08/34063

Industria y Comercio

SUPERINTENDENCIA

PCT

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

08-34063

SOLICITUD DE PATENTE DE INVENCIÓN

TITULO: NUEVAS PIRAZOLOPIRIMIDINAS COMO INHIBIDORES DE QUINASA DEPENDIENTES DE CICLINA

SOLICITANTE: SCHERING CORPORATION

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

A 61 K 31/519

APODERADO: CARLOS R. OLARTE

BOGOTÁ 3 Abril de 2008

P2008/000072

OLARTE RAISBECK

115

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-034063- -00000-0000
Fecha: 2008-04-04 16:28:48 Dep: 2020 NUECREACION
Tra: 11 PATENTE(YII Eve: 378 FASENACIONAL
Act: 411 PRESENTACION Folios: 1378

PETITORIO - FORMULARIO
PATENTE PCT
ENTRADA EN FASE NACIONAL **P2008/000072**

SOLICITUD DE:

(1)

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

[X] Capítulo I. [ ] Capítulo II.

(2)

SOLICITANTE (71)

Nombre: SCHERING CORPORATION

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

Nacionalidad o Domicilio: Estadounidense

Lugar de Constitución: Estados Unidos

Teléfono: _____ **Fax:** _____

E-mail: _____

IDENTIFICACIÓN

C.C. [ ] **NIT** [ ]

C.E. [ ] **Otro** [ ]

Cual _____

Número _____

REPRESENTANTE O APODERADO

Nombre: CARLOS R. OLARTE

Dirección: World Trade Center, Torre A, Calle 100 No. 8A-37 Piso 10.

Teléfono: 601-7700 **Fax:** 601-7799

E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN

C.C. [x] **NIT** [ ]

C.E. [ ] **Otro** [ ]

Cual _____

Número 79.782.747 Btá

TP 74.295

INVENTOR (ES) (72)

Nombre: VER PAGINA ADJUNTA

Dirección: VER PAGINA ADJUNTA

Nacionalidad o Domicilio: _____

(5)

PCT (86)

Solicitud Internacional No. PCT/US2006/038939 Fecha Octubre 4, 2006

Publicación Internacional No. WO 2007/044449 Fecha Abril 19, 2007

(6)

Título (54) **NUEVAS PIRAZOLOPIRIMIDINAS COMO INHIBIDORES DE QUINASA DEPENDIENTES DE CICLINA**

Clasificación Internacional (51) C07D 487/04, A61K 31/519, A61P 35/00

Prioridad

SI [X] **NO** [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitu
US	Octubre 6, 2005	11/245,401

(9)

Comprobante de pago No. 08-24,727 **Fecha** Marzo 26 de 2008

(0) **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. Ver expediente No. 06-120.230
- [ ] 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

(1) **FIGURA CARACTERÍSTICA:**

(2) 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.

LISTA DE IN VENTORES **PCT/US2006/038939**

1. **TIMOTHY J. GUZI,**
   48 Red Road, Chatham,
   NJ 07928
   Estados Unidos de América
   Nacionalidad: Estadounidense

2. **KAMIL PARUCH,**
   20 Third Avenue, Garwood,
   NJ 07027
   Estados Unidos de América
   Nacionalidad: Checo

3. **MICHAEL P. DWYER,**
   235 Katherine Street,
   Scotch Plains, NJ 07076
   Estados Unidos de América
   Nacionalidad: Estadounidense

4. **MARC LABROLI,**
   1405 August Circle, Mount
   Laurel, NJ 08054
   Estados Unidos de América
   Nacionalidad: Estadounidense

5. **KARTIK M. KEERTIKAR,**
   24 Columbia Avenue,
   East Windsor, NJ 08520
   Estados Unidos de América
   Nacionalidad: Estadounidense

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 08-034063- -00000-0000

Fecha: 2008-01-04 16:28:46 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIY# Eve: 378 FASENACIONALI
Act: 411 PRESENTACION Folios: 1376

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 900176089-2

) OFICIAL DE CAJA : 08 - 24,727
: MARZO 26 DE 2008

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

ITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
: RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	107000	26/03/2008	4,811,000.00

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

RENTISTICO	CONCEPTO		TOTAL CONCEPTO
50005-01-01 SOLICITUDES	: TRAMITES DE SOL. DE PATENTE DE IN		501,000.00
	TOTAL :	$	501,000.00

QUINIENTOS UN MIL PESOS

CAJERO : _____

) 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

6

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

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

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

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

CERTIFIED

5. AT TRENTON, NEW JERSEY

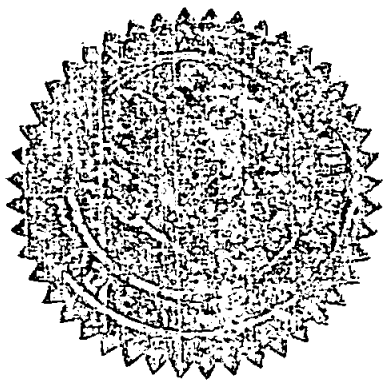
6. THE 29TH DAY OF AUGUST 2003

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

8. NO. A180345

9. SEAL/STAMP:

10. SIGNATURE



OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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

www.olarteraisbeck.com

Power of Attorney

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

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

Poder

El suscrito,

domiciliado en
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

WORLD TRADE CENTER – TORRE C
CALLE 100 NO. 8A-55 PISO 10
BOGOTA, COLOMBIA
TELEPHONE: +57-1 638-8200
FAX: +57-1 638-8201

www.olarteraisbeck.com

Notarial Certification

On this date, August 7, 2003

The undersigned Notary Public certifies:

1. That Edward H. Mazer

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

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

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

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

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):
Power of Attorney, dated November 4, 2002.

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

mayor de edad y domiciliado

suscribió el documento que antecede.

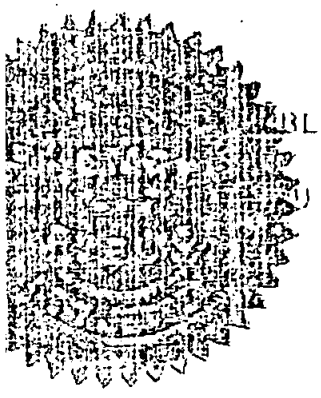
2. Que el otorgante ha suscrito el referido documento en su carácter de

de

4. Que
con sede principal ubicada en
está legalmente constituida, que tiene existencia legal vigente y que los propósitos para los cuales se otorga el poder se encuentra dentro de los que comprenden su objeto social.

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

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



BLIC (Signature): Marguerite LaCorte

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

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

(19) World Intellectual Property Organization
International Bureau

PCT

(43) International Publication Date
19 April 2007 (19.04.2007)

(10) International Publication Number
WO 2007/044449 A2

(51) International Patent Classification:
C07D 487/04 (2006.01) *A61P 35/00* (2006.01)
A61K 31/519 (2006.01)

(21) International Application Number:
PCT/US2006/038939

(22) International Filing Date: 4 October 2006 (04.10.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
11/245,401 6 October 2005 (06.10.2005) US

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

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: GUZI, Timothy, J. [US/US]; 48 Red Road, Chatham, NJ 07928 (US). PARUCH, Kamil [CZ/US]; 20 Third Avenue, Garwood, NJ 07027 (US). DWYER, Michael, P. [US/US]; 235 Katherine Street, Scotch Plains, NJ 07076 (US). LABROLI, Marc [US/US]; 1405 August Circle, Mount Laurel, NJ 08054 (US). KEERTIKAR, Kartik, M. [US/US]; 24 Columbia Avenue, East Windsor, NJ 08520 (US).

(74) Agent: KALYANARAMAN, Palaiyur, S.; SCHERING-PLOUGH CORPORATION, Patent Department, K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

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

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, 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*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NOVEL PYRAZOLOPYRIMIDINES AS CYCLIN DEPENDENT KINASE INHIBITORS

(57) Abstract: In its many embodiments, the present invention provides a novel class of pyrazolo[1,5-a]pyrimidine compounds as inhibitors of cyclin dependent kinases, methods of preparing such compounds, pharmaceutical compositions containing one or more such compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention, inhibition, or amelioration of one or more diseases associated with the CDKs using such compounds or pharmaceutical compositions.

WO 2007/044449 A2

NOVEL PYRAZOLOPYRIMIDINES AS CYCLIN DEPENDENT KINASE INHIBITORS

Field of the Invention

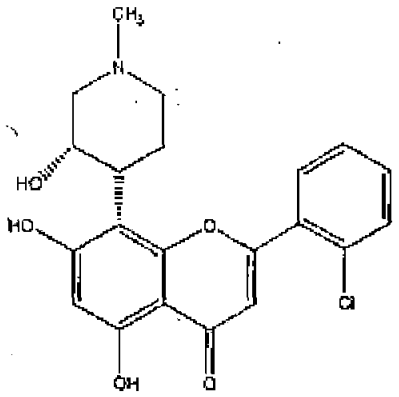
The present invention relates to pyrazolo[1,5-a]pyrimidine compounds useful as protein kinase inhibitors (such as for example, the inhibitors of the cyclin-dependent kinases, mitogen-activated protein kinase (MAPK/ERK), glycogen synthase kinase 3(GSK3beta) and the like), pharmaceutical compositions containing the compounds, and methods of treatment using the compounds and compositions to treat diseases such as, for example, cancer, inflammation, arthritis, viral diseases, neurodegenerative diseases such as Alzheimer's disease, cardiovascular diseases, and fungal diseases. This application claims benefit of priority from U.S. provisional patent applications, Serial No. 60/408,027 filed September 4, 2002, and Serial No. 60/421,959 filed October 29, 2002.

Background of the Invention

Protein kinase inhibitors include kinases such as, for example, the inhibitors of the cyclin-dependent kinases (CDKs), mitogen activated protein kinase (MAPK/ERK), glycogen synthase kinase 3 (GSK3beta), and the like. Protein kinase inhibitors are described, for example, by M. Hale *et* al in WO02/22610 A1 and by Y. Mettey *et* al in *J. Med. Chem.*, (2003) 46 222-236. The cyclin-dependent kinases are serine/threonine protein kinases, which are the driving force behind the cell cycle and cell proliferation. Individual CDK's, such as, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6 and CDK7, CDK8, CDK9 and the like, perform distinct roles in cell cycle progression and can be classified as either

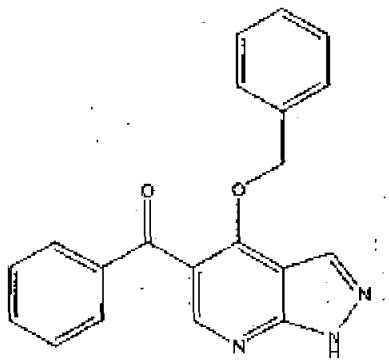
G1, S, or G2M phase enzymes. Uncontrolled proliferation is a hallmark of cancer cells, and misregulation of CDK function occurs with high frequency in many important solid tumors. CDK2 and CDK4 are of particular interest because their activities are frequently misregulated in a wide variety of human cancers. CDK2 activity is required for progression through G1 to the S phase of the cell cycle, and CDK2 is one of the key components of the G1 checkpoint. Checkpoints serve to maintain the proper sequence of cell cycle events and allow the cell to respond to insults or to proliferative signals, while the loss of proper checkpoint control in cancer cells contributes to tumorgenesis. The CDK2 pathway influences tumorgenesis at the level of tumor suppressor function (e.g. p52, RB, and p27) and oncogene activation (cyclin E). Many reports have demonstrated that both the coactivator, cyclin E, and the inhibitor, p27, of CDK2 are either over – or underexpressed, respectively, in breast, colon, nonsmall cell lung, gastric, prostate, bladder, non-Hodgkin's lymphoma, ovarian, and other cancers. Their altered expression has been shown to correlate with increased CDK2 activity levels and poor overall survival. This observation makes CDK2 and its regulatory pathways compelling targets for the development years, a number of adenosine 5'-triphosphate (ATP) competitive small organic molecules as well as peptides have been reported in the literature as CDK inhibitors for the potential treatment of cancers. U.S. 6,413,974, col. 1, line 23- col. 15, line 10 offers a good description of the various CDKs and their relationship to various types of cancer.

CDK inhibitors are known. For example, flavopiridol (Formula I) is a nonselective CDK inhibitor that is currently undergoing human clinical trials, A. M. Sanderowicz *et al*, *J. Clin. Oncol.* (1998) 16, 2986-2999.



Formula I

Other known inhibitors of the CDKs include, for example, olomoucine (J. Vesely *et al, Eur. J. Biochem.*, (1994) 224, 771-786) and roscovitine (I. Meijer *et al, Eur. J. Biochem.*, (1997) 243, 527-536). U.S. 6,107,305 describes certain pyrazolo[3,4-b] pyridine compounds as CDK inhibitors. An illustrative compound from the '305 patent has the Formula II:



Formula II

K. S. Kim *et al, J. Med. Chem.* 45 (2002) 3905-3927 and WO 02/10162 disclose certain aminothiazole compounds as CDK inhibitors.

Pyrazolopyrimidines are known. For Example, WO92/18504, WO02/50079, WO95/35298, WO02/40485, EP94304104.6, EP0628559 (equivalent to US Patents 5,602,136, 5,602,137 and 5,571,813), U.S. 6,383,790, *Chem. Pharm. Bull.*, (1999) 47 928, *J. Med. Chem.*, (1977) 20, 296, *J. Med. Chem.*, (1976) 19 517 and *Chem. Pharm. Bull., (1962)* 10 620 disclose various pyrazolopyrimidines. Other publications of interest are: WO 03/101993

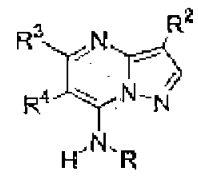
(published December 11, 2003), WO 03/091256 (published November 6, 2003), and DE 10223917 (published December 11, 2003).

There is a need for new compounds, formulations, treatments and therapies to treat diseases and disorders associated with CDKs. It is, therefore, an object of this invention to provide compounds useful in the treatment or prevention or amelioration of such diseases and disorders.

Summary of the Invention

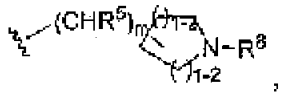
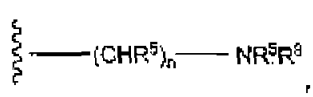
In its many embodiments, the present invention provides a novel class of pyrazolo[1,5-a]pyrimidine compounds as inhibitors of cyclin dependent kinases, methods of preparing such compounds, pharmaceutical compositions comprising one or more such compounds, methods of preparing pharmaceutical formulations comprising one or more such compounds, and methods of treatment, prevention, inhibition or amelioration of one or more diseases associated with the CDKs using such compounds or pharmaceutical compositions.

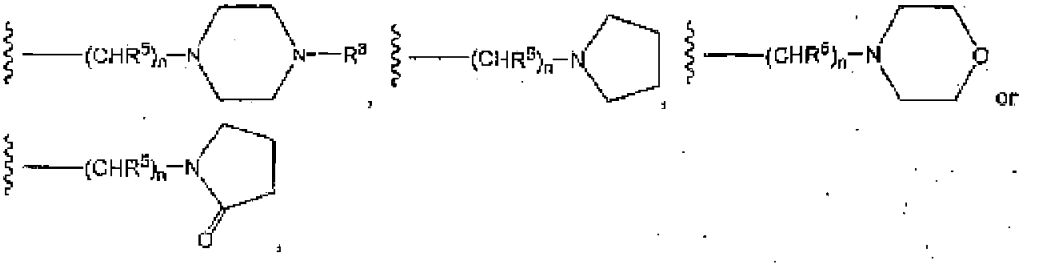
In one aspect, the present application discloses a compound, or pharmaceutically acceptable salts or solvates of said compound, said compound having the general structure shown in Formula III:



Formula III

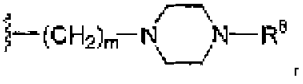
wherein:

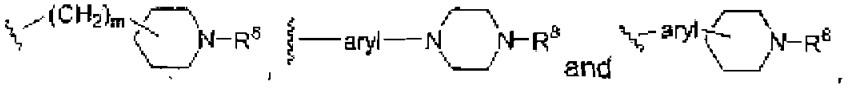
R is H, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, cycloalkyl, cycloalkylalkyl, alkenylalkyl, alkynylalkyl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl (including N-oxide of said heteroaryl), -$(CHR^5)_n$-aryl, -$(CHR^5)_n$-heteroaryl,  ,  ,



wherein each of said alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocyclyl, and heteroaryl 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, heterocyclylalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^{10}$, $-C(R^4R^5)_p-R^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^{10}$, $-SO_3H$, $-SR^{10}$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^{10}$;

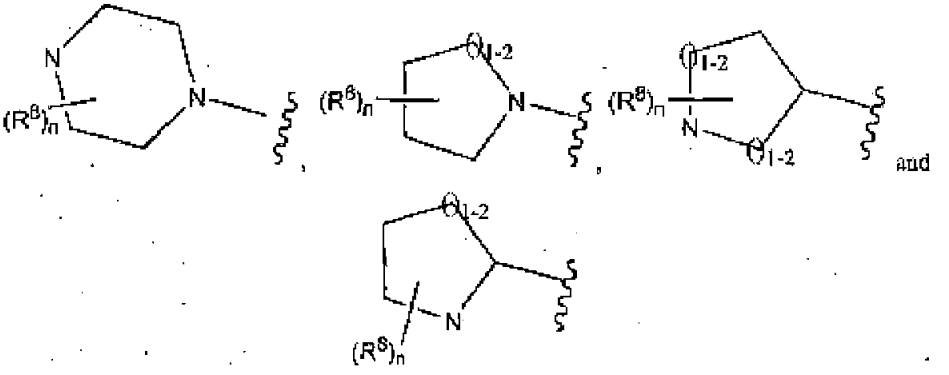
R^2 is selected from the group consisting of H, R^9, alkyl; alkenyl, alkynyl, CF_3, heterocyclyl, heterocyclylalkyl, halogen, haloalkyl, aryl, arylalkyl, heteroarylalkyl, alkynylalkyl, cycloalkyl, heteroaryl, alkyl substituted with 1-6 R^9 groups which can be the same or different and are independently selected from the list of R^9 shown below, aryl substituted with 1-3 aryl or heteroaryl groups which can be the same or different and are independently selected from phenyl, pyridyl, thiophenyl, furanyl and thiazolo groups, aryl fused with an aryl or heteroaryl group, heteroaryl substituted with 1-3 aryl or heteroaryl groups which can be the same or different and are independently selected from phenyl, pyridyl, thiophenyl, furanyl and thiazolo groups, heteroaryl fused with an aryl or heteroaryl group,





wherein one or more of the aryl and/or one or more of the heteroaryl in the above-noted definitions for R^2 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, -CN, $-OR^5$, $-SR^5$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-NR^5R^6$, $-C(O)NR^5R^6$, CF_3, alkyl, aryl and OCF_3;

R^3 is selected from the group consisting of H, halogen, $-NR^5R^6$, $-OR^6$, $-SR^6$, $-C(O)N(R^5R^6)$, alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl,



and

wherein each of said alkyl, cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl and heteroarylalkyl for R^3 and the heterocyclyl moieties whose structures are shown immediately above for R^3 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, aryl, cycloalkyl, CF_3, CN, $-OCF_3$, $-(CR^4R^5)_pOR^5$, $-OR^5$, $-NR^5R^6$, $-(CR^4R^5)_pNR^5R^6$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^6$, $-SR^5$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$, $-N(R^5)C(R^4R^5)_nN(R^5R^6)$ and $-N(R^5)C(O)NR^5R^6$, with the proviso that no carbon adjacent to a nitrogen atom on a heterocyclyl ring carries a $-OR^5$ moiety;

R^4 is H, halo or alkyl;

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

R^6 is selected from the group consisting of H, Boc, alkyl, alkenyl, aryl, arylalkyl, arylalkenyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl, wherein each of said alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl 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, heterocyclylalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^{10}$, $-C(R^4R^5)_p-R^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^9$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^{10}$, $-SO_3H$, $-SR^{10}$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^{10}$;

R^{10} is selected from the group consisting of H, alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl, wherein each of said alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, and heteroarylalkyl 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, heterocyclylalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^4R^5$, $-C(R^4R^5)_p-R^9$, -N(R^5)Boc, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)NR^4R^5$, $-C(O)R^5$, $-SO_3H$, $-SR^5$, $-S(O_2)R^7$, $-S(O_2)NR^4R^5$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^4R^5$;

or optionally (i) R^5 and R^{10} in the moiety $-NR^5R^{10}$, or (ii) R^5 and R^6 in the moiety $-NR^5R^6$, may be joined together to form a cycloalkyl or heterocyclyl moiety, with each of said cycloalkyl or heterocyclyl moiety being unsubstituted or optionally independently being substituted with one or more R^9 groups;

R^7 is selected from the group consisting of alkyl, cycloalkyl, aryl, arylalkenyl, heteroaryl, arylalkyl, heteroarylalkyl, heteroarylalkenyl, and heterocyclyl, wherein each of said alkyl, cycloalkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl 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, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^{10}$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^{10}$, $-C(O)R^5$, $-SR^{10}$, $-S(O_2)R^{10}$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^{10}$, $-N(R^5)C(O)R^{10}$ and $-N(R^5)C(O)NR^5R^{10}$;

R^8 is selected from the group consisting of R^6, $-OR^6$, $-C(O)NR^5R^{10}$, $-S(O_2)NR^5R^{10}$, $-C(O)R^7$, $-C(=N-CN)-NH_2$, $-C(=NH)-NHR^5$, heterocyclyl, and $-S(O_2)R^7$;

R^9 is selected from the group consisting of halogen, -CN, $-NR^5R^{10}$, -SCN, $-NO_2$, $-C(O)R^5$, $-C(O_2)R^6$, $-C(O)NR^5R^{10}$, $-OR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$and $-N(R^5)C(O)NR^5R^{10}$;

m is 0 to 4;

n is 1 to 4; and

p is 1 to 4,

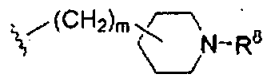
with the proviso that when R^2 is phenyl, R^3 is not alkyl, alkynyl or halogen, and that when R^2 is aryl, R is not  , and with the further proviso that when R is arylalkyl, then any heteroaryl substituent on the aryl of said arylalkyl contains at least three heteroatoms.

The compounds of Formula III can be useful as protein kinase inhibitors and can be useful in the treatment and prevention of proliferative diseases, for example, cancer, inflammation and arthritis. They may also be useful in the treatment of neurodegenerative diseases such Alzheimer's disease, cardiovascular diseases, viral diseases and fungal diseases.

Detailed Description

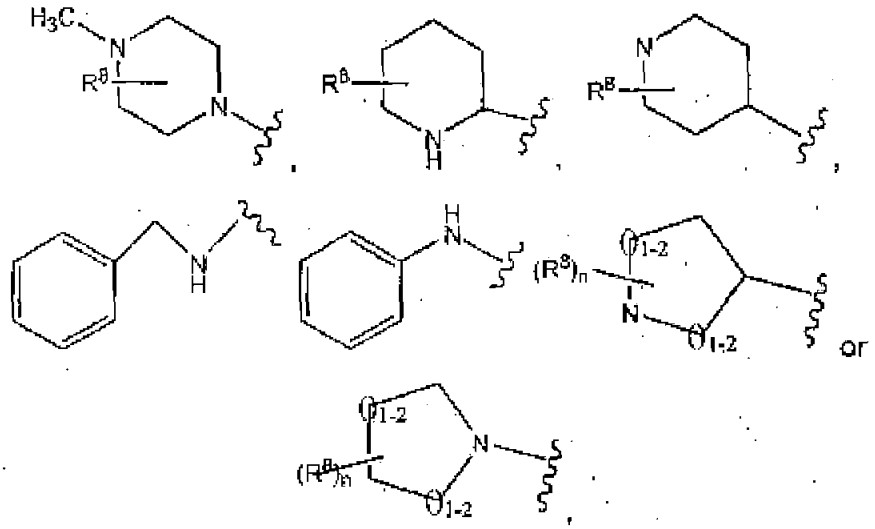
In one embodiment, the present invention discloses pyrazolo[1,5-a]pyrimidine compounds which are represented by structural Formula III, or a pharmaceutically acceptable salt or solvate thereof, wherein the various moieties are as described above.

In another embodiment, R is $-(CHR^5)_n$-aryl, $-(CHR^5)_n$-heteroaryl, $-(CHR^5)_n$-heteroaryl (with said heteroaryl being substituted with an additional, same or different, heteroaryl), $-(CHR^5)_n$-heterocyclyl (with said heterocyclyl being substituted with an additional, same or different, heterocyclyl), or



In another embodiment, R^2 is halogen, CF_3, CN, lower alkyl, alkyl substituted with $-OR^6$, alkynyl, aryl, heteroaryl or heterocyclyl.

In another embodiment, R^3 is H, lower alkyl, aryl, heteroaryl, cycloalkyl, $-NR^5R^6$,



wherein said alkyl, aryl, heteroaryl, cycloalkyl and the heterocyclyl structures shown immediately above for R^3 are 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, CF_3, OCF_3, lower alkyl, CN, $-C(O)R^5$, $-S(O_2)R^5$, $-C(=NH)-NH_2$, $-C(=CN)-NH_2$, hydroxyalkyl, alkoxycarbonyl, $-SR^5$, and OR^5, with the proviso that no carbon adjacent to a nitrogen atom on a heterocyclyl ring carries a $-OR^6$ moiety.

In another embodiment, R^4 is H or lower alkyl.

In another embodiment, R^5 is H, lower alkyl or cycloalkyl.

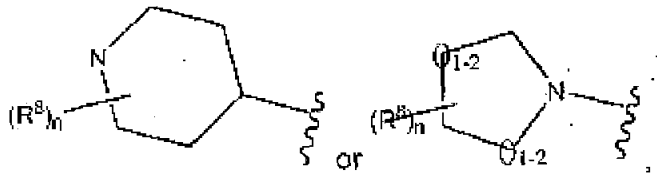
In another embodiment, n is 1 to 2.

In an additional embodiment, R is $-(CHR^5)_n$-aryl, $-(CHR^5)_n$-heteroaryl.

In an additional embodiment, R^2 is halogen, CF_3, CN, lower alkyl, alkynyl, or alkyl substituted with $-OR^6$.

In an additional embodiment, R^2 is lower alkyl, alkynyl or Br.

In an additional embodiment, R^3 is H, lower alkyl, aryl,



wherein said alkyl, aryl and the heterocyclyl moieties shown immediately above for R^3 are 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, CF_3, lower alkyl, hydroxyalkyl, alkoxy, $-S(O_2)R^5$, and CN.

In an additional embodiment, R^4 is H.

In an additional embodiment, R^5 is H, ethyl, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

In an additional embodiment, R^5 is alkyl or hydroxyalkyl.

In an additional embodiment, n is 1.

In an additional embodiment, p is 1 or 2.

In another embodiment, R is H.

In another embodiment, R^2 is halogen.

In another embodiment, R^2 is thiophene, furan, pyridine, pyrazole, alkylthio or arylthio, wherein each of said alkyl and aryl of R^2 can independently be unsubstituted or substituted as defined above.

In another embodiment, R^2 is thiophene, furan, pyridine or pyrazole.

In another embodiment, R^2 is an amide which can be unsubstituted or substituted as defined above.

In another embodiment, R^2 is an urea, which may be unsubstituted or substituted as defined above.

In another embodiment, R^2 is an alkenyl.

In another embodiment, R^2 is an alkynyl.

In another embodiment, R3 is $-NR^5R^6$.

In another embodiment, R^4 is H.

In another embodiment, R^4 is unsubstituted lower alkyl.

In another embodiment, R^4 is alkyl substituted with $-OR^6$.

In another embodiment, R^4 is halo.

In another embodiment, R^4 is -F, -Cl or -Br.

In another embodiment, both R^2 and R^4 are halogen.

In another embodiment, both R^2 and R^4 are halo and R is H.

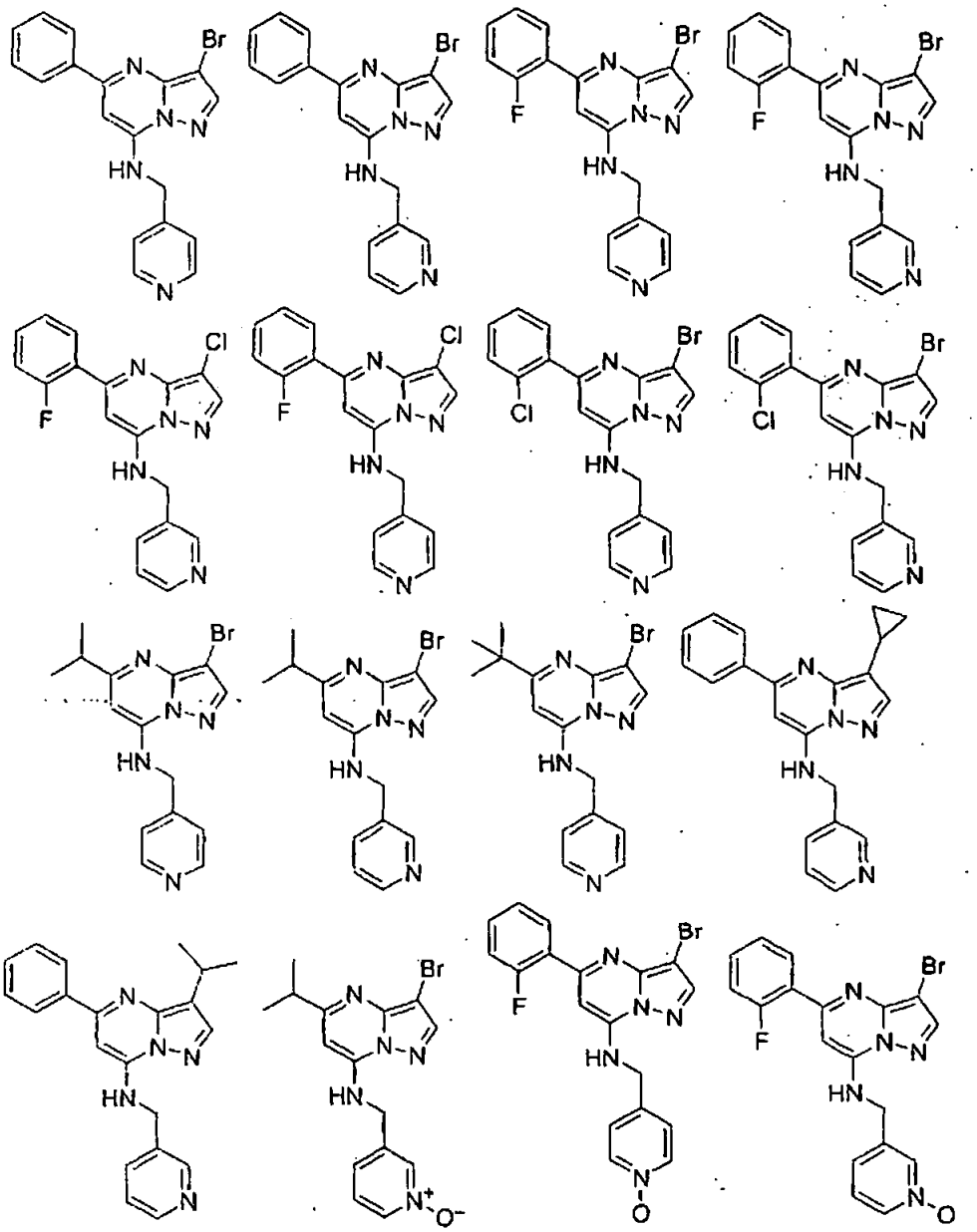
In another embodiment, R is H, R^2 is halo and R^3 is heteroaryl.

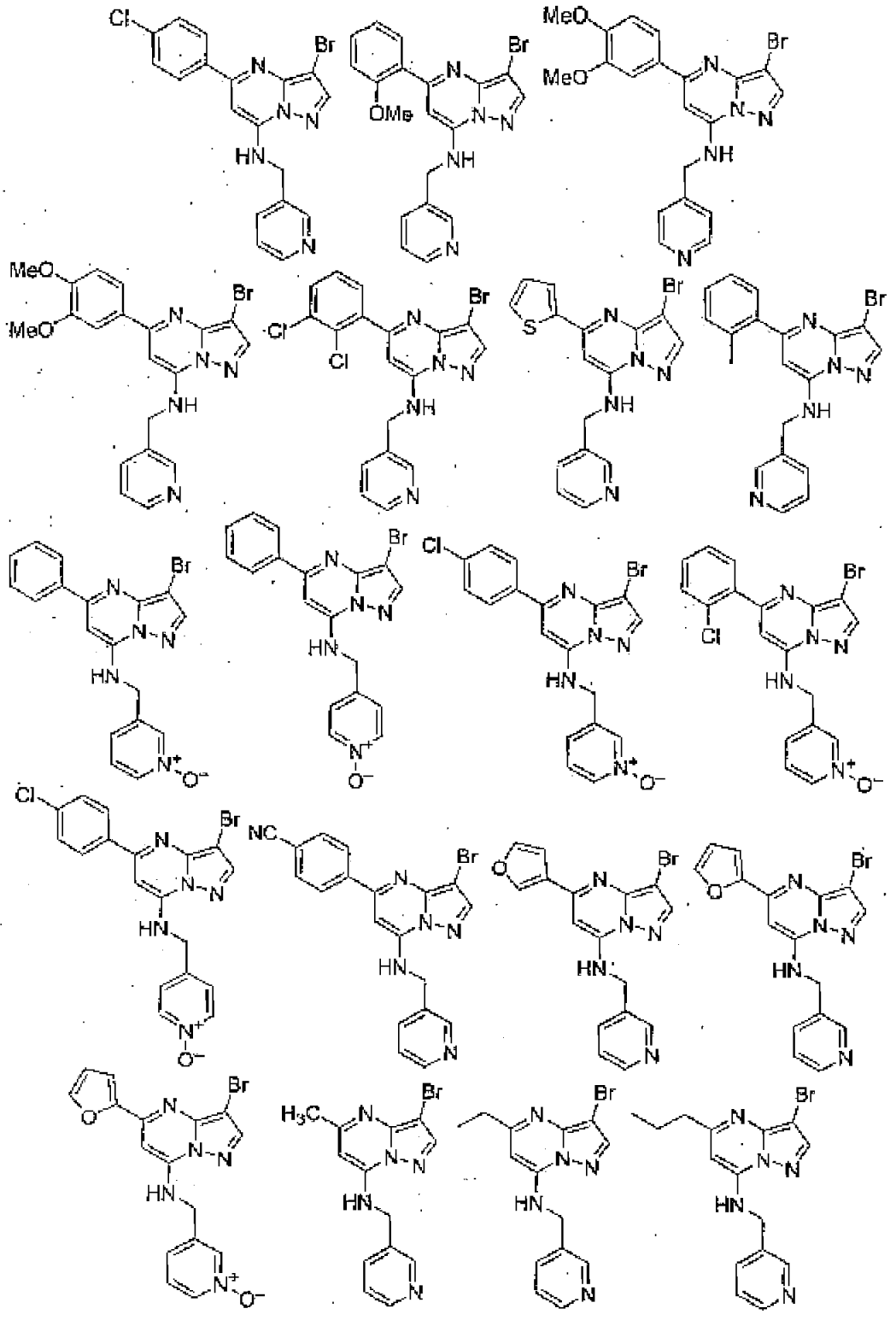
In another embodiment, R is H, R^2 is halo and R^3 is aryl.

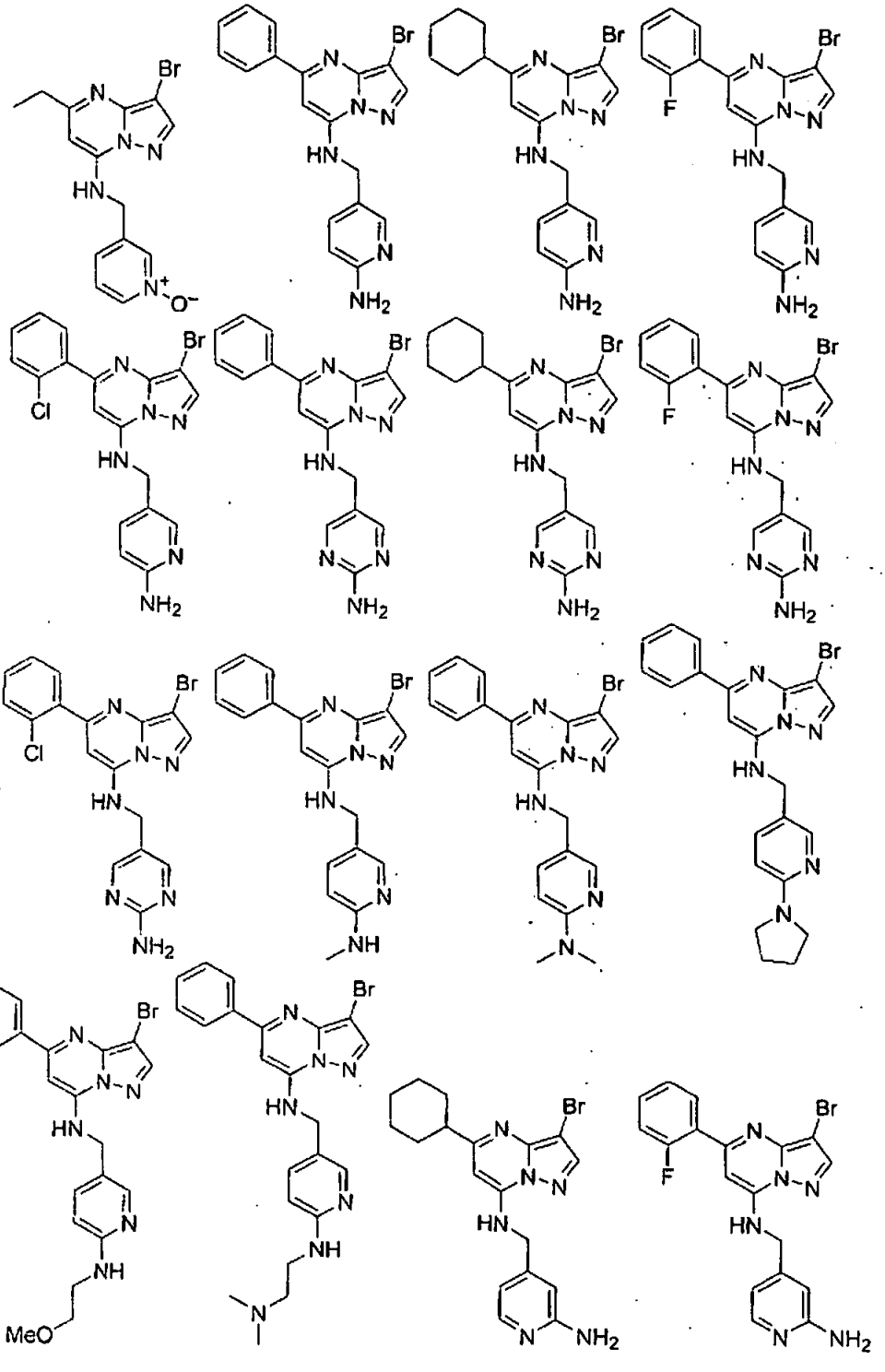
In another embodiment, R is H, R^2 is halo and R^3 is heterocyclyl.

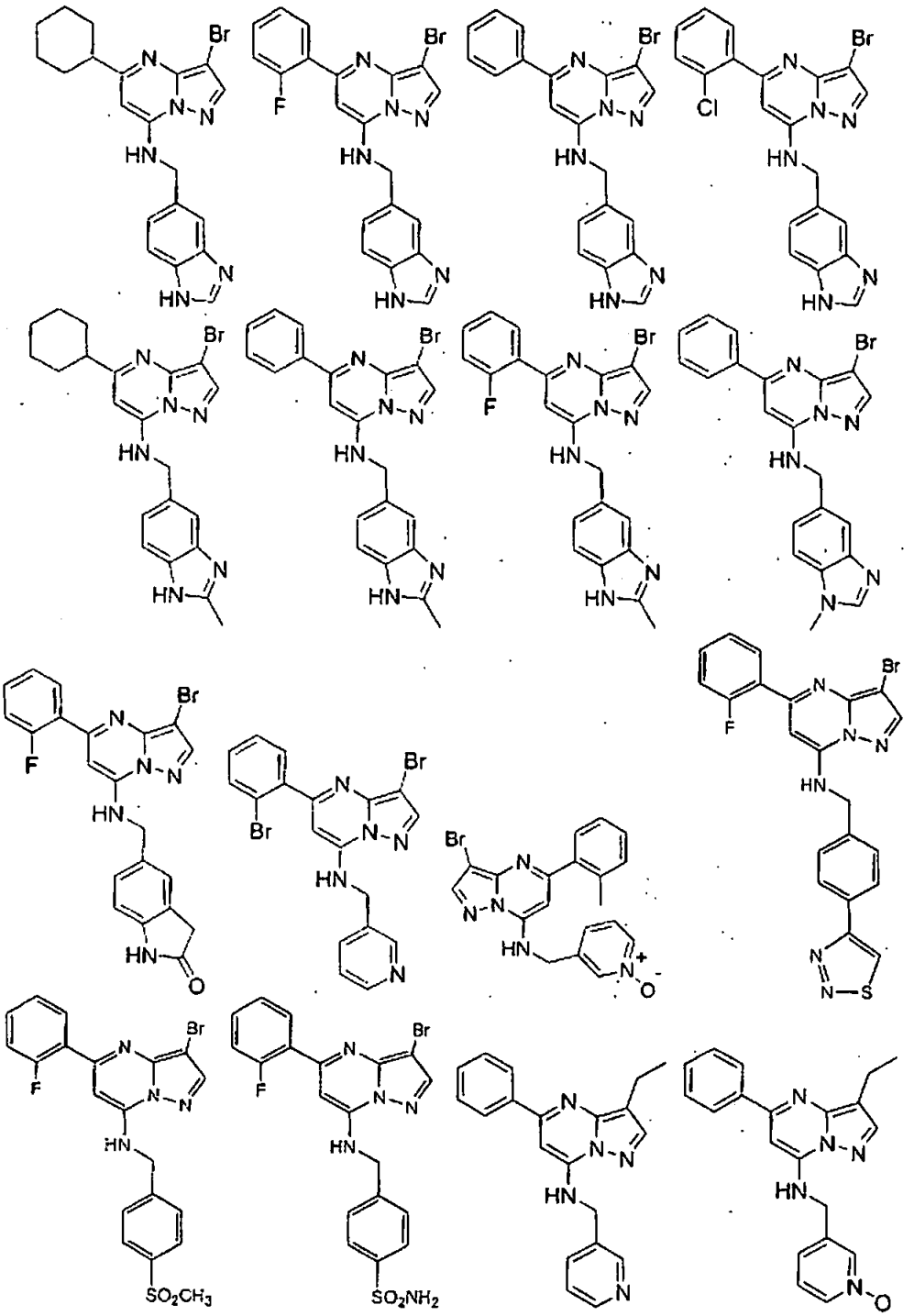
Another embodiment discloses the inventive compounds shown in **Table 1**, which exhibited CDK2 inhibitory activity of about 0.0001μM to > about 5 μM. The assay methods are described later (from page 333 onwards).

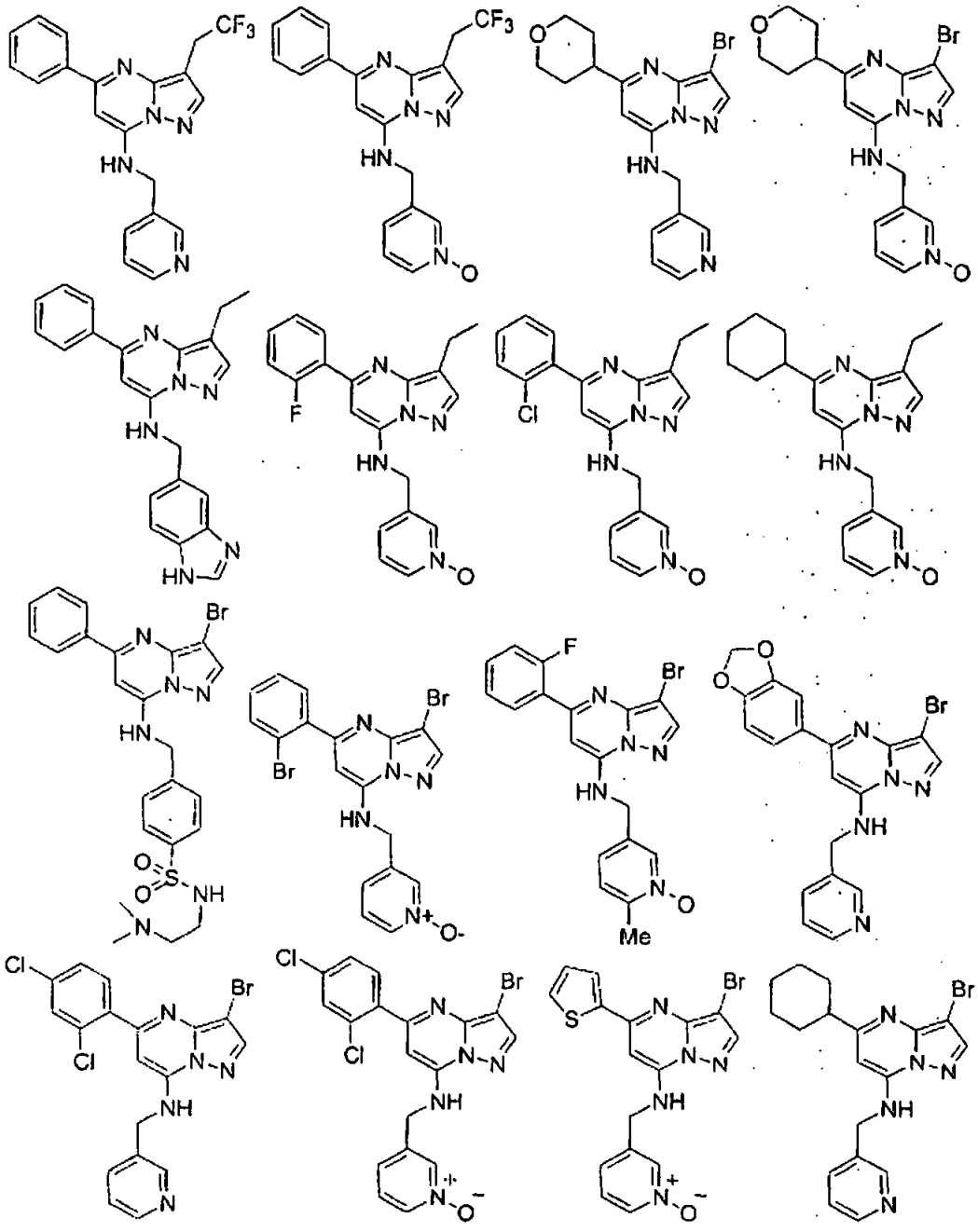
Table 1

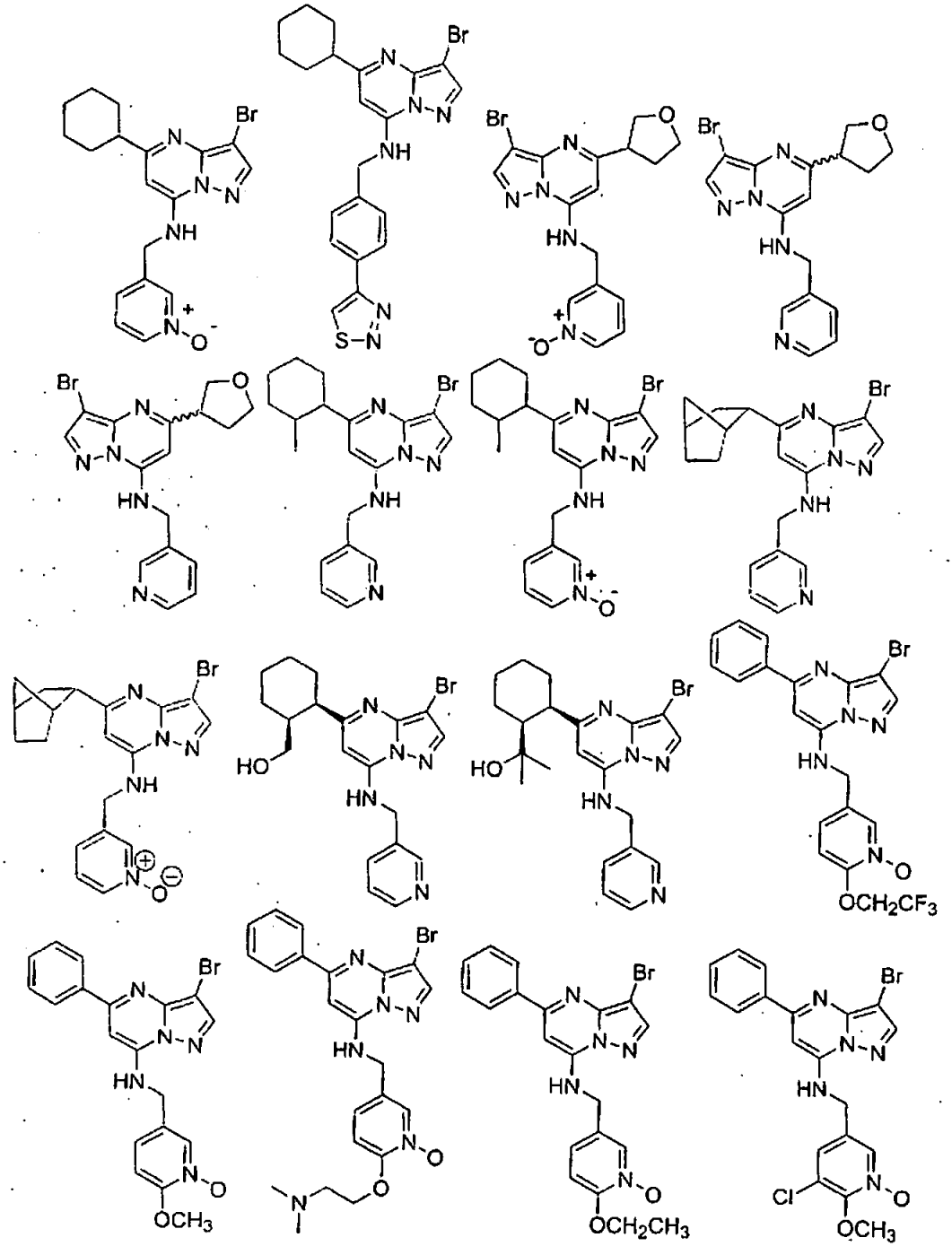


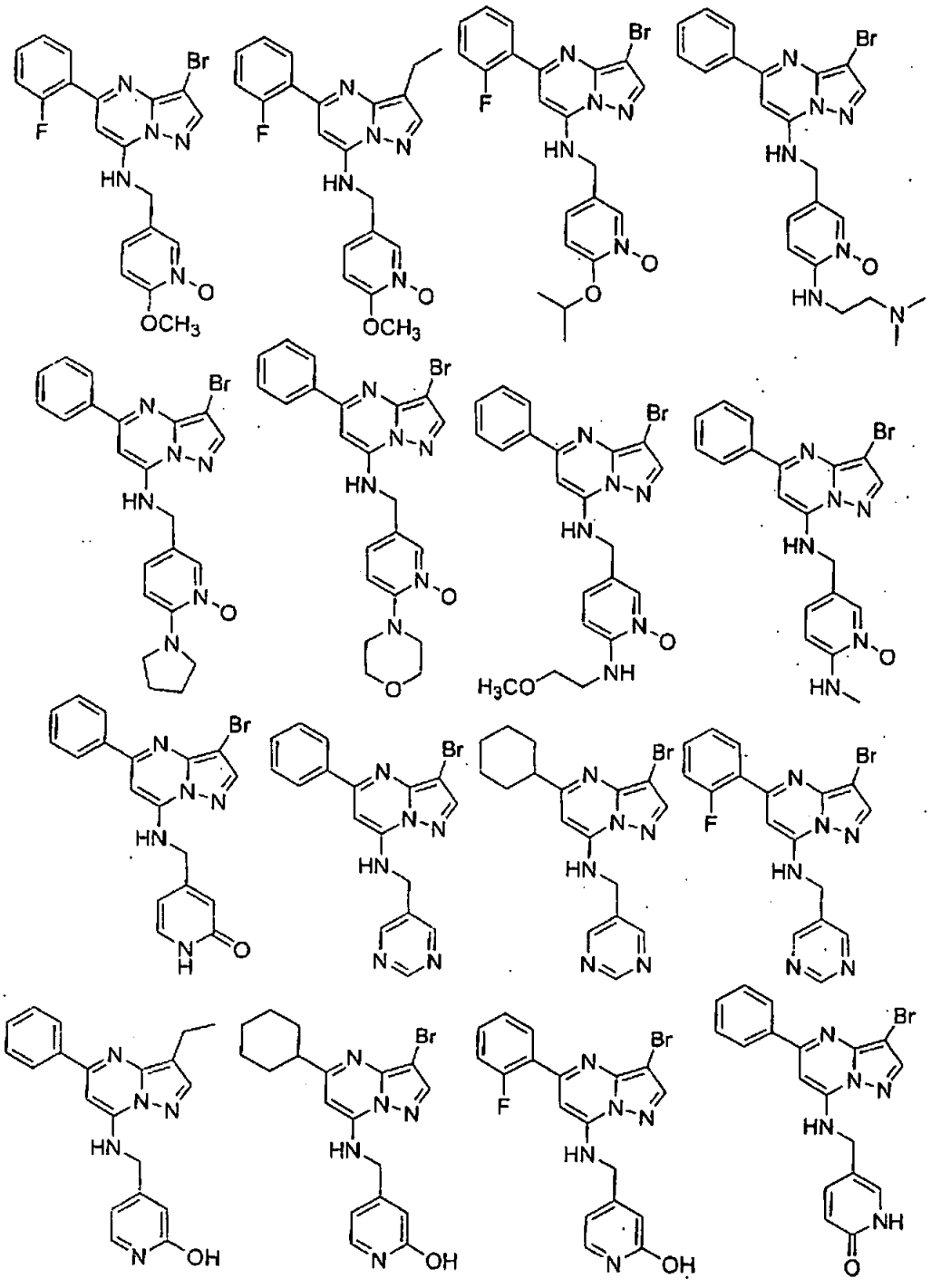


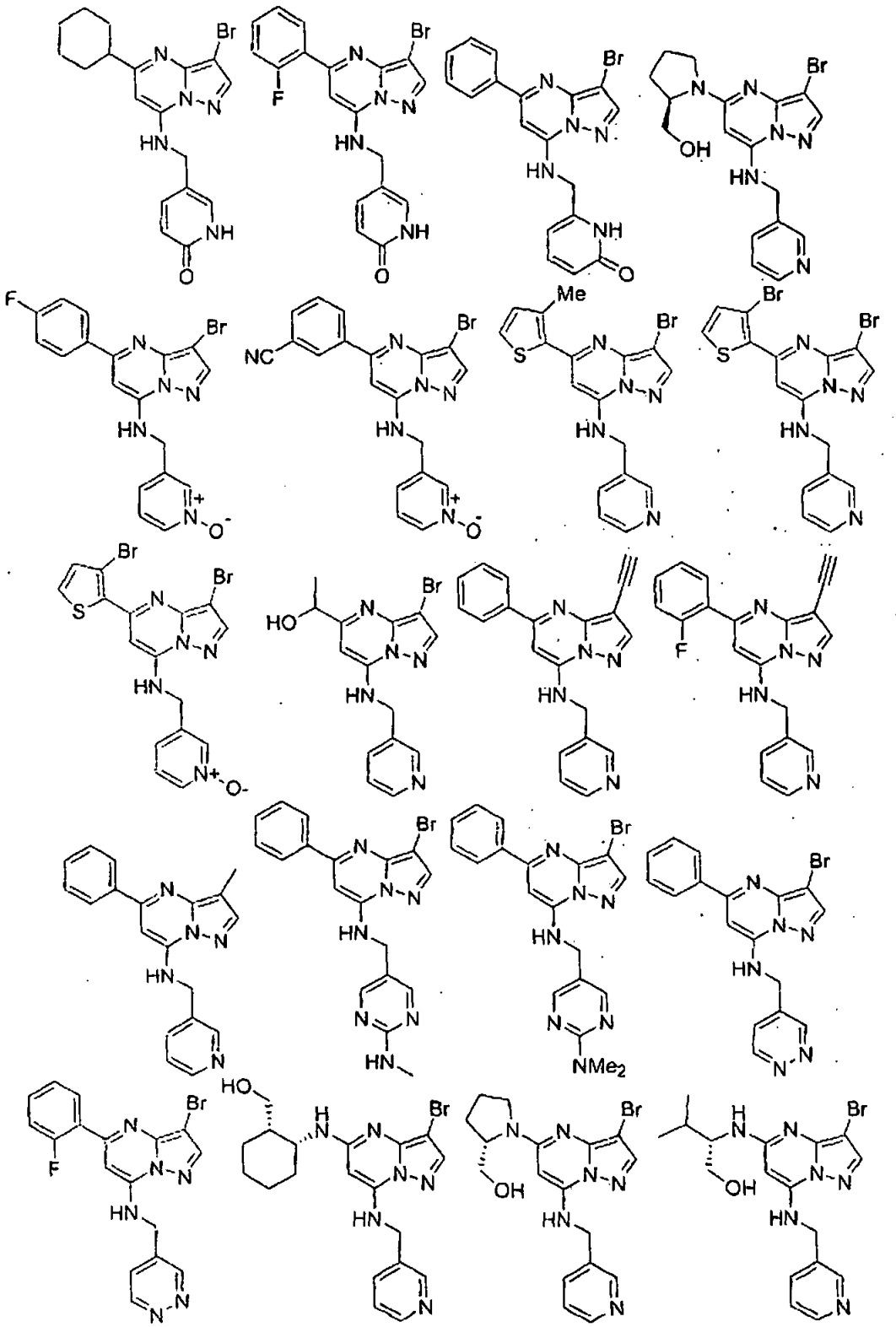




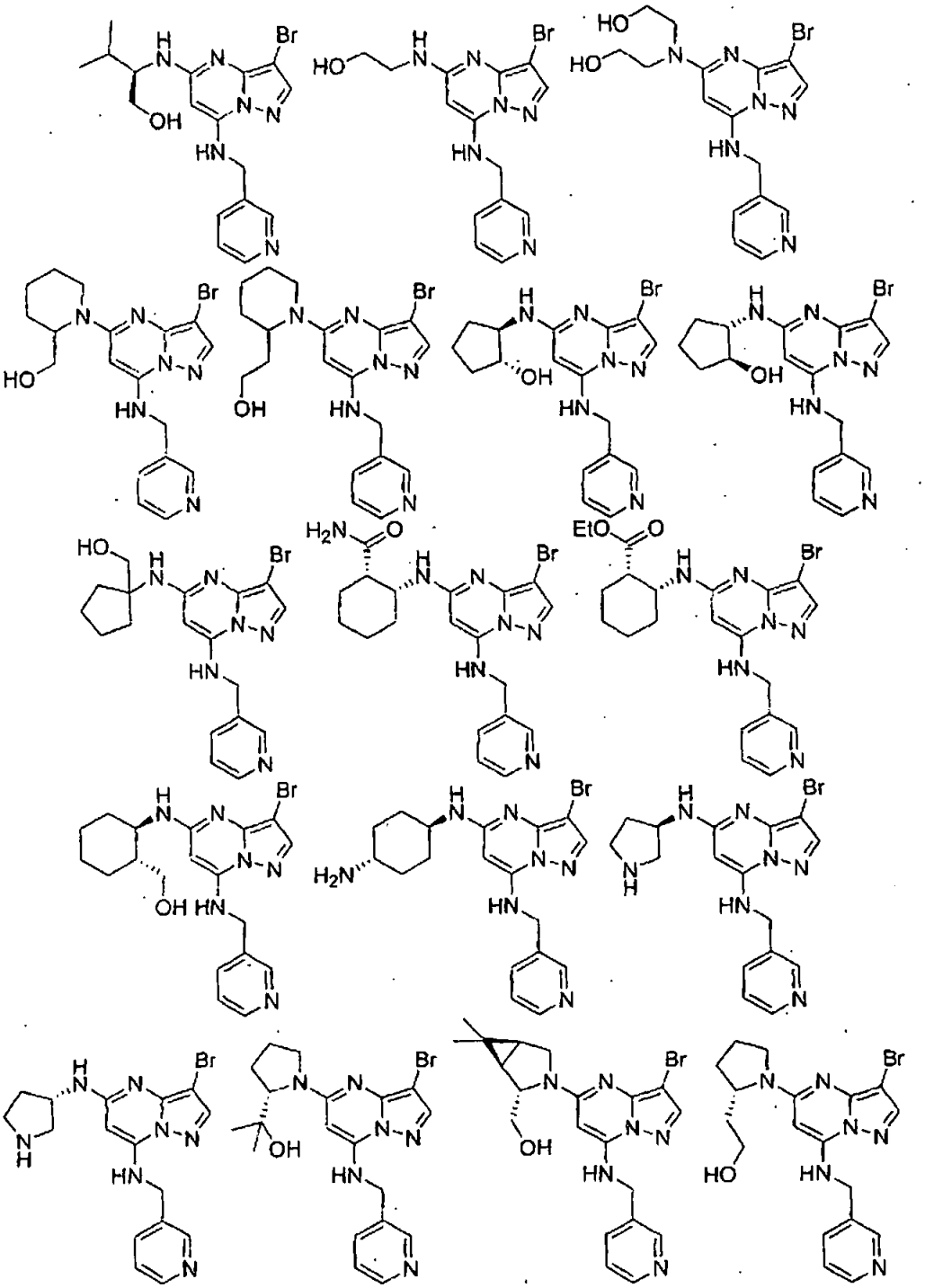




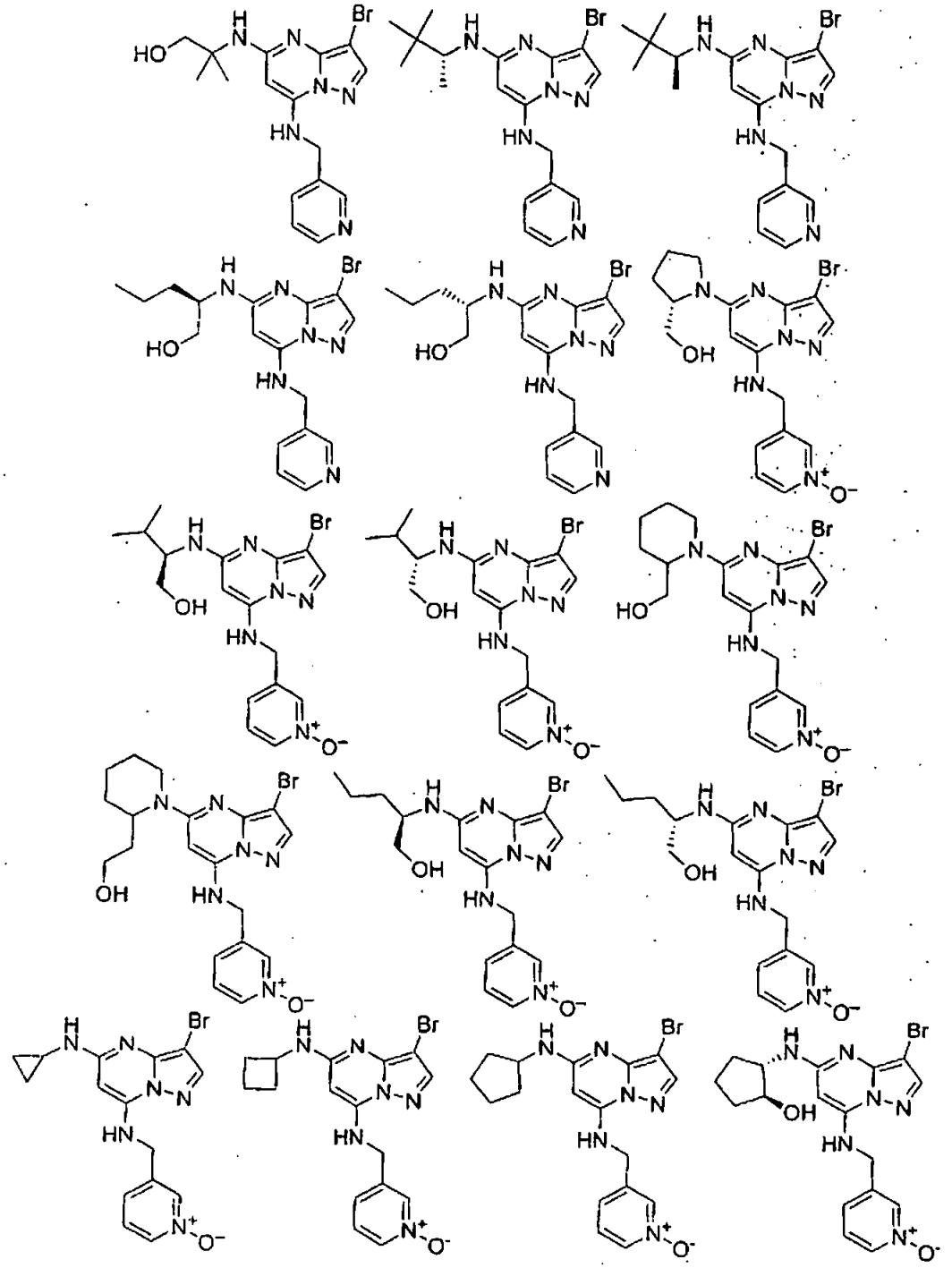




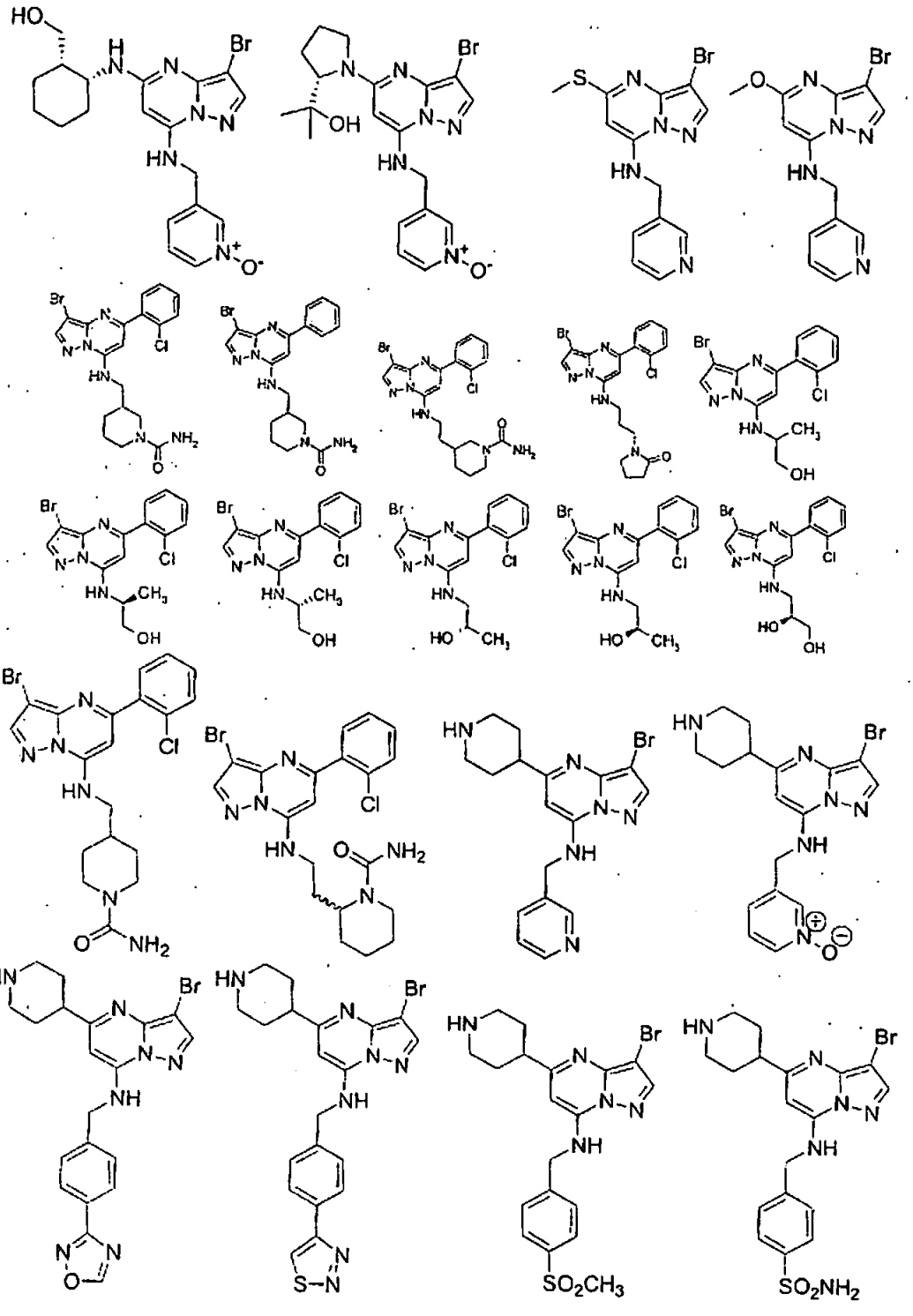
5



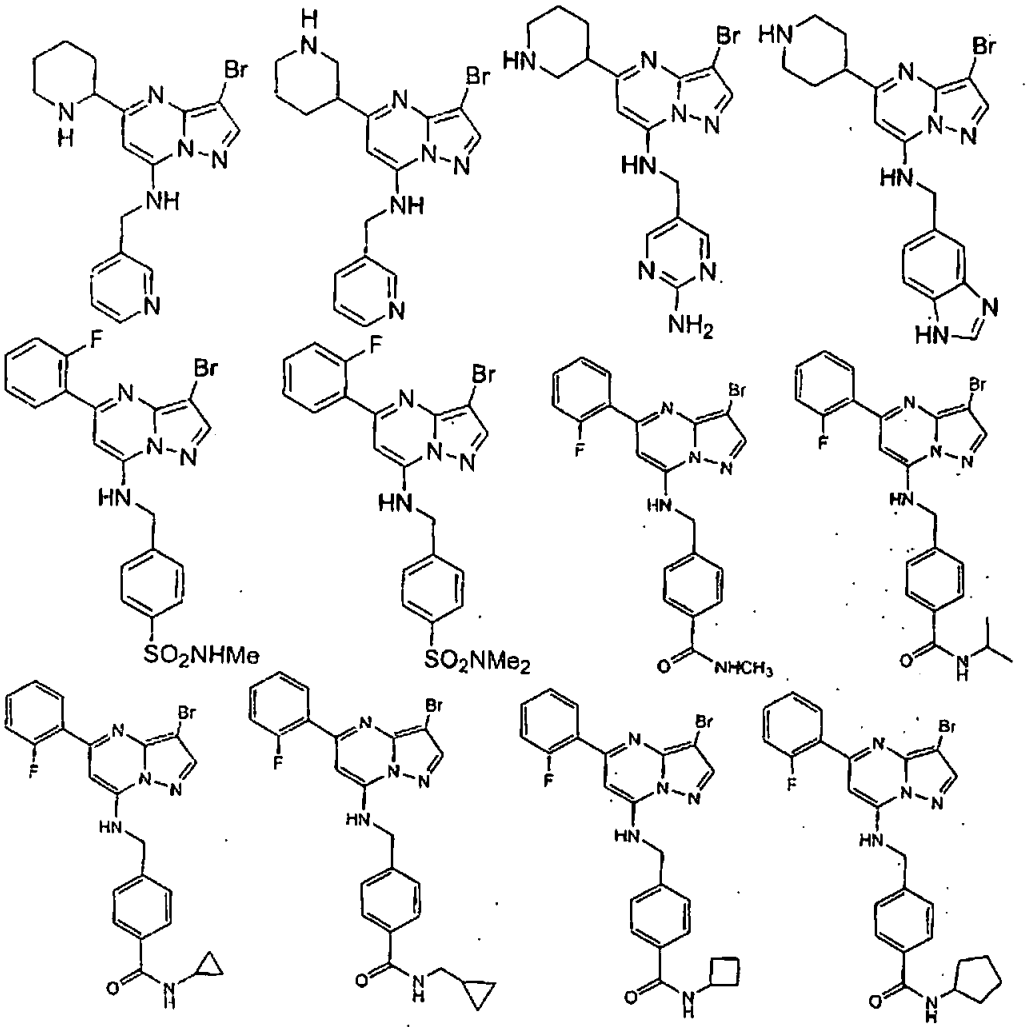
5

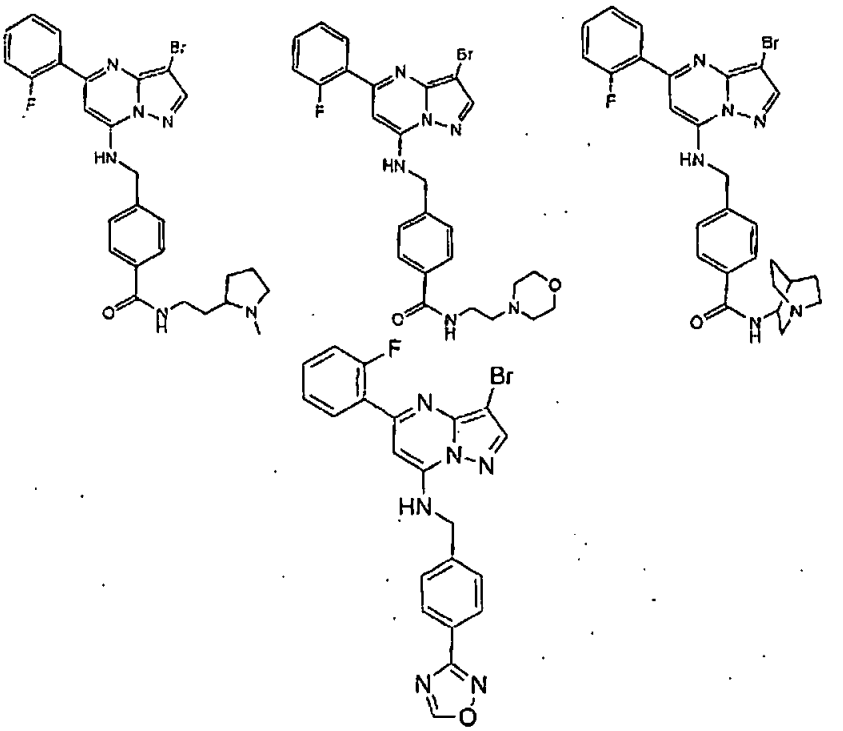


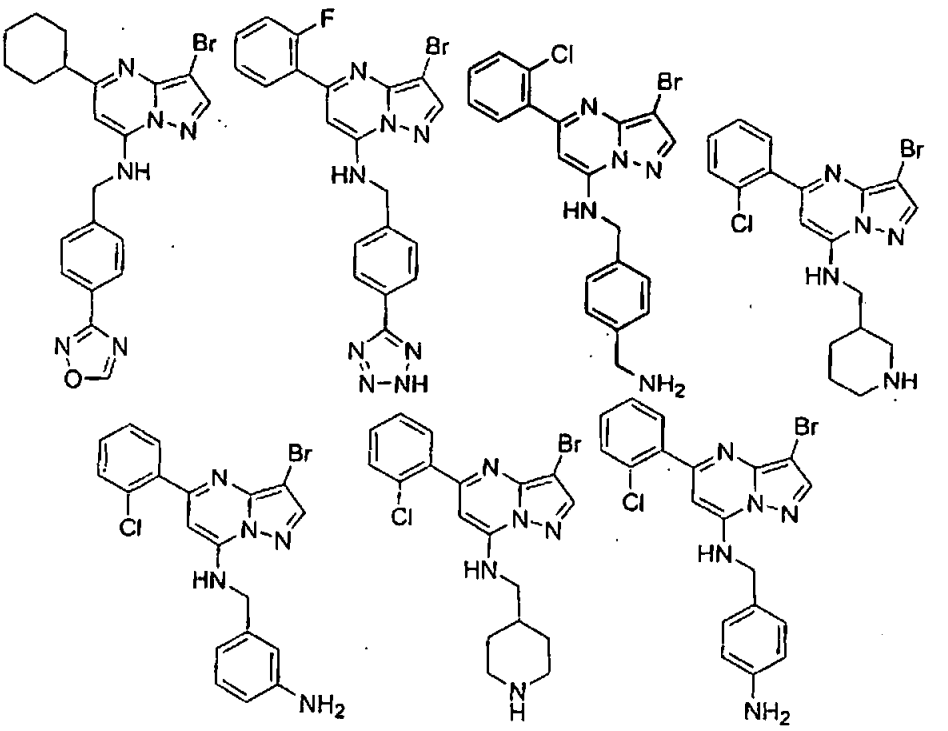
5



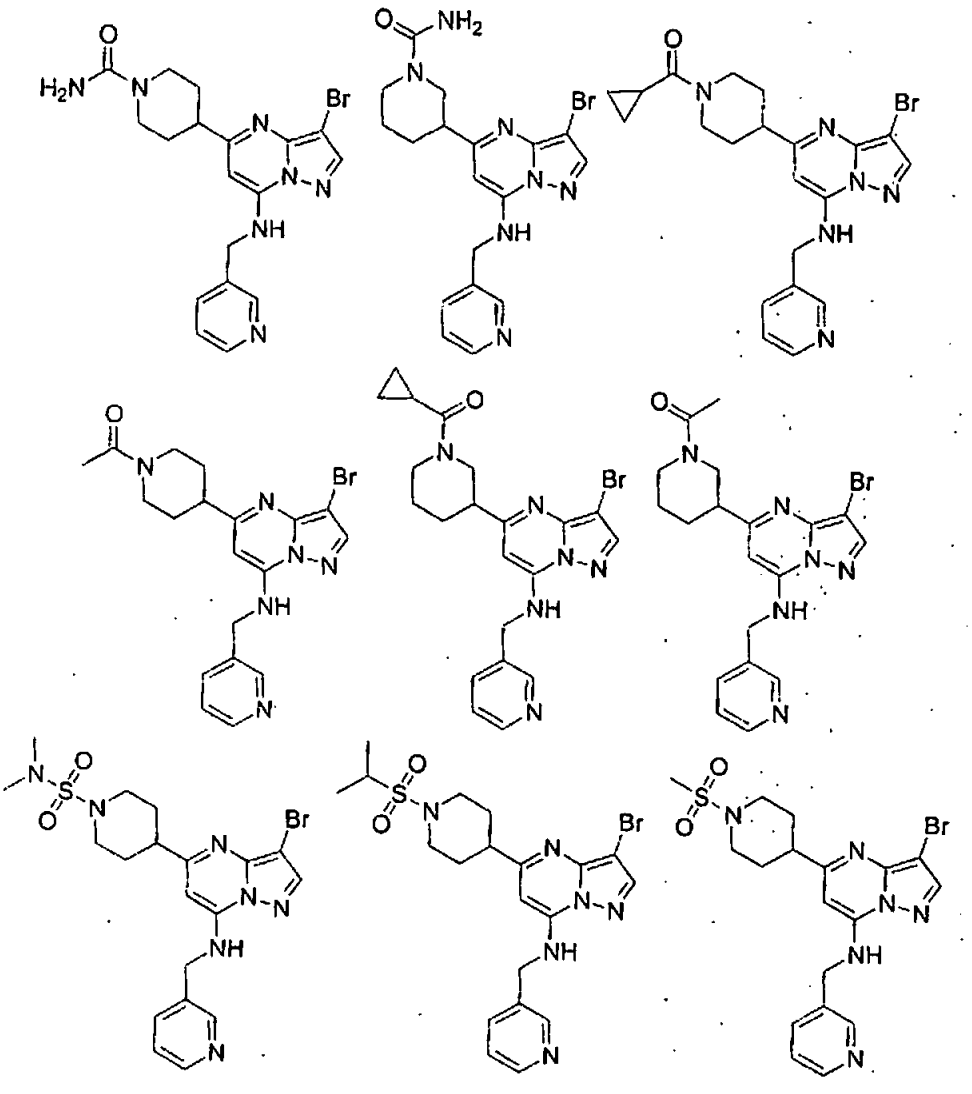
5

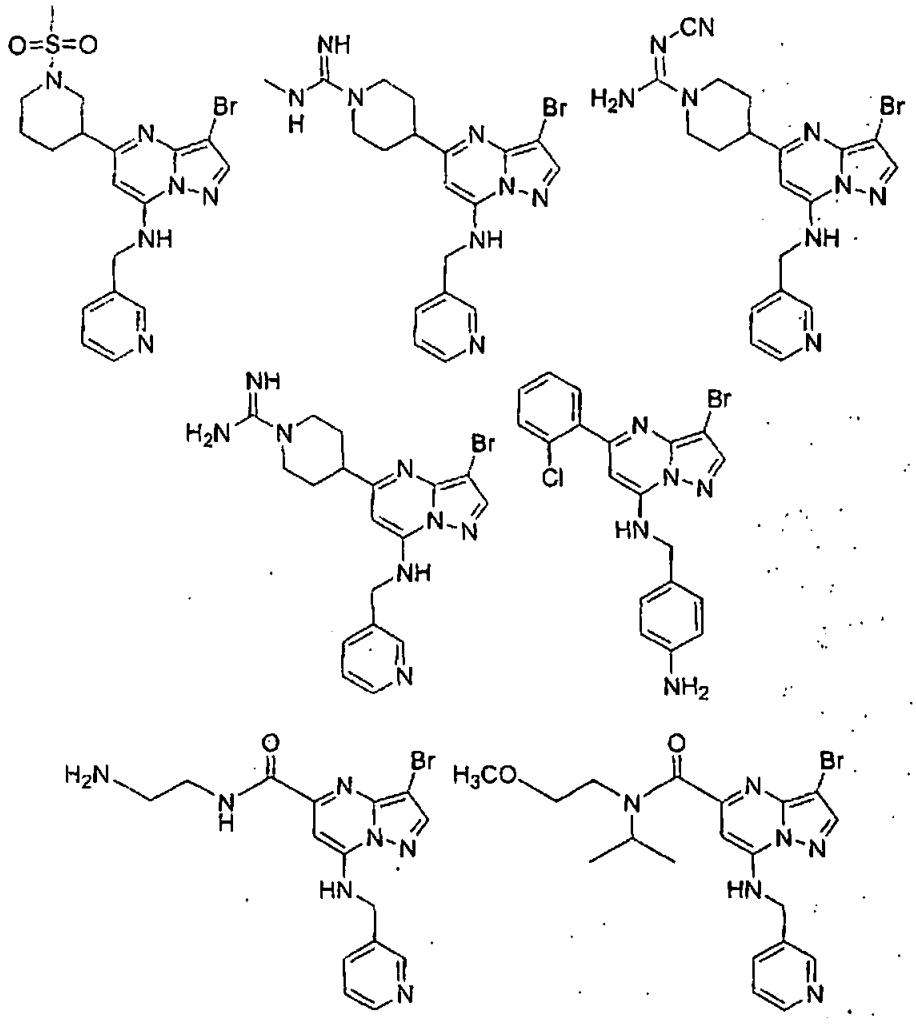

Br
NH
HN
F
SO_2NHMe
SO_2NMe_2
$NHCH_3$
NH_2



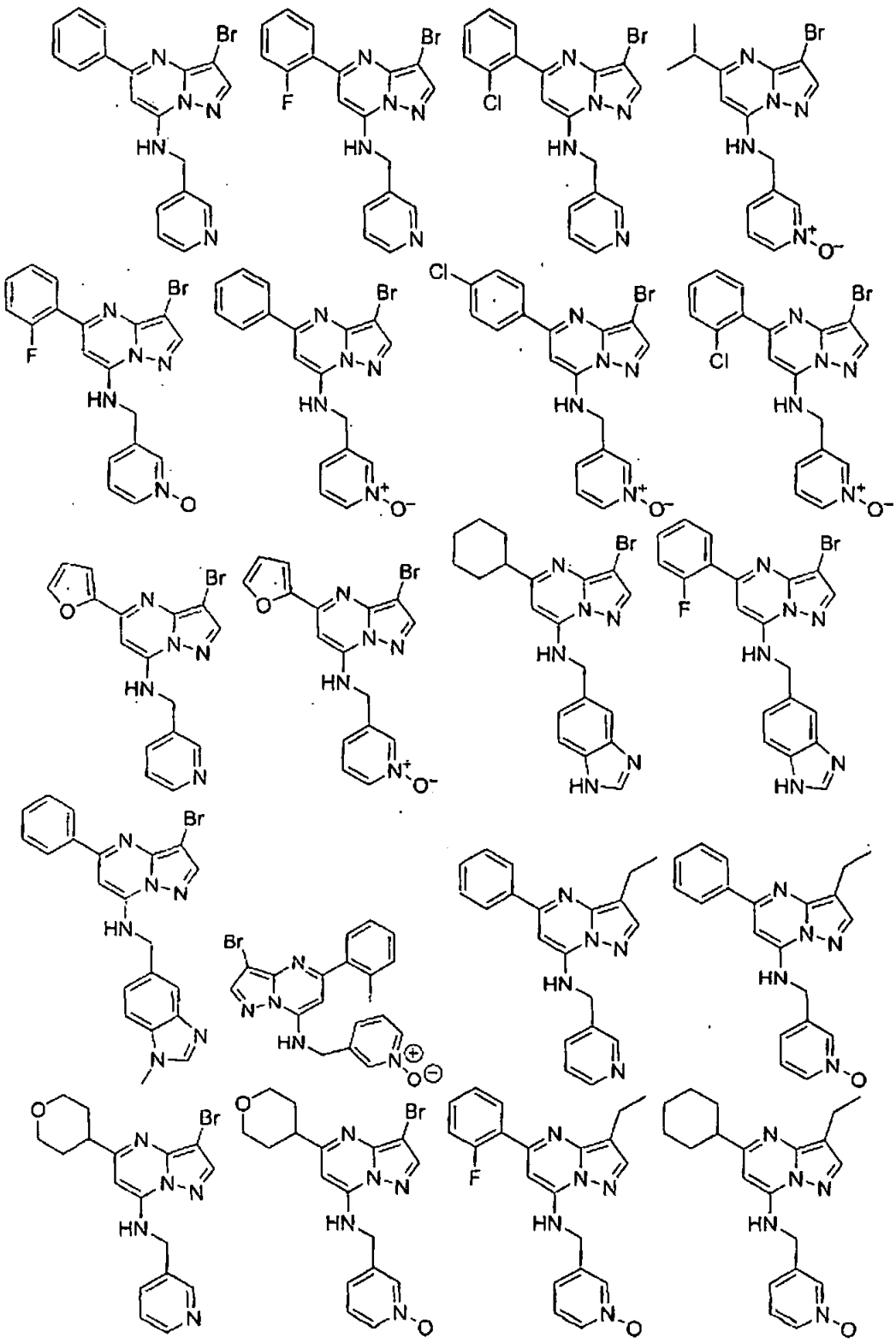


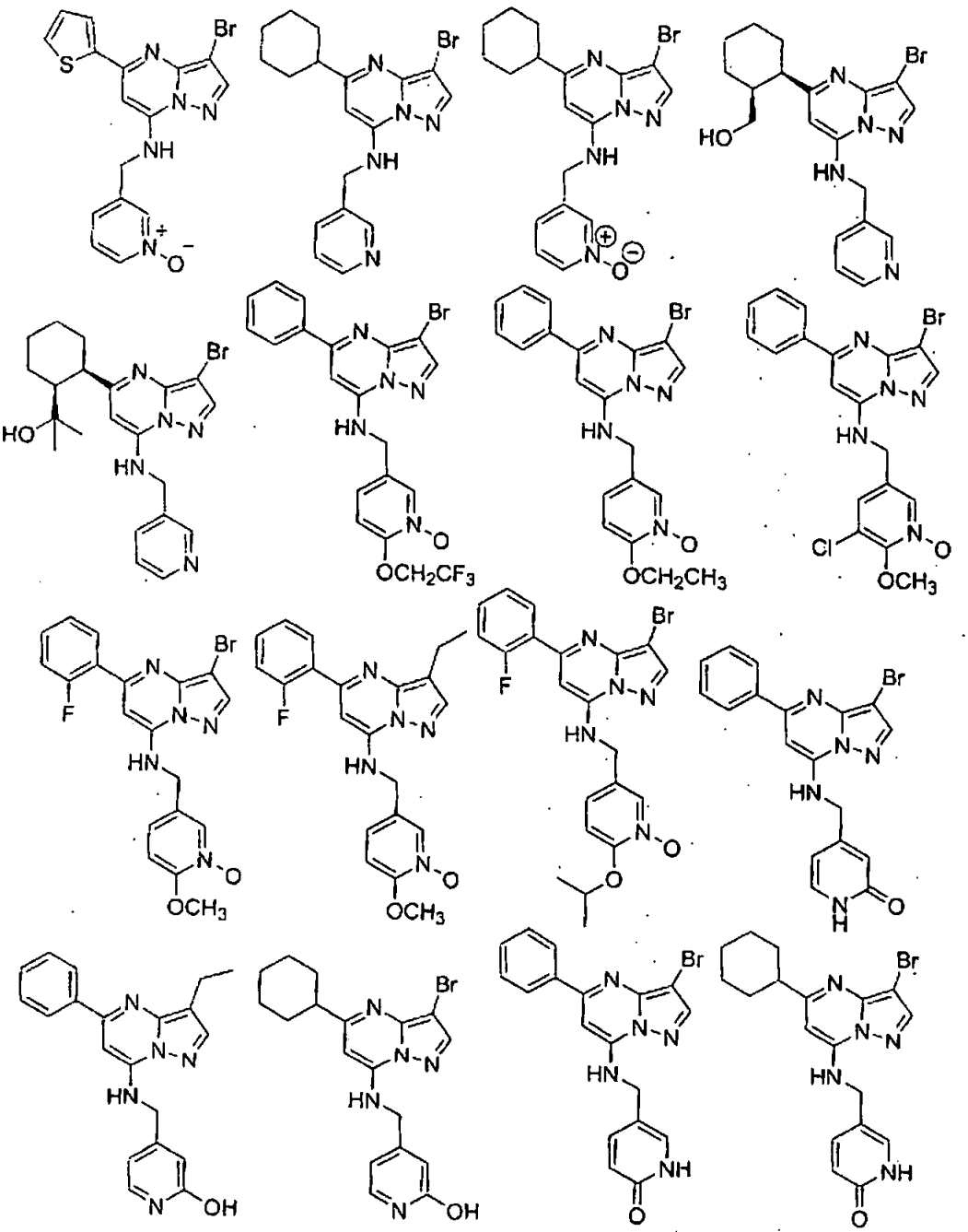
5

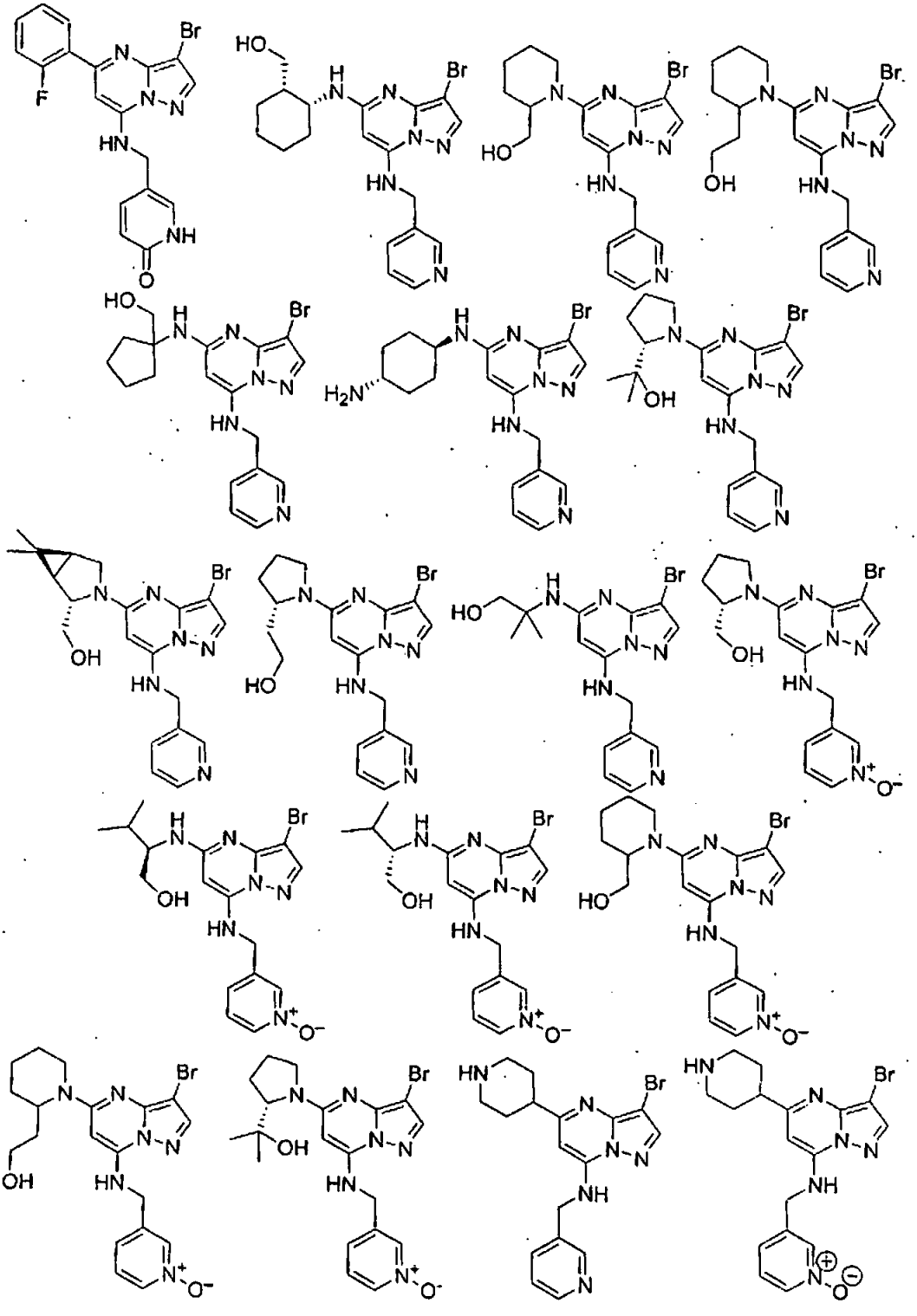


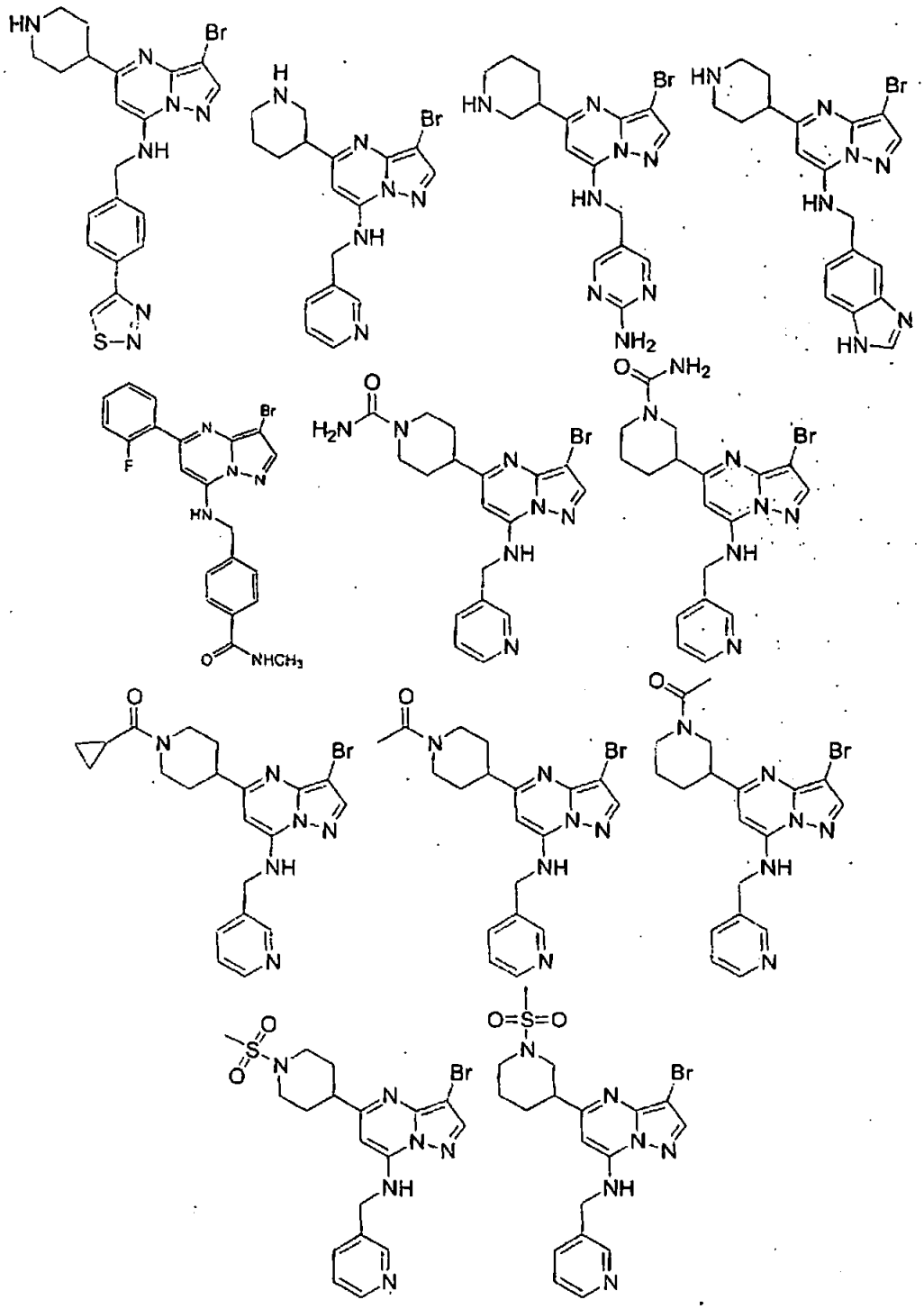


Another embodiment of the invention discloses the following compounds, which exhibited CDK2 inhibitory activity of about 0.0001μM to about 0.5μM:

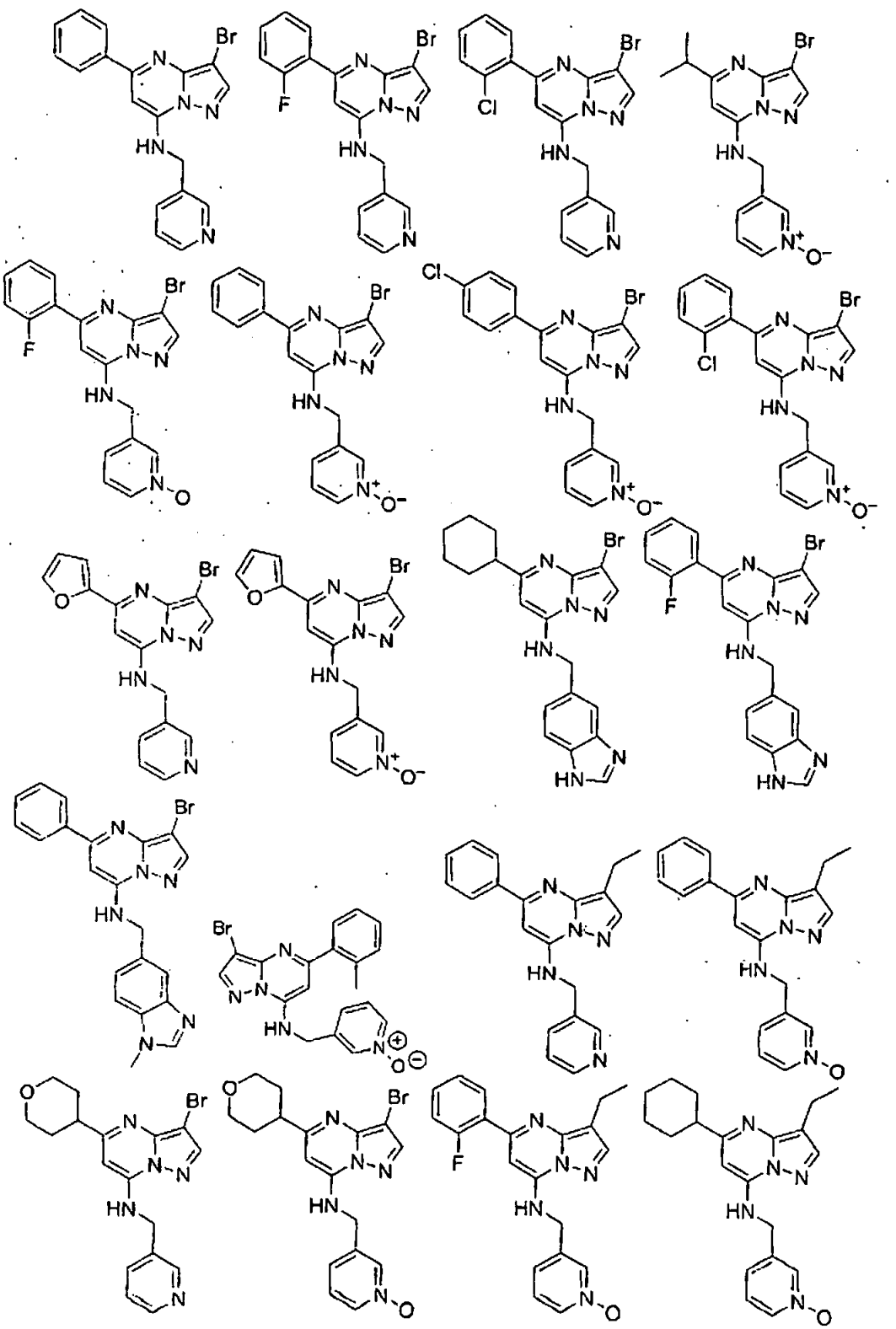




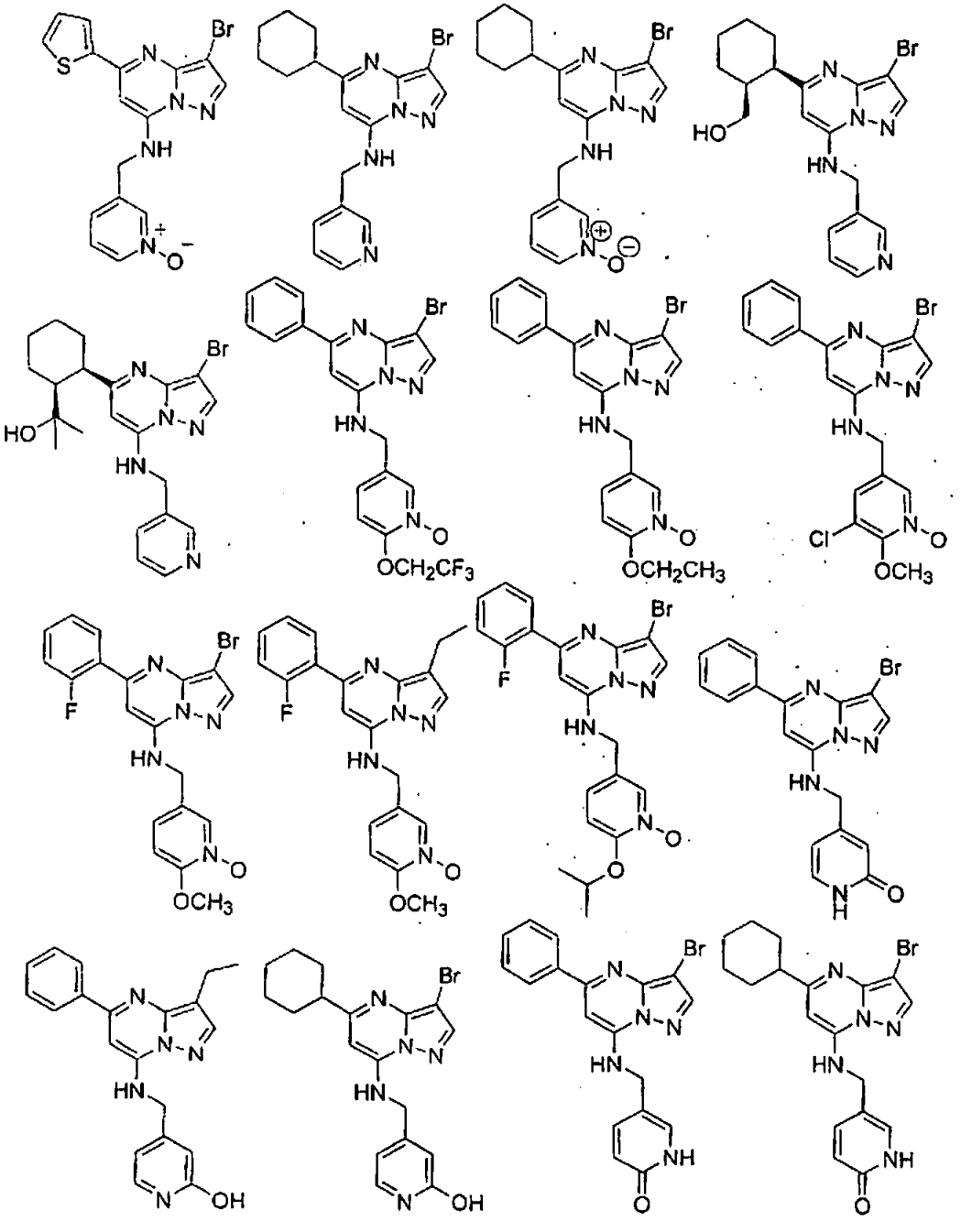


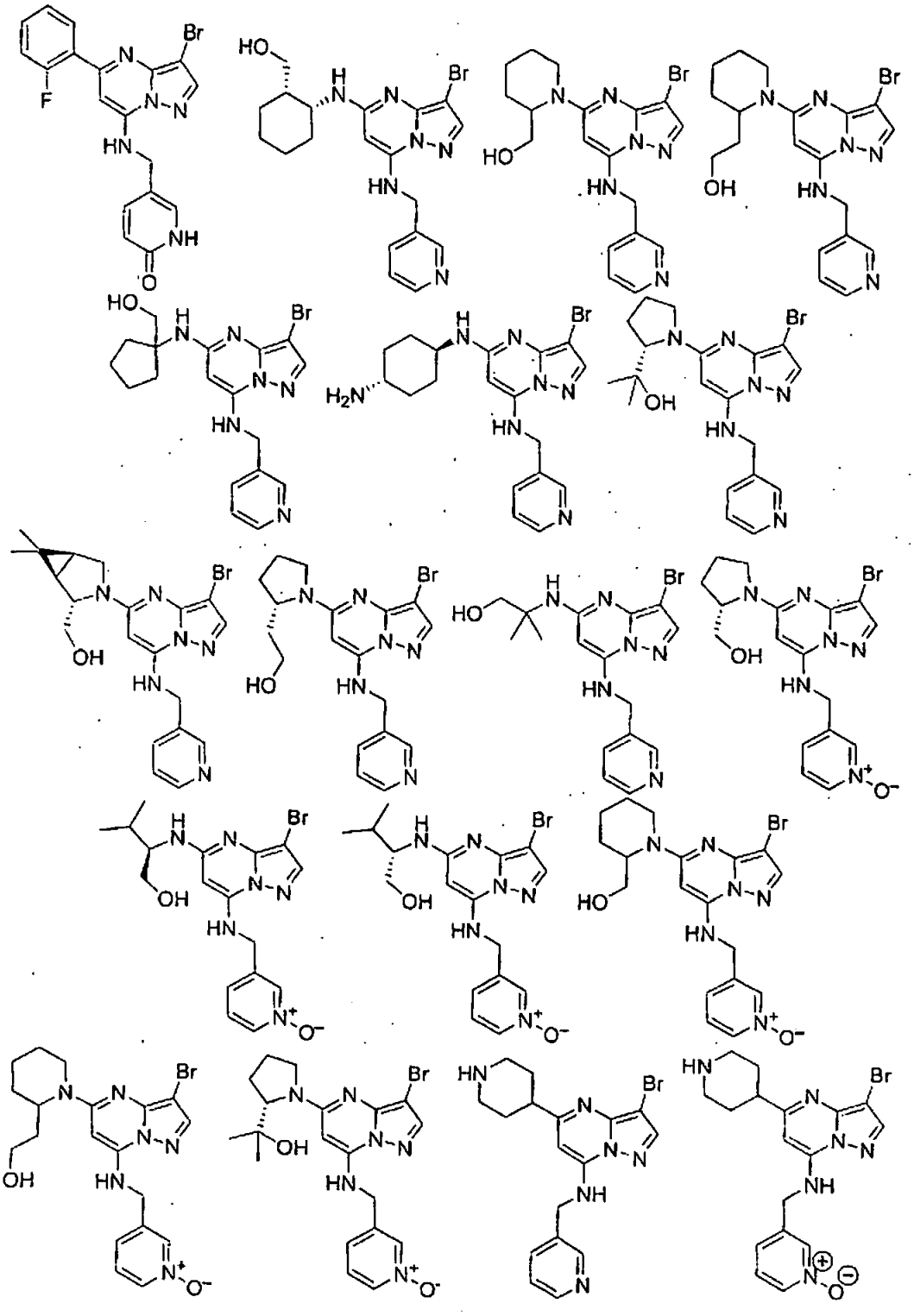


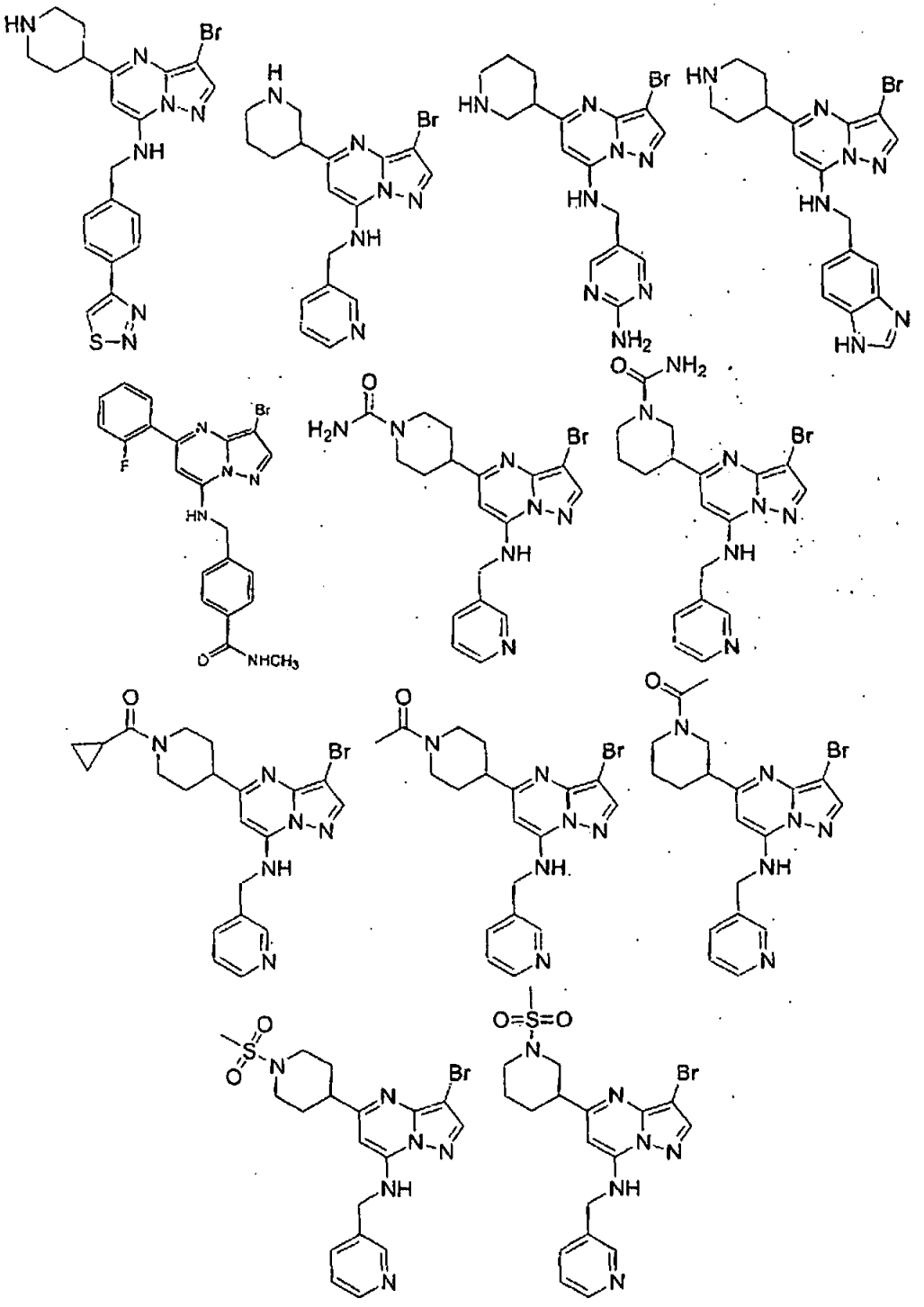
Another embodiment of the invention discloses the following compounds, which exhibited CDK2 inhibitory activity of about 0.0001μM to about 0.1μM:



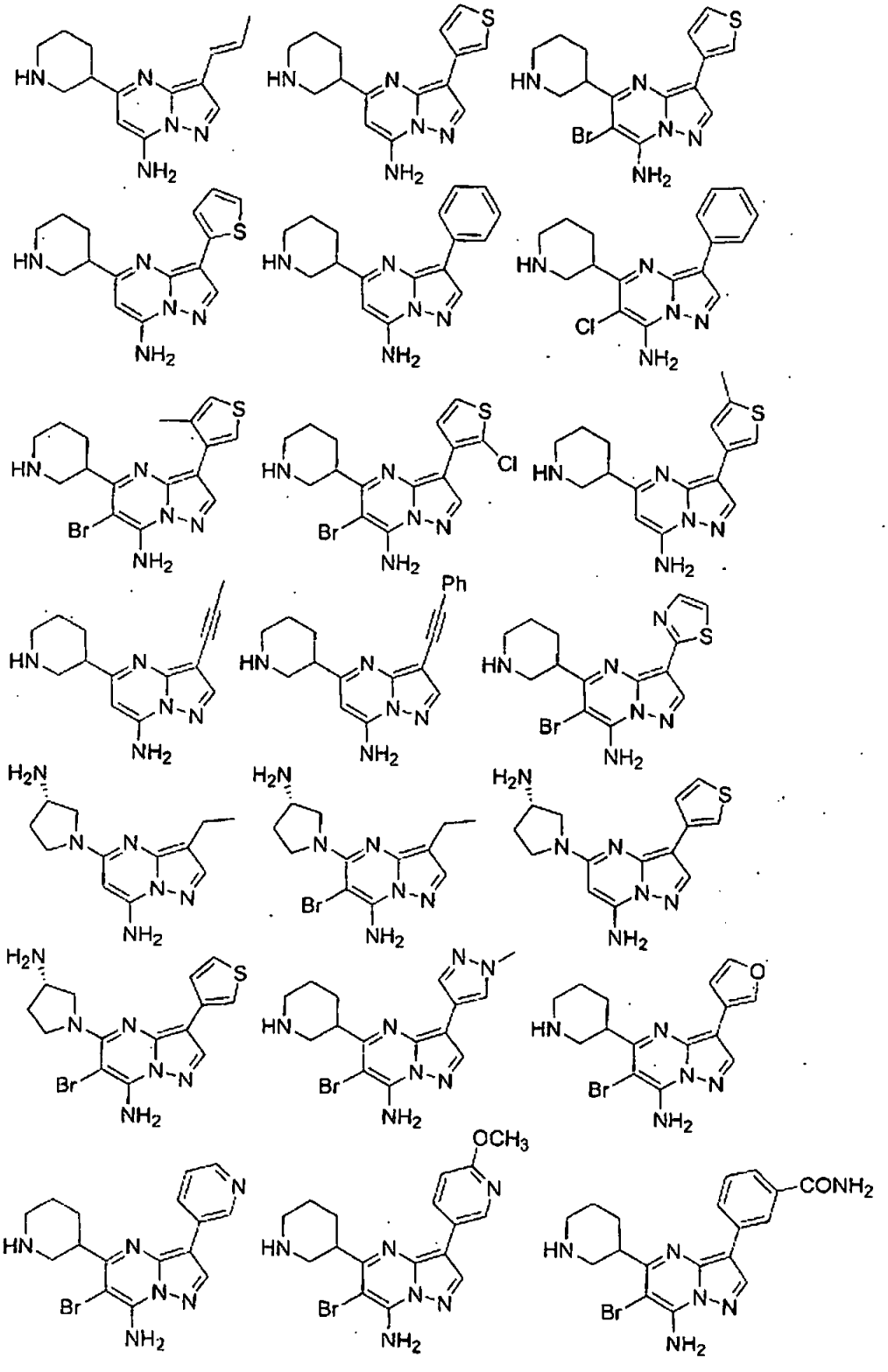
5

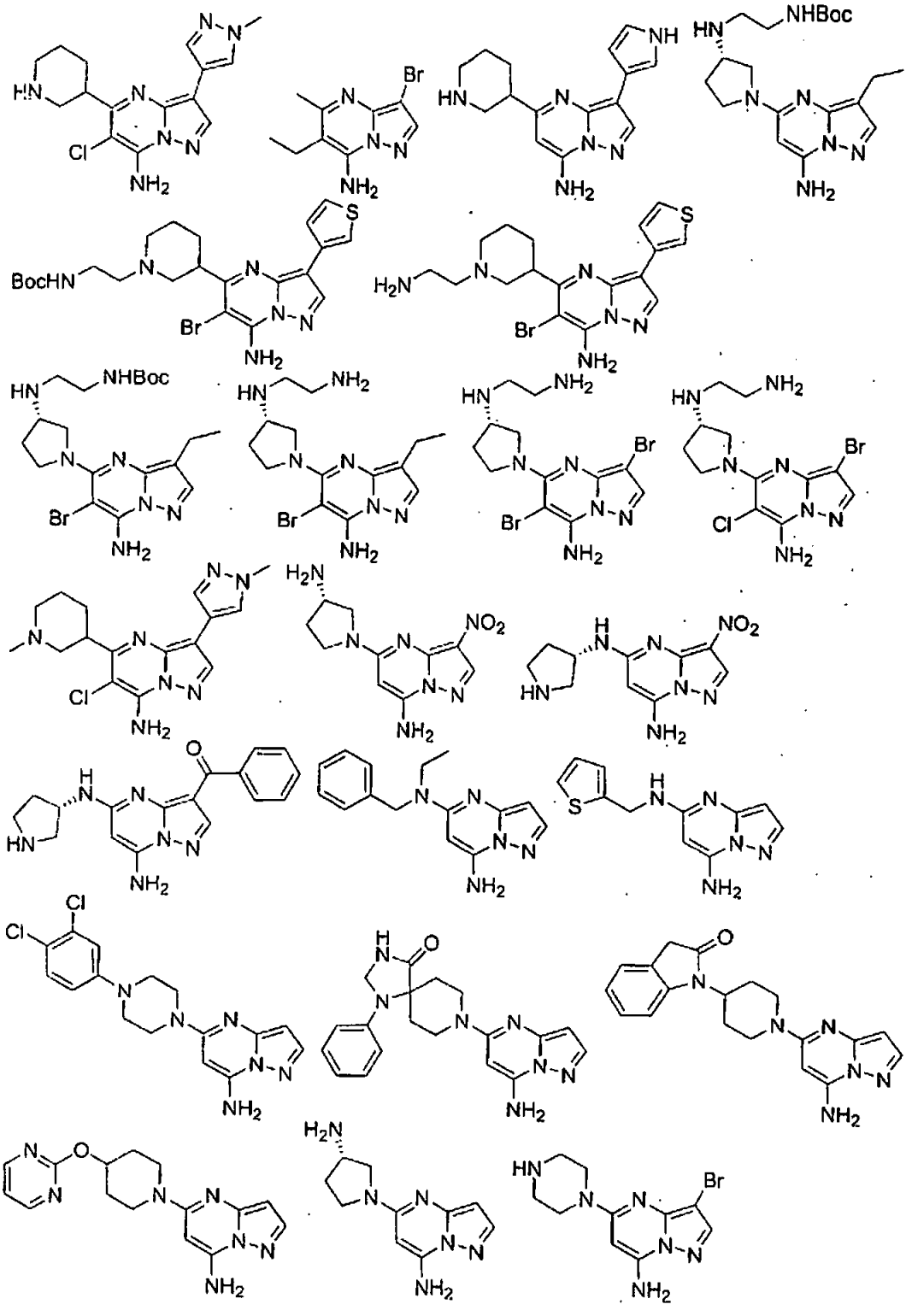


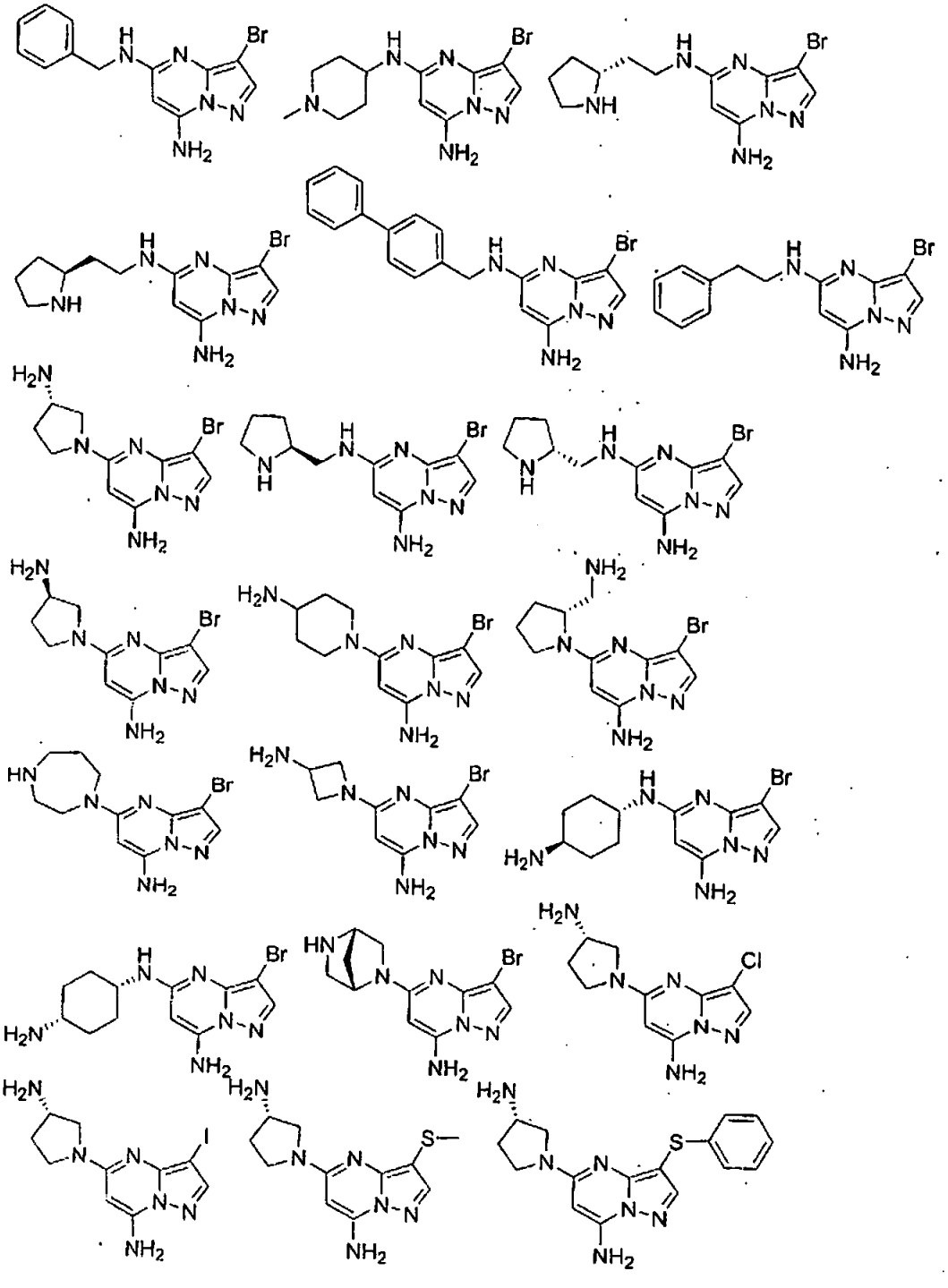


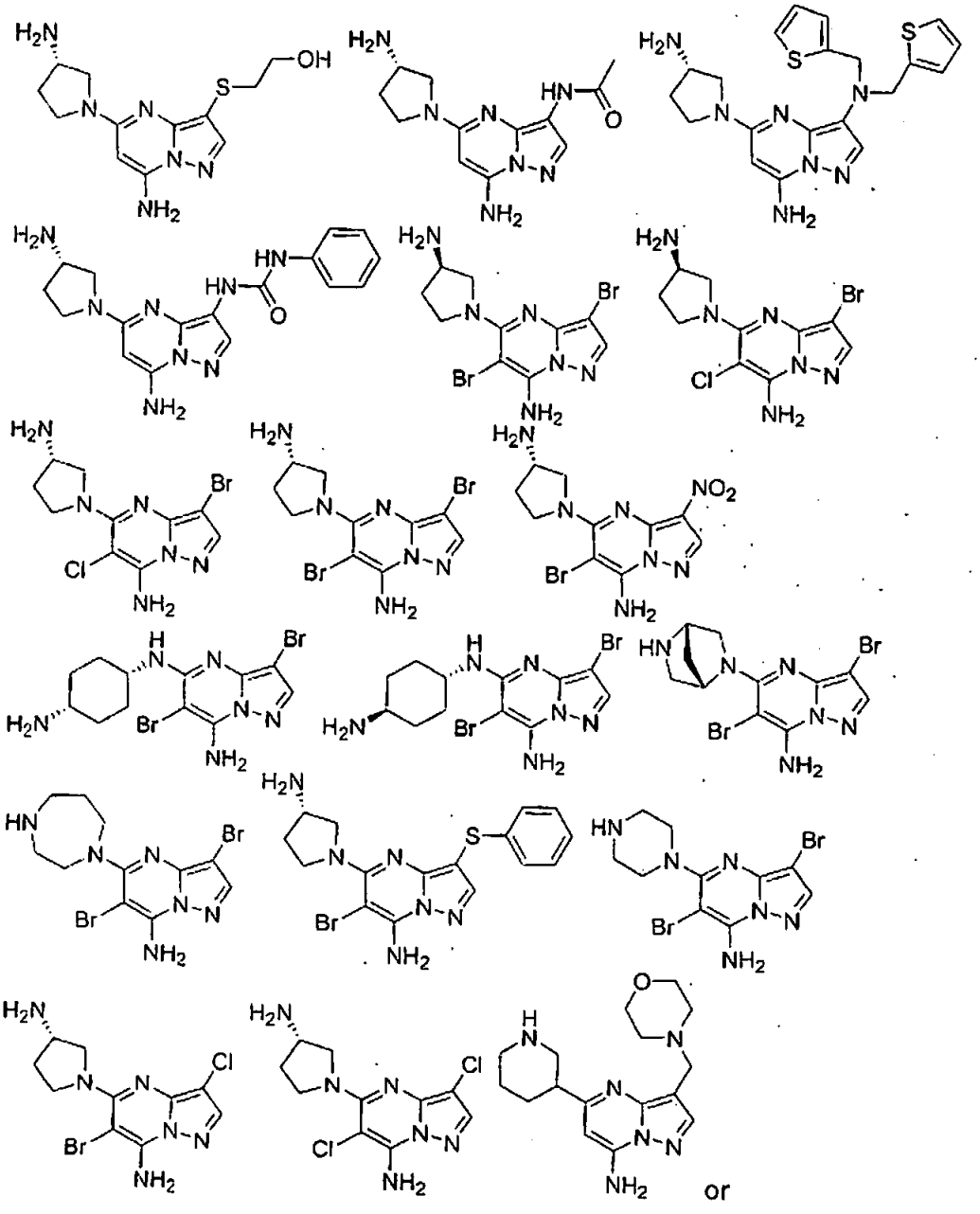


Still additionally disclosed are the following compounds:

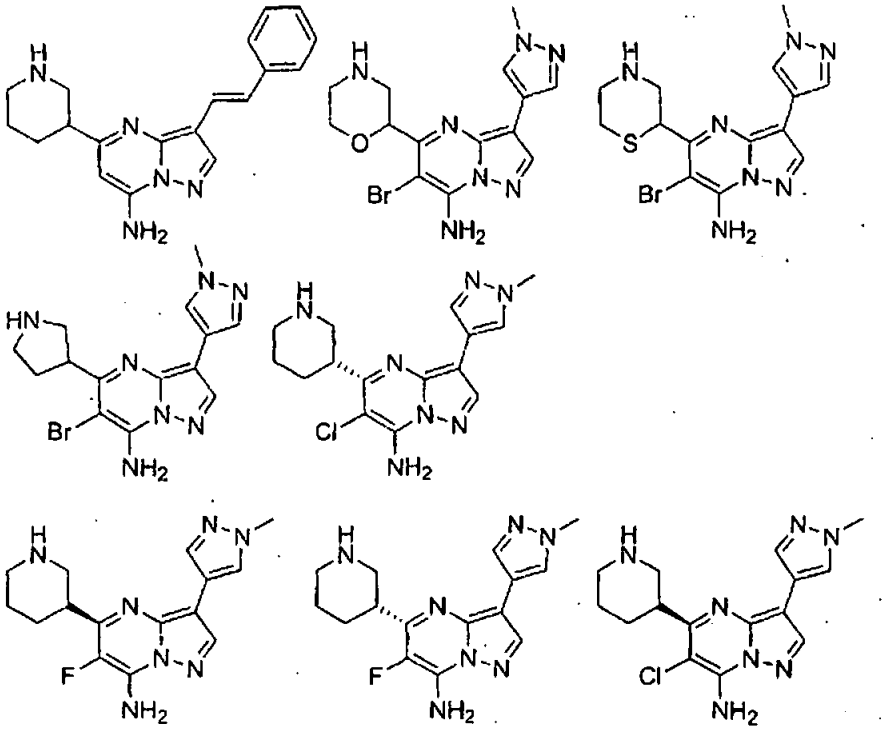








or



or a pharmaceutically acceptable salt or solvate thereof.

As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"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, -NH(alkyl), -NH(cycloalkyl), -N(alkyl)$_2$,

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.

"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. 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.

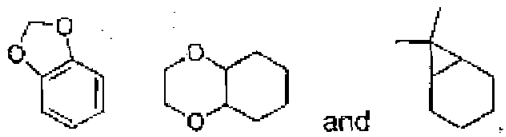
"Cycloalkenyl" means a non-aromatic mono or multicyclic ring system comprising about 3 to about 10 carbon atoms, preferably about 5 to about 10 carbon atoms which contains at least one carbon-carbon double bond. Preferred cycloalkenyl rings contain about 5 to about 7 ring atoms. The cycloalkenyl can be optionally substituted with one or more "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, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alkyl), 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 hydrogens 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:

 and

"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 hydrogens on the same carbon atom on a ring system. Example of such moiety is pyrrolidone:

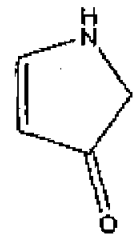


"Heterocyclylalkyl" means a heterocyclyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core. Non-limiting examples of suitable heterocyclylalkyls include piperidinylmethyl, piperazinylmethyl and the like.

"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-

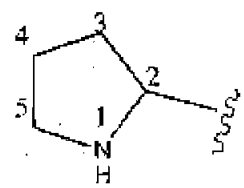
tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, dihydroimidazolyl, dihydrooxazolyl, dihydrooxadiazolyl, dihydrothiazolyl, 3,4-dihydro-2H-pyranyl, dihydrofuranyl, fluorodihydrofuranyl, 7-oxabicyclo[2.2.1]heptenyl, dihydrothiophenyl, dihydrothiopyranyl, and the like.

"Heterocyclenyl" may also mean a single moiety (e.g., carbonyl) which simultaneously replaces two available hydrogens on the same carbon atom on a ring system. Example of such moiety is pyrrolidinone:



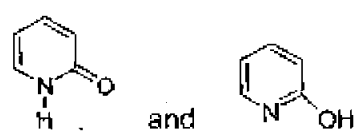
"Heterocyclenylalkyl" means a heterocyclenyl moiety as defined above linked via an alkyl moiety (defined above) to a parent core.

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:



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.

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

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

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

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 Formula III, 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 Formula (III) 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 Formula (III) 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 Formula (III) 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 Formula (III) 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) describe the preparation of the solvates of the antifungal fluconazole in ethyl acetate as well as from water. Similar preparations of solvates, hemisolvate, hydrates and the like are described by E. C. van Tonder *et al, AAPS PharmSciTech.*, 5(1), article 12 (2004); and A. L. Bingham *et al, Chem. Commun.*, 603-604 (2001). A typical, non-limiting, process involves dissolving the inventive compound in desired amounts of the desired solvent (organic or water or mixtures thereof) at a higher than ambient temperature, and cooling the solution at a rate sufficient to form

crystals which are then isolated by standard methods. Analytical techniques such as, for example I. R. spectroscopy, show the presence of the solvent (or water) in the crystals as a solvate (or hydrate).

"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 Formula III can form salts which are also within the scope of this invention. Reference to a compound of Formula III herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic salts formed with inorganic and/or organic acids, as well as basic salts formed with inorganic and/or organic bases. In addition, when a compound of Formula III 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 the Formula III may be formed, for example, by reacting a compound of Formula III 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 Formula III, 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 Formula (III) may contain asymmetric or chiral centers, and, therefore, exist in different stereoisomeric forms. It is intended that all stereoisomeric forms of the compounds of Formula (III) 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 Formula (III) 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 Formula (III) 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 Formula (III) 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 Formula (III) 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 Formula (III) (e.g., those labeled with ^{3}H and ^{14}C) are useful in compound and/or substrate tissue distribution assays. Tritiated (i.e., ^{3}H) and carbon-14 (i.e., ^{14}C) isotopes are particularly preferred for their ease of preparation and detectability. Further, substitution with heavier isotopes such as deuterium (i.e., ^{2}H) may afford certain therapeutic advantages resulting from greater metabolic stability (e.g., increased in vivo half-life or reduced dosage requirements) and hence may be preferred in some circumstances. Isotopically labelled compounds of Formula (III) can generally be prepared by following procedures analogous to those disclosed in

the Schemes and/or in the Examples hereinbelow, by substituting an appropriate isotopically labelled reagent for a non-isotopically labelled reagent.

Polymorphic forms of the compounds of Formula III, and of the salts, solvates, esters and prodrugs of the compounds of Formula III, are intended to be included in the present invention.

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

The compounds according to the invention have pharmacological properties; in particular, the compounds of Formula III can be inhibitors of protein kinases such as, for example, the inhibitors of the cyclin-dependent kinases, mitogen-activated protein kinase (MAPK/ERK), glycogen synthase kinase 3(GSK3beta) and the like. The cyclin dependent kinases (CDKs) include, for example, CDC2 (CDK1), CDK2, CDK4, CDK5, CDK6, CDK7 CDK8 and CDK9. The novel compounds of Formula III are expected to be useful in the therapy of proliferative diseases such as cancer, autoimmune diseases, viral diseases, fungal diseases, neurological/neurodegenerative disorders, arthritis, inflammation, anti-proliferative (e.g., ocular retinopathy), neuronal, alopecia and cardiovascular disease. Many of these diseases and disorders are listed in U.S. 6,413,974 cited earlier, the disclosure of which is incorporated herein.

More specifically, the compounds of Formula III can be useful in the treatment of a variety of cancers, including (but not limited to) the following:

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

hematopoietic tumors of lymphoid lineage, including 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;

hematopoietic tumors of myeloid lineage, including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia;

tumors of mesenchymal origin, including fibrosarcoma and rhabdomyosarcoma;

tumors of the central and peripheral nervous system, including astrocytoma, neuroblastoma, glioma and schwannomas; and

other tumors, including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctanthoma, thyroid follicular cancer and Kaposi's sarcoma.

Due to the key role of CDKs in the regulation of cellular proliferation in general, inhibitors could act as reversible cytostatic agents which may be useful in the treatment of any disease process which features abnormal cellular proliferation, e.g., benign prostate hyperplasia, familial adenomatosis polyposis, neuro-fibromatosis, atherosclerosis, pulmonary fibrosis, arthritis, psoriasis, glomerulonephritis, restenosis following angioplasty or vascular surgery, hypertrophic scar formation, inflammatory bowel disease, transplantation rejection, endotoxic shock, and fungal infections.

Compounds of Formula III may also be useful in the treatment of Alzheimer's disease, as suggested by the recent finding that CDK5 is involved in the phosphorylation of tau protein (*J. Biochem*, (1995) 117, 741-749).

Compounds of Formula III may induce or inhibit apoptosis. The apoptotic response is aberrant in a variety of human diseases. Compounds of Formula III, as modulators of apoptosis, will be useful in the treatment of cancer (including

but not limited to those types mentioned hereinabove), viral infections (including but not limited to herpevirus, poxvirus, Epstein- Barr virus, Sindbis virus and adenovirus), prevention of AIDS development in HIV-infected individuals, autoimmune diseases (including but not limited to systemic lupus, erythematosus, autoimmune mediated glomerulonephritis, rheumatoid arthritis, psoriasis, inflammatory bowel disease, and autoimmune diabetes mellitus), neurodegenerative disorders (including but not limited to Alzheimer's disease, AIDS-related dementia, Parkinson's disease, amyotrophic lateral sclerosis, retinitis pigmentosa, spinal muscular atrophy and cerebellar degeneration), myelodysplastic syndromes, aplastic anemia, ischemic injury associated with myocardial infarctions, stroke and reperfusion injury, arrhythmia, atherosclerosis, toxin-induced or alcohol related liver diseases, hematological diseases (including but not limited to chronic anemia and aplastic anemia), degenerative diseases of the musculoskeletal system (including but not limited to osteoporosis and arthritis) aspirin-sensitive rhinosinusitis, cystic fibrosis, multiple sclerosis, kidney diseases and cancer pain.

Compounds of Formula III, as inhibitors of the CDKs, can modulate the level of cellular RNA and DNA synthesis. These agents would therefore be useful in the treatment of viral infections (including but not limited to HIV, human papilloma virus, herpesvirus, poxvirus, Epstein-Barr virus, Sindbis virus and adenovirus).

Compounds of Formula III may also 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.

Compounds of Formula III may also be useful in inhibiting tumor angiogenesis and metastasis.

Compounds of Formula III may also act as inhibitors of other protein kinases, e.g., protein kinase C, her2, raf 1, MEK1, MAP kinase, EGF receptor, PDGF receptor, IGF receptor, PI3 kinase, wee1 kinase, Src, Abl and thus be effective in the treatment of diseases associated with other protein kinases.

Another aspect of this invention is a method of treating a mammal (*e.g.*, human) having a disease or condition associated with the CDKs by administering a therapeutically effective amount of at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound to the mammal.

A preferred dosage is about 0.001 to 500 mg/kg of body weight/day of the compound of Formula III. An especially preferred dosage is about 0.01 to 25 mg/kg of body weight/day of a compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound.

The compounds of this invention may also be useful in combination (administered together or sequentially) with one or more of anti-cancer treatments such as radiation therapy, and/or one or more anti-cancer agents selected from the group consisting of cytostatic agents, cytotoxic agents (such as for example, but not limited to, DNA interactive agents (such as cisplatin or doxorubicin)); taxanes (e.g. taxotere, taxol); topoisomerase II inhibitors (such as etoposide); topoisomerase I inhibitors (such as irinotecan (or CPT-11), camptostar, or topotecan); tubulin interacting agents (such as paclitaxel, docetaxel or the epothilones); hormonal agents (such as tamoxifen); thymidilate synthase inhibitors (such as 5-fluorouracil); anti-metabolites (such as methoxtrexate); alkylating agents (such as temozolomide (TEMODAR™ from Schering-Plough Corporation, Kenilworth, New Jersey), cyclophosphamide); Farnesyl protein transferase inhibitors (such as, SARASAR™(4-[2-[4-[(11R)-3,10-dibromo-8-chloro-6,11-dihydro-5H-benzo[5,6]cyclohepta[1,2-b]pyridin-11-yl-]-1-piperidinyl]-2-oxoehtyl]-1-piperidinecarboxamide, or SCH 66336 from Schering-Plough Corporation, Kenilworth, New Jersey), tipifarnib (Zarnestra® or R115777 from Janssen Pharmaceuticals), L778,123 (a farnesyl protein transferase inhibitor from Merck & Company, Whitehouse Station, New Jersey), BMS 214662 (a farnesyl protein transferase inhibitor from Bristol-Myers Squibb Pharmaceuticals, Princeton, New Jersey); signal transduction inhibitors (such as, Iressa (from Astra Zeneca Pharmaceuticals, England), Tarceva (EGFR kinase inhibitors), antibodies to EGFR (e.g., C225), GLEEVEC™ (C-abl kinase inhibitor from Novartis Pharmaceuticals, East Hanover, New Jersey); interferons such as,

for example, intron (from Schering-Plough Corporation), Peg-Intron (from Schering-Plough Corporation); hormonal therapy combinations; aromatase combinations; ara-C, adriamycin, cytoxan, and gemcitabine.

Other anti-cancer (also known as anti-neoplastic) agents include but are not limited to Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, oxaliplatin, leucovirin, oxaliplatin (ELOXATIN™ from Sanofi-Synthelabo Pharmaceuticals, France), Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17α-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrazole, Letrazole, Capecitabine, Reloxafine, Droloxafine, Hexamethylmelamine, Avastin, herceptin, Bexxar, Velcade, Zevalin, Trisenox, Xeloda, Vinorelbine, Porfimer, Erbitux, Liposomal, Thiotepa, Altretamine, Melphalan, Trastuzumab, Lerozole, Fulvestrant, Exemestane, Fulvestrant, Ifosfomide, Rituximab, C225 (or Cetuximab from Merck KGaA, Darmstadt, Germany), and Campath.

The compounds of this invention may specifically be useful in combination (administered together, concurrently or sequentially) with temozolomide and/or radiation therapy.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the dosage range described herein and the other pharmaceutically active agent or treatment within its dosage range. For example, the CDC2 inhibitor olomucine has been found to act synergistically with

known cytotoxic agents in inducing apoptosis (*J. Cell Sci.*, (1995) 108, 2897. Compounds of Formula III may also be administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of Formula III may be administered either prior to or after administration of the known anticancer or cytotoxic agent. For example, the cytotoxic activity of the cyclin-dependent kinase inhibitor flavopiridol is affected by the sequence of administration with anticancer agents. *Cancer Research*, (1997) 57, 3375. 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 at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate thereof, and an amount of one or more anti-cancer treatments and anti-cancer agents listed above wherein the amounts of the compounds/ treatments result in desired therapeutic effect.

The pharmacological properties of the compounds of this invention may be confirmed by a number of pharmacological assays. The exemplified pharmacological assays which are described later have been carried out with the compounds according to the invention and their salts.

This invention is also directed to pharmaceutical compositions which comprise at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate 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.

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 component, e.g., an effective amount to achieve the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 1 mg to about 100 mg, preferably from about 1 mg to about 50 mg, more preferably from about 1 mg to about 25 mg, according to the particular application.

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the

skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

The amount and frequency of administration of the compounds of the invention and/or the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended daily dosage regimen for oral administration can range from about 1 mg/day to about 500 mg/day, preferably 1 mg/day to 200 mg/day, in two to four divided doses.

Another aspect of this invention is a kit comprising a therapeutically effective amount of at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound and a pharmaceutically acceptable carrier, vehicle or diluent.

Yet another aspect of this Invention is a kit comprising an amount of at least one compound of Formula III, or a pharmaceutically acceptable salt or solvate of said compound and an amount of at least one anticancer therapy and/or anti-cancer agent listed above, wherein the amounts of the two or more ingredients result in desired therapeutic effect.

The invention disclosed herein is exemplified by the following preparations and examples which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures will be apparent to those skilled in the art.

Where NMR data are presented, ^1H spectra were obtained on either a Varian VXR-200 (200 MHz, ^1H), Varian Gemini-300 (300 MHz) or XL-400 (400 MHz) and are reported as ppm down field from Me_4Si with number of protons, multiplicities, and coupling constants in Hertz indicated parenthetically. Where LC/MS data are presented, analyses was performed using an Applied Biosystems API-100 mass spectrometer and Shimadzu SCL-10A LC column: Altech platinum C18, 3 micron, 33mm x 7mm ID; gradient flow: 0 min – 10% CH_3CN, 5 min – 95% CH_3CN, 7 min – 95% CH_3CN, 7.5 min – 10% CH_3CN, 9 min – stop. The retention time and observed parent ion are given.

The following solvents and reagents may be referred to by their abbreviations in parenthesis:

Thin layer chromatography: TLC

dichloromethane: CH_2Cl_2

ethyl acetate: AcOEt or EtOAc

methanol: MeOH

trifluoroacetate: TFA

triethylamine: Et_3N or TEA

butoxycarbonyl: n-Boc or Boc

nuclear magnetic resonance spectroscopy: NMR

liquid chromatography mass spectrometry: LCMS

high resolution mass spectrometry: HRMS

milliliters: mL

millimoles: mmol

microliters: µl

grams: g

milligrams: mg

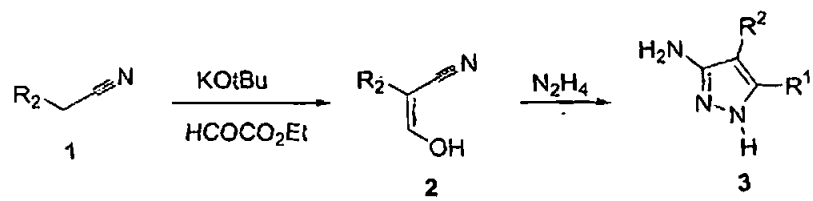
room temperature or rt (ambient): about 25°C.

dimethoxyethane: DME

EXAMPLES

In general, the compounds described in this Invention can be prepared through the general routes described below in Scheme 1. Treatment of the

Scheme 1

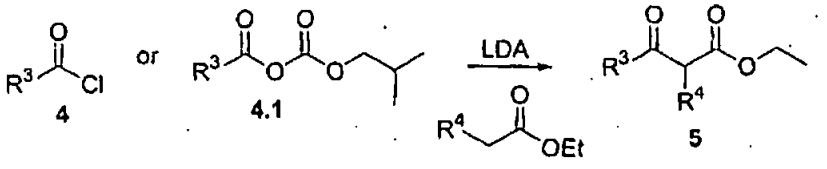


1 2 3

starting nitrile with potassium t-butoxide and ethyl formate gives rise to the intermediate enol 2 which upon treatment with hydrazine gives the desired substituted 3-aminopyrazole. Condensation of compounds of type 3 with the appropriately functionalized keto ester of type 5 gives rise to the pyridones 6 as

shown in Scheme 3. The keto esters used in this general route are either commercially available or can be made as illustrated in Scheme 2.

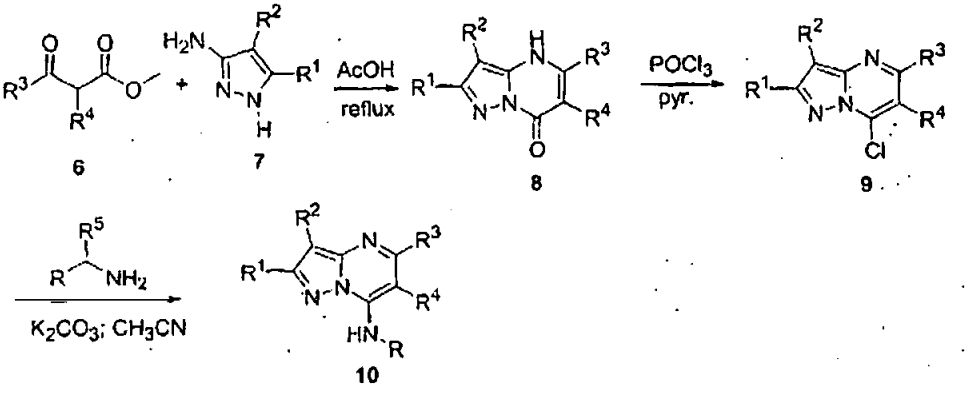
Scheme 2



The chlorides of type 9 can be prepared by treatment of the pyridones 8 with $POCl_3$. When R^2 is equal to H, substitution in this position is possible on the compounds of type 9 by electrophilic halogenation, acylation, and various other electrophilic aromatic substitutions.

Introduction of the N7-amino functionality can be accomplished through displacement of the chloride of compounds of type 9 by reaction with the appropriate amine as shown in Scheme 3.

Scheme 3



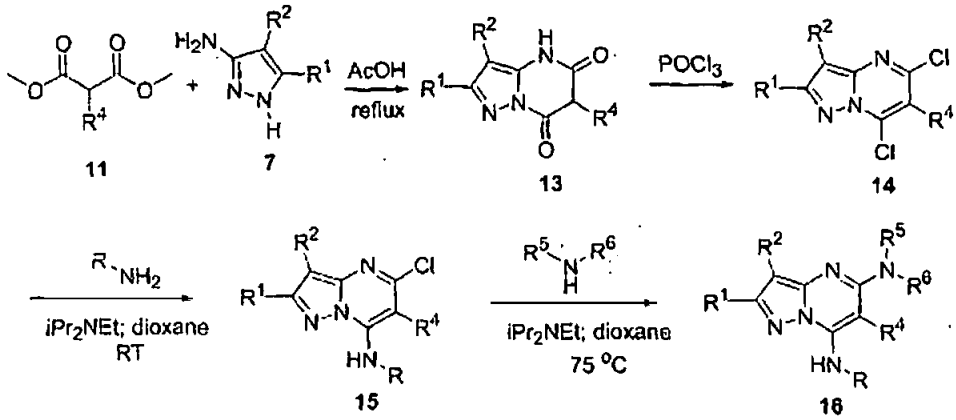
Condensation of compounds of type 7 with the appropriately functionalized malonate ester of type 11 gives rise to the pyridones 13 as shown in Scheme 4.

The chlorides of type 14 can be prepared by treatment of the pyridones 13 with $POCl_3$. When R^2 is H, substitution in this position is possible on compounds of type 9 by electrophilic halogenation, acylation, and various other electrophilic aromatic substitutions.

Incorporation of the N7-amino functionality can be accomplished through regioselective displacement of the chloride of compounds of type 14.

Incorporation of the N5-amino functionality by addition of an appropriate amine at higher temperature.

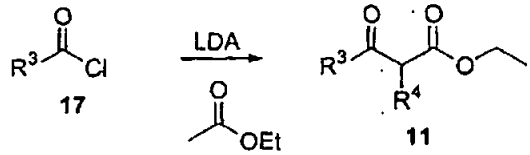
Scheme 4



11 7 13 14 15 16

Alternatively, condensations of the aminopyrazoles of type 7 with an appropriately functionalize keto ester as prepared in Scheme 5, leads to compounds of type 13 as shown in Scheme 4.

Scheme 5



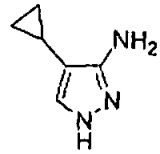
17 11

The chlorides of type 14 can be prepared by treatment of the pyridones 13 with $POCl_3$. When R^2 is equal to H, substitution in this position is possible on compounds of type 14 by electrophilic halogenation, acylation, and various other electrophilic aromatic substitutions.

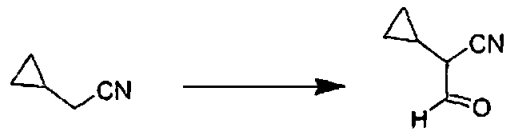
Incorporation of the N7-amino functionality can be accomplished through displacement of the chloride of compounds of type 15.

Preparative Examples:

PREPARATIVE EXAMPLE 1:

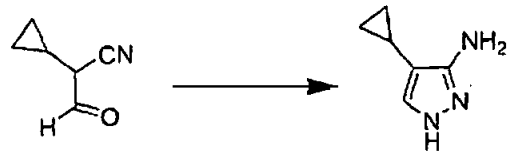


Step A:



A procedure in German patent DE 19834047 A1, p 19 was followed. To a solution of KOtBu (6.17 g, 0.055 mol) in anhydrous THF (40 mL) was added, dropwise, a solution of cyclopropylacetonitrile (2.0 g, 0.025 mol) and ethyl formate (4.07 g, 0.055 mol) in anhydrous THF (4 mL). A precipitate formed immediately. This mixture was stirred for 12 hr. It was concentrated under vacuum and the residue stirred with Et_2O (50 mL). The resulting residue was decanted and washed with Et_2O (2 x 50 mL) and Et_2O removed from the residue under vacuum. The residue was dissolved in cold H_2O (20 mL) and pH adjusted to 4 – 5 with 12 N HCl. The mixture was extracted with CH_2Cl_2 (2 x 50 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under vacuum to give the aldehyde as a tan liquid.

Step B:

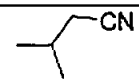
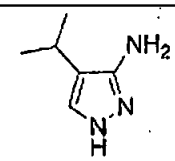
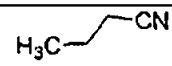
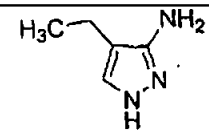
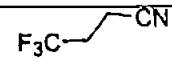
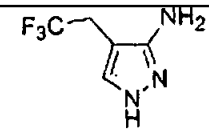


The product from Preparative Example 1, Step A (2.12 g, 0.0195 mol), $NH_2NH_2 \cdot H_2O$ (1.95 g, 0.039 mol) and 1.8 g (0.029 mole) of glacial CH_3CO_2H (1.8 g, 0.029 mol) were dissolved in EtOH (10 mL). It was refluxed for 6 hr and concentrated under vacuum. The residue was slurried in CH_2Cl_2 (150 mL) and the pH adjusted to 9 with 1N NaOH. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under vacuum to give the product as a waxy orange solid.

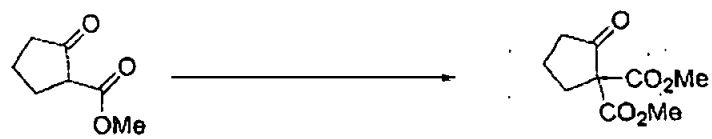
PREPARATIVE EXAMPLES 2-4:

By essentially the same procedure set forth in Preparative Example 1, only substituting the nitrile shown in Column 2 of Table 2, the compounds in Column 3 of Table 2 were prepared:

TABLE 2

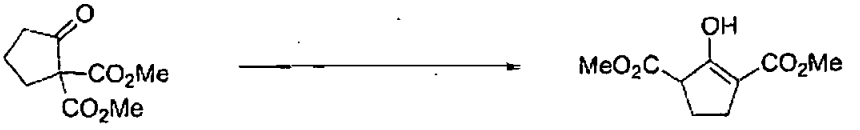
Prep. Ex.	Column 2	Column 3
2		
3		
3.10		

PREPARATIVE EXAMPLE 4



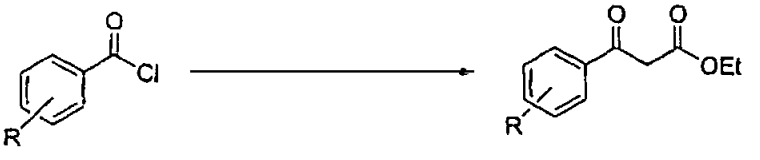
2-Carbomethoxycyclopentanone (6.6 ml, 0.05 mol) in THF (15 ml) was added dropwise to a vigorously stirred suspension of NaH (60% in mineral oil, 4 g, 0.1 mol) in THF (100 ml) at 0 – 10 °C. When bubbling ceased, the reaction mixture was treated at the same temperature with ClCOOMe (7.8 ml, 0.1 mol) in THF (15 ml). The resulted off-white suspension was stirred for 30 minutes at room temperature and 30 minutes under reflux. The reaction was monitored by TLC for disappearance of starting material. The reaction mixture was quenched with water carefully and partitioned between ethyl acetate and saturated solution of ammonium chloride in a funnel. Shaken and separated, the organic layer was washed with brine and dried over anhydrous sodium sulfate. Solvents were removed, and the residue was purified by flash chromatography, eluted with 5% and then 10% ethyl acetate in hexane. 9.4 g colorless oil was obtained with 94% yield. ^{1}H NMR ($CDCl_3$) δ 3.90(s, 3H), 3.73(s, 3H), 2.65(m, 4H), 1.98(m, 2H).

PREPARATIVE EXAMPLE 5



To lithium diisopropylamide solution in THF (2.0 N, 0.04 mol) at –65 °C, was added dropwise 2,2-dicarbomethoxycyclopentanone (4 g, 0.02 mol) in THF (60 ml). The resulted reaction mixture was stirred at the same temperature before adding methyl chloroformate (1.54 ml, 0.02 mol). Reaction mixture stirred for an hour and poured into saturated ammonium chloride solution with some ice. This solution was extracted three times with ether, and the combined ethearal layers were dried over sodium sulfate. Solvents were removed in vacuo, and the residue was purified by flash chromatography, eluted with 30% increased to 50% ethyl acetate in hexane. 2.3 g yellowish oil was obtained with 58% yield. ^{1}H NMR ($CDCl_3$) δ 3.77(s, 6H), 3.32(t, 1H), 3.60-3.10(m, 4H).

PREPARATIVE EXAMPLE 6:

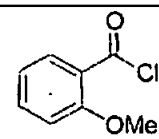
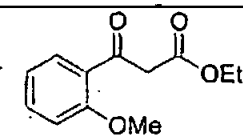
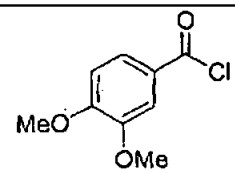
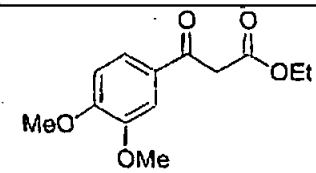
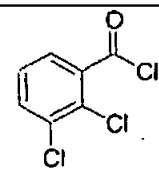
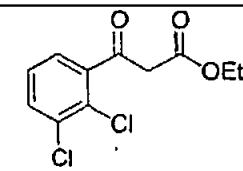
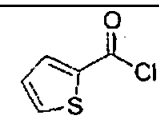
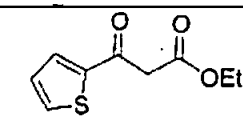
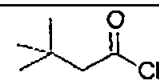
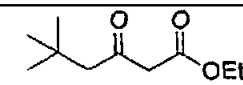
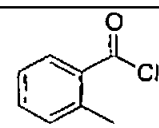
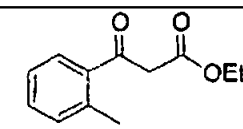
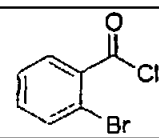
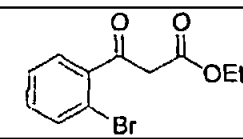
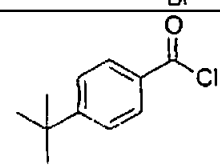
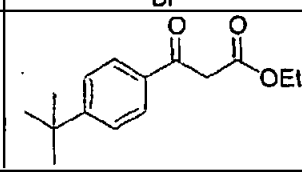


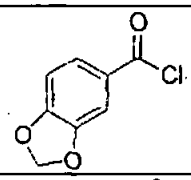
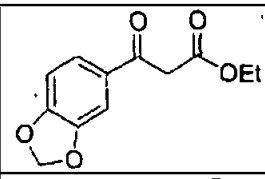
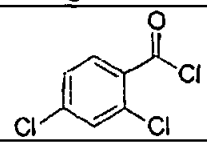
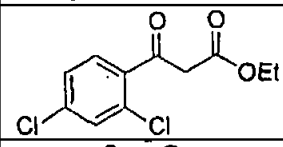
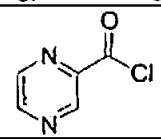
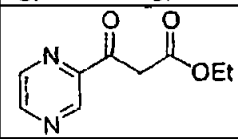
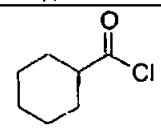
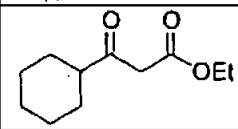
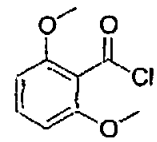
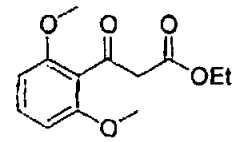
The reactions were done as outlined in (K. O. Olsen, *J. Org. Chem.*, (1987) 52, 4531 – 4536). Thus, to a stirred solution of lithium diisopropylamide in THF at -65 to –70 C was added freshly distilled ethyl acetate, dropwise. The resulting solution was stirred for 30 min and the acid chloride was added as a solution in THF. The reaction mixture was stirred at –65 to –70° C for 30 min and then terminated by the addition of 1 N HCl solution. The resulting two-phased mixture was allowed to warm to ambient temperature. The resulting mixture was diluted with EtOAc (100 mL) the organic layer was collected. The aqueous layer was extracted with EtOAc (100 mL). The organic layers were combined, washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give the crude β-keto esters, which were used in the subsequent condensations.

PREPARATIVE EXAMPLES 7-19:

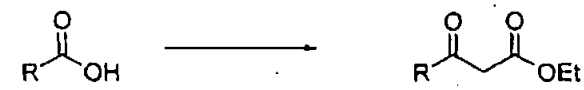
By essentially the same procedure set forth in Preparative Example 6 only substituting the acid chlorides shown in Column 2 of Table 3, the β-keto esters shown in Column 3 of Table 3 were prepared:

TABLE 3

Prep. Ex.	Column 2	Column 3	DATA
7			LCMS: MH^+ = 223
8			LCMS: MH^+ = 253
9			LCMS: MH^+ = 261
10			MH^+ = 199
11			
12			
13			LCMS: MH^+ = 271
14			Yield = quant MH^+ =249

15			Yield = quant MH^+ =237
16			Yield = quant MH^+ = 262
17			Yield = 48 MH^+ = 195
18			Yield = 99 MH^+ =199
19			Yield=77% ^1H NMR ($CDCl_3$) δ 7.42(t, 1H), 6.68(d, 2H), 4.29(q, 2H), 3.97(d, 2H), 3.95(s, 3H), 1.38(t, 3H).

PREPARATIVE EXAMPLE 20:

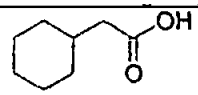
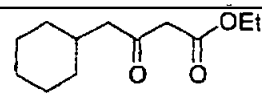
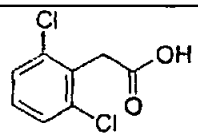
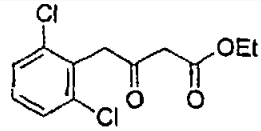
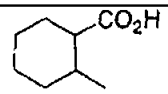
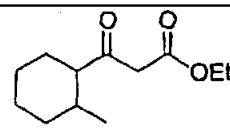
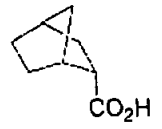
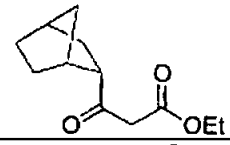
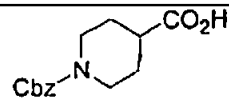
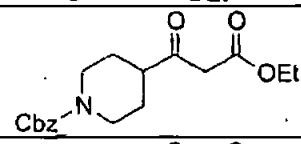
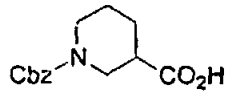
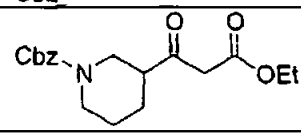
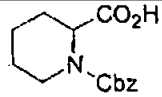
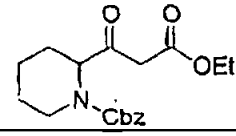
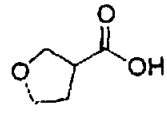
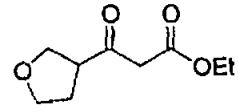


To a solution of the acid in THF was added Et_3N, followed by isobutyl chloroformate at –20 to –30°C. After the mixture was stirred for 30 min at –20 to –30°C, triethylamine hydrochloride was filtered off under argon, and the filtrate was added to the LDA-EtOAc reaction mixture (prepared as outlined in Method A) at –65 to –70°C. After addition of 1 N HCl, followed by routine workup of the reaction mixture and evaporation of the solvents, the crude β-keto esters were isolated. The crude material was used in the subsequent condensations.

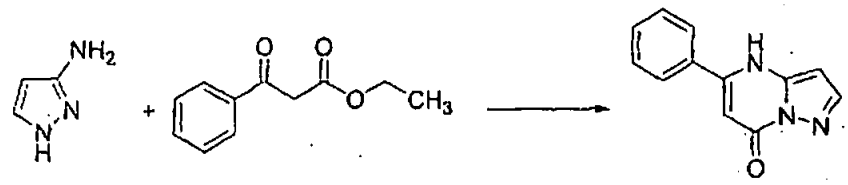
PREPARATIVE EXAMPLES 21 - 28:

By essentially the same conditions set forth in Preparative Example 20 only substituting the carboxylic acid shown in Column 2 of Table 4, the compounds shown in Column 3 of Table 4 were prepared:

TABLE 4

Prep. Ex.	Column 2	Column 3	CMPD
21			Yield = 99% MH^+ = 213
22			Yield = 70% MH^+ = 275
23			Yield = quant MH^+ =213
24			Yield = quant MH^+ =211
25			Yield = 99 MH^+ = 334
26			Yield = 99 MH^+ = 334
27			Yield = 99 MH^+ = 334
28			Yield=77% ^1H NMR ($CDCl_3$) δ 4.21(q, 2H), 3.95(d, 2H), 3.93-3.79(m, 4H), 3.52(s, 2H), 2.65(m, 1H), 1.25(t, 3H), 1.23-1.2(m, 2H).

PREPARATIVE EXAMPLE 29:

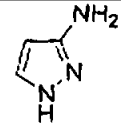
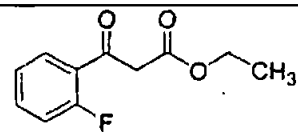
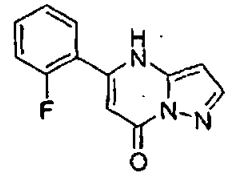
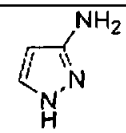
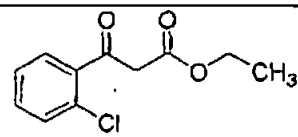
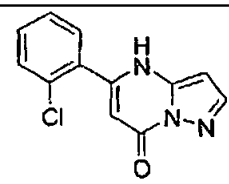
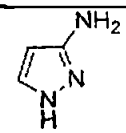
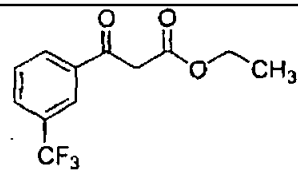
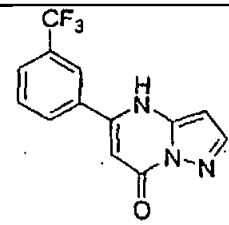


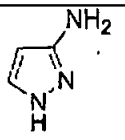
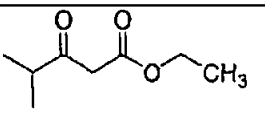
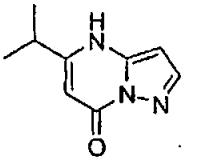
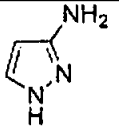
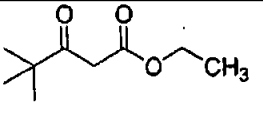
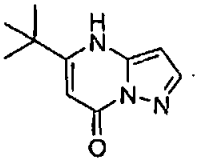
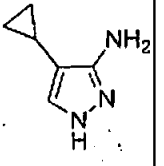
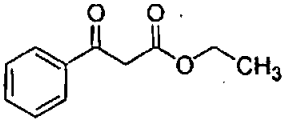
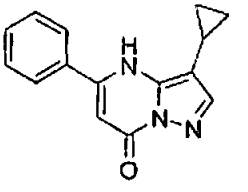
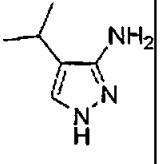
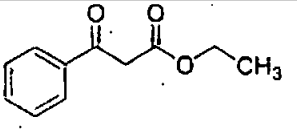
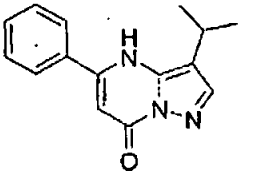
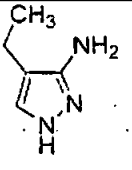
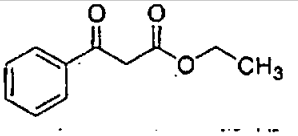
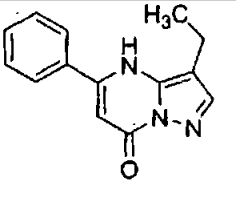
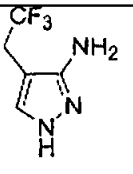
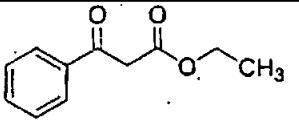
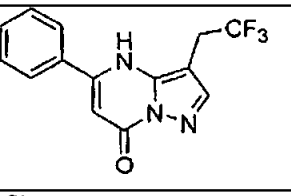
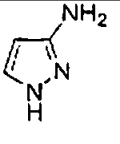
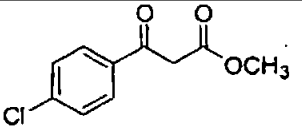
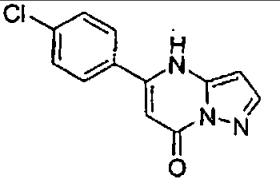
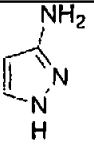
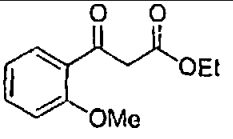
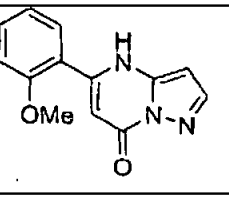
A solution of 3-aminopyrazole (2.0g, 24.07 mmol) and ethyl benzoylacetate (4.58 mL, 1.1 eq.) in AcOH (15 mL) was heated at reflux for 3 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The resulting solid was diluted with EtOAc and filtered to give a white solid (2.04 g, 40% yield).

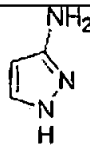
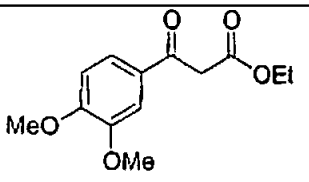
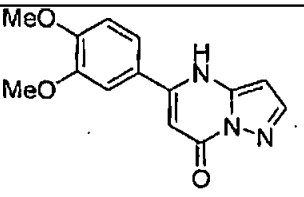
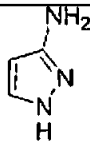
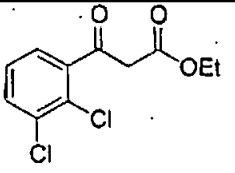
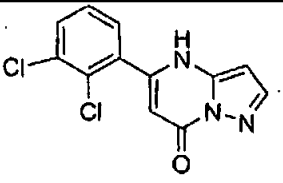
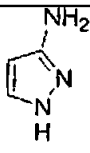
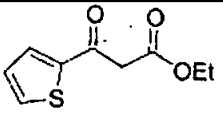
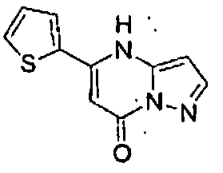
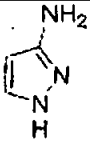
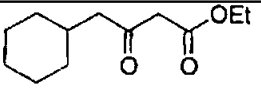
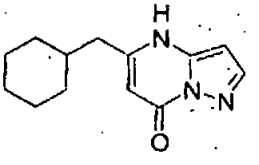
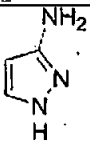
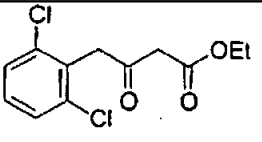
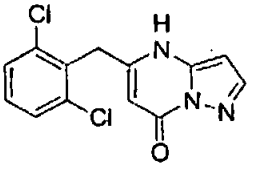
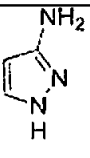
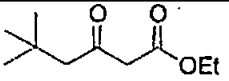
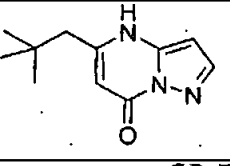
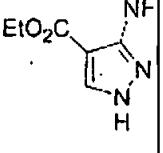
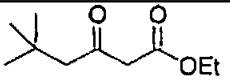
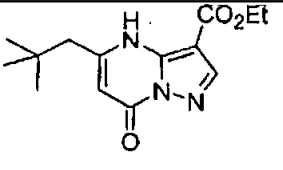
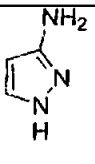
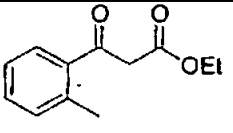
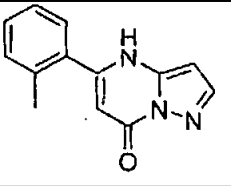
PREPARATIVE EXAMPLES 30-73:

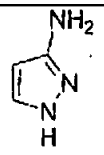
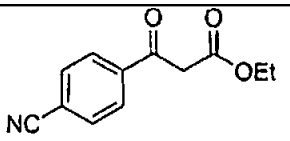
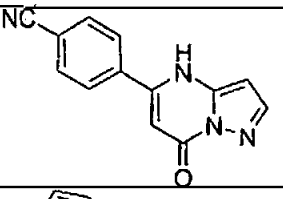
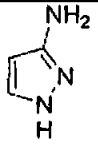
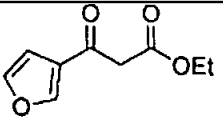
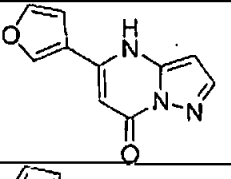
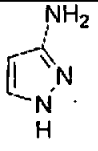
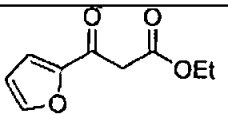
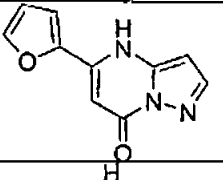
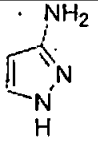
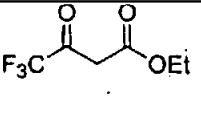
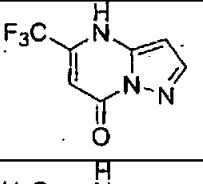
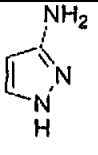
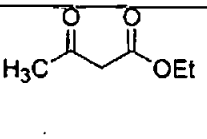
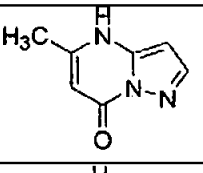
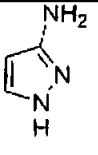
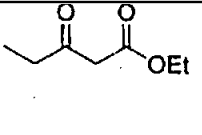
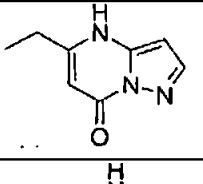
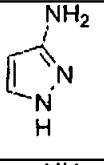
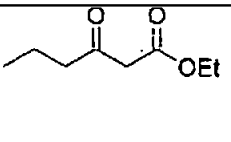
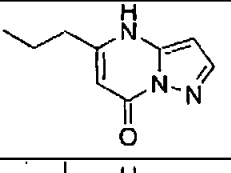
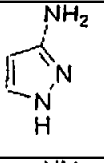
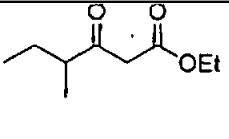
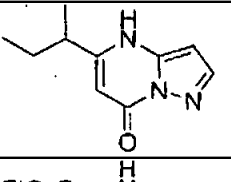
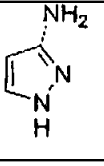
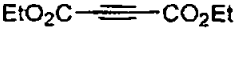
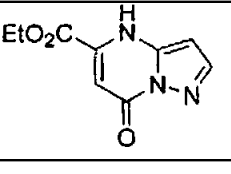
By essentially the same procedure set forth in Preparative Example 29 only substituting the aminopyrazole shown in Column 2 of Table 5 and the ester shown in Column 3 of Table 5, the compounds shown in Column 4 of Table 5 were prepared:

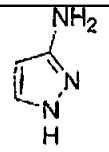
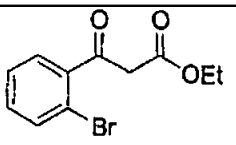
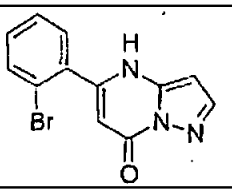
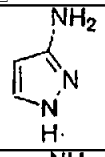
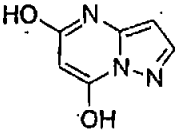
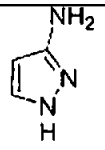
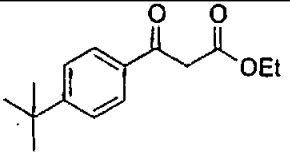
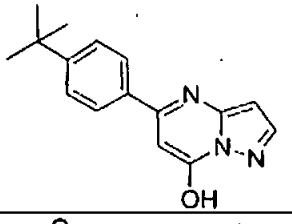
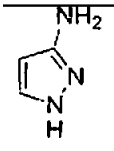
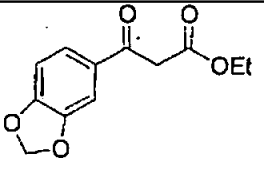
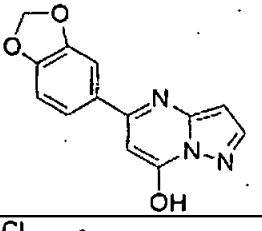
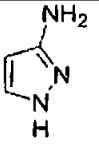
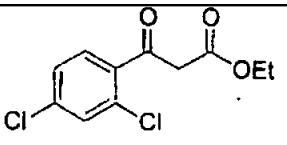
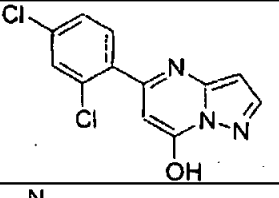
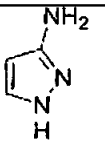
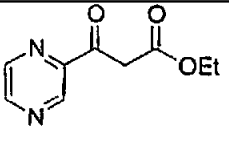
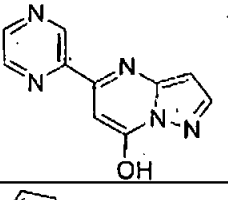
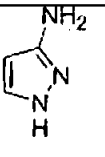
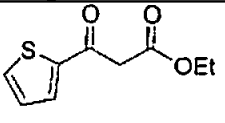
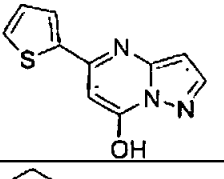
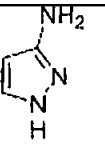
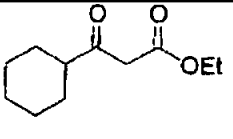
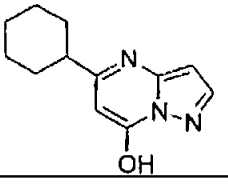
TABLE 5

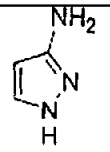
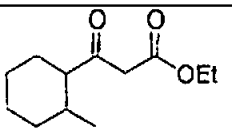
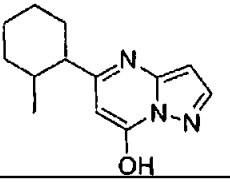
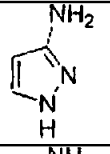
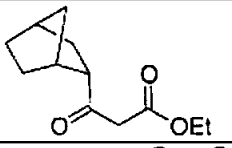
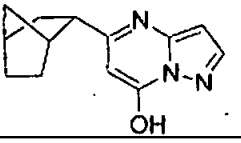
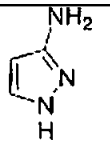
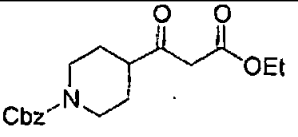
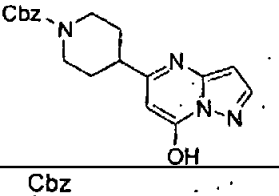
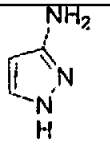
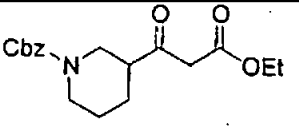
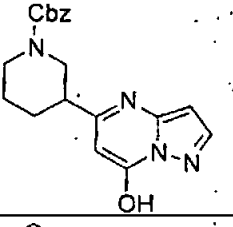
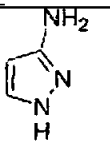
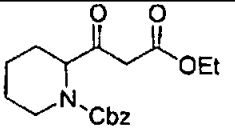
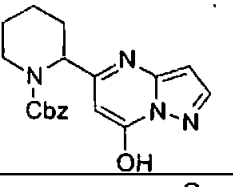
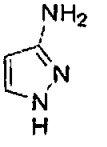
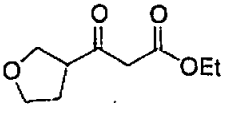
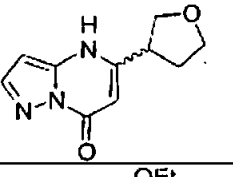
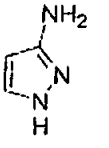
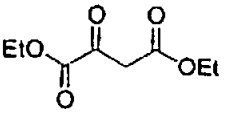
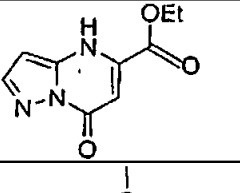
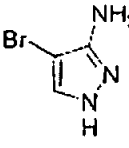
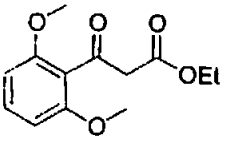
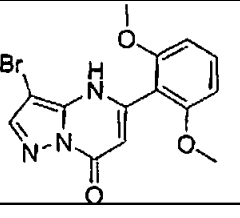
Prep. Ex.	Column 2	Column 3	Column 4	Column 5
30				
31				
32				

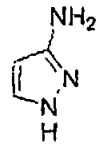
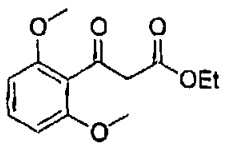
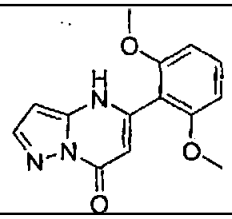
33				
34				
35				
36				
37				
37.10				
38				
39				

40				
41				
42				
43				
44				
45				
46				
47				

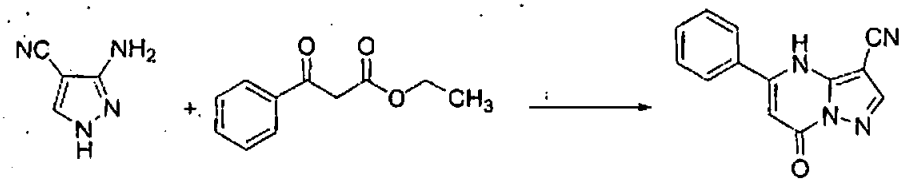
48				
49				
50				
51				
52				
53				
54				
55				
56				

57				
58				Yield = 68 MH^+ = 152
59				Yield = 46 MH^+ = 268
60				Yield = 63 MH^+ = 255
61				Yield = 80 MH^+ = 280
62				Yield =72 MH^+ = 214
63				Yield = 51 MH^+ = 218
64				Yield = 82 MH^+ =218

65				Yield = 39 MH^+ =232
66				Yield = 30 MH^+ =230
67				Yield = 80 MH^+ =353
68				Yield = 49 MH^+ =353
69				Yield = 42 MH^+ =353
70				
71				
72				

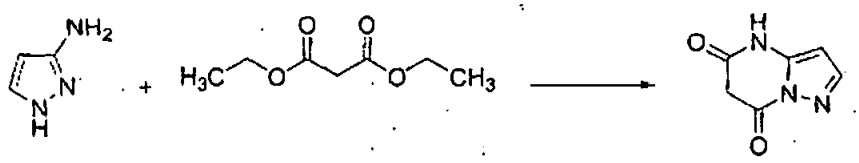
73				

PREPARATIVE EXAMPLE 74:



Ethyl benzoylacetate (1.76 mL, 1.1 eq.) and 3-amino-4-cyanopyrazole (1.0 g, 9.25 mmol) in AcOH (5.0 mL) and H_2O (10 mL) was heated at reflux 72 hours. The resulting solution was cooled to room temperature, concentrated *in vacuo*, and diluted with EtOAc. The resulting precipitate was filtered, washed with EtOAc, and dried *in vacuo* (0.47 g, 21% yield).

PREPARATIVE EXAMPLE 75

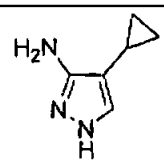
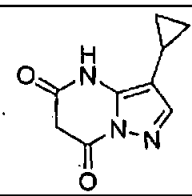
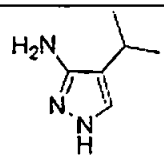
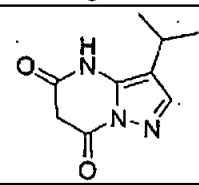
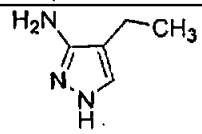
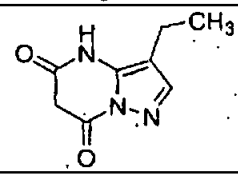


A procedure in US patent 3,907,799 was followed. Sodium (2.3 g, 2 eq.) was added to EtOH (150 mL) portionwise. When the sodium was completely dissolved, 3-aminopyrazole (4.2 g, 0.05 mol) and diethyl malonate (8.7 g, 1.1 eq.) were added and the resulting solution heated to reflux for 3 hours. The resulting suspension was cooled to room temperature and filtered. The filter cake was washed with EtOH (100 mL) and dissolved in water (250 mL). The resulting solution was cooled in an ice bath and the pH adjusted to 1-2 with concentrated HCl. The resulting suspension was filtered, washed with water (100 mL) and dried under vacuum to give a white solid (4.75 g, 63% yield).

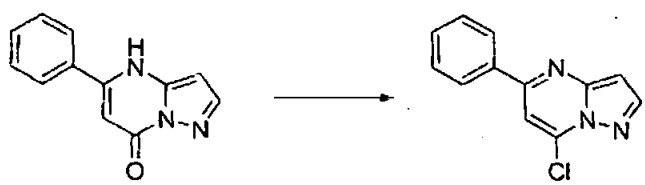
PREPARATIVE EXAMPLES 76-78:

By essentially the same procedure set forth in Preparative Example 75 only substituting the compound shown in Column 2 of Table 6, the compounds shown in Column 3 of Table 6 are prepared:

TABLE 6

Prep. Ex.	Column 2	Column 3
76		
77		
78		

PREPARATIVE EXAMPLE 79:

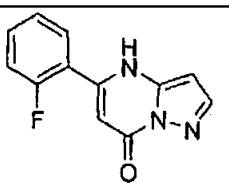
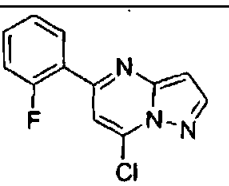
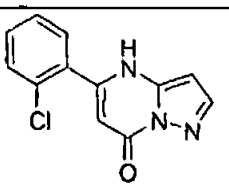
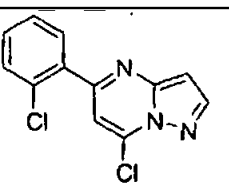
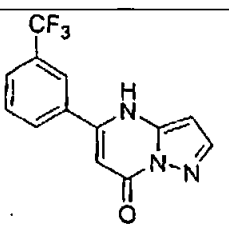
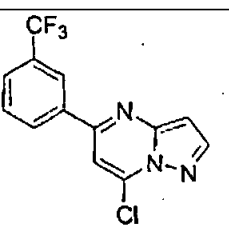
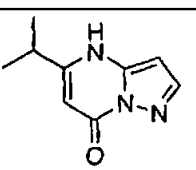
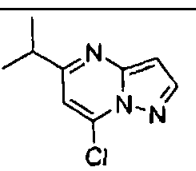
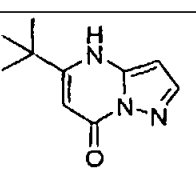
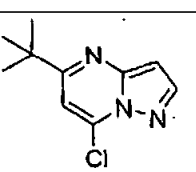
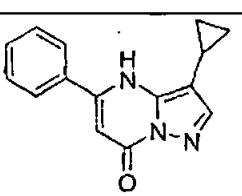
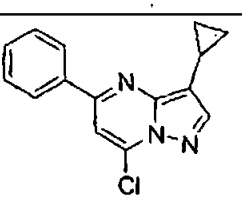
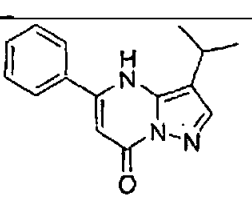
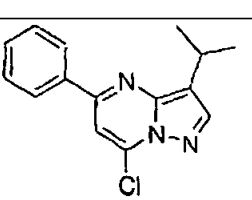


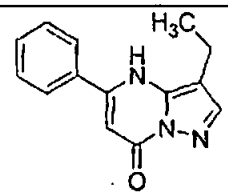
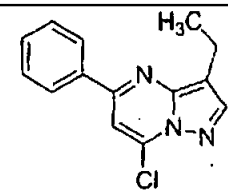
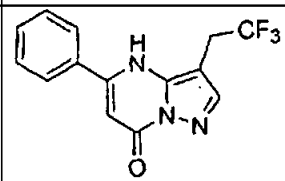
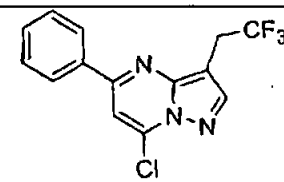
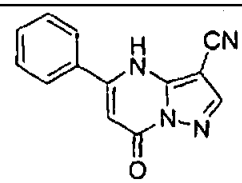
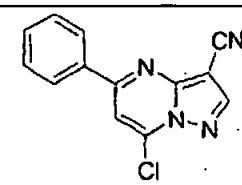
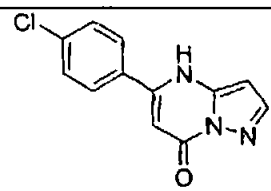
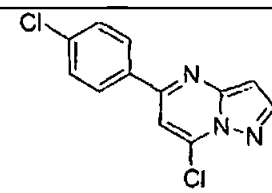
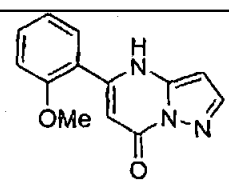
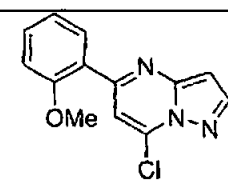
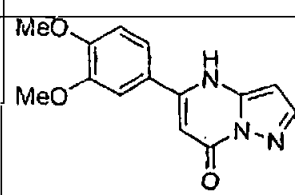
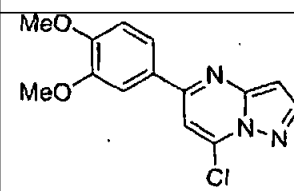
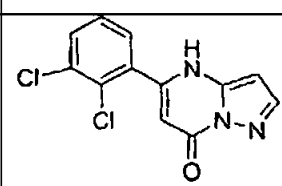
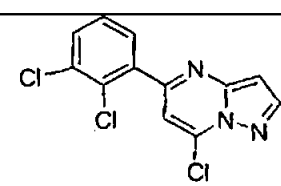
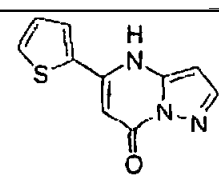
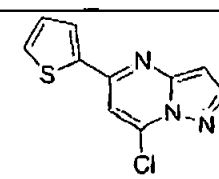
A solution of the compound prepared in Preparative Example 29 (1.0 g, 4.73 mmol) in $POCl_3$ (5 mL) and pyridine (0.25 mL) was stirred at room temperature 3 days. The resulting slurry was diluted with Et_2O, filtered, and the solid residue washed with Et_2O. The combined Et_2O washings were cooled to 0°C and treated with ice. When the vigorous reaction ceased, the resulting mixture was diluted with H_2O, separated, and the aqueous layer extracted with Et_2O. The combined organics were washed with H_2O and saturated NaCl, dried over Na_2SO_4, filtered, and concentrated to give a pale yellow solid (0.86 g, 79% yield). LCMS: MH^+=230.

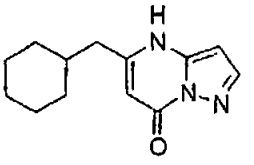
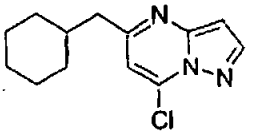
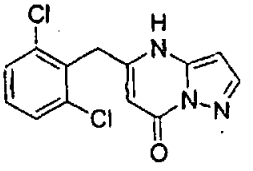
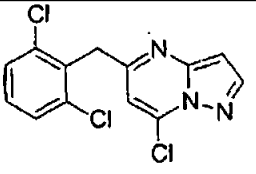
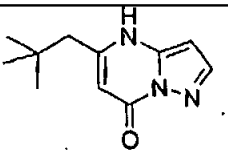
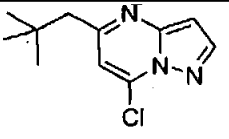
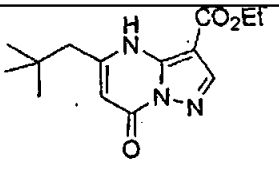
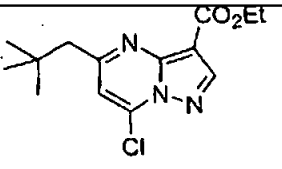
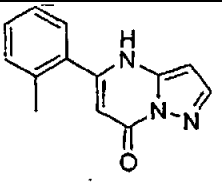
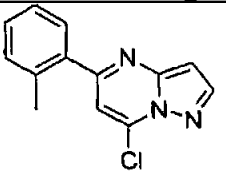
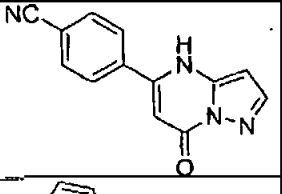
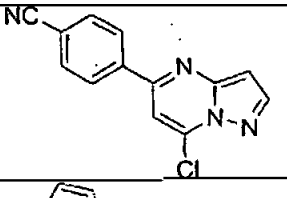
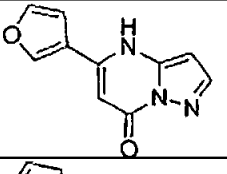
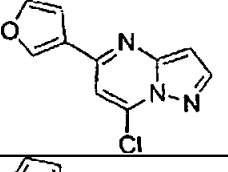
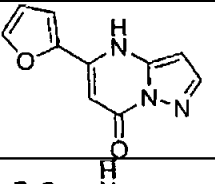
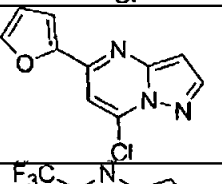
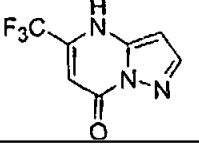
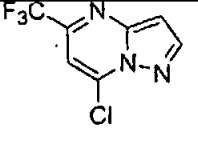
PREPARATIVE EXAMPLE 80-122:

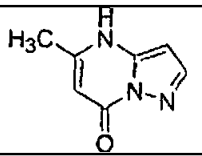
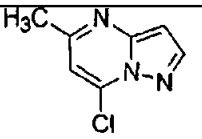
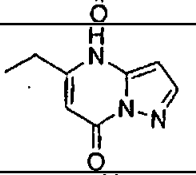
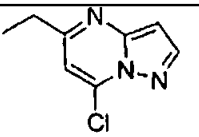
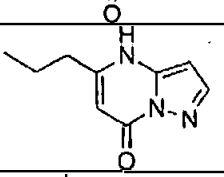
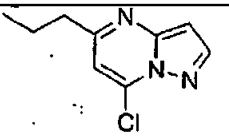
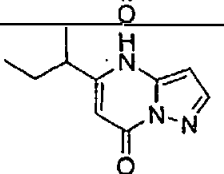
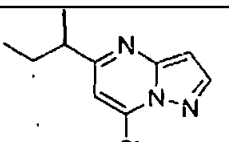
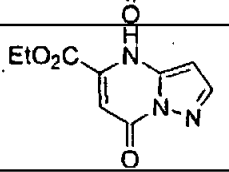
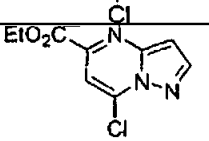
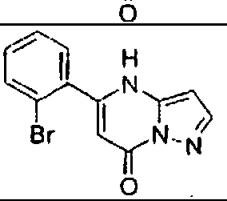
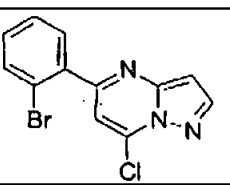
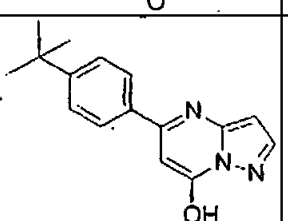
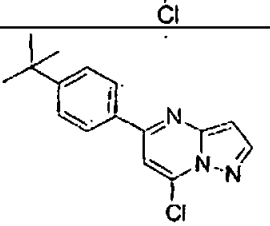
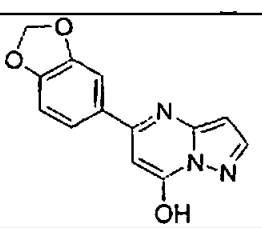
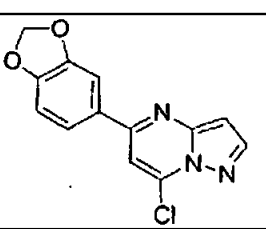
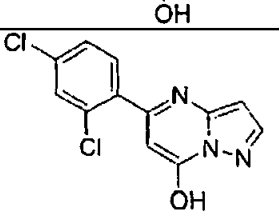
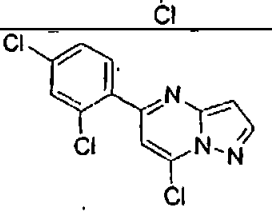
By essentially the same procedure set forth in Preparative Example 79, only substituting the compound shown in Column 2 of Table 7, the compounds shown in Column 3 of Table 7 were prepared:

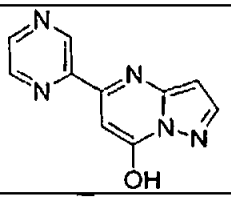
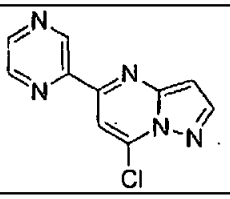
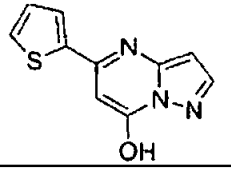
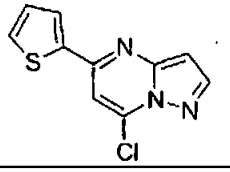
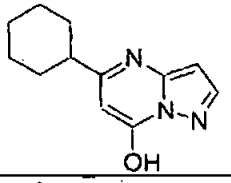
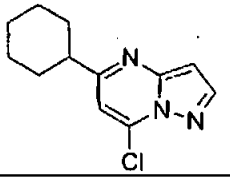
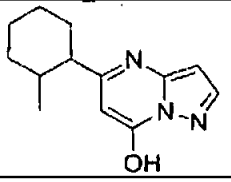
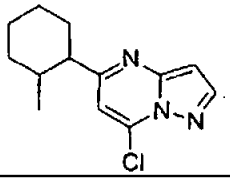
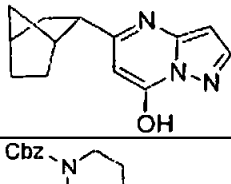
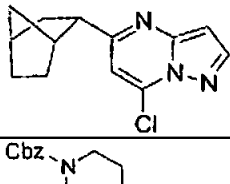
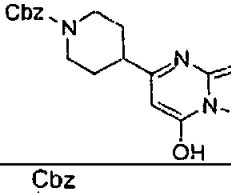
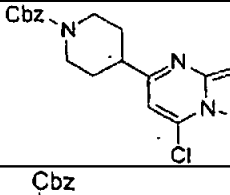
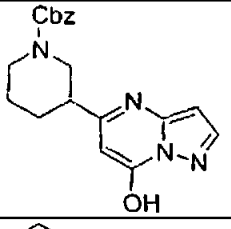
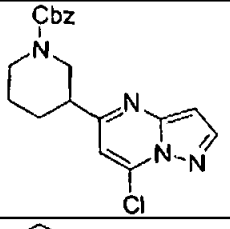
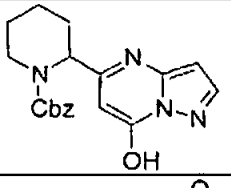
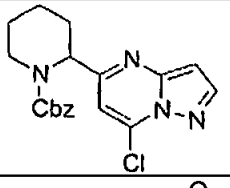
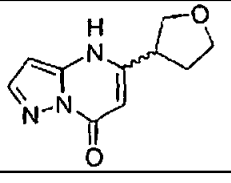
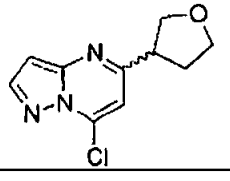
TABLE 7

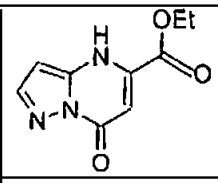
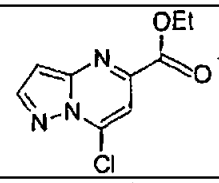
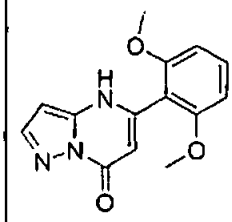
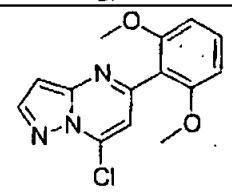
Prep. Ex.	Column 2	Column 3	CMPD
80			MS: MH^+=248
81			
82.			MS: MH^+=298
83			MS: MH^+=196
84			MS: MH^+=210
85			
86			MS: MH^+=272

87			
87.10			
88			MS: MH^+=255
89			
90			Yield = 65% MS: MH^+ = 260
91			Yield = 35% MS: MH^+ = 290
92			Yield = 32%. MS: MH^+ = 298
93			Yield = 45% MS: MH^+ = 236

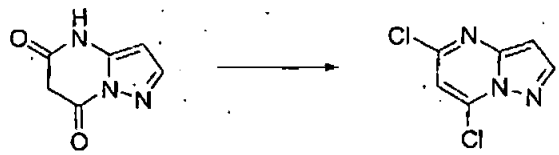
94			Yield = 100% LCMS: MH^+ = 250
95			Yield = 88% MS: MH^+ = 314
96			Yield=43% MS: MH^+=223
97			Yield=30% MS: MH^+=295
98			Yield=98% MS: MH^+=244
99			
100			
101			
102			

103			
104			
105			
106			
107			45% yield; MS: MH^+=226
108			MS: MH^+ = 308
109			Yield = quant MH^+ = 286
110			Yield = 50 MH^+ = 272
111			Yield = 85 MH^+ = 299

112			Yield = 97 MH^+ = 231
113			Yield = 45 MH^+ = 236
114			Yield = quant. MH^+ =236
115			Yield = 57 MH^+ =250
116			Yield = 89 MH^+ =248
117			Yield = 96 MH^+ =371
118			Yield = 99 MH^+ =371
119			Yield = 50 MH^+ =371
120			Yield=57% LCMS: MH^+=224

121			Yield=34% LCMS: MH^+=226
122			Yield=100% ^{1}H NMR ($CDCl_3$) δ 8.53(d, 1H), 7.66(t, 1H), 7.51(s, 1H), 7.45(d, 1H), 6.84(d, 2H).

PREPARATIVE EXAMPLE 123

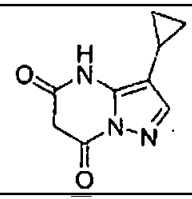
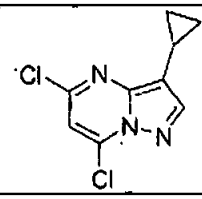
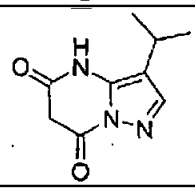
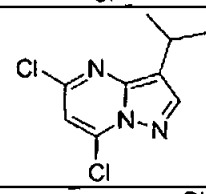
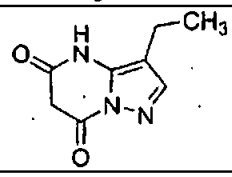
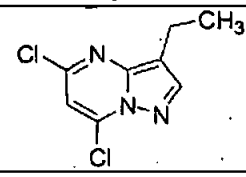


$POCl_3$ (62 mL) was cooled to 5 °C under nitrogen and dimethylaniline (11.4 g, 2.8 eq.) and the compound prepared in Preparative Example 75 (4.75 g, 0.032 mol). The reaction mixture was warmed to 60 °C and stirred overnight. The reaction mixture was cooled to 30 °C and the $POCl_3$ was distilled off under reduced pressure. The residue was dissolved in CH_2Cl_2 (300 mL) and poured onto ice. After stirring 15 minutes, the pH of the mixture was adjusted to 7-8 with solid $NaHCO_3$. The layers were separated and the organic layer was washed with H_2O (3 x 200 mL), dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography using a 50 : 50 CH_2Cl_2 : hexanes solution as eluent to elute the dimethyl aniline. The eluent was then changed to 75 : 25 CH_2Cl_2 : hexanes to elute the desired product (4.58 g, 77% yield). MS: MH^+=188.

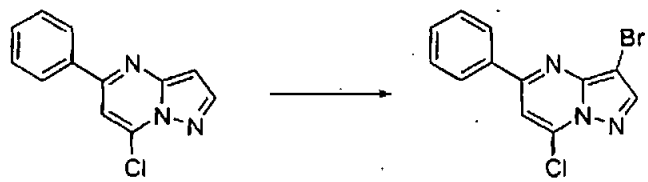
PREPARATIVE EXAMPLES 124-126

By essentially the same procedure set forth in Preparative Example 123 only substituting the compound in Column 2 of Table 8, the compounds shown in Column 3 of Table 8 are prepared:

TABLE 8

Prep. Ex.	Column 2	Column 3
124		
125		
126		

PREPARATIVE EXAMPLE 127:

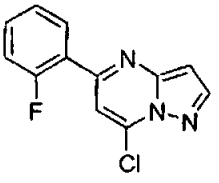
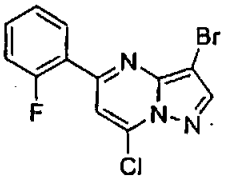
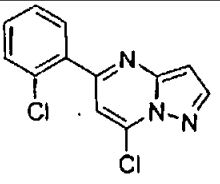
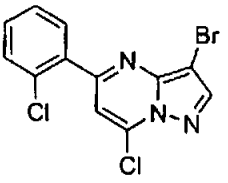
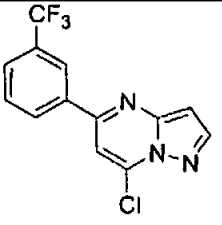
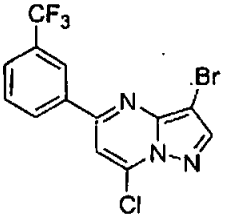
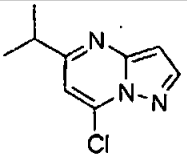
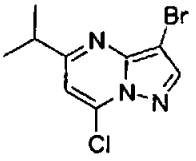
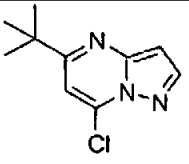
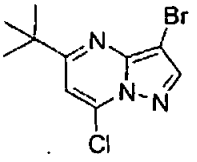
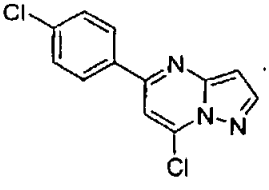
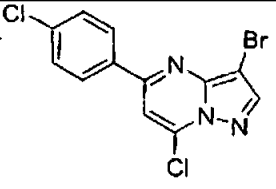
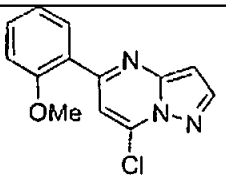
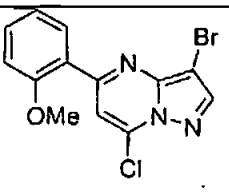


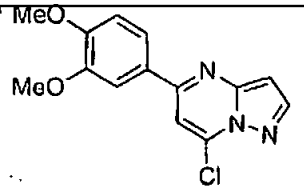
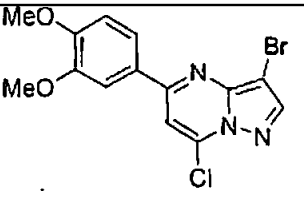
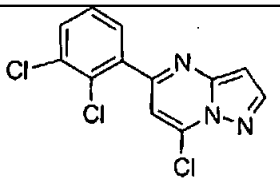
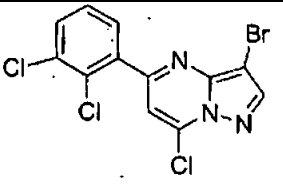
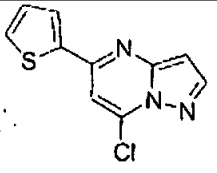
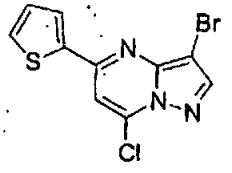
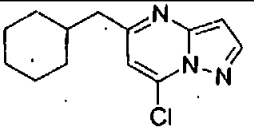
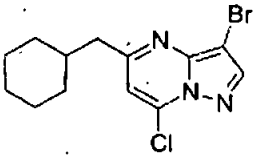
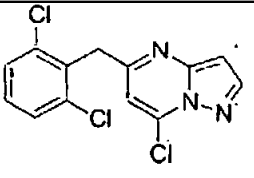
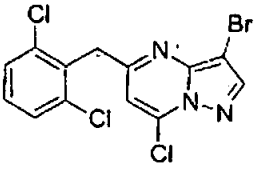
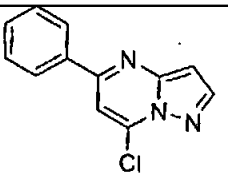
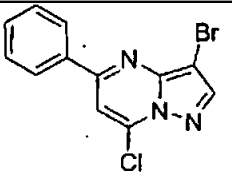
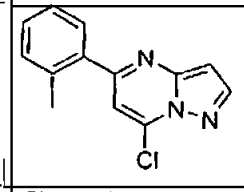
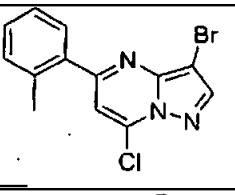
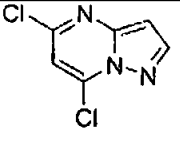
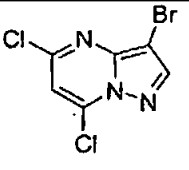
A solution of the compound prepared in Preparative Example 79 (0.10 g, 0.435 mmol) in CH_3CN (3 mL) was treated with NBS (0.085 g, 1.1 eq.). The reaction mixture was stirred at room temperature 1 hour and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 20% EtOAc-in-hexanes solution as eluent (0.13 g, 100% yield). LCMS:MH^+=308.

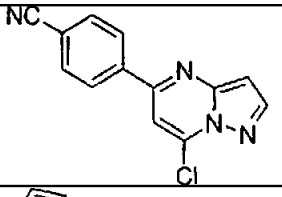
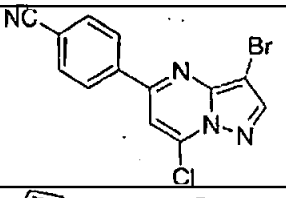
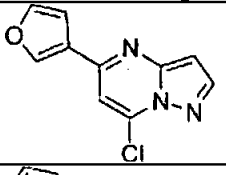
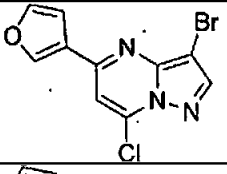
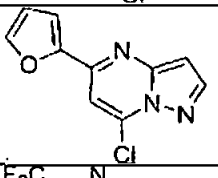
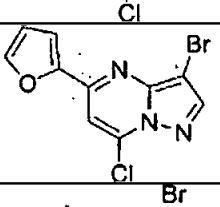
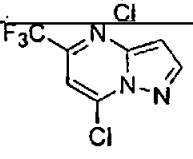
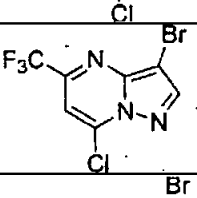
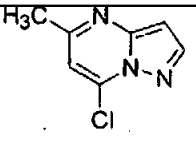
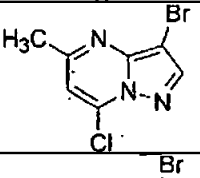
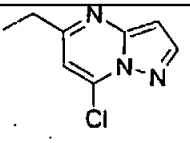
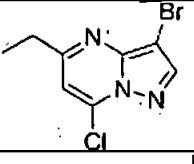
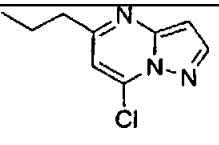
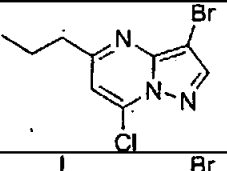
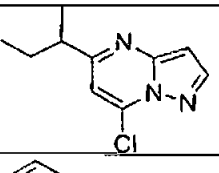
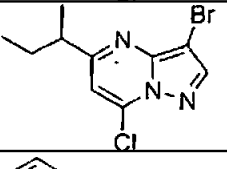
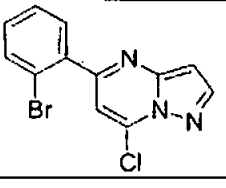
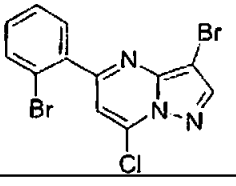
PREPARATIVE EXAMPLES 128-164:

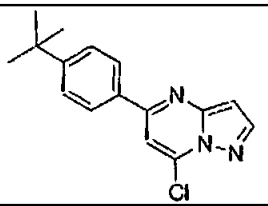
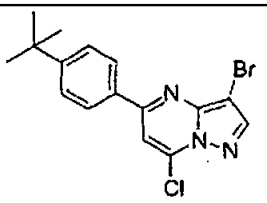
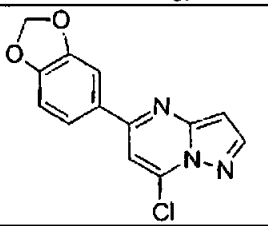
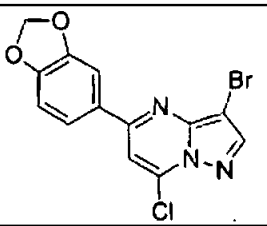
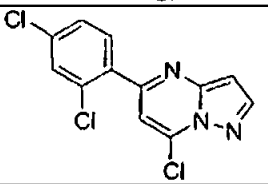
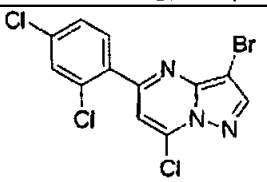
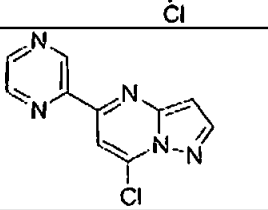
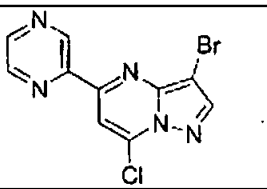
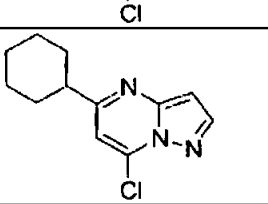
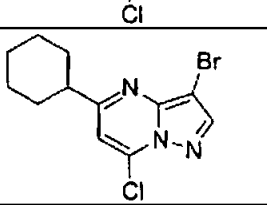
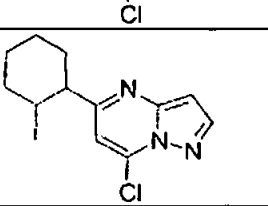
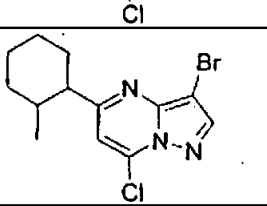
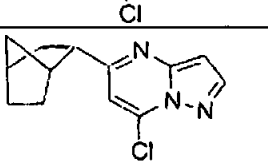
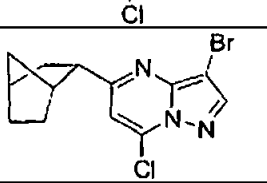
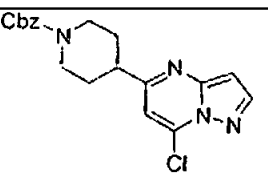
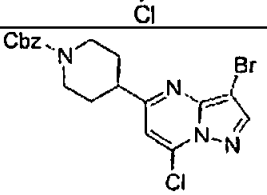
By essentially the same procedure set forth in Preparative Example 127 only substituting the compounds shown in Column 2 of Table 9, the compounds shown in Column 3 of Table 9 were prepared:

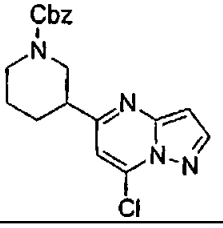
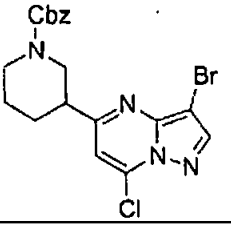
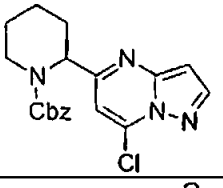
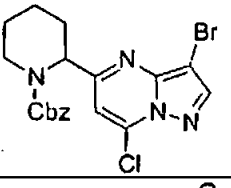
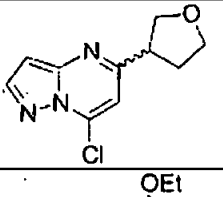
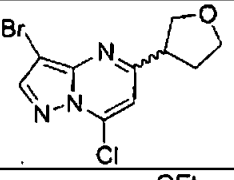
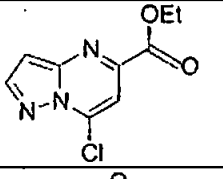
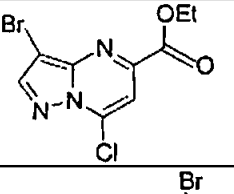
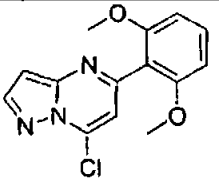
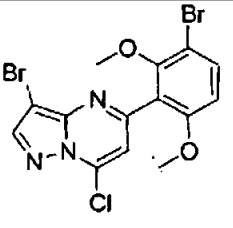
TABLE 9

Prep. Ex.	Column 2	Column 3	CMPD
128			MS: MH^+= 326
129			MS: MH^+= 342
130			MS: MH^+= 376
131			MS: MH^+=274
132			MS: MH^+=288
133			
134			Yield = 75% MS: MH^+ = 338

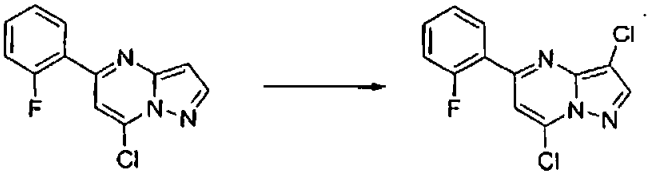
135			Yield = 52% MS: MH^+ = 368
136			Yield = 87% MS: MH^+ = 376
137			Yield = 100% MS: MH^+ = 316
138			Yield = 92% MS: MH^+ = 330
139			Yield = 82% MS: MH^+ = 395
140			Yield=88% MS: MH^+=308
141			Yield=100% MS: MH^+=322
142			MH^+=266

143			
144			
145			
146			
147			
148			
149			
150			
151			LCMS: MH^+ = 386

152			Yield = quant MH^+ = 364
153			Yield = quant MH^+ = 353
154			Yield = 95 MH^+ = 378
155			Yield = 77 MH^+ = 311
156			Yield =quant. MH^+ =314
157			Yield = 99 MH^+ =328
158			Yield = 98 MH^+ =326
159			Yield = 99 MH^+ =449

160			Yield = 95 MH^+ =449
161			Yield = 72 MH^+ =449
162			Yield=98% LCMS: MH^+=302
163			Yield=95% LCMS: MH^+=305
164			Yield=50% ^1H NMR ($CDCl_3$) δ 8.36(s, 1H), 7.72(d, 1H), 7.20(s, 1H), 6.82(d, 1H), 3.99(s, 3H), 3.90(s, 3H);

PREPARATIVE EXAMPLE 165:



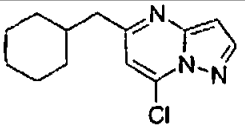
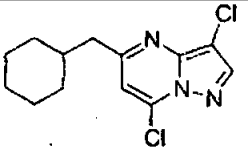
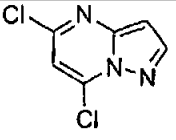
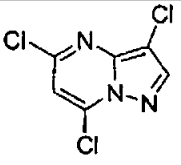
A solution of the compound prepared in Preparative Example 80 (0.3 g, 1.2 mmol) in CH_3CN (15 mL) was treated with NCS (0.18 g, 1.1 eq.) and the resulting solution heated to reflux 4 hours. Additional NCS (0.032 g, 0.2 eq.) added and the resulting solution was stirred at reflux overnight. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the residue

purified by flash chromatography using a 20% EtOAc in hexanes solution as eluent (0.28 g, 83% yield). LCMS: MH^+= 282.

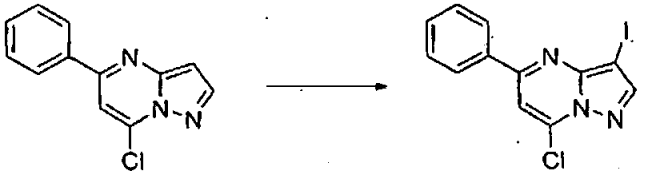
PREPARATIVE EXAMPLE 166-167:

By essentially the same procedure set forth in Preparative Example 165 only substituting the compound shown in Column 2 of Table 10, the compound shown in Column 3 of Table 10 was prepared:

TABLE 10

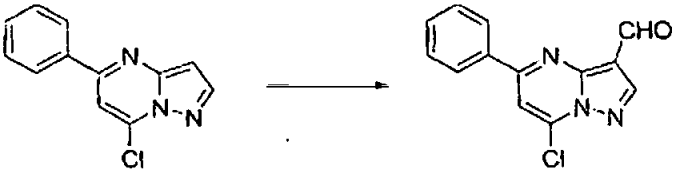
Prep. Ex.	Column 2	Column 3	CMPD
166			Yield = 82% LCMS: MH^+ = 286
167			

PREPARATIVE EXAMPLE 167.10:



By essentially the same procedure set forth in Preparative Example 165 only substituting N-iodosuccinimide, the above compound was prepared.

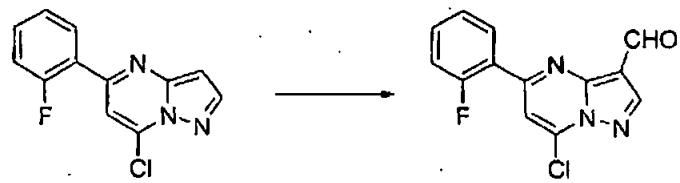
PREPARATIVE EXAMPLE 168:



To a solution of the compound from Preparative Example 79 (1.0 g, 4.35 mmol) in DMF (6 mL) was added $POCl_3$ (1.24 mL, 3.05 eq.) and the resulting mixture was stirred at room temperature overnight. The reaction mixture was cooled to 0°C and the excess $POCl_3$ was quenched by the addition of ice. The

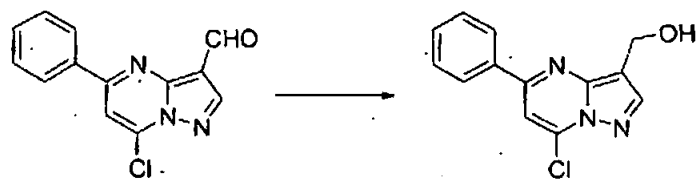
resulting solution was neutralized with 1N NaOH, diluted with H_2O, and extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography using a 5% MeOH in CH_2Cl_2 solution as eluent (0.95 g, 85% yield). LCMS: MH^+=258.

PREPARATIVE EXAMPLE 169:



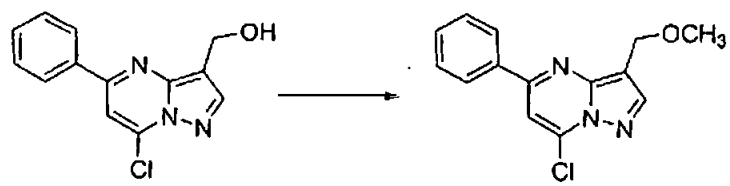
By essentially the same procedure set forth in Preparative Example 168 only substituting the compound prepared in Preparative Example 80, the above compound was prepared (0.45 g, 40% yield).

PREPARATIVE EXAMPLE 170:



To a solution of the product of Preparative Example 169 (0.25 g, 0.97 mmol) in THF was added $NaBH_4$ (0.041 g, 1.1 eq.) and the resulting solution was stirred at room temperature overnight. The reaction mixture was quenched by the addition of H_2O and extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 60: 40 hexanes : EtOAc mix as eluent (0.17 g, 69% yield). MS: MH^+=260.

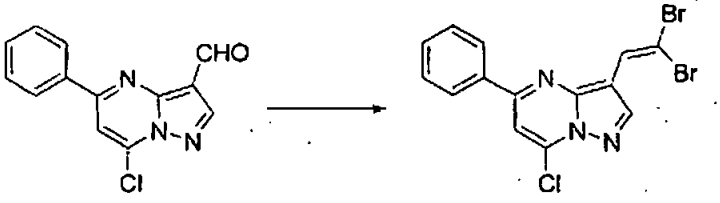
PREPARATIVE EXAMPLE 171:



A solution of the compound prepared in Preparative Example 170 (0.12 g, 0.462 mmol), dimethyl sulfate (0.088 mL, 2.0 eq), 50% NaOH (0.26 mL) and

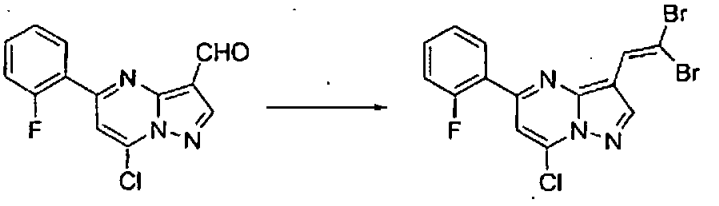
catalytic Bu_4NBr in CH_2Cl_2 (4 mL) was stirred at room temperature overnight. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 30% EtOAc-in-hexanes solution as eluent (0.062 g, 48% yield).

PREPARATIVE EXAMPLE 172



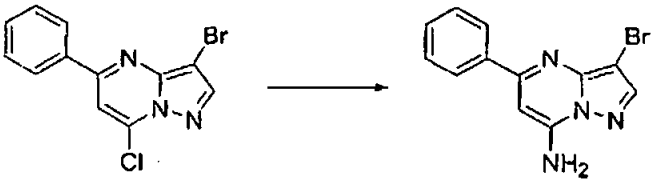
To a solution of PPh_3 (4.07 g, 4.0 eq.) and CBr_4 (2.57 g, 2.0 eq.) in CH_2Cl_2 (75 mL) at 0 °C was added the compound prepared in Preparative Example 168 (1.0 g, 3.88 mmol). The resulting solution was stirred at 0 °C for 1 hour and concentrated under reduced pressure. The residue was purified by flash chromatography using a 20% EtOAc in hexanes solution as eluent (1.07 g, 67% yield).

PREPARATIVE EXAMPLE 173:



By essentially the same procedure set forth in Preparative Example 172 only substituting the compound prepared in Preparative Example 169 the above compound was prepared (0.5 g, 70% yield).

PREPARATIVE EXAMPLE 174:



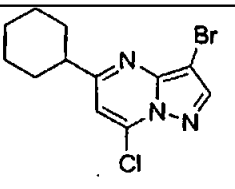
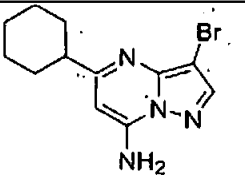
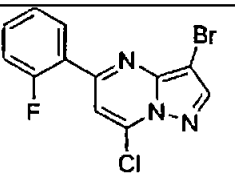
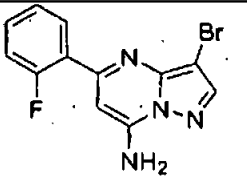
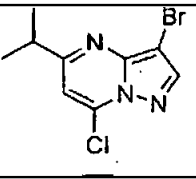
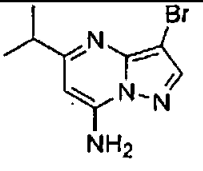
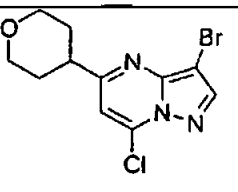
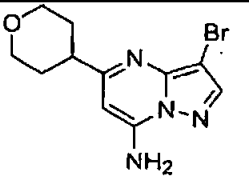
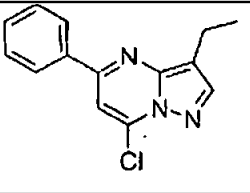
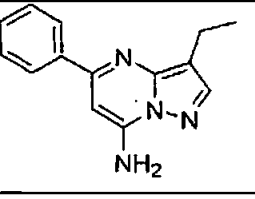
The compound prepared in Preparative Example 127 (3.08 g, 10.0 mmol), 2.0 M NH_3 in 2-propanol (50 mL, 100.0 mmol), and 37 % aqueous NH_3 (10.0 mL) were stirred in a closed pressure vessel at 50°C for 1 day. The solvent was

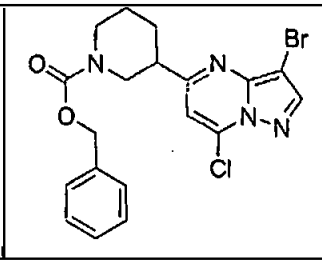
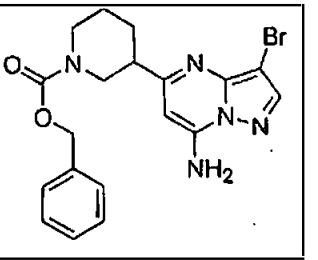
evaporated and the crude product was purified by flash chromatography using 3:1 CH_2Cl_2:EtOAc as eluent. Pale yellow solid (2.30 g, 80%) was obtained. LCMS: M^+=289.

PREPARATIVE EXAMPLES 175-180:

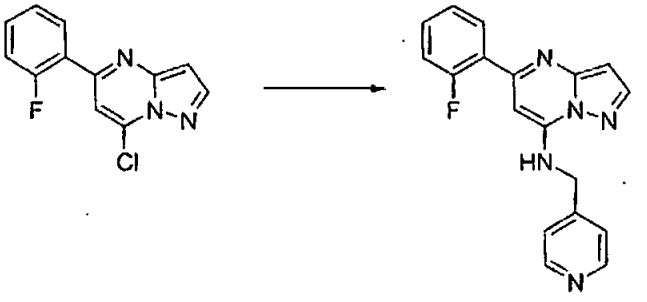
By essentially the same procedure set forth in Preparative Example 174 only substituting the compound shown in Column 2 of Table 11, the compounds shown in Column 3 of Table 11 were prepared.

TABLE 11

Prep. Ex.	Column 2	Column 3
175		
176		
177		
178		
179		

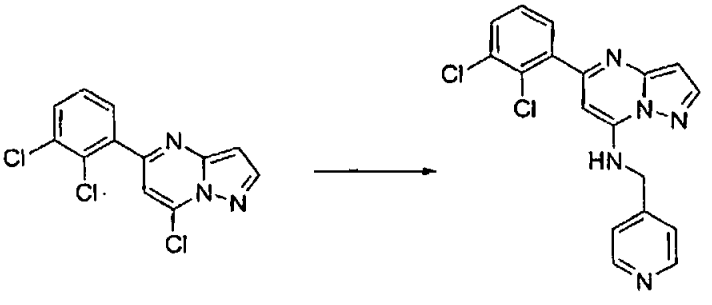
180		

PREPARATIVE EXAMPLE 181:



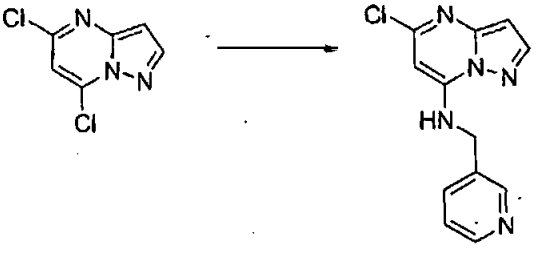
The compound prepared in Preparative Example 80 (0.3 g, 1.2 mmol), K_2CO_3 (0.33 g, 2 eq.), and 4-aminomethylpyridine (0.13 mL, 1.1 eq.) was heated to reflux overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with H_2O and extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered and, concentrated. The crude product was purified by flash chromatography using a 5% (10% NH_4OH in MeOH) solution in CH_2Cl_2 as eluent (0.051 g, 40% yield). LCMS: MH^+=320.

PREPARATIVE EXAMPLE 182:



By essentially the same procedure set forth in Preparative Example 181 only substituting the compound described in Preparative Example 92, the above compound was prepared. LCMS: MH^+=370.

PREPARATIVE EXAMPLE 183:

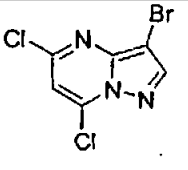
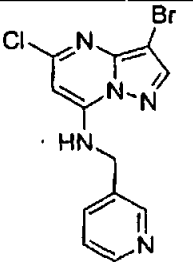


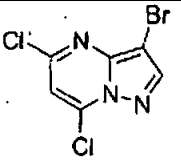
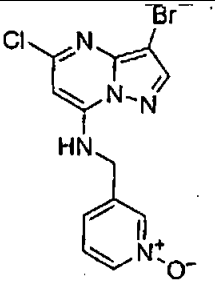
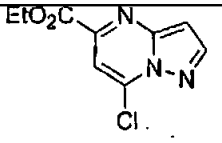
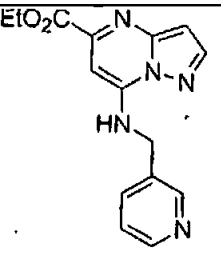
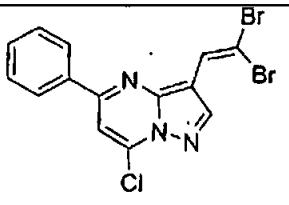
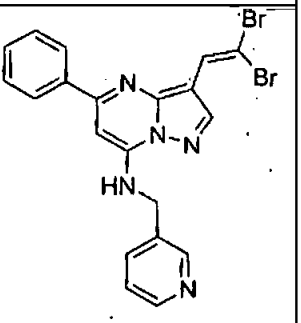
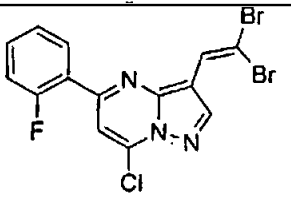
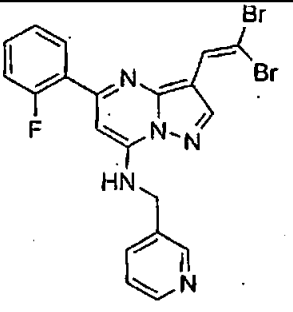
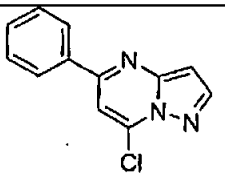
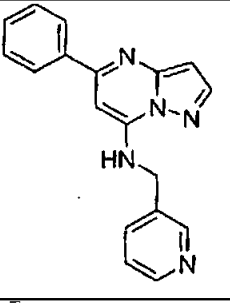
To a solution of the compound prepared in Preparative Example 123 (0.25 g, 1.3 mmol) in dioxane (5 mL) was added iPr_2NEt (0.47 mL, 2.0 eq.) and 3-aminomethylpyridine (0.15 ml, 1.1 eq.). The resulting solution was stirred at room temperature 72 hours. The reaction mixture was diluted with H_2O and extracted with EtOAc. The combined organics were washed with H_2O and saturated NaCl, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography using a 5% MeOH in CH_2Cl_2 solution as eluent (0.29 g, 83% yield). MS: MH^+=260.

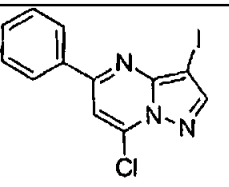
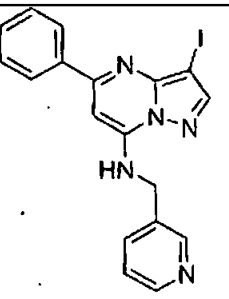
PREPARATIVE EXAMPLES 184-187:

By essentially the same procedure set forth in Preparative Example 183 only substituting the compound shown in Column 2 of Table 12, the compounds shown in Column 3 of Table 12 are prepared.

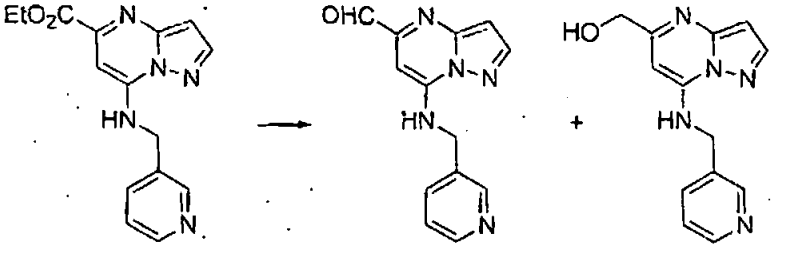
TABLE 12

Prep. Ex.	Column 2	Column 3
184		

184.1		
185		
186		
187		
187.1		

187.11		

PREPARATIVE EXAMPLE 188 and PREPARATIVE EXAMPLE 189:

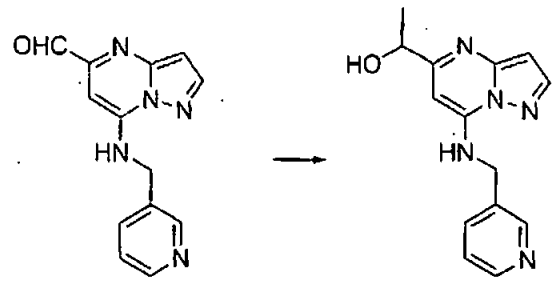


To a solution of the compound prepared in Preparative Example 185 (1.18 g, 3.98 mmol) in THF (35 mL) at -78 °C was added LAH (4.78 mL, 1M in Et_2O, 1.0 eq.) dropwise. The reaction mixture was stirred at -78 °C for 3 hours at which time additional LAH (2.0 mL, 1M in Et_2O, 0.42 eq.) was added dropwise. The reaction mixture was stirred an additional 1.25 hours and quenched by the addition of saturated Na_2SO_4 (8.5 mL). The reaction mixture was diluted with EtOAC (23 mL), H_2O (2 mL), and CH_3OH (50 mL). The resulting slurry was filtered through a plug of Celite. The Celite was washed with CH_3OH and the filtrate dried with Na_2SO_4, filtered, and concentrated. The product was purified by flash chromatography using a CH_2Cl_2 : CH_3OH (93 : 7) solution as eluent to yield aldehyde as the first eluting product and alcohol as the second eluting product.

Preparative Example 188: (aldehyde): 0.4 g, 39% yield. MS: MH^+ = 254.

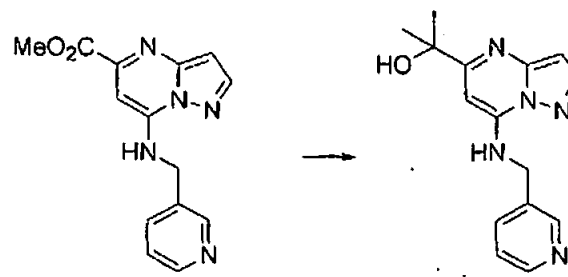
Preparative Example 189: (alcohol): 0.25 g, 24% yield. MS: MH^+ = 256.

PREPARATIVE EXAMPLE 190:



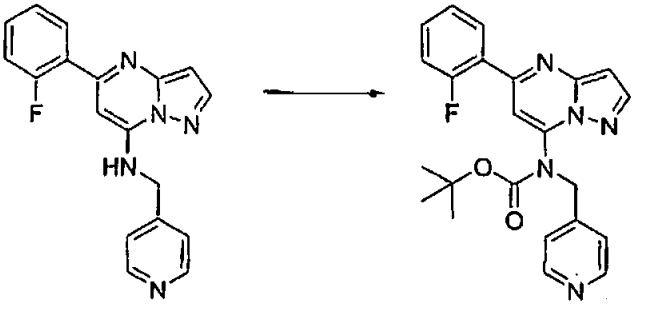
To a solution of the compound prepared in Preparative Example 188 (0.075 g, 0.30 mmol) in THF (2.0 mL) at 0 °C was added CH_3MgBr (0.3 mL, 3.0M solution in Et_2O, 3.0 eq.) dropwise. The resulting solution was stirred at 0 °C an additional 1.5 hours, warmed to room temperature, and stirred overnight. Additional CH_3MgBr (0.15 mL, 3.0M in Et_2O, 1. eq.) was added and the resulting solution stirred an additional 1.5 hours. The reaction mixture was cooled to 0 °C and quenched by the addition of saturated NH_4Cl. The resulting solution was diluted with CH_2Cl_2 and H_2O and extracted with CH_2Cl_2. The combined organics were washed with saturated NaCl and dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography using a CH_2Cl_2 : CH_3OH (90 : 10) solution as eluent (0.048 g, 60% yield). MS: MH^+ = 270.

PREPARATIVE EXAMPLE 191:



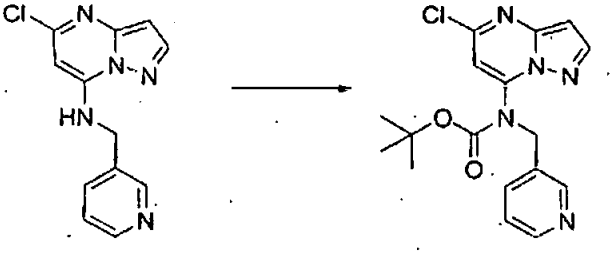
By essentially the same procedure set forth in Preparative Example 190 only substituting the compound prepared in Preparative Example 185 and using excess MeMgBr (5 eq.), the above compound was prepared.

PREPARATIVE EXAMPLE 192:



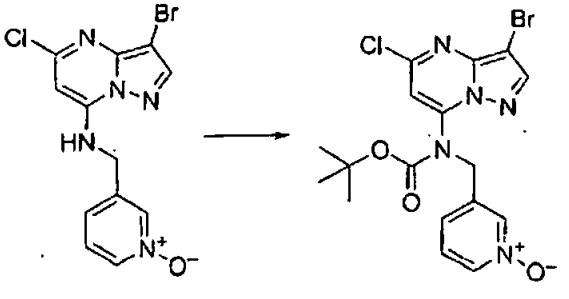
The compound prepared in Preparative Example 181 (0.29 g, 0.91 mmol), BOC_2O (0.22 g, 1.1 eq), and DMAP (0.13 g, 1.1 eq.) in dioxane (10 mL) was stirred at room temperature 3 days. Additional BOC_2O (0.10g, 0.5 eq.) was added and the reaction mixture was stirred 4 hours. The reaction mixture was concentrated *in vacuo*, diluted with saturated $NaHCO_3$ (15 mL), and extracted with CH_2Cl_2 (2 x 100 mL). The combined organics were dried over Na_2SO_4, filtered , and concentrated under reduce pressure. The crude product was purified by flash chromatography using a 5% (10% NH_4OH in MeOH) solution in CH_2Cl_2 as eluent (0.35 g, 91% yield). LCMS: MH^+= 420.

PREPARATIVE EXAMPLE 193:



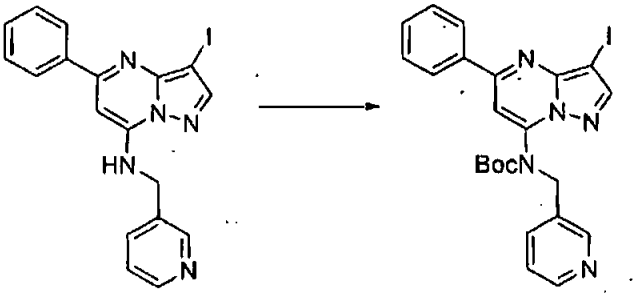
By essentially the same procedure set forth in Preparative Example 192 only substituting the compound prepared in Preparative Example 183, the above compound was prepared. MS: MH^+ = 360.

PREPARATIVE EXAMPLE 193.10:



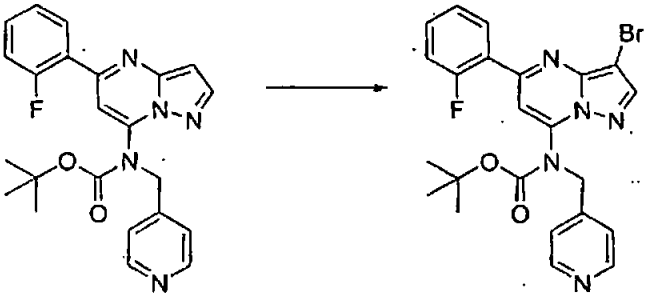
By essentially the same procedure set forth in Preparative Example 192 only substituting the compound prepared in Preparative Example 184.1, the above compound was prepared. MS: MH^+ = 454.

PREPARATIVE EXAMPLE 194:



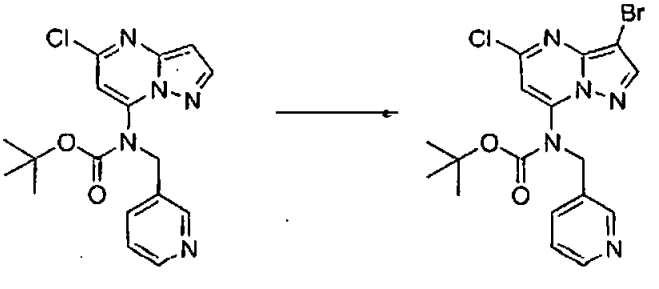
By essentially the same procedure set forth in Preparative Example 192 only substituting the above compound prepared in Preparative Example 187.11, the above compound was prepared (0.223 g, 88% yield). MS: MH^+ = 528.

PREPARATIVE EXAMPLE 195:



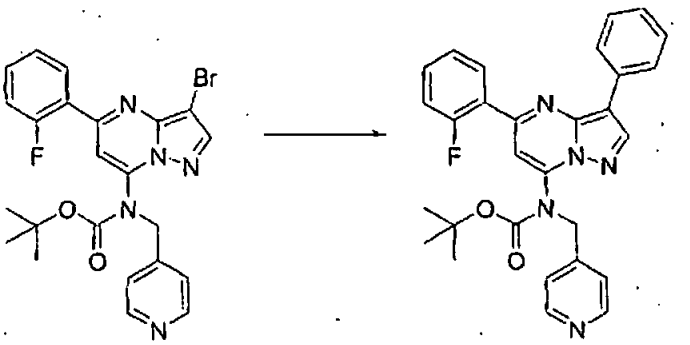
By essentially the same procedure set forth in Preparative Example 127 only substituting the compound prepared in Preparative Example 192, the above compound was prepared (0.38 g, 95% yield). LCMS: MH^+= 498.

PREPARATIVE EXAMPLE 196:



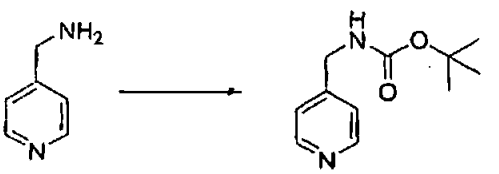
By essentially the same procedure set forth in Preparative Example 195, only substituting the compound prepared in Preparative Example 193, the above compound was prepared (0.3 g, 83% yield). MS: MH^+ = 438.

PREPARATIVE EXAMPLE 197:



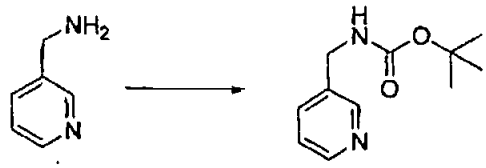
A solution of the compound prepared in Preparative Example 195 (0.15 g, 0.3 mmol), phenylboronic acid (0.073 g, 2.0 eq.), K_3PO_4 (0.19 g, 3.0 eq.), and $Pd(PPh_3)_4$ (0.017 g, 5 mol %) was heated at reflux in DME (16 mL) and H_2O (4 mL) 7 hours. The resulting solution was cooled to room temperature, diluted with H_2O (10 mL), and extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography using a 2.5% (10% NH_4OH in MeOH) in CH_2Cl_2 solution as eluent (0.16 g, 100% yield).

PREPARATIVE EXAMPLE 198:



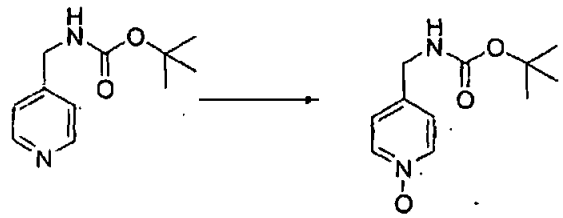
To a solution of 4-aminomethylpyridine (1.41 mL; 13.87 mmol) in CH_2Cl_2 (50 mL) was added BOC_2O (3.3 g, 1.1 eq.) and TEA and the resulting solution was stirred a room temperature 2 hours. The reaction mixture was diluted with H_2O (50 mL) and extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 5% (10% NH_4OH in MeOH) solution in CH_2Cl_2 as eluent to give a yellow solid (2.62 g, 91% yield). LCMS: MH^+= 209.

PREPARATIVE EXAMPLE 199:



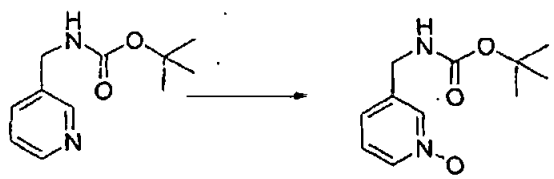
By essentially the same procedure set forth in Preparative Example 198 only substituting 3-aminomethylpyridine, the above compound was prepared as a yellow oil (2.66 g, 92% yield). LCMS: MH^+= 209.

PREPARATIVE EXAMPLE 200:



To a solution of the compound prepared in Preparative Example 198 (0.20 g, 0.96 mmol) in CH_2Cl_2 (5 mL) at 0°C was added *m*-CPBA (0.17 g, 1.0 eq) and the resulting solution stirred at 0°C 2 hours and stored at 4°C overnight at which time the reaction mixture was warmed to room temperature and stirred 3 hours. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography using a 10% (10% NH_4OH in MeOH) solution as eluent: LCMS: MH^+= 255.

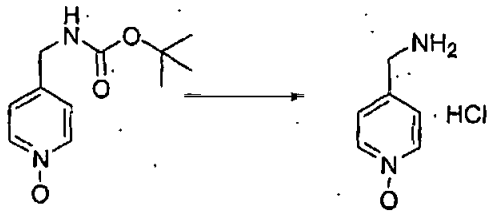
PREPARATIVE EXAMPLE 201:



A solution of oxone (58.6 g) in H_2O (250 mL) was added dropwise to the compound prepared in Preparative Example 199 (27 g, 0.13 mol) and $NaHCO_3$ (21.8 g, 2.0 eq.) in MeOH (200 mL) and H_2O (250 mL). The resulting solution was stirred at room temperature overnight. The reaction mixture was diluted with CH2Cl2 (500 mL) and filtered. The layers were separated and the aqueous layer extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4,

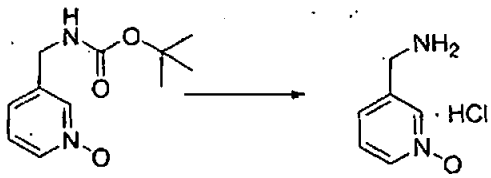
filtered, and concentrated under reduced pressure to give a white solid (21.0 g, 72% yield). MS: MH^+= 255.

PREPARATIVE EXAMPLE 202:



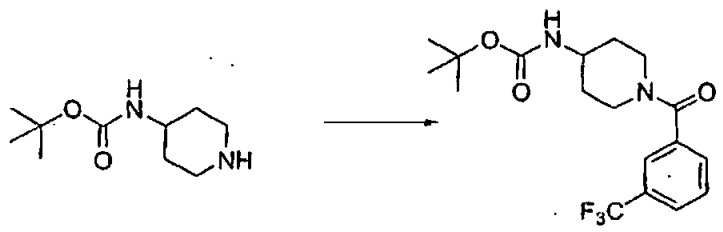
The compound prepared in Preparative Example 200 (0.29 g, 1.29 mmol) was stirred at room temperature in 4M HCl in dioxane (0.97 mL) 2 hours. The reaction mixture was concentrated *in vacuo* and used without further purification. LCMS: MH^+= 125.

PREPARATIVE EXAMPLE 203:



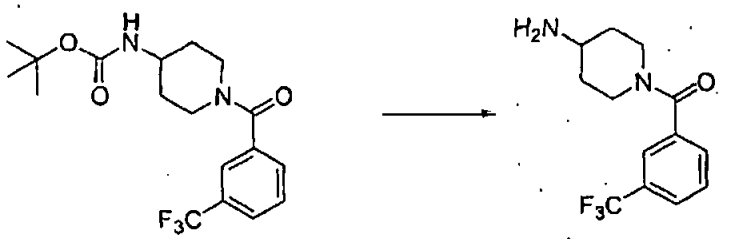
By essentially the same procedure set forth in Preparative Example 202 only substituting the compound prepared in Preparative Example 201, the compound shown above was prepared. LCMS: MH^+= 125.

PREPARATIVE EXAMPLE 204:



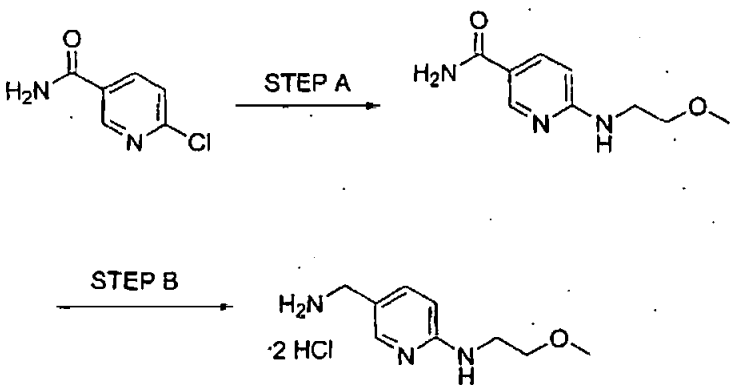
To 4-N-t-Butoxycarbonylaminopiperidine (0.8 g, 4.0 mmol) in CH_2Cl_2 (10 mL) at 0°C was added TEA (1.40 mL, 2.5 eq.) and 3-trifluoromethyl benzoyl chloride (1.05 g, 1.25 eq.). The resulting solution was stirred 15 minutes and warmed to room temperature and stirred 3 hours. The reaction mixture was diluted with CH_2Cl_2 and washed with 5% Na_2CO_3 (2 x 100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to yield a pale yellow solid (quantitative crude yield).

PREPARATIVE EXAMPLE 205:



To a solution of the compound prepared in Preparative Example 204 (1.0 g, 2.76 mmol) in CH_2Cl_2 (15 mL) at 0°C was added TFA (8 mL) and the resulting solution was stirred at 0°C for 30 minutes and room temperature 1 hour. The reaction mixture was poured onto Na_2CO_3 (40 g) and H_2O (400 mL) added and the resulting mixture was extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 20% (7N NH_3 in MeOH) solution in CH_2Cl_2 as eluent (0.6 g, 82% yield).

PREPARATIVE EXAMPLES 206:



STEP A:

To a solution of 6-chloronicotinamide (1g, 6.39 mmol) in isoamyl alcohol (15 mL) at rt was added Na_2CO_3 (0.81g, 7.67 mmol) followed by methoxyethylamine (0.67 mL, 7.67 mmol). The mixture was heat at 130 °C for 16h, cooled to rt, and was filtered thru a medium glass-fritted filter. The resulting filtrate was concentrated under reduced pressure and the resultant solid was triturated with Et_2O (2 x 10 mL). The crude solid was placed under high vacuum to afford 1.2 g (96%) of a light yellow solid. M+H = 196.

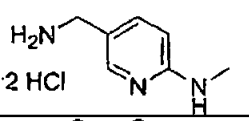
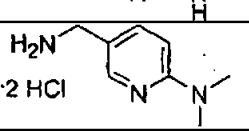
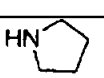
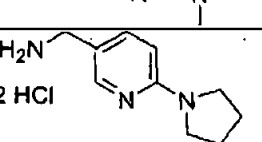
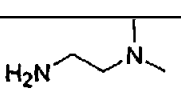
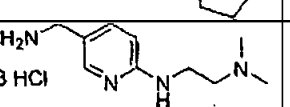
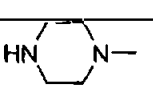
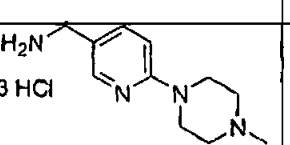
STEP B:

To a solution of amide (1.2 g, 6.12 mmol) from Preparative Example 206, Step A in THF (5 mL) at 0 °C was added a solution of BH_3-THF (43 mL; 43 mmol) dropwise over 10 min. The resultant solution was warmed to rt and stirred for 14 h. The mixture was cooled to 0 °C and was sequentially treated with 6M HCl (35 mL), water (30 mL), and MeOH (150 mL). The mixture was stirred for 8 h and was concentrated under reduced pressure. The crude residue was triturated with MeOH, concentrated under reduced pressure, and placed under high vacuum to afford 1.6 g (82%) of a white solid as the dihydrochloride salt. M+H (free base) = 182.0. This material was used crude in the coupling with 7-Cl adducts.

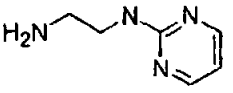
PREPARATIVE EXAMPLES 207-211:

By essentially the same known procedure set forth in Preparative Example 206 only by utilizing the amines shown in Column 2 of Table 13 and the amines shown in Column 3 of Table 13 were prepared:

TABLE 13

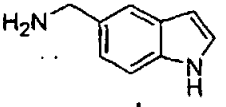
Prep.Ex.	Column 2 (Amine)	Column 3 (Amine)	CMPD M+H (free base)
207			M+H = 138
208			M+H = 152
209			M+H = 178
210			M+H = 195
211			M+H = 207

PREPARATIVE EXAMPLE 212:



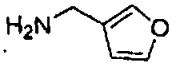
The above compound was prepared accordingly to the methods described in WO 91/18904.

PREPARATIVE EXAMPLE 213:



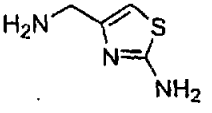
The above compound was prepared accordingly to the methods described in US 6,180,627 B1.

PREPARATIVE EXAMPLE 214:



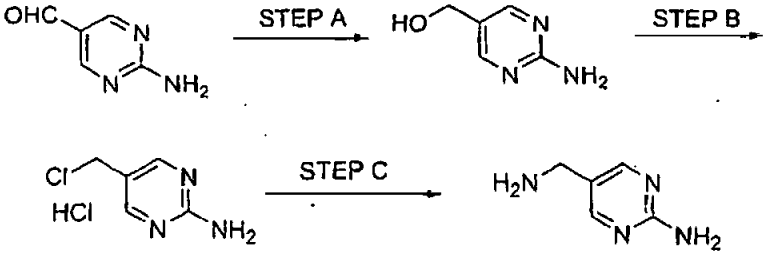
The known amine was prepared as described in *J. Med. Chem.* (2001), *44*, 4505-4508.

PREPARATIVE EXAMPLE 215:



The known amine was prepared as described in *J. Med. Chem.* (1997), *40*, 3726-3733.

PREPARATIVE EXAMPLE 216:



STEP A:

A solution of aldehyde (50 g, 0.41 mol) [WO 0232893] in MeOH (300 mL) was cooled to 0 °C and carefully treated with $NaBH_4$ (20g, 0.53 mol in 6 batches) over 20 minutes. The reaction was then allowed to warm to 20 °C and was stirred for 4 hours. The mixture was again cooled to 0 °C, carefully quenched with saturated aqueous NH_4Cl, and concentrated. Flash chromatography (5–10% 7N NH_3-MeOH/CH_2Cl_2) provided the primary alcohol (31g, 62%) as a light yellow solid.

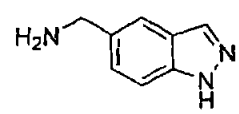
STEP B:

A slurry of alcohol (31 g, 0.25 mol) from Preparative Example 216, Step A in CH_2Cl_2 (500 mL) was cooled to 0 °C and slowly treated with $SOCl_2$ (55mL; 0.74 mol over 30 minutes). The reaction was then stirred overnight at 20 °C. The material was concentrated, slurried in acetone, and then filtered. The resulting beige solid was dried overnight in vacuo (38.4g, 52%, HCl salt).

STEP C:

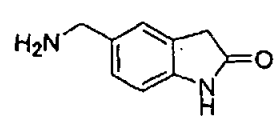
To a 15 mL pressure tube charged with a stir bar was added chloride (150 mg, 0.83 mmol) from Preparative Example 216, Step B followed by 7 M NH_3/MeOH (10 mL). The resulting solution was stirred for 48 h at rt where upon the mixture was concentrated under reduced pressure to afford a light yellow solid (0.146 g, 83%). M+H (free base) = 140.

PREPARATIVE EXAMPLE 217:



The above compound was prepared accordingly to methods described in WO 00/26210.

PREPARATIVE EXAMPLE 218:



The above compound was prepared accordingly to methods described in WO 99/10325.

PREPARATIVE EXAMPLE 219:

aq. NH_4Cl (3 mL). The mixture was concentrated under reduced pressure and the resultant aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The organic layers were combined, washed with brine (1 x 5 mL), dried (Na_2SO_4), and filtered. The organic layer was concentrated under reduced pressure to afford 417 mg (90% yield) of a white solid. M+H = 225.

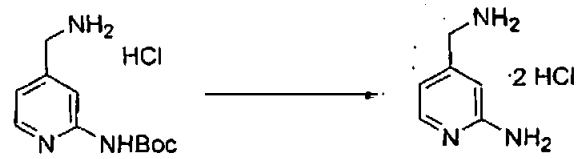
STEP B:

The crude alcohol from Preparative Example 222, step A (0.4 g, 1.78 mmol) in CH_2Cl_2 (4 mL) was added $SOCl_2$ (0.65 mL, 8.91 mmol) and the mixture was stirred for 2 h at rt. The mixture was concentrated under reduced pressure to afford 407 mg (94%) of a light yellow solid. M+H = 243. The crude product was taken on without further purification.

STEP C:

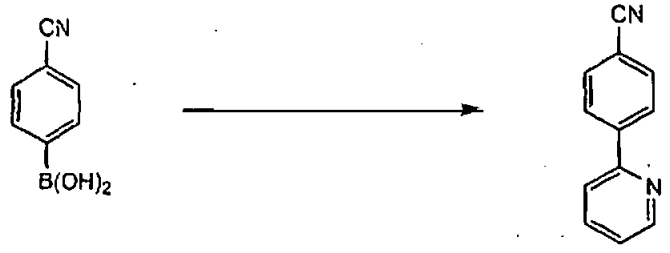
To a solution of crude chloride from Preparative Example 222, Step B (0.33 g, 1.36 mmol) in a pressure tube charged with 7M NH_3/MeOH (35 mL) and the mixture was stirred for 72 h. The mixture was concentrated under reduced pressure to afford 257 mg (85%) of a yellow semisolid. M+H (free base) = 224.

PREPARATIVE EXAMPLE 223:



To a round bottom flask charged with amine hydrochloride (0.24 g, 1.1 mmol) from Preparative Example 222 and a stir bar was added 4N HCl/dioxane (10 mL). The resulting solution was stirred for 12h at rt, concentrated under reduced pressure, and triturated with CH_2Cl_2 (3 x 5 mL). The crude product was filtered, washed with Et2O (2 x 5mL), and dried under high vacuum to afford 0.19g (91%) as the dihydrochloride salt. M+H (free base) = 124.

PREPARATIVE EXAMPLE 224:

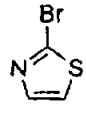
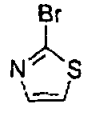
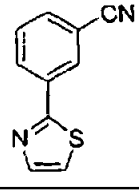


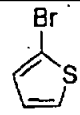
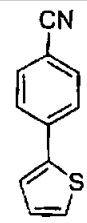
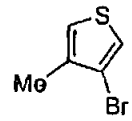
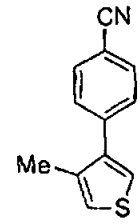
$Pd(PPh_3)_4$ (0.404 gm, 0.35 mmol) was added to a degassed solution of 4-cyanobenzene boronic acid (1.029 g, 7 mmol) and 2-bromopyridine (1.11 g, 7 mmol) in 75 mL acetonitrile. 0.4 M sodium carbonate solution (35 mL) was added to the reaction mixture and the resulting solution was refluxed at 90°C under Ar for 24 hours (progress of reaction was monitored by TLC). The reaction mixture was cooled and aqueous layer was separated. The organic layer containing the product and spent catalyst was mixed with silica gel (15 g) and concentrated to dryness. The 4-(2-pyridyl)-benzonitrile was isolated by column chromatography (0.850 g, 68%). LCMS: MH^+ = 181; ^1H NMR ($CDCl_3$) δ 8.85 (d, 1H), 8.7 (dd, 1H), 7.9 (dd, 1H), 7.75 (d, 2H), 7.7 (d, 2H), 7.4 (dd, 1H).

PREPARATIVE EXAMPLES 225-228:

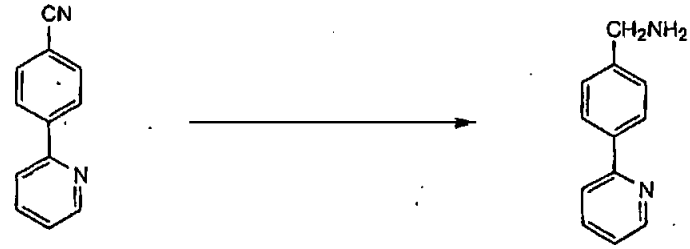
By following essentially same procedure described in Preparative Example 224, only substituting the bromides in column 2 of Table 14, compounds in column 3 of Table 14 were prepared.

Table 14

Prep. Ex.	Column 2	Column 3	Column 4
225			Yield = 70% LCMS: MH^+ = 187
226			Yield = 60% LCMS: MH^+ = 187

227			Yield = 70% LCMS: MH^+ = 186
228			Yield = 70% LCMS: MH^+ = 200

PREPARATIVE EXAMPLE 229:

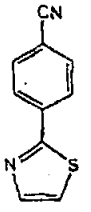
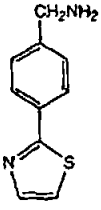
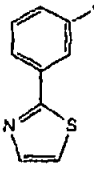
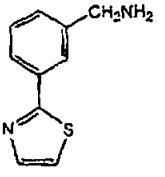
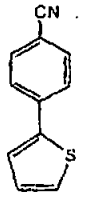
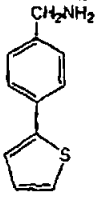
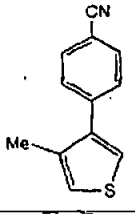
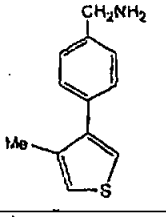


BH_3-THF solution (1 M, 24 mL, 5 eq) was added slowly to a stirring solution of 4-(2-pyridyl)-benzonitrile (0.85 g, 4.72 mmol) in anhydrous THF (25 mL) under Ar, and the resulting solution was refluxed for about 12 hr. The solution was cooled to 0°C using ice-water. Methanol (15 mL) was added drop-wise to the cold reaction mixture and stirred for 1 h to destroy excess BH_3. Added HCl – methanol (1M, 10 mL) slowly to the reaction mixture and refluxed for 5 h. Concentrated the solution to dryness and the residue was dissolved in 25 mL water and extracted with ether to remove any un-reacted material. The aqueous solution was neutralized with solid potassium carbonate to pH 10-11. The free amine, thus formed was extracted with ether, dried over potassium carbonate (0.45 g, 50%). LCMS: MH+ = 185; ^1H NMR ($CDCl_3$) δ 8.85 (d, 1H), 8.7 (dd, 1H), 7.9 (dd, 1H), 7.75 (d, 2H), 7.7 (d, 2H), 7.4 (dd, 1H), 3.7 (t, 2H), 1.7 (t, 2H).

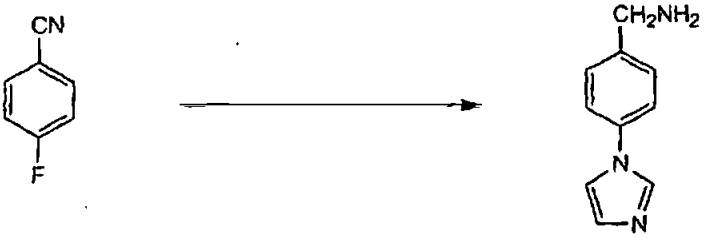
PREPARATIVE EXAMPLES 230-233:

By following essentially the same procedure set forth in Preparative Example 229, compounds in column 3 of Table 15 were prepared.

Table 15

Prep. Ex.	Column 2	Column 3	Column 4
230			Yield = 60% LCMS: MH^+ = 191
231			Yield = 60% LCMS: MH^+ = 191
232			Yield = 70% LCMS: MH^+ = 190
233			Yield = 70% LCMS: MH^+ = 204

PREPARATIVE EXAMPLE 234:



Step A:

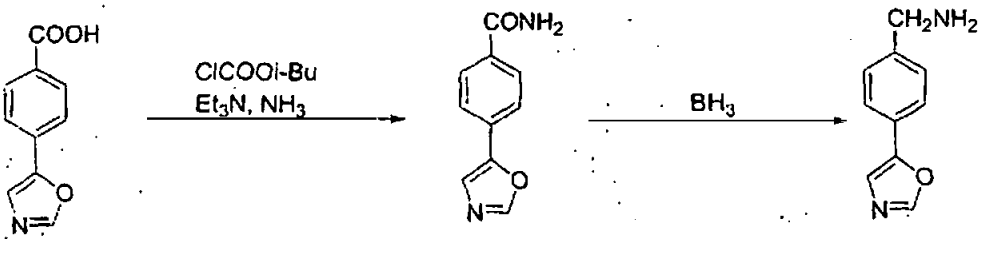
A mixture 4-fluorobenzonitrile (3 g, 25 mmol) and imidazolyl sodium (2.48 g, 27.5 mmol) in DMF (50 mL) was stirred at 80°C under Ar for 12 h. Progress of reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo* and the residue was diluted with 50 mL water and stirred. The aqueous mixture was extracted with EtOAc (2 x 50 mL). Combined EtOAc extracts was dried over

anhydrous MgSO4, concentrated, and the 4-(1-imidazolyl)-benzonitrile was isolated by column chromatography (3.6 g, 78%). LCMS: MH^+ = 170; ^1H NMR ($CDCl_3$) δ 8.0 (s, 1H), 7.5 (d, 2H), 7.4 (m, 3H), 7.3 (d, 1H)

Step B:

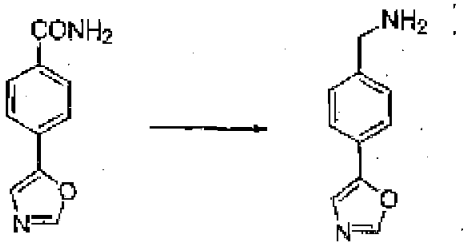
4-(1-imidazolyl)-benzonitrile (1g, 5.92 mmol) was dissolved in anhydrous THF (10 mL) and added drop-wise to a stirring solution of LAH –THF (1 M in THF, 18 mL) at room temperature. The reaction mixture was refluxed under Ar for 2 h and the progress was monitored by TLC. The mixture was cooled to 0°C and quenched by drop-wise addition of a saturated Na_2SO_4 – H_2O solution. The mixture was stirred for 1 h and filtered to remove lithium salts. The filtrate was dried over anhydrous $MgSO_4$ and concentrated to obtain 4-(1-imidazolyl)-benzylamine (0.8 g, 80%). LCMS: MH^+ = 174.

PREPARATIVE EXAMPLE 235:



A mixture of 4-(5-oxazolyl)benzoic acid (1.0 g, 5.46 mmol) and Et_3N (552 mg, 5.46 mmol) in 25 mL of THF was cooled to 0 °C and ClCOO*i*-Bu (745 mg, 5.46 mmol) was added dropwise. After the addition was over, the reaction mixture was stirred for additional 5 min and then aq NH_4OH (0.63 mL of 28% solution, 10.46 mmol) was added. After overnight stirring, the solvent was evaporated, the residue was taken up in water and basified to pH 9. The precipitated solid was filtered, washed with water and dried over P_2O_5 in a vacuum desiccator to provide 500 mg (48%) of the 4-(5-oxazolyl)-benzamide: ^1H NMR (DMSO-d6) δ 8.50 (s, 1H), 8.20-7.80 (m, 5H).

PREPARATIVE EXAMPLE 236:

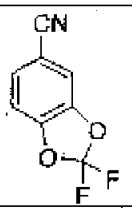
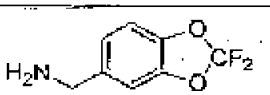
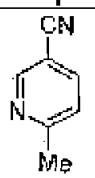
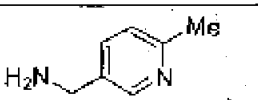


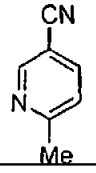
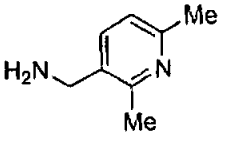
A suspension of 4-(5-oxazolyl)benzamide (500 mg, 2.657 mmol) in 10 mL of dry THF was cooled to 0 °C and 10 mL of 1 M BH_3.THF (10.00 mmol) was added. The contents were refluxed overnight and the excess borane was destroyed by dropwise addition of methanol. The solvent was evaporated and the residue was treated with methanolic HCl to decompose the amine-borane complex. After evaporation of the methanol, the residue was taken in water, basified to pH 10 and the product was extracted in to DCM. The DCM layer was dried (K_2CO_3) and the solvent was removed to provide 150 mg (32%) of 4-(5-oxazolyl)benzylamine: ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1H), 7.60 (d, 2H), 7.40 (d, 2H), 7.30 (s, 1H), 3.90 (s, 2H).

PREPARATIVE EXAMPLES 237-239:

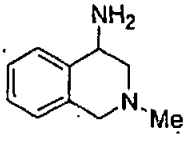
By essentially the same procedures set forth above, the compounds in Column 2 of Table 16 were reduced using the method indicated in Column 3 of Table 16 to give the amine indicated in Column 4 of Table 16.

Table 16

Prep. Ex.	Column 2	Column 3	Column 4	CMPD
237		BH_3		^{1}H NMR ($CDCl_3$) δ 7.15-6.90 (m, 3H), 3.85 (s, 2H), 1.45 (s, 2H)
238		H_2		^{1}H NMR ($CDCl_3$) δ 8.40(s, 1H), 7.55 (dd, 1H), 7.10 (d, 1H), 3.85 (s, 2H), 2.50 (s, 3H), 1.70 (bs, 2 H)

239		BH_3		

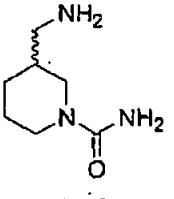
PREPARATIVE EXAMPLE 240



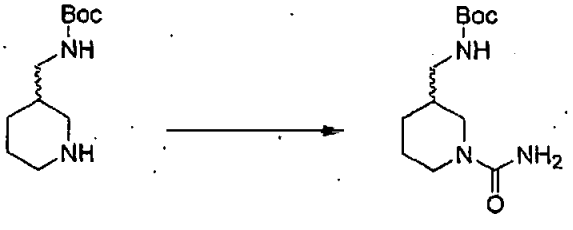
Prepared by the literature procedure (PCT Int. Appl, WO 0105783): ^{1}H NMR ($CDCl_3$) δ 7.35 (d, 1H), 7.24-7.10 (m, 2 H), 7.02 (d, 1H), 3.95 (t, 1H), 3.70 (d, 1H), 3.37 (d, 1H), 2.65 (m, 2H), 2.45 (s, 3H), 1.90 (bs, 2H)

PREPARATIVE EXAMPLE 241:

3-(AMINOMETHYL)PIPERIDINE-1-CARBOXAMIDE



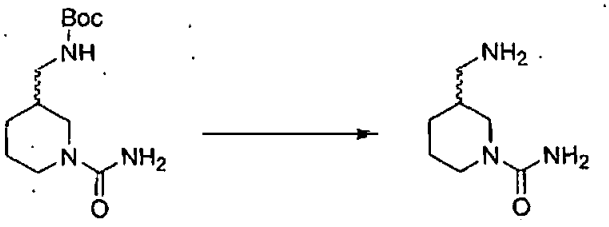
A. 3-(*tert*-BUTOXYCARBONYLAMINOMETHYL)PIPERIDINE-1-CARBOXAMIDE



3(R/S)-(*tert*-Butoxycarbonylaminomethyl)piperidine (3g, 14.0mmoles) was dissolved in anhydrous dichloromethane (50mL) and trimethylsilylisocyanate (9.68g, 11.4mL, 84.0mmoles) was added. The mixture was stirred under argon at 25°C for 68h. Additional trimethylsilylisocyanate (4.84g, 5.7mL, 42.0mmoles) was added and the mixture was stirred at 25°C for a total of 90h. The mixture was evaporated to dryness and chromatographed on a silica gel column (30x5cm) using 2% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give 3-(*tert*-

butoxycarbonylaminomethyl)piperidine-1-carboxamide (3.05g, 85%): FABMS: m/z 258.1 (MH^+); HRFABMS: m/z 258.1816 (MH^+). Calcd. for $C_{12}H_{24}O_3N_3$: m/z 258.1818; δ_H ($CDCl_3$) 1.22 91H, m, CH_2), 1.42 (9H, s, -COOC(CH_3)$_3$), 1.48 (1H, m, CH_2), 1.67 (2H, m, CH_2), 1.78 (1H, m, CH), 2.80 (1H, m, CH_2), 2.99, 3H, m, CH_2), 3.59 (1H, m, CH_20 3.69 (1H, m, CH_2), 4.76 (2H, bm, $CONH_2$) and 4.98ppm (1H, bm, NH); δ_C ($CDCl_3$) CH_3: 28.5, 28.5, 28.5; CH_2: 24.0, 28.3, 43.2, 45.1, 47.8; CH: 36.5; C: 79.4, 156.3, 158.5.

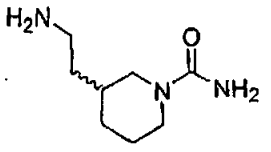
B. 3-(AMINOMETHYL)PIPERIDINE-1-CARBOXAMIDE



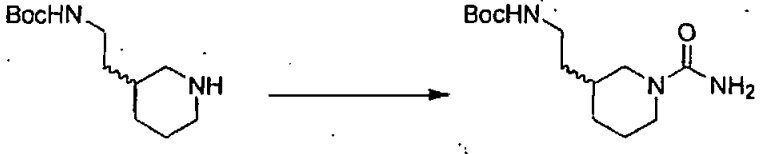
3-(*tert*-Butoxycarbonylaminomethyl)piperidine-1-carboxamide (150mg, 0.583mmoles) (prepared as described in Preparative Example 241, Step A above) was dissolved in methanol (3mL). 10% conc. sulfuric acid in 1,4-dioxane (7.9mL) was added and the mixture was stirred at 25°C for 1h. The mixture was diluted with methanol and BioRad AG1-X8 resin (OH^- form) was added until the pH was basic. The resin was filtered off, washed with methanol, evaporated to dryness and chromatographed on a silica gel column (15x2cm) using dichloromethane followed by 15% (10% conc, ammonium hydroxide in methanol)-dichloromethane as the eluant to give the 3-(aminomethyl)piperidine-1-carboxamide (80mg, 87%): FABMS: m/z 158.1 (MH^+); HRFABMS: m/z 158.1294 (MH^+). Calcd. for $C_7H_{16}N_3O$: m/z 158.1293; δ_H ($CDCl_3$ + drop CD_3OD) 1.20 (1H, m, CH_2), 1.48 (1H, m, CH_2), 1.60 (1H, m, CH), 1.68 (1H, m, CH_2), 1.83 (1H, m, CH_2), 2.64 (bm, 2H, -CH_2NH_2), 2.82 (1H, m, CH_2), 3.02 (1H, m, CH_2), 2.98 (2H, m, CH_2), 3.70 (1H, m, -CH_2NH_2), 3.78 (1H, m, -CH_2NH_2) and 5.24 ppm (1H, bs, NH); δ_C ($CDCl_3$ + drop CD_3OD) CH_2: 24.1, 28.6, 44.0, 44.8, 47.9; CH: 38.3; C: 159.0.

PREPARATIVE EXAMPLE 242:

3-(2-AMINOETHYL)PIPERIDINE-1-CARBOXAMIDE

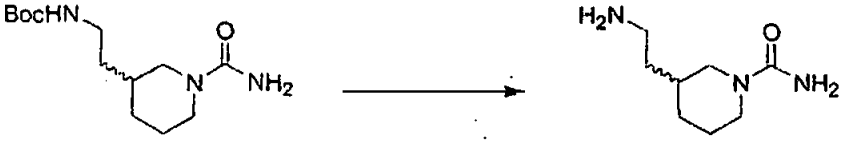


A. 3-(2-tert-BUTOXYCARBONYLAMINOETHYL)PIPERIDINE-1-CARBOXAMIDE



3-(2-*tert*-Butoxycarbonylaminoethyl)piperidine (500mg, 2.19mmoles) was dissolved in anhydrous dichloromethane (10mL) and trimethylsilylisocyanate (2.96mL, 21.9mmoles) was added. The mixture was stirred under argon at 25°C for 3.35h. The mixture was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$), filtered, evaporated to dryness and chromatographed on a silica gel column (15x5cm) using 5% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give 3-(2-*tert*-butoxycarbonylaminoethyl)piperidine-1-carboxamide (417.7mg, 70%): FABMS: m/z 272.0 (MH^+); HRFABMS: m/z 272.1979 (MH^+). Calcd. for $C_{13}H_{26}O_3$: m/z 272.1974; δ_H ($CDCl_3$) 1.16 (1H, m, CH_2), 1-30-1.60 (5H, m, CH/CH_2), 1.46 (9H, s, -COOC(CH_3)$_3$), 1.68 (1H, m, CH_2), 1 84 (1H, m, CH_2), 2.54 (1H, dd, CH_2), 2.73 (1H, m, CH_2), 3.08 (1H, m, CH_2), 3.42 (1H, m, CH_2), 4.02 (1H, m, CH_2), 4.10 (1H, m, CH_2), 4.84 (1H, m, NH) and 4.96 ppm (2H, bm; $CONH_2$); δ_C ($CDCl_3$) CH_3: 28.5, 28.5, 28.5; CH_2: 25.2, 31.7, 34.9, 37.3, 44.6, 50.3; CH: 32.9; C: 79.5, 156.4, 158.2.

B. 3-(2-AMINOETHYL)PIPERIDINE-1-CARBOXAMIDE

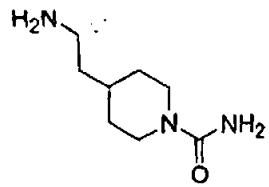


3-(2-*tert*-Butoxycarbonylaminoethyl)piperidine-1-carboxamide (392.7mg, 1.45mmoles) (prepared as described in Preparative Example 242, Step A above) was dissolved in methanol (7.5mL) and 10% conc. sulfuric acid in 1,4-dioxane (19.5mL) was added. The mixture was stirred at 25°C for 1.25h. The mixture was

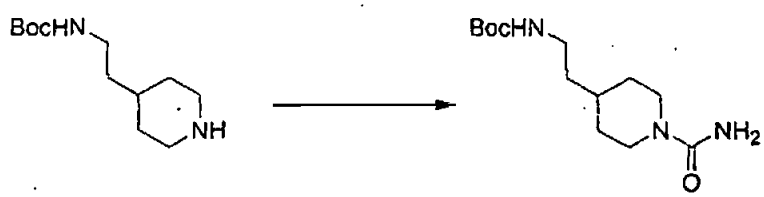
diluted with methanol and BioRad AG1-X8 resin (OH^- form) was added until the pH was basic. The resin was filtered off, washed with methanol, evaporated to dryness and chromatographed on a silica gel column (30x2.5cm) using 15% (10% conc, ammonium hydroxide in methanol)-dichloromethane as the eluant to give 3-(2-aminoethyl)piperidine-1-carboxamide (233mg, 94%): FABMS: m/z 172.1 (MH^+); HRFABMS: m/z 172.1444(MH^+). Calcd for $C_8H_{18}N_3O$ requires: m/z 172.1450; δ_H ($CDCl_3$ + 3% CD_3OD) 1.14 (1H, m, CH_2), 1.40 (2H, m, CH_2), 1.49 (1H, m, CH), 1.58 (1H, m, CH_2), 1.69 (1H, m, CH_2), 1.85 (1H, m, CH_2), 2.55 (1H, m, CH_2), 2.67 (5H, m, CH_2/NH_2), 2.76 (1H, bm, CH_2), 2.84 (1H, m, CH_2) and 3.82 ppm (2H, m, $CONH_2$); δ_C ($CDCl_3$ + 3% CD_3OD) CH_2: 24.8, 30.9, 36.6, 38.9, 44.9, 50.0; CH: 33.4.

PREPARATIVE EXAMPLE 243:

4-(2-AMINOETHYL)PIPERIDINE-1-CARBOXAMIDE



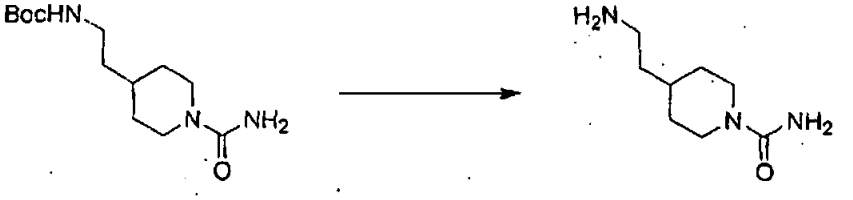
A. 4-(2-tert-BUTOXYCARBONYLAMINOETHYL)PIPERIDINE-1-CARBOXAMIDE



4-(2-*tert*-Butoxycarbonylaminoethyl)piperidine (500mg, 2.19mmoles) was dissolved in anhydrous dichloromethane (10mL) and trimethylsilylisocyanate (2.96mL, 21.9mmoles) was added. The mixture was stirred under argon at 25°C for 3.25h. The mixture was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$), filtered, evaporated to dryness and chromatographed on a silica gel column (15x5cm) using 5% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give 4-(2-*tert*-butoxycarbonylaminoethyl)piperidine-1-carboxamide (308.2mg, 52%): FABMS:

m/z 272.0 (MH^+); HRFABMS: m/z 272.1965 (MH^+). Calcd. for $C_{13}H_{26}O_3N_3$: m/z 272.1974; δ_H ($CDCl_3$) 1.20 (2H, m, CH_2), 1.47 (9H, s, -COOC(CH_3)$_3$), 1.45-1.55 (3H, m, CH/CH_2), 1.75 (2H, m, CH_2), 2.82 (2H, m, CH_2), 3.19 (2H, m, CH_2), 3.96 (2H, m, CH_2), 4.64 (2H, m, CH_2) and 4.70 ppm (1H, bm, NH); δ_C ($CDCl_3$) CH_3: 28.5, 28.5, 28.5; CH_2: 31.8, 31.8, 36.7, 38.0, 44.5, 44.5; CH: 33.4; C: 79.2, 156.7, 158.1.

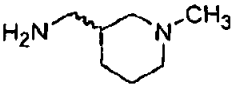
A. 3-(2-AMINOETHYL)PIPERIDINE-1-CARBOXAMIDE



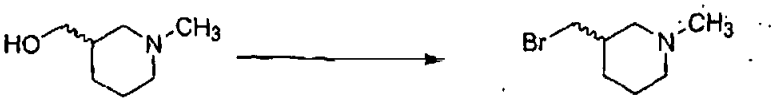
4-(2-*tert*-Butoxycarbonylaminoethyl)piperidine-1-carboxamide (283.3mg, 1.04mmoles) (prepared as described in Preparative Example 243, Step A above) was dissolved in methanol (5.4mL) and 10% conc. sulfuric acid in 1,4-dioxane (14.2mL) was added and the mixture was stirred at 25°C for 1.25h. The mixture was diluted with methanol and BioRad AG1-X8 resin (OH^- form) was added until the pH was basic. The resin was filtered off, washed with methanol, evaporated to dryness and chromatographed on a silica gel column (30x2.5cm) using 15% (10% conc, ammonium hydroxide in methanol)-dichloromethane as the eluant to give the 3-(2-aminoethyl)piperidine-1-carboxamide (170mg, 95%): FABMS: m/z 172.1 (MH^+); HRFABMS: m/z 172.1442. Calcd for $C_8H_{18}N_3O$ requires: m/z 172.1450; δ_H ($CDCl_3$ + 3% CD_3OD) 1.16 (2H, m, CH_2), 1.43 (2H, m, CH_2), 1.52 (1H, m, CH), 1.70 (2H, m, CH_2), 2.70-2.85 (8H, m, CH_2) and 3.92 ppm (2H, m, $CONH_2$); δ_C ($CDCl_3$ + 3% CD_3OD) CH_2: 31.9, 31.9, 39.0, 39.7, 44.4, 44.4; CH: 33.5; C: 158.7.

PREPARATIVE EXAMPLE 244:

3-(AMINOMETHYL)-1-METHYLPIPERIDINE

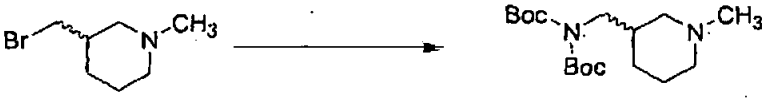


A. 3-(BROMOMETHYL)-1-METHYLPIPERIDINE



3-(Hydroxymethyl)-1-methylpiperidine (2g, 15.5mmoles) was dissolved in anhydrous acetonitrile (32mL) and anhydrous pyridine (2.02mL, 24.8mmoles) was added and the solution was cooled to 0°C. Dibromotriphenylphosphorane (8.49g, 20.2mmoles) was added at 0°C and the mixture was allowed to warm up to 25°C and was stirred for 94h. The mixture was evaporated to dryness and the residue was chromatographed on a silica gel column (30x5cm) using gradient elution with dichloromethane, 35% diethyl ether in dichloromethane and 5-10% methanol in dichloromethane as the eluant to give 3-(bromomethyl)-1-methylpiperidine (3.13g, 100%): FABMS: m/z 192.1 (MH^+); δ_H ($CDCl_3$) 1.52 (1H, m, CH_2), 1.99 (2H, m, CH_2), 2.43 (1H, m, CH_2), 2.75 (2H, m, CH_2), 2.82 (1H, m, CH), 2.86/2.88 (3H, s, NCH_3), 3.42/3.49 (2H, dd, -$C\underline{H}_2$Br) and 3.56 ppm (2H, m, CH_2); δ_C ($CDCl_3$) CH_3: 44.3; CH_2: 22.1, 26.6, 35.4, 54.8, 58.2; CH: 34.6.

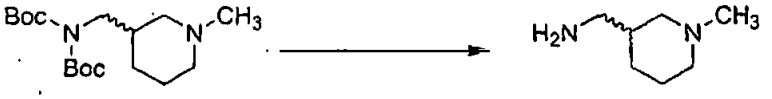
A. 3-(Di-tert-BUTOXYCARBONYLAMINOMETHYL)-1-METHYLPIPERIDINE



3-(Bromomethyl)-1-methylpiperidine (1.5g, 7.81mmoles) (from Preparative Example 244, Step A above) and di-*tert*-butyliminodicarboxylate (1.697g, 7.81mmoles) were dissolved in anhydrous acetonitrile (25mL). Cesium carbonate (5.1g, 15.6mmoles) and lithium iodide (52mg, 0.391mmoles) were added and the mixture was stirred at 70°C for 20h. The mixture was evaporated to dryness and the residue was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness. the residue was chromatographed on a silica gel column (30x5cm) using 3% methanol in dichloromethane as the eluant to

give 3-(di-*tert*-butoxycarbonylamino)-1-methylpiperidine (1.331g, 52%): FABMS: m/z 329.2 (MH^+); HRFABMS: m/z 329.2438 (MH^+). Calcd. for $C_{17}H_{33}N_2O_4$: m/z 329.2440; δ_H ($CDCl_3$) 1.10 (1H, m, CH_2), 1.54 (18H, s, -$COOC(CH_3)_3$), 1.86 (2H, m, CH_2), 2.01 (1H, m, CH_2), 2.19 (1H m, CH), 2.34 (2H, bm, CH_2), 2.59 (3H, -NCH_3), 3.19 (2H, m, CH_2) and 3.52/3.52 ppm (2H, -CH_2N-); δ_C ($CDCl_3$) CH_3: 28.5, 28.5, 28.5, 28.5, 28.5, 28.5, 47.2; CH_2: 25.4, 28.3, 50.4, 56.8, 60.8; CH: 37.2; C: 83.0, 83.0,153.5, 153.5.

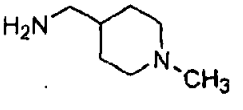
A. 3-(AMINOMETHYL)-1-METHYLPIPERIDINE



3-(Di-*tert*-butoxycarbonylamino)-1-methylpiperidine (500mg, 1.52mmoles) (from Preparative Example 244, Step B above) was dissolved in methanol (7.5mL) and 10% (v/v) conc. sulfuric acid in 1,4-dioxane (19.75mL) was added. The solution was stirred at 25°C for 0.5h. Methanol (300mL) was added, followed by BioRad AG1-X8 resin (OH^- form) until the pH was ~10. The resin was filtered off and washed with methanol (2x200mL). The combined eluates were evaporated to dryness and the residue was chromatographed on a silica gel column (30x2.5cm) using 10% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give 3-(aminomethyl)-1-methylpiperidine (69.2mg, 35%): FABMS: m/z 129.1 (MH^+); HRFABMS: m/z 129.1392 (MH^+). Calcd. for $C_7H_{17}N_2$: m/z 129.1392; δ_H ($CDCl_3$) 0.90 (2H, m, CH_2), 1.65 (2H, m, CH_2), 1.72 (1H, m, CH), 1.79 (1H, m, CH_2), 1.91 (1H, m, CH_2), 2.30 (3H, s, -NCH_3), 2.64 (2H, m, CH_2), 2.82 (1H, m, -$C\underline{H}_2NH_2$) and 2.92 ppm (1H, m, -$C\underline{H}_2NH_2$); δ_C ($CDCl_3$) CH_3: 46.7; CH_2: 25.2, 28.0, 46.3, 56.4, 60.3; CH: 39.9.

PREPARATIVE EXAMPLE 245:

4-(AMINOMETHYL)-1-METHYLPIPERIDINE

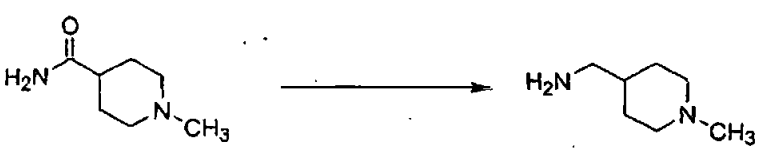


A. 1-METHYLISONIPECOTAMIDE



Isonipecotamide (10g, 78.0mmoles) was dissolved in distilled water (100mL) and 37% aqueous formaldehyde (7.6mL, equivalent to 2.81g HCHO, 93.6mmoles) was added. Wet 10% Pd-C (8 spoon spatulas) was added under argon and the mixture was hydrogenated at 25°C and 50psi for 43h. The catalyst was filtered off through Celite and the latter was washed with water and methanol. The combined filtrates were evaporated to dryness and the residue was chromatographed on a silica gel column (60x5cm) using 8%-10%-20% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give 1-methylisonipecotamide (7.15g, 64%): FABMS: m/z 143.1 (MH^+); HRFABMS: m/z 143.1184 (MH^+). Calcd. for $C_7H_{15}N_2O$: m/z 143.1184; δ_H (d_6-DMSO) 1.50/1.57 (4H, m, CH_2), 1.76/1.94 (4H, m, CH_2), 2.10 (3H, s, $-NCH_3$), 2.72 (1H, m; CH) and 6.68/7.18 ppm (2H, m, $CONH_2$); δ_C (d_6-DMSO) CH_3: 41.2; CH_2: 28.5, 28.5, 54.9, 54.9; CH: 46.2; C: 176.7.

B. 4-(AMINOMETHYL)-1-METHYLPIPERIDINE

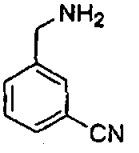


1-Methylisonipecotamide (6.75g, 47.5mmoles) (prepared as described in Preparative Example 245, Step A above) was dissolved in anhydrous THF (350mL) and the resulting mixture was added in portions to a stirred slurry of lithium aluminum hydride (1.8g, 47.5mmoles) in anhydrous THF (100mL) at 0°C under nitrogen. The mixture was stirred at 0°C for 30min and then heated at 66°C for 25h under nitrogen. Distilled water (1.88mL) was added dropwise to the

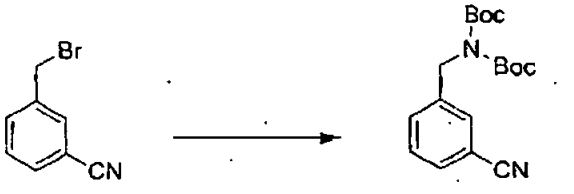
stirred mixture at 0°C, followed by 20% aqueous sodium hydroxide (1.42mL) and then distilled water (6.75mL) and the mixture was stirred for 15min. The mixture was filtered and the solids were washed with THF and dichloromethane. The combined filtrates were evaporated to dryness and chromatographed on a silica gel column (30x5cm) using 15%-20% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give 4-(aminomethyl)-1-methylpiperidine (0.678g, 11%): FABMS: m/z 129.1 (MH^+); HRFABMS: m/z 129.1389 (MH^+). Calcd. for $C_7H_{17}N_2$: m/z 129.1392; δ_H (d_6-DMSO): 2.08ppm (3H, s, $-NCH_3$); δ_C (d_6-DMSO): CH_3: under DMSO peaks; CH_2: 29.6, 29.6, 46.7, 55.2, 55.2; CH: 46.2.

PREPARATIVE EXAMPLE 246:

3-(AMINOMETHYL)BENZONITRILE



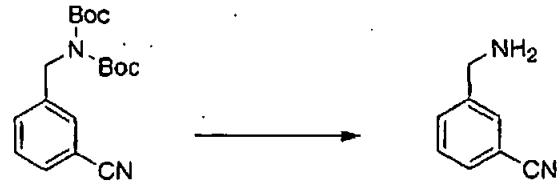
A. 3-(Di-*tert*-BUTOXYCARBONYLAMINO)BENZONITRILE



3-(Bromomethyl)benzonitrile (5g, 25.5mmoles) and di-tert-butyliminodicarboxylate (5.54g, 25.5mmoles) were dissolved in anhydrous THF (50mL) and cesium carbonate (16.62g, 25.5mmoles) and lithium iodide (170.5mg, 1.275mmoles) were added. The mixture was stirred at 70°C for 22h and the reaction was worked up as described in Preparative Example 89, Step B above. The residue was chromatographed on a silica gel column (60x5cm) using 5% ethyl acetate in hexane as the eluant to give 3-(di-*tert*-butoxycarbonylamino)benzonitrile (7.39g, 87%): FABMS: m/z 333.2 (MH^+);

HRFABMS: m/z 333.1815 (MH^+); Calcd. for $C_{18}H_{25}N_2O_4$: m/z 333.1814; δ_H ($CDCl_3$) 1.52 (18H, s, -$COOC(CH_3)_3$), 4.84 (2H, s, CH_2), 7.48 (1H, m, Ar-H), 7.60 (2H, m, Ar-H) and 7.65 ppm (1H, m, Ar-H); δ_C ($CDCl_3$) CH_3: 28.1, 28.1, 28.1, 28.1, 28.1, 28.1; CH_2: 48.4; CH: 129.2, 131.0, 131.0, 131.9; C: 83.2, 83.2, 112.5, 118.8, 140.1, 152.5, 152.5.

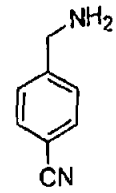
B. 3-(AMINOMETHYL)BENZONITRILE



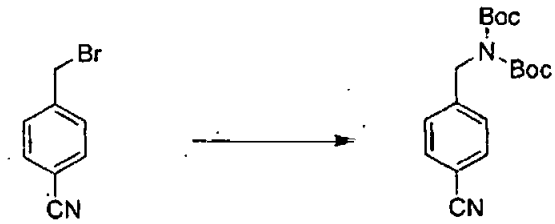
3-(Di-*tert*-butoxycarbonylamino)benzonitrile (2g, 6.0mmoles) (prepared as described in Preparative Example 246, Step A above) was dissolved in methanol (30mL) and 10%(v/v) (10% conc. sulfuric acid in 1,4-dioxane) (79mL) was added. The solution was stirred at 25°C for 0.25h and worked up as described in Preparative Example 89, Step C above). The residue was chromatographed on a silica gel column (15x5cm) using 3% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (651.4mg, 82%): FABMS: m/z 133.1 (MH^+); HRFABMS: m/z 133.0762 (MH^+). Calcd. for $C_8H_9N_2$: m/z 133.0766 ; δ_H ($CDCl_3$) 2.57 (2H, s, -$CH_2\underline{N}H_2$), 3.92 (2H, s, -$C\underline{H}_2NH_2$), 7.46 (1H, m, Ar-H), 7.57 (2H, m, Ar-H) and 7.64 ppm (1H, m, Ar-H); δ_C ($CDCl_3$) CH_2: 45.2; CH: 129.4, 130.7, 130.7, 131.8; C: 112.4, 118.8, 143.8.

PREPARATIVE EXAMPLE 247:

4-(AMINOMETHYL)BENZONITRILE

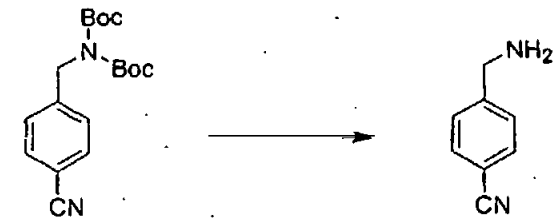


A. 3-(Di-*tert*-BUTOXYCARBONYLAMINOMETHYL)BENZONITRILE



4-(Bromomethyl)benzonitrile (5g, 25.5mmoles) and di-tert-butyliminodicarboxylate (5.54g, 25.5mmoles) were dissolved in anhydrous THF (50mL) and cesium carbonate (16.62g, 25.5mmoles) and lithium iodide (170.5mg, 1.275mmoles) were added. The mixture was stirred at 70°C for 23h and the reaction was worked up as described in Preparative Example 244, Step B above. The residue was chromatographed on a silica gel column (50x5cm) using 5% ethyl acetate in hexane as the eluant to give 4-(di-*tert*-butoxycarbonylaminomethyl)benzonitrile (7.07g, 83%): FABMS: m/z 333.2 (MH^+); HRFABMS: m/z 333.1816 (MH^+). Calcd. for $C_{18}H_{25}N_2O_4$: m/z 333.1814; δ_H ($CDCl_3$) 1.45 (18H, s, -COOC(CH_3)$_3$), 4.81 (2H, s, CH_2), 7.37 (2H, d, Ar-H) and 7.62 ppm (2H, d, Ar-H); δ_C ($CDCl_3$) CH_3: 28.1, 28.1, 28.1, 28.1, 28.1, 28.1; CH_2: 49.2 ; CH: 127.8, 127.8, 132.3, 132.3; C: 83.2, 83.2, 111.1, 118.9, 144.1, 152.4, 152.4.

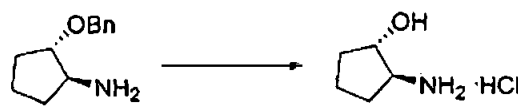
B. 4-(AMINOMETHYL)BENZONITRILE



4-(Di-*tert*-butoxycarbonylaminomethyl)benzonitrile (2g, 6.0mmoles) (prepared as described in Preparative Example 247, Step A above) was dissolved in TFA (4mL) and the solution was stirred at 25°C for 0.25h. The

reaction mixture was diluted with dichloromethane and extracted with 1N sodium hydroxide. The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness. The residue was chromatographed on a silica gel column (15x5cm) using 3% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give 4-(aminomethyl)benzonitrile (108mg, 68%): FABMS: m/z 133.1 (MH^+); HRFABMS: m/z133.0764 (MH^+). Calcd. for $C_8H_9N_2$: m/z 133.0766; δ_H ($CDCl_3$) 2.04 (2H, s, $-CH_2NH_2$), 3.89 (2H, s, $-CH_2NH_2$), 7.40 (2H , d, Ar-H) and 7.59 ppm (2H, d, Ar-H); δ_C ($CDCl_3$) CH_2: 45.7; CH: 127.8, 127.8, 132.4, 132.4; C: 110.6, 118.9, 148.0.

PREPARATIVE EXAMPLE 248



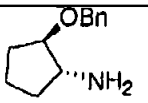
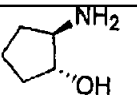
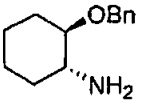
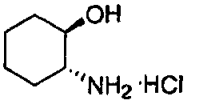
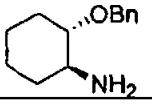
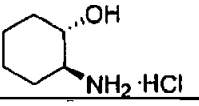
To a solution of (1*S*,2*S*)-2-benzyloxycyclopentyl amine (1.5 g, 7.84 mmol) in MeOH (50 mL) at rt was added 10 % Pd/C (50% wet, 1.0 g) followed by dropwise addition of conc. HCl (0.7 mL). The mixture was stirred under a balloon of H_2 for 14 h and the catalyst was filtered off thru a pad of Celite. The pad of Celite was washed with MeOH (2 x 10 mL) and the resulting filtrate was concentrated under reduced pressure to afford 0.97 g (90%) of a yellow semisolid; M+H (free base) = 102

PREPARATIVE EXAMPLES 249-251

In an analogous fashion to Preparative Example 248, the benzyl protected cycloalkyl amines (Column 2) were converted to the desired aminocycloalkanol hydrochloride derivatives (Column 3) as listed in Table 17.

TABLE 17

Ex.	Column 2 (Amine)	Column 3 (Cleavage method)	CMPD M+H

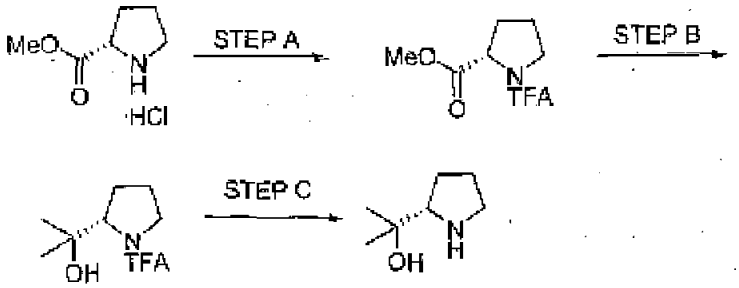
249			M+H = 102 (free base)
250			M+H = 116 (free base)
251			M+H = 116 (free base)

PREPARATIVE EXAMPLE 252



To a solution of ester (prepared according to *J. Org. Chem.* (1999), 64, 330) (0.5 g, 2.43 mmol) in THF (8 mL) at 0 °C was added $LiAlH_4$ (0.37 g, 9.74 mmol) in one portion. The resulting mixture was heated at reflux for 12h and was cooled to 0 °C. The mixture was treated sequentially with H_2O (1 mL), 1 M NaOH (1 mL), and H_2O (3 mL). CH_2Cl_2 (10 ml) was added to the mixture which was stirred vigorously for 30 min. The mixture was filtered thru a pad of Celite which was washed generously with CH_2Cl_2 (3 x 5 mL). The resulting filtrate was concentrated under reduced pressure to afford 0.41 g (85%) of a yellow/orange solid. M+H = 142.

PREPARATIVE EXAMPLE 253



STEP A:

To a solution of *L*-proline methyl ester hydrochloride (0.50 g, 3.0 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added Et_3N (1.1 mL, 7.55 mmol) followed by TFAA (0.56 mL, 3.92 mmol). The mixture was stirred for 12 h at rt and 1N HCl (25 mL) was added. The layers were separated and the organic layer was washed sequentially with sat. aq. $NaHCO_3$ (1 x 25 mL), and brine (1 x 25 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 0.72 g (100%) of a yellow oil. M+H = 226. The crude material was taken onto Step B without further purification.

STEP B:

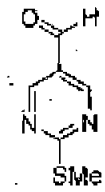
To a solution of the compound prepared in Preparative Example 253, Step A (0.68 g, 3.0 mmol) in THF (20 mL) at 0 °C was added MeMgI (5.1 mL, 3.0M in Et_2O) dropwise over 10 min. The resulting solution was stirred for 16 h at rt whereupon the mixture was quenched by addition of sat. aq. NH_4Cl. The mixture was concentrated to dryness and the resultant residue was stirred with EtOAc (100 mL) for 45 min and filtered. The filtrate was concentrated under reduced pressure to afford 0.68g (100%) of a yellow/orange oil. M+H = 226. The crude material was taken onto Step C without further purification.

STEP C:

To a solution of the compound prepared in Preparative Example 253, Step B (0.68 g, 3.0 mmol) in MeOH (5 mL) was added a solution of KOH (0.68 g, 12.1 mmol) in MeOH (5 mL). The mixture was stirred at reflux for 12h and rt for 72h whereupon the mixture was concentrated to dryness. The crude residue was suspended in EtOAc (50 mL) and was stirred vigorously for 30 min and was filtered. This procedure was repeated 2X more and the resultant filtrate was

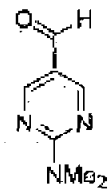
concentrated under reduced pressure to afford 128 mg (33%) of a maroon/orange oil. M+H = 130. This material was used without purification in the subsequent coupling step.

PREPARATIVE EXAMPLE 254:



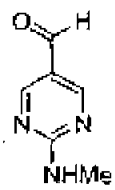
The aldehyde was prepared according to the procedure of Gupton (*J. Heterocyclic Chem.* (1991), *28*, 1281).

PREPARATIVE EXAMPLE 255



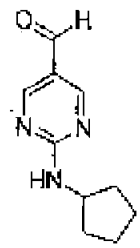
Using the aldehyde from Preparative Example 254, the procedure of Gupton (*J. Heterocyclic Chem.* (1991), *28*, 1281) was employed to prepare the title aldehyde.

PREPARATIVE EXAMPLE 256



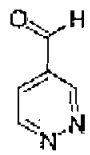
The title aldehyde was prepared according to the procedure of Ragan et. al *Synlett* (2000), *8*, 1172-1174.

PREPARATIVE EXAMPLE 257



The reaction of known cyclopentyl guanidine hydrochloride (*Org. Lett.* (2003), 5, 1369-1372) under the conditions of Ragan (*Synlett* (2000), 8, 1172-1174) afforded the title aldehyde.

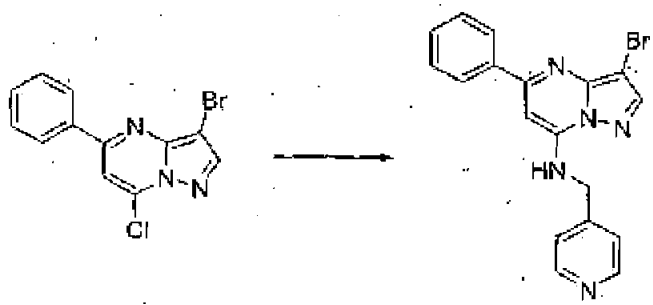
PREPARATIVE EXAMPLE 258



The title compound was prepared according to known literature *Monatshefte fur Chemie* (1973), *104*, 1372-1382.

EXAMPLES

EXAMPLE 1:

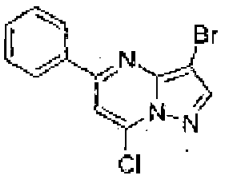
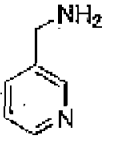
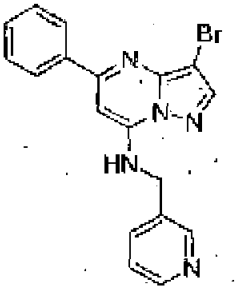
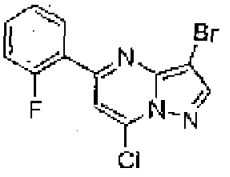
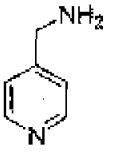
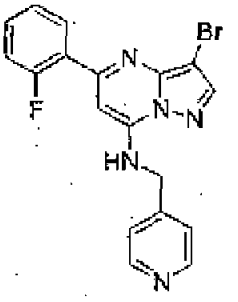
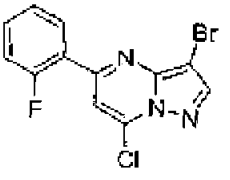
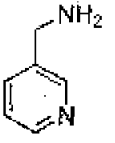
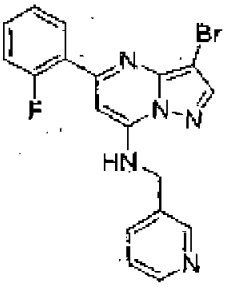


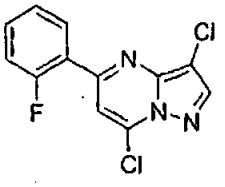
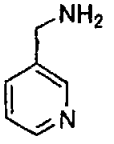
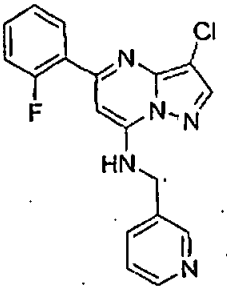
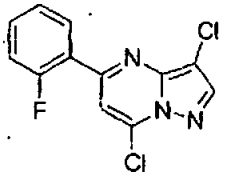
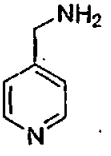
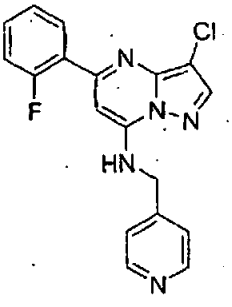
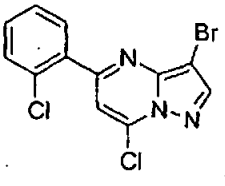
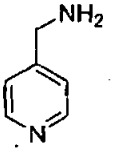
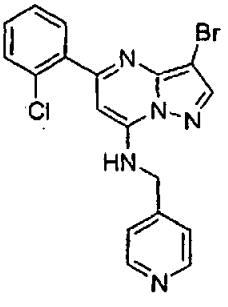
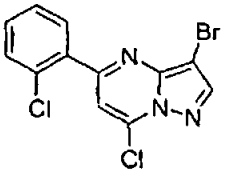
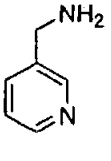
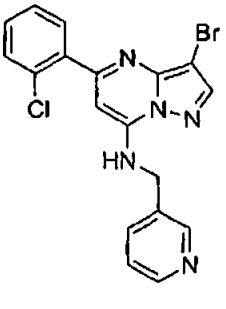
A solution of the product from Preparative Example 127 (0.27 g, 0.875 mmol), 4-aminomethylpyridine (0.12 g, 1.3 eq.), and K_2CO_3 (0.24 g, 2 eq.) in CH_3CN (5 mL) was stirred at room temperature 48 hours. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography using a 4% MeOH in CH_2Cl_2 solution as eluent (0.28 g, 93% yield). LCMS: MH^+=380; mp= >205°C (dec).

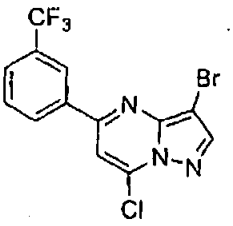
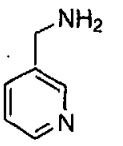
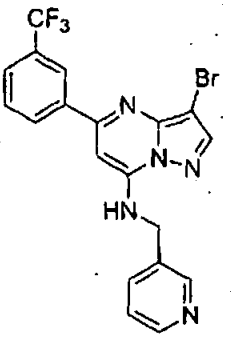
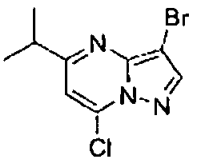
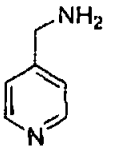
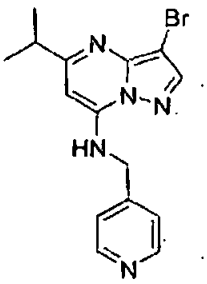
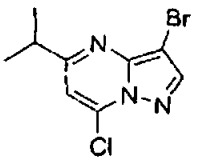
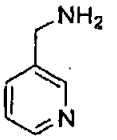
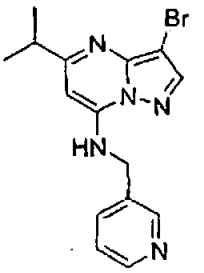
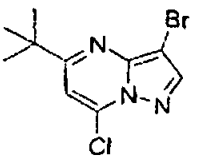
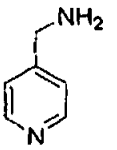
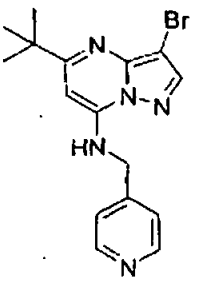
EXAMPLES 2-210:

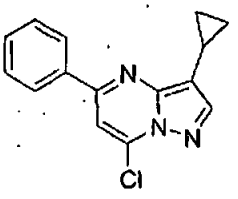
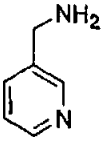
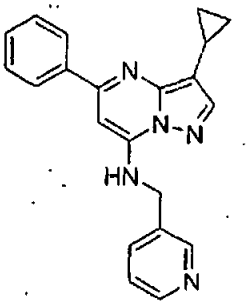
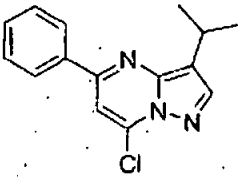
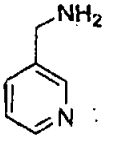
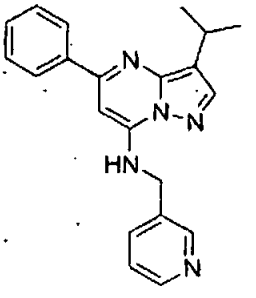
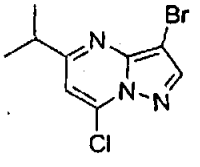
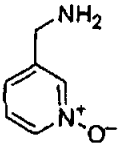
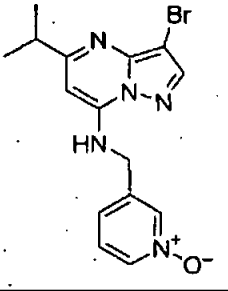
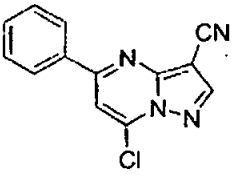
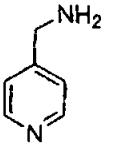
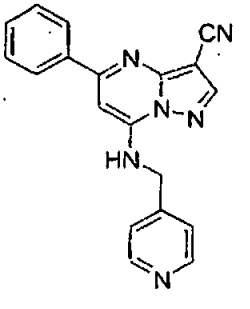
By following essentially the same procedure set forth in Example 1 only substituting the chlorides shown in Column 2 of Table 18 and the amines shown in Column 3 of Table 18, the compounds in Column 4 of Table 18 were prepared:

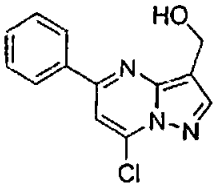
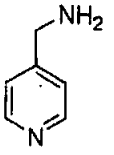
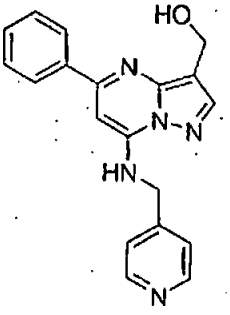
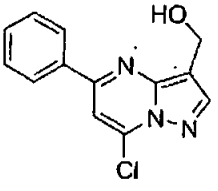
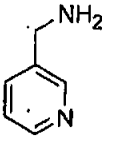
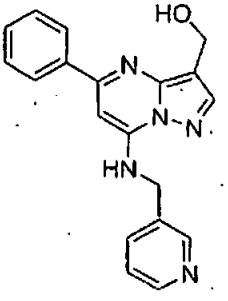
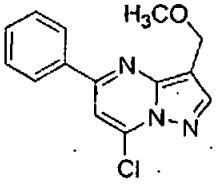
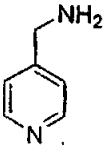
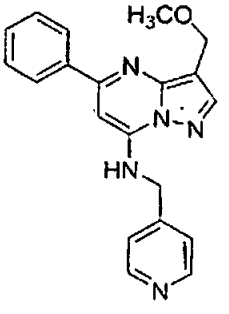
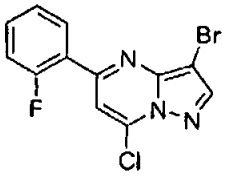
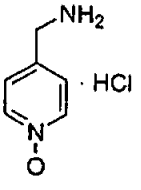
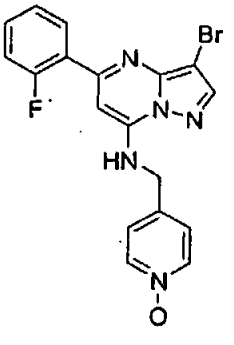
TABLE 18

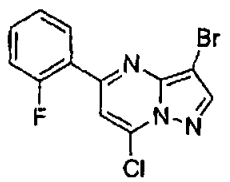
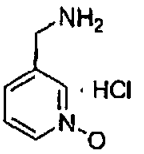
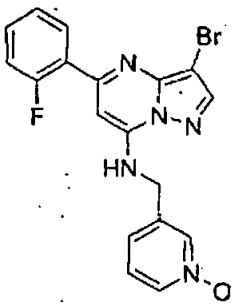
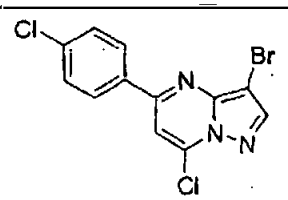
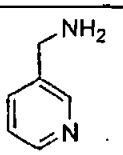
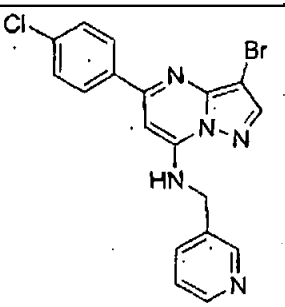
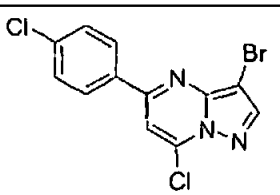
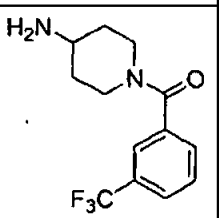
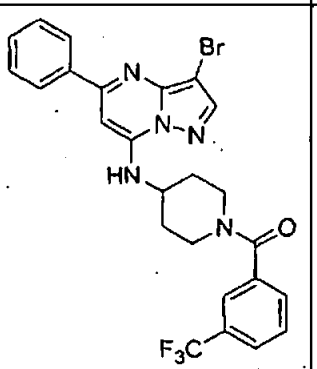
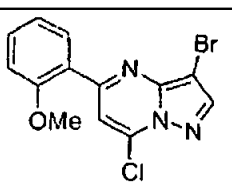
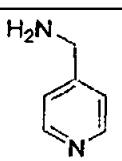
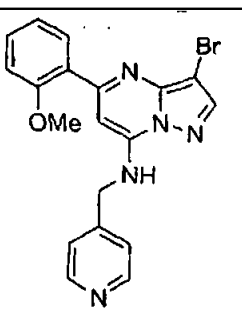
Ex.	Column 2	Column 3	Column 4	Data
2				LCMS: MH^+= 380; mp=175-176°C
3				LCMS: MH^+= 398; mp= 156-157°C
4				LCMS: MH^+= 398; mp= 45-49°C

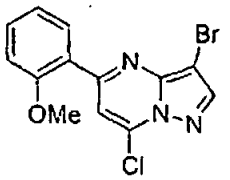
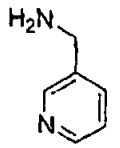
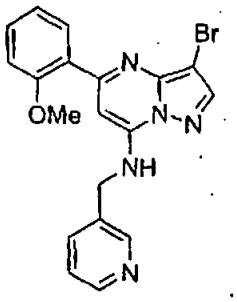
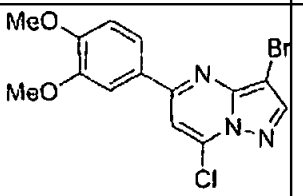
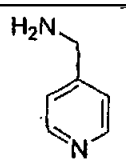
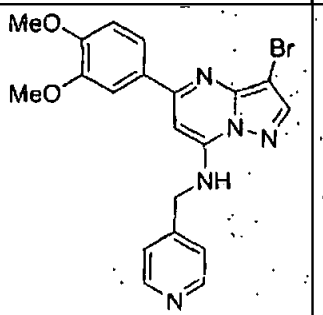
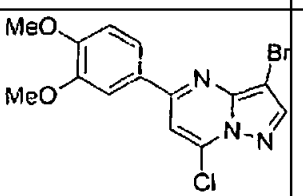
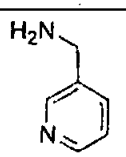
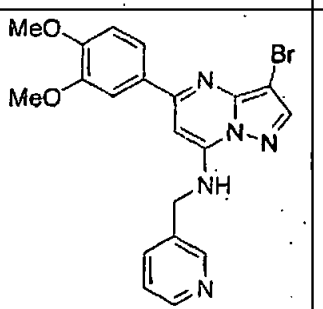
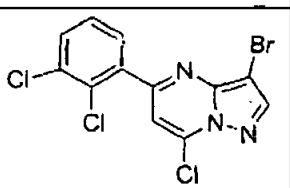
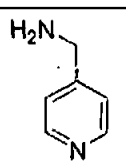
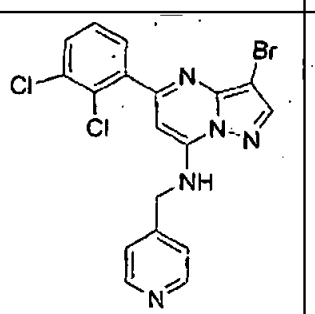
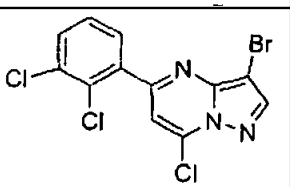
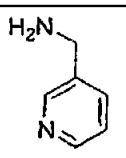
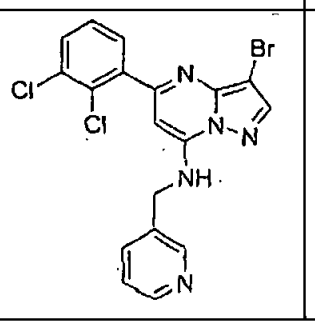
5				LCMS: MH^+= 354; mp= 43-46°C
6				LCMS: MH^+= 354; mp= 149-150°C
7				LCMS: MH^+= 414; mp= 86-92°C
8				LCMS: MH^+= 414; mp= 185-186°C

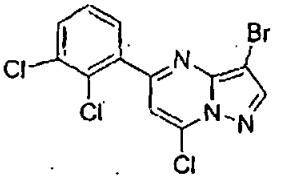
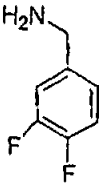
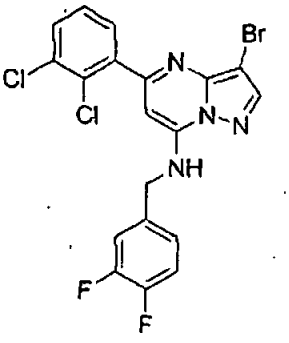
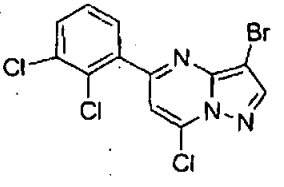
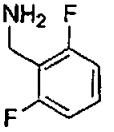
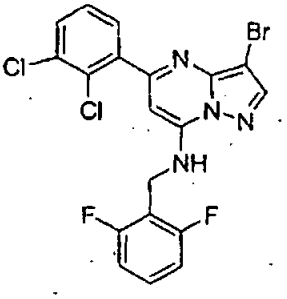
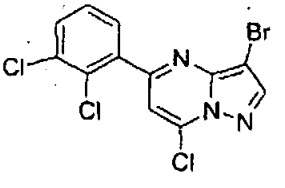
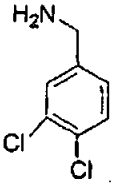
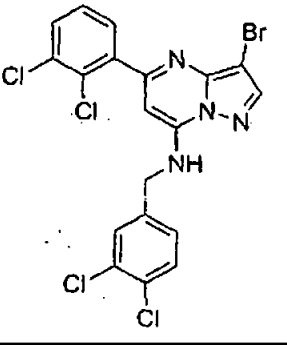
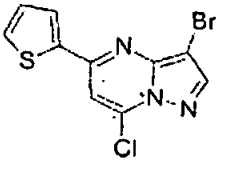
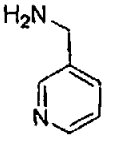
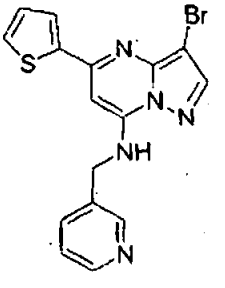
9				LCMS: MH^+= 448; mp= 167-168°C
10				LCMS: MH^+= 346; mp= 57-58°C
11				LCMS: MH^+= 347; mp=122.9-125.3 °C
12				LCMS: MH^+= 360; mp= 127-128°C

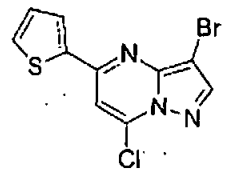
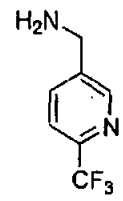
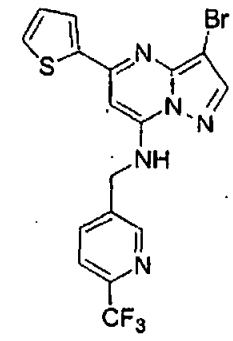
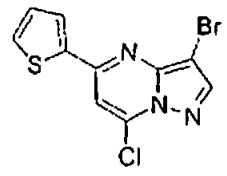
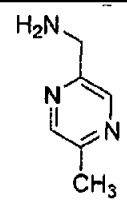
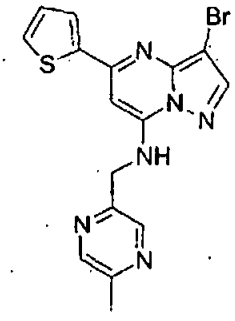
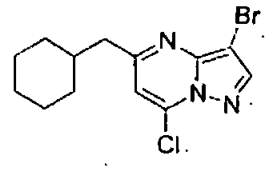
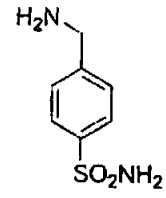
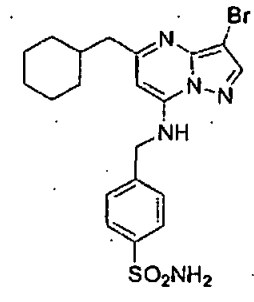
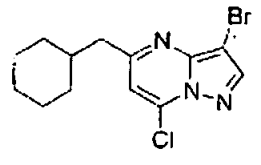
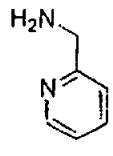
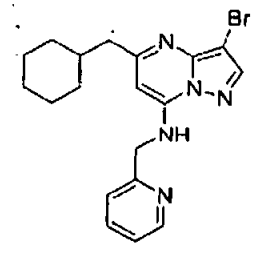
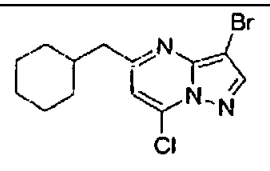
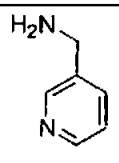
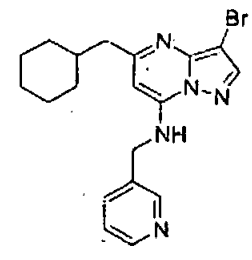
13				LCMS: MH^+= 342; mp= 133-135°C
14				LCMS: MH^+= 344; mp= 152-155°C
15				LCMS: MH^+= 362; mp= 164-167°C
16				LCMS: MH^+= 327; mp= 146-155°C

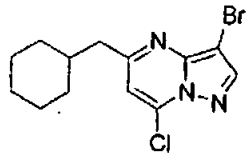
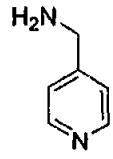
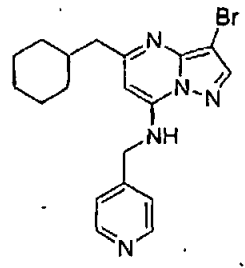
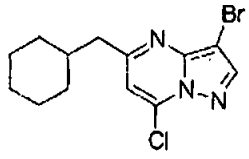
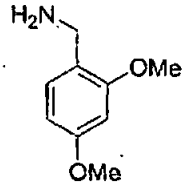
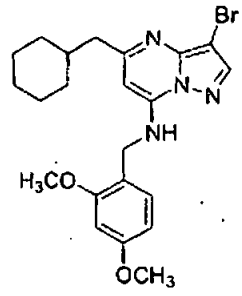
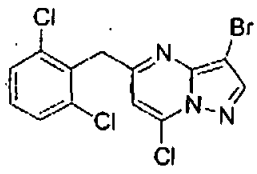
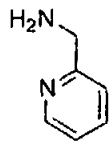
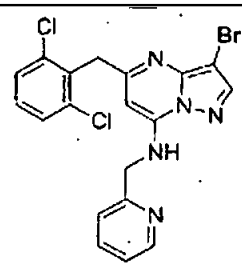
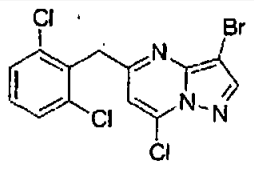
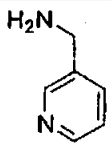
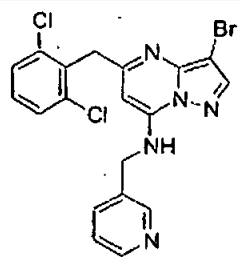
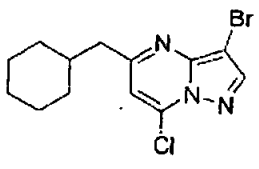
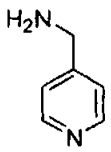
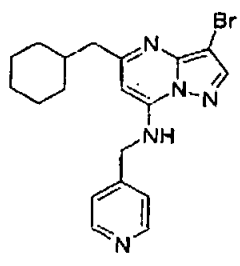
17				LCMS: MH^+= 332; mp= 71-82°C
17.1				MS: MH^+ = 332.
18				LCMS: MH^+= 346; mp= 58-65°C
19				LCMS: MH^+= 414; mp= 211-213°C

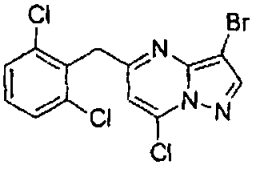
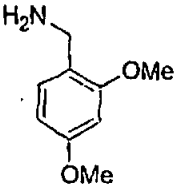
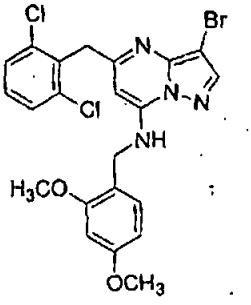
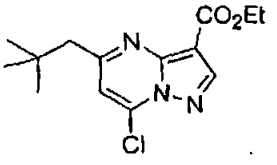
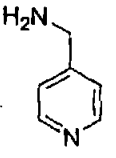
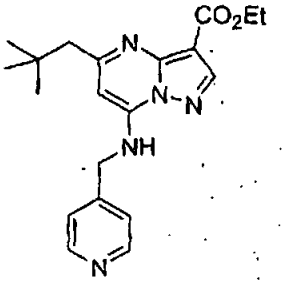
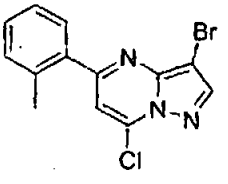
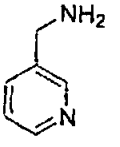
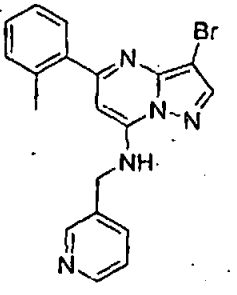
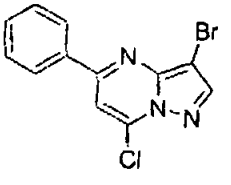
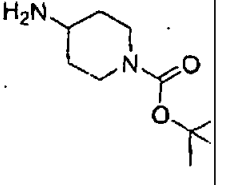
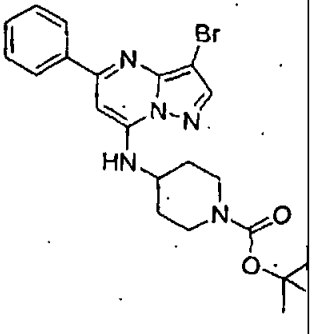
20				LCMS: MH^+= 414; mp= 194-197°C
21				MS: MH^+ = 414 m.p. 211 – 216°C
22				LCMS: MH^+= 544; mp= 104-107°C
23				Yield = 83% LCMS: MH^+ = 410.

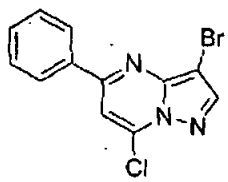
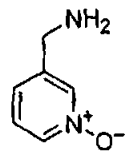
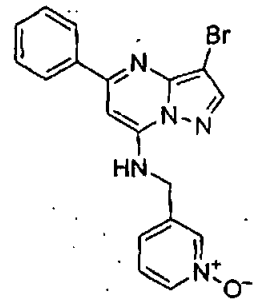
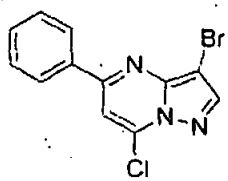
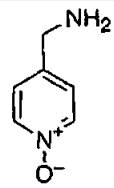
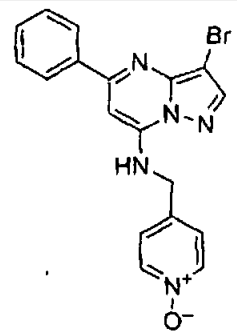
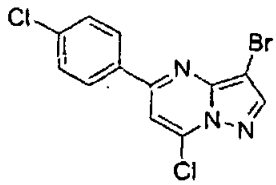
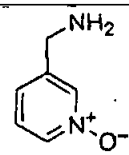
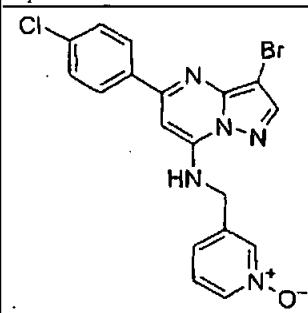
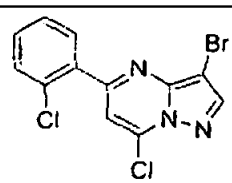
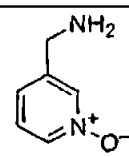
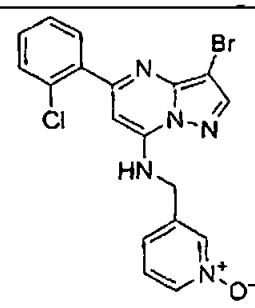
24				Yield = 84% LCMS: MH^+ = 410.
25				Yield = 96% LCMS: MH^+ = 440.
26				Yield = 99% LCMS: MH^+ = 440.
27				Yield = 89% LCMS: MH^+ = 448.
28				Yield = 78% LCMS: MH^+ = 448.

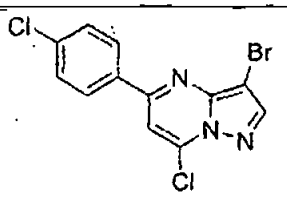
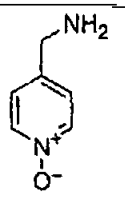
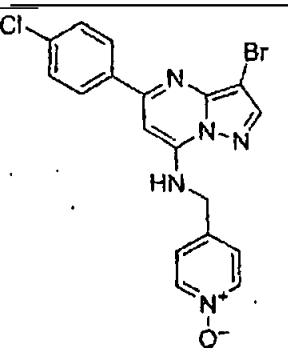
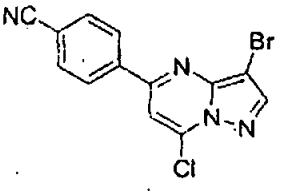
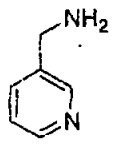
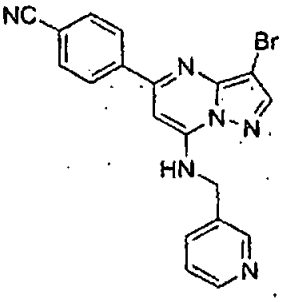
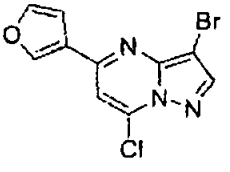
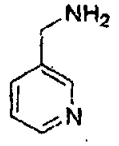
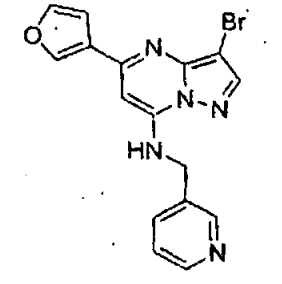
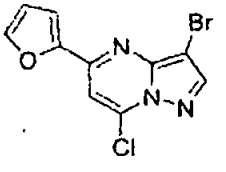
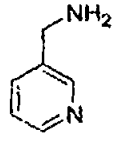
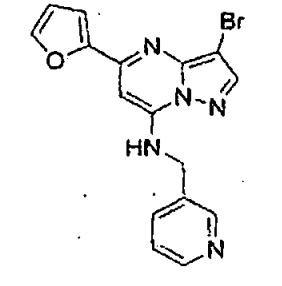
30				Yield = 96% LCMS: MH^+ = 483.
31				Yield = 35% LCMS: MH^+ = 483.
32				Yield = 77% LCMS: MH^+ = 515.
33				Yield = 100% m.p. 179°C LCMS: MH^+ = 388

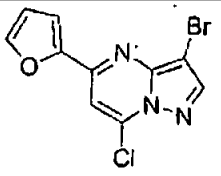
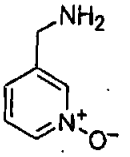
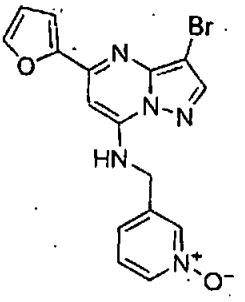
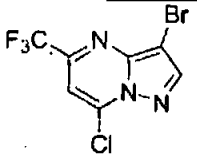
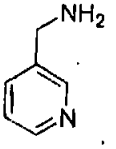
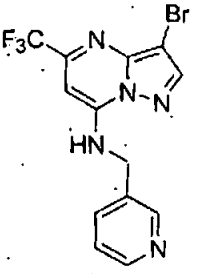
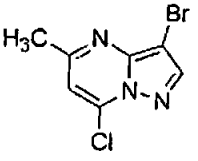
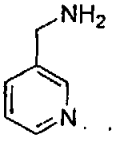
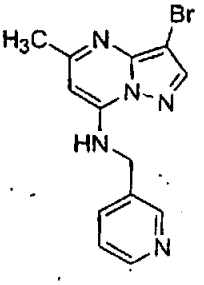
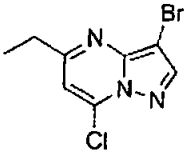
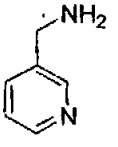
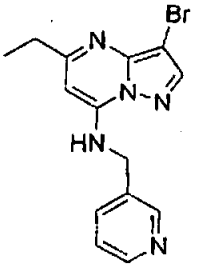
34				Yield = 99% m.p. 186°C LCMS: MH^+ = 456
35				Yield = 98% m.p. 181°C LCMS: MH^+ = 401
36				Yield = 63% m.p. 192°C LCMS: MH^+ = 480
37				Yield = 75% m.p. 126 -127°C LCMS: MH^+ = 400
38				Yield = 94% m.p. 132 -133°C LCMS: MH^+ = 400

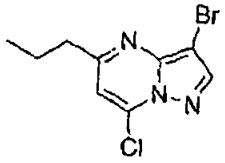
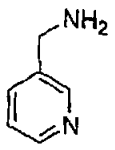
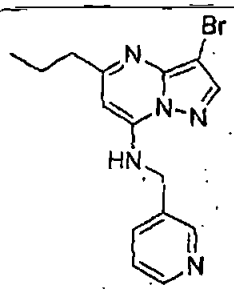
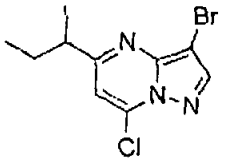
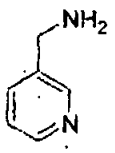
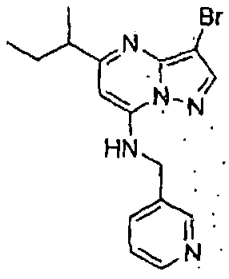
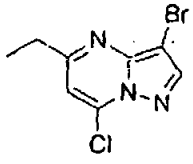
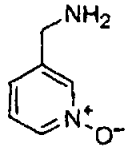
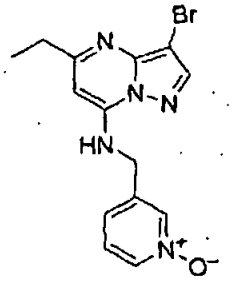
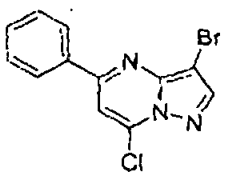
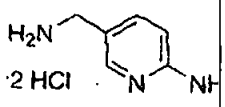
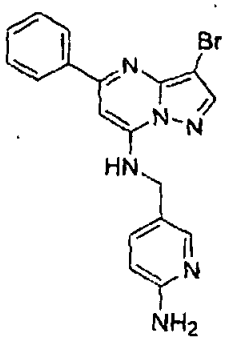
39				Yield = 95% m.p. 121 – 122°C LCMS: MH^+ = 400
40				Yield = 98% LCMS: MH^+ = 460
41				Yield = 87% m.p. 170 - 171°C LCMS: MH^+ = 464
42				Yield = 84% m.p. 216 -217°C LCMS: MH^+ = 464
43				Yield = 96% m.p. 214°C LCMS: MH^+ = 464

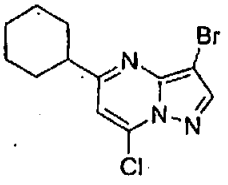
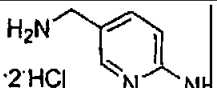
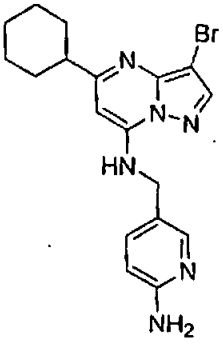
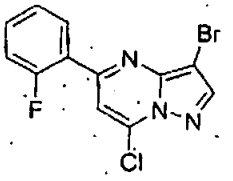
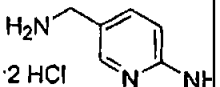
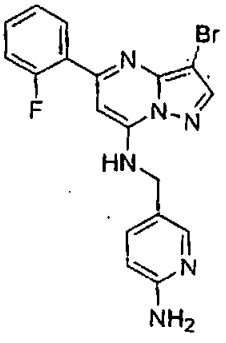
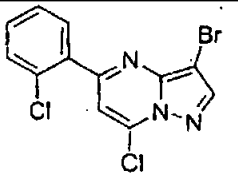
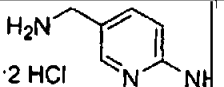
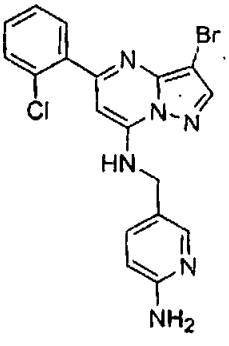
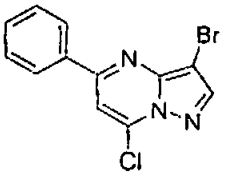
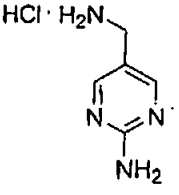
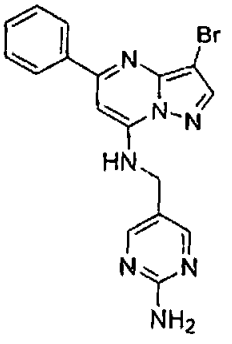
44				Yield = 95% m.p. 158°C LCMS: MH^+ = 522
45				Yield=90 % LCMS: MH^+= 278
46				Yield=100%; LCMS: MH^+=394
47				LCMS: MH+ = 473 m.p. 84 - 87°C

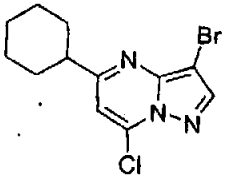
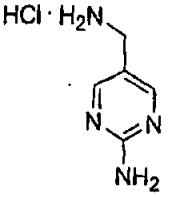
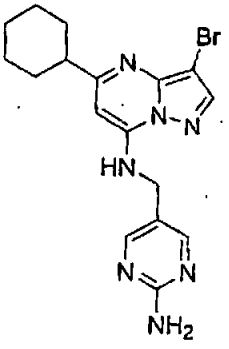
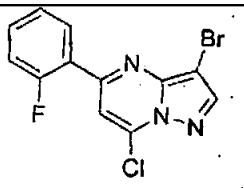
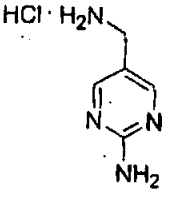
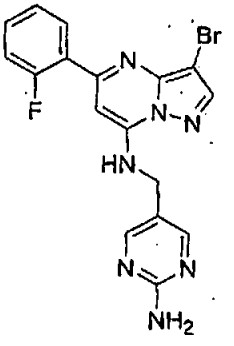
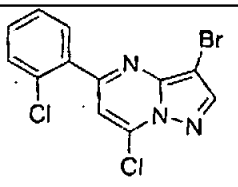
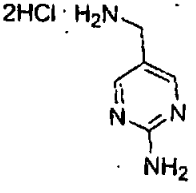
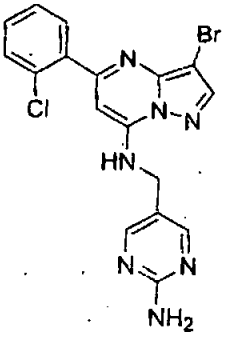
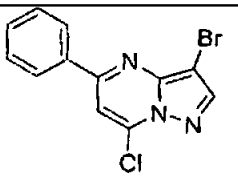
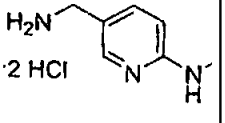
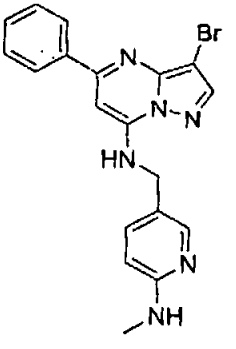
48				MS: MH^+ = 396 m.p. 91.5 – 93.3°C
49				MS: MH^+ = 396 m.p. 196 – 199°C
50				MS: MH^+ = 430 m.p. 242 – 244°C
51				MS: MH^+ = 430 m.p. 218°C

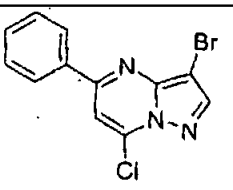
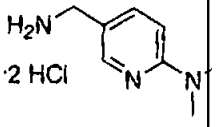
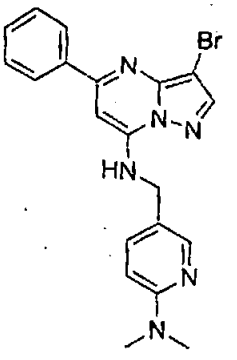
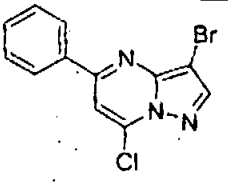
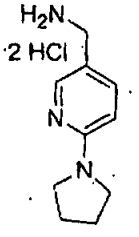
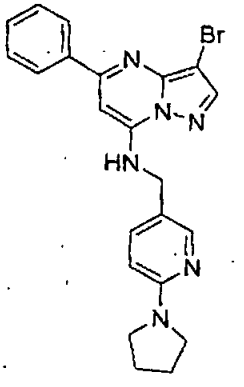
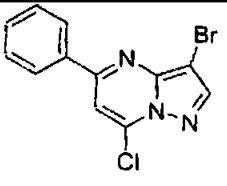
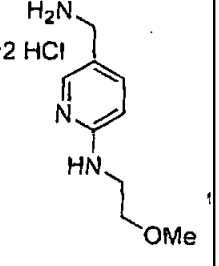
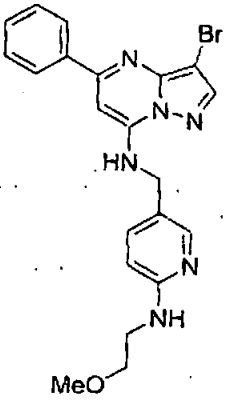
52				MS: MH^+ = 430 m.p. 230 – 233°C
54				MS: MH^+ = 405 m.p. 185 – 188°C
55				MS: MH^+ = 370 m.p. 229 – 232°C
56				MS: MH^+ = 370 m.p. 85 – 90°C

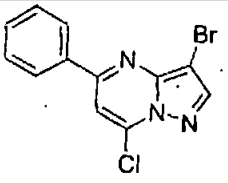
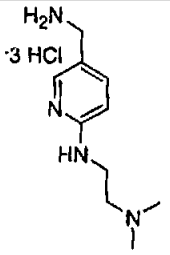
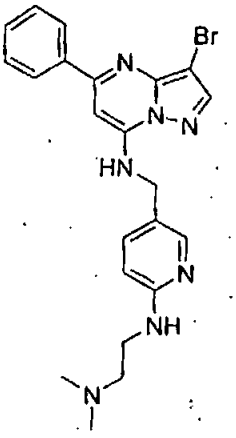
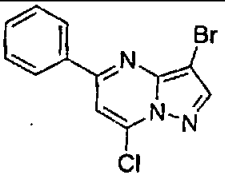
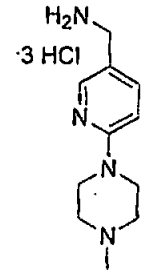
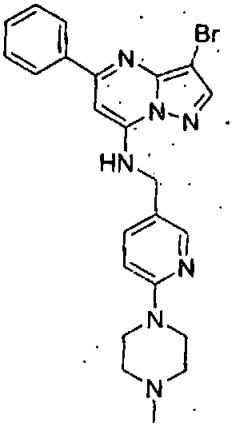
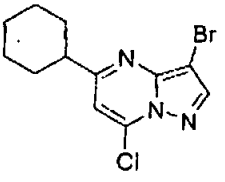
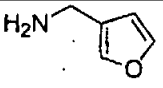
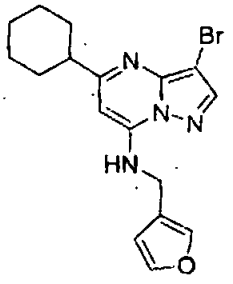
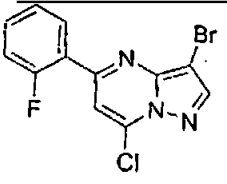
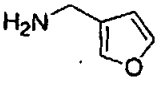
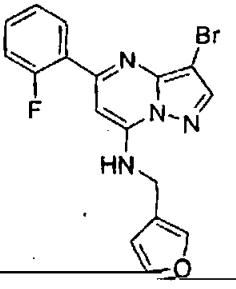
57				MS: MH^+ = 386 m.p. 227 – 230°C
58				MS: MH^+ = 372 m.p. 212 – 215°C
59				MS: MH^+ = 318 m.p. 169 – 171°C
60				MS: MH^+ = 332 m.p. 170 – 173°C

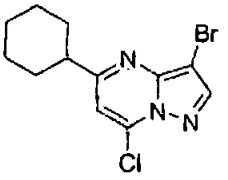
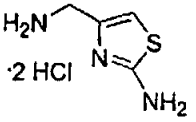
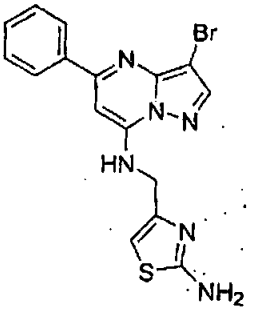
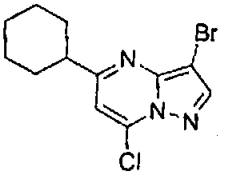
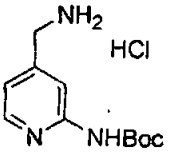
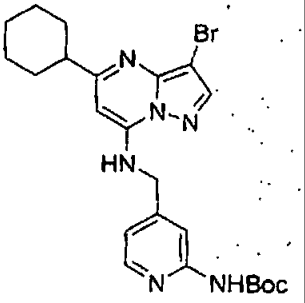
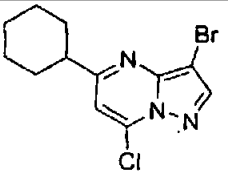
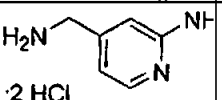
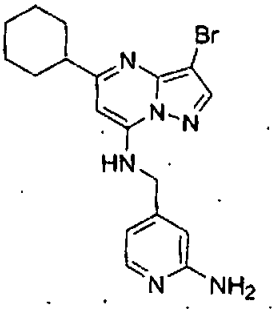
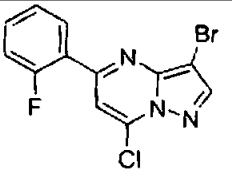
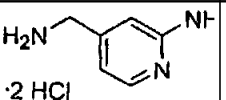
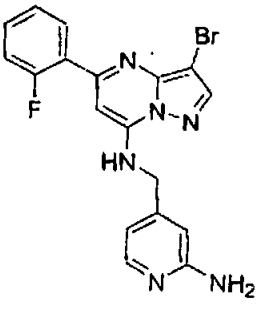
61				MS: MH^+ = 346 m.p. 156 – 159°C
62				MS: MH^+ = 360 m.p. 114 – 116°C
63				MS: MH^+ = 348 m.p. 197 – 200°C
64				1. mp = 230-232 2. M+H = 396

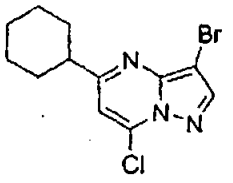
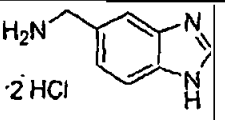
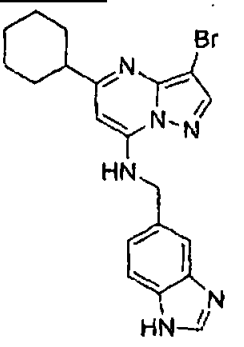
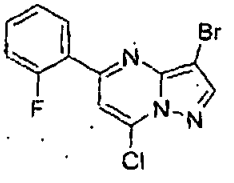
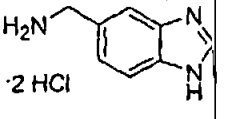
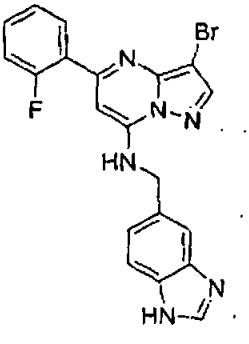
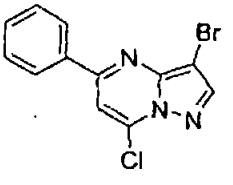
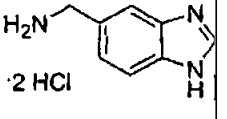
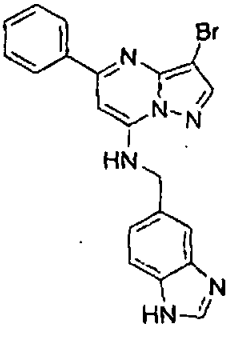
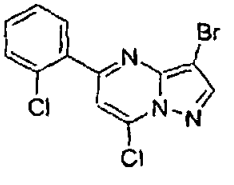
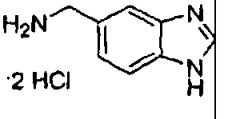
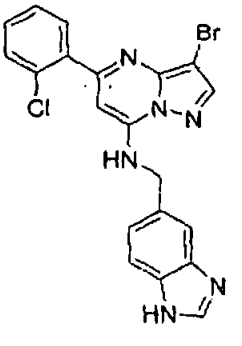
65				1. mp = 205-207 2. M+H = 402
66				1. mp = 220-223 2. M+H = 414
67				1. mp = 191-193 2. M+H = 431
68				1. mp = 235-237 2. M+H = 397

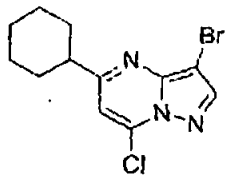
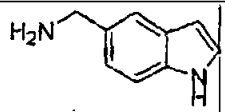
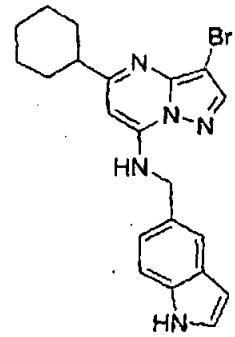
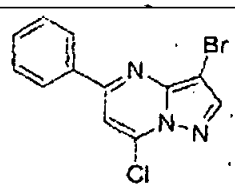
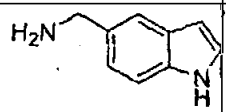
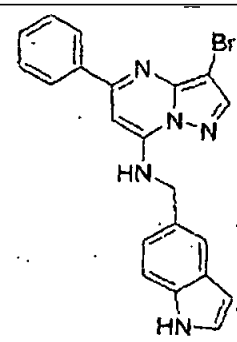
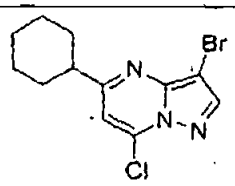
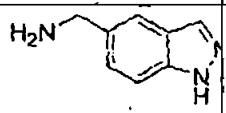
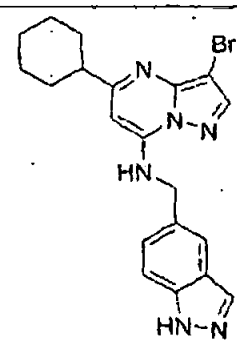
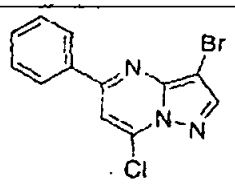
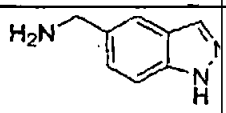
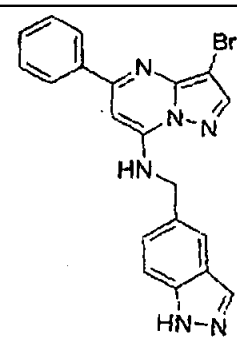
69				1. mp = >250 2. M+H = 403
70				1. mp = 230-232 2. M+H = 415
71				1. mp = 235-238 2. M+H = 431
72				1. mp = 186-188 2. M+H = 410

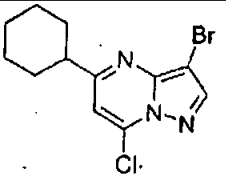
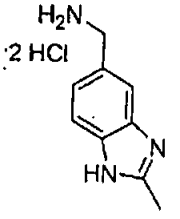
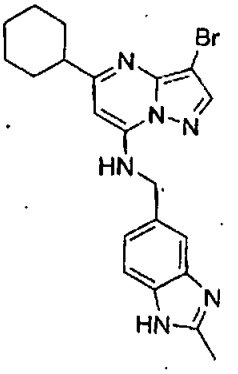
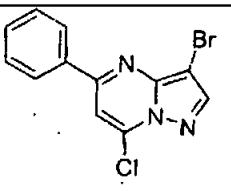
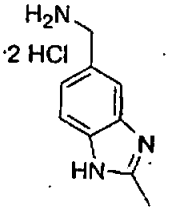
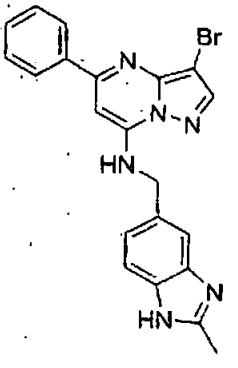
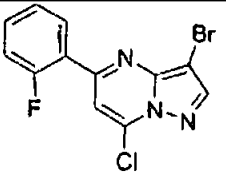
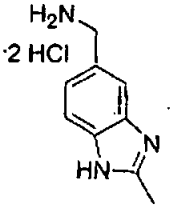
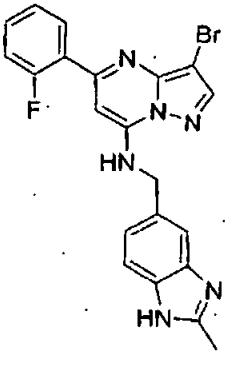
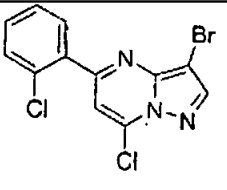
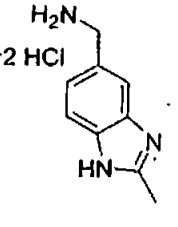
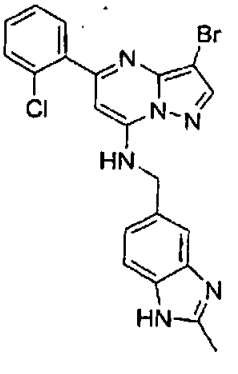
73				1. mp = 136-138 2. M+H = 424
74				1. mp = 192-195 2. M+H = 450
75				1. mp = 88-90 2. M+H = 454

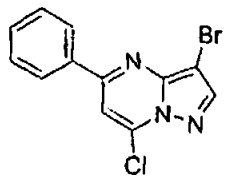
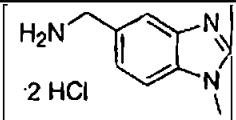
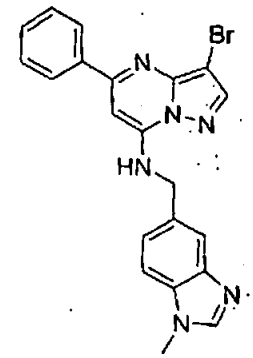
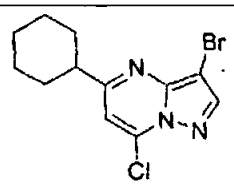
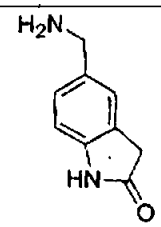
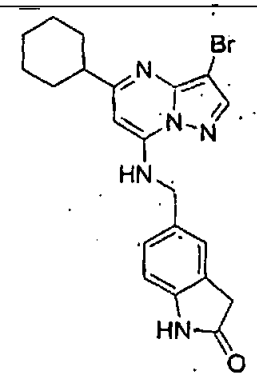
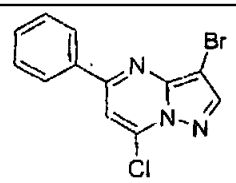
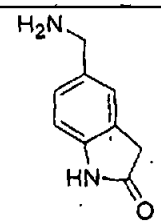
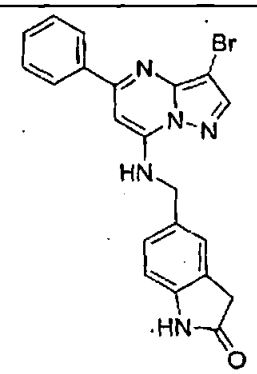
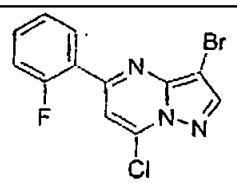
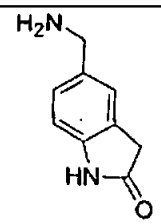
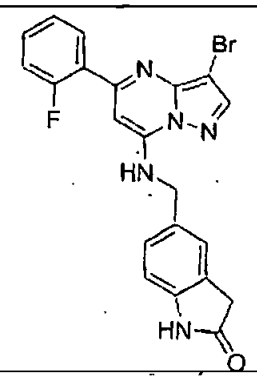
76				1. mp = 230-232 2. M+H = 467
77				1. mp = 131-133 2. M+H = 479
78				1. mp = 85-88 2. M+H = 376
79				1. mp = 131-133 2. M+H = 388

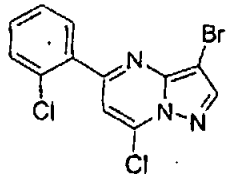
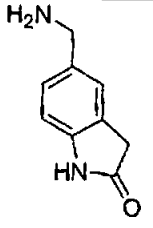
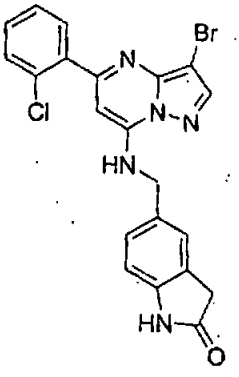
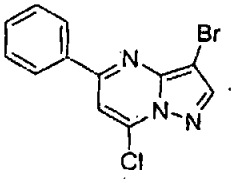
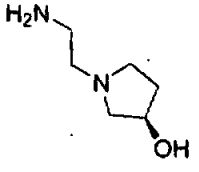
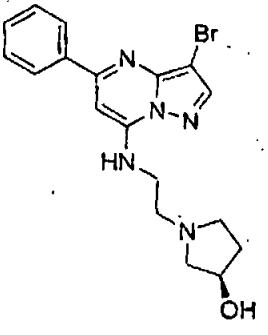
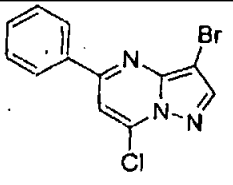
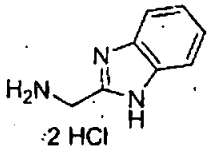
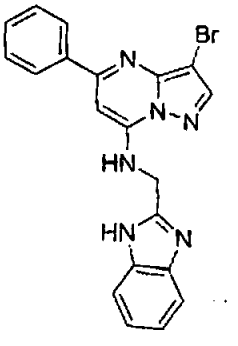
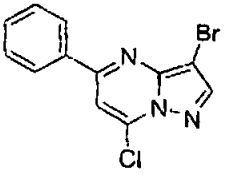
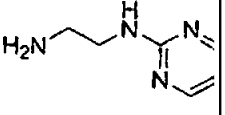
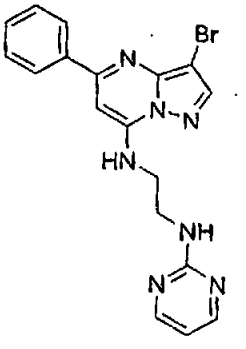
80				1. mp = 206-208 2. M+H = 408
81				1. mp = 108-110 2. M+H = 502
82				1. mp = 83-85 2. M+H = 402
83				1. mp = 220 2. M+H = 414

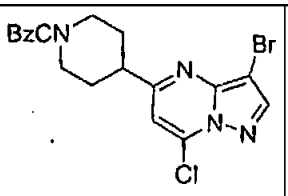
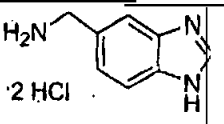
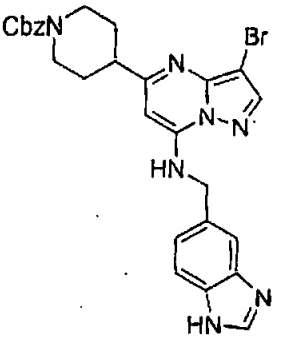
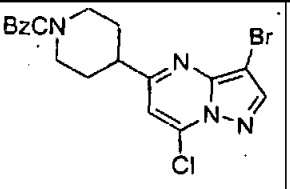
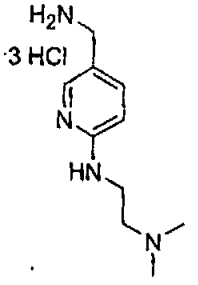
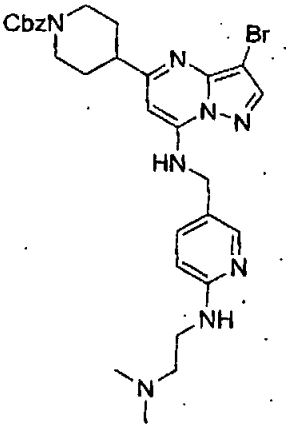
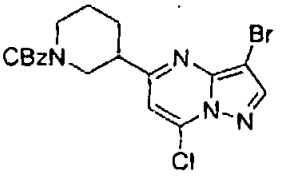
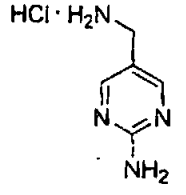
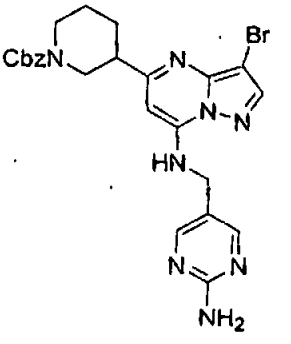
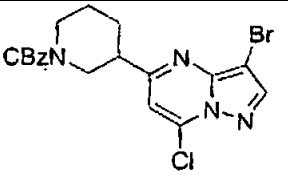
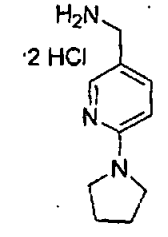
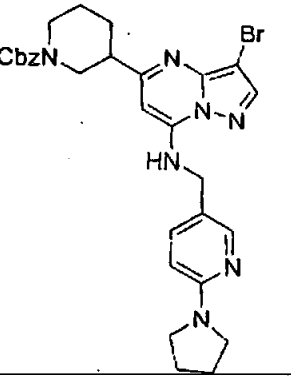
84				1. mp = 154-156 2. M+H = 426
85				1. mp = 152-153 2. M+H = 438
86				1. mp = 159-161 2. M+H = 420
87				1. mp = >220 2. M+H = 455

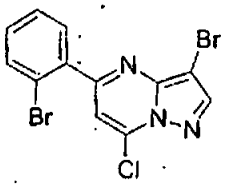
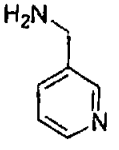
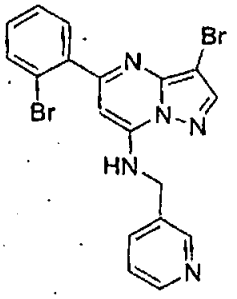
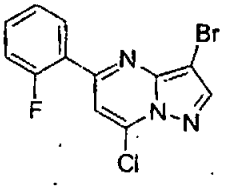
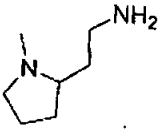
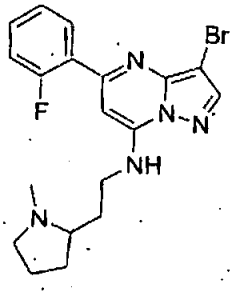
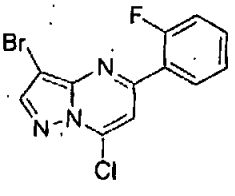
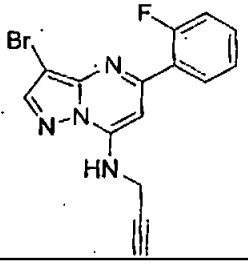
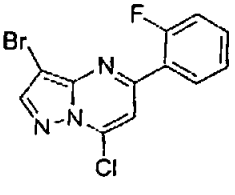
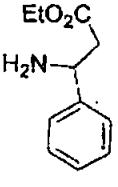
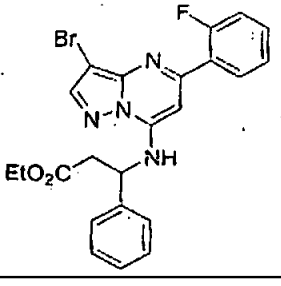
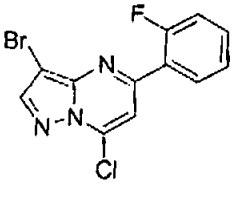
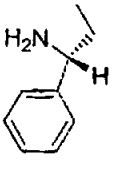
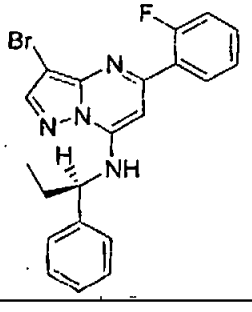
88				1. mp = 223-225 2. M+H = 425
89				1. mp = 199-201 2. M+H = 419
90				1. mp = 184-186 2. M+H = 426
91				1. mp = 196-198 2. M+H = 420

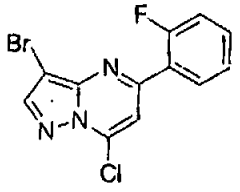
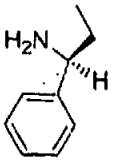
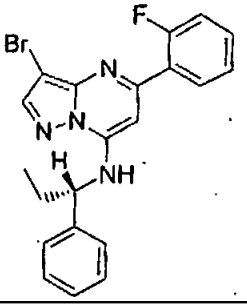
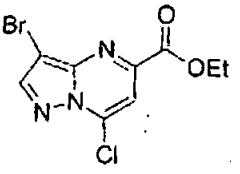
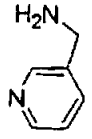
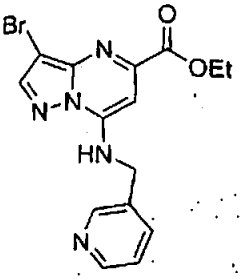
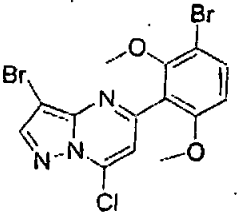
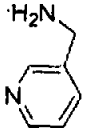
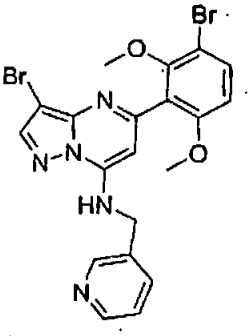
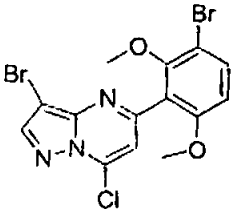
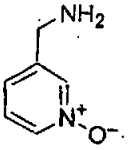
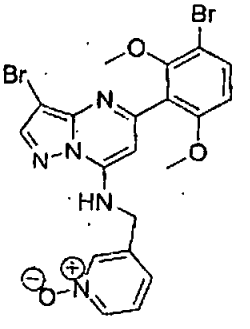
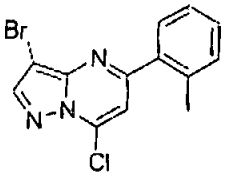
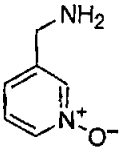
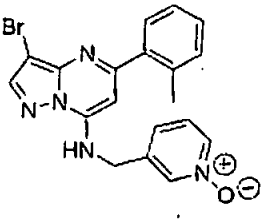
92				1. mp = 156-159 2. M+H = 440
93				1. mp = 173-176 2. M+H = 434
94				1. mp = 173-175 2. M+H = 452
95				1. mp = 174-176 2. M+H = 469

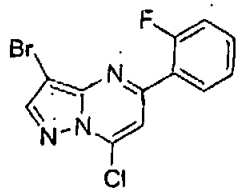
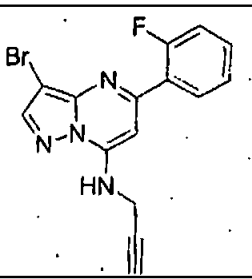
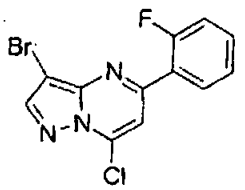
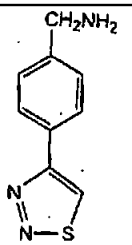
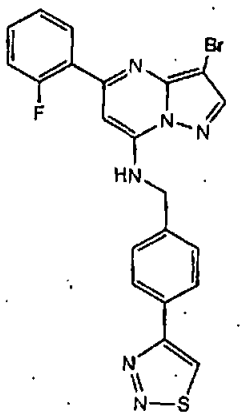
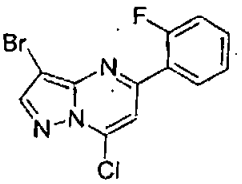
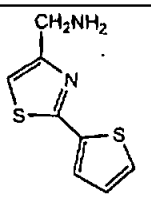
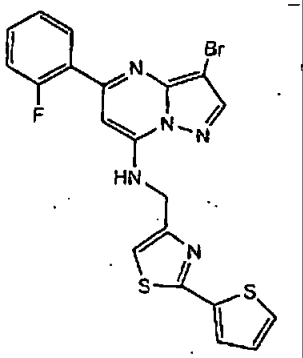
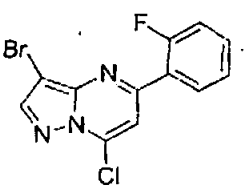
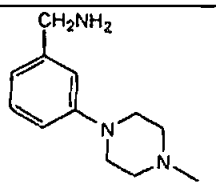
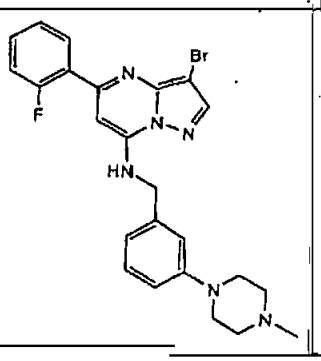
96		 2 HCl		1. mp = 230-234 2. M+H = 434
97				1. mp = 191-193 2. M+H = 441
98				1. mp = 202-205 2. M+H = 434
99				1. mp = 209-212 2. M+H = 453

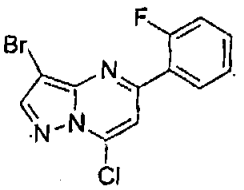
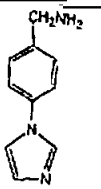
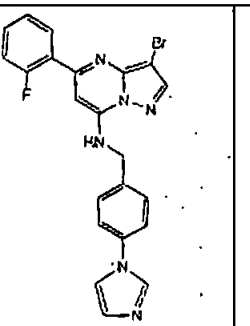
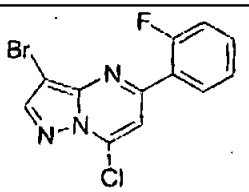
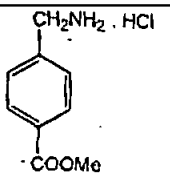
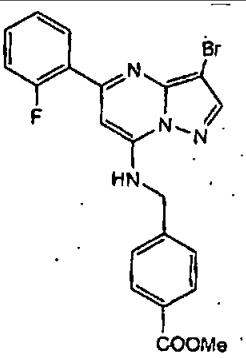
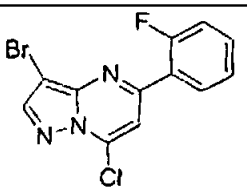
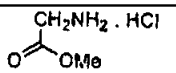
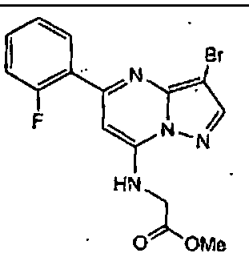
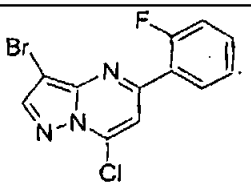
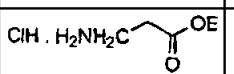
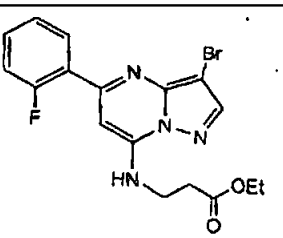
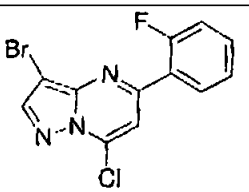
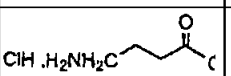
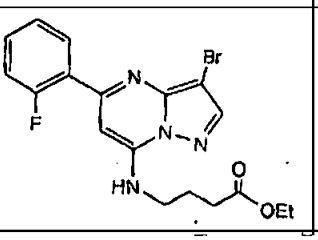
100				1. mp = 219-221 2. M+H = 469
101				1. mp = 64-66 2. M+H = 403
102				1. mp = 168-170 2. M+H = 420
103				1. mp = 213-216 2. M+H = 411

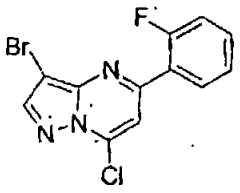
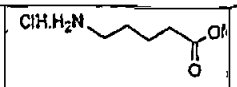
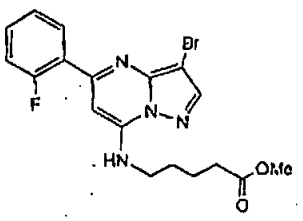
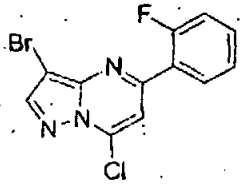
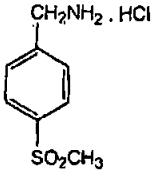
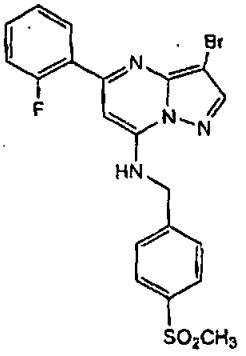
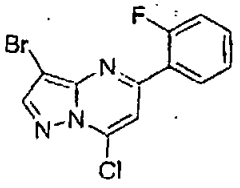
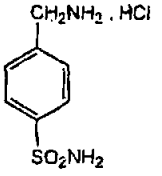
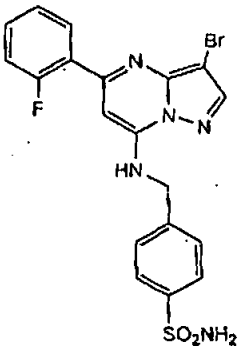
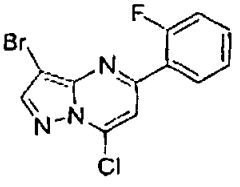
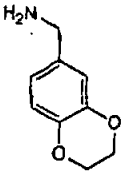
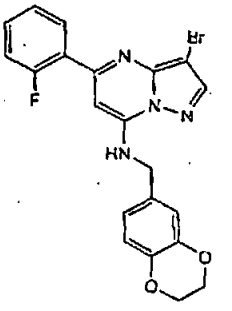
104				1. mp = 98-100 2. M+H = 561
105				1. mp 70-72 2. M+H = 608
106				1. mp 168-170 2. M+H = 538
107				1. mp 189-191 2. M+H = 592

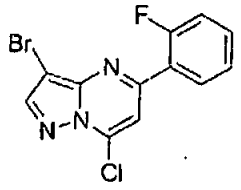
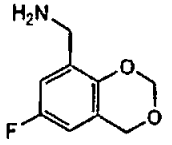
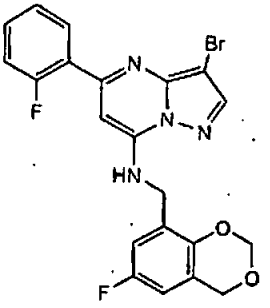
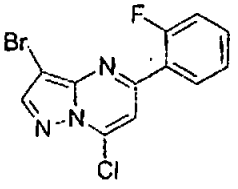
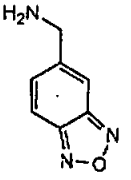
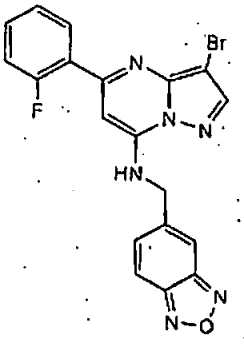
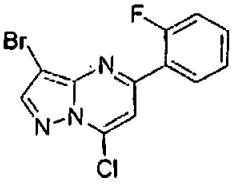
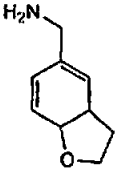
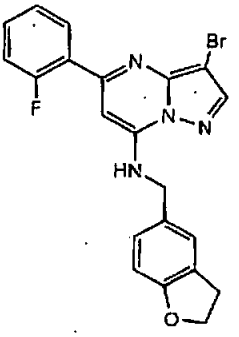
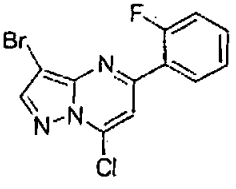
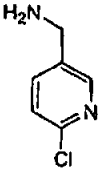
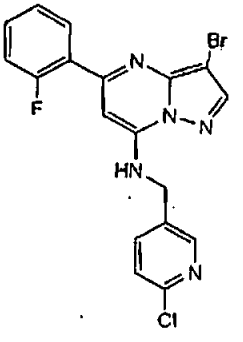
108				LCMS: MH^+ = 458;
109				Yield = 89 LCMS: MH^+ = 418 m. p. = 131-132 °C
110				Yield=95% LCMS: MH^+= 347
111				Yield=91% 3H); LCMS: MH^+= 484
112				Yield=87% LCMS: MH^+= 427

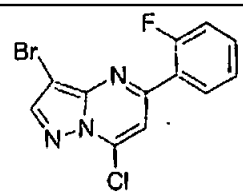
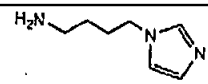
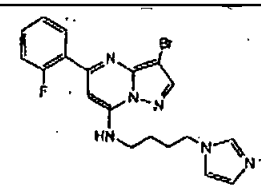
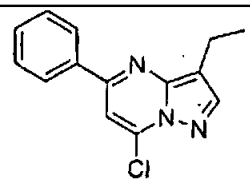
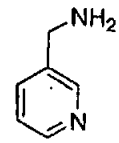
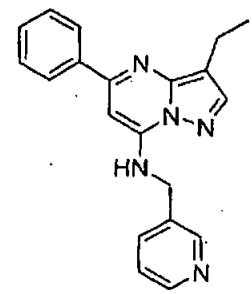
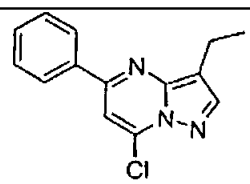
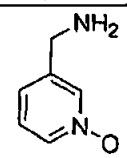
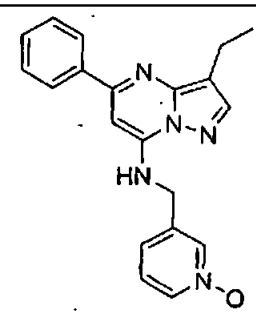
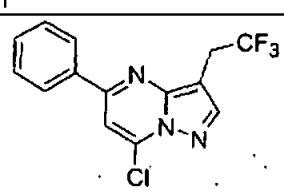
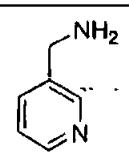
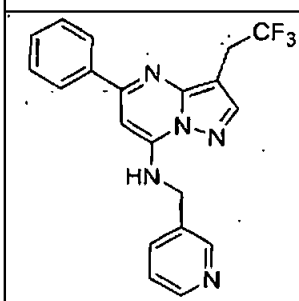
113				Yield=80% LCMS: MH^+= 427
114				Yield=91% LCMS: MH^+= 378
115				Yield=92% , 3H); LCMS: MH^+=520
116				Yield=98% LCMS: MH^+=536
117				Yield=82% LCMS: MH^+=410

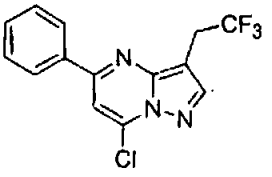
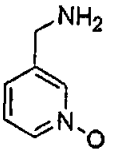
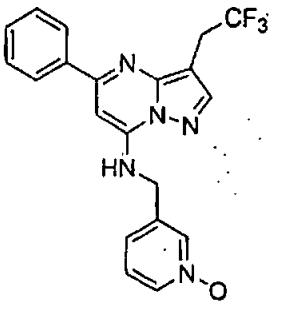
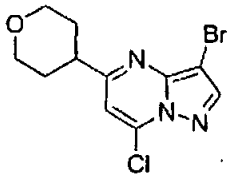
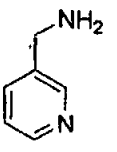
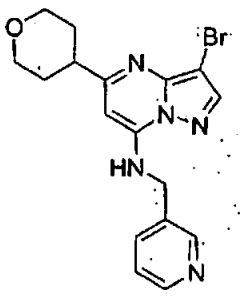
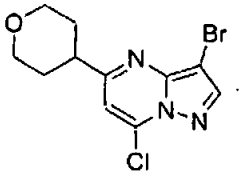
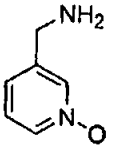
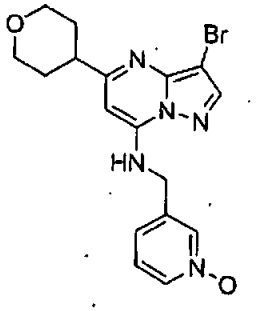
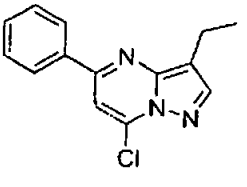
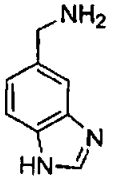
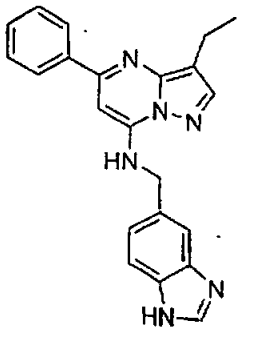
118				Yield=95% LCMS: MH^+= 347
121				Yield = 65% LCMS: MH^+ = 481.02
126				Yield=71% MH^+ = 486
127				Yield=71% MH^+ = 495.1

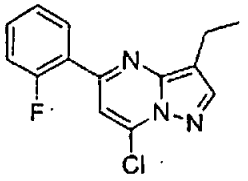
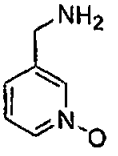
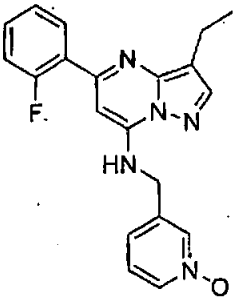
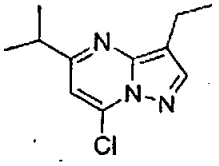
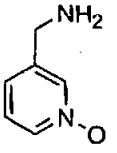
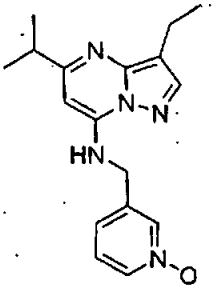
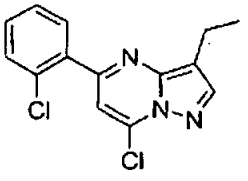
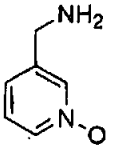
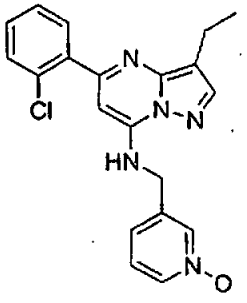
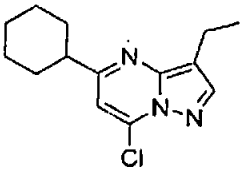
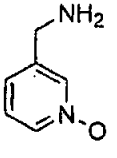
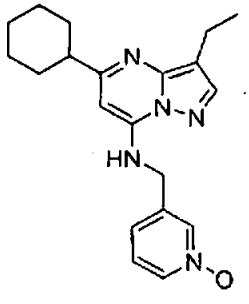
128				Yield=55% MH⁺ = 463
129				Yield = 77% LCMS: MH⁺ = 455
130				^{1}H NMR (Yield = 75% LCMS: MH⁺ = 379
131				Yield = 75% LCMS: MH⁺ = 407
132				Yield = 75% LCMS: MH⁺ = 421

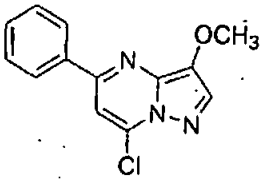
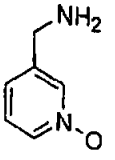
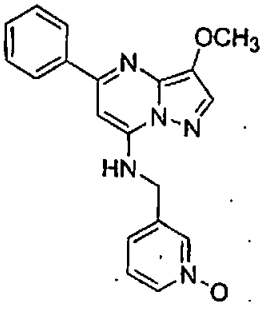
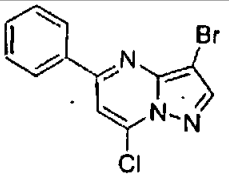
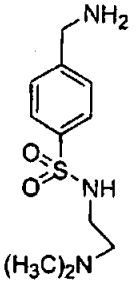
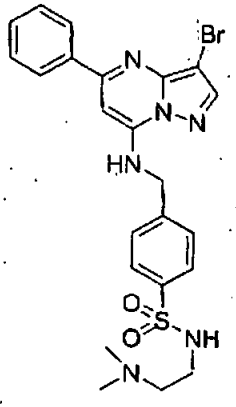
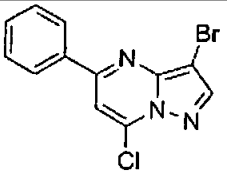
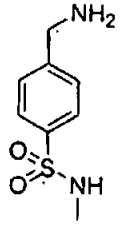
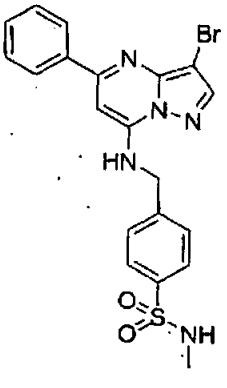
133				Yield = 70% LCMS: MH^+ = 421
134				Yield = 78% LCMS: MH^+ = 475
135				Yield = 75% LCMS: MH^+ = 476
136				Yield = 65% LCMS: MH^+ = 455

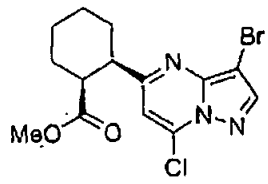
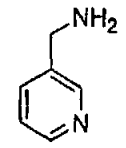
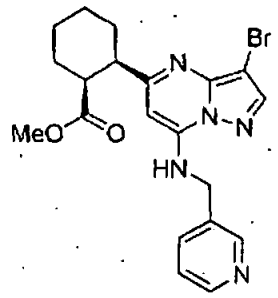
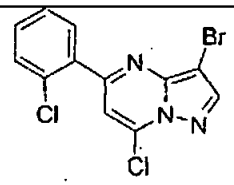
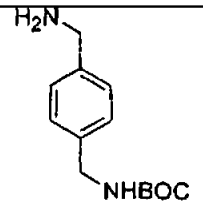
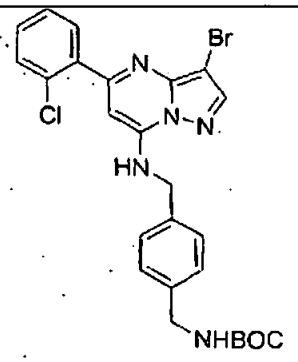
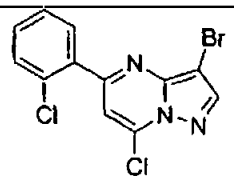
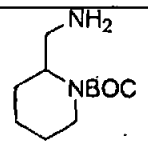
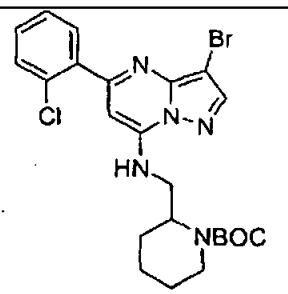
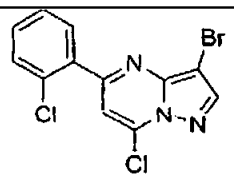
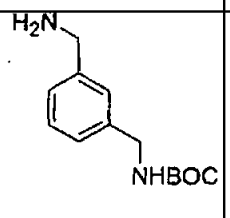
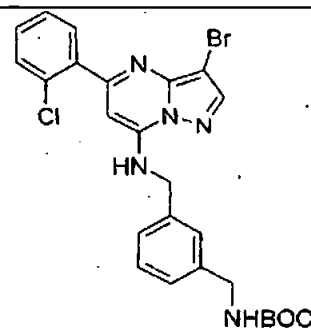
137				Yield = 55% LCMS: MH^+ = 473)
138				Yield = 60% LCMS: MH^+ = 439
139				Yield = 65% LCMS: MH^+ = 441
140				Yield = 80% LCMS: MH^+ = 432

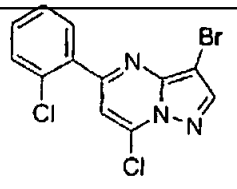
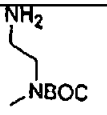
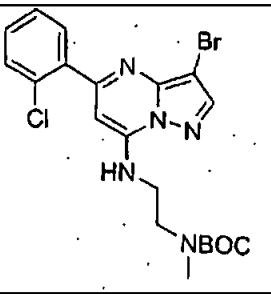
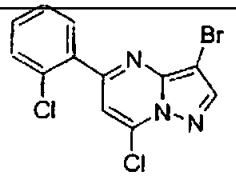
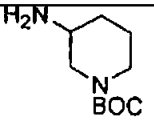
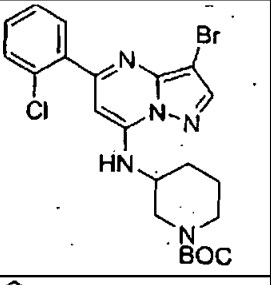
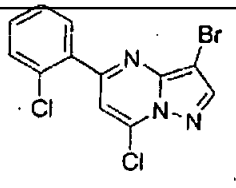
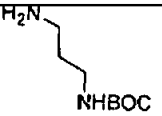
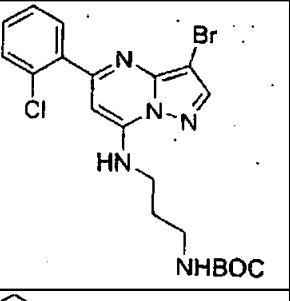
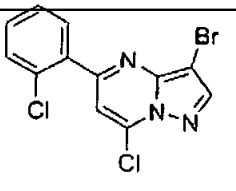
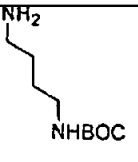
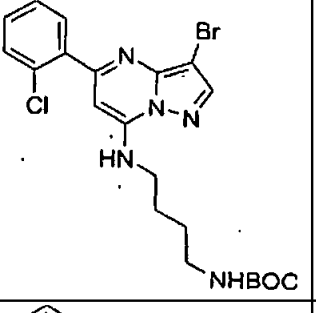
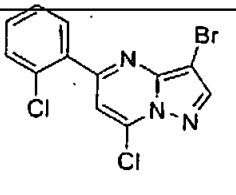
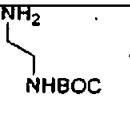
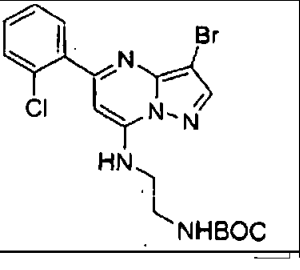
141				Yield = 60% LCMS: MH^+ = 429
142				LCMS: MH^+=330 ; mp=109-111°C
143				LCMS: MH^+=346 ; mp=186-188°C
144				LCMS: MH^+=384 ; mp=148-150°C

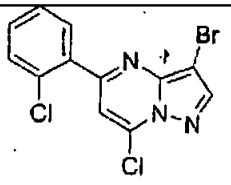
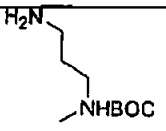
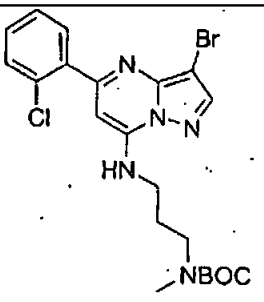
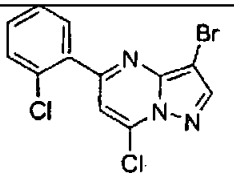
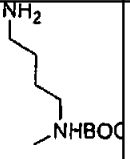
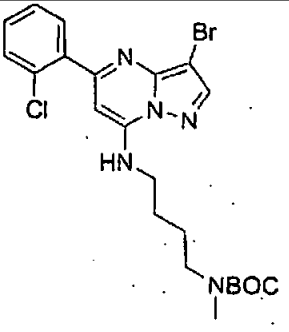
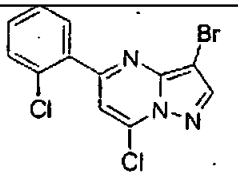
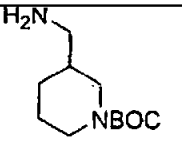
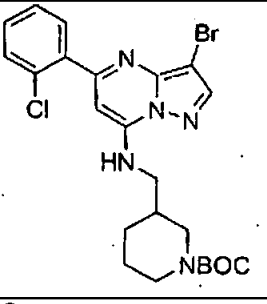
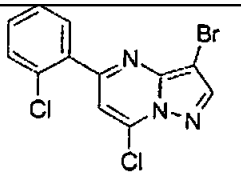
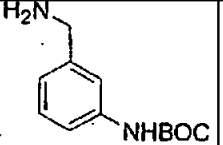
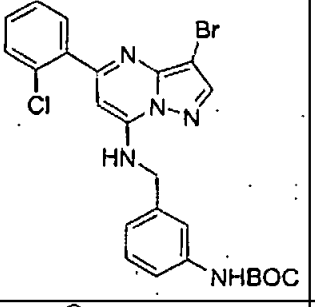
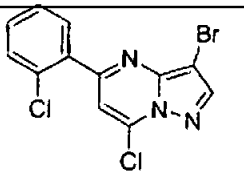
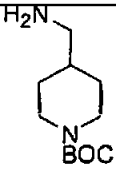
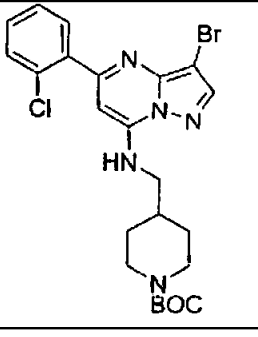
145				LCMS: MH^+=400; mp=186-188°C
146				LCMS: $M2H^+$=390; mp=192-194°C
147				LCMS: M^+=404; mp=220-222°C
148				LCMS: MH^+=369; mp>230° C

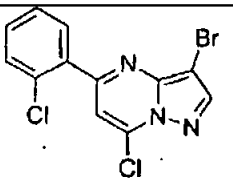
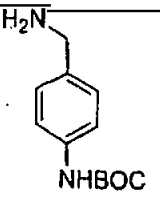
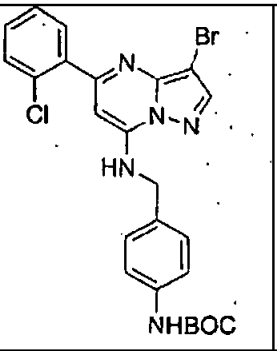
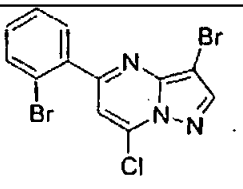
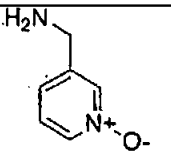
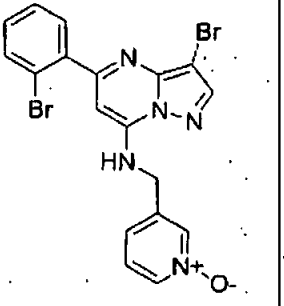
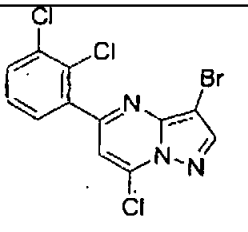
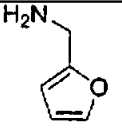
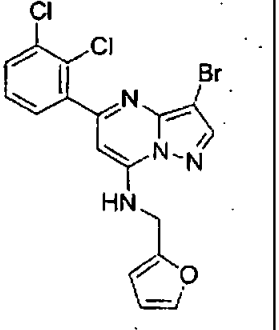
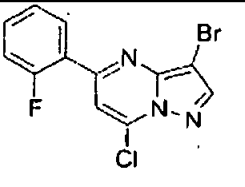
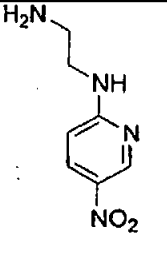
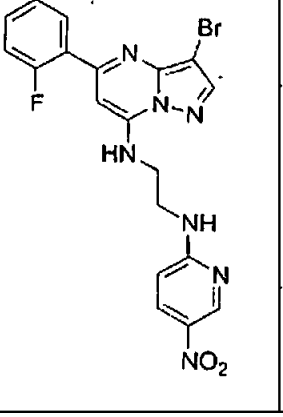
149				LCMS: MH^+=364 ; mp=186-188°C
150				LCMS: MH^+=312 ; mp=138-140°C
151				LCMS: M^+=380; mp=172-174°C
152				LCMS: MH^+=352 ; mp=201-203°C

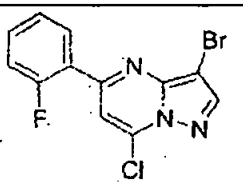
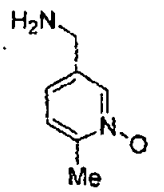
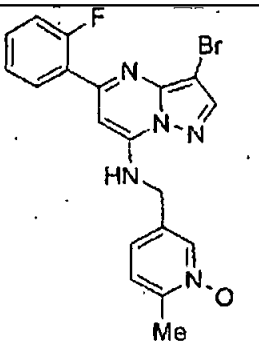
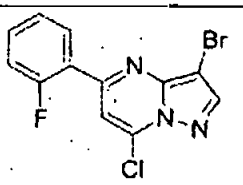
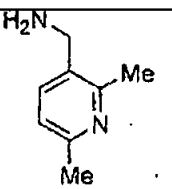
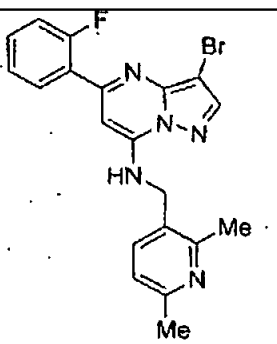
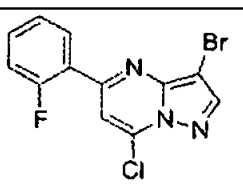
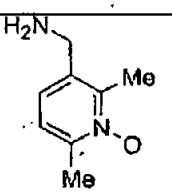
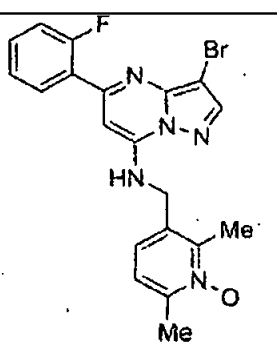
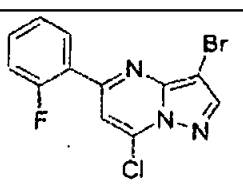
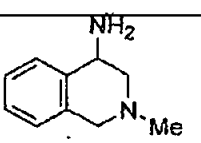
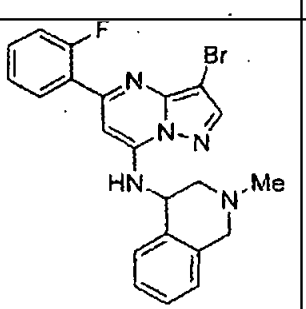
153				LCMS: MH^+=348; mp=166-168°C
154				LCMS: $M2H^+$=531; mp=78-80°C
155				LCMS: $M2H^+$=474; mp=161-163°C

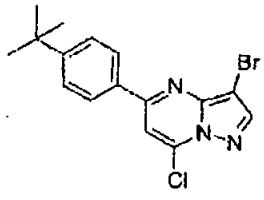
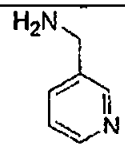
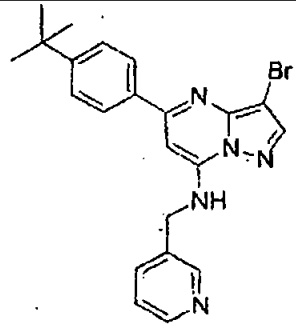
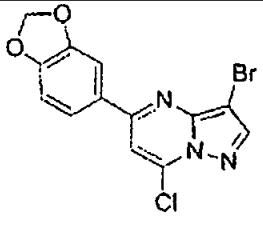
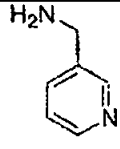
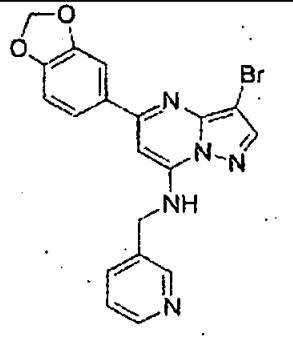
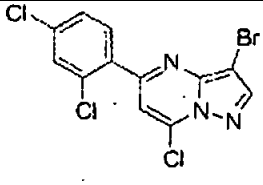
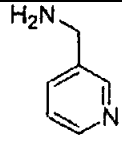
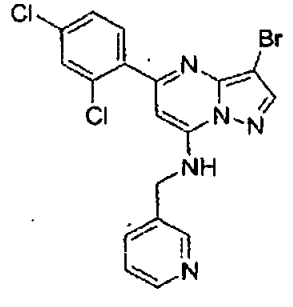
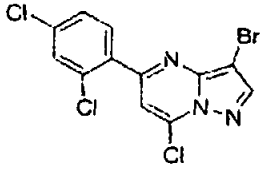
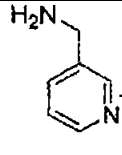
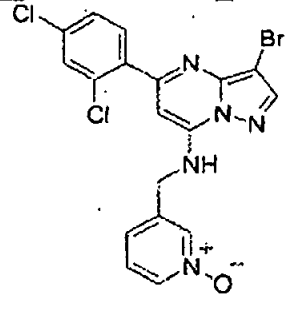
156				LCMS: M^+=444; mp=48-51°C
157				MH^+ = 542.1
158				MH^+ = 520.1
159				MH^+ = 542.1

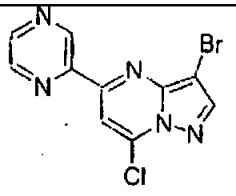
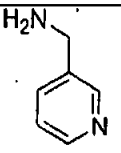
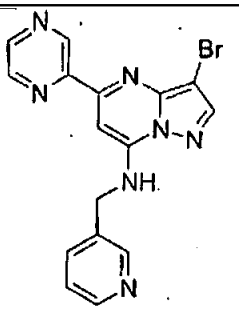
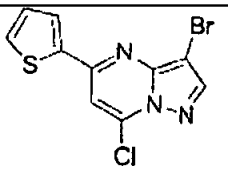
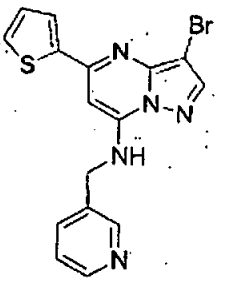
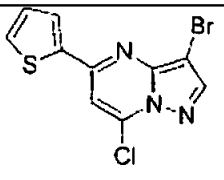
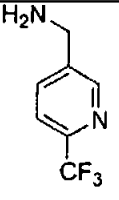
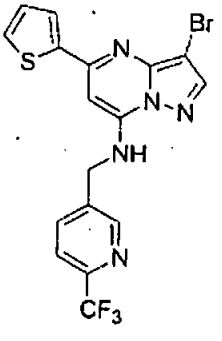
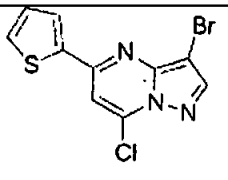
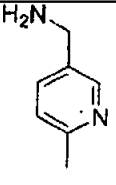
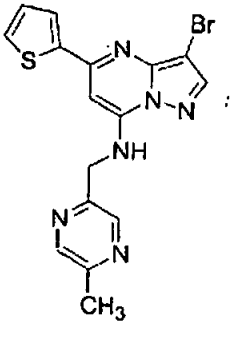
160				MH^+ = 480.1
161				MH^+ = 506.1
162				MH^+ = 480.1
163				MH^+ = 494.1
164				MH^+ = 466.1

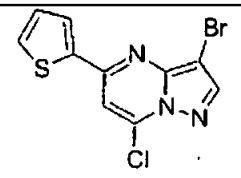
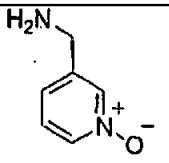
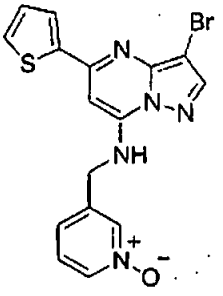
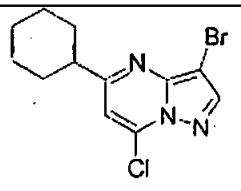
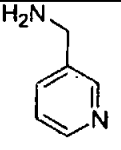
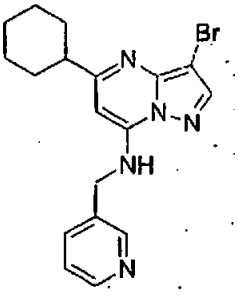
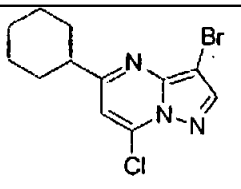
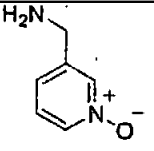
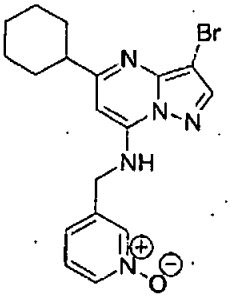
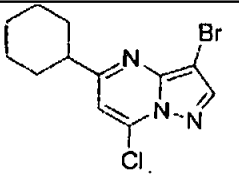
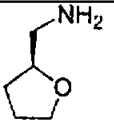
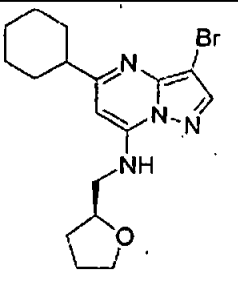
165				MH^+ = 494.1
166				MH^+ = 508.1
167				MH^+ = 520.1
168				MH^+ = 528.1
169				MH^+ = 520.1

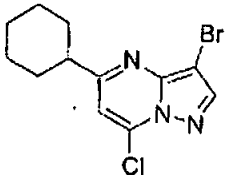
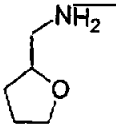
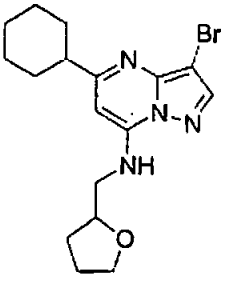
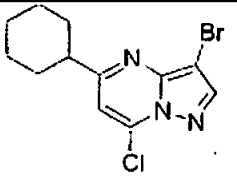
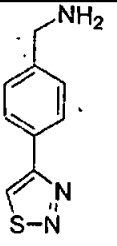
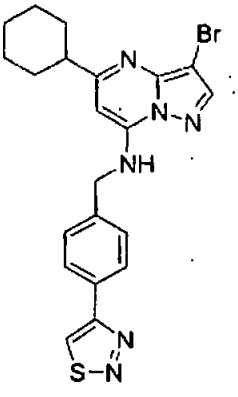
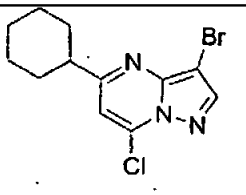
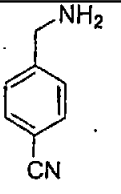
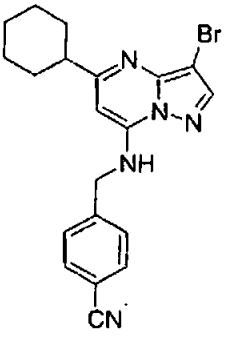
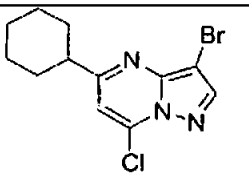
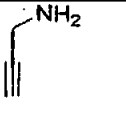
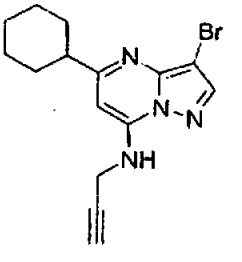
170				MH^+ = 528.1
171				LCMS: MH^+ = 474;
172				LCMS: MH^+ = 437;
173				LCMS: MH^+ = 472;

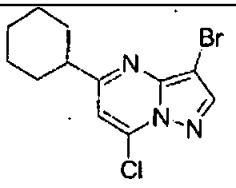
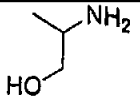
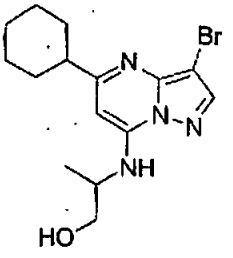
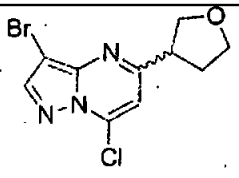
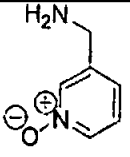
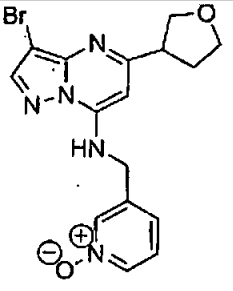
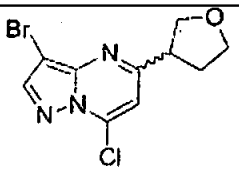
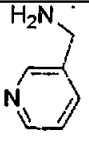
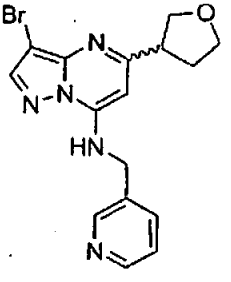
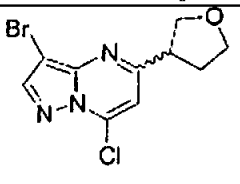
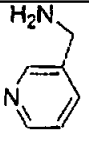
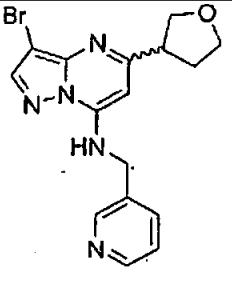
174				LCMS: MH^+ = 428.1
175				LCMS: MH^+ = 426.2
176				LCMS: MH^+ = 442.0
177				LCMS: MH^+ = 452.0

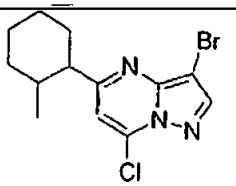
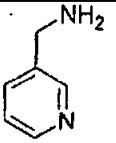
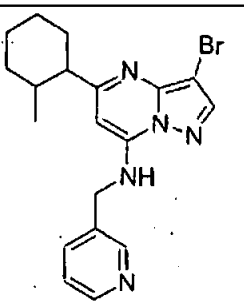
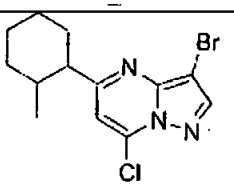
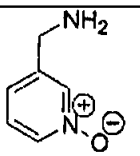
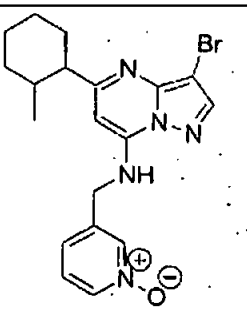
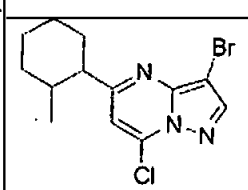
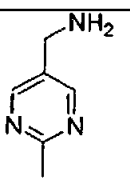
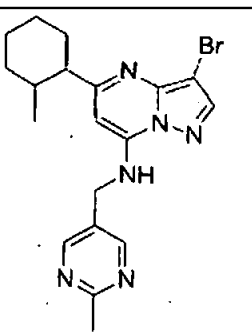
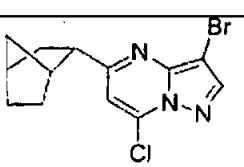
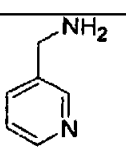
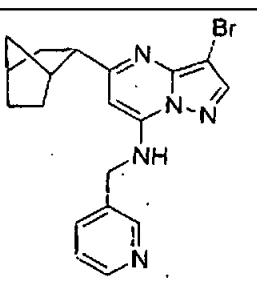
178				Yield = 90 MH^+ =436 m. pt. = 89.1 °C
179				MH^+ =424 m. pt. = 188.2 °C
180				MH^+ =448 m. pt. = 211.3 °C
181				Yield = quant. MH^+ = 464

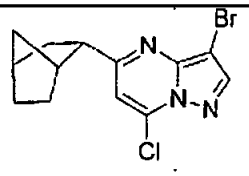
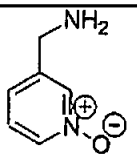
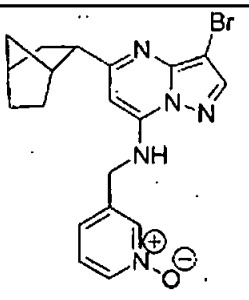
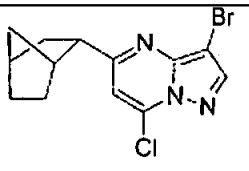
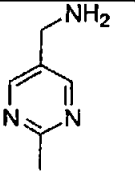
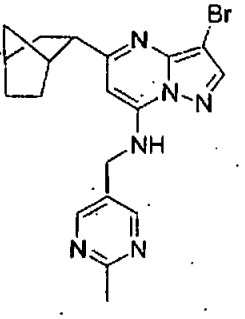
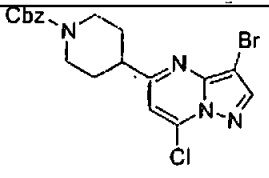
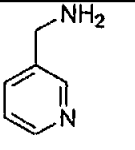
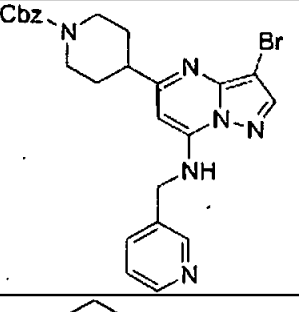
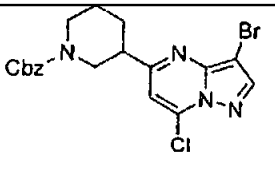
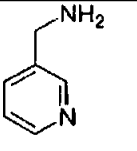
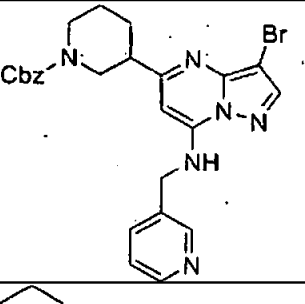
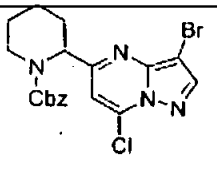
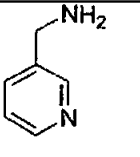
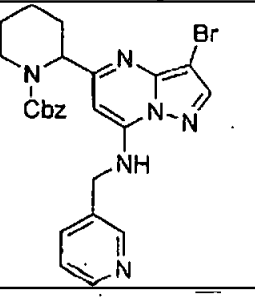
182				MH^+ = 382 m. pt. = 185.8 °C
183				MH^+ = 387 m. pt. = 181 – 182 °C
184				MH^- = 453
185				MH^+ = 401 m. pt. = 178.3 °C

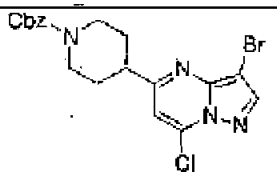
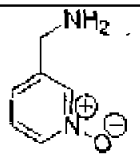
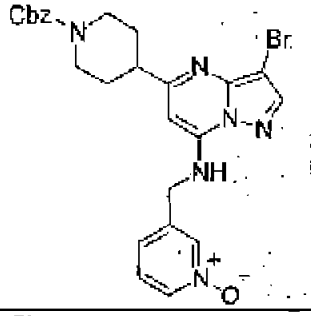
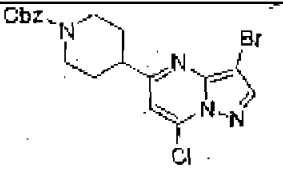
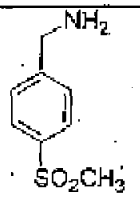
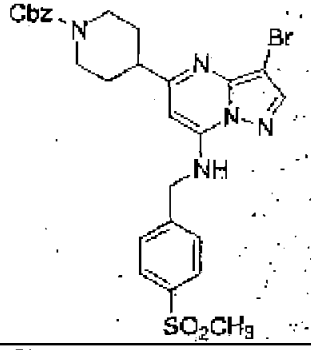
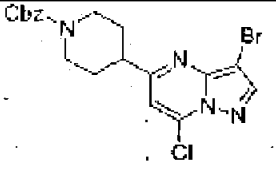
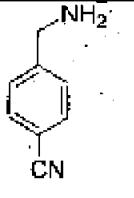
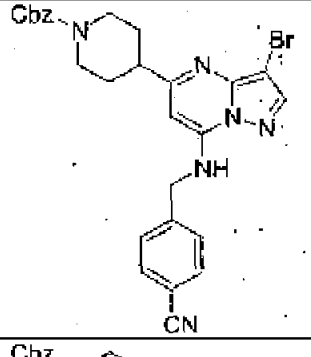
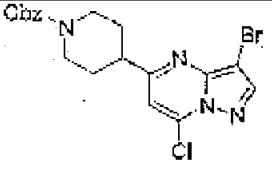
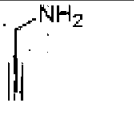
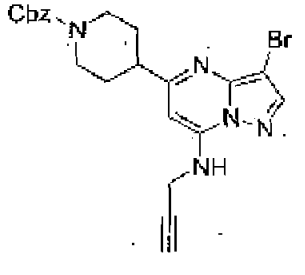
186				MH^+ = 402
187				Yield = 91 MH^+ = 386 m. pt. = 148.3 °C
188				Yield = 65 MH^+ = 402 m. pt. = 174.5 °C
189				MH^+ = 379 m. pt. = 82 – 83 °C

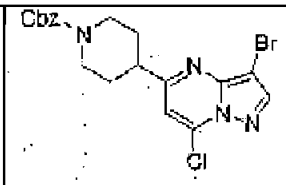
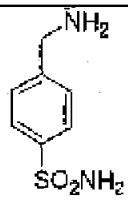
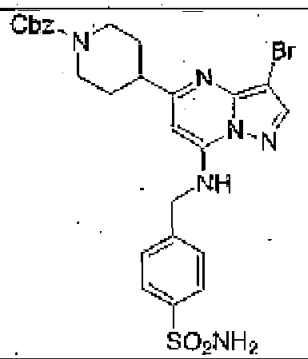
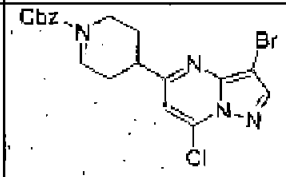
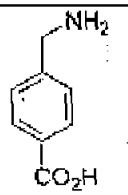
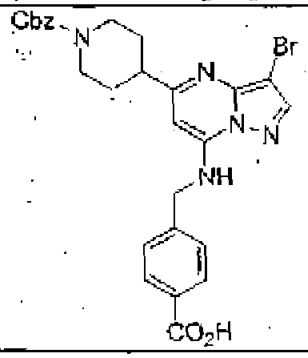
190				MH^+ = 379 m. pt. = 50.7 °C
191				Yield = 89 MH^+ = 469 m. pt. = 186.7°C
192				Yield = 93 MH^+ = 410 m. pt. = 86.7°C
193				Yield = 76 MH^+ = 333 m. pt. = 120.3°C

194				Yield = 86 MH^+ = 353 m. pt. = 188.9 °C
195				Yield=11% LCMS:374 MH^+= 390
196				Yield=88% LCMS:374 MH^+= 346
197				Yield=88% LCMS:374 MH^+= 346

198				Yield = MH+ = 400 m. pt. = 111.5 – 112.2 °C
199				MH+ = 416
200				MH+ = 415
201				MH+ =398 m.p. = 156.5°C

202				MH^+ = 414 m.p. = 89.5 °C
203				MH^+ = 413
204				Yield = 86 MH^+ = 521 m.p. = 79.9 °C
204 .10				
204 .11				Yield = 87 MH^+ = 521 m.p. = 128.6 °C

205				Yield = 99 MH^+ = 537 m.p. = 83.5 °C
206				Yield = 94 MH^+ = 598 m.p. = 110.8 °C
207				Yield = quant. MH^+ = 545
208				Yield = 96 MH^+ = 468 m.p. = 69.2 °C

209				MH^+ = 498 m.p. = 226.5 °C
210				MH^+ = 564 m.p. = 174.2 °C

Additional data for select examples given below.

Example 23: ^{1}H NMR (CD_3OD) δ 8.63 (d, J = 5.7 Hz, 2H), 8.18 (s, 1H), 7.81 (dd, J = 8.1 Hz, 2.1 Hz, 1H), 7.58 (d, J = 6.0 Hz, 2H), 7.48 (m, 1H), 7.15-7.10 (m, 2H), 6.50 (s, 1H), 4.86 (s, 2H), 3.70 (s, 3H)

Example 24: ^{1}H NMR ($CDCl_3$) δ 8.82 (s, 1H), 8.73 (d, J = 4.2 Hz, 1H), 8.11 (s, 1H), 8.06 (dd, J = 7.8 Hz, 1.8 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 7.53-7.47 (m, 2H), 7.20 (m, 1H), 7.08 (d, J = 8.1 Hz, 1H), 6.75 (s, 1H), 4.81 (d, J = 4.5 Hz, 2H), 3.86 (s, 3H)

Example 25: ^{1}H NMR ($CDCl_3$) δ 8.75 (d, J = 5.7 Hz, 2H), 8.12 (s, 1H), 7.81 (d, J = 2.1 Hz, 1H), 7.53 (dd, J = 8.4, 2.1 Hz, 1H), 7.45 (d, J = 6.0 Hz, 2H), 6.96 (t, J = 6.0 Hz, 2H), 6.33 (s, 1H), 4.85 (d, J = 6.0 Hz, 2H), 4.09 (s, 3H), 4.03 (s, 3H)

Example 26: ^{1}H NMR ($CDCl_3$) δ 8.82 (s, 1H), 8.72 (s, 1H), 8.09 (m, 1H), 7.87-7.83 (m, 2H), 7.60 (m, 1H), 7.45 (m, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.87 (s, 1H), 6.43 (s, 1H), 4.83 (d, J = 4.5 Hz, 2H), 4.11 (s, 3H), 4.04 (s, 3H)

Example 27: ^{1}H NMR ($CDCl_3$) δ 8.75 (d, J = 4.5 Hz, 2H), 8.19 (s, 1H), 7.63 (d, J = 7.8 Hz, 2H), 7.44-7.40 (m, 3H), 7.07 (m, 1H), 6.26 (s, 1H), 4.63 (d, J = 5.1 Hz, 2H)

Example 28: ^{1}H NMR ($CDCl_3$) δ 8.86 (s, 1H), 8.74 (m, 1H), 8.17 (s, 1H), 7.97 (m, 1H), 7.66-7.63 (m, 2H), 7.62 (m, 1H), 7.41 (m, 1H), 7.07 (m, 1H), 6.35 (s, 1H), 4.87 (d, J = 6.0 Hz, 2H)

Example 30: ^{1}H NMR ($CDCl_3$) δ 8.16 (s, 1H), 7.66-7.62 (m, 2H), 7.41 (m, 1H), 7.33-7.22 (m, 3H), 6.98 (t, J = 6.0 Hz, 1H), 6.33 (s, 1H), 4.73 (d, J = 6.0 Hz, 2H)

Example 31: ^{1}H NMR ($CDCl_3$) δ 8.13 (s, 1H), 7.66 (d, J = 7.8 Hz, 2H), 7.45-7.40 (m, 2H), 7.10-7.04 (m, 2H), 6.93 (t, J = 6.6 Hz, 1H), 6.60 (s, 1H), 4.84 (d, J = 6.6 Hz, 2H)

Example 32: ^{1}H NMR ($CDCl_3$) δ 8.16 (s, 1H), 7.66-7.62 (m, 2H), 7.57-7.55 (m, 2H), 7.41 (t, J = 7.8 Hz, 1H), 7.31 (dd, J = 7.8, 1.8 Hz, 1H), 6.99 (t, J = 6.0 Hz, 1H), 6.32 (s, 1H), 4.73 (d, J = 6.0 Hz, 2H)

Example 40: ^{1}H NMR ($CDCl_3$) δ 8.01 (s, 1H), 7.31 – 7.24 (d, J = 8.2 Hz, 1H), 6.72 – 6.64 (br t, J = 5.4 Hz, 1H), 6.62 – 6.52 (m, 2H), 6.05 – 6.01 (s, 1H), 5.56 – 4.64 (d, J = 6.0 Hz, 2H), 4.03 – 3.93 (s, 3H), 3.94 – 3.86 (s, 3H), 2.79 – 2.70 (d, J = 8.1 Hz, 2H), 2.02 – 1.66 (m, 6H), 1.43 –1.22 (m, 3H), 1.20 – 1.02 (m, 2H)

Example 45: ^{1}H NMR ($CDCl_3$) δ 8.73(d, 2H), 8.54(s, 1H), 7.41(d, 2H), 7.02(br, 1H), 5.90(s, 1H), 4.80(s, 2H), 4.48(q, 2H), 2.75(s, 2H), 1.50(t, 2H), 1.06(s, 9H);

Example 46: ^{1}H NMR ($CDCl_3$) δ 8.79(s, 1H), 8.72(d, 1H), 8.14(s, 1H), 7.84(d, 1H), 7.54-7.33(m, 4H), 6.97(t, 1H), 6.18(s, 1H), 4.79(d, 2H), 2.47(s, 3H)

Example 108: ^{1}H NMR ($CDCl_3$) δ 8.79 (s, 1H), 8.72 (d, J = 3.0 Hz, 1H), 8.16 (s, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.74 (d, J = 7.5 Hz, 2H), 7.55-7.35 (m, 3H), 6.92 (t, J = 6.3 Hz, 1H), 6.42 (s, 1H), 4.81 (d, J = 6.3 Hz, 2H)

Example 110: ^{1}H NMR ($CDCl_3$) δ 8.18(t, 1H), 8.03(s, 1H), 7.44(m, 1H), 7.30(t, 1H), 7.17(q, 1H), 6.66(s, 1H), 6.56(br, 1H), 4.28(d, 2H), 2.38(s, 1H)

Example 111: ^{1}H NMR ($CDCl_3$) δ 8.72(br, 1H), 8.59(d, 1H), 8.11(t, 1H), 8.06(s, 1H), 7.73(d, 1H), 7.44(d, 1H), 7.42-7.21(m, 3H), 7.07(q, 1H), 6.39(d, 1H), 5.21(q, 1H), 4.16(q, 2H), 3.08(d, 2H), 1.22(t, 3H)

Example 112: ^{1}H NMR ($CDCl_3$) δ 8.22(t, 1H), 8.15(s, 1H), 7.51-7.33(m, 7H), 7.21(q, 1H), 6.82(d, 1H), 6.51(s, 1H), 4.68(q, 1H), 2.18(m, 2H), 1.17(t, 3H)

Example 113: ^{1}H NMR ($CDCl_3$) δ 8.22(t, 1H), 8.14(s, 1H), 7.51-7.33(m, 7H), 7.21(q, 1H), 6.82(d, 1H), 6.51(s, 1H), 4.68(q, 1H), 2.18(m, 2H), 1.17(t, 3H)

Example 114: ^{1}H NMR ($CDCl_3$) δ 8.81(s, 1H), 8.75(d, 1H), 8.21(s, 1H), 7.84(d, 1H), 7.47(q, 1H), 6.96(s, 1H), 6.94(t, 1H), 4.85(d, 2H), 4.60(q, 2H), 1.58(t, 3H)

Example 115: ^{1}H NMR ($CDCl_3$) δ 8.77(s, 1H), 8.72(d, 1H), 8.14(s, 1H), 7.83(d, 1H), 7.65(d, 1H), 7.44(q, 1H), 7.80(t, 1H), 7.6(d, 1H), 6.18(s, 1H), 4.75(d, 2H), 3.91(s, 3H), 3.81(s, 3H)

Example 116: ^{1}H NMR ($CDCl_3$) δ 8.67(s, 1H), 8.55(d, 1H), 8.50(s, 1H), 7.92(d, 1H), 7.90(d, 1H), 7.78(t, 1H), 7.10(d, 1H), 6.97(s, 1H), 5.11(s, 2H), 3.77(s, 6H)

Example 117: ^{1}H NMR ($CDCl_3$) δ 8.38(s, 1H), 8.30(d, 1H), 8.17(s, 1H), 7.52-7.37(m, 6H), 6.97(t, 1H), 6.13(s, 1H), 4.77(d, 2H), 2.50(s, 3H)

Example 118: ^{1}H NMR ($CDCl_3$) δ 8.18(t, 1H), 8.03(s, 1H), 7.44(m, 1H), 7.30(t, 1H), 7.17(q, 1H), 6.66(s, 1H), 6.56(br, 1H), 4.28(d, 2H), 2.38(s, 1H);

Example 121: ^{1}H NMR ($CDCl_3$) δ 8.6 (S, 1H), 8.15 (dt,1H), 8.1 (s, 1H), 8.0 (d, 2H), 7.5 (d, 2H), 7.4 (dd, 1H), 7.2 (d, 1H), 7.15 (dd, 1H), 6.8 (t, 1H), 6.6 (s, 1H), 4.75 (d, 2H).

Example 126: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.5 (d, 1H), 7.42 – 7.35 (m, 2H), 7.3 –7.2 (m, 2H), 7.15 (dd, 1H), 7.1 (dd, 1H), 7.0 (t, 1H), 6.6 (s, 1H), 4.8 (d, 2H).

Example 127: ^{1}H NMR ($CDCl_3$) δ 8.2 (dt, 1H), 8.0 (s,1H), 7.4 (dd, 1H), 7.3- 7.25 (m, 3H), 7.1 (dd, 1H), 6.9 - 6.85 (m, 2H), 6.7 (t, 1H), 6.6 (s, 1H), 4.6 (d, 2H), 3.2 (m, 4H), 2.6 (m, 4H), 2.3 (s, 3H)

Example 128: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt,1H), 8.1 (s, 1H), 8.0 (d, 2H), 7.5 (d, 2H), 7.4 (m, 2H), 7.25 (d, 1H), 7.2 (s,1H), 7.15 (dd, 1H), 7.0 (s, 1H), 6.8 (t, 1H), 6.6 (s, 1H), 4.75 (d, 2H).

Example 129: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.05 (s, 1H), 8.0 (d, 2H), 7.5 (d, 2H), 7.4 (m, 1H), 7.3 (dd, 1H), 7.15 (dd, 1H), 6.9 (t, 1H), 6.5 (s, 1H), 4.75 (d, 2H), 3.85 (s, 3H)

Example 130: ^{1}H NMR ($CDCl_3$) δ 8.2 (dt,1H), 8.0 (s, 1H), 7.4 (dd, 1H), 7.3(dd, 1H), 7.15 (dd, 1H), 6.8 (t, 1H), 6.4 (s,1H), 4.2 (d, 2H), 3.8 (s, 3H).

Example 131: ^{1}H NMR ($CDCl_3$) δ 8.2 (dt, 1H), 8.0 (s,1H), 7.4 – 7.15 (m, 3H), 6.7 (t, 1H), 4.2 (q, 2H), 3.8 (dt, 2H), 2.8 (t, 2H), 1.2 (t, 3H)

Example 132: ^{1}H NMR ($CDCl_3$) δ 8.2 (dt, 1H), 8.0 (s,1H), 7.4 – 7.15 (m, 3H), 6.7 (t, 1H), 4.2 (q, 2H), 3.8 (dt, 2H), 2.8 (t, 2H), 2.05 (m, 2H) 1.2 (t, 3H)

Example 133: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s,1H), 7.4 (m, 1H), 7.3 (dd 1H), 7.2 (dd, 1H), 6.5 (s, 1H), 6.4 (t,1H), 3.7 (s, 3H), 3.5 (dd,2H),2.4 (t, 2H), 1.8 (m, 4H)

Example 134: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.95 (d, 2H), 7.6 (d, 2H), 7.4 (m, 1H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.9 (t, 1H), 6.5 (s, 1H), 4.8 (d, 2H), 3.0 (s, 3H)

Example 135: ^{1}H NMR (DMSO d6) δ 9.1 (bs, 2H), 8.4 (s,1H), 8.0 (t, 1H), 7.85 (d, 2H), 7.7 (d, 2H), 7.6 (m, 1H), 7.4 (m, 2H), 6.6 (s, 1H), 4.8 (bs, 2H)

Example 136: ^{1}H NMR ($CDCl_3$) δ 8.2 (dt, 1H), 8.0 (s,1H), 7.4 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 6.9 (m, 3H), 6.7 (t, 1H), 6.5 (s, 1H), 4.5 (d, 2H), 4.2 (s, 4H)

Example 137: ^{1}H NMR ($CDCl_3$) δ 8.2 (dt, 1H), 8.0 (s, 1H), 7.4 (m, 1H), 7.3 (dd, 1H), 7.2 (dd, 1H), 6.9 (dd, 1H), 6.8 (t, 1H), 6.7 (m, 1H), 6.6 (s, 1H), 5.3 (s, 2H), 4.85 (s, 2H), 4.6 (d, 2H).

Example 138: ^{1}H NMR ($CDCl_3$) δ 8.2 (dt, 1H), 8.0 (s, 1H), 7.9 (d,1H), 7.8 (d, 1H), 7.4 (m, 2H), 7.3 (dd, 1H), 7.1 (dd, 1H), 6.9 (t, 1H), 6.6 (s, 1H), 4.8 (d, 2H)

Example 139: ^{1}H NMR ($CDCl_3$) δ 8.2 (dt, 1H), 8.0 (s, 1H), 7.4 (m, 1H), 7.3 (m, 2H), 7.2 (dd, 1H), 7.1 (dd, 1H), 6.8 (d, 1H), 6.7 (t, 1H), 6.6(s, 1H), 4.6 (m, 4H), 3.2 (t, 2H)

Example 140: ^{1}H NMR ($CDCl_3$) δ 8.45 (s, 1H), 8.2 (dt, 1H), 8.0 (s, 1H), 7.7 (dd, 1H), 7.4 – 7.3 (m, 3H), 7.15 (dd, 1H), 6.8 (t, 1H), 6.6 (s,1H), 4.7 (d, 2H)

Example 141: ^{1}H NMR ($CDCl_3$) δ 8.2 (dt, 1H), 8.0 (s, 1H), 7.45 - 7.1 (m, 7H), 6.6 (s, 1H), 4.4 (dt, 2H), 2.6 (t, 2H), 1.8 (m, 2H), 1.4 (m, 2H)

Example 171: ^{1}H NMR (CD_3OD) δ 8.41 (s, 1H), 8.25 (d, J = 6.3 Hz, 1H), 8.15 (s, 1H), 7.67 (d, J = 7.8 Hz, 2H), 7.55-7.48 (m, 2H), 7.45 (dd, J = 7.5, 1.2 Hz, 1H), 7.34 (dd, J = 7.5, 1.8 Hz, 1H), 6.28 (s, 1H), 4.79 (s, 2H).

Example 172: ^{1}H NMR ($CDCl_3$) δ 8.64 (s, 1H), 7.68-7.64 (m, 2H), 7.52 (m, 1H), 7.43 (t, J = 7.8 Hz, 1H), 6.89 (t, J = 6.0 Hz, 1H), 6.51 (s, 1H), 6.48 (m, 2H), 4.74 (d, J = 6.0 Hz, 2H).

Example 173: ^{1}H NMR (DMSO-d_6) δ 8.86 (s, 1H), 8.46 (s, 1H), 8.32-8.28 (m, 2H), 7.97 (m, 1H), 7.87 (m, 1H), 7.52 (m, 1H), 7.35-7.24 (m, 2H), 6.57 (s, 1H), 6.46 (m, 1H), 3.65 (m, 4H).

Example 174: ^{1}H NMR ($CDCl_3$) d 8.37 (s, 1H), 8.16 (t, J = 7.5 Hz, 1H), 7.45-7.35 (m, 1H), 7.32-7.20 (m, 3H), 7.17-7.07 (m, 1H), 6.92 (t, J = 6 Hz, 1H), 6.48 (s, 1H), 4.65 (d, 2H), 2.50 (s, 3H).

Example 175: ^{1}H NMR ($CDCl_3$) d 8.16 (t, J = 9 Hz, 1H), 8.00 (s, 1H), 7.49 (d, J= 9 Hz, 1H), 7.46-7.36 (m, 1H), 7.18-7.08 (m, 1H), 7.00 (d, J = 9 Hz, 1H), 6.62-6.50 (m, 2H), 2.60 (s, 3H), 2.55 (s, 3H).

Example 176: ^{1}H NMR ($CDCl_3$) d 8.15 (t, J = 9 Hz, 1H), 8.00 (s, 1H), 7.45-7.35 (m, 1H), 7.32-7.20 (m, 1H), 7.20-7.05 (m, 3H), 6.80 (t, 1H), 6.50 (s, 1H), 4.65 (d, 2H), 2.65 (s, 3H), 2.50 (s, 3H).

Example 177: ^{1}H NMR ($CDCl_3$) d 8.20 (t, 1H), 7.90 (s, 1H), 7.50-7.05 (m, 8H), 6.80 (s, 1H), 5.05-4.90 (m, 2H), 3.80 (d, 1H), 3.45 (d, 1H), 3.00 (dd, 1H), 2.90 (dd, 1H), 2.50 (s, 3H).

Example 181: ^{1}H NMR (300MHz, $CDCl_3$) □ 8.41 (s, 1H), 8.28 – 8.23 (d, 1H), 8.15 (s, 1H), 7.89 –7.60 (d, 1H), 7.62 – 7.50 (m, 3H), 7.50 – 7.47 (dd, 1H), 6.35 (s, 1H), 5.36 (s, 1H), 4.80 (s, 2H).

Example 184: ^{1}H NMR (300MHz, $CDCl_3$) □8.96 - 8.90 (s, 1H), 8.08 (s, 1H), 8.04 (d, 1H), 7.72 (d, 1H), 7.70 – 7.61 (dd, 1H), 7.24 – 7.20 (dd, 1H), 6.92 – 6.84 (t, 1H), 6.36 (s, 1H), 4.96 – 4.89 (d, 2H).

Example 186: ^{1}H NMR (300MHz, $CDCl_3$) □8.96 - 8.90 (s, 1H), 8.08 (s, 1H), 8.44 (s, 1H), 8.27 – 8.24 (d, 1H), 8.02 (s, 1H), 7.78 – 7.76 (d, 1H), 7.73 – 7.70 (d, 1H), 7.58 – 7.51 (m, 2H), 7.13 –7.08 (dd, 1H), 5.51 (s, 2H).

Example 195: ^{1}H NMR (CD_3OD) δ 8.40(s, 1H), 8.27(d, 1H), 8.03(s, 1H), 7.75-7.50(m, 2H), 6.10(s, 1H), 4.76(s, 2H), 4.05(m, 2H), 3.88(m, 2H), 3.52(m, 1H), 2.33(m, 1H), 2.20(m, 1H).

Example 196: ^{1}H NMR (CD_3OD) δ 8.73(d, 1H), 8.58(q, 1H), 8.12(s, 1H), 8.00(d, 1H), 7.54(q, 1H), 6.19(s, 1H), 4.86(s, 2H), 4.22-4.08(m, 2H), 4.03-3.93(m, 2H), 3.63(m, 1H), 2.50-2.39(m, 1H), 2.32-2.21(m, 1H).

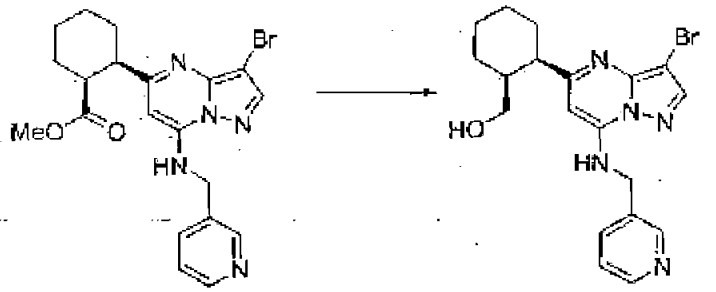
Example 197: ^{1}H NMR (CD_3OD) δ 8.73(d, 1H), 8.58(q, 1H), 8.12(s, 1H), 8.00(d, 1H), 7.54(q, 1H), 6.19(s, 1H), 4.86(s, 2H), 4.22-4.08(m, 2H), 4.03-3.93(m, 2H), 3.63(m, 1H), 2.50-2.39(m, 1H), 2.32-2.21(m, 1H).

Example 199: ^{1}H NMR (300MHz, $CDCl_3$) □8.29 (s, 1H), 8.15 (br s, 1H), 7.95 (s, 1H), 7.28 (d, 1H), 7.05 - 6.95 (appt t, 1H), 5.70 (s, 1H), 4.62 (d, 2H), 2.90 (m, 1H), 2.30 (m, 1H), 1.9 – 1.2 (m, 8H), 0.65 (d, 3H).

Example 200: ^{1}H NMR (300MHz, $CDCl_3$) □ 8.71 (s, 2H), 8.00 (s, 1H), 6.13 (s, 1H), 3.59 (s, 2H), 3.01 – 2.58 (m, 1H), 2.51 – 2.45 (m, 1H), 2.44 –2.30 (m,1H), 2.20 (s, 3H), 2.09 – 1.95 (m, 2H), 1.85 –1.70 (m, 2H), 0.80 – 0.76 (d, 3H).

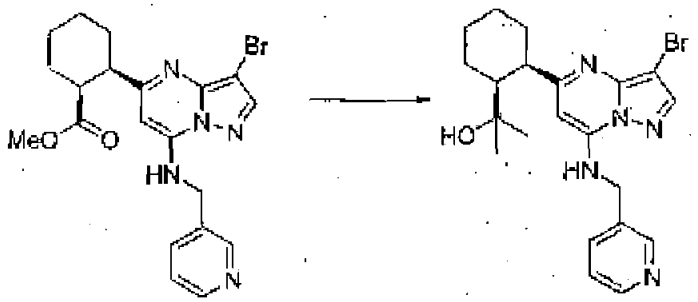
Example 203: ^{1}H NMR (300MHz, $CDCl_3$) □8.10 (s, 1H), 8.08 (s, 1H), 6.27 (s, 2H), 4.95 (s, 2H), 3.00 – 2.90 (dd, 2H), 2.60 (m, 2H), 2.48 (br s, 1H), 2.39 (s, 3h), 2.25 m, 1H), 1.95 – 1.70 (m, 3H).

EXAMPLE 211:



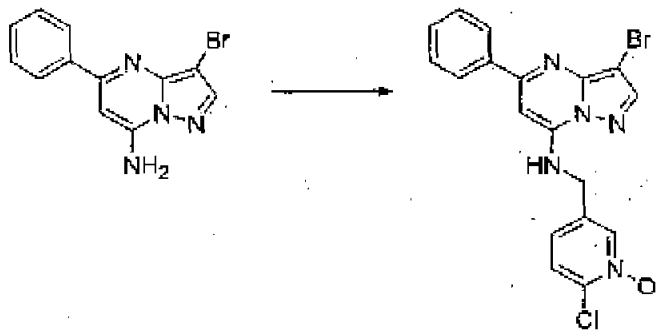
To a solution of the compound prepared in Example 156 (100 mg, 0.23 mmol) in dry THF (4 mL) was added $LiAlH_4$ (1.0 M in THF, 0.110 mL, 0.110 mmol) at 0°C under N_2. The mixture was stirred at 0°C for 1hr, warmed to 25°C, then additional $LiAlH_4$ (1.0 M in THF, 0.400 mL) was added, the mixture was stirred for 20 min and then quenched with MeOH (2.0 mL). The solvent was evaporated and the crude product was purified by flash chromatography using 10:1 CH_2Cl_2:MeOH as eluent. White solid (46 mg, 48%) was obtained. LCMS: M^+= 416. Mp=71-72 °C.

EXAMPLE 212:



To a solution of the compound prepared in Example 156 (70 mg, 0.16 mmol) in dry THF (3 mL) was added MeMgBr (3.0 M in Et_2O, 1.10 mL, 3.20 mmol) under N_2. The mixture was stirred at 25°C for 45 min and then quenched with saturated aqueous NH_4Cl (5.0 mL). The mixture was poured into saturated aqueous NH_4Cl (30 mL) and extracted with CH_2Cl_2 (3x20 mL). The extracts were dried over Na_2SO_4 and filtered. The solvent was evaporated and the crude product was purified by flash chromatography using 20:1 CH_2Cl_2:MeOH as eluent. White solid (25 mg, 36%) was obtained. LCMS: M^+= 444. Mp=76-80 °C.

EXAMPLE 213:



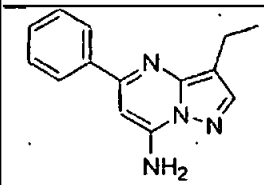
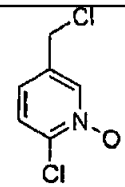
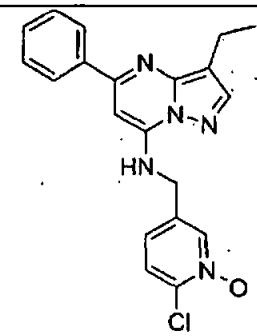
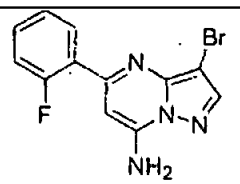
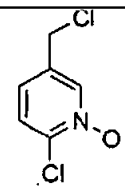
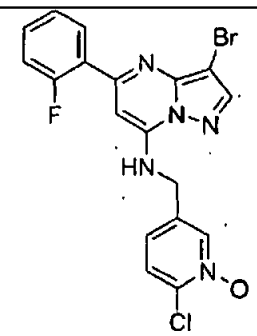
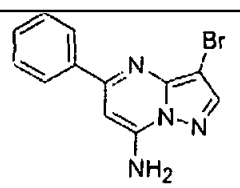
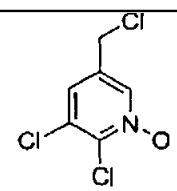
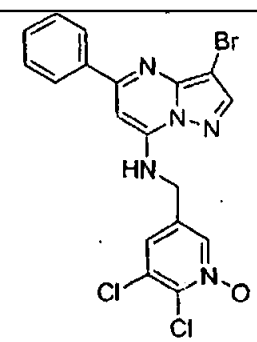
Anhydrous DMF (40 mL) was added under N_2 to the compound prepared in Preparative Example 174 (2.50 g, 8.65 mmol) and 60 % NaH in mineral oil (346 mg, 8.65 mmol). The mixture was stirred at 25°C for 1 hr, then 2-chloro-5-chloromethylpyridine N-oxide (1.54 g, 8.65 mmol) in anhydrous DMF (20 mL) was added slowly. The mixture was stirred at 25°C for 18 hr, the solvent was evaporated and the crude product was purified by flash chromatography using

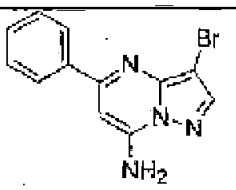
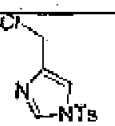
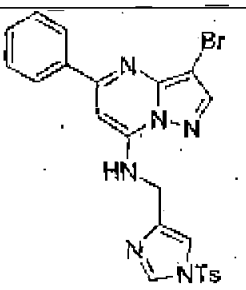
30:1 CH_2Cl_2:MeOH as eluent. So obtained solid was triturated by 50 mL of 1:1 EtOAc: hexane. Pale yellow solid (1.25 g, 34%) was obtained. LCMS: MH^+=432. Mp=224-226 °C.

EXAMPLES 214-217:

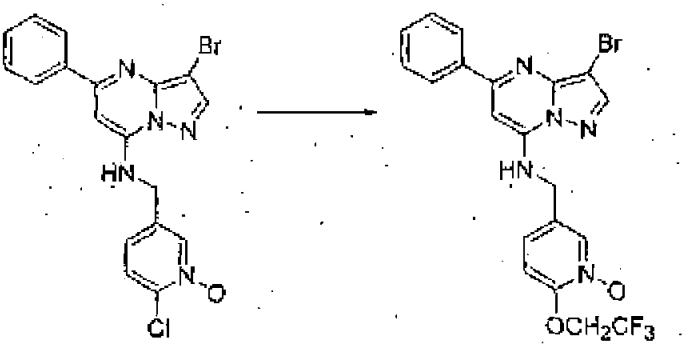
By essentially the same procedure set forth in Example 213 combining the compounds shown in Column 2 of Table 19 with compounds in Column 3 of Table 19, the compounds shown in Column 3 of Table 19 were prepared.

TABLE 19

Ex.	Column 2	Column 3	Column 4	CMPD
214				LCMS: MH^+=380; mp=°C
215				LCMS: MH^+=450; mp=218-222°C
216				LCMS: MH^+=466; mp=126-128°C

217				LCMS: M^+=523

EXAMPLE 218:



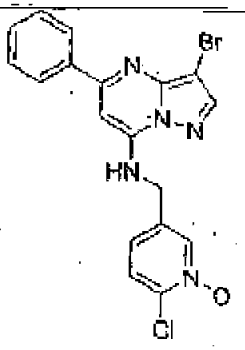
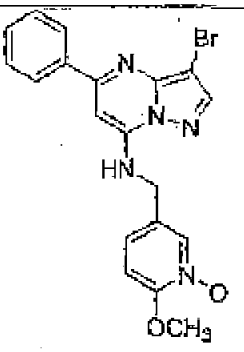
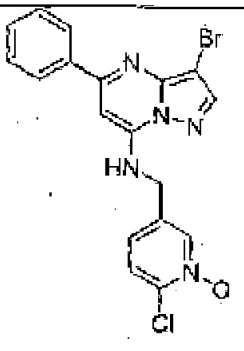
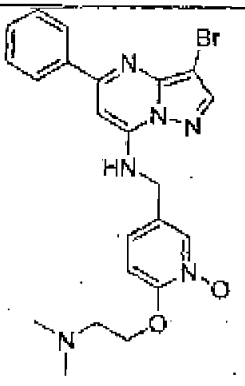
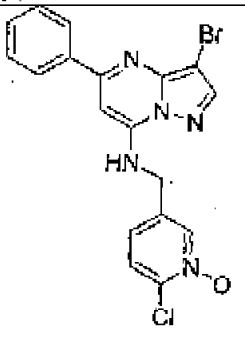
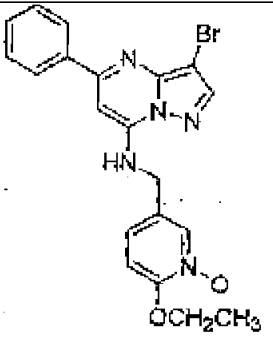
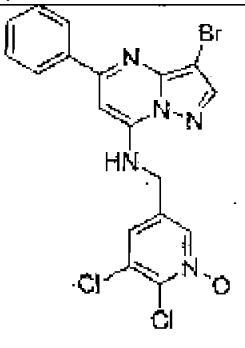
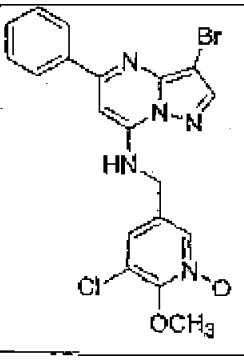
CF_3CH_2OH (3.0 mL) was added under N_2 to 60% NaH in mineral oil (40 mg, 1.0 mmol), the mixture was stirred for 20 min, then the product prepared in Example 213 (50 mg, 0.12 mmol) was added. The mixture was refluxed for 20 hr, the solvent was evaporated, and the residue was purified by flash chromatography using 20:1 CH_2Cl_2:MeOH as eluent to yield pale yellow solid (35 mg, 61%). LCMS: $M2H^+$=496. Mp=208-210 °C.

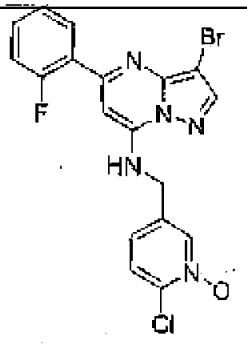
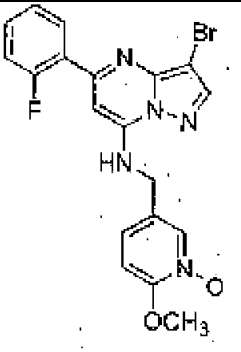
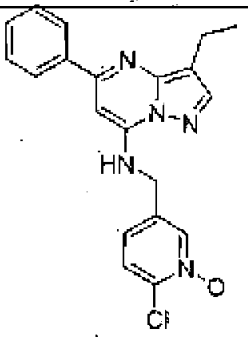
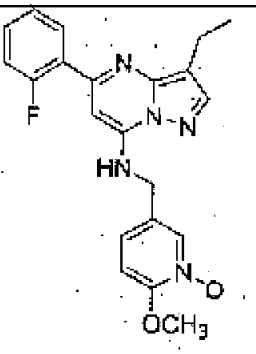
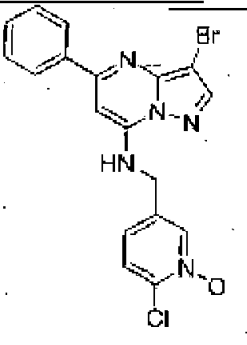
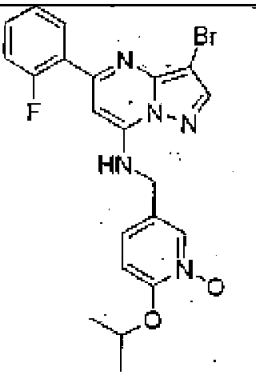
EXAMPLES 219-225:

By essentially the same procedure set forth in Example 218 combining the compounds shown in Column 1 of Table 20 with the appropriate alcohol , the compounds shown in Column 2 of Table 20 were prepared.

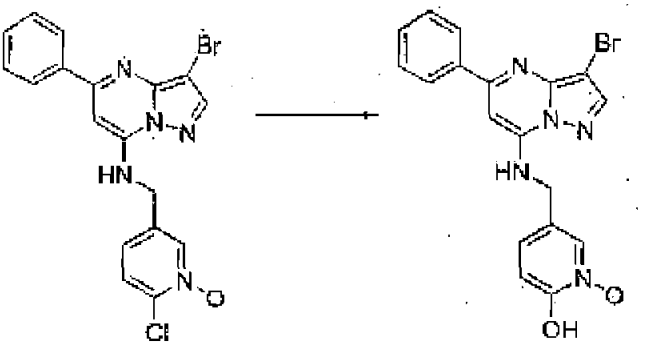
TABLE 20

Ex.	Column 1	Column 2	Data

219			LCMS: M^+=426; mp=126-128°C
220			LCMS: M^+=483; mp=89-91°C
221			LCMS: $M2H^+$=442 ; mp=112-114°C
222			LCMS: MH^+=462; mp=121-123°C

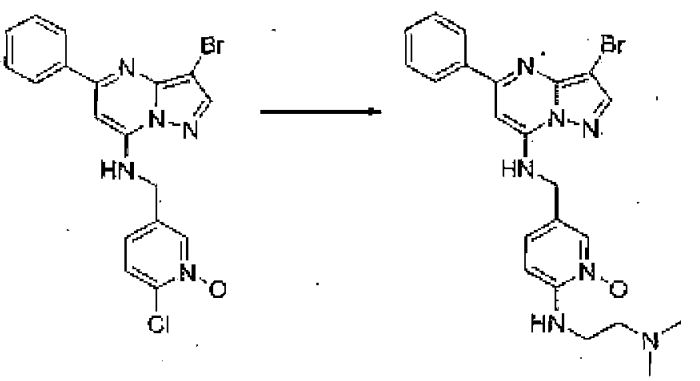
223			LCMS: MH^+=444; mp=112-114°C
224			LCMS: M^+=376; mp=°C
225			LCMS: MH^+=; mp=°C

EXAMPLE 226:



A mixture of the product prepared in Example 213 (100 mg, 0.23 mmol) and KOH (95 mg, 1.70 mmol) in 1,2-dimethoxyethane (3mL) and H_2O (1.5 mL) was refluxed under N_2 for 20 hr, quenched with acetic acid (0.30 mL), and the solvent was evaporated. The residue was suspended in H_2O (15 mL), filtered and the solid was washed with H_2O (15 mL) and Et_2O (10 mL). Then it was mixed with CH_2Cl_2 (2 mL) and Et_2O (2 mL) and filtered. Et_2O (5 mL) was added to the filtrate and the mixture was allowed to stand overnight. The solid was removed by filtration, washed with Et_2O and then dissolved in MeOH (5 mL). The solution was filtered and the solvent from the filtrate was evaporated. Off-white solid (5 mg, 5%) was obtained. LCMS: M^+=412. Mp= 206-208°C.

EXAMPLE 227:



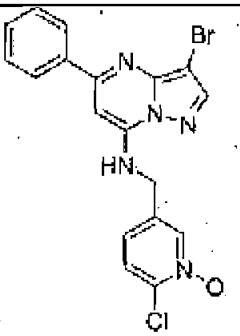
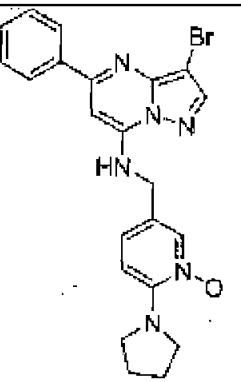
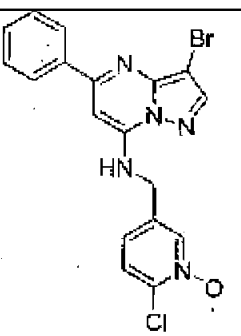
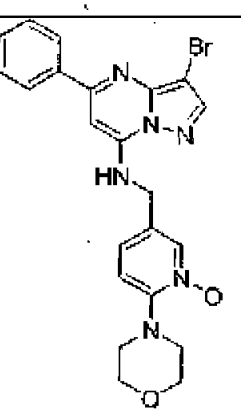
A mixture of the product prepared in Example 213 (129 mg, 0.30 mmol), N,N-dimethylethylenediamine (0.165 mL, 1.50 mmol), and diisopropylethylamine (0.10 mL) in anhydrous N-methylpyrrolidinone (1.0 mL) was stirred at 100°C for

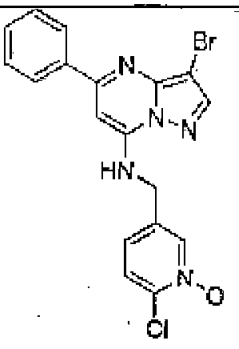
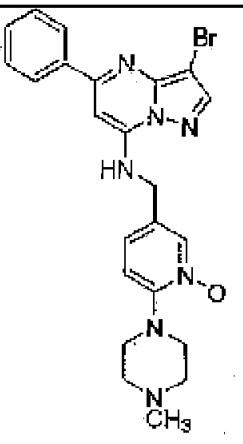
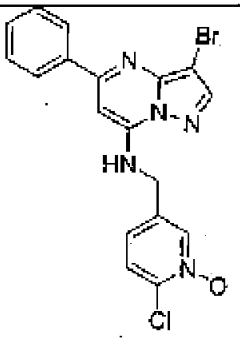
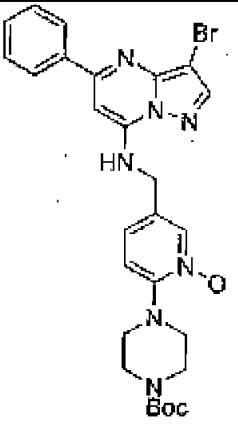
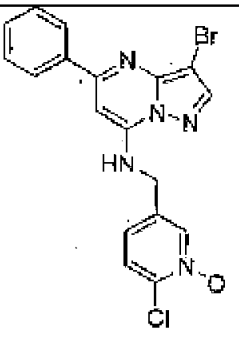
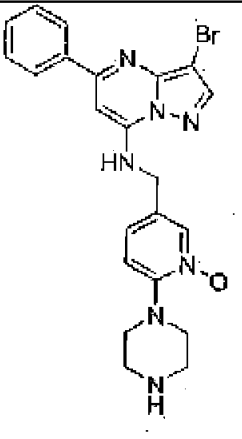
24 hr. The solvent was evaporated, and the residue was purified by flash chromatography using 20:1 CH_2Cl_2: 7N NH_3 in MeOH as eluent to yield pale yellow solid (110 mg, 76%). LCMS: M^+=482. Mp=76-78 °C.

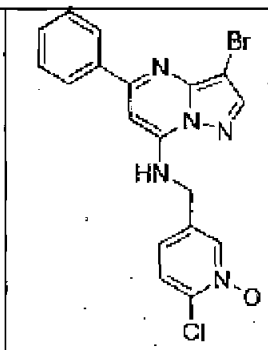
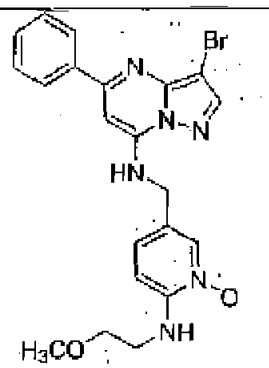
EXAMPLES 228-233:

By essentially the same procedure set forth in Example 227 combining the compounds shown in Column 1 of Table 21 with the appropriate amine, the compounds shown in Column 2 of Table 21 were prepared.

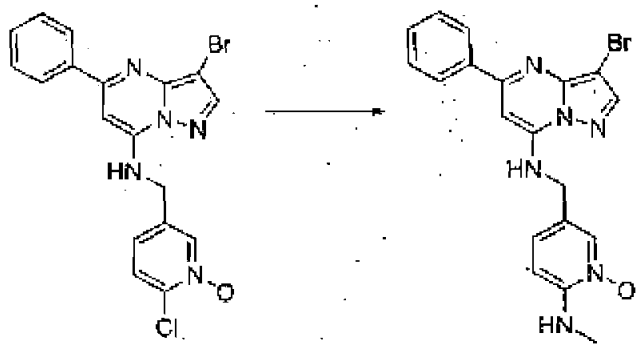
TABLE 21

Ex.	Column 1	Column 2	Data
228			LCMS: $M2H^+$=467 ; mp126-128=°C
229			LCMS: M^+=481; mp=128-130°C

230			LCMS: M^+=494; mp=108-110°C
231			LCMS: $M2H^+$=482 ; mp=129-133°C
232			LCMS: $M2H^+$=482 ; mp=124-126°C

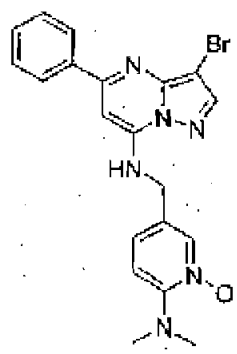
233			LCMS: $M2H^+$=471 ; mp=88-90°C

EXAMPLE 234:



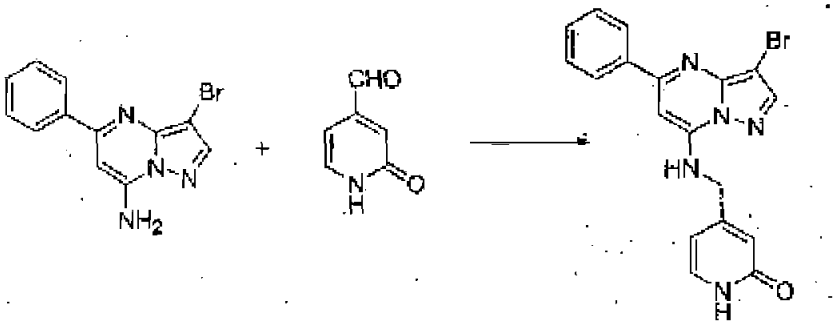
A mixture of the product prepared in Example 213 (80 mg, 0.19 mmol) and 2.0 M methylamine in THF was stirred in a closed pressure vessel at 50°C for 72 hr. The solvent was evaporated, and the residue was purified by flash chromatography using 10:1 CH_2Cl_2: MeOH as eluent to yield pale yellow solid (40 mg, 51%). LCMS: $M2H^+$=427. Mp=217-219 °C.

EXAMPLE 235:



By essentially the same procedure set forth in Example 234, the compound shown above was prepared. LCMS: $M2H^+$=441. Mp=98-101 °C.

EXAMPLE 236:



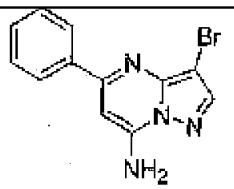
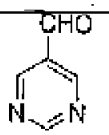
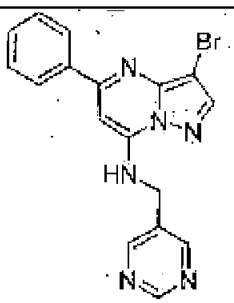
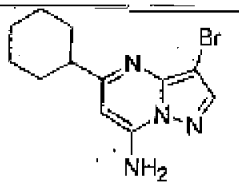
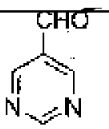
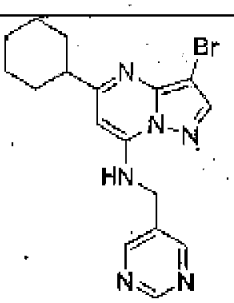
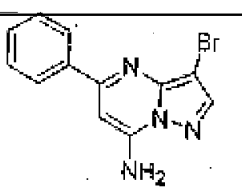
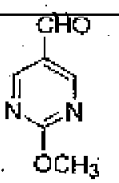
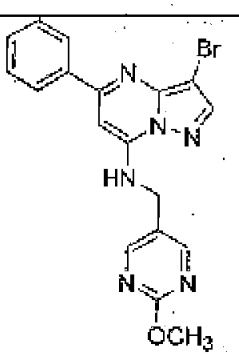
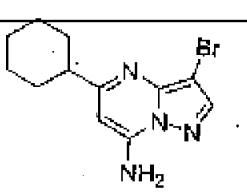
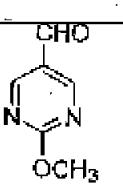
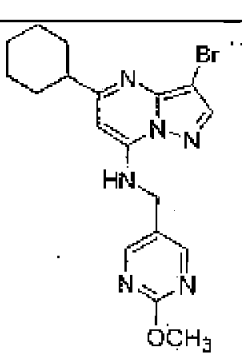
The compound prepared in Preparative Example 174 (140 mg, 0.48 mmol) and the aldehyde (71 mg, 0.58 mmol) were stirred in anhydrous THF (4 mL) at 50°C under N_2. $Ti(OiPr)_4$ (0.574 mL, 1.92 mmol) was added, the mixture was stirred at 50°C 3 hr, and cooled to 25°C. $NaBH_3CN$ (181 mg, 2.88 mmol) was added, the mixture was stirred for 2 more hr, then poured into 10 % aqueous Na_2CO_3 (100 mL), and extracted with CH_2Cl_2 (3 x 50 mL). Combined extracts were dried over Na_2SO_4, filtered, and the solvent was evaporated. The residue was purified by flash chromatography using 15:1 CH_2Cl_2:MeOH as eluent to yield pale yellow solid (40 mg, 21%). LCMS: MH^+=398. Mp>230 °C.

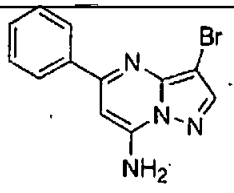
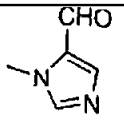
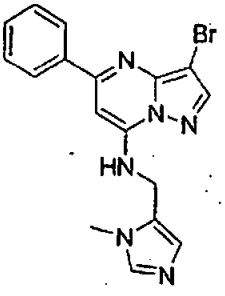
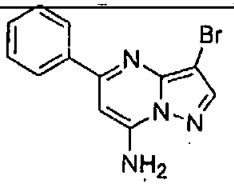
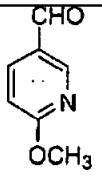
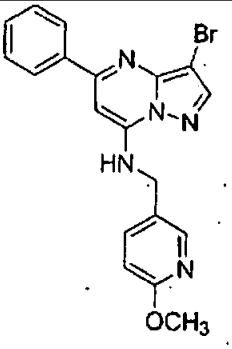
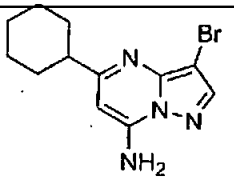
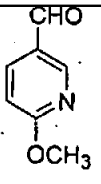
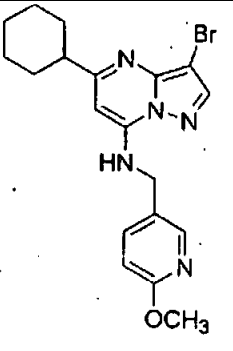
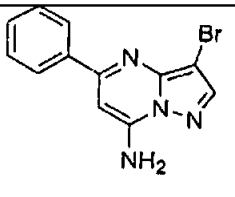
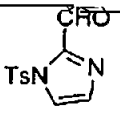
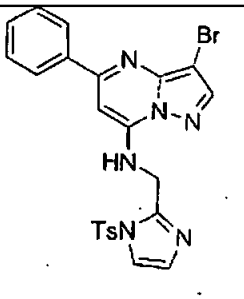
EXAMPLES 237-256:

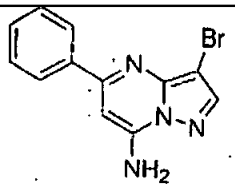
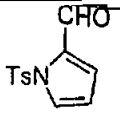
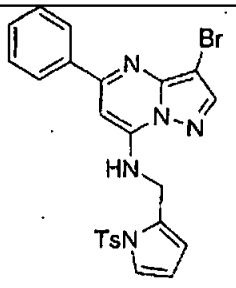
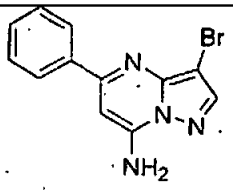
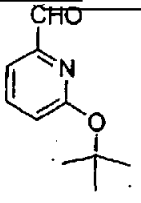
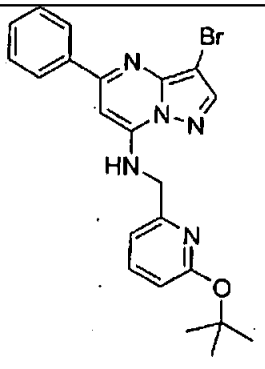
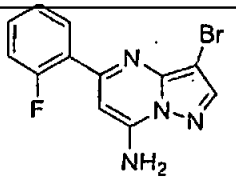
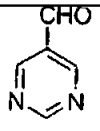
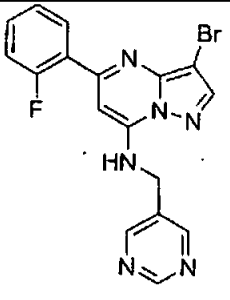
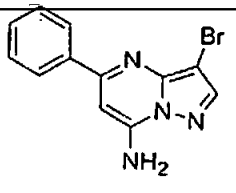
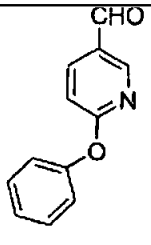
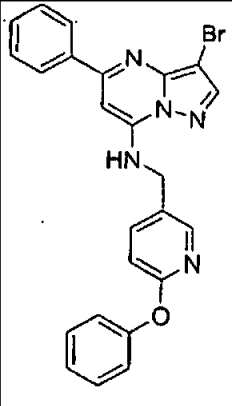
By essentially the same procedure set forth in Example 236 combining the compounds shown in Column 2 and 3 of Table 22, the compounds shown in Column 4 of Table 22 were prepared.

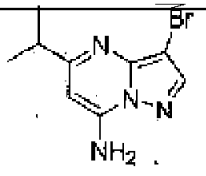
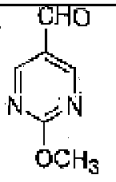
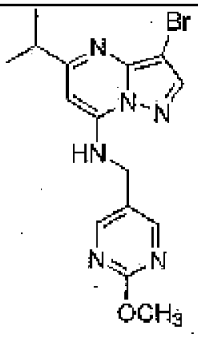
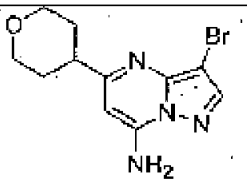
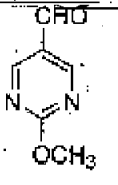
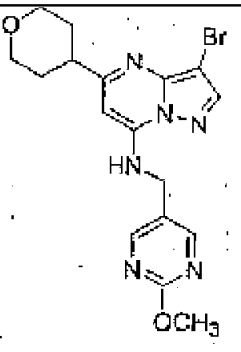
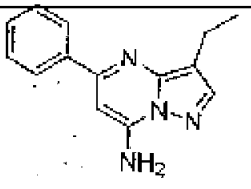
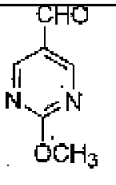
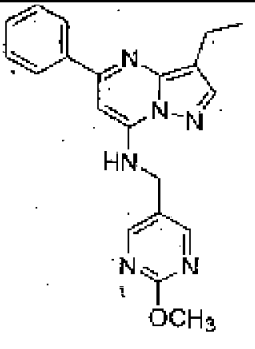
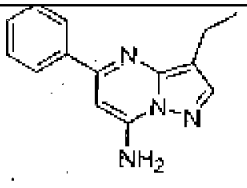
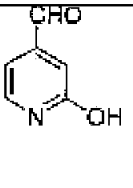
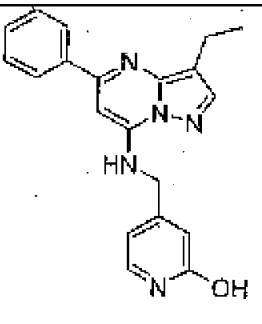
TABLE 22

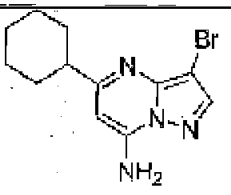
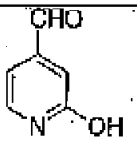
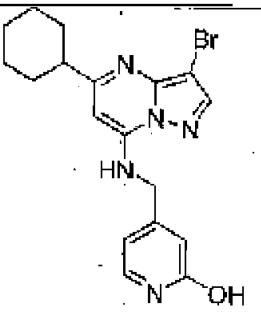
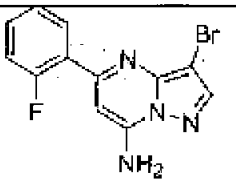
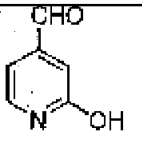
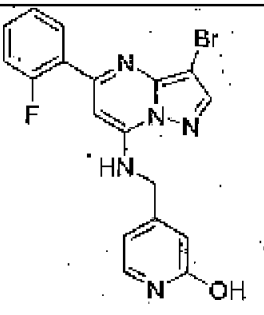
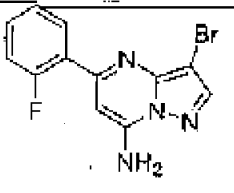
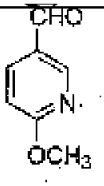
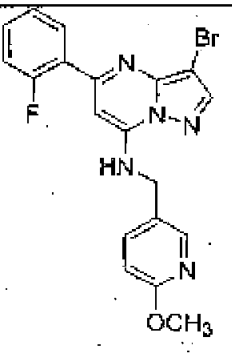
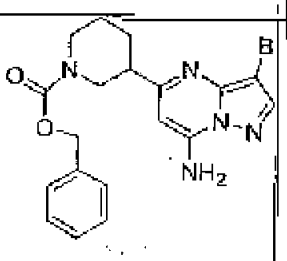
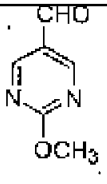
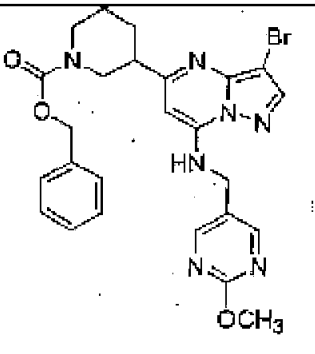
Ex.	Column 2	Column 3	Column 4	Data

237				LCMS: M^+=381; mp>200°C
238				LCMS: M^+=387; mp=°C
239				LCMS: MH^+=413; mp=157-159°C
240				LCMS: $M2H^+$=419; mp=77-79°C

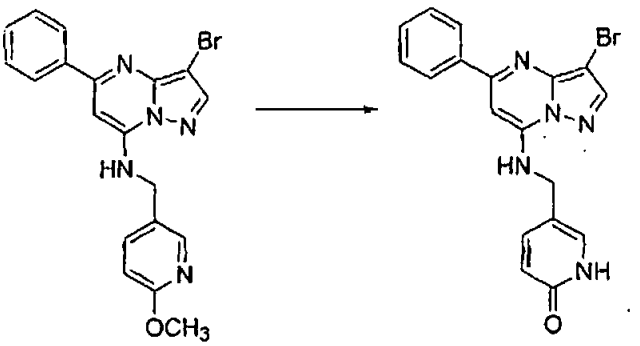
241				LCMS: $M2H^+$=385 ; mp=214-216°C
242				LCMS: MH^+=; mp=°C
243				LCMS: M^+=416; mp=80-82°C
244				

245				
246				LCMS: M^+=452; mp=54-56°C
247				LCMS: MH^+= 401; mp>200°C
248				LCMS: $M2H^+$= 474; mp>200.0. °C dec.

249				LCMS: MH^+= 377; mp= 65-67°C
250				LCMS: $M2H^+$=421; mp=87-93°C
251				LCMS: MH^+=361; mp>225°C
252				LCMS: MH^+=346; mp=270-271°C

253				LCMS: MH^+=402; mp=250-255°C
254				LCMS: MH^+=416; mp=210-215°C
255				LCMS: MH^+=428; mp=145°C
256				LCMS: MH^+=; mp=°C

EXAMPLE 257:

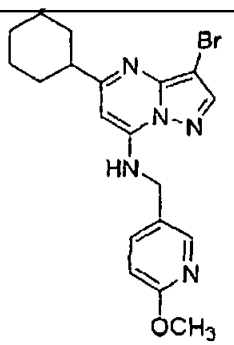
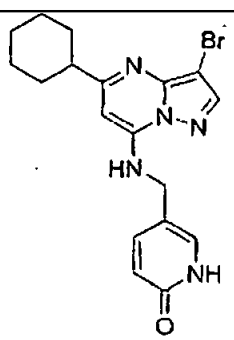


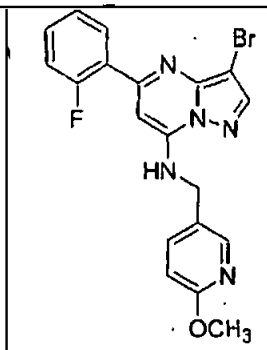
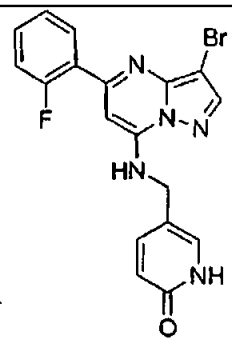
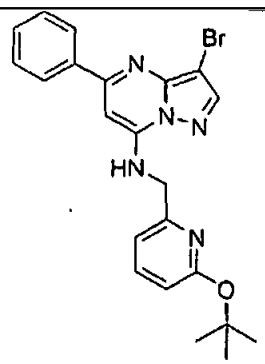
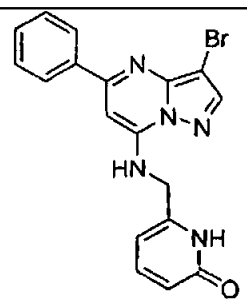
A mixture of the compound prepared in Example 242 (100 mg, 0.24 mmol), conc. aqueous HCl (1.0 mL) and acetic acid (2.0 mL) were stirred at 100°C under N_2 for 2 hr, then poured onto Na_2CO_3 (15 g), and extracted with 1:1 acetone:CH_2Cl_2 (3 x 30 mL). Combined extracts were filtered, and the solvent was evaporated. The residue was purified by flash chromatography using 10:1 CH_2Cl_2:MeOH as eluent to yield pale yellow solid (36 mg, 37%). LCMS: $M2H^+$=398.

EXAMPLES 258-260:

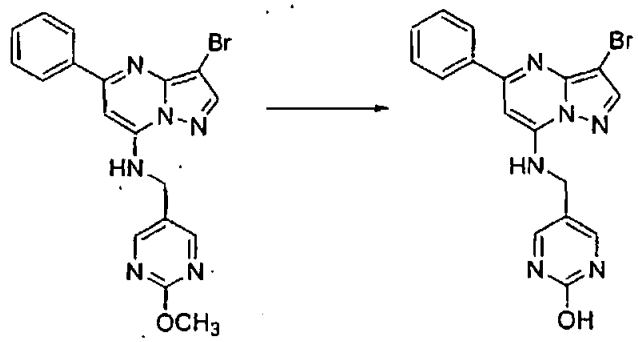
By essentially the same procedure set forth in Example 257 starting from the compounds shown in Column 1 of Table 23, the compounds shown in Column 2 of Table 23 were prepared.

TABLE 23

Ex.	Column 1	Column 2	Data
258			LCMS: M^+=402; mp=229-231°C

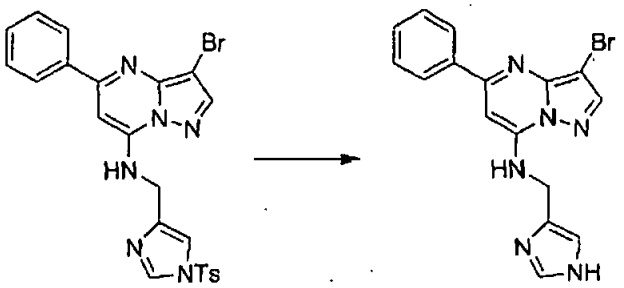
259			LCMS: MH^+=416; mp=215-218°C
260			LCMS: $M2H^+$=398 mp>230°C

EXAMPLE 261:



To a stirred solution of the compound prepared in Example 239 (41 mg, 0.10 mmol) in CH_2Cl_2 was added 1.0 M BBr_3 (0.30 mL, 0.30 mmol) in CH_2Cl_2 at -78°C. The mixture was stirred at -78°C for 5 min, then at 24°C for 3 hr, then MeOH (2.0 mL) was added and the mixture was stirred for 10 min. The solvent was evaporated and the residue was purified by flash chromatography using 5:1:0.1 CH_2Cl_2:MeOH:conc. NH_4OH as eluent to yield white solid (39 mg, 99%). LCMS: M^+=397. Mp>230 °C.

EXAMPLE 262:

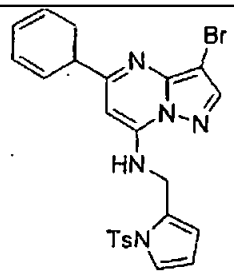
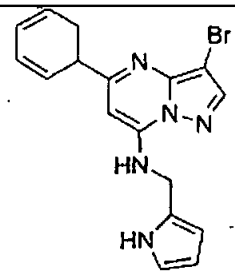


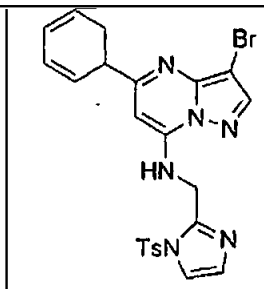
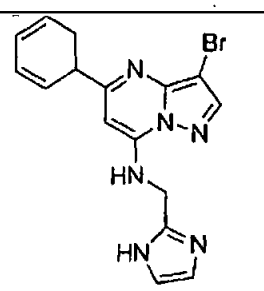
A mixture of the product prepared in Example 217 (40 mg, 0.077 mmol) and 5.0 M aqueous NaOH (0.8 mL) in MeOH (3.0 mL) was refluxed under N_2 for 1 hr. $NaHCO_3$ (700 mg) was added, the solvent evaporated, and the residue was purified by flash chromatography using 10:1:0.1 CH_2Cl_2: MeOH: conc. NH_4OH as eluent to yield white solid (10 mg, 35%). LCMS: $M2H^+$=371. Mp=237-239 °C.

EXAMPLES 263-264:

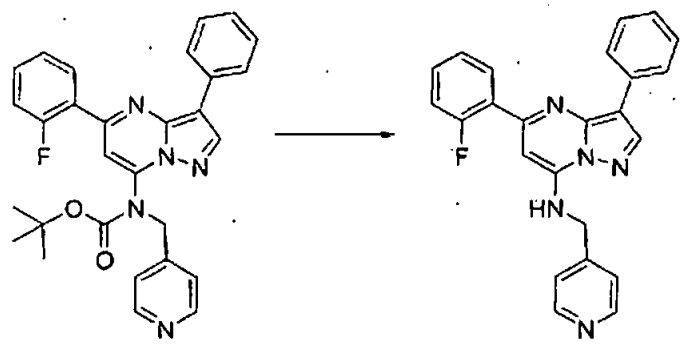
By essentially the same procedure set forth in Example 262 starting from the compounds shown in Column 1 of Table 24, the compounds shown in Column 2 of Table 24 were prepared.

TABLE 24

Ex.	Column 1	Column 2	Data
263			LCMS: $M2H^+$=370 ; mp=166-168°C

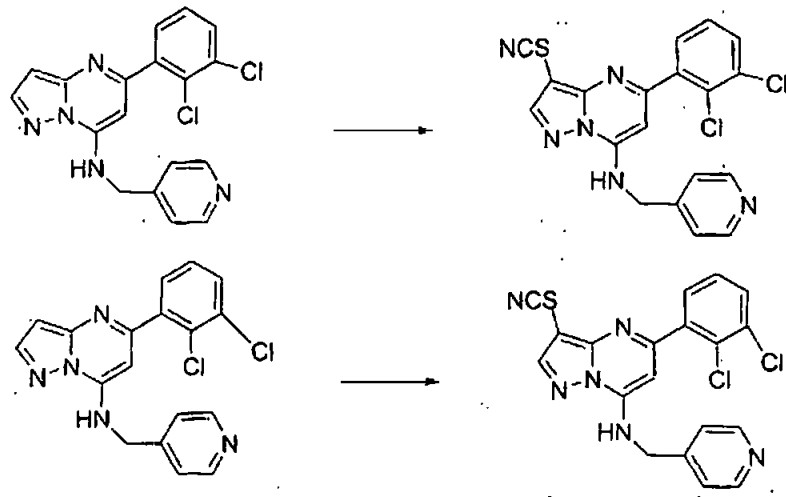
264			LCMS: $M2H^+$=371 ; mp=180-182°C

EXAMPLE 265:



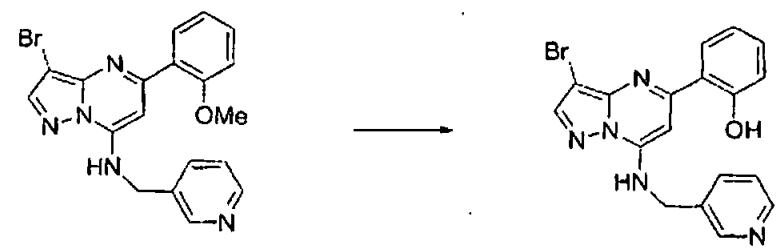
TFA (0.5 mL) was added to a solution of the compound prepared in Preparative Example 197 (0.08 g, 0.16 mmol) in CH_2Cl_2 (2.0 mL) at 0°C and the resulting solution stirred 2.5 hours and stored at 4°C overnight at which time additional TFA (0.5 mL) was added. The resulting solution was stirred 4 hours and concentrated *in vacuo*. The residue was neutralized with 1N NaOH and extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 2.5% (10% NH_4OH in MeOH) in CH_2Cl_2 solution as eluent (0.009 g, 15% yield). LCMS: MH^+=396; mp= 53-54°C.

EXAMPLE 266:



A solution of the compound prepared in Preparative Example 182 (26 mg, 0.070 mmol) and potassium thiocyanate (13 mg, 0.14 mmol) in MeOH (1 mL) was cooled in a cold water bath. To it was added a solution of bromine (22 mg, 0.14mmol) in MeOH (0.7 mL) dropwise. The resulting reaction mixture was stirred for 4 h at room temperature and the volatiles were removed under reduced pressure. The residue obtained was suspended in a small amount of CH_2Cl_2. The potassium bromide was filtered off and pH of the filtrate was adjusted to about 7 by the addition of aqueous ammonia. It was concentrated under reduced pressure and the residual oil was purified by preparative thin-layer chromatography using 15% MeOH in CH_2Cl_2 as eluent (26 mg, 87% yield). ^{1}H NMR ($CDCl_3$) δ 8.75 (d, J = 4.2 Hz, 2H), 8.38 (s, 1H), 7.68-7.64 (m, 2H), 7.46-7.39 (m, 3H), 7.22 (t, J = 6.3 Hz, 1H), 6.43 (s, 1H), 4.84 (d, J = 6.3 Hz, 2H); LCMS: MH^+ = 427.

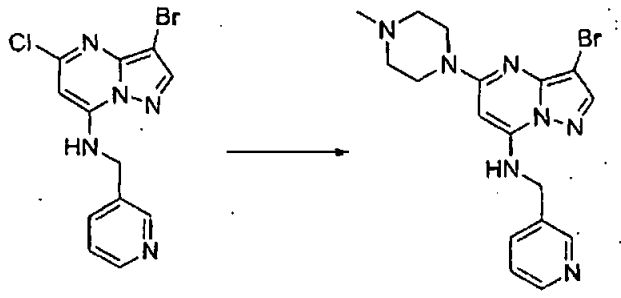
EXAMPLE 267:



Boron tribromide (1 M in CH_2Cl_2, 0.60 mL, 0.60 mmol) was added dropwise to an ice-cold stirred solution of the compound prepared in Example 24 (50 mg, 0.12 mmol) in CH_2Cl_2 (1.5 mL) under an argon atmosphere. The

resulting reaction mixture was stirred at 0°C for 30 minutes, allowed to warm up to room temperature, and stirred overnight. The mixture was quenched by the addition of a small amount of water and extracted with CH_2Cl_2. The organic layer was dried over magnesium sulfate and concentrated *in vacuo* (45 mg, 94% yield). ^1H NMR (CD_3OD) δ 9.16 (s, 1H), 8.95 (s, 1H), 8.88 (d, J = 8.1 Hz, 1H), 8.24 (t, J = 6.9 Hz, 1H), 8.18 (s, 1H), 7.95 (d, J = 7.8 Hz, 1H), 7.40 (t, J = 7.8 Hz, 1H), 7.00-6.96 (m, 2H), 6.86 (s, 1H), 5.28 (s, 2H); LCMS: MH^+ = 396.

EXAMPLE 268:



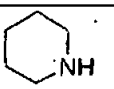
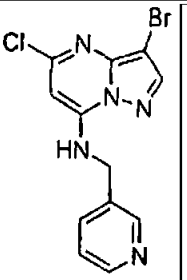
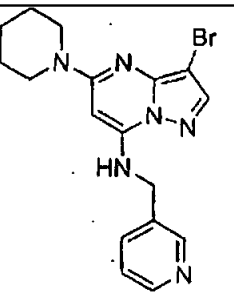
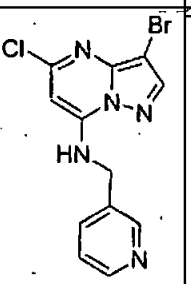
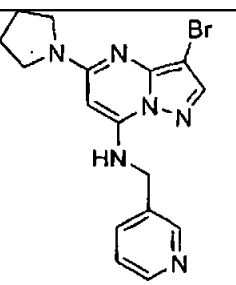
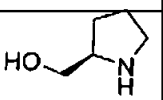
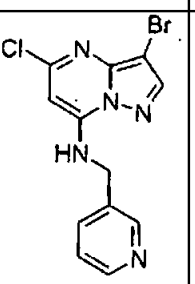
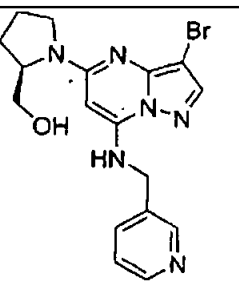
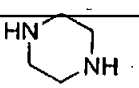
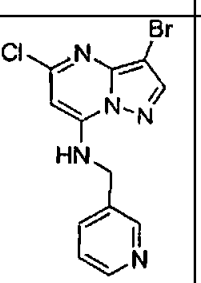
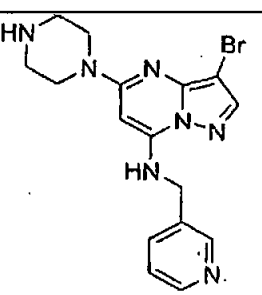
A solution of the compound from Preparative Example 184 (0.05 g, 0.15 mmol), N-methylpiperazine (20 μL, 1.2 eq.) and iPr_2Et (52 μL, 2.0 eq.) in dioxane (1 mL) was heated to 70 °C overnight. The reaction mixture was cooled to room temperature and diluted with H_2O and saturated $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2, the combined organics dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by Preparative TLC using a 5% (10% NH_4OH in MeOH) in CH_2Cl_2 solution as eluent (0.028 g, 47% yield). MS: MH^+= 402. mp = 210 °C (dec.)

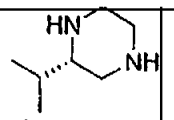
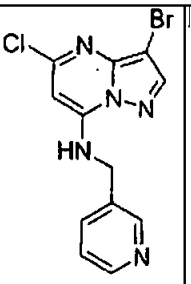
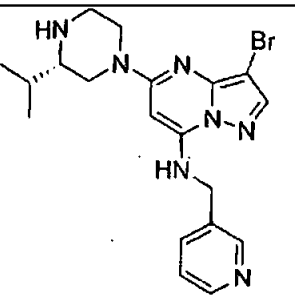
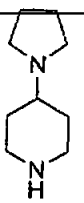
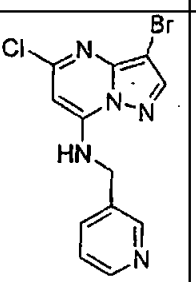
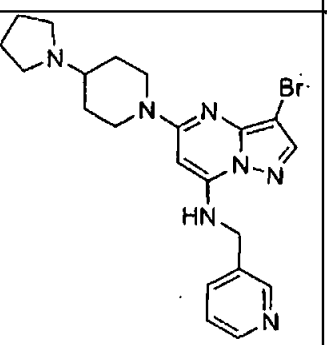
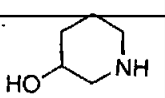
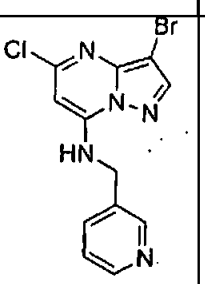
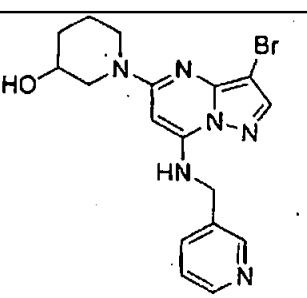
EXAMPLES 269-275:

By essentially the same procedure set forth in Example 268 only substituting the amine in Column 2 of Table 25 and the chlorides in Column 3 of Table 25, the compounds shown in Column 4 of Table 25 are prepared:

TABLE 25

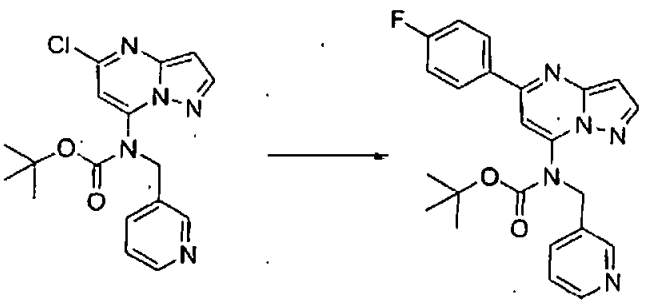
Ex.	Column 2	Column 3	Column 4	CMPD

269				MS: MH^+ = 387 m.p. 182 – 183°C
270				MS: MH^+ = 373 m.p. 190 – 191 °C
271				MS: MH^+ = 403 m.p. 227 – 230 °C
272				MS: MH^+ = 388 m.p. 198 – 201 °C

273				MS: MH^+ = 430 m.p. 100-103 °C
274				MS: MH^+ = 456 m.p. 175 – 178 °C
275				MS: MH^+ = 403 m.p. 218 °C

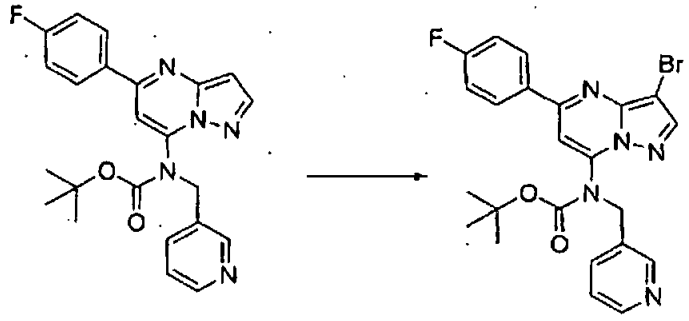
EXAMPLE 276:

Step A:



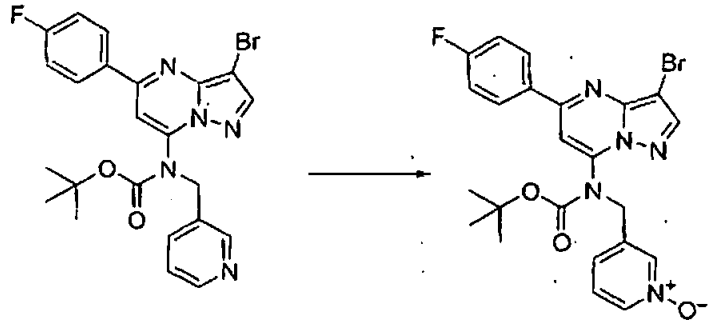
4-Fluorophenyl magnesium bromide (0.68 mL, 1.2 eq.) was added to the compound prepared in Preparative Example 193 (0.20 g, 0.55 mmol) and $PdCl_2(dppf)_2$ (0.037 g, 10 mol%) in THF and the resulting solution was stirred at room temperature 72 hours. The reaction mixture was dilute with saturated NH_4Cl and extracted with EtOAc. The combined organics were washed with saturated NaCl, dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash chromatography using neat EtOAc as eluent (0.15 g, 65% yield). MS: MH^+ = 420.

Step B:



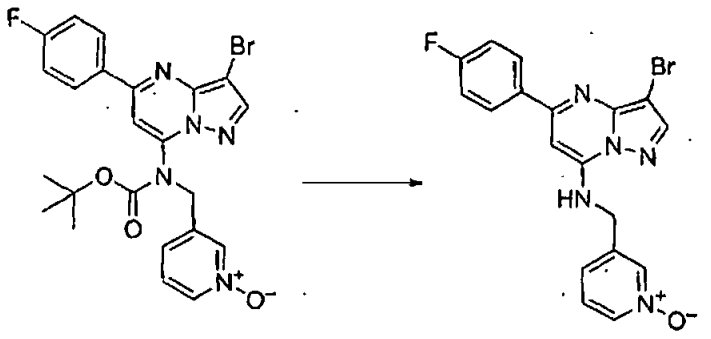
By essentially the same procedure set forth in Preparative Example 127 only substituting the compound prepared in Example 276, Step A, the above compound was prepared (0.17 g, 94% yield).

Step C:



By essentially the same procedure set forth in Preparative Example 200 only substituting the compound prepared in Example 276, Step B, the above compound was prepared (0.1g, 100% yield).

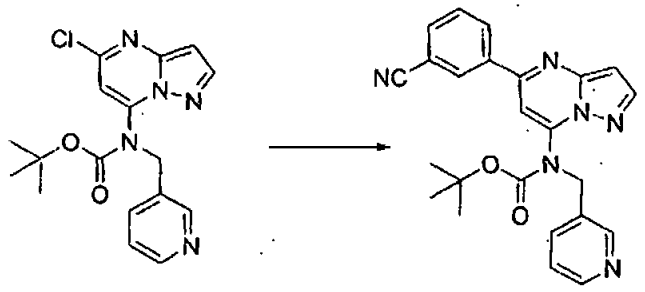
Step D:



By essentially the same procedure set forth in Example 265 only substituting the compound prepared in Example 276, Step C, the above compound was prepared (0.049 g, 62% yield). MS: MH^+ = 414; mp = 110-115 °C.

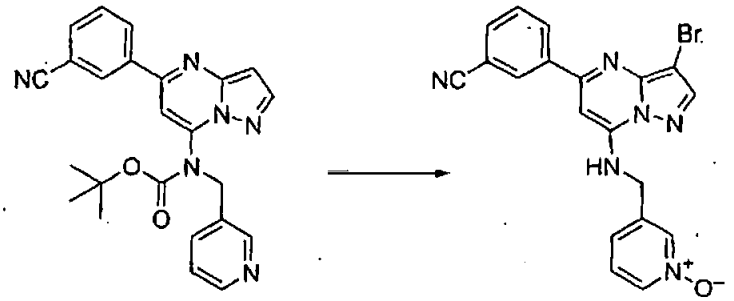
EXAMPLE 277:

Step A:



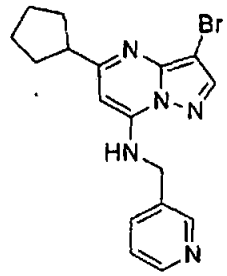
$Pd(PPh_3)_4$ (0.065 g, 10 mol%) was added to 3-cyanophenyl zinc iodide (2.2 mL, 0.5 M solution in THF, 2 eq.) and the compound prepared in Preparative Example 193 (0.2 g, 0.56 mmol) in DMF (2.0 mL) and the resulting solution heated to 80 °C g for 144 hours. The reaction mixture was cooled to room temperature, diluted with saturated NH_4Cl and extracted with EtOAc. The combined organics were washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using a neat EtOAC solution as eluent (0.07 g, 29% yield). MS: MH^+ = 427.

Step B through Step D:



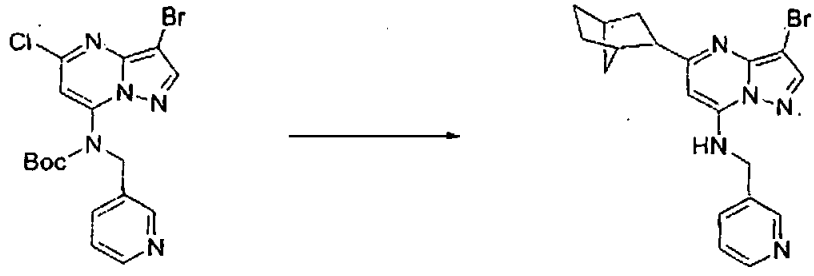
By essentially the same procedures set forth in Example 276, Step B through Step D, the above compound was prepared (0.023 g, 53% yield). MS: MH^+ = 421; mp = 230 °C (dec.)

EXAMPLE 278:



By essentially the same procedure set forth in Example 276 only substituting the appropriate cyclopropylmagnesium bromide in Step A, the compound was prepared. MS: MH^+ = 372; m. p. = 96-98 °C.

EXAMPLE 279:



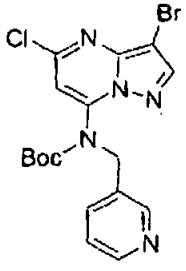
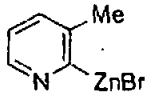
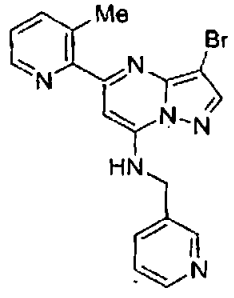
The palladium-catalyzed zinc cross-coupling reaction was carried out in a manner similar to the procedure described in *J. Org. Chem.* (1999), 453. A solution of the chloropyrazolopyrimidine (200 mg, 0.458 mmol), $Pd(PPh_3)_4$ (53

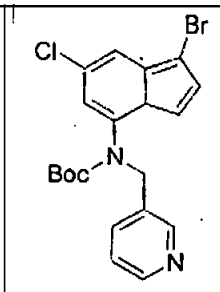
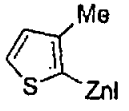
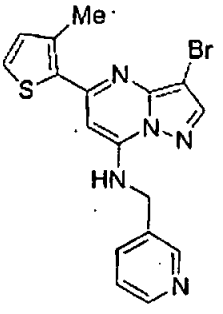
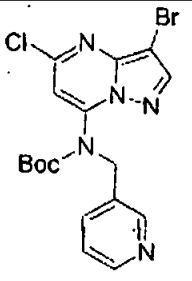
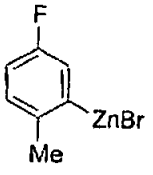
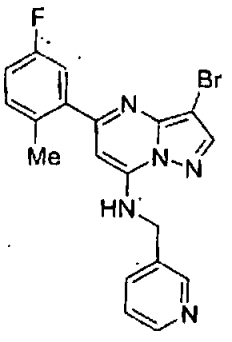
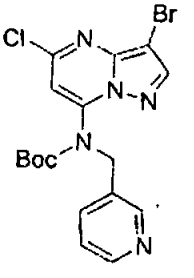
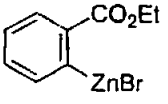
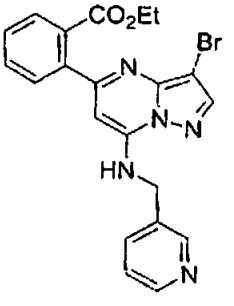
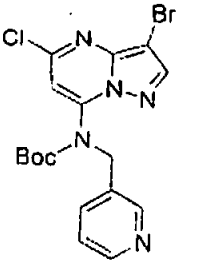
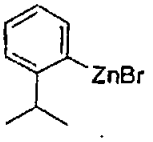
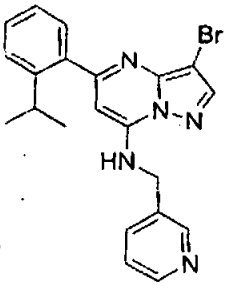
mg, 0.046 mmol), and *exo*-2-norbonylzinc bromide (0.5 M in THF, 0.95 mL, 0.47 mmol) in DMF (2 mL) was refluxed at 100°C (oil bath temp.) overnight. The reaction mixture was quenched with half-saturated NH_4Cl and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography using a 50% EtOAc in hexanes solution as eluent. A solution of the obtained *N*-Boc-protected product (121 mg, 53% yield, LCMS: MH^+ = 498) and TFA (1 mL) in CH_2Cl_2 (2 mL) was stirred at room temperature for 2 hr. The volatiles were removed under reduced pressure. The residue was dissolved in CH_2Cl_2, neutralized with saturated $NaHCO_3$, and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* (96 mg, 99% yield). LCMS: MH^+ = 398; ^1H NMR ($CDCl_3$) δ 8.78 (s, 1H), 8.71 (d, J = 4.2 Hz, 1H), 8.04 (d, J = 3.9 Hz, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.44 (m, 1H), 6.73 (m, 1H), 5.98 (d, J = 7.5 Hz, 1H), 4.74 (d, J = 5.4 Hz, 2H), 3.40-1.00 (m, 11H).

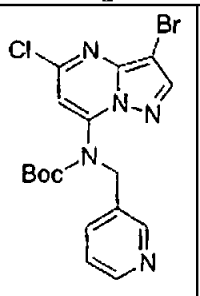
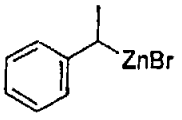
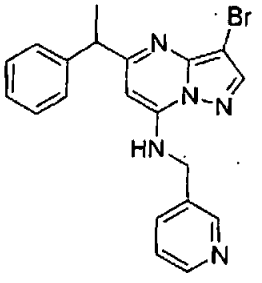
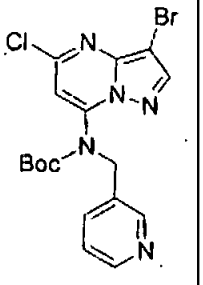
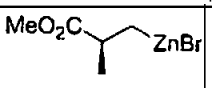
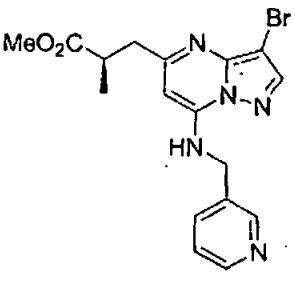
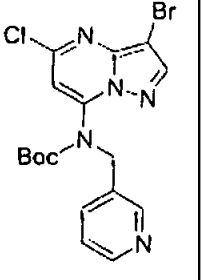
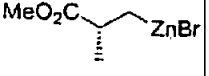
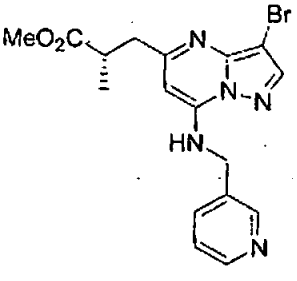
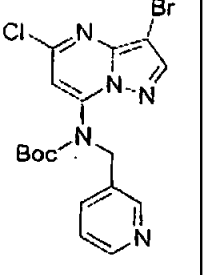
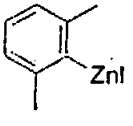
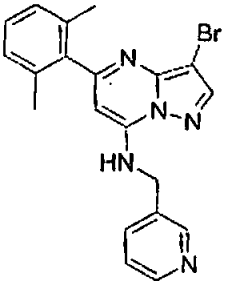
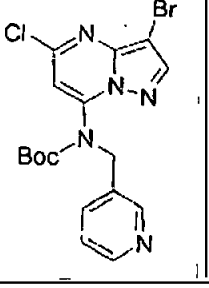
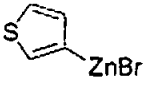
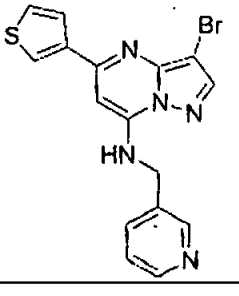
EXAMPLES 280-294:

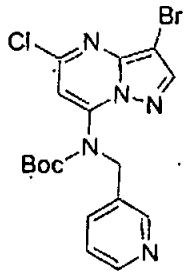
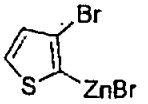
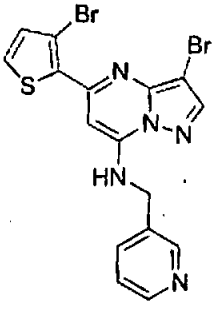
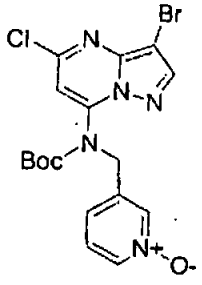
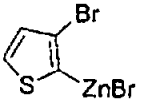
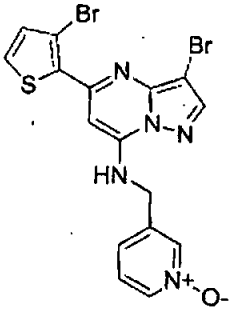
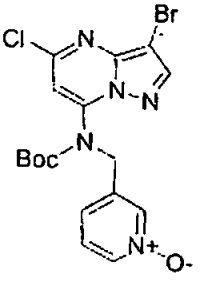
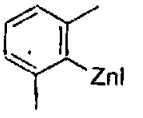
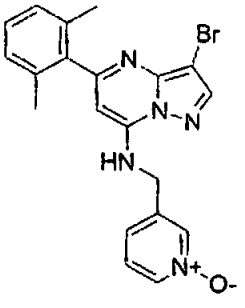
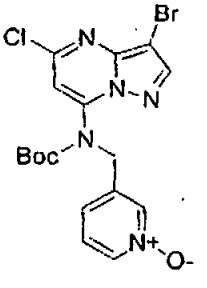
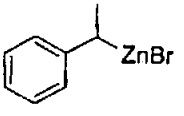
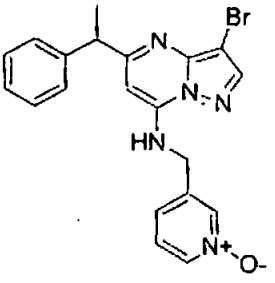
By following essentially the same procedure set forth in Example 279 only substituting the chlorides shown in Column 2 of Table 26 and the organozinc reagents shown in Column 3 of Table 26, the compounds in Column 4 of Table 26 were prepared:

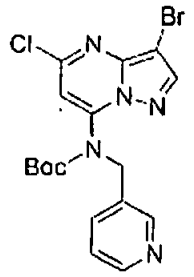
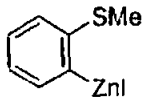
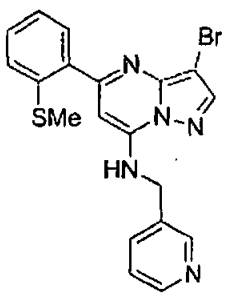
Table 26

Ex.	Column 2	Column 3	Column 4	Data
280				LCMS: MH^+ = 395

281				LCMS: MH^+ = 400
282				LCMS: MH^+ = 412
283				LCMS: MH^+ = 452
284				LCMS: MH^+ = 422

285				LCMS: MH^+ = 408
286				LCMS: MH^+ = 404
287				LCMS: MH^+ = 404
288				LCMS: MH^+ = 408
289				LCMS: MH^+ = 386

290				LCMS: MH^+ = 464
291				LCMS: MH^+ = 480
292				LCMS: MH^+ = 424
293				LCMS: MH^+ = 424

294				LCMS: MH^+ = 426

Additional data for select compounds is shown below.

EXAMPLE 280: ^{1}H NMR ($CDCl_3$) δ 8.65 (s, 1H), 8.57 (d, J = 4.2 Hz, 1H), 8.50 (d, J = 4.5 Hz, 1H), 8.01 (s, 1H), 7.69 (d, J = 7.5 Hz, 1H), 7.61 (d, J = 7.8 Hz, 1H), 7.31-7.22 (m, 2H), 6.77 (m, 2H), 4.71 (d, J = 5.4 Hz, 2H), 2.68 (s, 3H).

EXAMPLE 281: ^{1}H NMR ($CDCl_3$) δ 8.80 (s, 1H), 8.72 (d, J = 4.8 Hz, 1H), 8.08 (s, 1H), 7.85-7.40 (m, 3H), 7.02 (d, J = 5.1 Hz, 1H), 6.90 (t, J = 6.0 Hz, 1H), 6.29 (s, 1H), 4.79 (d, J = 6.0 Hz, 2H), 2.61 (s, 3H).

EXAMPLE 282: ^{1}H NMR ($CDCl_3$) δ 8.67 (s, 1H), 8.61 (d, J = 3.9 Hz, 1H), 8.03 (s, 1H), 7.72-7.31 (m, 3H), 7.22-7.00 (m, 2H), 6.81 (t, J = 6.0 Hz, 1H), 6.03 (s, 1H), 4.68 (d, J = 6.0 Hz, 2H), 2.28 (s, 3H).

EXAMPLE 283: ^{1}H NMR ($CDCl_3$) δ 8.68 (s, 1H), 8.63 (d, J = 4.0 Hz, 1H), 8.00 (s, 1H), 7.80-7.72 (m, 2H), 7.54-7.47 (m, 3H), 7.35 (m, 1H), 6.74 (t, J = 6.0 Hz, 1H), 6.19 (s, 1H), 4.67 (d, J = 6.0 Hz, 2H), 4.21 (q, J = 7.2 Hz, 2H), 1.13 (t, J = 7.2 Hz, 3H).

EXAMPLE 284: ^{1}H NMR ($CDCl_3$) δ 7.97 (s, 1H), 7.65 (d, J = 7.2 Hz, 1H), 7.33-7.15 (m, 5H), 6.73 (t, J = 5.4 Hz, 1H), 5.99 (s, 1H), 4.61 (d, J = 5.4 Hz, 2H), 3.09 (sept, J = 6.9 Hz, 1H), 1.11 (d, J = 6.9 Hz, 6H).

EXAMPLE 285: ^{1}H NMR ($CDCl_3$) δ 8.56-8.55 (m, 2H), 7.94 (s, 1H), 7.54 (m, 1H), 7.30-7.22 (m, 6H), 6.59 (t, J = 5.7 Hz, 1H), 5.66 (s, 1H), 4.47 (d, J = 5.7 Hz, 2H), 4.26 (q, J = 7.2 Hz, 1H), 1.68 (d, J = 7.2 Hz, 3H).

EXAMPLE 286: ^{1}H NMR ($CDCl_3$) δ 8.67 (m, 2H), 7.94 (s, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.34 (m, 1H), 6.63 (t, J = 5.7 Hz, 1H), 5.87 (s, 1H), 4.62 (d, J = 5.7 Hz, 2H), 3.64 (s, 3H), 3.13 (m, 2H), 2.82 (m, 1H), 1.22 (m, 3H).

EXAMPLE 287: ^{1}H NMR ($CDCl_3$) δ 8.66 (m, 2H), 7.94 (s, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.34 (m, 1H), 6.62 (t, J = 6.0 Hz, 1H), 5.87 (s, 1H), 4.62 (d, J = 6.0 Hz, 2H), 3.64 (s, 3H), 3.13 (m, 2H), 2.81 (m, 1H), 1.22 (m, 3H).

EXAMPLE 288: ^{1}H NMR ($CDCl_3$) δ 8.64 (s, 1H), 8.60 (d, J = 3.6 Hz, 1H), 8.04 (s, 1H), 7.68 (m, 1H), 7.31 (m, 1H), 7.16 (m, 1H), 7.07-7.05 (m, 2H), 6.80 (t, J = 6.3 Hz, 1H), 5.93 (s, 1H), 4.64 (d, J = 6.3 Hz, 2H), 2.08 (s, 6H).

EXAMPLE 289: ^{1}H NMR ($CDCl_3$) δ 8.72 (s, 1H), 8.62 (d, J = 4.8 Hz, 1H), 7.99-7.97 (m, 2H), 7.73-7.69 (m, 2H), 7.40-7.33 (m, 2H), 6.67 (t, J = 6.0 Hz, 1H), 6.29 (s, 1H), 4.71 (d, J = 6.0 Hz, 2H).

EXAMPLE 290: ^{1}H NMR ($CDCl_3$) δ 8.73 (s, 1H), 8.62 (d, J = 4.5 Hz, 1H), 8.01 (s, 1H), 7.76 (m, 1H), 7.41 (d, J = 5.1 Hz, 1H), 7.34 (dd, J = 8.1, 5.1 Hz, 1H), 7.05 (d, J = 5.1 Hz, 1H), 7.01 (s, 1H), 6.79 (t, J = 6.0 Hz, 1H), 4.74 (d, J = 6.0 Hz, 2H).

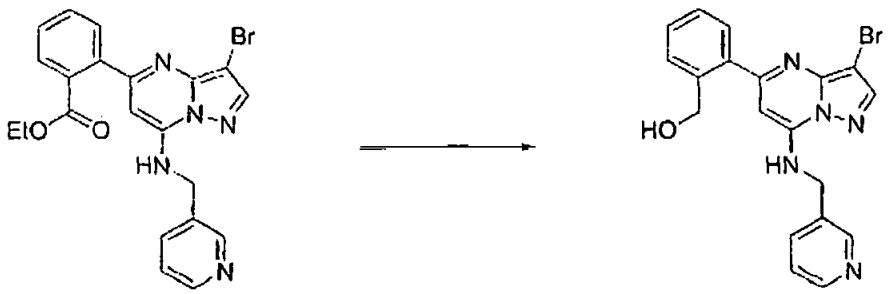
EXAMPLE 291: ^{1}H NMR (DMSO-d_6) δ 9.12 (s, 1H), 8.40 (s, 1H), 8.33 (s, 1H), 8.13 (m, 1H), 7.82 (d, J = 5.1 Hz, 1H), 7.40-7.39 (m, 2H), 7.22 (d, J = 5.1 Hz, 1H), 6.86 (s, 1H), 4.86 (s, 2H).

EXAMPLE 292: ^{1}H NMR ($CDCl_3$) δ 8.23 (s, 1H), 8.16 (d, J = 6.0 Hz, 1H), 8.06 (s, 1H), 7.31-7.05 (m, 5H), 6.86 (m, 1H), 5.87 (s, 1H), 4.62 (d, J = 6.3 Hz, 2H), 2.09 (s, 6H).

EXAMPLE 293: ^{1}H NMR ($CDCl_3$) δ 8.14 (s, 1H), 8.12 (d, J = 6.3 Hz, 1H), 7.94 (s, 1H), 7.29-7.16 (m, 6H), 7.07 (m, 1H), 6.78 (t, J = 6.0 Hz, 1H), 5.54 (s, 1H), 4.44 (d, J = 6.0 Hz, 2H), 4.24 (t, J = 7.2 Hz, 1H), 1.68 (d, J = 7.2 Hz, 3H).

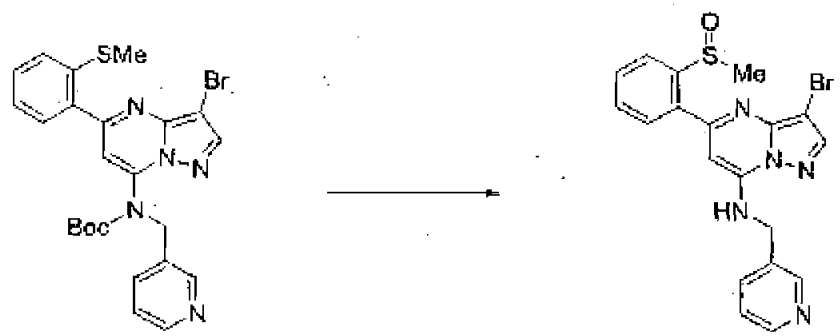
EXAMPLE 294: ^{1}H NMR ($CDCl_3$) δ 8.67 (s, 1H), 8.59 (d, J = 4.8 Hz, 1H), 8.01 (s, 1H), 7.71 (m, 1H), 7.52 (dd, J = 7.8, 1.8 Hz, 1H), 7.40-7.19 (m, 4H), 6.78 (t, J = 6.0 Hz, 1H), 6.32 (s, 1H), 4.67 (d, J = 6.0 Hz, 2H), 2.38 (s, 3H).

EXAMPLE 295:



To a suspension of lithium aluminum hydride (10 mg, 0.26 mmol) in anhydrous THF (2 mL) at 0°C was added dropwise a solution of the compound prepared in Example 283 (20 mg, 0.044 mmol) in anhydrous THF (2 mL). The resulting mixture was refluxed for 1 hr and stirred at room temperature overnight, neutralized with dilute sulfuric acid, and extracted with EtOAc. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by preparative thin-layer chromatography using a 5% MeOH in EtOAc solution as eluent (15 mg, 83% yield). LCMS: MH^+ = 410; ^1H NMR ($CDCl_3$) δ 8.69 (s, 1H), 8.61 (d, J = 3.9 Hz, 1H), 8.05 (d, J = 2.1 Hz, 1H), 7.74 (d, J = 7.8 Hz, 1H), 7.52-7.31 (m, 5H), 6.97 (t, J = 6.3 Hz, 1H), 6.55 (d, J = 2.7 Hz, 1H), 6.20 (s, 1H), 4.71 (d, J = 6.3 Hz, 2H), 4.52 (s, 2H).

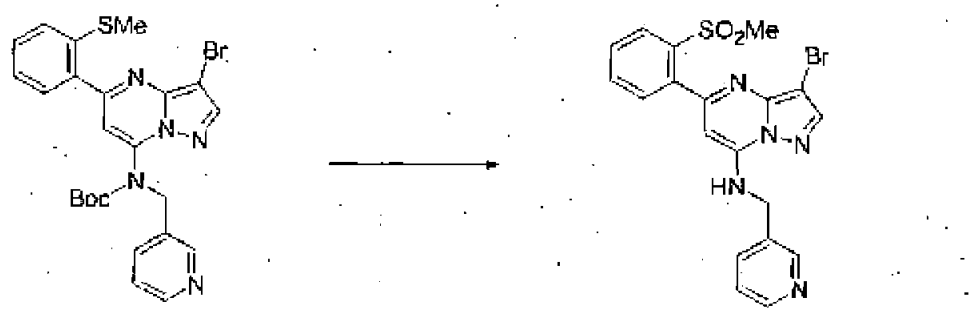
EXAMPLE 296:



To a solution of the *N*-Boc-protected compound prepared in Example 294 (45 mg, 0.085 mmol) in CH_2Cl_2 (4 mL) at –50°C was added *m*-CPBA (18 mg, 0.10 mmol). After stirring for 1 hr at –50°C more *m*-CPBA (4 mg, 0.02 mmol) was added. The mixture was stirred for a further 2 hr, diluted with CH_2Cl_2 (20 mL), and washed with saturated $NaHCO_3$ (20 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography using a 2.5% MeOH in CH_2Cl_2 solution as eluent. A solution of the obtained *N*-Boc-protected product (37 mg, 80% yield, LCMS: MH^+ = 542) and TFA (1 mL) in CH_2Cl_2 (2 mL) was stirred at room temperature for 2 hr. The volatiles were removed under reduced pressure. The residue was dissolved in CH_2Cl_2, neutralized with saturated $NaHCO_3$, and

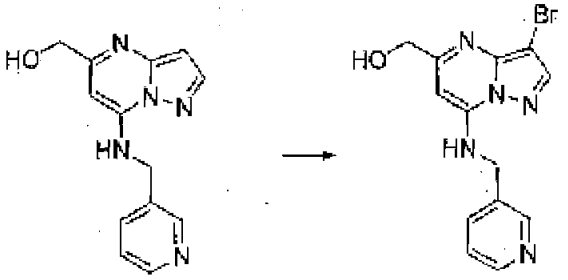
extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by preparative thin-layer chromatography using a 5% MeOH in EtOAc solution as eluent (26 mg, 89% yield). LCMS: MH^+ = 442; ^1H NMR ($CDCl_3$) δ 8.71 (s, 1H), 8.64 (d, J = 3.9 Hz, 1H), 8.41 (m, 1H), 8.03 (s, 1H), 7.75-7.54 (m, 4H), 7.36 (dd, J = 8.1, 5.1 Hz, 1H), 6.81 (t, J = 6.0 Hz, 1H), 6.34 (s, 1H), 4.74 (d, J = 6.0 Hz, 2H), 3.25 (s, 3H).

EXAMPLE 297:



To a solution of the *N*-Boc-protected compound prepared in Example 294 (56 mg, 0.11 mmol) in CH_2Cl_2 (4 mL) at 0°C was added *m*-CPBA (42 mg, 0.24 mmol). After stirring for 2 hr at room temperature more *m*-CPBA (13 mg, 0.075 mmol) was added. The mixture was stirred at room temperature overnight, diluted with CH_2Cl_2 (20 mL), and washed with saturated $NaHCO_3$ (20 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by preparative thin-layer chromatography using a 2.5% MeOH in EtOAc solution as eluent. A solution of the obtained *N*-Boc-protected product (29 mg, 49% yield, LCMS: MH^+ = 558) and TFA (1 mL) in CH_2Cl_2 (2 mL) was stirred at room temperature for 2 hr. The volatiles were removed under reduced pressure. The residue was dissolved in CH_2Cl_2, neutralized with saturated $NaHCO_3$, and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by preparative thin-layer chromatography using a 2.5% MeOH in EtOAc solution as eluent (21 mg, 90% yield). LCMS: MH^+ = 458; ^1H NMR ($CDCl_3$) δ 8.64 (s, 2H), 8.20 (m, 1H), 8.01 (s, 1H), 7.73-7.60 (m, 3H), 7.46 (m, 1H), 7.35 (s, 1H), 6.82 (t, J = 5.9 Hz, 1H), 6.17 (s, 1H), 4.65 (d, J = 5.7 Hz, 2H), 3.60 (s, 3H).

EXAMPLE 298

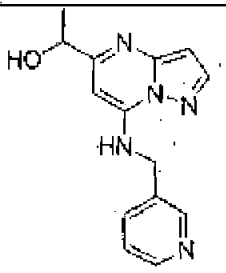
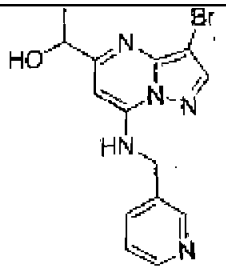
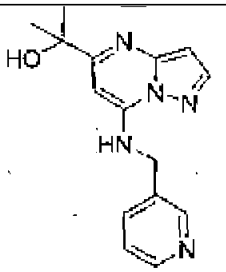
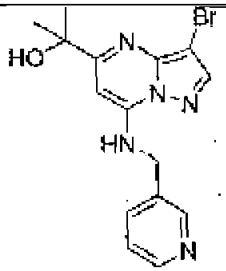


By essentially the same procedure set forth in Preparative Example 127 only substituting the compound prepared in Preparative Example 189, the above compound was prepared. MS: MH^+ = 334; mp = 170-173 °C.

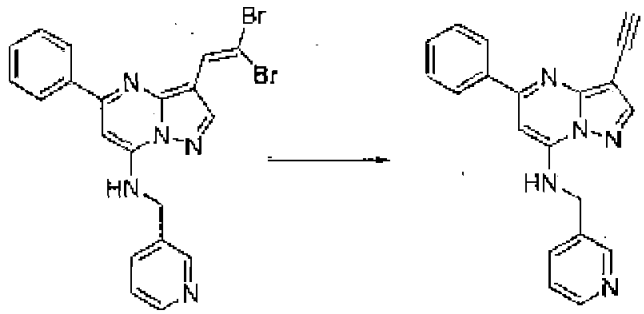
Examples 299-300:

By essentially the same procedure set forth in Example 298 only substituting the compound shown in Table 27, Column 2, the compounds shown in Table 27, Column 3 were prepared:

Table 27

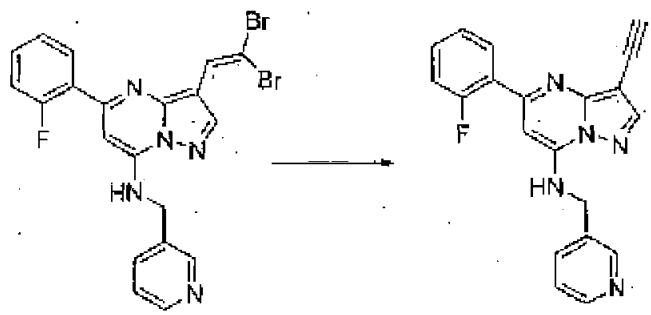
Ex.	Column 2	Column 3	CMPD
299			MS: MH^+ = 348 m.p. = 73 – 83 °C
300			MS: MH^+ = 362 m.p. = 165 – 175 °C

EXAMPLE 301:



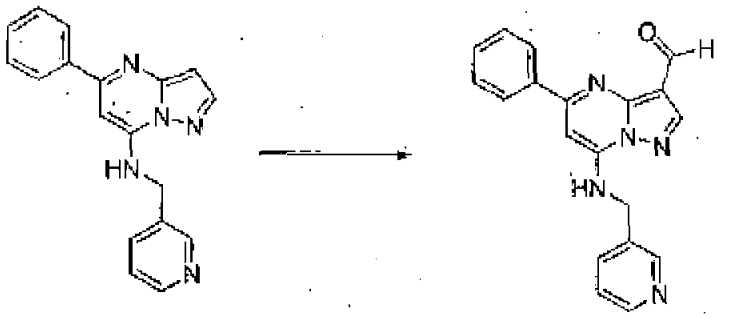
To a solution of the compound prepared in Preparative Example 186 (0.1 g, 0.21 mmol) in THF (4.0 mL) at -78 °C was added nBuLI (0.57 mL, 2.16M in hexanes, 5.0 eq.) at -78 °C. The reaction mixture was stirred 2 hours at -78 °C, quenched with H_2O, warmed to room temperature, and extracted with EtOAc. The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by Preparative TLC using a 2.5% (10%NH_4OH in CH_3OH) solution in CH_2Cl_2 as eluent (0.013 g, 20% yield). MS: MH^+ = 326; mp = 71-72 °C.

EXAMPLE 302:



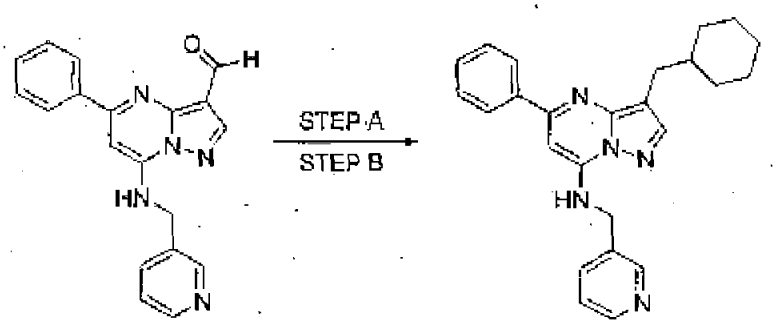
By essentially the same procedure set forth in Example 301 only substituting the compound from Preparative Example 187, the above compound was prepared (0.049 g, 68% yield).MS: MH^+ = 344; mp = 69-71 °C.

EXAMPLE 303:



To a solution of 3-H adduct from Preparative Example 187.1 (0.70 g, 2.32 mmol) in DMF (4.2 mL) at 0 °C was added $POCl_3$ (0.67 mL, 7.2 mmol) dropwise. The mixture was stirred for 14h at rt, cooled to 0 °C, and was quenched by addition of ice. 1N NaOH was carefully added to adjust pH to 8 and the mixture was extracted with CH_2Cl_2 (3 x 25 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was recrystallized from EtOAc to afford 0.43 g (56%) of a yellow solid. mp 181-183 °C; M+H = 330.

EXAMPLE 304:



STEP A:

To a solution of aldehyde (100 mg, 0.30 mmol) from Example 303 in THF (1 mL) at 0 °C was added cyclohexyl magnesium bromide (0.46 mL, 2.0M in Et_2O) dropwise over 5 min. The resulting mixture was stirred at 0 °C for 2h and at rt for 12h. The mixture was cooled to 0 °C and was treated with sat. aq. NH_4Cl (3 mL) and CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, washed with brine (1 x 5 mL), dried (Na_2SO4), filtered and concentrated under

reduced pressure to afford 110 mg (89%) of a light yellow semisolid. M+H = 414. This material was carried on crude to Step B without further purification.

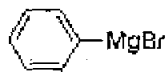
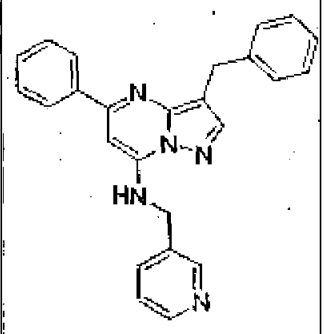
STEP B:

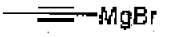
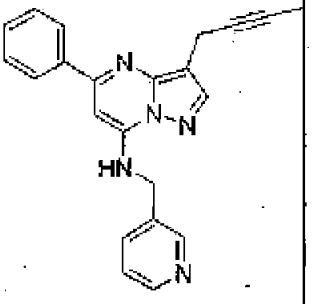
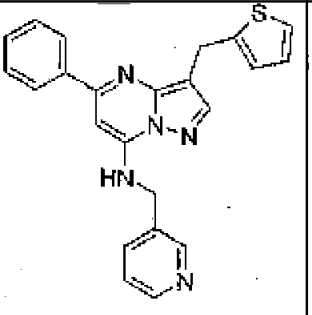
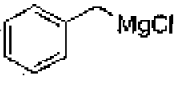
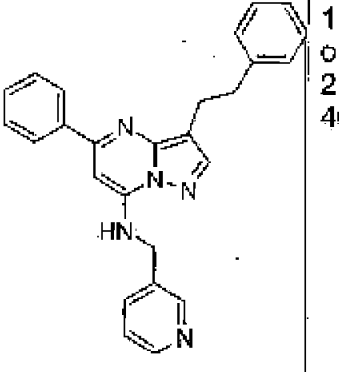
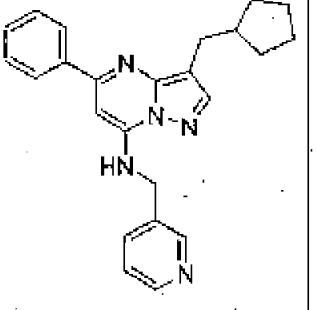
To a solution of alcohol (53 mg, 0.13 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added Et_3SiH (24 µL, 0.15 mmol) followed by TFA (24 µL, 0.30 mmol). The mixture was stirred for 2 h at 0 °C and rt for 2 h whereupon additional portions of Et_3SiH (24 µL, 0.15 mmol) and TFA (24 µL, 0.30 mmol) were added and the mixture was stirred for 3 h at rt (until complete by TLC). The mixture was concentrated under reduced pressure and the crude residue was partitioned between CH_2Cl_2 (5 mL) and sat. aq. $NaHCO_3$ (2.5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, washed with brine (1 x 5 mL), dried (Na_2SO4), filtered and concentrated under reduced pressure. The crude product was purified by prep TLC (8 x 1000 mM) eluting with CH_2Cl_2/MeOH (22:1) to afford 29 mg (56%) of a yellow semisolid. M+H = 398.

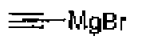
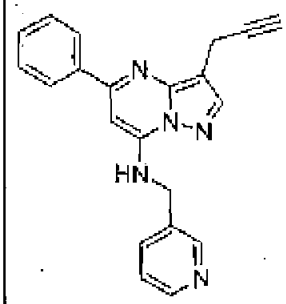
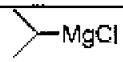
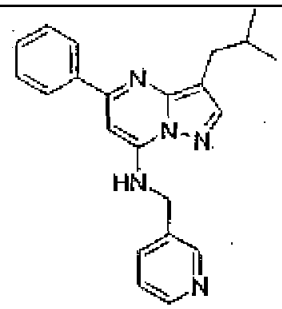
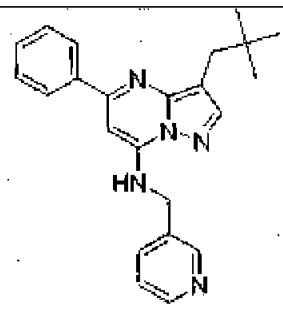
EXAMPLES 305-312:

By essentially the same procedure set forth in Example 304, utilizing the aldehyde from Example 303 and substituting the Grignard or organolithium reagents shown in Column 2 of Table 28, the compounds in Column 3 of Table 28 were prepared:

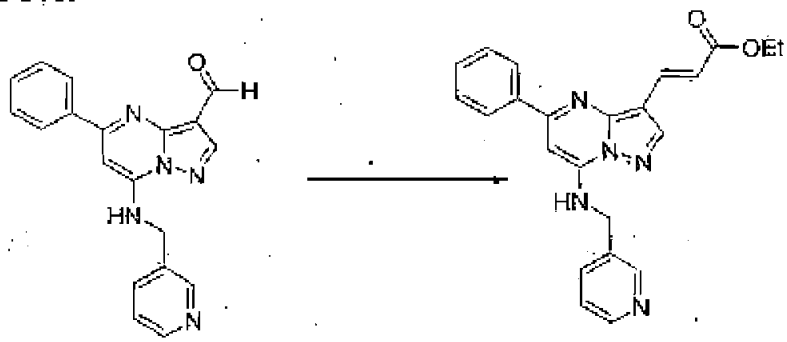
TABLE 28

Ex.	Column 2 (Organometallic)	Column 3 (Final Structure)	CMPD 1. mp (°C) 2. M+H
305			1. yellow oil 2. M+H = 392

306			1. red oil 2. M+H = 353
307			1. red oil 2. M+H = 398
308			1. yellow oil 2. M+H = 406
309			1. yellow semisolid 2. M+H = 384

310			1. semisolid 2. M+H = 340
311			1. mp = 141-143 2. M+H = 358
312			1. mp = 148-150 2. M+H = 372

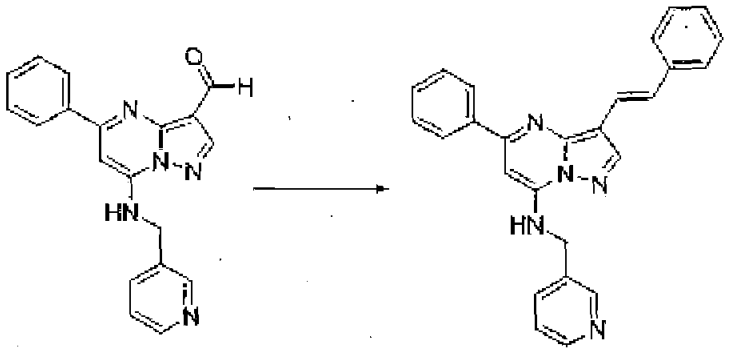
EXAMPLE 313:



To solution of aldehyde (81 mg, 0.25 mmol) from Example 303 in benzene (2.5 mL) was added carboethoxymethylene triphenyl phosphorane

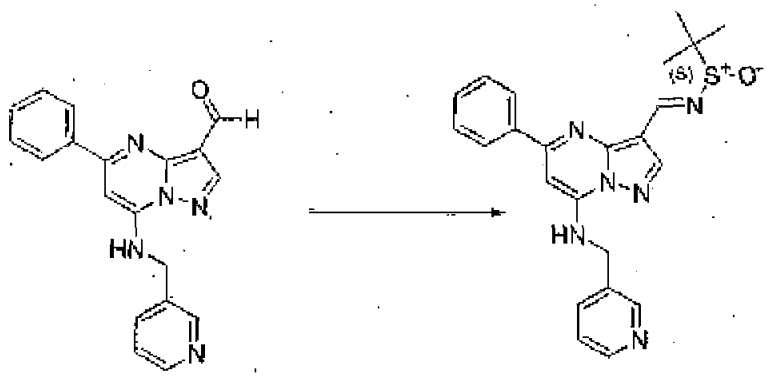
(0.12 g, 0.33 mmol) in one portion. The mixture was heated at reflux for 24h, cooled to rt, and concentrated under reduced pressure. The mixture was diluted CH_2Cl_2 (5 mL), brine (2 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 4 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by preparative TLC (8 x 1000 μM) eluting with CH_2Cl_2/MeOH (20:1) to afford 98 mg (100%) of white solid. mp 151-153 °C; M+H = 400.

EXAMPLE 314:



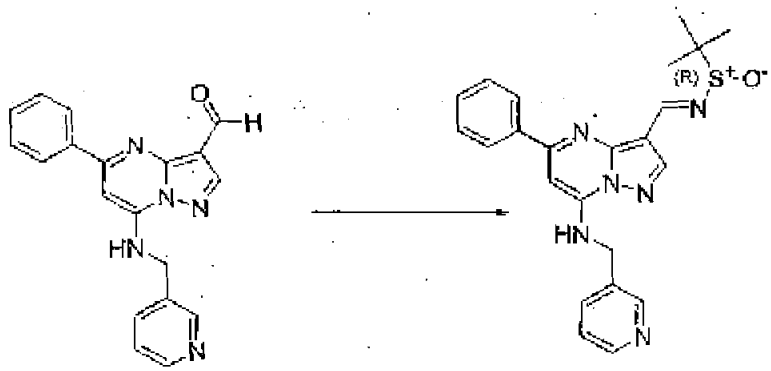
To a mixture of benzyltriphenylphosphonium bromide (0.59 g, 1.37 mmol) in THF (3 mL) was added NaH (55 mg, 1.37 mmol) and the mixture was stirred for 30 min. The aldehyde (0.15 g, 0.46 mmol) from Example 303 was added in a single portion and the mixture was heated at reflux for 36h. The mixture was cooled to rt and was concentrated under reduced pressure. The mixture was diluted CH_2Cl_2 (5 mL), brine (2 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 4 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by preparative TLC (8 x 1000 μM) eluting with CH_2Cl_2/MeOH (20:1) to afford 58 mg (32%) of yellow solid. mp 138-141 °C; M+H = 404.

EXAMPLE 315:



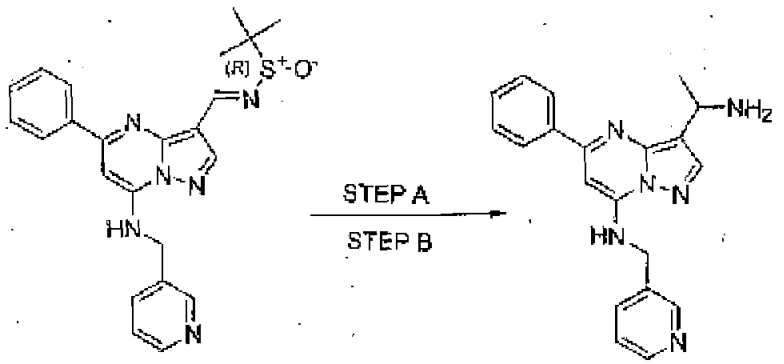
To a solution of aldehyde (0.20 g, 0.60 mmol) from Example 303 in THF (3 mL) was added Ti (i-OPr)$_4$ (0.36 mL, 1.21 mmol) dropwise followed by addition of (*S*)-(-)-2-methyl-2-propanesulfinamide (74 mg, 0.61 mmol). The resulting mixture was stirred for 18h at reflux, cooled to rt, and quenched with brine (2 mL). The mixture was filtered thru a pad of Celite which was washed with EtOAc (2 x 2 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 4 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by preparative TLC (8 x 1000 μM) eluting with CH_2Cl_2/MeOH (20:1) to afford 0.21 g (80%) of yellow solid. mp 108-110 °C; M+H = 433.

EXAMPLE 316:



Prepared in the same fashion as Example 315 except substituting (*R*)-(-)-2-methyl-2-propanesulfinamide to afford 0.25 g (94%) as a yellow solid. mp 107-109 °C; M+H = 433.

EXAMPLE 317:



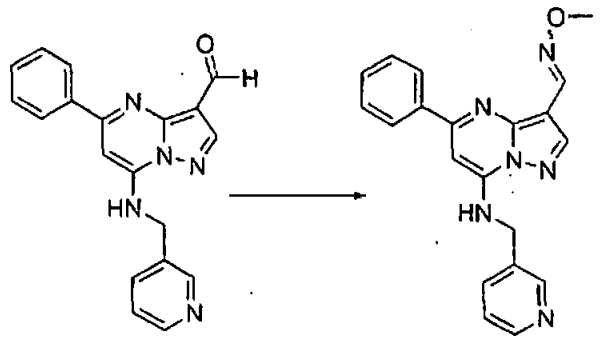
STEP A:

To a solution of sulfinimine (50 mg, 0.12 mmol) from Example 316 in CH_2Cl_2 (2.5 mL) at -40 °C was added MeMgBr (96 mL, 0.29 mmol) dropwise. The mixture was stirred for 5h at -40 °C and was stirred at rt for 12h. An additional portion of MeMgBr (96 mL, 0.29 mmol) and the mixture was stirred for 12 h. Sat. aq. NH_4Cl (2 mL) was added and the mixture was extracted with EtOAc (3 x 4 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 30 mg (58%) of crude residue. This material was taken onto the next step without purification.

STEP B:

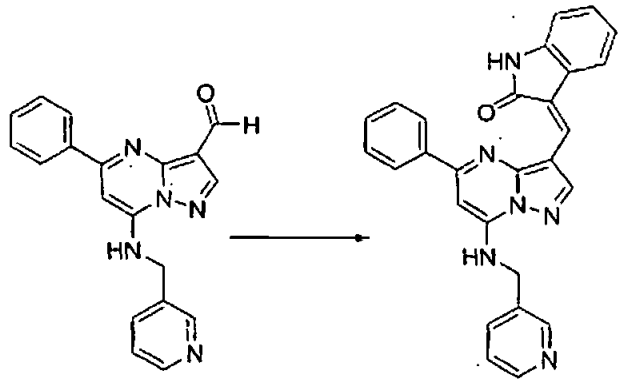
The crude material from Step A (30 mg, 0.067 mmol) in MeOH (2 mL) was added conc. HCl (2 mL). The mixture was stirred at rt for 12h and the mixture was concentrated to dryness. The crude material was partitioned between CH_2Cl_2 (3 mL) and sat. aq. $NaHCO_3$ (2 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 3 mL) and the organic layers were combined. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 6 mg (24%) of the title compound as a light yellow solid. mp 100-102 °C; M + H = 345.

EXAMPLE 318:



To a solution of aldehyde (75 mg, 0.23 mmol) from Example 300 in THF/CH_2Cl_2 (5 mL/1mL) at rt was added $MeONH_2$·HCl (38 mg, 0.46 mmol) followed by dropwise addition of pyridine (46 μL, 0.57 mmol). The mixture was stirred for 72h at rt whereupon the mixture was concentrated to dryness. The crude material was partitioned between CH_2Cl_2 (3 mL) and sat. aq. $NaHCO_3$ (2 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 3 mL) and the organic layers were combined. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by preparative TLC (3 x 1000 μM) eluting with CH_2Cl_2/MeOH (22:1) to afford 90 mg (100%) of light yellow solid. mp 173-175 °C ; M + H = 359.

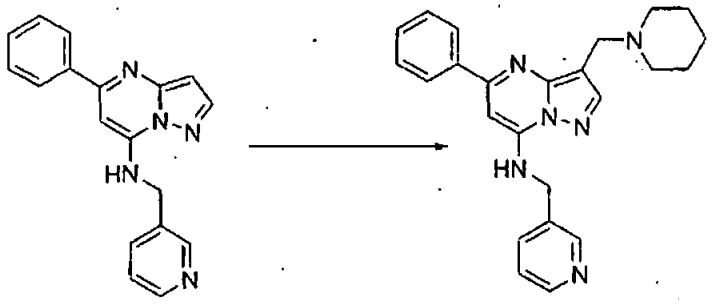
EXAMPLE 319:



To solution of aldehyde (60 mg, 0.18 mmol) from Example 303 at EtOH (2.5 mL) was added oxindole (48 mg, 0.37 mmol) followed by piperidine (3 drops). The mixture was heated at reflux for 14h and the mixture was cooled to

rt. The resultant precipitate was filtered and washed with cold EtOH (2 x 2 mL). The product was dried under high vacuum to afford 81 mg (100%) of the title compound as an orange/brown solid. mp 182-185 °C; M+H = 445.

EXAMPLE 320:

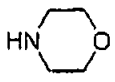


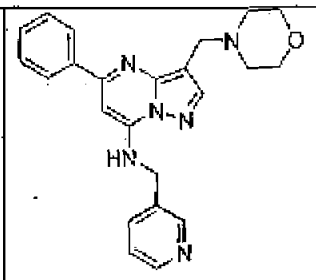
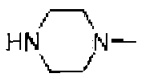
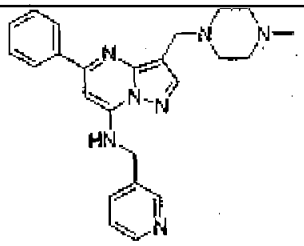
To a solution of 3-H analog (106 mg, 0.35 mmol) from Preparative Example 187.10 in AcOH (2 mL) was added 37% aqueous formaldehyde (1.5 ml; 1.40 mmol) followed by piperidine (100 μL; 0.37 mmol). The resulting mixture was stirred at rt for 24h and the AcOH was removed under reduced pressure. The mixture was diluted with water (2 mL) and neutralized with 2M NaOH until pH = 8. The aqueous layer was extracted with CH_2Cl_2 (3 x 7 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 to afford 96 mg (69%) of an off-white solid. mp 88-90 °C; M+H 399.

EXAMPLES 321-322:

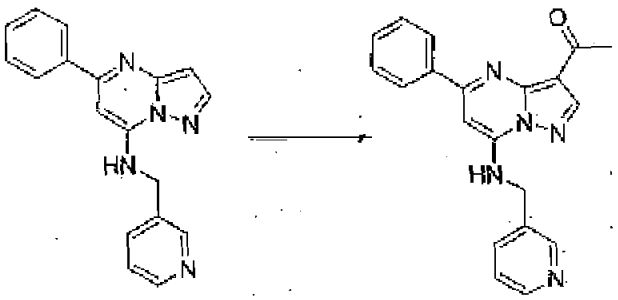
By essentially the same procedure set forth in Example 320 only substituting the amines in Column 2 of Table 29 and employing the 3-H adduct from Preparative Example 187.10, the compounds in Column 3 of Table 29 were prepared:

TABLE 29

Ex.	Column 2 (Amine)	Column 3 (Final Structure)	CMPD 1. mp (°C) 2. M+H
321			1. mp = 178-180 2. M+H = 401

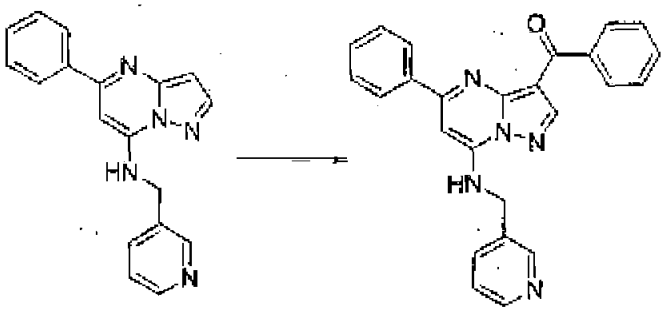
			
322			1. mp = 102-104 2. M+H. = 414

EXAMPLE 323:



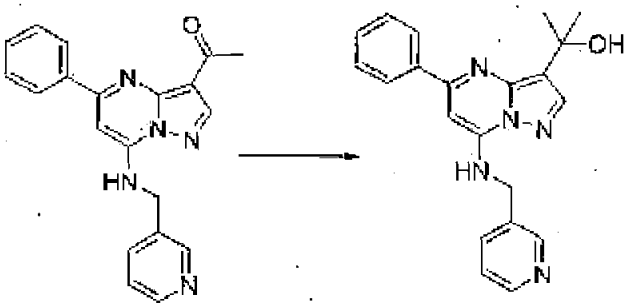
To a solution of 3-H analog (113 mg, 0.38 mmol) from Preparative Example 187.10 in CH_2Cl_2 (5 mL) at rt was added $AlCl_3$ (215 mg, 1.61 mmol) followed by AcCl (100 mL, 1.40 mmol). The mixture was heated at reflux for 12h and was cooled to rt. The mixture was treated sequentially with 3M HCl (3 mL) followed by sat. aq. $NaHCO_3$ (until pH = 8). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by preparative TLC (8 x 1000 mM) eluting with CH_2Cl_2/MeOH (20:1) to afford 68 mg (52%) of white solid. mp 220-221 °C; M+H = 344.

EXAMPLE 324:



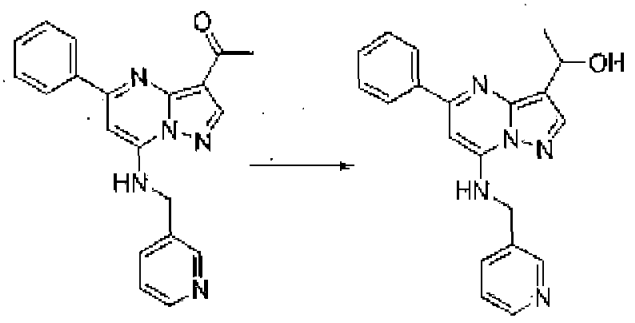
Utilizing the method described in Example 323, except employing benzoyl chloride, the title compound was prepared in 61% yield as a white solid. mp 172-175 °C; M+H = 406.

EXAMPLE 325:



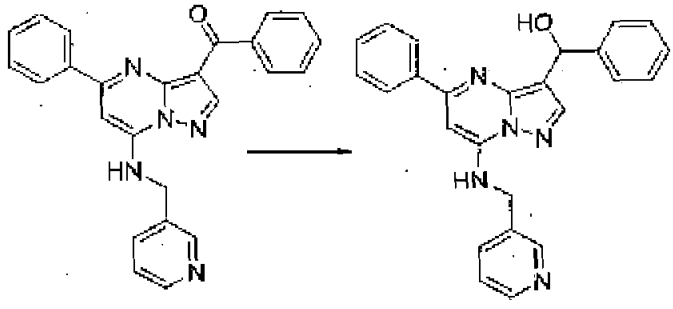
To a solution of ketone (100 mg, 0.29 mmol) from Example 323 in CH_2Cl_2 (2.5 mL) at 0 °C was added MeMgBr (0.35 mL, 3.0M in Et_2O) dropwise. The resulting mixture was stirred for 18h at rt and was carefully quenched by addition of sat. aq. NH_4Cl (2 mL) and CH_2Cl_2 (2 mL) were added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 4 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by preparative TLC (8 x 1000 μM) eluting with CH_2Cl_2/MeOH (10:1) to afford 68 mg (52%) of a yellow solid. mp 160-162 °C; M+H = 360.

EXAMPLE 326:



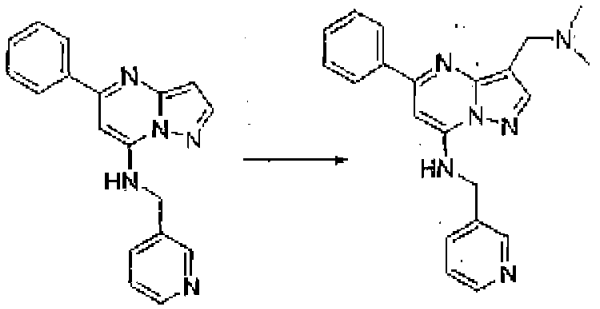
To a solution of ketone (84 mg, 0.24 mmol) from Example 323 in MeOH/THF (1:1; 2 mL total) at 0 °C was added $NaBH_4$ (12 mg, 0.30 mmol) in one portion. The resulting mixture was stirred for 18h at rt whereupon and additional portion of $NaBH_4$ (12 mg, 0.30 mmol) was added. The mixture was stirred for 12h whereupon the mixture was quenched with ice followed by addition of 1M NaOH to adjust the pH = 9. The mixture was diluted with CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 4 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by preparative TLC (8 x 1000 μM) eluting with CH_2Cl_2/MeOH (10:1) to afford 25 mg (30%) of a yellow solid. mp 148-150 °C; M+H = 346.

EXAMPLE 327:



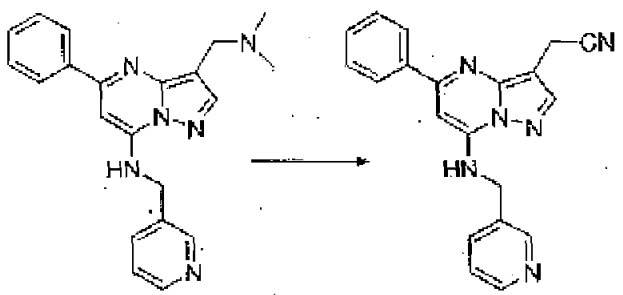
Using the same procedure as outlined in Example 326, the ketone (84 mg, 0.21 mmol) was converted to 53 mg (62%) as a light yellow solid. mp 78-80 °C; M+H = 408.

EXAMPLE 328:



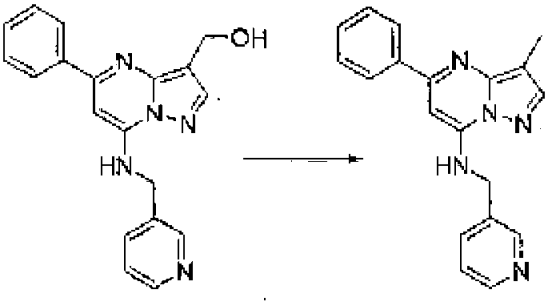
To a solution of 3-H adduct (1.3 g, 4.31 mmol) from Preparative Example 187.10 in CH_2Cl_2 (50 mL) was added Eschenmoser's salt (0.79 g, 4.31 mmol) followed by dropwise addition of TFA (0.56 mL, 7.33 mmol). The mixture was stirred at rt for 48 h and was diluted with CH_2Cl_2 (250 mL). The organic layer was washed with sat. aq. $NaHCO_3$ (2 x 125 mL) to afford 1.41 h (92%) of a yellow solid. mp 231-233 °C; M+H = 359.

EXAMPLE 329:



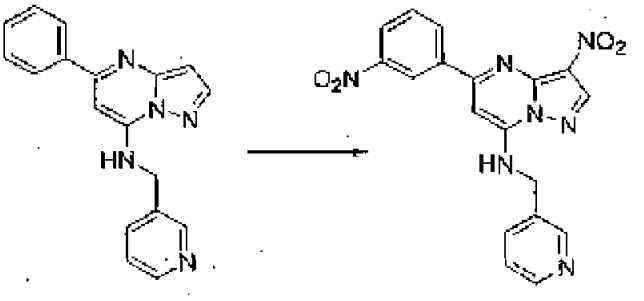
To a solution of tertiary amine adduct (100 mg, 0.28 mmol) from Example 328 in 50% aq. DMF (5 mL) in a pressure tube was added KCN (0.15 g, 2.32 mmol). The tube was capped and heated at 100 °C for 96h. The mixture was cooled to rt and was diluted with EtOAc (25 mL). The organic layer was washed with brine (1 x 5 mL) and water (1 x 5 mL). The organic layers was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by preparative TLC (4 x 1000 μM) eluting with EtOAc to afford 21 mg (30%) of brown solid. mp 152-155 °C; M+H = 341.

EXAMPLE 330:



To a solution of alcohol (45 mg, 0.14 mmol) from Example 17.10 in CH_2Cl_2 (0.7 mL) at 0 °C was added Et_3SiH (26 μL, 0.16 mmol) followed by TFA (25 μL, 0.33 mmol). The mixture was stirred for 2 h at 0 °C and rt for 2 h whereupon additional portions of Et_3SiH (26 μL, 0.16 mmol) and TFA (25 μL, 0.33 mmol) were added and the mixture was stirred for 4 h at rt (until complete by TLC). The mixture was concentrated under reduced pressure and the crude residue was partitioned between CH_2Cl_2 (3 mL) and sat. aq. $NaHCO_3$ (1.5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 4 mL). The organic layers were combined, washed with brine (1 x 5 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by prep TLC (4 x 1000 mM) eluting with CH_2Cl_2/MeOH (20:1) to afford 21 mg (48%) of a yellow solid. mp 146-148 °C; M+H = 316.

EXAMPLE 331:

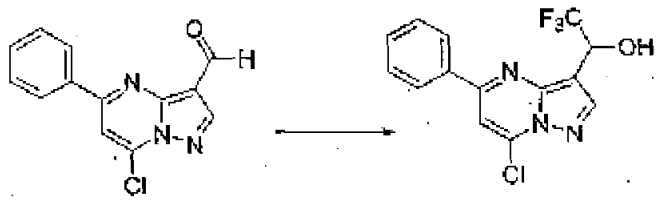


To a solution of 3-H adduct (90 mg, 0.30 mmol) from Preparative Example 187.10 in conc. H_2SO_4 (2 mL) at 0 °C was added fuming HNO_3 (30 μL, 0.72 mmol) dropwise. The resulting mixture was stirred for 1 h at 0 °C whereupon ice

(~1g) was added to the mixture. The resulting precipitate was collected and was washed with water (2 x 2 mL) and CH_2Cl_2 (2 x 2 mL). The crude product was dried under high vacuum to afford 67 mg (60%) of the monosulfate salt as a yellow/orange solid. mp 250 °C; M+H (free base) = 392.

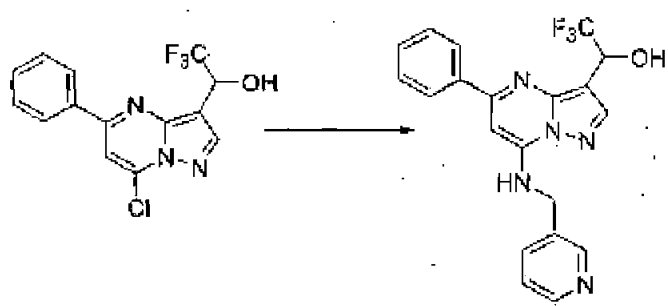
EXAMPLE 332:

Step A:



To a solution of aldehyde (0.10 g, 0.39 mmol) from Preparative Example 168 in THF (2.5 mL) at 0 °C was added CF_3TMS (64 mL, 0.43 mmol) followed by CsF (10 mg). The resulting mixture was stirred for 2 h at 0 °C and 2h at rt. 1M HCl (5 mL) was added and the mixture was diluted with 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 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 127 mg (99%) of a yellow semisolid. M+H =328. The crude product was carried on without further purification.

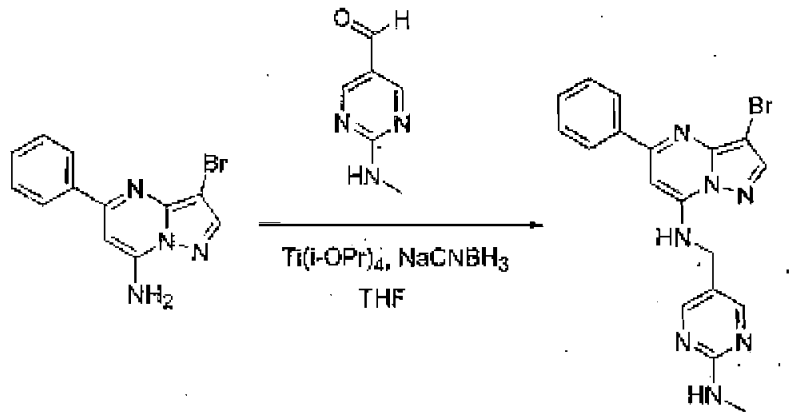
Step B:



By utilizing the general procedure set forth in Example 1, the 7-Cl adduct (127 mg, 0.39 mmol) from Example 332, Step A was reacted with 3-

(aminomethyl)pyridine (73 µL, 0.43 mmol) to afford 80 mg (51%) of the title compound as a light yellow solid. mp 68-72 °C; M+H = 400.

EXAMPLE 333:



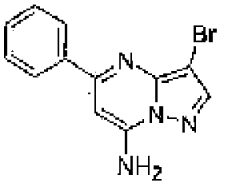
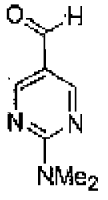
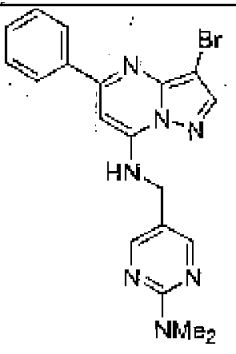
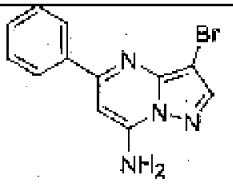
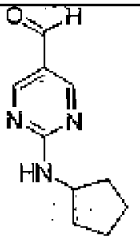
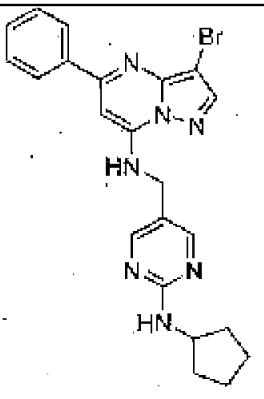
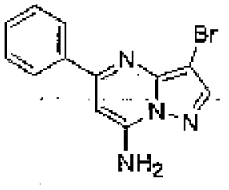
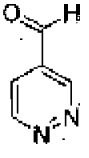
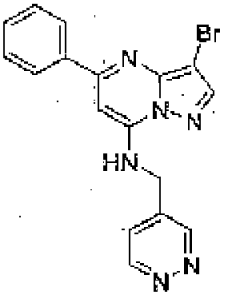
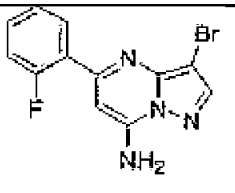
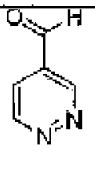
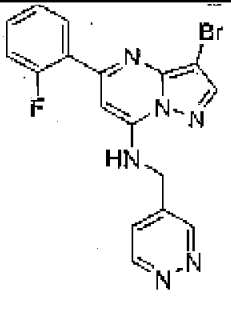
To a solution of aniline (200 mg, 0.69 mmol) from Preparative Example 174 in THF (6 mL) at rt was added aldehyde (114 mg, 0.83 mmol) from Preparative Example 256 followed by dropwise addition of Ti(*i*-OPr)$_4$ (0.82 mL, 2.77 mmol). The mixture was stirred at reflux for 4 h and was cooled to rt. $NaCNBH_3$ (347 mg, 5.53 mmol) was added and the mixture was stirred for 2 h at rt. The mixture was cooled to 0 oC, treated with 1M NaOH (4 mL) and brine (1 mL) and stirred for 30 min. The mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the organic layers were combined. The organic layer was washed with brine (1 x 7 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by preparative thin-layer chromatography (8 x 1000 uM plates) eluting with CH_2Cl_2/MeOH (25:1) to afford 89 mg (31%) of the title compound as a yellow solid. mp 210-213 °C ; M+H = 411.

EXAMPLES 334-337:

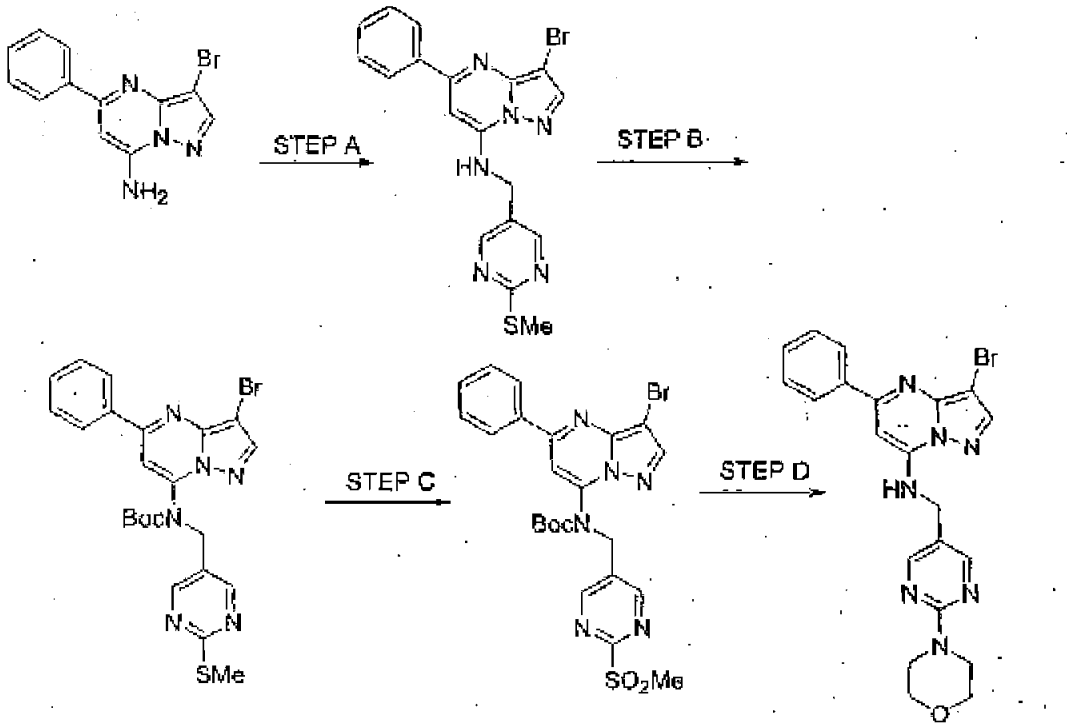
By essentially the same procedure set forth in Example 333 only by utilizing the anilines shown in Column 2 of Table 30 and the aldehydes shown in Column 3 of Table 30, the compounds in Column 4 of Table 30 were prepared:

TABLE 30

Ex.	Column 2 (Aniline)	Column 3 (Aldehyde)	Column 4 (Final Structure)	CMPD 1. mp (°C) 2. M+H

334				1. mp = 85-87 2. M+H = 425
335				1. mp = 160-162 2. M+H = 451
336				1. mp = 117-119 2. M+H = 382
337				1. mp = 171-175 2. M+H = 400

EXAMPLE 338:



STEP A:

Reaction of aniline (0.20 g, 0.69 mmol) with aldehyde (0.13 g, 0.83 mmol) under the reaction conditions described in Example 333 afforded 70 mg (23%) of thiomethyl derivative as a yellow solid. M+H = 428.

STEP B:

To a solution of thiomethyl derivative (60 mg, 0.14 mmol) from Example 338, Step A in dioxane (2 mL) was added Boc_2O (61 mg, 0.28 mmol) followed by DMAP (21 mg, 0.17 mmol). The mixture was stirred for 14h at rt and was concentrated under reduced pressure. The crude product was purified by preparative thin-layer chromatography (6 x 1000 μM plates) eluting with hexanes/EtOAc (4:1) to afford 61 mg (83%) of the title compound as a yellow solid. M+H = 528.

STEP C:

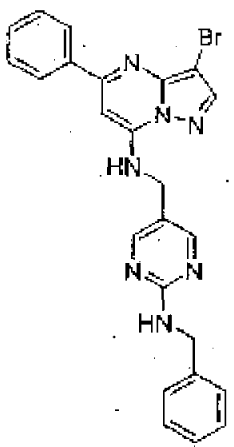
To a solution of thiomethyl derivative from Example 338, Step B (41 mg, 0.078 mmol) in CH_2Cl_2 (2 mL) was added MCPBA (33 mg, 0.19 mmol) in one portion. The resulting mixture was stirred for 3h at rt and the mixture was diluted

with CH_2Cl_2 (5 mL) and sat. aq. $NaHCO_3$ (2.5 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL), and the organic layers were combined. The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 40 mg (92%) of the sulfone adduct as a light yellow solid. M+H = 560.

STEP D:

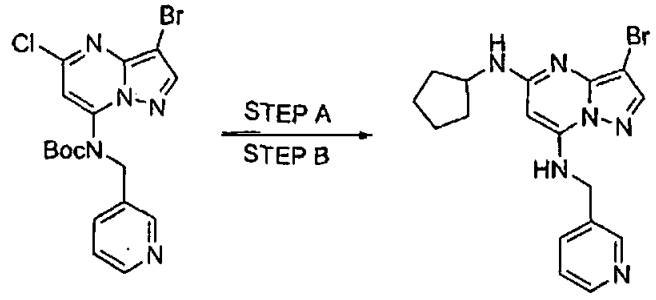
To a flask charged with sulfone from Example 338, Step C (75 mg, 0.13 mmol) and a stir bar was added morpholine (2 ml; 22 mmol). The mixture was heated at reflux for 12h, cooled to rt, and concentrated to dryness under high vacuum. The crude product was purified by preparative thin-layer chromatography (6 x 1000 μM plates) eluting with CH_2Cl_2/MeOH (40:1) to afford 41 mg (68%) of the title compound as a yellow solid. mp 209-210 °C; M+H = 466.

EXAMPLE 339:



The title compound was prepared according to the procedure outlined in Example 338 except using benzyl amine to afford 12 mg (70%) of a white solid. mp 194-196; M+H = 487.

EXAMPLE 340:



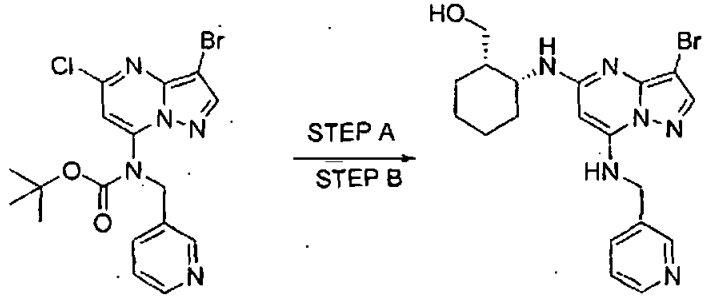
STEP A:

To a solution of 5-chloro adduct (0.15 g, 0.34 mmol) in dioxane/DIPEA (2.5mL/1.0mL) at rt was added cyclopentylamine (0.041 μL, 0.41 mmol) dropwise. The resulting solution was stirred at reflux for 16h, cooled to rt, and concentrated under reduced pressure. The crude material was purified by preparative thin-layer chromatography (8 x 1000 μM) eluting with CH_2Cl_2/MeOH (25:1) to afford 148 mg (89%) of a yellow oil. M+H = 489.

STEP B: Removal of the t-butoxycarbonyl protecting group with TFA

To a solution of the compound prepared in Example 340, Step A (135 mg, 0.28 mmol) in CH_2Cl_2 (2 mL) at rt was added TFA (0.54 mL, 7.0 mmol) dropwise. The resulting solution was stirred for 18 h at rt and was concentrated under reduced pressure. The crude material was redissolved in CH_2Cl_2 (5 mL) and the organic layer was sequentially washed with sat. aq. $NaHCO_3$ (2 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 material was purified by preparative thin-layer chromatography (8 x 1000 μM) eluting with CH_2Cl_2/MeOH (20:1) to afford 105 mg (97%) of white solid. mp 120-122 °C; M+H = 389.

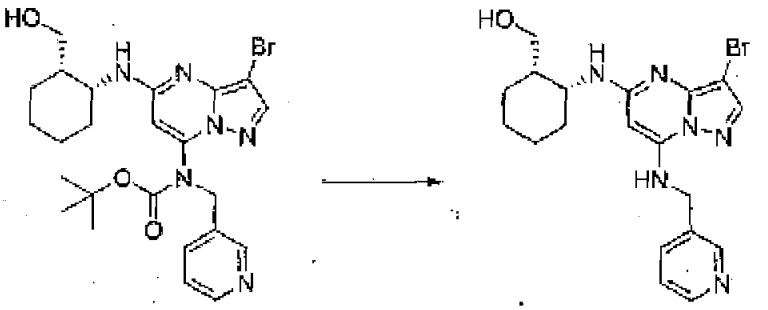
EXAMPLE 341:



Step A:

By essentially the same procedure set forth in Example 340 only substituting the appropriate amine, the above compound was prepared. MS: MH^+ = 431.

Step B: Removal to t-butoxycarbonyl protecting group with KOH.

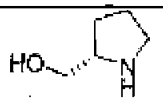
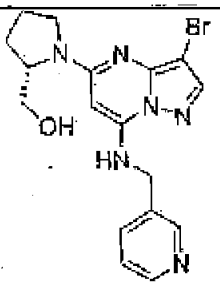
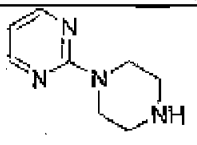
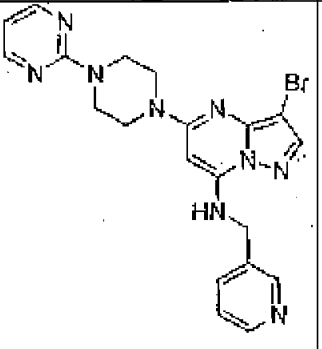
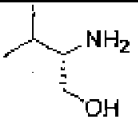
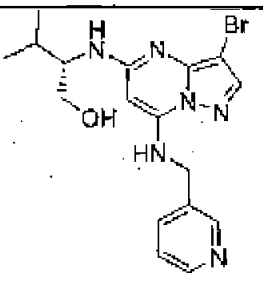
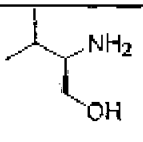
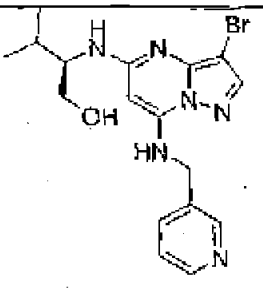


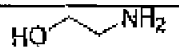
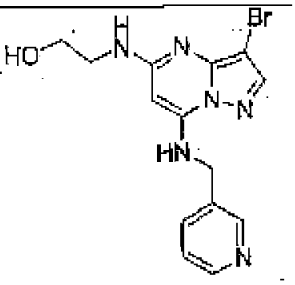
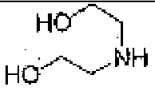
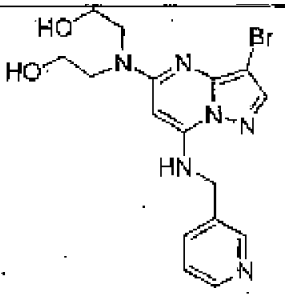
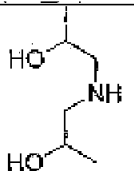
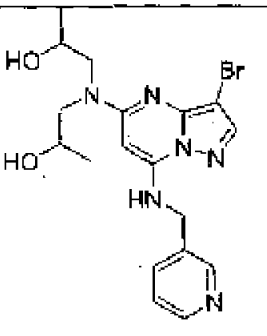
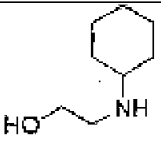
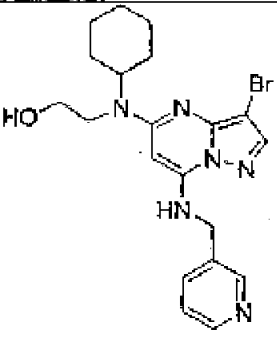
To a mixture of the compound prepared in Example 341, Step A (0.14 g, 0.26 mmol) in EtOH : H_2O (3 mL, 2 : 1) was added KOH (0.29 g, 20 eq.) in one portion. The resulting solution was stirred at reflux 14 hours, cooled to room temperature, and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (5 mL) and diluted with saturated $NaHCO_3$ (2 mL). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (2 x 4 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by preparative TLC (8 x 1000 μM) eluting with 5% MeOH in CH_2Cl_2 solution (0.066 g, 59% yield). MS: MH^+ = 432; mp = 219-221°C.

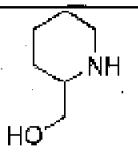
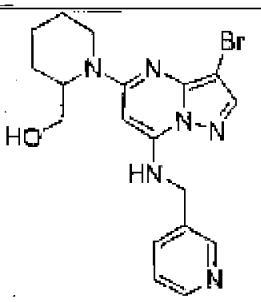
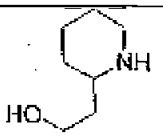
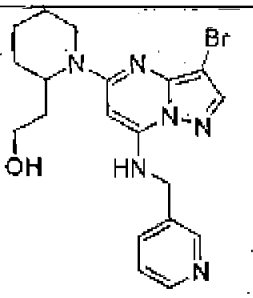
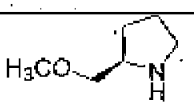
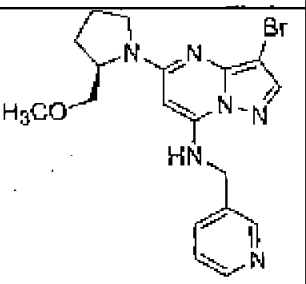
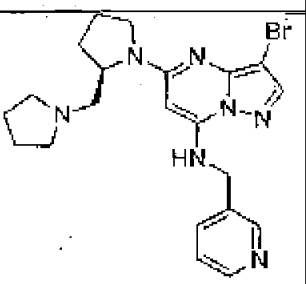
EXAMPLES 342-397:

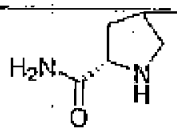
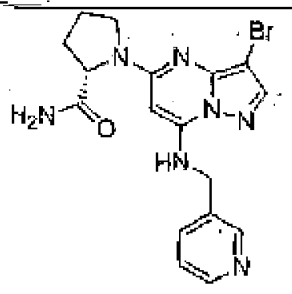
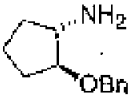
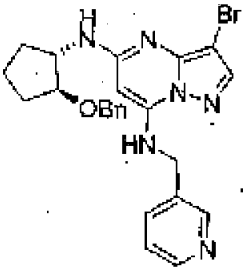
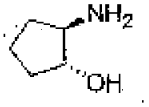
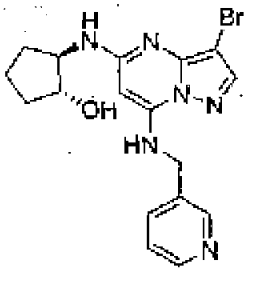
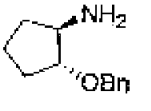
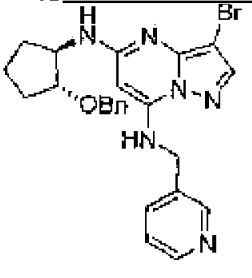
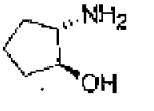
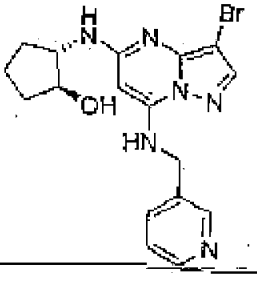
By essentially the same procedure set forth in Example 340 only substituting the chlorides in Column 2 of Table 31 and removing the t-butoxycarbonyl protecting group by the method shown in Column 3 of Table 31, the compounds shown in Column 4 of Table 31 were prepared.

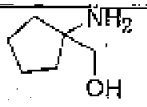
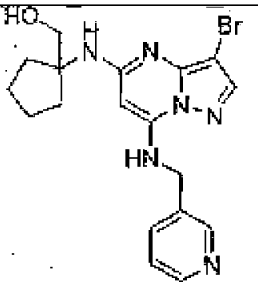
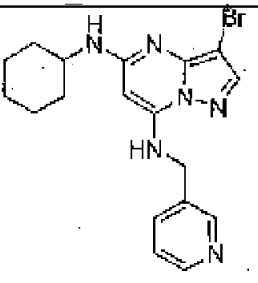
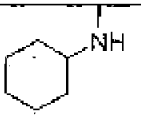
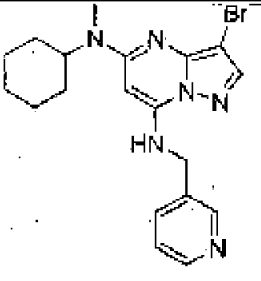
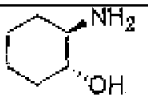
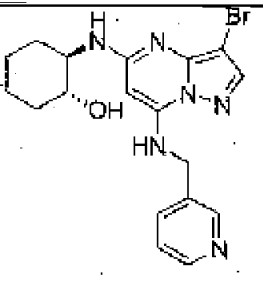
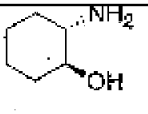
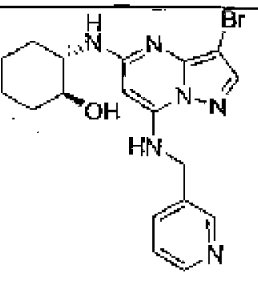
Table 31

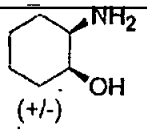
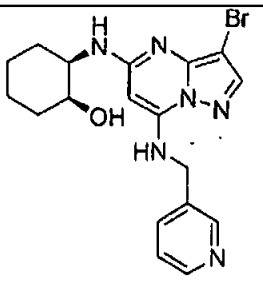
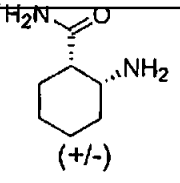
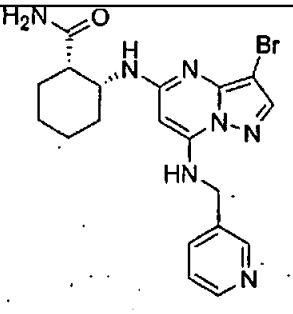
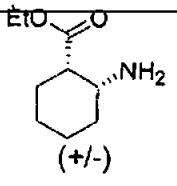
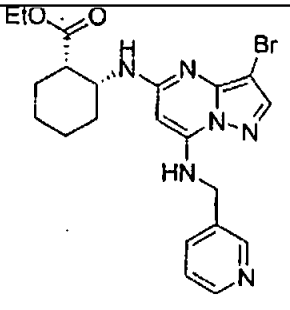
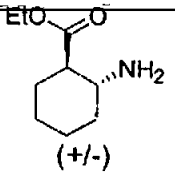
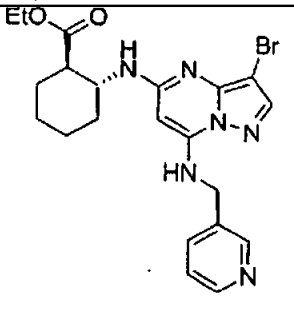
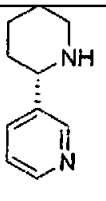
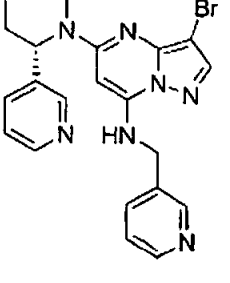
Ex.	Column 2	Column 3	Column 4	CMPD
342		HCl		MS: MH$^+$ = 403 m.p. 151 – 157 °C
343		HCl		MS: MH$^+$ = 466 m.p. 212 – 217 °C
344		HCl		MS: MH$^+$ = 405 m.p. 53 – 58 °C
345		HCl		MS: MH$^+$ = 405 m.p. 63 – 69 °C

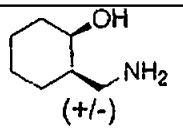
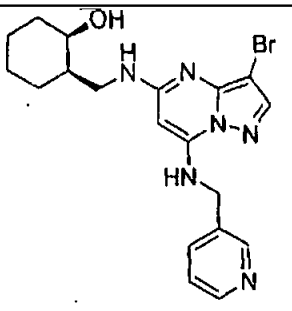
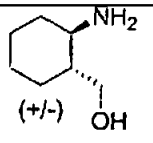
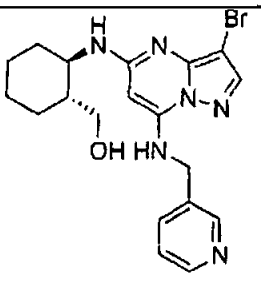
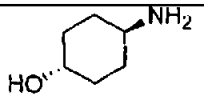
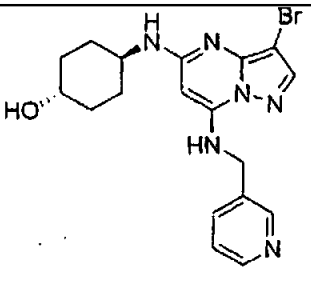
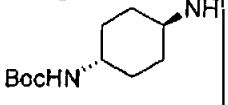
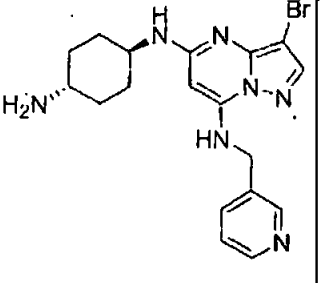
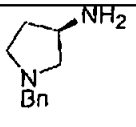
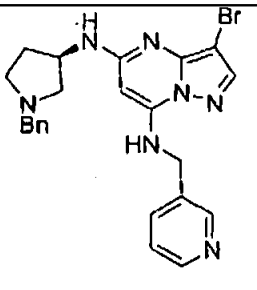
346		HCl		MS: MH^+ = 363 m.p. 170 – 171 °C
347		HCl		MS: MH^+ = 407 m.p. 148 – 151 °C
348		HCl		MS: MH^+ = 435 m.p. 56 – 59 °C
349		HCl		MS: MH^+ = 445 m.p. 66 – 68 °C

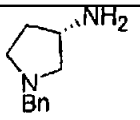
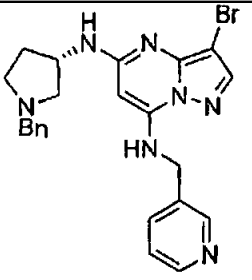
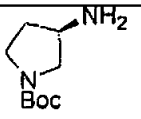
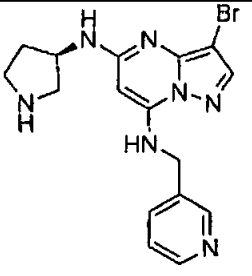
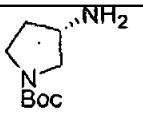
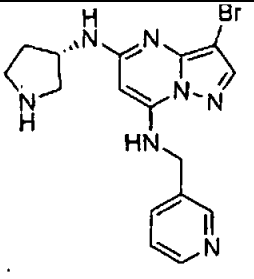
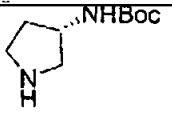
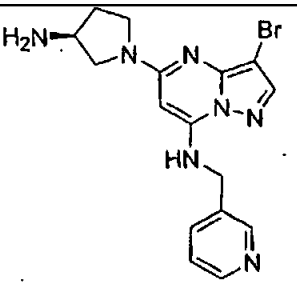
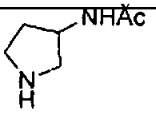
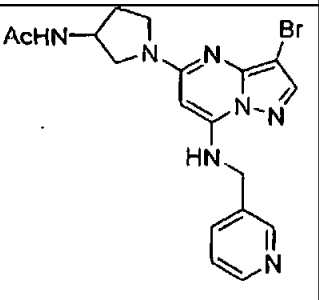
350		KOH		MS: MH^+ = 417 m.p. 149 – 151 °C
351		KOH		MS: MH^+ = 431 m.p. 111 – 114 °C
352		KOH		MS: MH^+ = 417 m.p. 53 – 58 °C
353		KOH		MS: MH^+ = 456 m.p. 186 – 189 °C

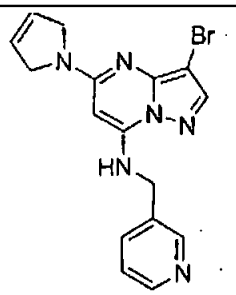
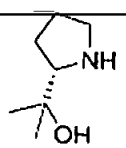
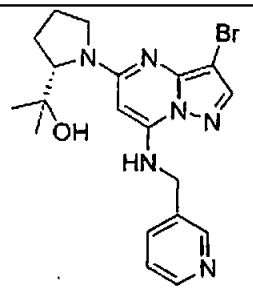
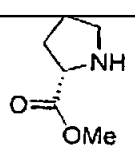
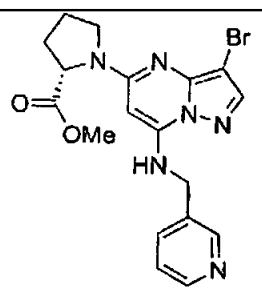
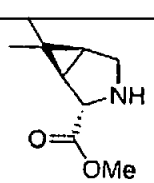
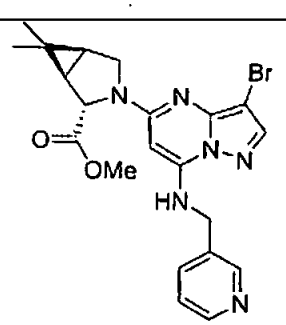
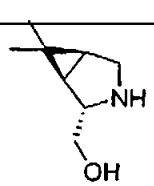
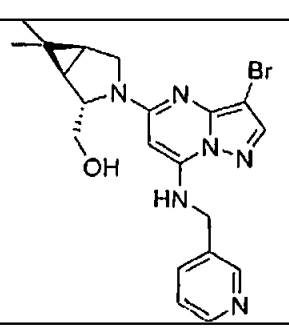
354		KOH		MS: MH^+ = 416 m.p. 210 – 213 °C
355		TFA		1. mp = 68-70 2. M+H = 494
356		KOH		1. mp = 181-183 2. M+H = 404
357		TFA		1. mp = 69-71 2. M+H = 494
358		KOH		1. mp = 182-184 2. M+H = 404

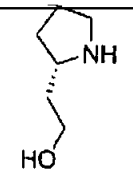
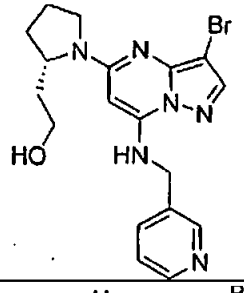
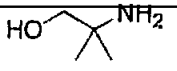
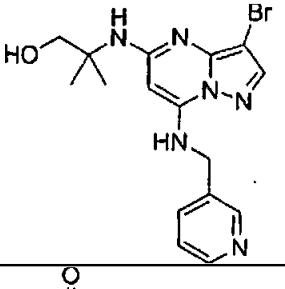
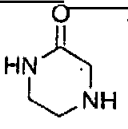
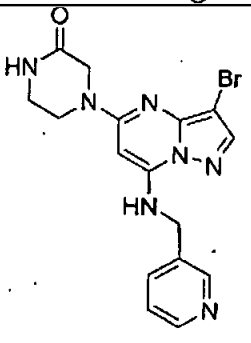
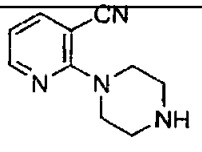
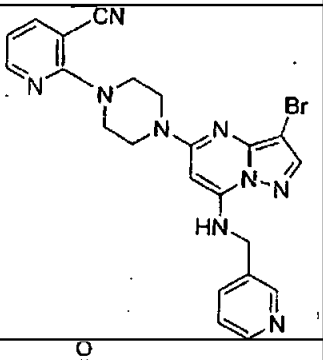
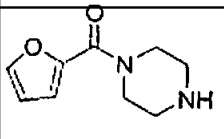
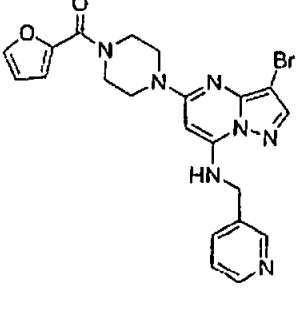
359		KOH		1. mp = 202-204 2. M+H = 418
360		TFA		1. mp = 160-162 2. M+H = 402
361		TFA		1. mp = 151-153 2. M+H = 416
362		KOH		1. mp = 140-143 2. M+H = 418
363		KOH		1. mp = 139-142 2. M+H = 418

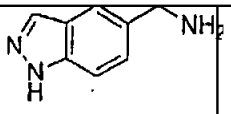
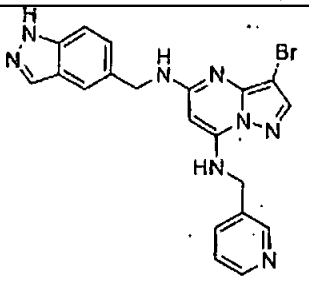
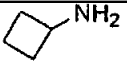
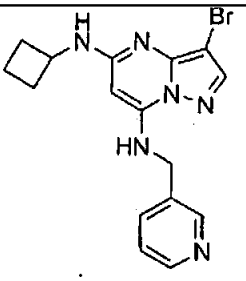
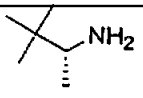
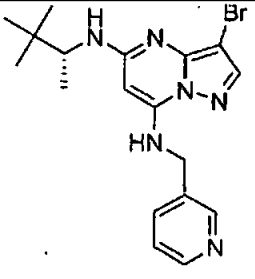
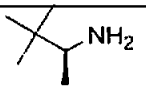
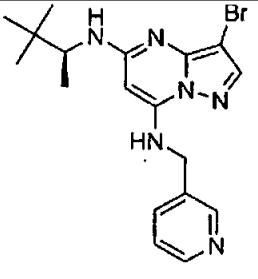
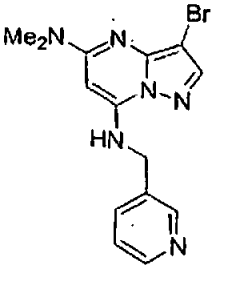
364		KOH		1. mp = 115-117 2. M+H = 418
366		TFA		1. mp = 102-104 2. M+H = 445
367		TFA		1. mp = 118-120 2. M+H = 474
368		TFA		1. mp = 106-108 2. M+H = 474
369		TFA		1. mp = 160-161 2. M+H = 464

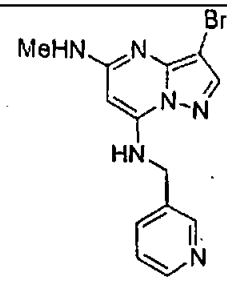
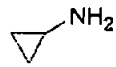
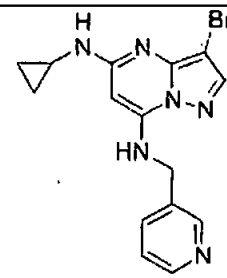
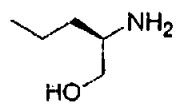
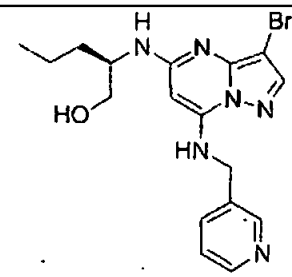
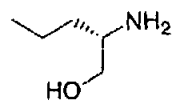
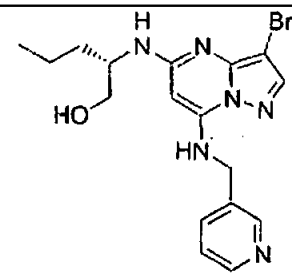
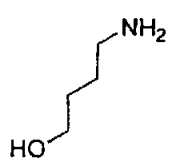
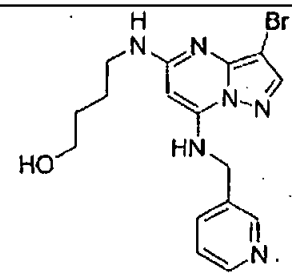
370		TFA		1. mp = 93-95 2. M+H = 432
371		KOH		1. mp = 108-110 2. M+H = 432
372		KOH		1. mp = 180-182 2. M+H = 418
373		TFA		1. mp = 169-170 2. M+H = 417
374		TFA		1. mp = 77-79 2. M+H = 479

375		TFA		1. mp = 76-79 2. M+H = 479
376		TFA		1. mp = 105-107 2. M+H = 389
377		TFA		1. mp = 105-107 2. M+H = 389
378		TFA		1. mp = 130-133 2. M+H = 389
379		TFA		1. mp = 132-135 2. M+H = 431

380		TFA		1. mp = 135-137 2. M+H = 372
381		KOH		1. mp = 78-82 2. M+H = 432
382		TFA		1. mp = 101-103 2. M+H = 432
383		TFA		1. mp = 92-95 2. M+H = 472
384		TFA		1. mp = 107-111 2. M+H = 444

384.10		TFA		1. mp = 2. M+H = 417
384.11		TFA		1. mp = 210-212 2. M+H = 391
385		TFA		1. mp = 122-124 2. M+H = 403
386		TFA		1. mp = 186-188 2. M+H = 491
387		TFA		1. mp = 173-175 2. M+H = 483

388		TFA		1. mp = 167-169 2. M+H = 450
389		TFA		1. mp = 90-92 2. M+H = 374
390		TFA		1. mp = 113-115 2. M+H = 404
391		TFA		1. mp = 114-116 2. M+H = 404
392		TFA		LCMS: MH^+ = 347;

393	H_2NMe	TFA		LCMS: MH^+ = 333;
394		TFA		LCMS: MH^+ = 359;
395		TFA		LCMS: MH^+ = 405;
396		TFA		LCMS: MH^+ = 405;
397		TFA		LCMS: MH^+ = 391;

Additional data for select example shown below:

Example 392: ^{1}H NMR (DMSO-d_6) δ 8.65 (s, 1H), 8.46 (d, J = 3.3 Hz, 1H), 8.21 (t, J = 6.6 Hz, 1H), 7.90 (s, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.35 (dd, J = 7.8, 4.8 Hz, 1H), 5.46 (s, 1H), 4.61 (d, J = 6.9 Hz, 2H), 3.01 (s, 6H).

Example 393: ^{1}H NMR ($CDCl_3$) δ 8.65 (s, 1H), 8.60 (d, J = 4.8 Hz, 1H), 7.76 (s, 1H), 7.70 (m, 1H), 7.32 (dd, J = 8.1, 4.8 Hz, 1H), 6.43 (t, J = 6.0 Hz, 1H), 5.08 (s, 1H), 4.80 (m, 1H), 4.56 (d, J = 6.0 Hz, 2H), 2.96 (d, J = 5.1 Hz, 3H).

Example 394: ^{1}H NMR ($CDCl_3$) δ 8.68 (s, 1H), 8.60 (d, J = 4.8 Hz, 1H), 7.76 (s, 1H), 7.72 (m, 1H), 7.32 (dd, J = 7.8, 5.4 Hz, 1H), 6.55 (t, J = 5.7 Hz, 1H), 5.53 (s, 1H), 5.35 (s, 1H), 4.62 (d, J = 5.7 Hz, 2H), 2.49 (m, 1H), 0.75 (m, 2H), 0.51 (m, 2H).

Example 395: ^{1}H NMR ($CDCl_3$) δ 8.65 (s, 1H), 8.60 (d, J = 4.0 Hz, 1H), 7.75 (s, 1H), 7.69 (m, 1H), 7.33 (dd, J = 8.1, 5.1 Hz, 1H), 6.45 (t, J = 6.0 Hz, 1H), 5.07 (s, 1H), 4.69 (m, 1H), 4.54 (d, J = 6.0 Hz, 2H), 3.98 (m, 1H), 3.79 (dd, J = 10.8, 2.4 Hz, 1H), 3.59 (dd, J = 11.1, 7.2 Hz, 1H), 1.59-1.36 (m, 4H), 0.94 (t, J = 6.9 Hz, 3H).

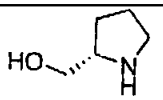
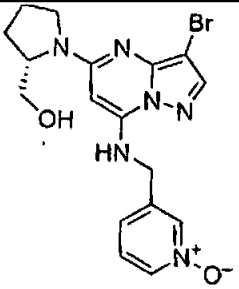
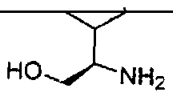
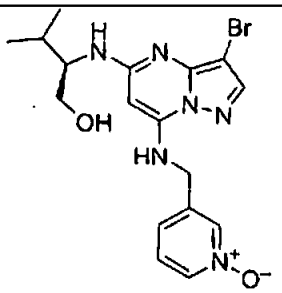
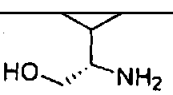
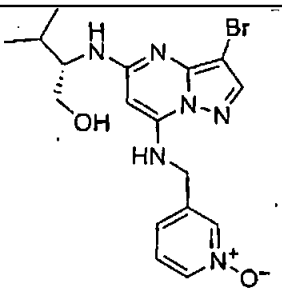
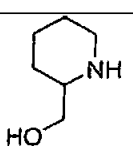
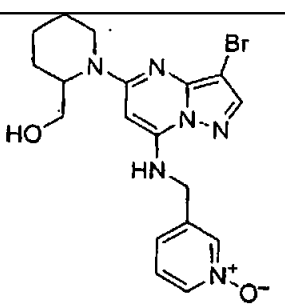
Example 396: ^{1}H NMR ($CDCl_3$) δ 8.60 (s, 1H), 8.56 (d, J = 4.2 Hz, 1H), 7.73 (s, 1H), 7.66 (m, 1H), 7.31 (dd, J = 7.8, 4.8 Hz, 1H), 6.51 (t, J = 6.0 Hz, 1H), 5.05 (s, 1H), 4.86 (d, J = 6.6 Hz, 1H), 4.50 (d, J = 6.0 Hz, 2H), 3.94 (m, 1H), 3.78 (dd, J = 11.1, 2.4 Hz, 1H), 3.57 (dd, J = 11.1, 7.2 Hz, 1H), 1.57-1.34 (m, 4H), 0.91 (t, J = 7.2 Hz, 3H).

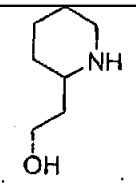
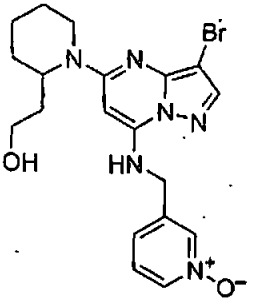
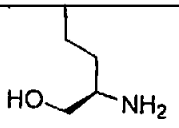
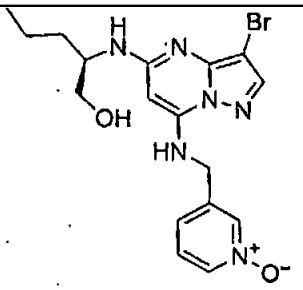
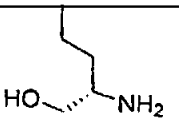
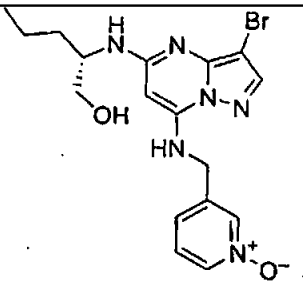
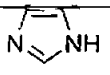
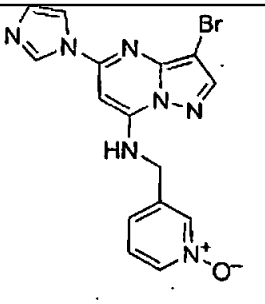
Example 397: ^{1}H NMR ($CDCl_3$) δ 8.65 (s, 1H), 8.59 (d, J = 4.5 Hz, 1H), 7.75 (s, 1H), 7.69 (m, 1H), 7.31 (m, 1H), 6.43 (t, J = 6.0 Hz, 1H), 5.06 (s, 1H), 4.88 (m, 1H), 4.55 (d, J = 6.0 Hz, 2H), 3.70 (m, 2H), 3.38 (m, 2H), 1.79-1.61 (m, 4H).

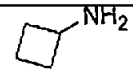
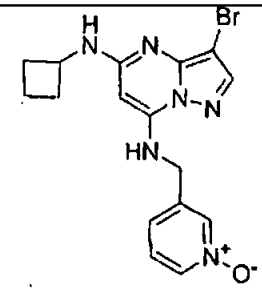
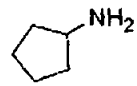
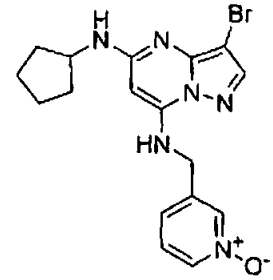
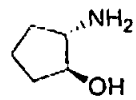
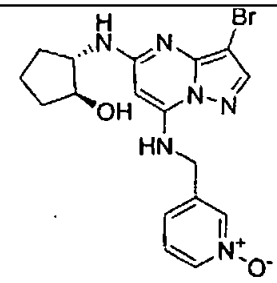
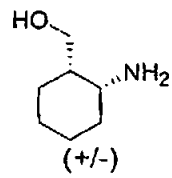
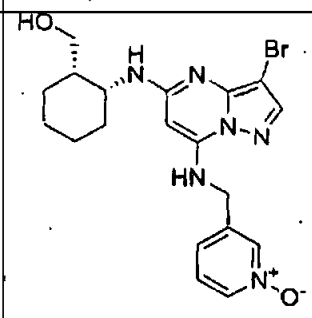
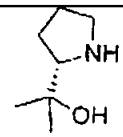
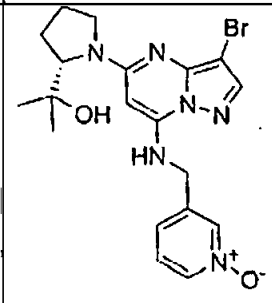
EXAMPLES 398-416:

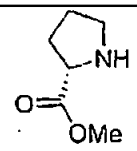
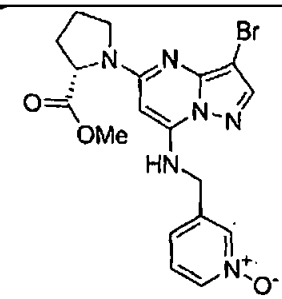
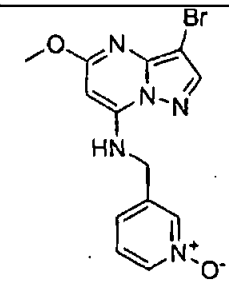
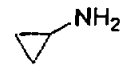
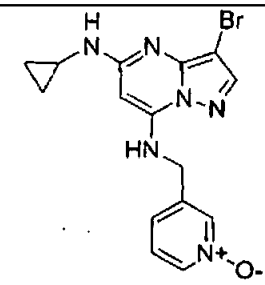
By essentially the same conditions set forth in Example 341, Steps A and B only substituting the compound prepared in Preparative Example 193.10, the compounds in Column 4 of Table 32 were prepared.

Table 32

Ex.	Column 2	Column 3	Column 4	CMPD
398				MS: MH^+ = 419 m.p. 102 – 105 °C
399				MS: MH^+ = 421 m.p. 79 – 81 °C
400				MS: MH^+ = 421 m.p. 78 – 79 °C
401				MS: MH^+ = 433 m.p. 228-231 °C

402				MS: MH^+ = 447 m.p. 97-102 °C
403				MS: MH^+ = 421 m.p. °C
404				MS: MH^+ = 421 m.p. °C
405				MS: MH^+ = 386 m.p. °C

407		KOH		1. mp = 98-100 2. M+H = 390
408		TFA		1. mp = 170-173 2. M+H = 404
409		KOH		1. mp = 218-221 2. M+H = 420
410		KOH		1. mp = 110-112 2. M+H = 448
411		TFA		1. mp = 81-83 2. M+H = 448

412		TFA		1. mp = 136-138 2. M+H = 448
413	NaOMe	KOH		1. mp = 107-110 2. M+H = 351
414				LCMS: MH^+ = 375;

Additional data for select examples shown below:

Example 414: ^{1}H NMR (DMSO-d_6) δ 8.26 (s, 1H), 8.23 (m, 1H), 8.13 (m, 1H), 7.90 (s, 1H), 7.40-7.27 (m, 3H), 5.34 (s, 1H), 4.49 (d, J = 6.3 Hz, 2H), 2.56 (m, 1H), 0.67 (m, 2H), 0.35 (m, 2H).

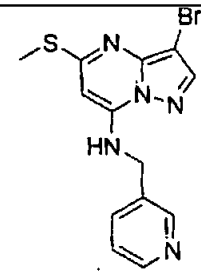
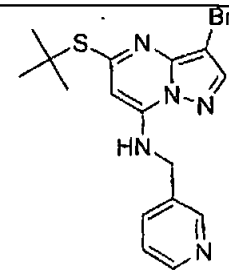
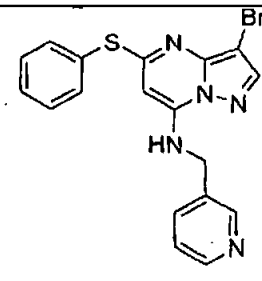
Example 403: ^{1}H NMR (DMSO-d_6+$CDCl_3$) δ 8.08 (s, 1H), 7.90 (d, J = 6.3 Hz, 1H), 7.49 (s, 1H), 7.34 (t, J = 6.3 Hz, 1H), 7.16-7.09 (m, 2H), 5.65 (d, J = 6.6 Hz, 1H), 4.97 (s, 1H), 4.90 (s, 1H), 4.29 (d, J = 6.3 Hz, 2H), 3.70 (m, 1H), 3.46 (m, 1H), 3.34 (m, 1H), 1.35-1.17 (m, 4H), 0.71 (t, J = 7.2 Hz, 3H).

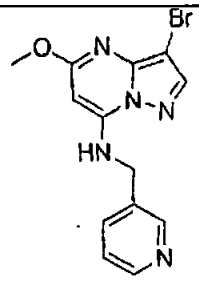
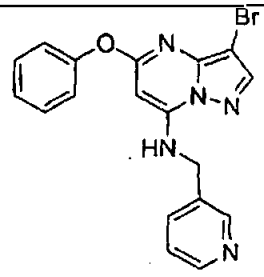
Example 404: ^{1}H NMR (DMSO-d_6) δ 8.21 (s, 1H), 8.12 (d, J = 6.6 Hz, 1H), 8.06 (m, 1H), 7.86 (s, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 6.73 (d, J = 8.7 Hz, 1H), 5.28 (s, 1H), 4.70 (t, J = 5.1 Hz, 1H), 4.41 (d, J = 6.6 Hz, 2H), 4.00 (s, 1H), 3.39 (m, 1H), 1.53 (m, 1H), 1.36-1.25 (m, 3H), 0.86 (t, J = 7.0 Hz, 3H).

EXAMPLES 417—421:

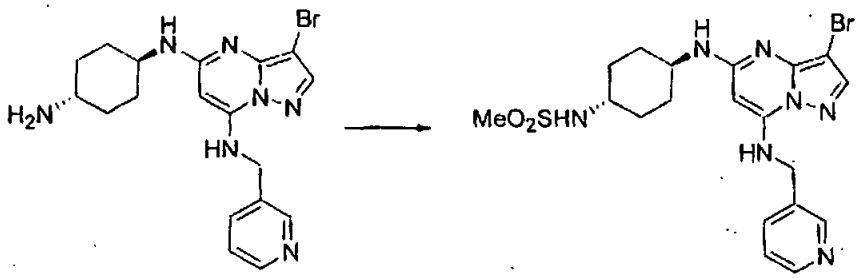
By the procedure set forth in *Chem. Pharm. Bull.* **1999**, *47*, 928-938. utilizing the oxygen or sulfur nucleophiles shown in Column 2 as described of Table 33 and by employing the cleavage method listed in Column 3 of Table 33, the compounds in Column 4 of Table 33 were prepared:

TABLE 33

Ex.	Column 2 (Nucleophile)	Column 3 (Cleavage method)	Column 4 (Final Structure)	CMPD 1. mp. 2. M+H
417	NaSMe	TFA		1. mp = 172-175 2. M+H = 351
418	NaSt-Bu	TFA		1. mp = 165-168 2. M+H = 392
419	NaSPh	TFA		1. mp = 154-156 2. M+H = 412
420	NaOMe	TFA		1. mp = 161-163 2. M+H = 335

				
421	NaOPh	TFA		1. mp = 64-66 2. M+H = 397

EXAMPLE 422:

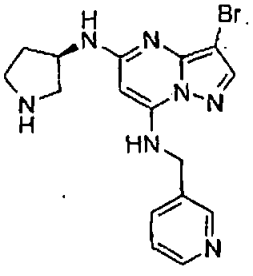
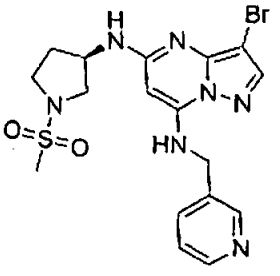
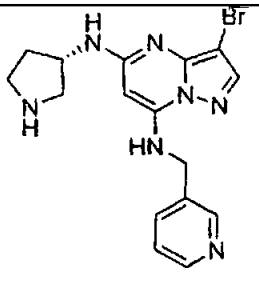
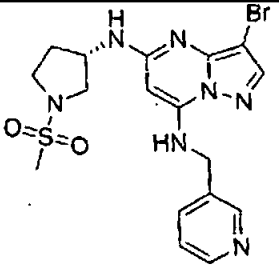


To a solution of amino compound (18 mg, 0.043 mmol) from Example 373 in CH_2Cl_2 (1 mL) at rt was added DIPEA (10 μL, 0.056 mmol) followed by $MeSO_2Cl$ (4 mL, 0.052 mmol). The mixture was stirred at rt for 12 h and was diluted with CH_2Cl_2 (2 mL) and sat. aq. $NaHCO_3$ (2 mL). The layers were separated and the organic layer was extracted with brine (1 x 2 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was purified by preparative thin-layer chromatography (4 x 1000 μM) eluting with CH_2Cl_2/MeOH (20:1) to afford 16 mg (75%) of white solid. mp 152-154 °C; M+H = 495.

EXAMPLES 423-424:

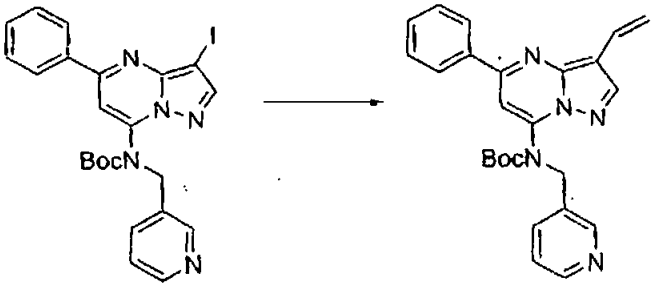
Utilizing the procedure outlined in Example 422, the amino compounds (Column 2) were converted to the corresponding methylsulfonamides (Column 3) in Table 34:

TABLE 34

Ex.	Column 2 (Amine)	Column 3 (Final Structure)	CMPD 1. mp. 2. M+H
423			1. mp = 166-168 2. M+H = 467
424			1. mp = 165-168 2. M+H = 467

EXAMPLE 425:

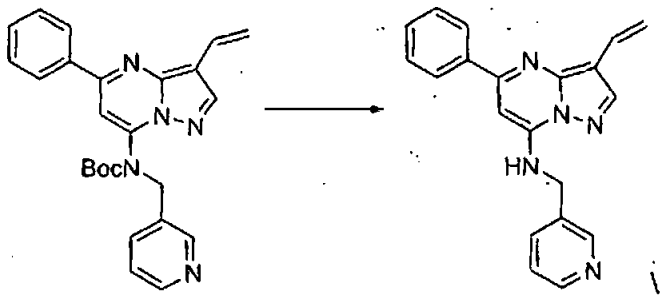
STEP A:



A mixture of the compound prepared in Preparative Example 194 (132 mg, 0.25 mmol), tributylvinyltin (95 mg, 0.30 mmol) and

tetrakis(triphenylphospine) palladium (29 mg, 0.025 mmol) in anhydrous dioxane (5 mL) was refluxed under N_2 for 24 hr. The solvent was evaporated and the residue was purified by flash chromatography using 2:1 CH_2Cl_2:EtOAc as eluent to yield yellow waxy solid (53 mg, 50%). LCMS: MH^+=428.

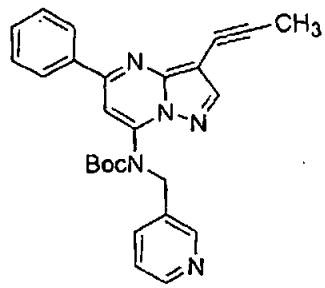
STEP B:



A mixture of the compound prepared in Example 425, Step A (50 mg, 0.12 mmol) and KOH (100 mg, 1.80 mmol) in ethanol (3 mL) and H_2O (0.6 mL) was stirred at 70°C under N_2 for 24 hr. $NaHCO_3$ (1.0 g), Na_2SO_4 (2.0g), and CH_2Cl_2 (20 mL) were added, the mixture was shaken and then filtered. The solvent was evaporated and the residue was purified by flash chromatography using 20:1:0.1 CH_2Cl_2:MeOH:conc.NH_4OH as eluent to yield yellow waxy solid (17 mg, 45%). LCMS: MH^+=328. Mp=48-51 °C.

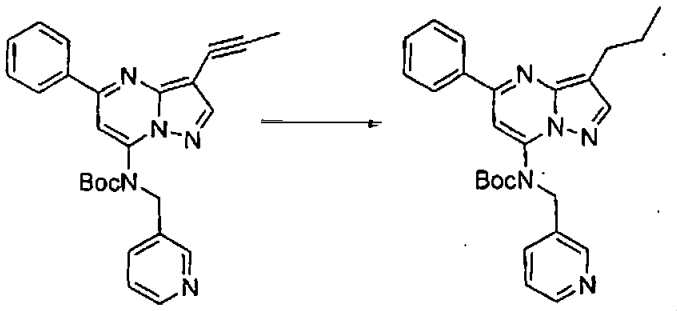
EXAMPLE 426:

STEP A:



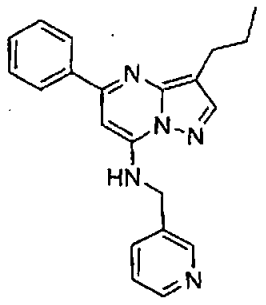
By essentially the same procedure set forth in Example 425, Step A only using tributylmethylethynyltin, the compound shown above was prepared.

STEP B:



A mixture of the compound prepared in Example 426, Step A (150 mg, 0.34 mmol) and PtO2 (30 mg, 0.13 mmol) in glacial acetic acid (5 mL) was stirred under 1 atmosphere of H_2 for 20 hr. The mixture was filtered, fresh PtO2 (30 mg, 0.13 mmol) was added and the mixture was stirred under 1 atmosphere of H_2 for 2.5 hr. The mixture was poured onto Na_2CO_3 (20 g) and H_2O (200 mL) and it was extracted with CH_2Cl_2 (4x20 mL). The combined extracts were dried over Na_2SO_4 and filtered. The solvent was evaporated and the residue was purified by flash chromatography using 1:1 CH_2Cl_2:EtOAc as eluent to yield yellow waxy solid (68 mg, 45%).

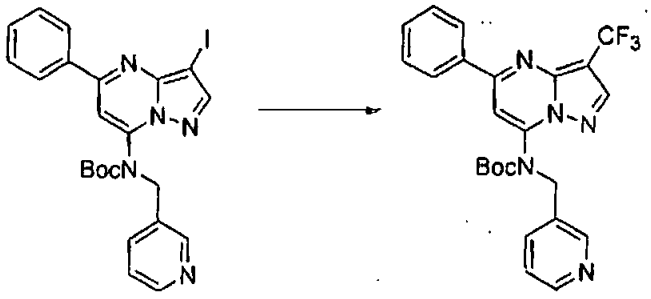
STEP C:



By essentially the same procedure set forth in Example 425, Step B only substituting the compound prepared in Example 426, Step B, the compound shown above was prepared, MS: MH^+=344. Mp=110-112 °C.

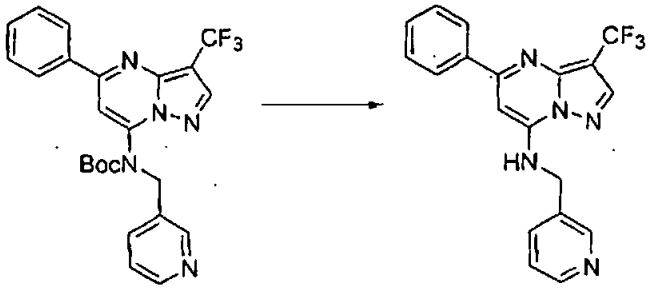
EXAMPLE 427:

STEP A:



A mixture of the compound prepared in Preparative Example 194 (527 mg, 1.00 mmol), triethyl(trifluoromethyl)silane (666 mg, 3.60 mmol), potassium fluoride (210 mg, 3.60 mmol), and CuI (850 mg, 4.46 mmol) in anhydrous DMF (4 mL) was stirred in a closed pressure vessel at 80°C for 72 hr. CH2Cl2 (80 mL) was added and the mixture was filtered through Celite. The solvent was evaporated and the residue was purified by flash chromatography using 2:1 CH_2Cl_2: EtOAc as eluent to yield pale orange waxy solid (70 mg, 15%). LCMS: M^+=470.

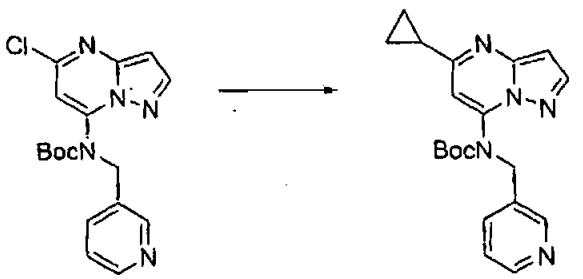
STEP B:



TFA (0.70 mL) was added at 0°C under N_2 to a stirred solution of the compound prepared in Example 427, Step A (70 mg, 0.15 mmol), in anhydrous CH_2Cl_2 (3 mL). The mixture was stirred at 0°C for 10 min, then at 25°C for 2 hr. It was poured into 10 % aqueous Na_2CO_3 (50 mL), extracted with CH_2Cl_2 (3x15 mL), dried over Na_2SO_4, and filtered. The solvent was evaporated and the residue was purified by flash chromatography using EtOAc as eluent to yield off-white solid (40 mg, 73%). LCMS: M^+=370. Mp=156-158 °C.

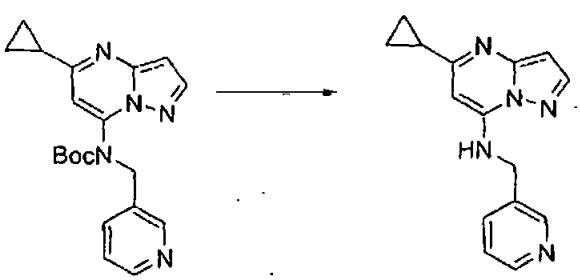
EXAMPLE 428:

STEP A:



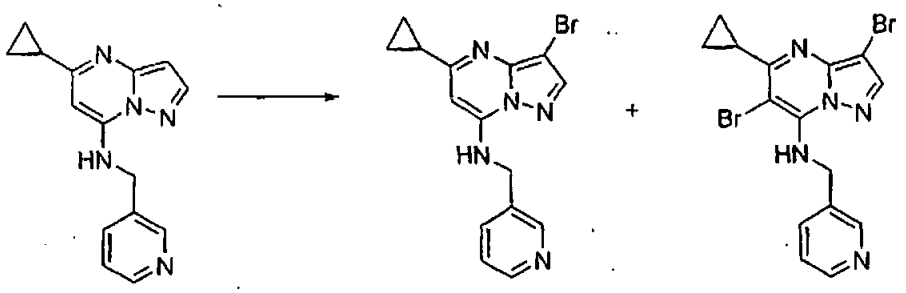
A mixture of the compound prepared in Preparative Example 193 (100 mg, 0.28 mmol), tetracyclopropyltin (91 mg, 0.32 mmol), Pd_2dba_3 (8.0 mg, 0.009 mmol) and $Pd(Pt\text{-}Bu_3)_2$ (9.0 mg, 0.017 mmol) in anhydrous dioxane (3 mL) was refluxed under N_2 for 27 hr. The solvent was evaporated and the residue was purified by flash chromatography using 1:1 CH_2Cl_2:EtOAc as eluent to yield colorless waxy solid (38 mg, 38%). LCMS: MH^+=366.

STEP B:



A mixture of the compound prepared in Example 428, Step A (36 mg, 0.10 mmol) and KOH (300 mg, 5.40 mmol) in ethanol (3 mL), 1,2-dimethoxyethane (3.0 mL0 and H_2O (0.8 mL) was refluxed under N_2 for 4 hr. It was poured into saturated aqueous $NaHCO_3$ (100 mL), extracted with CH_2Cl_2 (5x10 mL), dried over Na_2SO_4, and filtered. The solvent was evaporated and the residue was purified by flash chromatography using 30:1. EtOAc:MeOH as eluent to yield colorless waxy (18 mg, 69%). LCMS: MH^+=266.

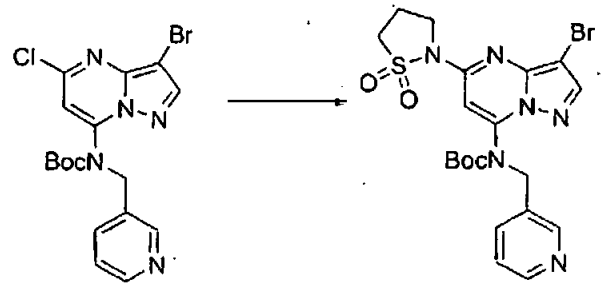
STEP C:



N-bromosuccinimide (12 mg, 0.068 mmol) in anhydrous CH_3CN (2 mL) was added under N_2 to a stirred solution of the compound prepared in Example 428, Step B (18 mg, 0.068 mmol), in anhydrous CH_3CN (2 mL). The mixture was stirred at 25°C for 2 hr. The solvent was evaporated and the residue was purified by flash chromatography using EtOAc as eluent to yield 5 mg (17%) of the dibromo compound (white solid, LCMS: MH^+=370, mp= 150-152°C) and 8 mg (34%) of the monobromo compound (colorless solid, LCMS: M^+=344, mp= 196-198°C).

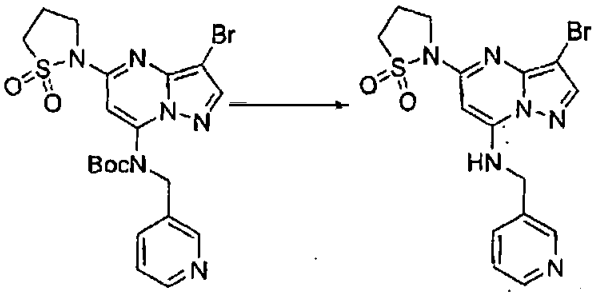
EXAMPLE 429:

STEP A:



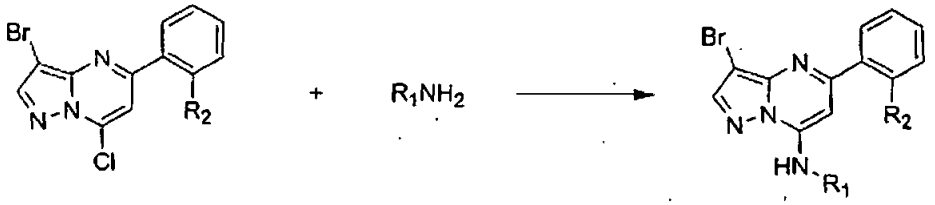
1,3-propanesultam (72 mg, 0.60 mmol) in anhydrous DMF (3 mL) was added under N_2 to 60 % NaH in mineral oil (36 mg, 0.90 mmol). The mixture was stirred for 20 min, then the compound prepared in Preparative Example 196 (200 mg, 0.46 mmol) was added. The mixture was stirred at 100°C for 30 min, the solvent was evaporated and the residue was purified by flash chromatography using EtOAc as eluent to yield colorless solid (150 mg, 63%). LCMS: M^+=523.

STEP B:



TFA (1.5 mL) was added at 0°C under N_2 to a stirred solution of the compound prepared in Preparative Example 196 (140 mg, 0.27 mmol), in anhydrous CH_2Cl_2 (5 mL). The mixture was stirred at 0°C for 10 min, then at 25°C for 2 hr. It was poured onto Na_2CO_3 (10 g), extracted with CH_2Cl_2 (3x50 mL), and filtered. The solvent was evaporated and the residue was purified by flash chromatography using 40:1 EtOAc:MeOH as eluent to yield white solid (32 mg, 28%). LCMS: M^+=423. Mp=218-220 °C.

EXAMPLE 430:



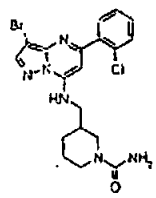
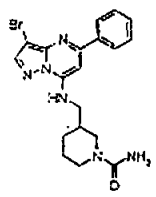
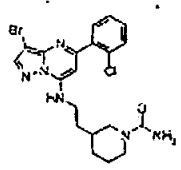
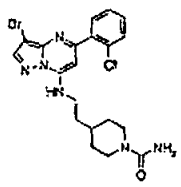
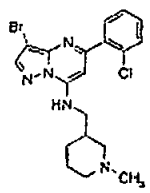
Where: R_2=H, or Cl

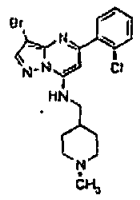
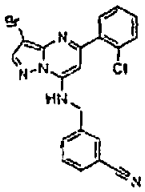
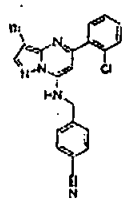
3-Bromo-7-chloro-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidine (1 equivalent) (prepared as described in Preparative Example 129), or 3-Bromo-7-chloro-5-phenylpyrazolo[1,5-a]pyrimidine (1 equivalent) (prepared as described in Preparative Example 127), R_1NH_2 (1.2 equivalents) and diisopropyl ethylamine (2 equivalents) were dissolved in anhydrous 1,4-dioxane and the mixture was heated at 75°C for the time given in Table 97. The solution was evaporated to dryness and the residue was chromatographed on a silica gel column as described in Table 97, to give the title compound.

Using the appropriate reactants and essentially the same procedure as described above, the products of Examples 431 to 438 were prepared. Variations in the reaction conditions are noted in Table 35.

279

TABLE 35

Ex.	Structure	MW	FABMS MH^+	Reaction Conditions	Yield	Chromatographic Data
431		463.8	463.0	75°C / 26h	52%	15x2.5cm 0.5-2% (10% Conc. ammonium hydroxide in methanol)-dichloromethane
432		429.3	429.2	75°C / 26h 25°C / 39h	53%	15x5cm Dichloromethane; 1.5% (10% Conc. ammonium hydroxide in methanol)-dichloromethane
433		477.8	477.1	75°C / 26h	48%	15x5cm Dichloromethane; 3.5-15% (10% Conc. ammonium hydroxide in methanol)-dichloromethane
434		477.8	477.0	75°C / 26h	50%	15x5cm Dichloromethane; 3.5-15% (10% Conc. ammonium hydroxide in methanol)-dichloromethane
435		434.8	434.1	75°C / 24h 25°C / 65h	53%	15x2.5cm 3% (10% Conc. ammonium hydroxide in methanol)-dichloromethane
436		434.8	434.2	75°C / 27h	31%	15x2.5cm 3% (10% Conc. ammonium hydroxide in methanol)-dichloromethane

						
437		438.7	438.1	75°C / 21h 25°C / 46h	97%	15x2.5cm 0.25% (10% Conc. ammonium hydroxide in methanol)-dichloromethane
438		438.7	438.1	75°C / 28h -20°C / 72h	95%	60x2.5cm 20% Ethyl acetate in hexane

Additional physical data for the compounds are given below:

EXAMPLE 431: Reactants: 3-Bromo-7-chloro-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidine (110mg, 0.318mmoles) (prepared as described in Preparative Example 129); 3-(aminomethyl)piperidine-1-carboxamide (60mg, 0.382mmoles) (prepared as described in Preparative Example 241 above); diisopropyl ethylamine (0.111mL, 0.636mmoles); anhydrous 1,4-dioxane (2.5mL). Physical properties: HRFABMS: m/z 463.0628 (MH^+). Calcd. for $C_{19}H_{21}N_6OBrCl$: m/z 463.0649: δ_H ($CDCl_3$) 1.38 (1H, m, CH_2), 1.52 (1H, m, CH_2), 1.73 (1H, m, CH), 1.93 (1H, m, CH_2), 2.02 (1H, m, CH_2), 2.98 (1H, m, CH_2), 3.06 (1H, m, CH_2), 3.37 (2H, m, CH_2), 3.58 (1H, m, CH_2), 3.82 (1H, m, CH_2), 4.87 (2H, bm, $CONH_2$), 6.28 (1H, s, H_6), 7.02 (1H, m, NH), 7.36 (2H, m, Ar-H), 7.45 (1H, m, Ar-H), 7.68 (1H, m, Ar-H) and 8.00 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 23.7, 28.1, 44.6, 45.5, 47.2; CH: 35.2, 87.4, 127.2, 130.1, 130.3, 131.6, 143.9: C: 83.1, 132.1, 138.6, 145.5, 146.5, 158.0, 158.4.

EXAMPLE 432: Reactants: 3-Bromo-7-chloro-5-phenylpyrazolo[1,5-a]pyrimidine (500mg, 1.62mmoles) (prepared as described in Preparative Example 127); 3-(aminomethyl)piperidine-1-carboxamide (306mg, 1.944mmoles) (prepared as described in Preparative Example 241 above); diisopropyl ethylamine (0.566mL, 3.24mmoles); anhydrous 1,4-dioxane (13mL). Physical properties: HRFABMS: m/z 429.1031 (MH^+). Calcd. for $C_{19}H_{22}N_6OBr$: m/z 429.1038; δ_H ($CDCl_3$) 1.44 (1H, m, CH_2), 1.59 (1H, m, CH_2), 1.79 (1H, m, CH), 2.01 (1H, m, CH_2), 2.08 (1H, m, CH_2), 3.03 (1H, m, CH_2), 3.13 (1H, m, CH_2), 3.39 (1H, m, CH_2), 3.47 (1H, m, CH_2), 3.63 (1H, m, CH_2), 3.90 (1H, m, CH_2), 4.88 (2H, bm, $CONH_2$), 6.40 (1H, s, H_6), 6.90 (1H, m, NH), 7.53 (2H, m, Ar-H), 8.02 (1H, s, H_2) and 8.12 (1H, m, Ar-H); δ_C ($CDCl_3$) CH_2: 23.7, 28.2, 44.7, 45.5, 47.3; CH: 35.2, 82.9, 127.5, 127.5, 128.7, 128.7, 130.0, 143.9; C: 83.0, 138.5, 145.8, 147.1, 158.3, 158.5.

EXAMPLE 433: Reactants: 3-Bromo-7-chloro-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidine (347mg, 1.01mmoles) (prepared as described in Preparative Example 129); 3-(aminoethyl)piperidine-1-carboxamide (208mg, 1.21mmoles) (prepared as described in Preparative Example 242 above); diisopropyl ethylamine (0.393mL, 2.02mmoles); anhydrous 1,4-dioxane (9mL). Physical properties: δ_H ($CDCl_3$) 1.24 (1H, m, CH_2), 1.55 (1H, m, CH), 1.72 (4H, m, CH_2), 1.93 (1H, m, CH_2), 2.69 (1H, m, CH_2), 2.94 (1H, m, CH_2), 3.55 (2H, m, CH_2), 3.73 (1H, m, CH_2), 3.98 (1H, m, CH_2), 4.83 (2H, bm, $CONH_2$), 6.55 (1H, s, H_6), 6.78 (1H, m, NH), 7.41 (2H, m, Ar-H), 7.50 (1H, m, Ar-H), 7.75 (1H, m, Ar-H) and 8.04 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 24.6, 30.7, 32.6, 39.9, 45.3, 49.3; CH: 33.3, 87.5, 127.4, 130.1, 130.2, 131.6, 143.8; C: 83.2, 132.1, 138.8, 145.7, 146.2, 158.1, 158.1.

EXAMPLE 434: Reactants: 3-Bromo-7-chloro-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidine (275mg, 0.803mmoles) (prepared as described in Preparative Example 129); 4-(aminoethyl)piperidine-1-carboxamide (165mg, 0.963mmoles) (prepared as described in Preparative Example 243 above); diisopropyl ethylamine (0.311mL, 0.963mmoles); anhydrous 1,4-dioxane (7.2mL). Physical properties: δ_H (d_6-DMSO) 1.00 (2H, m, CH_2), 1.50 (1H, m, CH), 1.59 (2H, m,

CH_2), 1.67 (2H, m, CH_2), 2.60 (2H, m, CH_2), 3.48 (2H, m, CH_2), 3.70 (2H, m, CH_2), 5.84 (2H, bs, $CONH_2$), 6.43 (1H, s, H_6), 7.50 (2H, m, Ar-H), 7.62 (2H, m, Ar-H), 8.30 (1H, s, H_2) and 8.36 ppm (1H, m, NH); δ_C (d_6-DMSO) CH_2: 31.5, 31.5, 34.8, 43.5, 43.5, 43.5; CH: 32.8, 86.8, 127.1, 129.7, 130.3, 131.0; 143.3; CH: 81.3, 131.0, 138.7, 145.1, 146.4, 157.3, 157.8.

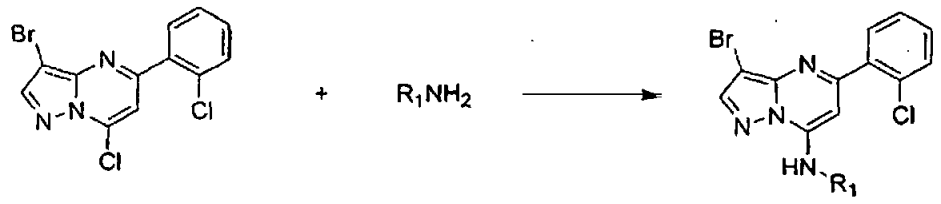
EXAMPLE 435: Reactants: 3-Bromo-7-chloro-5-phenylpyrazolo[1,5-a]pyrimidine (174mg, 0.507mmoles) (prepared as described in Preparative Example 129) and 3-(aminomethyl)-1-methylpiperidine (65mg, 0.507mmoles) (prepared as described in Preparative Example 244 above); diisopropyl ethylamine (0.178mL, 1.014mmoles); anhydrous 1,4-dioxane (2.5mL). Physical properties: HRFABMS: m/z 434.0742 (MH^+). Calcd. for $C_{19}H_{22}N_5BrCl$: m/z 434.0747; δ_H ($CDCl_3$) 1.18 (1H, m, CH_2), 1.68 (1H, m, CH_2), 1.80 (1H, m, CH_2), 1.87 (1H, m, CH_2), 1.96 (1H, m, CH), 2.14 (2H, m, CH_2), 2.32 (3H, s, NCH_3), 2.75 (1H, m, CH_2), 2.29 (1H, m, CH_2), 3.42 (2H, m, -NHC$\underline{H_2}$CH), 6.36 (1H, s, H_6), 6.64 (1H, bm, NH), 7.41 (2H, m, Ar-H), 7.51 (1H, m, Ar-H), 7.74 (1H, m, Ar-H) and 8.06 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 46.6; CH_2: 24.4, 27.9, 46.1, 56.1, 59.6; CH: 36.0, 87.4, 127.1, 130.1, 130.2, 131.6, 143.8; C: 83.2, 132.1, 138.9, 145.6, 146.4, 158.2.

EXAMPLE 436: Reactants: 3-Bromo-7-chloro-5-phenylpyrazolo[1,5-a]pyrimidine (111.4mg, 0.325mmoles) (prepared as described in Preparative Example 129); 4-(aminomethyl)-1-methylpiperidine (50mg, 0.39mmoles) (prepared as described in Preparative Example 245 above); diisopropyl ethylamine (0.1135mL, 0.65mmoles); anhydrous 1,4-dioxane (1.5mL). Physical data: HRFABMS: m/z 434.0735 (MH^+). Calcd. for $C_{19}H_{22}N_5BrCl$: m/z 434.0747; δ_H ($CDCl_3$) 1.42 (2H, m, CH_2), 1.72 (1H, m, CH), 1.82 (2H, m, CH_2), 1.93 (2H, m, CH_2), 2.20 (3H, s, NCH_3), 2.89 (2H, m, CH_2), 3.34 (2H, m, -NHC$\underline{H_2}$CH), 6.31 (1H, s, H_6), 6.46 (1H, m, NH), 7.36 (2H, m, Ar-H), 7.46 (1H, m, Ar-H), 7.70 (1H, m, Ar-H) and 8.00 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 46.4; CH_2: 30.2, 30.2, 48.0, 55.3, 55.3; CH: 35.4, 87.5, 127.2, 130.2, 130.2, 131.6, 143.8; C: 83.3, 132.2, 138.9, 145.7, 146.4, 158.1.

EXAMPLE 437: Reactants: 3-Bromo-7-chloro-5-phenylpyrazolo[1,5-a]pyrimidine (191mg, 0.557mmoles) (prepared as described in Preparative Example 129); 3-(aminomethyl)benzonitrile (88.3mg, 0.668mmoles) (prepared as described in Preparative Example 246 above); diisopropyl ethylamine (0.192mL, 1.114mmoles); anhydrous 1,4-dioxane (4.5mL). Physical data: HRFABMS: m/z 438.0125 (MH^+). Calcd. for $C_{19}H_{12}N_5BrCl$: m/z 438.0121; δ_H ($CDCl_3$) 4.76 (2H, d, -C<u>H</u>$_2$NH-), 6.32 (1H, s, H_6), 7.00 (1H, m, -CH_2N<u>H</u>-), 7.40 (2H, m, Ar-H), 7.46 (1H, m, Ar-H), 7.55 (1H, m, Ar-H), 7.67 (2H, m, Ar-H), 7.71 (1H, m, Ar-H), 7.75 (1H, m Ar-H) and 8.10 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 45.5; CH: 88.2, 127.2, 130.0, 130.2, 130.4, 130.6, 131.4, 131.6, 131.9, 144.1; C: 83.8, 113.4, 118.3, 132.0, 137.8, 138.3, 145.6, 145.9, 158.0.

EXAMPLE 438: Reactants: 3-Bromo-7-chloro-5-phenylpyrazolo[1,5-a]pyrimidine (233.5mg, 0.681mmoles) (prepared as described in Preparative Example 129); 4-(aminomethyl)benzonitrile (108mg, 0.817mmoles) (prepared as described in Preparative Example 247 above); diisopropyl ethylamine (0.235mL, 1.362mmoles); anhydrous 1,4-dioxane (5.3mL). Physical data: HRFABMS: m/z 438.0117 (MH^+) Calcd. for $C_{20}H_{14}N_5BrCl$: m/z 438.0121; δ_H ($CDCl_3$) 4.80 (2H, d, CH_2), 6.30 (1H, s, H_6), 7.01 (1H, m, NH), 7.40 (2H, m, Ar-H), 7.47 (1H, m, Ar-H), 7.70 (2H, m, Ar-H), 7.72 (2H, m, Ar-H), 7.80 (1H, m, Ar-H) and 8.10 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 45.8; CH: 88.2, 127.2, 127.7, 127.7, 130.2, 130.4, 131.6, 132.9, 132.9, 144.1; C: 83.8, 112.2, 118.4, 132.0, 138.2, 141.5, 145.5, 146.0, 158.0.

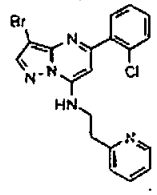
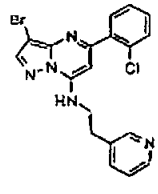
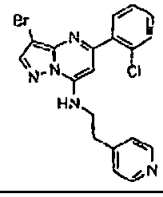
EXAMPLE 439:

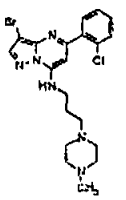
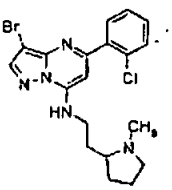
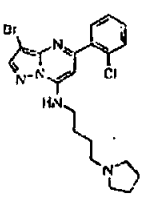
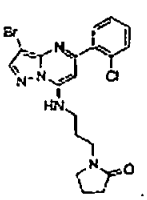
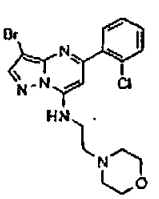


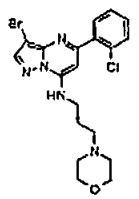
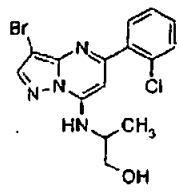
3-Bromo-7-chloro-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidine (50mg, 0.146mmoles) (prepared as described in Preparative Example 129) was dissolved in anhydrous 1,4-dioxane (5mL) in a GeneVac Technologies carousel reaction tube. PS-diisopropyl ethylamine resin (161mg, 0.5828mmoles) was

added to each tube. A freshly prepared 1M solution of the appropriate amine R_1NH_2 in anhydrous 1,4-dioxane (0.2185mL, 0.2185mmoles) was added to each tube and the tubes were sealed and heated at 70°C for 78h with magnetic stirring in the reaction block. Each tube was filtered and the resin was washed with anhydrous 1,4-dioxane and then dichloromethane. The combined individual filtrates from each tube were evaporated to dryness and the residues were each re-dissolved in anhydrous 1,4-dioxane (5mL) and placed in GeneVac reaction tubes. To each tube was added PS-isocyanate resin (594mg, 0.8742mmoles) and PS-trisamine resin (129mg, 0.4371mmoles) and the tubes were stirred at 25°C for 20h in the reaction block. The resins were filtered off and washed with anhydrous 1,4-dioxane and dichloromethane. The filtrates from each tube were evaporated to dryness and the residues were each chromatographed on a silica gel column using the column size and the eluant shown in Table 36, to give the title compounds.

TABLE 36

Ex.	Structure	MW	FABMS MH^+	Yield	Chromatographic Data
440		428.7	428.0	81%	15x2.5cm Dichloromethane; 0.5% Methanol in dichloromethane
441		428.7	428.0	48%	20x2cm Dichloromethane; 1.5% Methanol in dichloromethane
442		428.7	428.0	24%	15x2.5cm Dichloromethane; 1.5% Methanol in dichloromethane

443		463.8	463.0	44%	15x2.2cm Dichloromethane; 5% Methanol in dichloromethane
444		434.8	434.1	63%	15x2.5cm 5% Methanol in dichloromethane
445		448.8	448.2	65%	15x2.5cm 5% Methanol in dichloromethane
446		448.8	448.1	40%	15x2.5cm Dichloromethane; 0.5% Methanol in dichloromethane
447		436.7	436.1	72%	15x2.5cm 0.5% Methanol in dichloromethane

448		450.8	450.0	53%	20x2cm Dichloromethane; 0.5% Methanol in dichloromethane
449		381.7	381.0	44%	20x2cm 1.5% Methanol in dichloromethane

Additional physical data for the compounds are given below:

EXAMPLE 440: Physical properties: HRFABMS: m/z 428.0272 (MH^+). Calcd. for $C_{19}H_{16}N_5BrCl$: m/z 428.0278; δ_H ($CDCl_3$) 3.28 (2H, dd, $C_5H_4NC\underline{H_2}CH_2NH$-), 3.94 (2H, ddd, $C_5H_4NCH_2C\underline{H_2}NH$-), 6.40 (1H, s, H_6), 7.22-7.29 (3H, m, Ar-H), 7.38-7.44 (2H, m, Ar-H), 7.51 (1H, m, Ar-H), 7.68 (1H, ddd, Ar-H), 7.73 (1H, Ar-H), 8.18 (1H, s, H_2) and 8.68ppm (1H, NH); δ_C ($CDCl_3$) CH_2: 36.4, 41.5; CH: 87.3, 122.1, 123.6, 127.1, 130.1, 130.1, 131.6, 137.0, 143.8, 149.5; C: 83.1, 132.1, 138.9, 145.7, 146.3, 158.0, 158.1.

EXAMPLE 441: Physical properties: HRFABMS: m/z 428.0272 (MH^+). Calcd. for $C_{19}H_{16}N_5BrCl$: m/z 428.0278; δ_H ($CDCl_3$) 3.12 (2H, dd, $C_5H_4NC\underline{H_2}CH_2NH$-), 3.77 (2H, ddd, $C_5H_4NCH_2C\underline{H_2}NH$-), 6.40 (1H, s, H_6), 6.59 (1H, m, Ar-H), 7.34 (1H, bm, Ar-H), 7.39-7.45 (2H, m, Ar-H), 7.52 (1H, m, Ar-H), 7.62 (1H, m, Ar-H), 7.75 (1H, m, Ar-H), 8.05 (1H, s, H_2) and 8.63ppm (1H, m, NH); δ_C ($CDCl_3$) CH_2: 32.7, 43.1; CH: 87.5, 127.2, 130.2, 130.3, 131.6, 136.4, 142.9, 148.3, 149.8; C: 83.5, 132.0, 138.6, 145.6, 145.9, 158.1.

EXAMPLE 442: Physical properties: HRFABMS: m/z 428.0275 (MH^+). Calcd. for $C_{19}H_{16}N_5BrCl$: m/z 428.0278; δ_H ($CDCl_3$) 3.13 (2H, dd, $C_5H_4NC\underline{H_2}CH_2NH$-), 3.80 (2H, ddd, $C_5H_4NCH_2C\underline{H_2}NH$-), 6.42 (1H, s, H_6), 6.53 (1H, m, Ar-H), 7.23 (2H, m, Ar-H), 7.40-7.46 (2H, m, Ar-H), 7.62 (1H, m, Ar-H), 7.76 (1H, m, Ar-H), 8.07 (1H,

s, H_2) and 8.63ppm (1H, m, NH); δ_C ($CDCl_3$) CH_2: 34.7, 42.5; CH: 87.4, 124.5, 124.5, 127.2, 130.2, 130.3, 131.6, 144.0, 150.2, 150.2; C: 83.5, 132.0, 138.6, 145.6, 145.9, 146.6, 158.1.

EXAMPLE 443: Physical properties: HRFABMS: m/z 463.1003 (MH^+): Calcd. for $C_{20}H_{25}N_6BrCl$: m/z 463.1013; δ_H ($CDCl_3$) 1.98 (2H, m, $=NCH_2C\underline{H}_2CH_2NH$-), 2.43 (3H, s, NCH_3), 2.67 (2H, m, $=NC\underline{H}_2CH_2CH_2NH$-), 2.70 (8H, piperazine CH_2), 3.58 (2H, m, $=NCH_2CH_2C\underline{H}_2NH$-), 6.32 (1H, s, H_6), 7.37-7.43 (2H, m, Ar-H), 7.50 (1H, m, Ar-H), 7.73 (1H, m, Ar-H), 8.06 (1H, s, H_2) and 8.60ppm (1H, m, NH); δ_C ($CDCl_3$) CH_3: 46.1; CH_2: 24.1, 42.8, 53.3, 54.6, 54.6, 57.5, 57.5; CH: 87.1, 127.0, 130.0, 130.1, 131.5, 143.4; C: 82.7, 132.1, 139.2, 145.7, 146.7, 158.0.

EXAMPLE 444: Physical properties: HRFABMS: m/z 434.0742 (MH^+). Calcd. for $C_{19}H_{22}N_5BrCl$: m/z 434.0747; δ_H ($CDCl_3$) 1.72 (1H, m, CH/CH_2), 1.78-1.90 (2H, m, CH/CH_2), 2.02 (3H, m, CH/CH_2), 2.50 (1H, m, CH/CH_2), 2.45 (3H, s, NCH_3), 2.51 (1H, m, CH/CH_2), 3.23 (1H, m, CH/CH_2), 3.54 (1H, m, CH/CH_2), 3.60 (1H, m, CH/CH_2), 6.32 (1H, s, H_6), 7.38-7.44 (2H, m, Ar-H), 7.51 (1H, m, Ar-H), 7.75 (1H, m, Ar-H), 7.96 (1H, bm, NH) and 8.05 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 40.7; CH_2: 22.7, 29.3, 30.1, 39.4, 57.0; CH: 64.2, 87.1, 127.1, 130.0, 130.1, 131.6, 143.8; C: 82.8, 132.1, 139.1, 145.7, 146.4, 158.0.

EXAMPLE 445: Physical properties: HRFABMS: m/z 448.0910 (MH^+). Calcd. for $C_{20}H_{24}N_5BrCl$: m/z 448.0904; δ_H ($CDCl_3$) 1.90 (4H, m, CH_2), 2.00 (4H, m, CH_2), 2.84 (2H, m, CH_2), 2.95 (4H, m, CH_2), 3.51 (2H, m, CH_2), 6.32 (1H, s, H_6), 7.05 (1H, bm, NH), 7.37-7.43 (2H, m, Ar-H), 7.50 (1H, m, Ar-H), 7.73 (1H, m, Ar-H) and 8.04 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 23.4, 23.4, 24.8, 26.4, 41.8, 53.9, 53.9, 55.2; CH: 87.3, 127.1, 130.1, 130.2, 131.6, 143.7; C: 83.0, 132.0, 138.9, 145.7, 146.3, 158.1.

EXAMPLE 446: Physical properties: HRFABMS: m/z 448.0548 (MH^+). Calcd. for $C_{19}H_{20}N_5OBrCl$: m/z 448.0540; δ_H ($CDCl_3$) 1.94 (2H, m, CH_2), 2.09 (2H, m, CH_2), 2.49 (2H, m, CH_2), 3.45 (2H, m, CH_2), 3.51 (4H, m, CH_2), 6.32 (1H, s, H_6), 7.37-7.44 (3H, m, Ar-H/NH), 7.51 (1H, m, Ar-H), 7.75 (1H, m, Ar-H) and 8.10 ppm

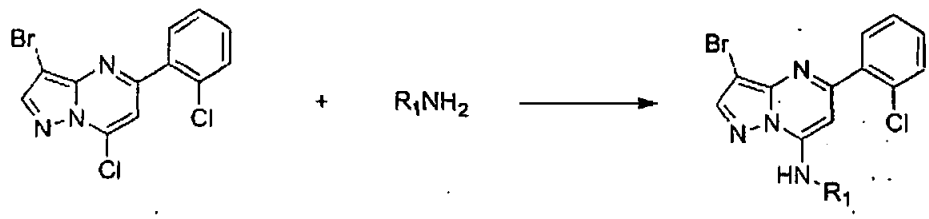
(1H, s, H_2); δ_C ($CDCl_3$) CH_2: 18.0, 26.3, 30.8, 39.2, 39.9, 47.5; CH: 87.0, 127.1, 130.1, 130.1, 131.6, 144.1; C: 82.9, 132.1, 138.9, 145.6, 146.2, 157.9, 176.2.

EXAMPLE 447: Physical properties: HRFABMS: m/z 436.0532 (MH^+). Calcd. for $C_{18}H_{20}N_5OBrCl$: m/z 436.0540; δ_H ($CDCl_3$) 2.60 (4H, bm, -N($C\underline{H}_2CH_2)_2O$), 2.83 (2H, m, =$NC\underline{H}_2CH_2NH$-), 3.57 (2H, m, =$NCH_2C\underline{H}_2NH$-), 3.83 (4H, m, -$N(CH_2C\underline{H}_2)_2O$), 6.37 (1H, s, H_6), 6.99 (1H, bm, NH), 7.38-7.45 (2H, m, Ar-H), 7.51 (1H, m, Ar-H), 7.75 (1H, m, Ar-H) and 8.09 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 38.2, 53.3, 53.3, 56.2, 66.9, 66.9; CH: 87.6, 127.1, 130.1, 130.2, 131.6, 143.9; C; 83.1, 132.1, 138.9, 145.7, 146.2, 158.1.

EXAMPLE 448: Physical properties: HRFABMS: m/z 450.0688 (MH^+). Calcd. for $C_{19}H_{22}N_5OBrCl$: m/z 450.0696; δ_H ($CDCl_3$) 1.98 (2H, m, =$NCH_2C\underline{H}_2CH_2NH$-), 2.58 (4H, m, -$N(C\underline{H}_2CH_2)_2O$), 2.67 (2H,m, =$NC\underline{H}_2CH_2CH_2NH$-), 3.59 (2H, m, =$NCH_2CH_2C\underline{H}_2NH$-), 3.94 (4H, m, -$N(CH_2C\underline{H}_2)_2O$), 6.31 (1H, s, H_6), 7.37-7.44 (2H, Ar-H), 7.51 (1H, m, Ar-H), 7.78 (1H, m, Ar-H), 8.08 (1H, s, H_2) and 8.60 ppm (1H, bm, NH); δ_C ($CDCl_3$) CH_2: 23.7, 42.7, 52.9, 52.9, 58.0, 66.6, 66.6; CH: 87.0, 127.1, 130.0, 130.1, 131.5, 143.6; C: 82.8, 132.1, 139.1, 145.7, 146.7, 158.0.

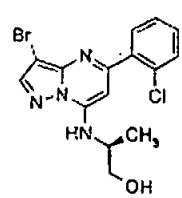
EXAMPLE 449: Physical properties: HRFABMS: m/z 381.0114 (MH^+). Calcd. for $C_{15}H_{15}N_4OBrCl$: m/z 381.0118; δ_H ($CDCl_3$) 1.39 (3H, d, $CHC\underline{H}_3$), 2.76 (1H, bm, -OH), 3.71 (1H, m, =$CHC\underline{H}_2OH$), 3.81 (1H, m, =$CHC\underline{H}_2OH$), 3.88 (1H, m, =$C\underline{H}CH_2OH$), 6.38 (1H, s, H_6), 7.38 (2H, m, Ar-H), 7.48 (1H, m, Ar-H), 7.68 (1H, m, Ar-H) and 8.02 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 16.9; CH_2: 65.0; CH: 50.0, 88.0, 127.1, 130.1, 130.3, 131.4, 143.8; C: 83.0, 132.0, 138.5, 145.6, 146.0, 158.2.

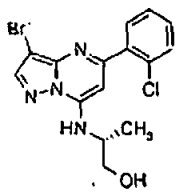
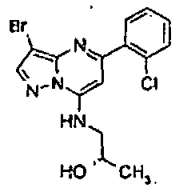
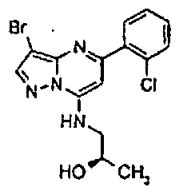
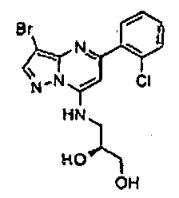
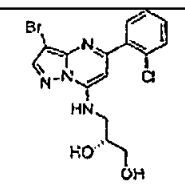
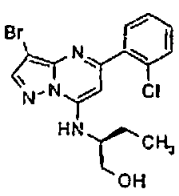
EXAMPLE 450:

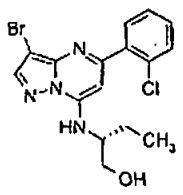
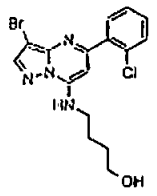


3-Bromo-7-chloro-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidine (50mg, 0.146mmoles) (prepared as described in Preparative Example 129) was dissolved in anhydrous 1,4-dioxane (5mL) in a GeneVac Technologies carousel reaction tube. PS-diisopropyl ethylamine resin (161mg, 0.5828mmoles) was added to each tube. A freshly prepared solution of the appropriate amine R_1NH_2 (0.219mmoles) in anhydrous 1,4-dioxane (0.3mL) was added to each tube, with the exception of Example 99-5 in which the amine was dissolved in 10% MeOH in 1,4-dioxane (0.3mL), and the tubes were sealed and heated at 70°C for 74h with magnetic stirring in the reaction block. Each tube was filtered and the resin was washed with anhydrous 1,4-dioxane and then dichloromethane. The combined individual filtrates from each tube were evaporated to dryness and the residues were each re-dissolved in anhydrous 1,4-dioxane (5mL) and placed in GeneVac reaction tubes. To each tube was added PS-isocyanate resin (594mg, 0.8742mmoles) and PS-trisamine resin (129mg, 0.4371mmoles) and the tubes were stirred at 25°C for 20h in the reaction block. The resins were filtered off and washed with anhydrous 1,4-dioxane and dichloromethane. The filtrates from each tube were evaporated to dryness and the residues were each chromatographed on a silica gel column using the column size and the eluant shown in Table 37, to give the title compounds.

TABLE 37

Ex.	Structure	MW	FABMS MH^+	Yield	Chromatographic Data
451		381.7	380.9	66%	15x2.5cm; 0.5% Methanol in dichloromethane

452		381.7	380.9	60%	20x2cm; 0.5% Methanol in dichloromethane
453		381.7	380.9	69%	15x2.5cm; 0.35% Methanol in dichloromethane
454		381.7	380.9	75%	15x2.5cm; 0.35% Methanol in dichloromethane
455		397.7	397.2	84%	15x2.5cm; 1.5% Methanol in dichloromethane
456		397.7			
457		395.7	395.0	60%	15x2.5cm; 0.35% Methanol in dichloromethane

458		395.7	396.3	50%	15x2.5cm; 0.35% Methanol in dichloromethane
459		395.7	396.0	76%	15x2.5cm; 0.35% Methanol in dichloromethane

Additional physical data for the compounds are given below:

EXAMPLE 451: Physical properties: HRFABMS: m/z 381.0115 (MH^+). Calcd. for $C_{15}H_{15}N_4OBrCl$: m/z 381.0118; $[\alpha]_D^{25°C}$ +1.4° (c=0.25 , MeOH); δ_H ($CDCl_3$) 1.44 (3H, d, -CHC<u>H</u>$_3$), 3.77 3.89 (1H, dd, CHC<u>H</u>$_2$OH), (1H, dd, CHC<u>H</u>$_2$OH), 3.94 (1H, m, C<u>H</u>CH$_2$OH), 6.41 (1H, s, H_6), 6.58 (1H, d, NH), 7.41 (2H, m, Ar-H), 7.51 (1H, m, Ar-H), 7.74 (1H, m, Ar-H) and 8.04 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 17.1; CH_2: 65.5; CH: 49.9, 88.0, 127.1, 130.1, 130.2, 131.6, 143.8; C: 83.2, 132.1, 138.7, 145.6, 145.8, 158.1.

EXAMPLE 452: Physical properties: HRFABMS: m/z 381.0115 (MH^+). Calcd. for $C_{15}H_{15}N_4OBrCl$: m/z 381.0118; $[\alpha]_D^{25°C}$ +6.5° (c=0.32 , MeOH); δ_H ($CDCl_3$) 1.44 (3H, d, -CHC<u>H</u>$_3$), 3.78 (1H, dd, CHC<u>H</u>$_2$OH), 3.89 (1H, dd, CHC<u>H</u>$_2$OH), 3.96 (1H, m, C<u>H</u>CH$_2$OH), 6.41 (1H, s, H_6), 6.58 (1H, d, NH), 7.41 (2H, m, Ar-H), 7.51 (1H, m, Ar-H), 7.75 (1H, m, Ar-H) and 8.04 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 17.1; CH_2: 65.5; CH: 49.9, 88.0, 127.1, 130.1, 130.3, 131.6, 143.8; C: 83.2, 132.1, 138.6, 145.6, 145.8, 158.1.

EXAMPLE 453: Physical properties: HRFABMS: m/z 381.0115 (MH^+). Calcd. for $C_{15}H_{15}N_4OBrCl$: m/z 381.0118; $[\alpha]_D^{25°C}$ +9.4° (c=0.27, MeOH); δ_H ($CDCl_3$) 1.33 (3H, d, CH_3), 2.25 (1H, bs, OH), 3.37 (1H, dd, CH_2), 3.51 (1H, m, CH_2), 4.16 (1H, m, C<u>H</u>OH), 6.35 (1H, s, H_6), 6.93 (1H, m, NH), 7.40 (2H, m, Ar-H), 7.50 (1H, m,

Ar-H), 7.70 (1H, m, Ar-H) and 8.04 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 20.8; CH_2: 49.2; CH: 65.7, 87.8, 127.1, 130.1, 130.2, 131.2, 143.9; C: 83.1, 132.1, 138.5, 145.6, 146.6, 158.3.

EXAMPLE 454: Physical properties: HRFABMS: m/z 381.0112 (MH^+). Calcd. for $C_{15}H_{15}N_4OBrCl$: m/z 381.0118; $[\alpha]_D^{25°C}$ -3.2° (c=0.29 ; MeOH); δ_H ($CDCl_3$) 1.32 (3H, d, CH_3), 2.48 (1H, bs, OH), 3.35 (1H, dd, CH_2), 3.49 (1H, m, CH_2), 4.15 (1H, m, C<u>H</u>OH), 6.34 (1H, s, H_6), 6.93 (1H, m, NH), 7.39 (2H, m, Ar-H), 7.49 (1H, m, Ar-H), 7.68 (1H, m, Ar-H) and 8.03 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 20.8; CH_2: 49.2; CH: 65.7, 87.7, 127.1, 130.1, 130.3, 131.4, 143.9; C: 83.0, 132.0, 138.6, 145.6, 146.6, 158.3.

EXAMPLE 455: Physical properties: HRFABMS: m/z 397.0054 (MH^+). Calcd. for $C_{15}H_{15}N_4O_2BrCl$: m/z 397.0067; $[\alpha]_D^{25°C}$ -9.5° (c= 0.28, MeOH); δ_H ($CDCl_3$) 3.18 (2H, bs, OH), 3.47 (1H, dd, CH_2), 3.58 (1H, dd, CH_2), 3.63 (1H, dd, C<u>H</u>$_2$OH), 3.70 (1H, dd, C<u>H</u>$_2$OH), 3.98 (1H, m, CH), 6.35 (1H, s, H_6), 7.10 (1H, m, NH), 7.37 (2H, m, Ar-H), 7.46 (1H, m, Ar-H), 7.64 (1H, m, Ar-H) and 8.01 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 44.7, 64.0; CH: 69.7, 87.7, 127.0, 130.1, 130.3, 131.3, 143.9; C: 82.9, 132.0, 138.4, 145.4, 146.7, 158.3.

EXAMPLE 456: This enantiomer may be prepared by essentially the same manner as described above.

EXAMPLE 457: Physical properties: HRFABMS: m/z 395.0260 (MH^+). Calcd. for $C_{16}H_{17}N_4OBrCl$: m/z 395.0274; $[\alpha]_D^{25°C}$ -34.3° (c= 0.28, MeOH); δ_H ($CDCl_3$) 1.08 (3H, dd, CH_3), 1.78 (1H, m, CH_2), 1.86 (1H, m, CH_2), 2.35 (1H, bs, CH_2O<u>H</u>), 3.71 (1H, m, C<u>H</u>NH), 3.81 (1H, dd, C<u>H</u>$_2$OH), 3.90 (1H, dd, C<u>H</u>$_2$OH), 6.42 (1H, s, H_6), 6.53 (1H, m, NH), 7.41 (2H, m, Ar-H), 7.51 (1H, Ar-H), 7.75 (1H, m, Ar-H) and 8.04 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 10.5; CH_2: 24.5, 63.7; CH: 55.9, 88.0, 127.1, 130.1, 130.2, 131.6, 143.8; C: 83.2, 132.1, 138.6, 145.6, 146.3, 158.1.

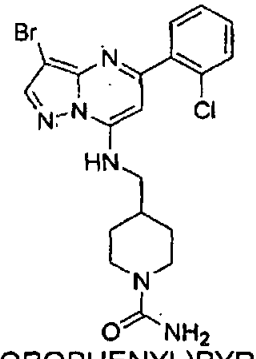
EXAMPLE 458: Physical properties: HRFABMS: m/z 395.0274 (MH^+). Calcd. for $C_{16}H_{17}N_4OBrCl$: m/z 395.0274; $[\alpha]_D^{25°C}$ +27.5° (c= 0.25, MeOH); δ_H ($CDCl_3$) 1.05

(3H, dd, CH_3), 1.76 (1H, m, CH_2), 1.85 (1H, m, CH_2), 2.28 (1H, bs, CH_2OH), 3.67 (1H, m, CHNH), 3.77 (1H, dd, CH_2OH), 3.84 (1H, dd, CH_2OH), 6.49 (1H, s, H_6), 6.66 (1H, m, NH), 7.39 (2H, m, Ar-H), 7.49 (1H, Ar-H), 7.71 (1H, m, Ar-H) and 8.04 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 10.5; CH_2: 24.3, 63.3; CH: 56.1, 88.0, 127.1, 130.1, 130.3, 131.5, 143.8; C: 83.0, 132.1, 138.6, 145.6, 146.3, 158.2.

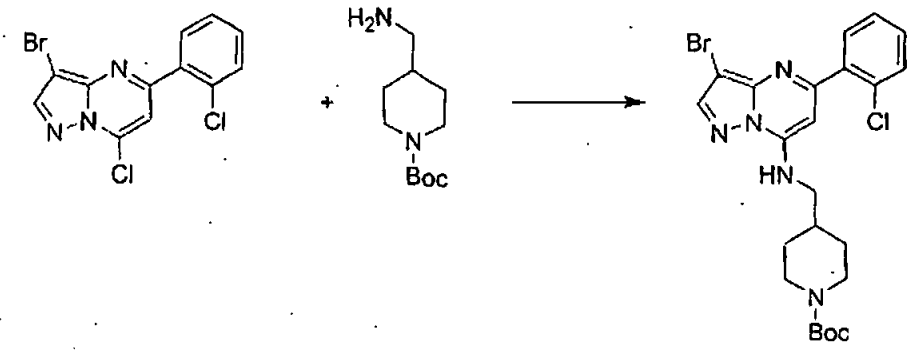
EXAMPLE 459: Physical properties: HRFABMS: m/z 395.0264 (MH^+). Calcd. for $C_{16}H_{17}N_4OBrCl$: m/z 395.0274; δ_H ($CDCl_3$) 1.77 (2H, m, -$NHCH_2CH_2CH_2CH_2OH$), 1.90 (1H, bm, -$NHCH_2CH_2CH_2CH_2OH$), 1.93 (2H, m, -$NHCH_2CH_2CH_2CH_2OH$), 3.54 (2H, m, -$NHCH_2CH_2CH_2CH_2OH$), 3.77 (2H, m, -$NHCH_2CH_2CH_2CH_2OH$), 6.37 (1H, s, H_6), 6.72 (1H, m, -$NHCH_2CH_2CH_2CH_2OH$), 7.41 (2H, m, Ar-H), 7.51 (1H, m, Ar-H), 7.75 (1H, m, Ar-H) and 8.06 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 25.7, 29.7, 42.2, 62.2; CH: 87.4, 127.1, 130.1, 130.2, 131.6, 143.8; C: 83.1, 132.1, 138.8, 145.6, 146.3, 158.1.

EXAMPLE 460:

4-{[3-BROMO-5-(2-CHLOROPHENYL)PYRAZOLO[1,5-a]PYRIMIDIN-7-YLAMINO]METHYL}PIPERIDINE-1-CARBOXYLIC ACID AMIDE:

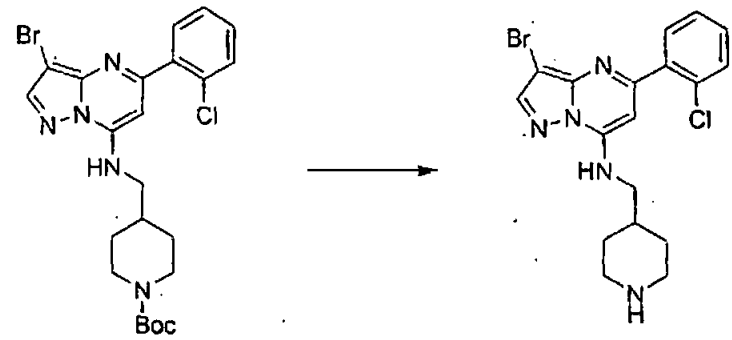


A. 4-{[3-BROMO-5-(2-CHLOROPHENYL)PYRAZOLO[1,5-a]PYRIMIDIN-7-YLAMINO]METHYL}PIPERIDINE-1-CARBOXYLIC ACID *tert*-BUTYL ESTER:



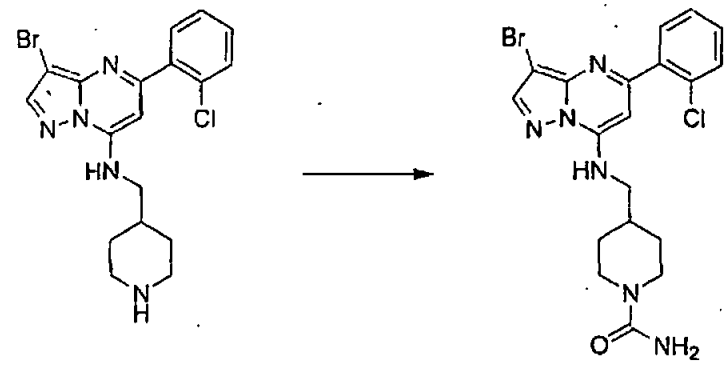
3-Bromo-7-chloro-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidine (300mg, 0.875mmoles) (prepared as described in Preparative Example 129) was dissolved in anhydrous 1,4-dioxane (6.8mL). 4-(aminomethyl)piperidine-1-carboxylic acid *tert*-butyl ester (225mg, 1.05mmoles) and diisopropyl ethylamine (0.3055mL, 1.75mmoles) were added and the mixture was heated at 75°C for 24h. The solution was evaporated to dryness and the residue was chromatographed on a silica gel column (15x5cm) using dichloromethane as the eluant to give 4-{[3-bromo-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidin-7-ylamino]methyl}piperidine-1-carboxylic acid *tert*-butyl ester (461.2mg, 100%): FABMS: m/z 520.1 (MH^+); HRFABMS: m/z 520.1111 (MH^+). Calcd. for $C_{23}H_{28}N_5O_2BrCl$: m/z 520.1115; δ_H ($CDCl_3$) 1.30 (2H, m, CH_2), 1.51 (9H, s, -$COOC(CH_3)_3$), 1.85 (2H, d, CH_2), 1.95 (1H, m , CH), 2.76 (2H, m, CH_2), 3.40 (2H, m, CH_2), 6.37 (1H, s, H_6), 6.55 (1H, m, NH), 7.42 (2H, m, Ar-H), 7.52 (1H, m, Ar-H), 7.76 (1H, m, Ar-H) and 8.07 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 28.5, 28.5, 28.5; CH_2: 29.1, 29.1, 43.5, 43.5, 47.9; CH: 36.3, 87.5, 127.2, 130.2, 130.3, 131.6, 143.9; C: 79.7, 83.3, 132.1, 138.6, 145.4, 146.3, 154.7, 158.1.

B. [3-BROMO-5-(2-CHLOROPHENYL)PYRAZOLO[1,5-a]PYRIMIDIN-7-YL]PIPERIDIN-4-YLMETHYLAMINE:



4-{[3-Bromo-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidin-7-ylamino]methyl}piperidine-1-carboxylic acid *tert*-butyl ester (441mg, 0.847mmoles) (prepared as described in Example 460, Step A above) was dissolved in methanol (4.5mL) and 10% (v/v) conc. sulfuric acid in 1,4-dioxane (11.46mL) was added. The mixture was stirred at 25°C for 0.5h. The product was worked up as described in Preparative Example 241, step B and chromatographed on a silica gel column (15x5cm) using 8% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give [3-bromo-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidin-7-yl]piperidin-4-ylmethylamine (314.4mg, 88%): FABMS: m/z 420.0 (MH^+); HRFABMS: m/z 420.0585 (MH^+). Calcd. for $C_{18}H_{20}N_5BrCl$: m/z 420.0591; δ_H ($CDCl_3$) 1.34 (2H, m, CH_2), 1.86 (2H, m, CH_2), 1.91 (1H, m, CH), 2.10 (1H, bm, piperidine-NH), 2.67 (2H, m, CH_2), 3.18 (2H, m, CH_2), 3.38 (2H, m, CH_2), 6.37 (1H, s, H_6), 6.53 (1H, m, NH), 7.42 (2H, m, Ar-H), 7.52 (1H, m, Ar-H), 7.76 (1H, m, Ar-H) and 8.06 ppm (1H, s Ar-H); δ_C ($CDCl_3$) CH_2: 31.2, 31.2, 46.2, 46.2, 48.4; CH: 36.4, 89.5, 127.1, 130.1, 130.5, 131.6, 143.8; C: 83.2, 132.1, 138.9, 145.6, 146.4, 158.1.

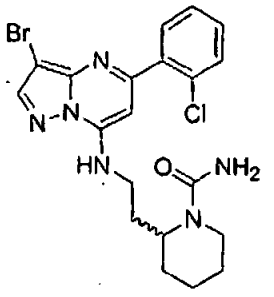
C. 4-{[3-BROMO-5-(2-CHLOROPHENYL)PYRAZOLO[1,5-a]PYRIMIDIN-7-YLAMINO]METHYL}PIPERIDINE-1-CARBOXYLIC ACID AMIDE:



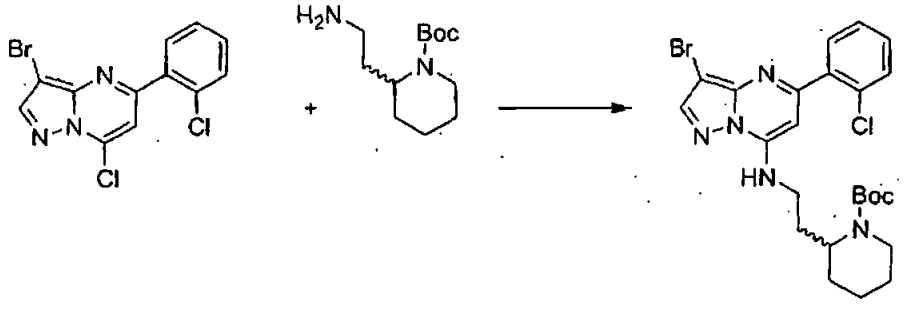
[3-Bromo-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidin-7-yl]piperidin-4-ylmethylamine (57mg, 0.136mmoles) (prepared as described in Example 460, Step B above) was dissolved in anhydrous dichloromethane (1.2mL) and trimethylsilylisocyanate (0.091mL, 0.679mmoles) was added. The mixture was stirred at 25°C for 2.5h. The mixture was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness. The residue was chromatographed on a silica gel column (30x2.5cm) using 3% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give 4-{[3-bromo-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidin-7-ylamino]methyl}piperidine-1-carboxylic acid amide (53.7mg, 86%): FABMS: m/z 463.1 (MH^+); HRFABMS: m/z 463.0647 (MH^+). Calcd. for $C_{19}H_{21}N_6OBrCl$: m/z 463.0649; δ_H (d_6-DMSO) 1.09 (2H, m, CH_2), 1.63 (2H, m, CH_2), 1.87 (1H, m, CH), 2.60 (2H, m, CH_2), 3.53 (2H, bm, $CONH_2$), 3.91 (2H, d, CH_2), 6.52 (1H, s, H_6), 7.50 (2H, m, Ar-H), 7.62 (2H, m, Ar-H), 8.33 (1H, s, H_2) and 8.52 ppm (1H, m, NH); δ_C (d_6-DMSO).CH_2: 30.1, 30.1, 44.2, 44.2, 47.7; CH: 36.4, 88.2, 128.1, 130.7, 131.4, 132.1, 147.9; C: 82.1, 132.1, 139.4, 145.7, 147.9, 158.1, 158.8.

EXAMPLE 461:

2-{2-[3-BROMO-5-(2-CHLOROPHENYL)PYRAZOLO[1,5-a]PYRIMIDIN-7-YLAMINO]ETHYL}PIPERIDINE-1-CARBOXYLIC ACID AMIDE:



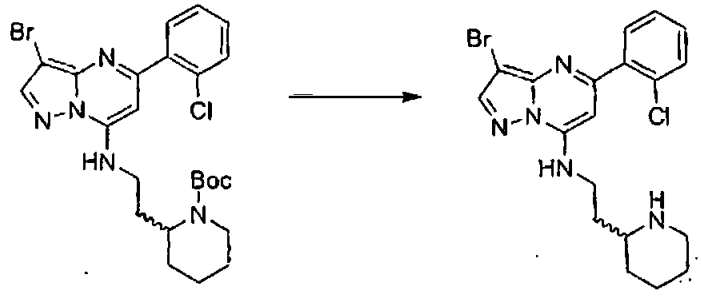
A. 2-{2-[3-BROMO-5-(2-CHLOROPHENYL)PYRAZOLO[1,5-a]PYRIMIDIN-7-YLAMINO]ETHYL}PIPERIDINE-1-CARBOXYLIC ACID *tert*-BUTYL ESTER:



3-Bromo-7-chloro-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidine (400mg, 1.166mmoles) (prepared as described in Preparative Example 129) was dissolved in anhydrous 1,4-dioxane (5.7mL). 2- Aminoethylpiperidine-1-carboxylic acid *tert*-butyl ester (266mg, 1.166mmoles) and diisopropyl ethylamine (0.409mL, 2.33mmoles) were added and the mixture was heated at 75°C for 48h. Additional diisopropyl ethylamine (0.204mL, 1.166mmoles) was added and the heating was continued for a total of 58h. The solution was evaporated to dryness and the residue was chromatographed on a silica gel column (15x5cm) using dichloromethane followed by 0.3% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give 2-{[3-bromo-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidin-7-ylamino]ethyl}piperidine-1-carboxylic acid *tert*-butyl ester (491.1mg, 79%): FABMS: m/z 534.1 (MH^+); HRESIMS: m/z 534.12797 (MH^+). Calcd. for $C_{24}H_{30}N_5O_2BrCl$: m/z 534.12714; δ_H ($CDCl_3$) 1.50 (1H, m, CH_2), 1.51 (9H, s, $COOC(CH_3)_3$), 1.57 (2H, m, CH_2), 1.68 (2H, m, CH_2), 1.76 (2H, m, CH_2), 2.24 (1H, bm, CH_2), 2.82/3.40/3.54/4.08/4.51 (5H, m, CH/CH_2), 6.34 (1H, s, H_6), 7.41 (2H, m, Ar-H),

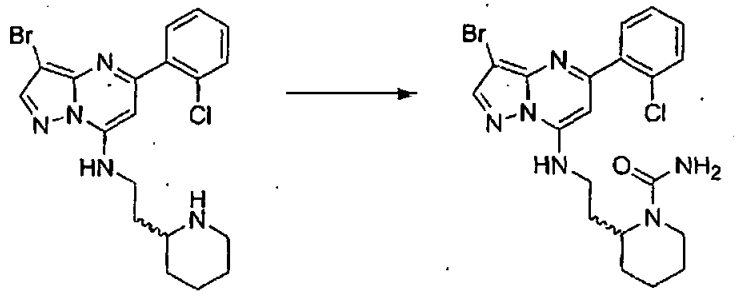
7.51 (1H, m, Ar-H), 7.76 (1H, m, Ar-H) and 8.08 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 28.5, 28.5, 28.5; CH_2: 19.2, 25.5, 29.2, 29.2, 39.2, 67.1; CH: ~47.4, 87.1, 127.1, 130.1, 130.1, 131.6, 143.9; C: 80.0, 83.0, 132.1, 138.9, 145.7, 146.2, 158.0.

B. [3-BROMO-5-(2-CHLOROPHENYL)PYRAZOLO[1,5-a]PYRIMIDIN-7-YL]-(2-PIPERIDIN-2-YLETHYL)AMINE:



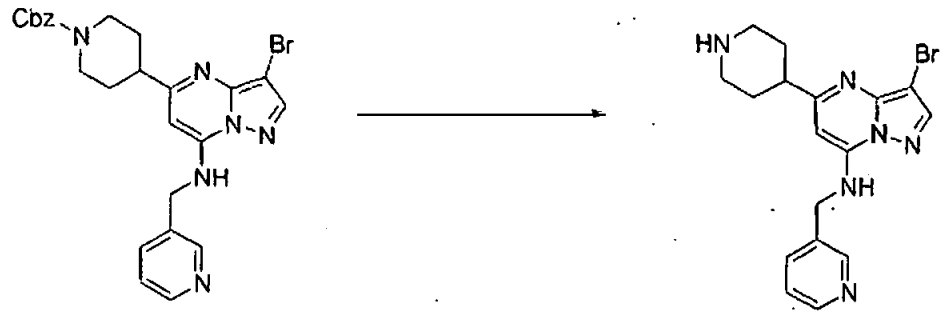
2-{[3-Bromo-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidin-7-ylamino]ethyl}piperidine-1-carboxylic acid *tert*-butyl ester (465mg, 0.869mmoles) (prepared as described in Example 461, Step A above) was dissolved in methanol (4.5mL) and 10% (v/v) conc. sulfuric acid in 1,4-dioxane (11.76mL) was added. The mixture was stirred at 25°C for 1.5h. The product was worked up as described in Preparative Example 241, step B and chromatographed on a silica gel column (15x5cm) using 3.5% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give [3-bromo-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidin-7-yl]piperidin-2-ylethyl)amine (365.6mg, 97%): FABMS: m/z 434.1 (MH^+); HRFABMS: m/z 434.0726 (MH^+). Calcd. for $C_{19}H_{22}N_5BrCl$: m/z 434.0747; δ_H ($CDCl_3$) 1.24 (1H, m, CH_2), 1.41 (1H, m, CH_2), 1.49 (1H, m, CH_2), 1.66 (1H, m, CH_2), 1.73 (1H, m, CH_2), 1.81 (1H, m, CH_2), 1.88 (2H, m, CH_2), 2.68 (1H, m, CH_2), 2.78 (1H, m, CH_2), 3.20 (1H,m, CH), 3.55 (1H, m, CH_2), 3.60 (1H, m, CH_2), 6.32 (1H, s, H_6), 7.41 (2H, m, Ar-H), 7.51 (1H, m, Ar-H), 7.74 (1H, m, Ar-H), 7.78 (1H, m, NH) and 8.05 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 24.7, 26.8, 33.1, 35.2, 40.3, 47.0; CH: 55.7, 87.2, 127.1, 130.0, 130.1, 131.5, 143.8; C: 82.9, 132.1, 139.0, 145.7, 146.5, 158.1.

C. 2-{2-[3-BROMO-5-(2-CHLOROPHENYL)PYRAZOLO[1,5-a]PYRIMIDIN-7-YLAMINO]ETHYL}PIPERIDINE-1-CARBOXYLIC ACID AMIDE:



[3-Bromo-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidin-7-yl]piperidin-2-ylethyl)amine (200mg, 0.46mmoles) (prepared as described in Example 461, Step B above) was dissolved in anhydrous dichloromethane (2mL) and trimethylsilylisocyanate (0.31mL, 2.3mmoles) was added. The mixture was stirred at 25°C for 1.25h. Additional trimethylsilylisocyanate (0.155mL, 1.15mmoles) was added and the stirring was continued for a total of 3h. The mixture was diluted with dichloromethane and washed with saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness. The residue was chromatographed on a silica gel column (30x2.5cm) using 2% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give 2-{2-[3-bromo-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidin-7-ylamino]ethyl}piperidine-1-carboxylic acid amide (106.3mg, 48%): FABMS: m/z 477.0 (MH^+); HRFABMS: m/z 477.0804 (MH^+). Calcd. for $C_{20}H_{23}N_6OBrCl$: m/z 477.0805; δ_H (d_6-DMSO) 1.29 (1H, m, CH_2), 1.52 (5H, m, CH_2), 1.72 (1H, m, CH_2), 2.05 (1H, m, CH_2), 2.51 (2H, s, $CONH_2$), 2.79 (1H, dd, CH), 3.31 (1H, m, CH_2), 3.34 (1H, m, CH_2), 3.76 (1H, m, CH_2), 4.30 (1H, bm, CH_2), 6.42 (1H, s, H_6), 7.50 (2H, m, Ar-H), 7.60 (1H, m, Ar-H), 7.63 (1H, m, Ar-H), 8.29 (1H, s, H_2) and 8.38 ppm (1H, dd, NH); δ_C (d_6-DMSO) CH_2: 18.6, 25.2, 28.2, 38.4, 38.6, 54.8; CH: 46.7, 86.6, 127.1, 129.7, 130.3, 131.0, 143.4; C: 81.2, 131.0, 138.7, 145.1, 146.4, 158.2.

EXAMPLE 462:

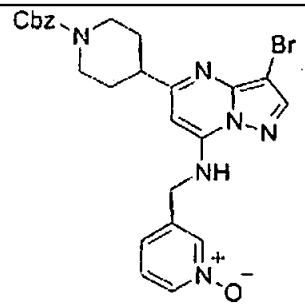
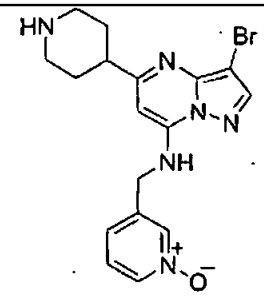


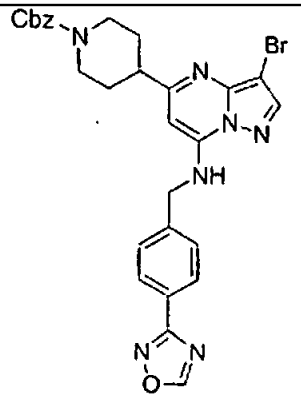
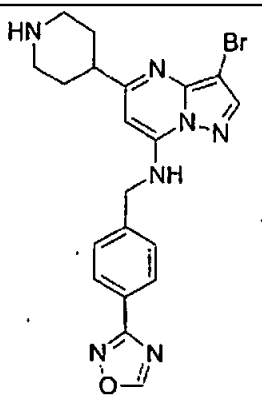
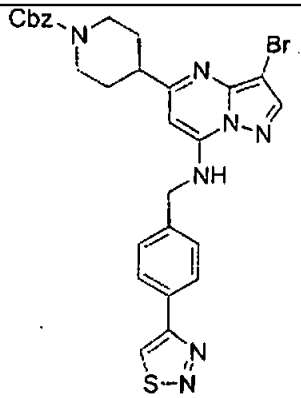
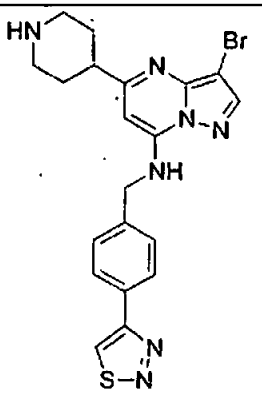
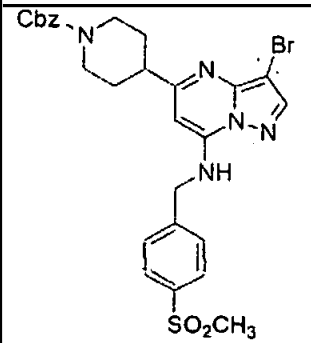
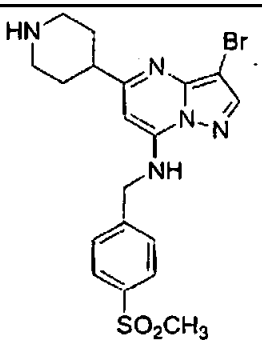
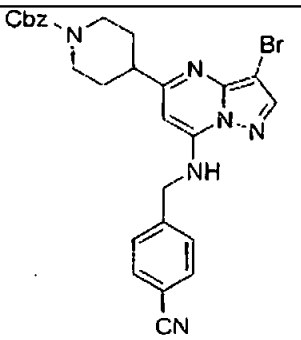
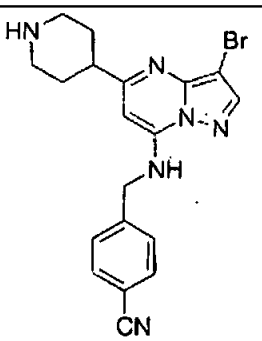
To a solution of the compound prepared in Example 204 (1.11 g, 2.12 mmol) in anhydrous acetonitrile (20 mL) was added TMSI (1.70 g, 8.52 mmol), dropwise at ambient temperature. After 10 minutes the acetonitrile was removed *in vacuo*. The resulting yellow foam was treated with 2 N HCl solution (7 mL) and then washed immediately with Et_2O (5X). The pH of the aqueous was adjusted to 10 with 50 % NaOH (aq) and the product was isolated by saturation of the solution with NaCl (s) followed by extraction with CH_2Cl_2 (5X) to give the crystalline product (733 mg, 89% yield). MH^+ = 387; m. p. = 207.5 °C

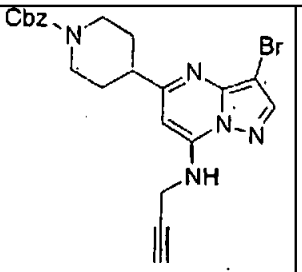
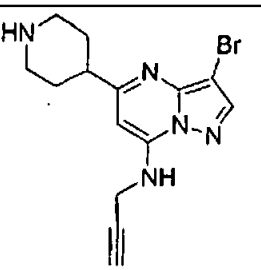
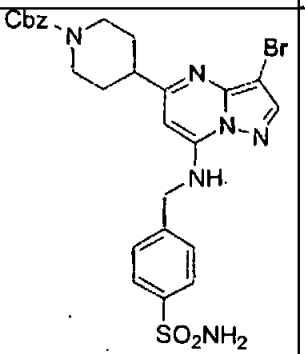
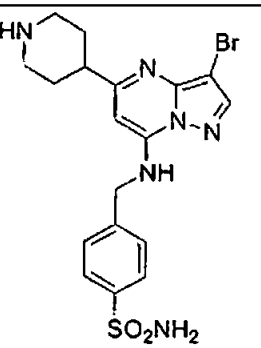
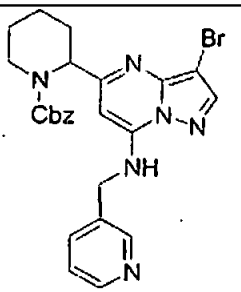
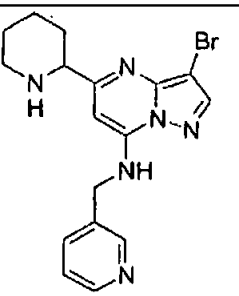
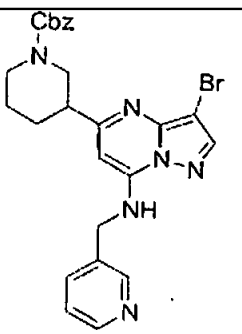
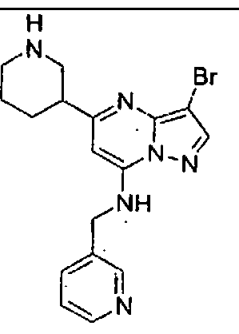
EXAMPLES 463-472:

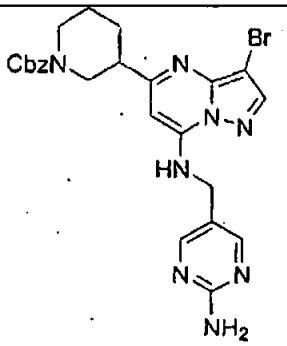
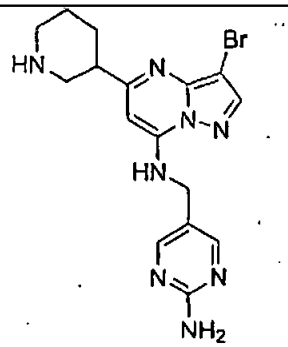
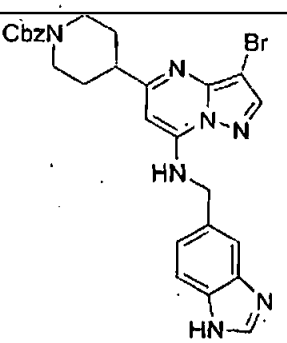
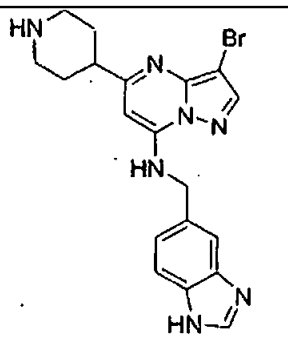
By essentially the same procedure set forth in Example 462 only substituting the compounds shown in Column 2 of Table 38, the compounds shown in Column 3 of Table 38 were prepared.

TABLE 38

Ex.	Column 2	Column 3	CMPD
463			MH^+ = 403 ^1H NMR (300MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.38 (d, 1H), 8.04 (s, 1H), 7.78 (d, 1H), 7.65 (t, 1H), 6.18 (s, 1H), 4.89 (s, 2H), 3.26 –3.21 (d, 2H), 2.96 – 2.70 (m, 3H), 2.05 –1.78 (m, 4H).

464			MH^+ = 454 m. p. = 175.4 °C
465			Yield = 87 MH^+ = 470 m. p. = 220 °C m. pt (hydrochloride salt) = 164.3 °C
466			MH^+ = 464 m. p. = 206 °C
467			MH^+ = 411 m. p. = 169.5 °C

468			MH^+ = 334 m. p. = 176.2 °C
469			MH^+ = 465 m. p. = 250.4 °C
470			MH^+ = 387 m. p. = 68.5 °C
471			MH^+ = 387 m. p. = 59.4 °C

472			1. mp = 230-232 2. M+H = 396
472.10			1. mp = 157-160 2. M+H = 427

EXAMPLE 473:

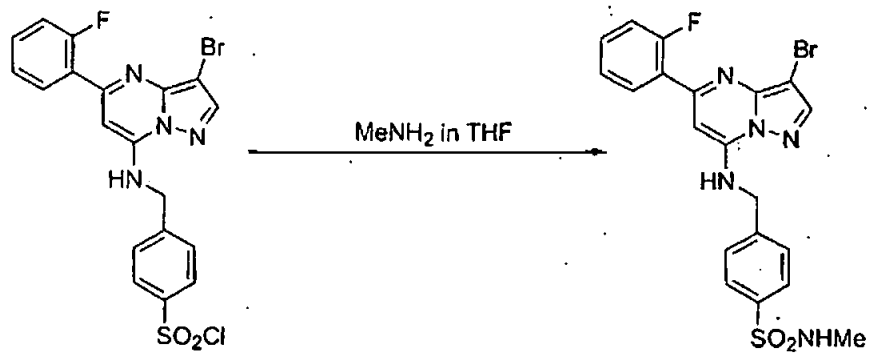
Step A:



A solution of the sulfonic acid (560 mg, 1.17 mmol) in 5 mL of dry DMF was cooled to 0 °C and $SOCl_2$ (278 mg, 2.34 mmol) was added. The reaction mixture was brought to RT and stirred overnight. The next day the contents were poured on ice and the pH was carefully adjusted to 8. The product was extracted in to EtOAc and the solvent was removed after drying (Na_2SO_4) to provide 240 mg (41%) of the crude sulfonyl chloride which was used for the next

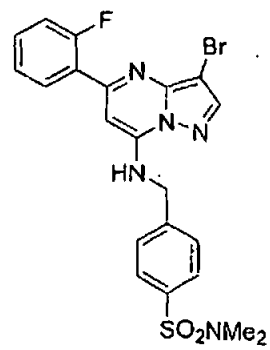
step without further purification. ^{1}H NMR ($CDCl_3$) δ 8.20-8.10 (m,1H), 8.10-7.95 (m, 3H), 7.65 (d, 2H), 7.45-7.35 (m, 1H), 7.35-7.20 (m, 1H), 7.15-7.05 (m, 1H), 6.95 (t, 1H), 4.85 (d, 2H).

Step B:



A solution of compound prepared in Example 473, Step A (120 mg, 0.24 mmol) in 10 mL of THF was treated with 2 mL of 1 M $MeNH_2$ (2.00 mmol) in THF at RT overnight. The solvent was removed and the residue was purified by chromatography (silica, hexane:EtOAc (4:1→1:1)) to provide 56 mg (48%) of the sulfonamide. ^{1}H NMR (DMSO-d6) δ 9.05 (t, J = 9 Hz, 1H), 8.35 (s, 1H), 7.90 (t, J = 7.5 Hz, 1H), 7.75 (d, J = 9 Hz, 2H), 7.62 (d, J = 9 Hz, 2H), 7.55-7.46 (m, 1H), 7.45-7.38 (m, 1H), 7.38-7.25 (m, 1H), 6.50 (s, 1H), 4.80 (d, 2H), 3.30 (s, 3H) LCMS: MH^+ = 492.1

EXAMPLE 474:

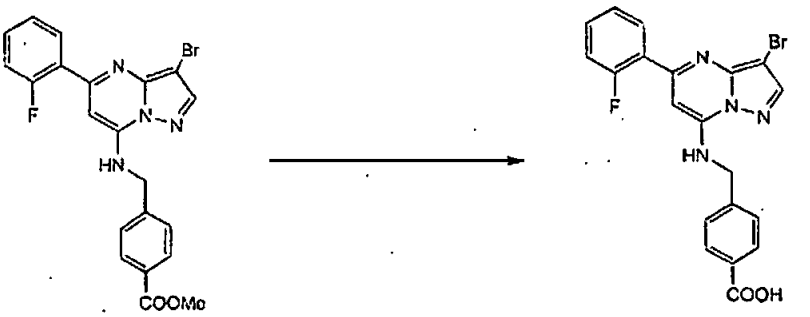


By essentially the same procedure set forth in Example 473, only substituting dimethylamine, the above compound was prepared. ^{1}H NMR ($CDCl_3$)

δ 8.14 (t, J = 9 Hz, 1H), 8.00 (s, 1H), 7.76 (d, J = 9 Hz, 2H), 7.54 (d, J = 9 Hz, 2H), 7.34-7.44 (m, 1H), 7.26 (t, J = 9 Hz, 1H), 7.14-7.04 (m, 1H), 6.93 (t, J= 6 Hz, 1H), 6.45 (s, 1H), 4.75 (d, 2H), 2.70 (s, 6H)

LCMS: MH^+ = 504.2

EXAMPLE 475:

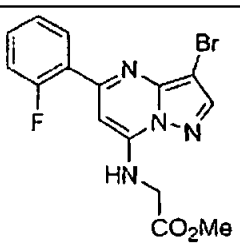
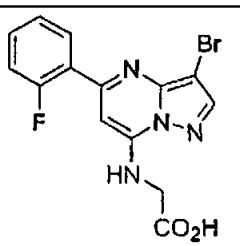


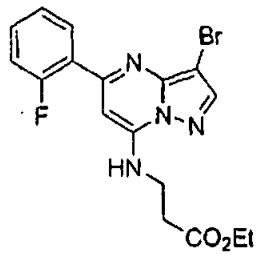
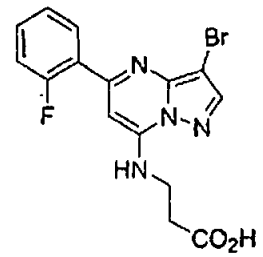
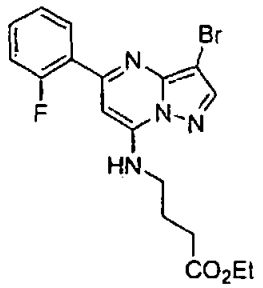
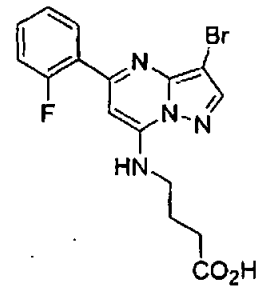
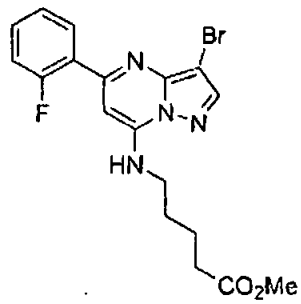
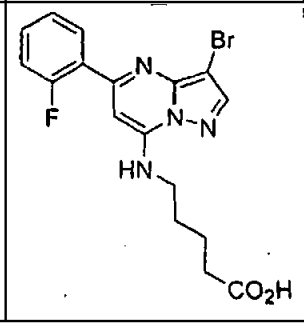
A mixture of the compound prepared in Example 129 (300 mg, 0.66 mmol), NaOH (5 g), CH_3OH –H_2O (100 mL; 90:10) was stirred at 25 C for about 15 h. Progress of hydrolysis was checked by TLC. Reaction mixture was concentrated to remove methanol. The concentrate was diluted with 50 mL water, and extracted with ether to remove any un-reacted ester. Aqueous solution, thus obtained, was neutralized with 3 N HCl to pH 4 to obtain free acid, filtered and washed repeatedly with water. The acid was dried under vacuum (270 mg, 93%) and used without further purification.

Example 476-479:

By essentially the same procedure set forth in Example 475 only substituting the compounds in Column 2 of Table 39, the compounds in Column 3 of Table 39 were prepared.

Table 39

Ex.	Column 2	Column 3	CMPD
476			Yield = 82% LCMS: MH^+ = 365

477			Yield = 82% LCMS: MH^+ = 379
478			Yield = 72% LCMS: MH^+ = 393
479			Yield = 70% LCMS: MH^+ = 407

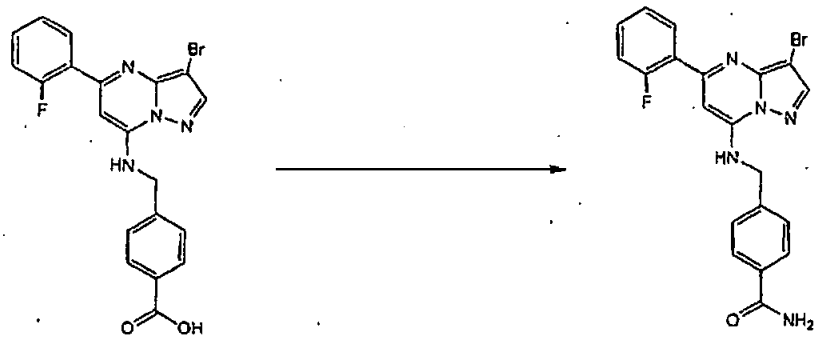
Additional data for select examples shown below:

Example 476: ^{1}H NMR ($CDCl_3$) δ 8.15 (m, 2H), 8.0 (m, 1H), 7.6 (m, 1H), 7.3 (m, 2H), 6.6 (s, 1H), 4.2 (d, 2H).

Example 477: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.4 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 7.0 (t, 1H), 6.5 (s, 1H), 3.8 (dt, 2H), 2.6 (t, 2H).

Example 479: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.4 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 6.8 (t, 1H), 3.5 (dt, 2H), 2.4 (t, 2H), 1.8 (m, 4H).

EXAMPLE 480:

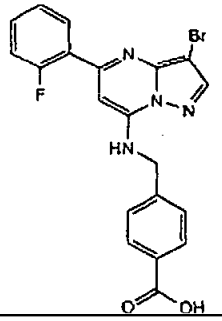
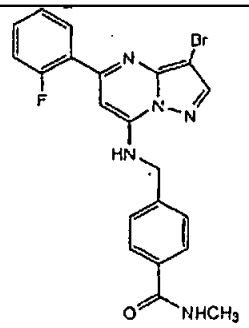


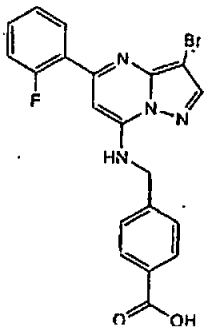
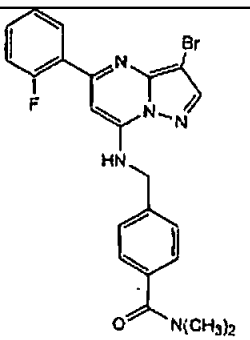
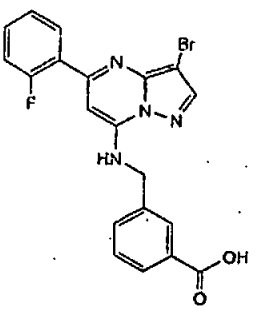
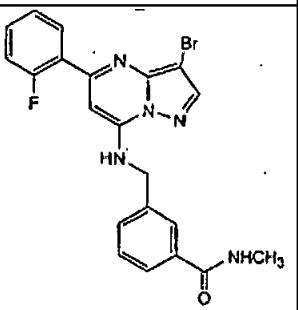
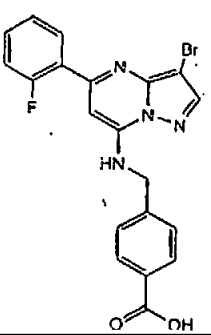
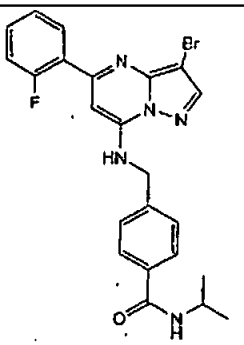
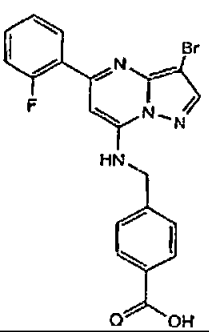
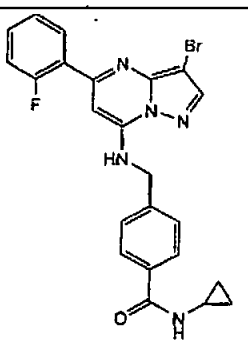
A mixture of the acid from Example 475 (85mg, 0.193 mmol) and Et_3N (20 mg, 0.193 mmol) in THF (20 mL) was stirred at 25 C for 15 min. Isobutyryl chloroformate (28mg, 0.205 mmol) was added to the reaction mixture and stirred for 10 min followed by addition of NH4OH solution (0.5 mL). The reaction mixture was stirred for 1 hr and concentrated to dryness. The dry mass was purified by column chromatography.

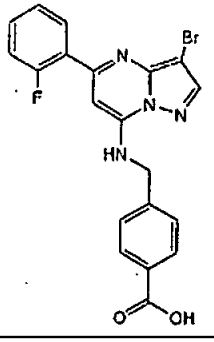
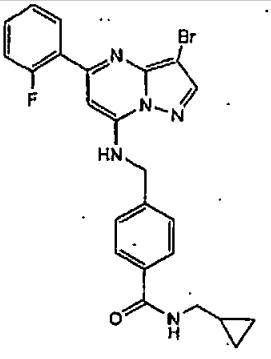
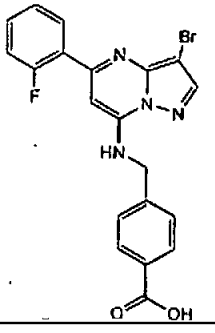
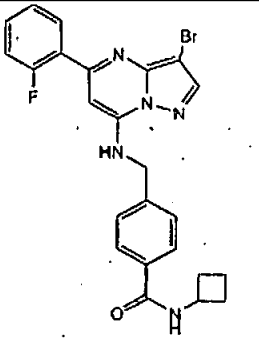
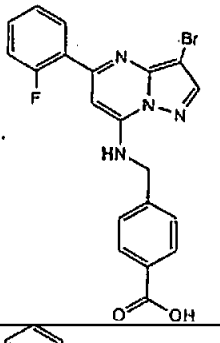
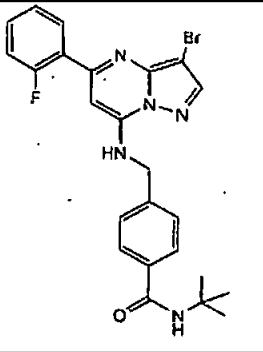
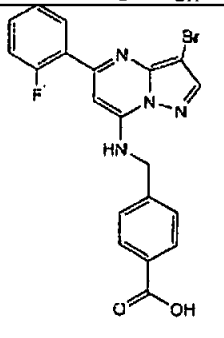
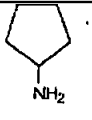
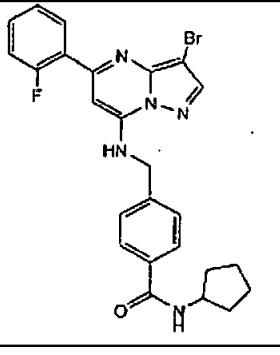
EXAMPLES 481-509:

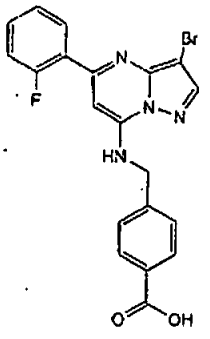
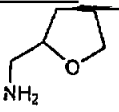
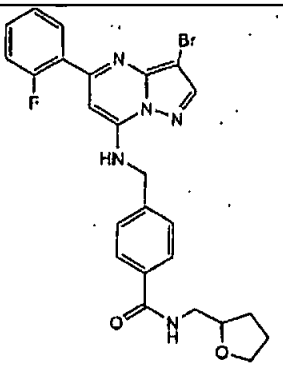
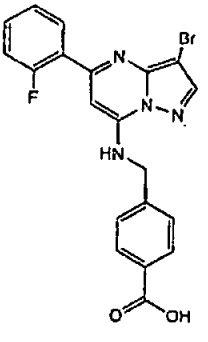
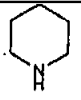
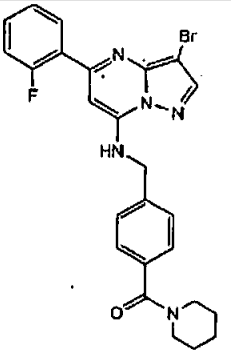
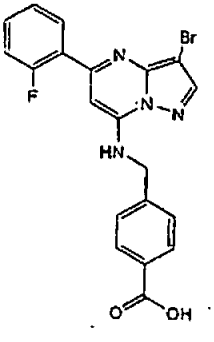
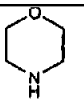
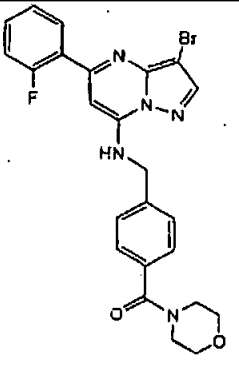
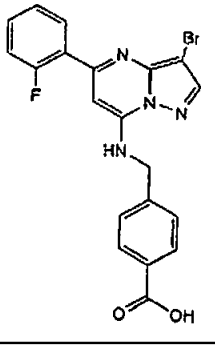
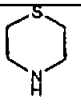
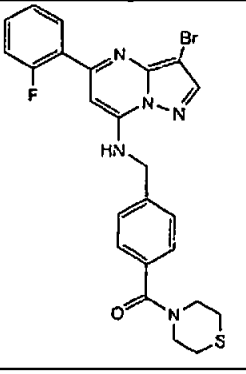
By essentially the same procedure set forth in Example 480 only substituting the carboxylic acid shown in Column 2 of Table 40 and the amine shown in Column 3 of Table 40, the compounds shown in Column 4 of Table 40 were prepared.

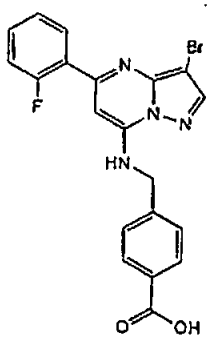
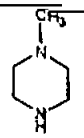
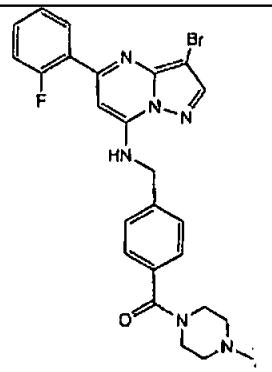
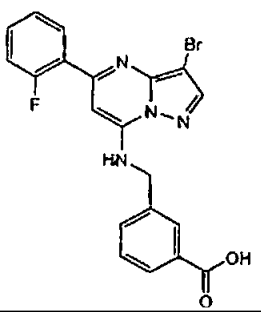
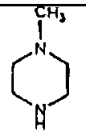
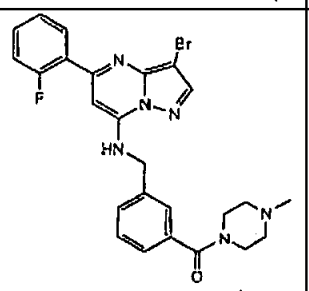
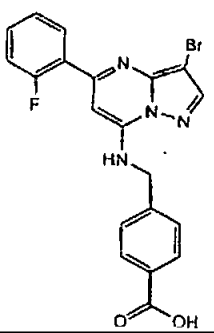
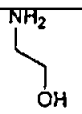
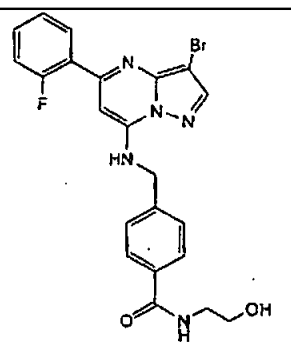
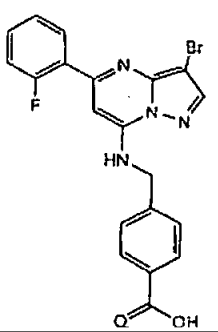
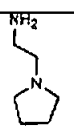
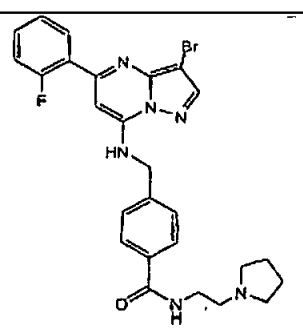
Table 40

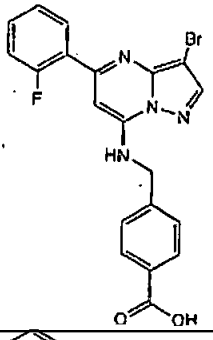
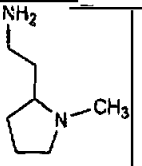
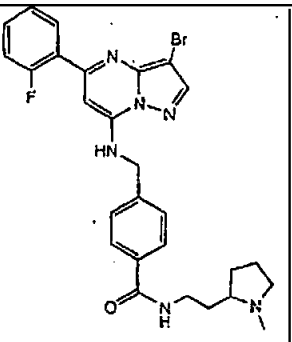
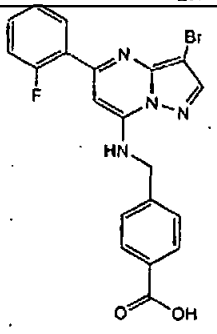
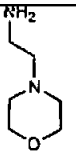
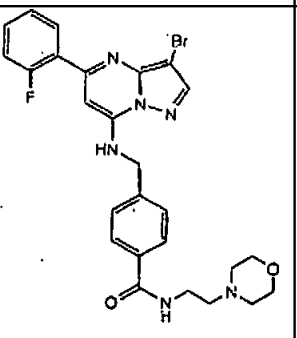
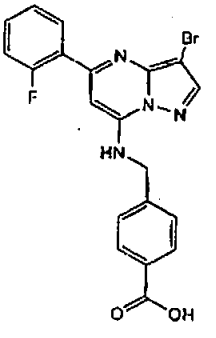
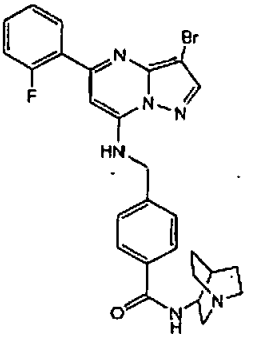
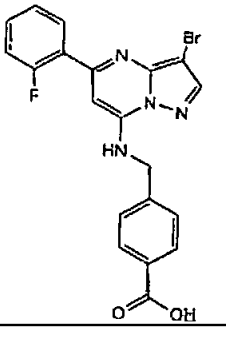
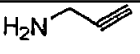
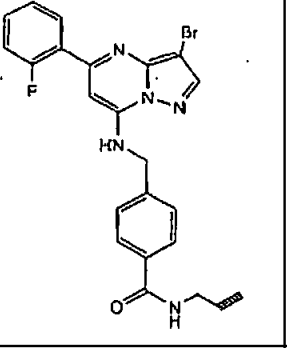
Ex.	Column 2	Column 3	Column 4	CMPD
481		CH_3NH_2		Yield = 88% LCMS: MH^+ = 454

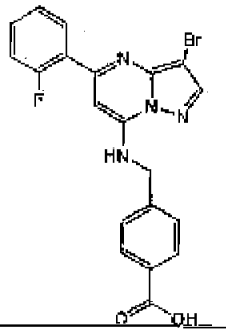
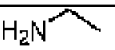
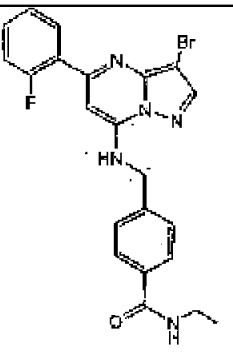
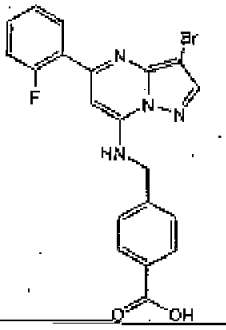
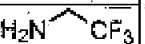
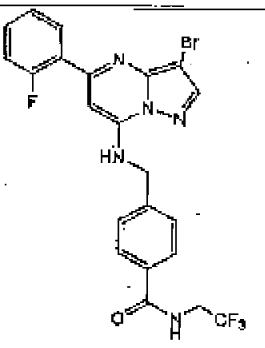
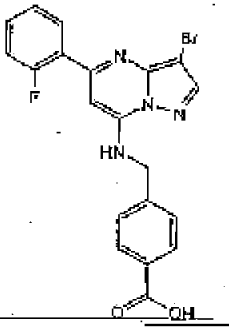
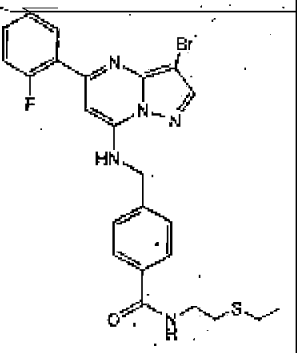
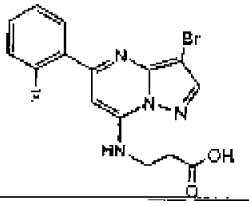
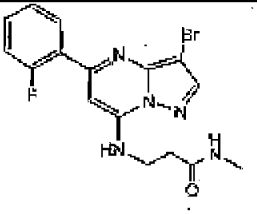
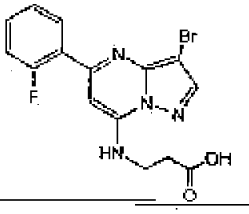
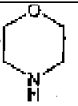
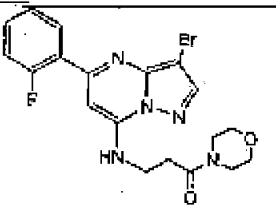
482		$(CH_3)_2NH$		Yield=80 % LCMS MH^+ = 468
483		CH_3NH_2		Yield=70 % LCMS MH^+ = 454.
484				Yield=75 % LCMS MH^+ = 482.1
485				Yield=71 % LCMS MH^+ = 480.1

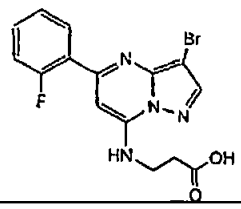
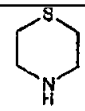
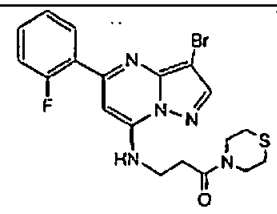
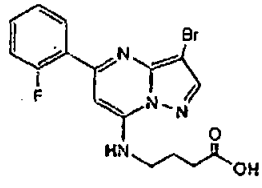
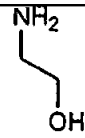
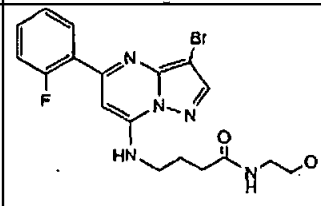
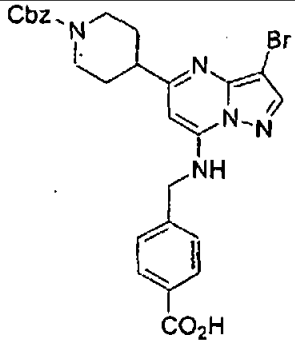
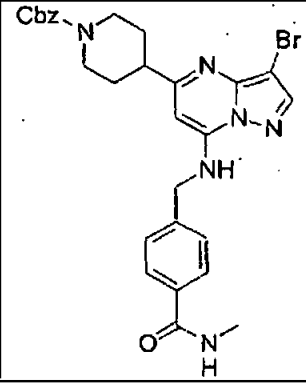
486				Yield=75 % LCMS MH^+ = 494.1
487				Yield=75 % MH^+ = 494.1
488				Yield=75 % MH^+ = 496.1
489				Yield=75 % LCMS MH^+ = 508.1

490				Yield=78 % LCMS MH^+ = 524.1
491				Yield=73 % LCMS MH^+ = 508.1
492				Yield=73 % LCMS MH^+ = 510.1
493				Yield=76 % LCMS MH^+ = 526.1

494				Yield=76 % MH^+ = 523.1
495				Yield=76 % MH^+ = 523.1
496				Yield=51 % LCMS MH^+ = 484.1
497				Yield=66 % MH^+ = 537.1

498				Yield=76 % LCMS MH^+ = 551.2
499				Yield=79 % LCMS MH^+ = 552.1
500				Yield=80 % MH^+ = 549.1
501				Yield=80 % LCMS MH^+ = 478.1

502				Yield=80 % LCMH$^+$ = 468.1
503				Yield=80 % MH$^+$ = 522.1
504				Yield=82 % LCMS MH$^+$ = 528.1
505		CH_3NH_2		Yield=60 % MH$^+$ = 392
506				Yield=60 % LCMH$^+$ = 448.1

507				Yield=70 % MH^+ = 464.1
508				Yield=50 % LCMS MH^+ = 436.1
508.10		CH_3NH_2		Yield = 92 MH^+ = 577

Additional data for select examples given below:

Example 481: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.7 (d, 2H), 7.4 (s, 1H), 7.35 (d, 2H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.95 (t, 1H), 6.5 (s, 1H), 6.25 (bs, 1H), 4.7 (d, 2H), 3.0 (d, 3H).

Example 482: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H),8.0 (s, 1H), 7.45 – 7.35 (m, 4H), 7.25 (d, 2H), 7.15 (dd, 1H), 6.7 (t, 1H), 6.5 (s, 1H), 4.7 (d, 2H), 3.1 (s, 3H), 3.0 (s, 3H).

Example 483: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.8 (bs, 1H), 7.7 (d, 1H), 7.5 – 7.3 (m, 3H), 7.25 (d, 1H), 7.15 (dd, 1H), 6.75 (t, 1H), 6.5 (s, 1H), 6.2 (bs, 1H), 4.7 (d, 2H), 3.0 (d, 3H).

Example 484: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.7 (d, 2H), 7.4 (d, 2H), 7.35 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 6.8 (t, 1H), 6.5 (s, 1H), 6.0 bs, 1H), 4.7 (d, 2H), 4.25 (m, 1H), 1.2 (d, 6H).

Example 485: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.7 (d, 2H), 7.4 (d, 2H), 7.35 (s, 1H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.9 (t, 1H), 6.5 (s, 1H), 6.3 (t, 1H), 4.7 (d, 2H), 2.9 (m, 1H), 0.8 (bt, 2H), 0.6 (bt, 2H).

Example 486: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.8 (d, 2H), 7.4 (d, 2H), 7.35 (d, 1H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.9 (t, 1H), 6.5 (s, 1H), 6.2 (t, 1H), 4.7 (d, 2H), 3.3 (dd, 2H), 1.05 (m, 1H), 0.5 (m, 2H), 0.25 (m, 2H).

Example 487: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.7 (d, 2H), 7.4 (d, 2H), 7.35 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 6.85 (t, 1H), 6.5 (s, 1H), 6.2 (bs, 1H), 4.7 (d, 2H), 4.6 (m, 1H), 2.4 (m, 2H), 1.95 (m, 1H), 1.75 (m, 2H).

Example 488: ^{1}H NMR ($CDCl_3$) δ 8.5 (t, 1H), 8.15 (dt, 1H), 8.0 (s, 1H), 7.7 (d, 2H), 7.4 (d, 2H), 7.35 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 6.8 (t, 1H), 6.5 (s, 1H), 5.9 (bs, 1H), 4.7 (d, 2H), 1.4 (s, 9H).

Example 489: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.7 (d, 2H), 7.4 (d, 2H), 7.35 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 6.8 (t, 1H), 6.5 (s, 1H), 6.0 bs, 1H), 4.7 (d, 2H), 4.4 (m, 1H), 2.05 (m, 2H), 1.7 (m, 4H), 1.4 (m, 2H).

Example 490: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.7 (d, 2H), 7.4 (d, 2H), 7.35 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 6.8 (t, 1H), 6.5 (s, 1H), 6.5 (bs, 2H), 4.7 (d, 2H), 4.1 (m, 1H), 3.9 – 3.7 (m, 3H), 3.3 (m, 1H), 2.0 – 1.9 (m, 4H).

Example 491: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.45 – 7.35 (m, 5H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.8 (t, 1H), 6.5 (s, 1H), 4.7 (d, 2H), 3.7 (bs, 2H),3.3 (bs, 2H), 1.7 (bs, 4H), 1.5 (bs, 2H).

Example 492: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.45 – 7.35 (m, 5H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.85 (t, 1H), 6.5 (s, 1H), 4.7 (d, 2H), 3.8 – 3.4 (bm, 8H).

Example 493: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.45 – 7.35 (m, 5H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.80 (t, 1H), 6.5 (s, 1H), 4.7 (d, 2H), 4.0 (m, 2H), 3.6 (m, 2H), 2.8 – 2.45 (m, 4H).

Example 494: ^{1}H NMR (CH3OD) δ 8.15 (s, 1H), 8.0 (dt, 1H), 7.45 – 7.35 (m, 5H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.80 (t, 1H), 6.5 (s, 1H), 4.7 (d, 2H), 3.7 (bs, 2H), 3.4 (bs, 2H), 2.5 – 2.4 (m, 4H), 2.2 (s, 3H).

Example 495: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.45 – 7.35 (m, 5H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.80 (t, 1H), 6.5 (s, 1H), 4.7 (d, 2H), 3.75 (bs, 2H), 3.35 (bs, 2H), 2.4 (bs, 2H), 2.3 (s, 3H), 2.2 (bs, 2H).

Example 496: ^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1H), 7.9 (dt, 1H), 7.8 (t, 1H), 7.7 (d, 2H), 7.15 (m, 4H), 7.05 (dd,1H), 6.9 (dd, 1H), 6.2 (s,1H), 4.5 (d, 2H), 3.6 (t, 2H), 3.3 (dt, 2H).

Example 497: ^{1}H NMR (CH3OD) δ 8.1 (s, 1H), 7.9 (dt, 1H), 7.8 (d, 2H), 7.5 (d, 2H), 7.4 (m, 1H), 7.3 (dd, 1H), 7.2 (dd, 1H), 6.4 (s, 1H), 4.7 (d, 2H), 3.5 (t, 2H), 2.7 (m, 2H), 2.6 (bs, 4H), 1.8 (bs, 4H).

Example 498: ^{1}H NMR ($CDCl_3$) δ 8.5 (t, 1H), 8.15 (dt, 1H), 8.0 (s, 1H), 7.8 (d, 2H), 7.4 (d, 2H), 7.35 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 6.8 (t, 1H), 6.5 (s, 1H), 4.7 (d, 2H), 3.7 – 2.5 (m, 4H), 2.35 (s, 3H), 2.2 (m, 1H), 1.9 – 1.6 (m, 6H).

Example 499: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.8 (d, 2H), 7.4 (d, 2H), 7.35 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 6.8 (t, 1H), 6.5 (s, 1H), 4.7 (d, 2H), 3.7 (m, 4H), 3.5 (dt, 2H), 2.6 (t, 2H), 2.5 (m, 4H).

Example 500: ^{1}H NMR (CH3OD) δ 8.15 (s, 1H), 7.9 (dt, 1H), 7.8 (d, 2H), 7.45 (d, 2H), 7.4 (m, 1H),7.25 (dd, 1H), 7.15 (dd, 1H), 6.4 (s, 1H), 4.75 (d, 2H), 4.2 (m, 1H), 3.4 – 2.8 (m, 7H), 1.9 – 1.6 (m, 4H).

Example 501: ^{1}H NMR ($CDCl_3$) δ 8.05 (dt, 1H), 8.0 (s, 1H), 7.6 (d, 2H), 7.4 (s, 1H), 7.35 (d, 2H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.9 (t, 1H), 6.5 (s, 1H), 6.4 (t,1H), 4.7 (d, 2H), 4.2 (d, 2H), 2.3 (bs, 1H).

Example 502: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.75 (d, 2H), 7.45 (s, 1H), 7.4 (d, 2H), 7.3 (dd, 1H), 7.1(dd, 1H), 6.8 (t, 1H), 6.5 (s, 1H), 6.1(bs, 1H), 4.7 (d, 2H), 3.5 (dq, 2H), 1.2 (t, 3H).

Example 503: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.8 (d, 2H), 7.4 (d, 2H), 7.35 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 6.9 (t, 1H), 6.5 (s, 1H), 6.4 (t, 1H), 4.75 (d, 2H), 4.1 (m, 2H).

Example 504: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.8 (d, 2H), 7.45 (d, 2H), 7.4 (m, 1H), 7.25 (dd, 1H), 7.1 (dd, 1H), 6.8 (t, 1H), 6.6 (t, 1H), 6.5 (s, 1H), 4.7 (d, 1H), 3.6 (m, 2H), 2.8 (t, 2H), 2.6 (q, 2H), 1.3 (t, 3H).

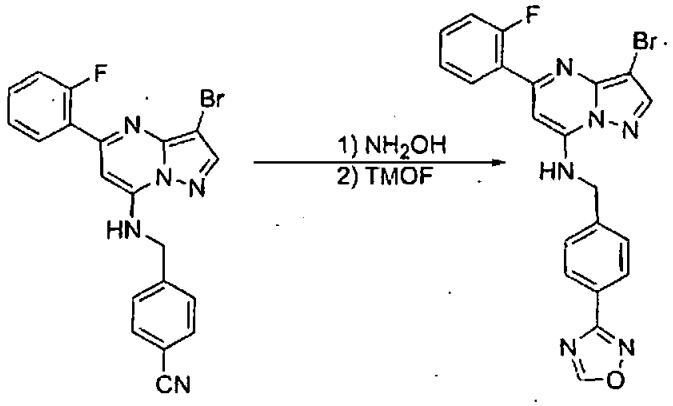
Example 505: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.4 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 7.0 (t, 1H), 6.5 (s, 1H), 3.8 (m, 2H), 2.7 (t, 2H), 3.0 (d, 3H).

Example 506: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.4 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 7.0 (t, 1H), 6.5 (s, 1H), 3.8 (m, 2H), 3.6 (m, 6H), 3.4 (m, 2H), 2.7 (t, 2H).

Example 507: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.4 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 7.0 (t, 1H), 6.5 (s, 1H), 3.9 (t, 2H), 3.8 (dt, 2H), 3.7 (t, 2H), 2.7 (t, 2H), 2.6 (m, 4H).

Example 508: ^{1}H NMR (CH_3OD) δ 8.1 (s, 1H), 7.95 (dt, 1H), 7.5 (m, 1H), 7.35 – 7.2 (m, 2H), 6.5 (s, 1H),3.6 (m, 4H), 3.25 (m, 4H), 2.4 (t, 2H), 2.05 (dt, 2H).

EXAMPLE 509:

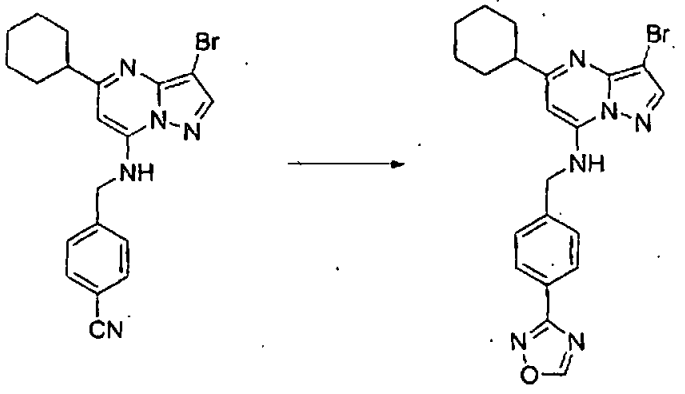


A solution of NaOH (59 mg, 1.47 mmol) in 1 mL of water was added to a suspension of $NH_2OH.HCl$ (102 mg, 1.47 mmol) in 10 mL of methanol at 0 °C. After 5 min, the compound prepared in Example 210.10 (208 mg, 0.49 mmol) was added and the reaction mixture was refluxed overnight. The solvent was removed *in vacuo* and the residue was partitioned between water and EtOAc. The EtOAc layer was dried (Na_2SO_4) and the solvent was evaporated. The resulting crude amidoxime was suspended in trimethyl orthoformate containing catalytic amount of PTS acid and refluxed overnight. The solvent was removed and the residue was taken up in EtOAc. The EtOAc layer was washed with aq $NaHCO_3$ followed by water and brine. The solvent was evaporated and the residue was purified by chromatography (silica, hexane:EtOAc (1:1)) to provide

80 mg (35%) of the oxadiazole. ^{1}H NMR ($CDCl_3$) δ 8.75 (s, 1H), 8.20-8.10 (m, 3H), 8.03 (s, 1H), 7.53 (d, J = 9 Hz, 2H), 7.45-7.36 (m, 1H), 7.30-7.22 (m, 2H), 7.16-7.08 (m, 1H), 6.80 (t, J = 5 Hz, 1H), 6.56 (s, 1H).

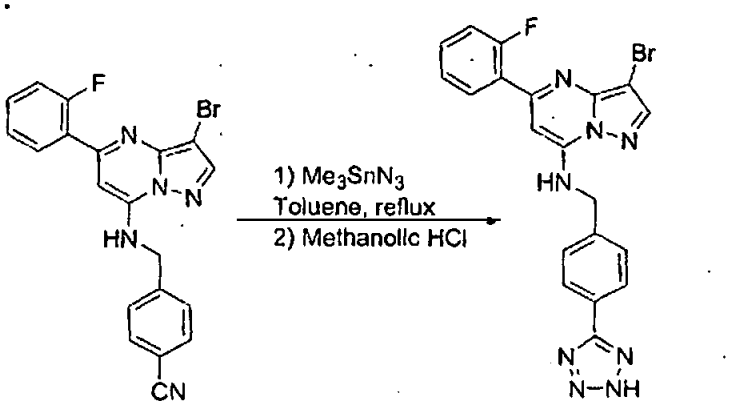
LCMS: MH^+ = 465.2

Example 510:



By essentially the same procedure set forth in Example 509 only substituting the compound prepared in Preparative Example 192, the above compound was prepared. yield = 75; MH^+ = 453; m. p. = 79.3°C.

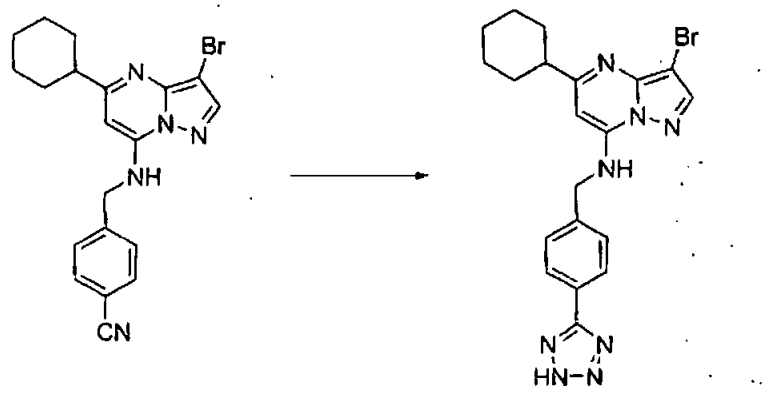
EXAMPLE 511:



A mixture of the nitrile (235 mg, 0.56 mmol) and Me_3SnN_3 (343 mg, 1.67 mmol) in 20 mL of dry toluene was refluxed for 2 days under Ar. The solvent was removed *in vacuo* and the residue was dissolved in dry methanol. HCl gas was bubbled through the solution for 15 min and the reaction mixture allowed to stand at overnight at RT. The next day, the solvent was removed, the residue was taken in water and the pH was adjusted to 5. The precipitated product was

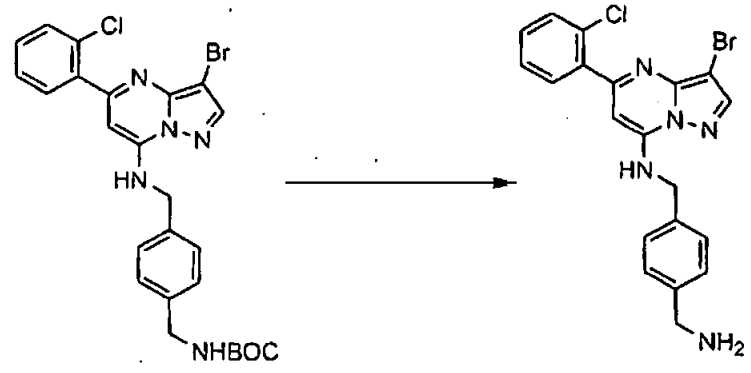
extracted into EtOAc. Evaporation of the EtOAc layer after drying (Na_2SO_4) provided the residue which was purified by chromatography (silica, DCM:MeOH (98:2→95:5)) to yield 50 mg (19%) of the pure tetrazole. ^1H NMR (CD_3OD) δ 8.10 (s, 1H), 8.00 (d, J = 9 Hz, 2H), 7.90 (t, J = 7 Hz, 1H), 7.65 (d, J = 9 Hz, 2H), 7.50-7.40 (m, 1H), 7.30-7.10 (m, 2H), 6.45 (s, 1H), 4.80 (s, 2H); LCMS: MH^+ = 465.0

EXAMPLE 512:



By essentially the same procedure set forth in Example 511 only substituting the compound prepared in Example 192, the above compound was prepared. Yield = 64; MH^+ = 453; m. p. = 238.9°C.

EXAMPLE 513:



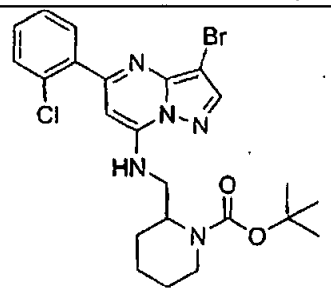
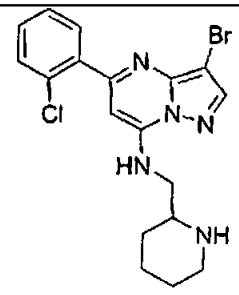
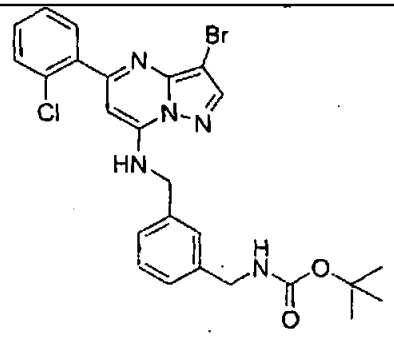
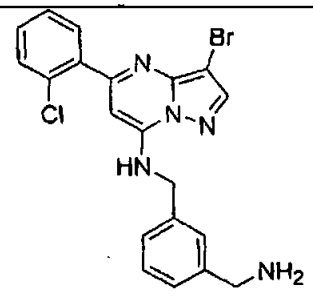
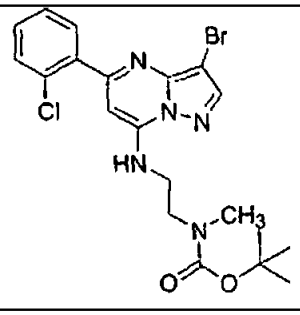
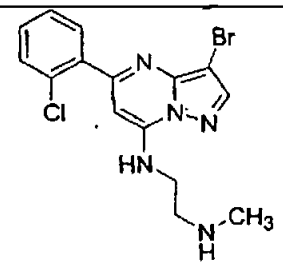
The compound prepared in Example 157 was dissolved in dioxane (30 mL) and a HCl-dioxane solution (4 M, 30 mL) was added. The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was evaporated under reduced pressure and ethyl acetate (200 mL) was added. The organic

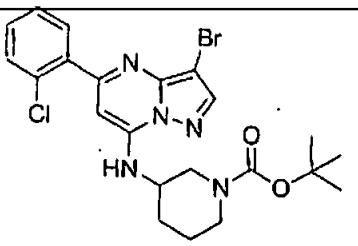
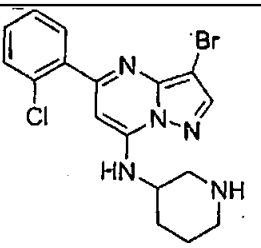
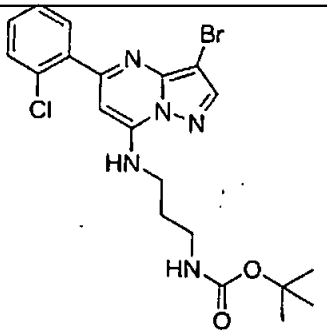
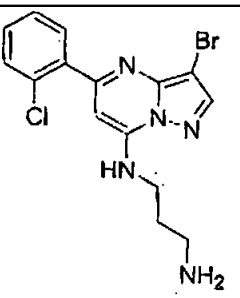
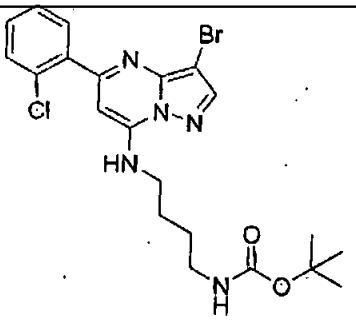
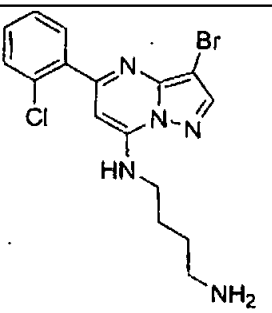
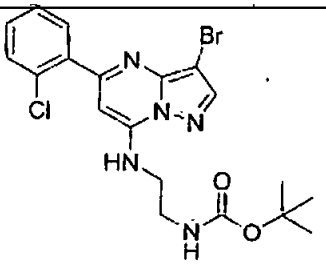
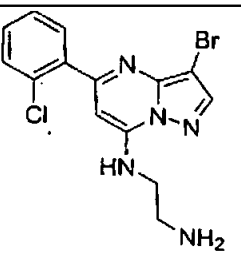
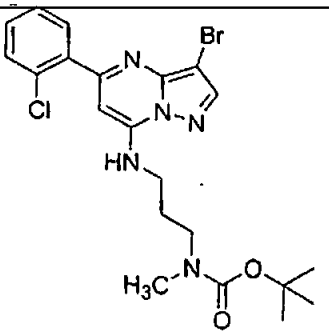
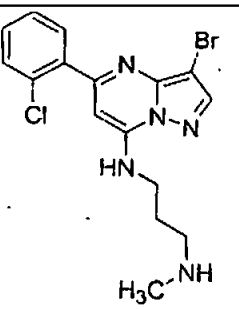
solution was washed with 1 N sodium hydroxide followed by saturated brine. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. MH^+ = 442.1

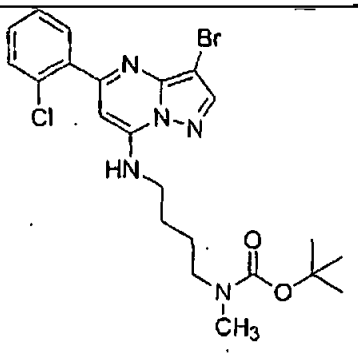
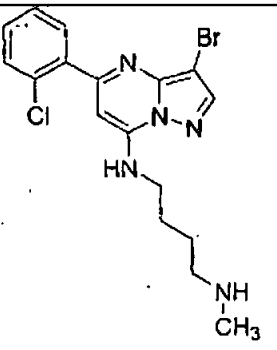
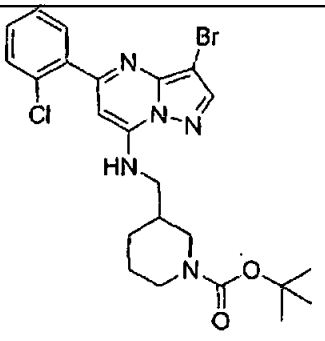
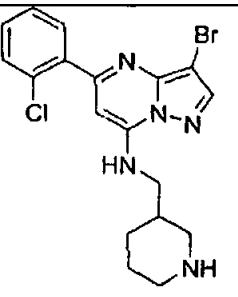
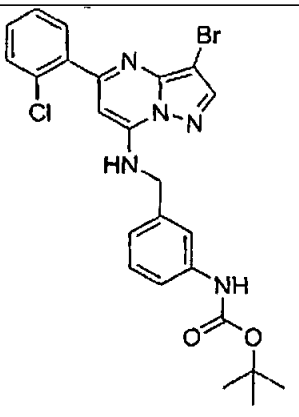
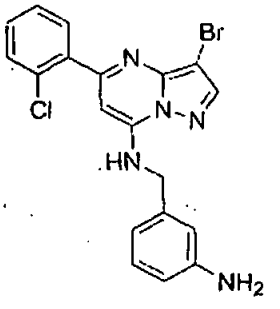
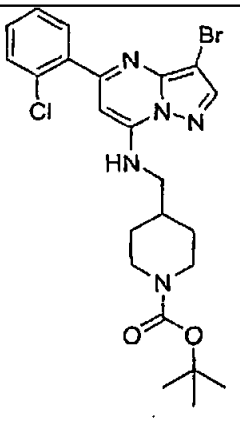
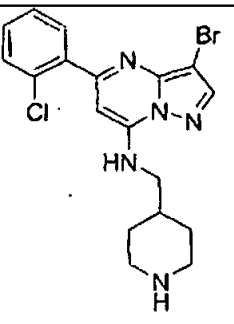
EXAMPLE 514-526:

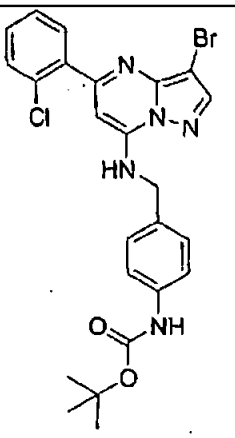
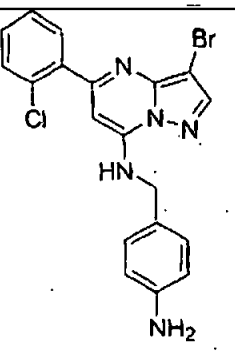
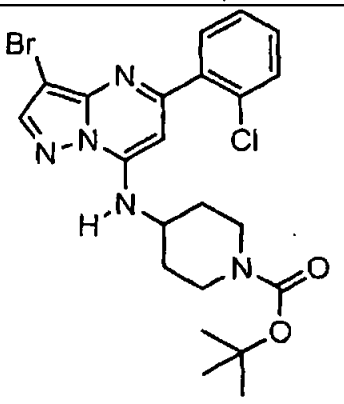
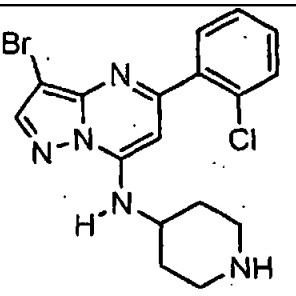
By essentially the same procedure set forth in Example 513, only substituting the compounds shown in Column 2 of Table 41, the compounds shown in Column 3 of Table 41 were prepared.

TABLE 41

Ex.	Column 2	Column 3	CMPD
514			MH^+ = 420.1
515			MH^+ = 442.1
516			MH^+ = 380.1

517			MH^+ = 406.1
518			MH^+ = 380.1
519			MH^+ = 394.1
520			MH^+ = 366
521			MH^+ = 394

522			MH^+ = 408.1
523			MH^+ = 420.1
524			
525			MH^+ = 420.1

526			MH^+ = 428.1
526.10			

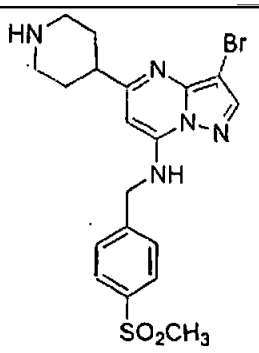
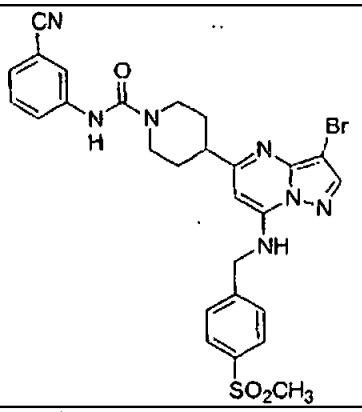
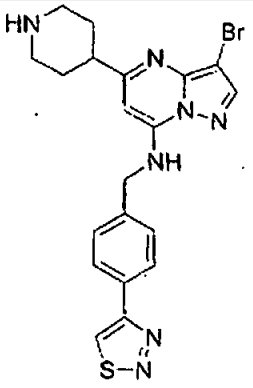
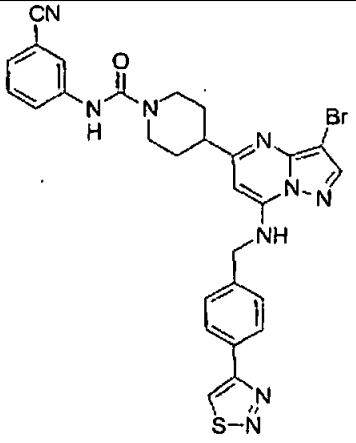
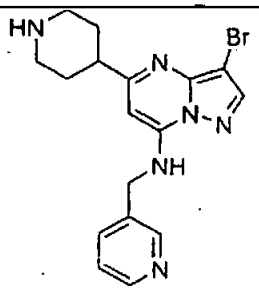
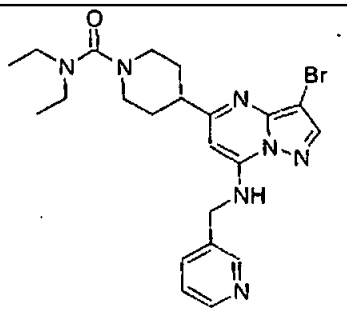
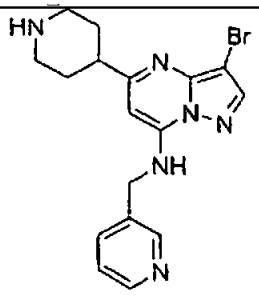
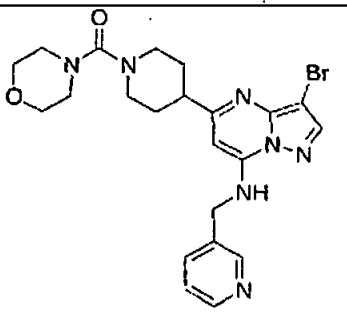
EXAMPLES 528-564:

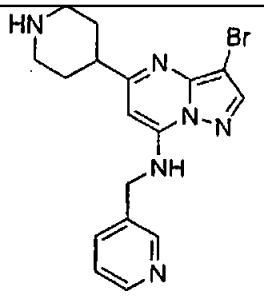
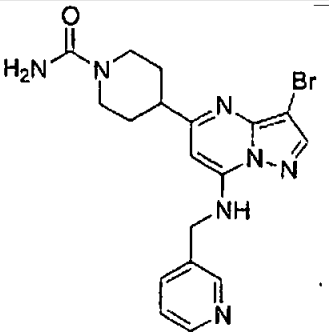
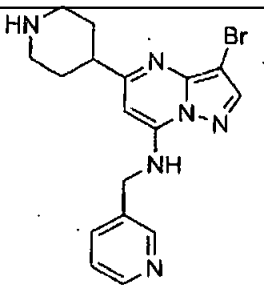
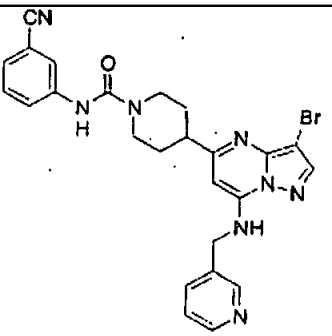
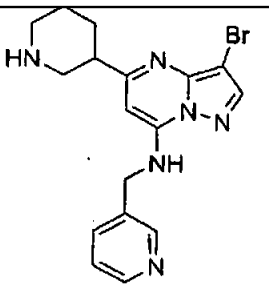
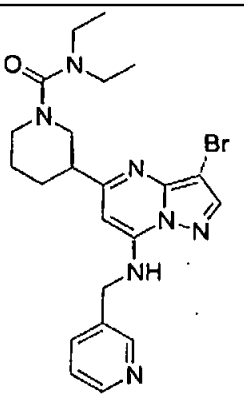
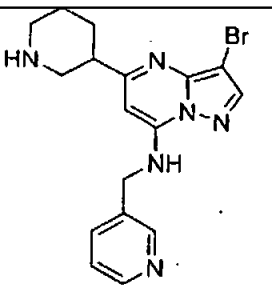
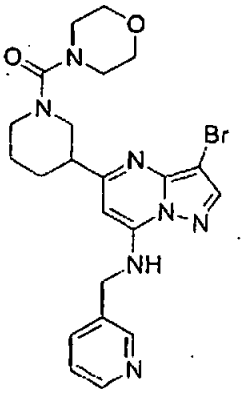
General procedure for 5-piperidinyl parallel library formation:

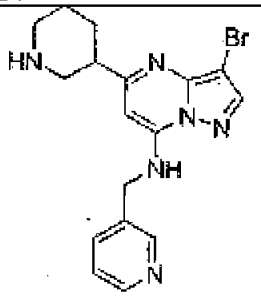
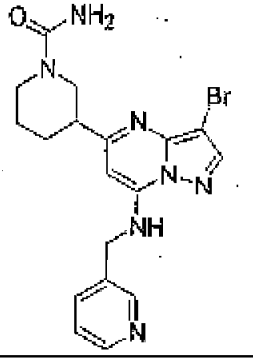
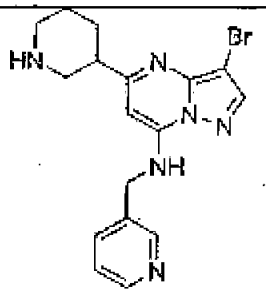
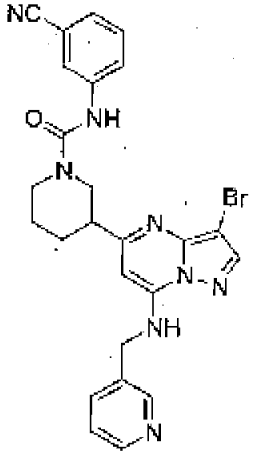
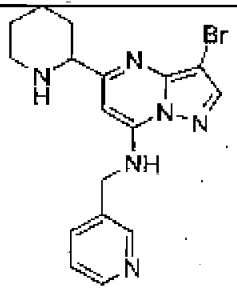
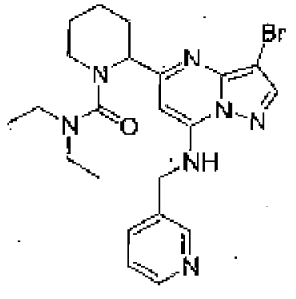
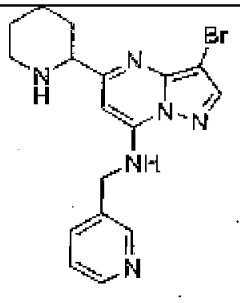
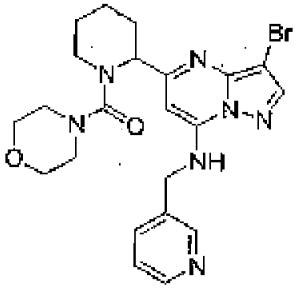
To a mixture of the starting material (80 mg, 0.21 mmol) shown in Column 2 of Table 42 in anhydrous CH_2Cl_2 (1.5 mL) was added DIPEA (75 μL, 0.42 mmol) and the appropriate capping reagent (1.1 equiv., 0.23 mmol). After 1 to 2 h, the reaction mixture was applied to 1000 micron preparatory TLC plate and was subsequently developed using a 8 – 10 % EtOH – CH_2Cl_2 as eluent to afford the compounds shown in Column 3 of Table 42.

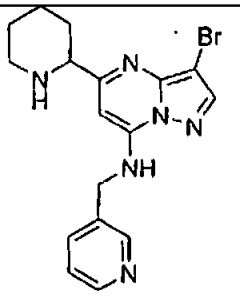
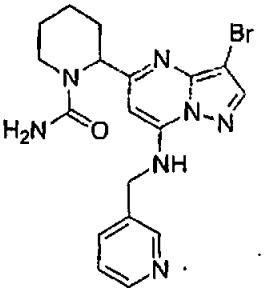
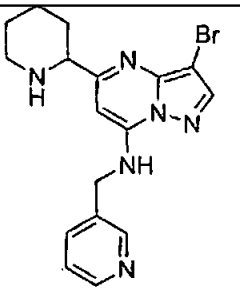
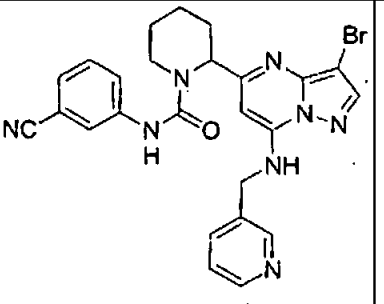
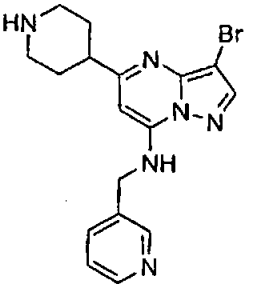
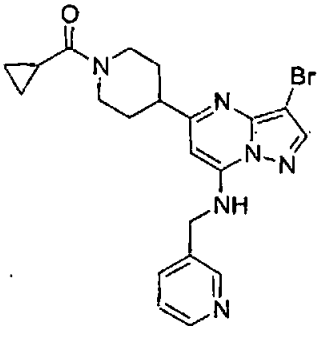
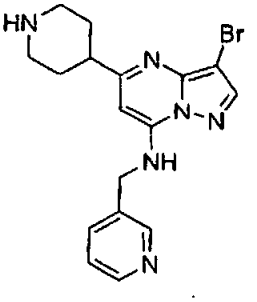
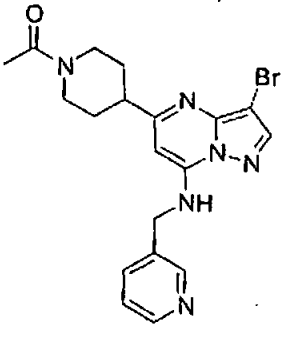
TABLE 42

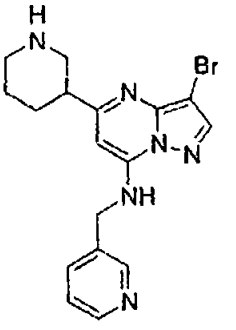
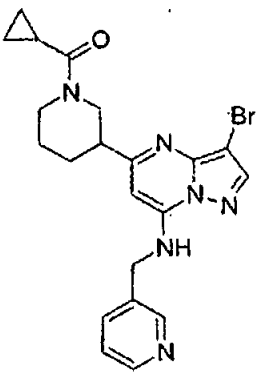
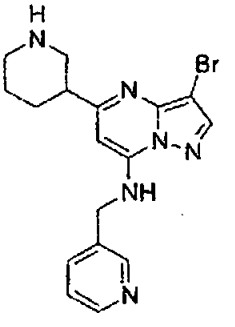
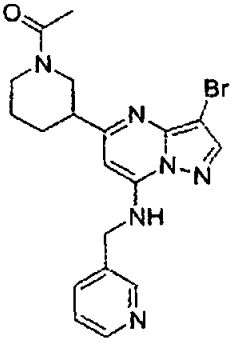
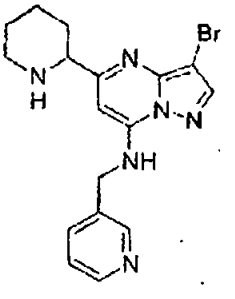
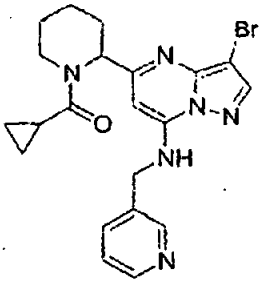
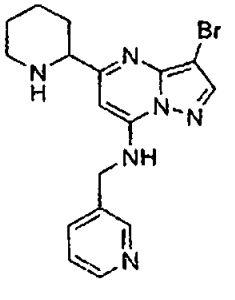
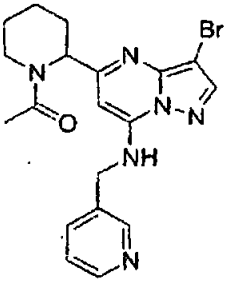
Ex.	Column 2	Column 3	CMPD

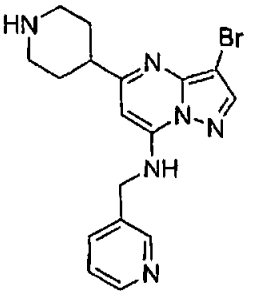
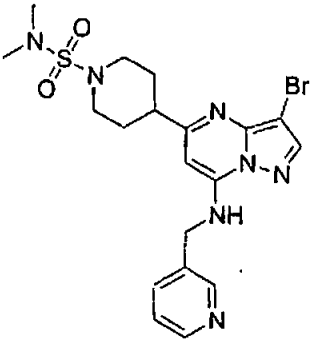
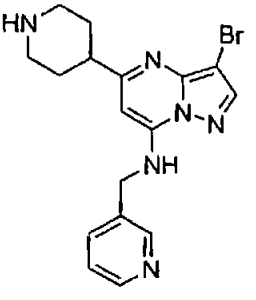
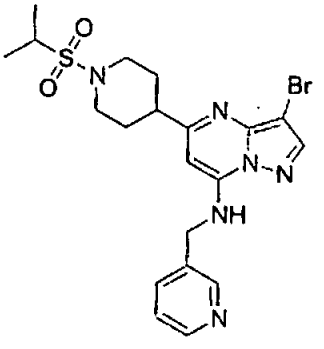
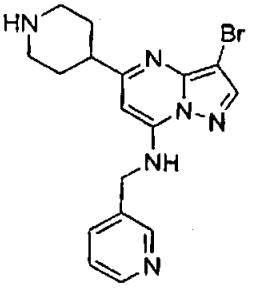
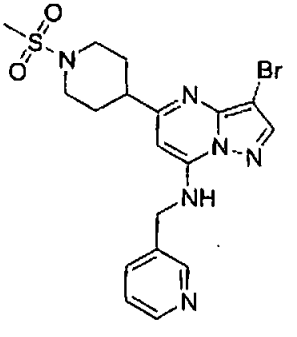
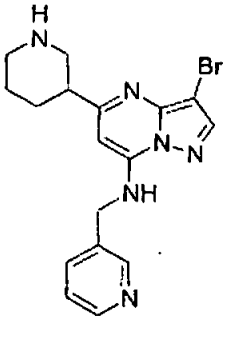
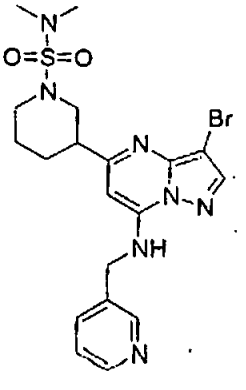
528			MH^+ = 608 m. p. = 230.1 °C
529			Yield = 82 MH^+ = 614 m. p. = 235.4 °C
530			MH^+ = 486 m. p. = 60.5 °C
531			MH^+ = 500 m. p. = 113.6 °C

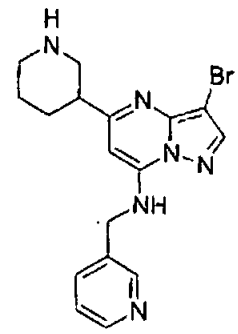
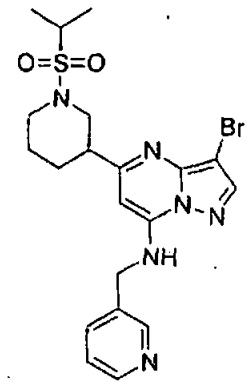
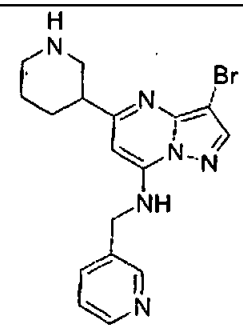
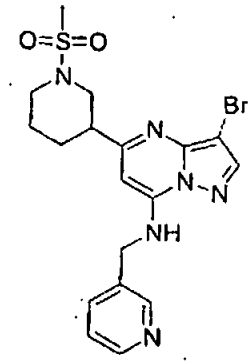
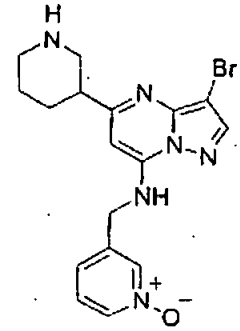
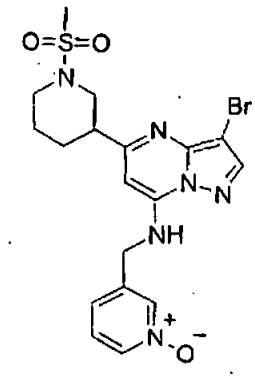
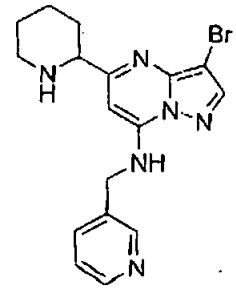
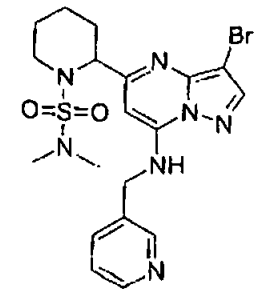
532			MH^+ = 430 m. p. = 158.3 – 159.2 °C
533			MH^+ = 531 m. p. =105.9 °C
534			MH^+ = 486
535			MH^+ = 500

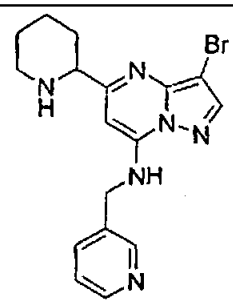
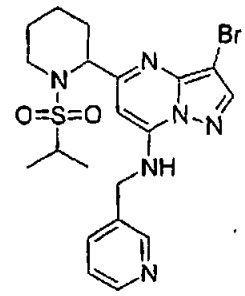
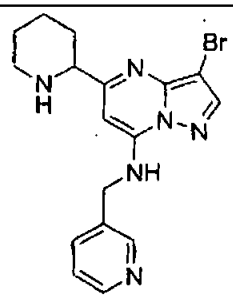
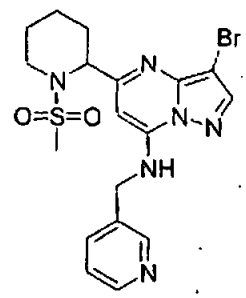
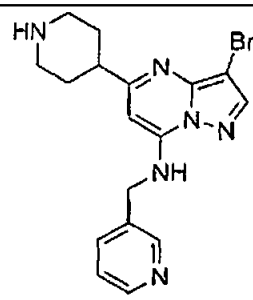
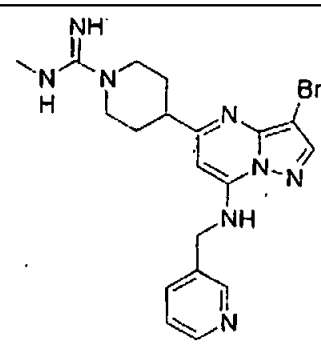
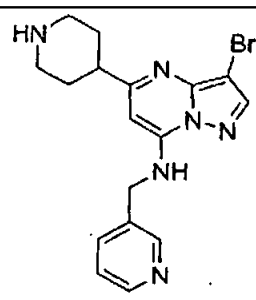
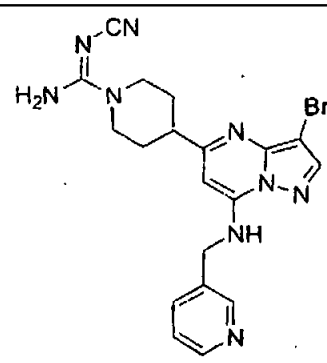
536			MH^+ = 430
537			MH^+ = 531
538			MH^+ = 486 m. p. = 69.6 °C
539			MH^+ = 500 m. p. = 82.3 °C

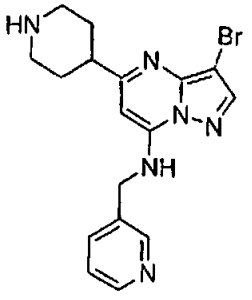
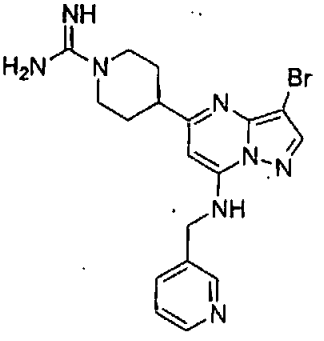
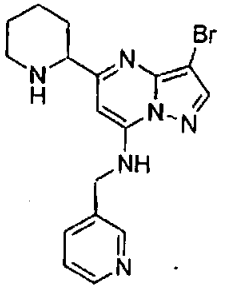
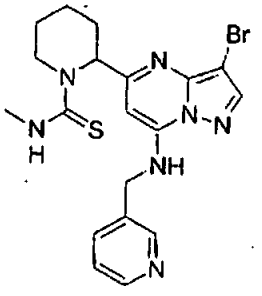
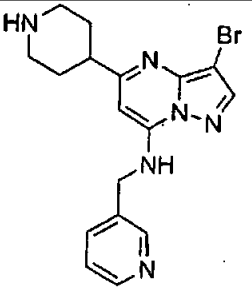
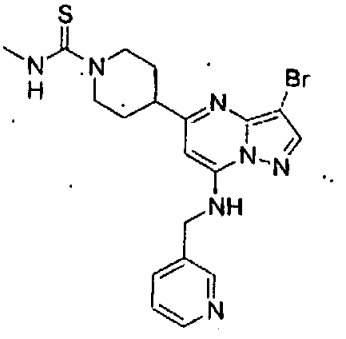
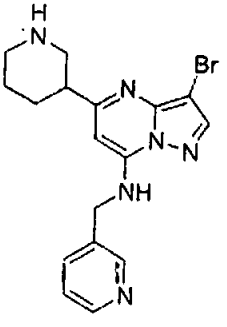
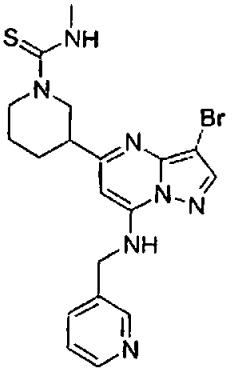
540			MH^+ = 430 m. p. = 223.6 °C
541			MH^+ = 531 m. p. = 118.1 °C
542			MH^+ = 455 m. p. = 109 – 110 °C
543			MH^+ = 429 m. p. = 111.5 °C

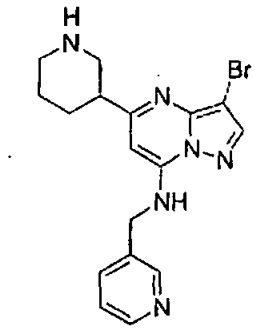
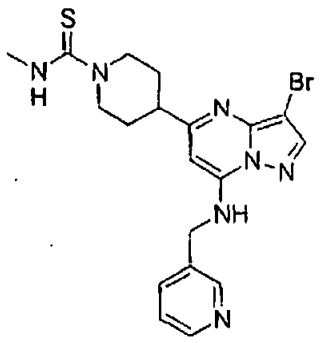
544			MH^+ = 455
545			MH^+ = 429
546			MH^+ = 455 m. p. =80.1 °C
547			MH^+ = 429 m. p. = 64.7 °C

548			MH^+ = 494 m. p. = 76.5 °C
549			MH^+ = 493 m. p. = 83.6 °C
550			MH^+ = 465 m. p. =207.5 °C
551			MH^+ = 494

552			MH^+ = 493
553			MH^+ = 465
554			MH^+ = 481 m. p. = 102.7 °C
555			MH^+ = 494 m. p. = 85.3 °C

556			MH^+ = 493 m. p. = 89.1 °C
557			MH^+ = 465 m. p. = 83.8 °C
558			Yield = quant. MH^+ = 443 m. p. = 98.3 °C (HCl salt)
559			MH^+ = 454

560			Yield = quant. MH^+ = 429 m. p. = 111.5 – 112. 6 °C
561			MH^+ = 460 m. p. = 122.7 °C
562			MH^+ = 460 m. p. = 95.4 °C
563			MH^+ = 460

564			MH^+ = 460 m. p. = 95.4 °C

Additional data for select examples given below.

Example 534: ^{1}H NMR (300MHz, $CDCl_3$) δ 8.66 – 8.62 (s, 1H), 8.62 – 8.58 (d, 1H), 7.95 (s, 1H), 7.72 – 7.68 (d, 1H), 7.36 – 7.31 (dd, 1H), 6.66 – 6.62 (t, 1H), 5.93 (s, 1H), 4.65 – 4.62 (d, 2H), 3.86 – 3.82 (d, 1H), 3.65 – 3.58 (m, 1H), 3.26 – 3.12 (dd, 4H), 3.02 – 2.80 (m, 3H), 2.10 – 2.00 (m, 1H), 1.67 – 1.57 (m, 3H).

Example 535: ^{1}H NMR (300MHz, $CDCl_3$) δ 8.66 – 8.62 (s, 1H), 8.62 – 8.58 (d, 1H), 7.95 (s, 1H), 7.72 – 7.67 (d, 1H), 7.36 – 7.30 (dd, 1H), 6.70 – 6.64 (t, 1H), 5.90 (s, 1H), 4.63 – 4.61 (d, 2H), 3.93 – 3.86 (m, 1H), 3.69 – 3.61 (m, 4H), 3.27 – 3.23 (m, 4H), 3.10 – 3.01 (dd, 1H), 2.93 – 2.84 (m, 2H), 2.08 – 2.03 (m, 1H), 1.90 – 1.57 (m, 4H).

Example 536: ^{1}H NMR (300MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.62 – 8.58 (d, 1H), 7.96 (s, 1H), 7.72 – 7.68 (d, 1H), 7.36 – 7.30 (dd, 1H), 6.79 – 6.72 (t, 1H), 5.96 (s, 1H), 4.86 (br s, 2H), 4.66 – 4.63 (d, 2H), 3.89 – 3.73 (m, 2H), 3.55 – 3.32 (m, 2H), 3.00 – 2.89 (m, 1H), 2.10 – 1.97 (m, 2H), 1.70 – 1.53 (m, 2H).

Example 537: ^{1}H NMR (300MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.62 – 8.58 (d, 1H), 7.98 (s, 1H), 7.77 – 7.76 (t, 1H), 7.72 – 7.69 (d, 1H), 7.63 – 7.59 (m, 1H), 7.56 (s, 1H), 7.36 – 7.29 (dd, 1H), 6.83 – 6.79 (t, 1H), 5.96 (s, 1H), 4.67 – 4.64 (d, 2H), 3.98 – 3.93 (dd, 1H), 3.79 – 3.68 (m, 2H), 3.37 – 3.28 (m, 1H), 3.03 – 2.94 (m, 1H), 2.12 – 1.99 (m, 1H), 1.76 – 1.56 (m, 3H).

Example 544: ^{1}H NMR (300MHz, $CDCl_3$) δ 8.66 – 8.62 (d, 1H), 8.61 – 8.58 (dd, 1H), 7.95 (s, 1H), 7.72 – 7.67 (d, 1H), 7.36 – 7.30 (dd, 1H), 6.80 – 6.62 (br s, 1H), 5.88 (s, 1H), 4.63 (s, 2H), 3.08 – 2.95 (m, 2H), 2.87 – 2.80 (m, 2H), 2.04 (m,

1H), 1.85 – 1.78 (m, 4H), 1.52 – 1.44 (m, 1H), 0.87 – 0.82 (m, 2H), 0.72 – 0.66 (m, 2H).

Example 545: ^{1}H NMR (300MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.62 – 8.58 (br t, 1H), 7.97 (s, 1H), 7.73 – 7.68 (d, 1H), 7.36 – 7.30 (br t, 1H), 6.79 – 6.72 (br t, 1H), 5.96 (s, 1H), 4.64 (br s, 2H), 4.59 – 4.46 (br d, 1H), 3.95 – 3.74 (br m, 1H), 3.57 – 3.49 (dd, 1H), 3.10 – 3.01 (dd, 1H), 2.86 – 2.70 (m, 2H), 2.13 (s, 3H), 2.06 – 2.00 (m, 2H), 1.65 – 1.48 (m, 2H).

Example 551: ^{1}H NMR (300MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.63 – 8.59 (d, 1H), 7.96 (s, 1H), 7.74 – 7.69 (d, 1H), 7.36 – 7.30 (dd, 1H), 6.69 – 6.64 (t, 1H), 5.95 (s, 1H), 4.67 – 4.63 (d, 2H), 3.85 3.65 (m,1H), 3.75 – 3.65 (m, 1H), 3.25 – 3.18 (dd, 1H), 3.03 – 2.90 (m, 2H), 2.81 (s, 6H), 2.03 – 1.95 (m, 1H), 1.89 – 1.68 (m, 3H).

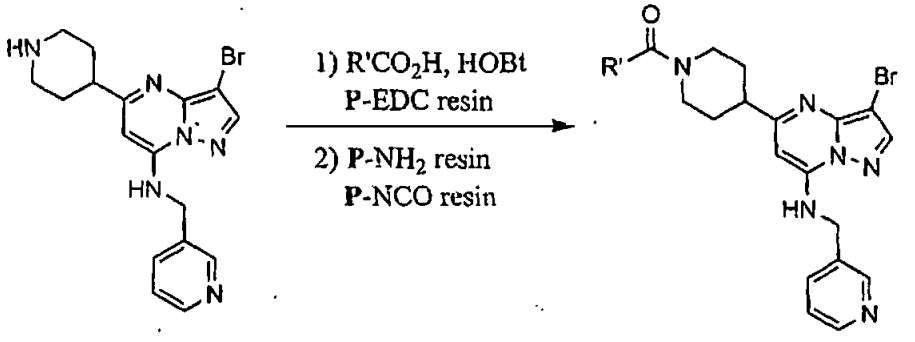
Example 552: ^{1}H NMR (300MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.62 – 8.59 (d, 1H), 7.95 (s, 1H), 7.74 – 7.69 (d, 1H), 7.36 – 7.31 (dd, 1H), 6.67 – 6.60 (t, 1H), 5.98 (s, 1H), 4.67 – 4.63 (d, 2H), 3.92 – 3.86 (m, 1H), 3.85 – 3.75 (m, 1H), 3.40 – 3.30 (dd, 1H), 3.27 – 3.16 (m, 1H), 3.10 – 2.86 (m, 2H), 2.10 – 1.78(m, 3H), 1.40–1.30 (d, 6H).

Example 553: ^{1}H NMR (300MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.62 (br s, 1H), 7.96 (s, 1H), 7.74 – 7.69 (d, 1H), 7.36 – 7.31 (dd, 1H), 6.70 – 6.66 (t, 1H), 5.98 (s, 1H), 4.67 – 4.63 (d, 2H), 3.88 – 3.81 (m, 1H), 3.71 – 3.65 (m, 1H), 3.20 – 3.11 (dd, 1H), 3.02 – 2.91 (m, 1H), 2.90 – 2.80 (m, 4H), 2.01 – 1.80 (m, 3H).

Example 559: ^{1}H NMR (300MHz, $CDCl_3$) δ 8.66 –8.60 (d, 1H), 8.50 – 8.44 (dd, 1H), 8.01 (s, 1H), 7.93 (m, 1H), 7.48 – 7.40 (dd, 1H), 6.08 (s, 1H), 4.80 – 7.74 (s, 2H), 4.32 –4.19 (br d, 2H), 3.10 – 2.86 (m, 2H), 1.95 – 1.68 (m, 4H).

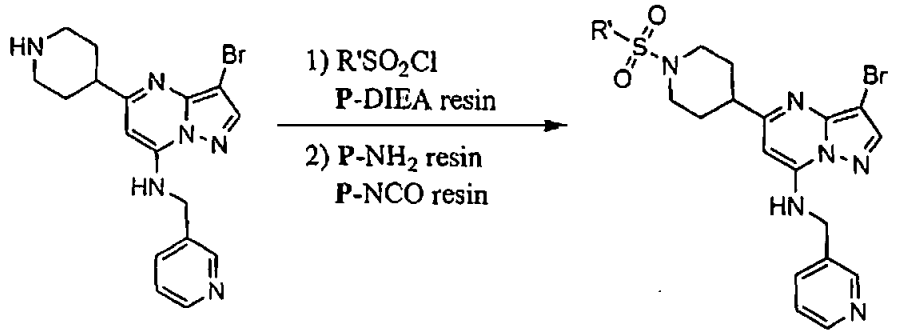
Example 563: ^{1}H NMR (300MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.62 – 8.58 (d, 1H), 7.96 (s, 1H), 7.73 – 7.68 (d, 1H), 7.36 – 7.30 (dd, 1H), 6.96 – 6.86 (br s, 1H), 6.79 – 6.74 (t, 1H), 6.00 (s, 1H), 4.67 – 4.64 (d, 2H), 4.37 – 4.30 (dd, 1H), 4.22 – 4.13 (m, 1H), 3.97 – 3.86 (dd, 1H), 3.73 – 3.64 (m, 1H), 3.17 – 3.14 (d, 3H), 3.07 – 2.99 (m, 1H), 2.20 – 1.97 (m, 2H), 1.68 – 1.48 (m, 2H).

GENERAL PROCEDURE 1: Procedure for the amide formation parallel synthesis:



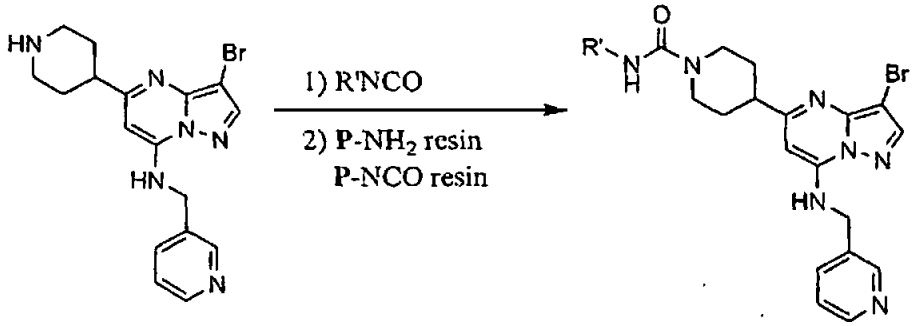
Parallel synthesis was conducted in polypropylene 96-well reaction blocks with removable top seal and fixed bottom seal. Each reaction well was fitted with a 20 micron polypropylene bottom frit and the maximum volume was 3 mL. Collection block was not fitted with bottom frit. To each reaction well was added a solution of an amine (0.021 mmol) dissolved in a DMF-THF-MeCN mixture (4:3:3 v/v, 0.95 mL), EDC resin (**P**-EDC, Polymer Laboratories Ltd., 43 mg, 0.063 mmol), 1-hydroxybenzotriazole (HOBt, 5.67 mg, 0.042 mmol) and a solution of a carboxylic acid in dimethylformamide (1 M, 0.0315 mL, 0.0315 mmol). The reaction mixture was agitated at room temperature for 16 h. The crude product solution was filtered into a reaction well loaded with trisamine resin (**P**-NH2, Argonaut Tech. Inc., 30 mg, 0.126 mmol) and isocyanate resin (**P**-NCO, Argonaut Tech. Inc., 35 mg, 0.063 mmol). The reaction mixture was agitated at room temperature for 16 h and filtered into the collection block. The product solution was evaporated under reduced pressure to afford the desired amide product.

GENERAL PROCEDURE 2: Procedure for the sulfonamide formation parallel synthesis



Parallel synthesis was conducted in polypropylene 96-well reaction blocks with removable top seal and fixed bottom seal. Each reaction well was fitted with a 20 micron polypropylene bottom frit and the maximum volume was 3 mL. Collection block was not fitted with bottom frit. To each reaction well was added a solution of an amine (0.021 mmol) dissolved in a DMF-THF-MeCN mixture (3:2:2 v/v, 0.95 mL), DIEA resin (P-DIEA, Argonaut Tech. Inc., 18 mg, 0.063 mmol) and a solution of a sulfonyl chloride in dimethylformamide (1 M, 0.0315 mL, 0.0315 mmol). The reaction mixture was agitated at room temperature for 16 h. The crude product solution was filtered into a reaction well loaded with trisamine resin (P-NH2, Argonaut Tech. Inc., 30 mg, 0.126 mmol) and isocyanate resin (P-NCO, Argonaut Tech. Inc., 35 mg, 0.063 mmol). The reaction mixture was agitated at room temperature for 16 h and filtered into the collection block. The product solution was evaporated under reduced pressure to afford the desired sulfonamide product.

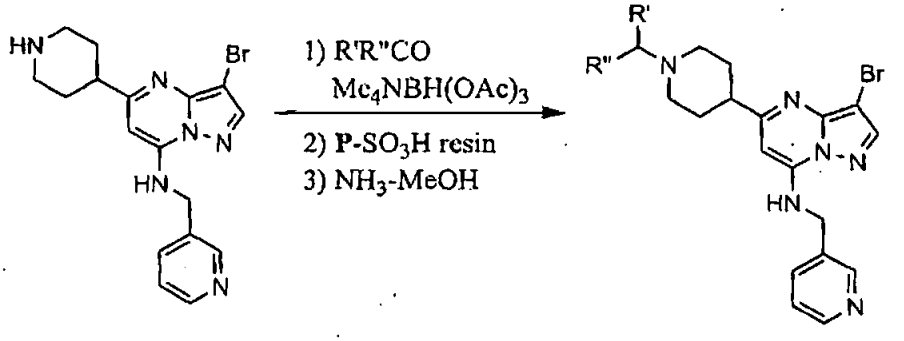
GENERAL PROCEDURE 3: Procedure for the urea formation parallel synthesis



Parallel synthesis was conducted in polypropylene 96-well reaction blocks with removable top seal and fixed bottom seal. Each reaction well was fitted with

a 20 micron polypropylene bottom frit and the maximum volume was 3 mL. Collection block was not fitted with bottom frit. To each reaction well was added a solution of an amine (0.021 mmol) dissolved in a DMF-MeCN mixture (1:1 v/v, 0.95 mL) and a solution of an isocyanate in dichloromethane (0.33 M, 0.126 mL, 0.042 mmol). The reaction mixture was agitated at room temperature for 16 h. The crude product solution was filtered into a reaction well loaded with trisamine resin (**P**-NH2, Argonaut Tech. Inc., 30 mg, 0.126 mmol) and isocyanate resin (**P**-NCO, Argonaut Tech. Inc., 35 mg, 0.063 mmol). The reaction mixture was agitated at room temperature for 16 h and filtered into the collection block. The product solution was evaporated under reduced pressure to afford the desired urea product.

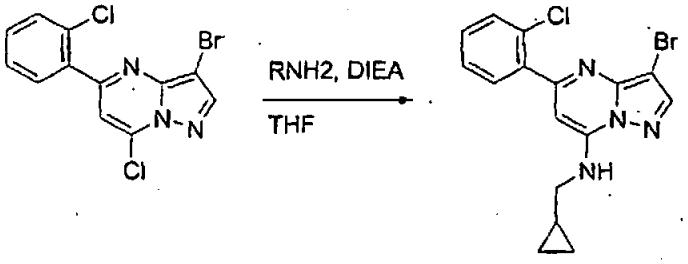
GENERAL PROCEDURE 4: Procedure for the reductive alkylation parallel synthesis



Parallel synthesis was conducted in polypropylene 96-well reaction blocks with removable top seal and fixed bottom seal. Each reaction well was fitted with a 20 micron polypropylene bottom frit and the maximum volume was 3 mL. Collection block was not fitted with bottom frit. To each reaction well was added a solution of an amine (0.021 mmol) dissolved in AcOH-DCE mixture (1:99 v/v, 0.5 mL), a solution of an aldehyde or ketone in dichloroethane (1 M, 0.147 mL, 0.147 mmol), and a solution of tetramethylammonium triacetoxyborohydride (11 mg, 0.042 mmol) dissolved in AcOH-DCE mixture 1:99 v/v, 0.5 mL). The reaction mixture was agitated at room temperature for 3 days. The crude product solution was filtered into a reaction well loaded with sulfonic acid resin Lanterns (**P**-SO_3H, MimotopesPty Ltd., 0.3 mmol). The reaction mixture was agitated at room temperature for 2 h and decanted. The product resin Lanterns

were washed with methanol (1 mL) for three times. A solution of ammonia in methanol (2 M, 1.2 mL) was added. The reaction mixture was agitated at room temperature for 30 min. and filtered into the collection block. The product solution was evaporated under reduced pressure to afford the desired tertiary amine product.

GENERAL PROCEDURE 5: Procedure for the parallel synthesis of 7,N-substituted pyrazolo[1,5a]pyrimidines

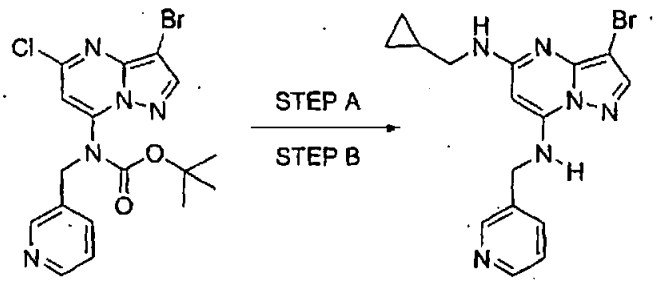


To 3-bromo-7-chloro-5-(2-chloro-phenyl)-pyrazolo[1,5-a]pyrimidine (9.0 mg, 0.03 mmol) in tetrahydrofuran were added di-*iso*-propylethylamine (12 μL, 0.07), followed by cyclopropylmethylamine (70 μL, .07 mmol; 1M solution in DMF). The reaction mixture was heated to 70 °C for 36 h and then cooled to rt. The mixture was treated with (P-NCO, Argonaut Tech. Inc 70 mg, 0.12 mmol), and P-CO_3^- (Argonaut Tech. Inc 70 mg, 0.24 mmol) and shaken at rt for 12-18 h. The solution was filtered and evaporated to dryness to provide the product. observed m/z 375.21.

GENERAL PROCEDURE 6: Procedure for the parallel synthesis of 5,N-substituted pyrazolo[1,5a]pyrimidines

General protocols:

Parallel synthesis was performed in a 96 well polypropylene blocks as described elsewhere. In the instance that heating was required, reactions were conducted in 2.5 mL glass tubes individually sealed with a polypropylene mat and heating achieved by a 96 well heat transfer block.



STEP A:

To the 3-bromo-5-chloro-7-N-Boc-alkylamino-pyrazolo[1,5-a]pyrimidine (17 mg, 0.04 mmol) in *p*-dioxane were added DIEA (9 μL, 0.05), followed by cyclopropyl-methylamine (80 μL, .08 mmol; 1M solution in isopropanol). The reaction mixture was heated to 90 °C for 36 h and then cooled to rt. The mixture was treated with P-NCO (Argonaut Tech. Inc. 70 mg, 0.12 mmol) and P-CO_3 (Argonaut Tech. Inc. 70 mg, 0.24 mmol) and shaken at rt for 12-18 h. The solution was filtered and evaporated to dryness to provide the product.

STEP B(acidic):

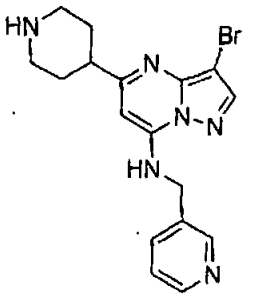
The product from STEP A was taken up in 35% TFA/DCM and agitated for 4 h followed by concentration under high vacuum. The residue was treated with 10% HCl(aq) in MeOH agitated for 2 h and then concentrated to give the desired product. . observed m/z 375.21.

STEP B(basic):

The product from step A was taken up in EtOH and treated with Ambersep® 900-OH ion exchange resin (Acros, 100mg), heated at reflux for 48 h with gently stirring. The reaction mixture was cooled to rt, filtered and concentrated to provide the desired product.

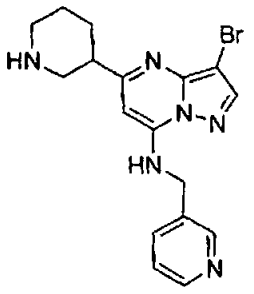
EXAMPLE 565:

By utilizing the procedure set forth in General Procedure 1 and the compound from Example 462 shown below, the compounds with the observed m/z shown in Table 43 were prepared.



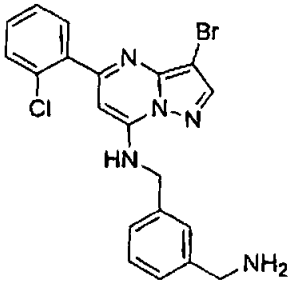
EXAMPLE 566:

By utilizing the procedure set forth in General Procedure 1 and the compound from Example 471 shown below, the compounds shown in Table 44 with the observed m/z were prepared.



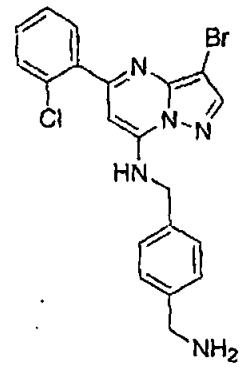
EXAMPLE 567:

By utilizing the procedure set forth in General Procedure 1 and the compound from Example 515 shown below, the compounds shown in Table 45 with the observed m/z were prepared.



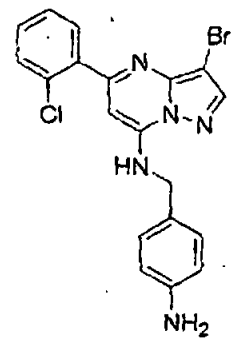
EXAMPLE 568:

By utilizing the procedure set forth in General Procedure 1 and the compound from Example 513 shown below, the compounds shown in Table 46 with the observed m/z were prepared.



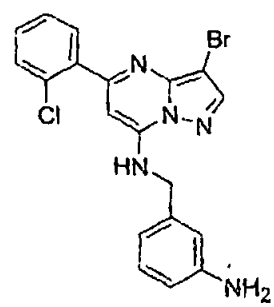
EXAMPLE 569:

By utilizing the procedure set forth in General Procedure 1 and the compound from Example 526 shown below, the compounds shown in Table 47 with the observed m/z were prepared.



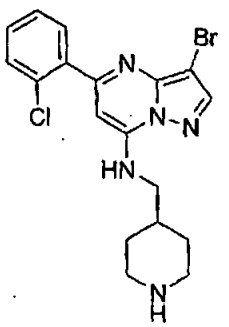
EXAMPLE 570:

By utilizing the procedure set forth in General Procedure 1 and the compound from Example 524 shown below, the compounds shown in Table 48 with the observed m/z were prepared.



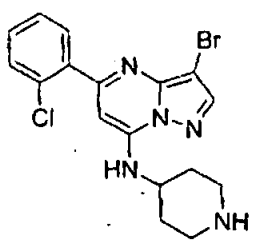
EXAMPLE 571:

By utilizing the procedure set forth in General Procedure 1 and the compound from Example 525 shown below, the compounds shown in Table 49 with the observed m/z were prepared.



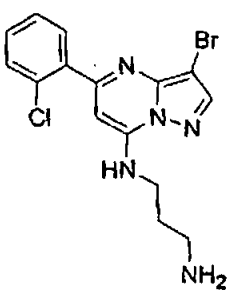
EXAMPLE 572:

By utilizing the procedure set forth in General Procedure 1 and the compound from Example 526.10 shown below, the compounds shown in Table 50 with the observed m/z were prepared.



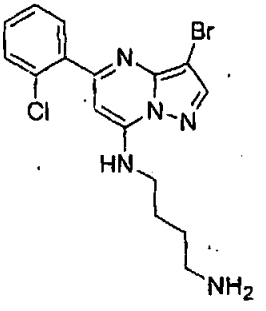
EXAMPLE 573:

By utilizing the procedure set forth in General Procedure 1 and the compound from Example 518 shown below, the compounds shown in Table 51 with the observed m/z were prepared.



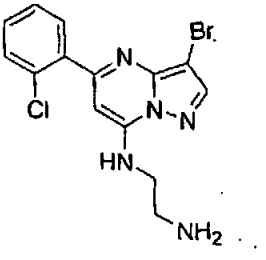
EXAMPLE 574:

By utilizing the procedure set forth in General Procedure 1 and the compound from Example 519 shown below, the compounds shown in Table 52 with the observed m/z were prepared.



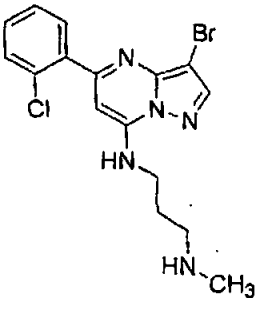
EXAMPLE 575:

By utilizing the procedure set forth in General Procedure 1 and the compound from Example 520 shown below, the compounds shown in Table 53 with the observed m/z were prepared.



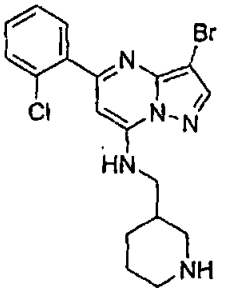
EXAMPLE 576:

By utilizing the procedure set forth in General Procedure 1 and the compound from Example 522 shown below, the compounds shown in Table 54 with the observed m/z were prepared.



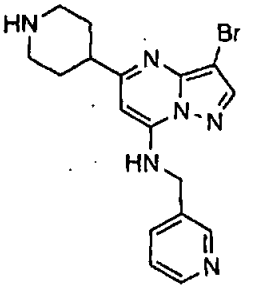
EXAMPLE 577:

By utilizing the procedure set forth in General Procedure 1 and the compound from Example 523 shown below, the compounds shown in Table 55 with the observed m/z were prepared.



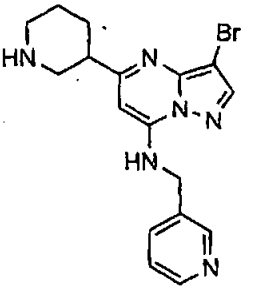
EXAMPLE 578:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 462 shown below, the compounds shown in Table 56 with the observed m/z were prepared.



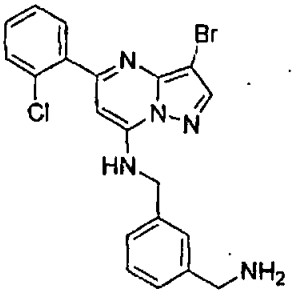
EXAMPLE 579:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 471 shown below, the compounds shown in Table 57 with the observed m/z were prepared.



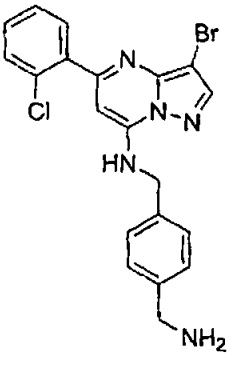
EXAMPLE 580:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 515 shown below, the compounds shown in Table 58 with the observed m/z were prepared.



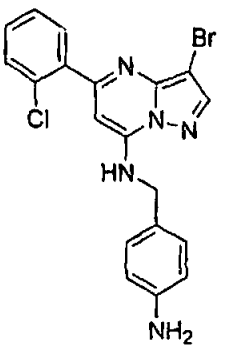
EXAMPLE 581:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 513 shown below, the compounds shown in Table 59 with the observed m/z were prepared.



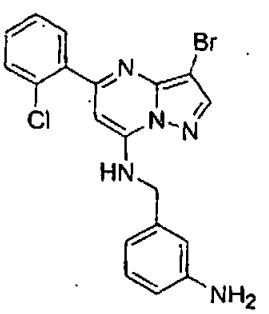
EXAMPLE 582:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 513 shown below, the compounds shown in Table 60 with the observed m/z were prepared.



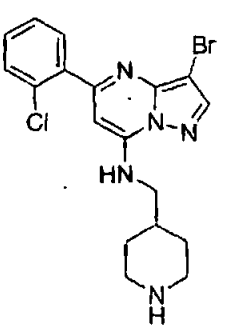
EXAMPLE 583:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 524 shown below, the compounds shown in Table 61 with the observed m/z were prepared.



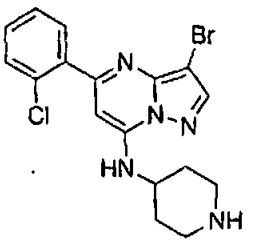
EXAMPLE 584:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 525 shown below, the compounds shown in Table 62 with the observed m/z were prepared.



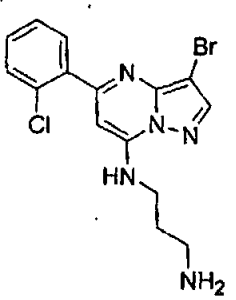
EXAMPLE 585:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 526.10 shown below, the compounds shown in Table 63 with the observed m/z were prepared.



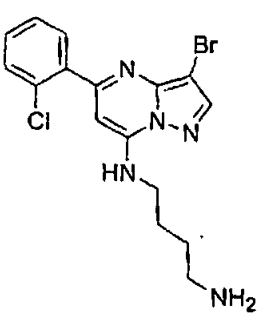
EXAMPLE 586:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 518 shown below, the compounds shown in Table 64 with the observed m/z were prepared.



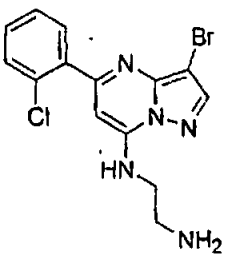
EXAMPLE 587:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 519 shown below, the compounds shown in Table 65 with the observed m/z were prepared.



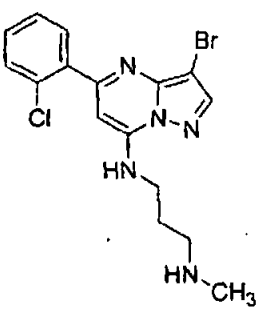
EXAMPLE 588:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 520 shown below, the compounds shown in Table 67 with the observed m/z were prepared.



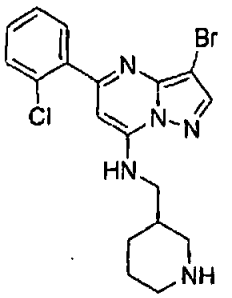
EXAMPLE 589:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 521 shown below, the compounds shown in Table 68 with the observed m/z were prepared.



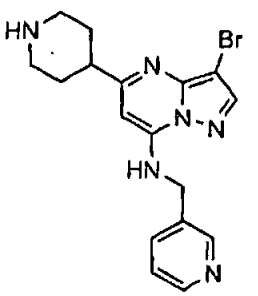
EXAMPLE 590:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 523 shown below, the compounds shown in Table 69 with the observed m/z were prepared.



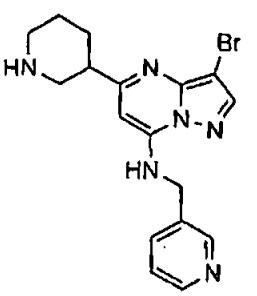
EXAMPLE 591:

By utilizing the procedure set forth in General Procedure 3 and the compound from Example 462 shown below, the compounds shown in Table 70 with the observed m/z were prepared.



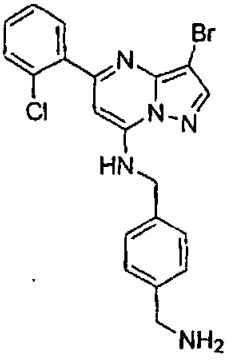
EXAMPLE 592:

By utilizing the procedure set forth in General Procedure 3 and the compound from Example 471 shown below, the compounds shown in Table 71 with the observed m/z were prepared.



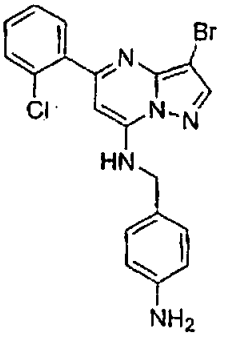
EXAMPLE 593:

By utilizing the procedure set forth in General Procedure 3 and the compound from Example 513 shown below, the compounds shown in Table 72 with the observed m/z were prepared.



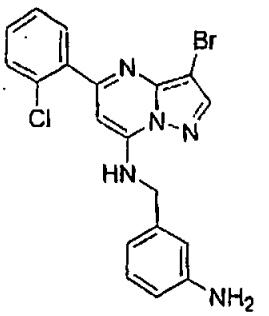
EXAMPLE 594:

By utilizing the procedure set forth in General Procedure 3 and the compound from Example 524 shown below, the compounds shown in Table 73 with the observed m/z were prepared.



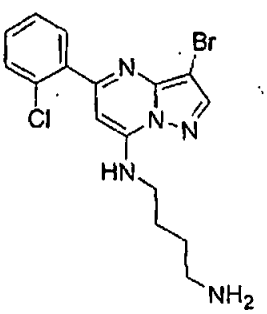
EXAMPLE 595:

By utilizing the procedure set forth in General Procedure 3 and the compound from Example 524 shown below, the compounds shown in Table 74 with the observed m/z were prepared.



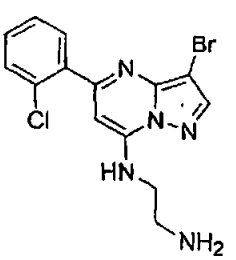
EXAMPLE 596:

By utilizing the procedure set forth in General Procedure 3 and the compound from Example 519 shown below, the compounds shown in Table 75 with the observed m/z were prepared.



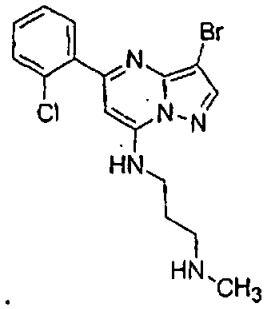
EXAMPLE 597:

By utilizing the procedure set forth in General Procedure 3 and the compound from Example 520 shown below, the compounds shown in Table 76 with the observed m/z were prepared.



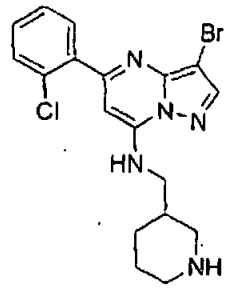
EXAMPLE 598:

By utilizing the procedure set forth in General Procedure 3 and the compound from Example 521 shown below, the compounds shown in Table 77 with the observed m/z were prepared.



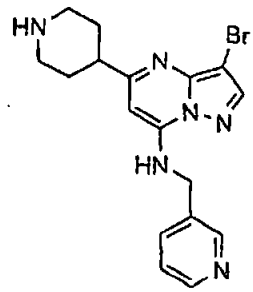
EXAMPLE 599:

By utilizing the procedure set forth in General Procedure 3 and the compound from Example 523 shown below, the compounds shown in Table 78 with the observed m/z were prepared.



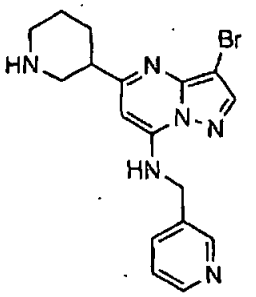
EXAMPLE 600:

By utilizing the procedure set forth in General Procedure 4 and the compound from Example 462 shown below, the compounds shown in Table 79 with the observed m/z were prepared.



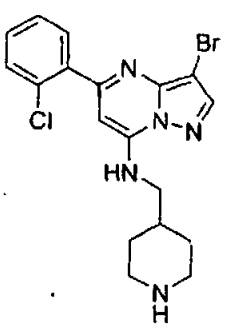
EXAMPLE 601:

By utilizing the procedure set forth in General Procedure 4 and the compound from Example 471 shown below, the compounds shown in Table 80 with the observed m/z were prepared.



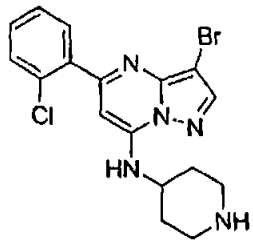
EXAMPLE 602:

By utilizing the procedure set forth in General Procedure 4 and the compound from Example 525 shown below, the compounds shown in Table 81 with the observed m/z were prepared.



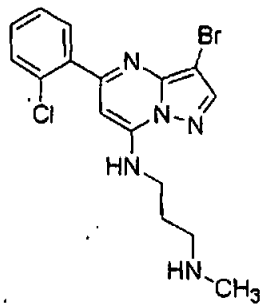
EXAMPLE 603:

By utilizing the procedure set forth in General Procedure 4 and the compound from Example 526.10 shown below, the compounds shown in Table 82 with the observed m/z were prepared.



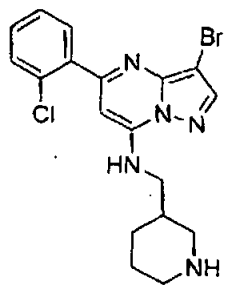
EXAMPLE 604:

By utilizing the procedure set forth in General Procedure 4 and the compound from Example 521 shown below, the compounds shown in Table 83 with the observed m/z were prepared.



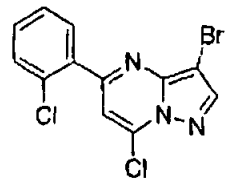
EXAMPLE 605:

By utilizing the procedure set forth in General Procedure 4 and the compound from Example 523 shown below, the compounds shown in Table 84 with the observed m/z were prepared.



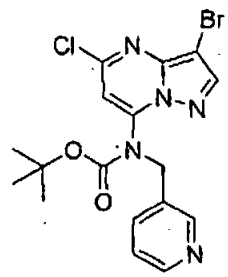
EXAMPLE 606:

By utilizing the procedure set forth in General Procedure 5 and the compound from Preparative Example 81 shown below, the compounds shown in Table 85 with the observed m/z were prepared.

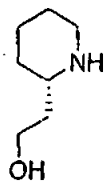


EXAMPLE 607:

By utilizing the procedure set forth in General Procedure 6 and the compound from Preparative Example 196, the compounds shown in Table 86 with the observed m/z were prepared.

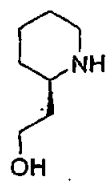


PREPARATIVE EXAMPLE 500



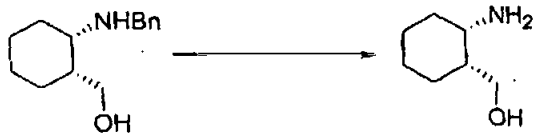
Piperidine-2-ethanol (127 g, 980 mmol) in 95% EtOH (260 mL) was added to *(S)*-(+)-camphorsulfonic acid (228.7 g, 1.0 eq.) in 95% EtOH (150 mL) and the resulting solution was warmed to reflux. To the warm solution was added Et_2O (600 mL) and the solution cooled to room temperature and let stand 3 days. The resulting crystals were filtered and dried *in vacuo* (25 g): mp 173-173 °C (lit. 168 °C). The salt was then dissolved in NaOH (3M, 100 mL) and stirred 2 hours and the resulting solution was extracted with CH_2Cl_2 (5 x 100 mL). The combined organics were dried over Na_2SO_4, filtered, filtered and concentrated under reduced pressure to give *(S)*-piperidine-2-ethanol (7.8 g) a portion of which was recrystallized from Et_2O: mp= 69-70 °C (lit. 68-69 °C); $[\alpha]_D$ = 14.09° ($CHCl_3$, c=0.2).

PREPARATIVE EXAMPLE 501



Bye essentially the same procedure set forth in Preparative Example 500 only substituting *(R)*-(-)-camphorsulfonic acid, *(R)*-piperidine-2-ethanol was prepared. (1.27 g): $[\alpha]_D$ = 11.3° ($CHCl_3$, c=0.2).

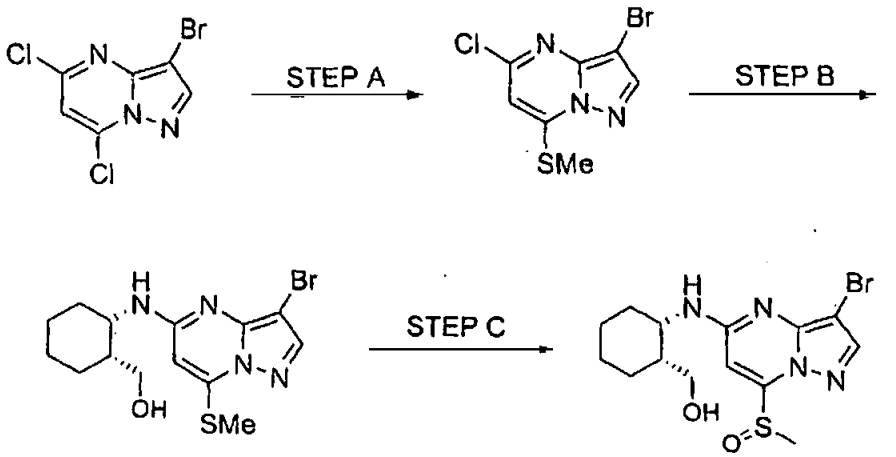
PREPARATIVE EXAMPLE 502



To pressure bottle charged with a solution of *cis*-(1*R*,2*S*)-(+)-2-(Benzylamino) cyclohexanemethanol (1g, 4.57 mmol) in MeOH (35 mL) was added 20% wt $Pd(OH)_2$ (0.3g, >50% wet) in one portion. The mixture was shaken under 50 psi of H_2 in a Parr hydrogenation apparatus for 12 h. The

mixture was purged to N_2 and was filtered through a pad of Celite. The pad was generously washed with MeOH (2 x 25 mL) and the resulting filtrate was concentrated under reduces pressure to afford 0.57g (97%) of a white solid. M+H = 130.

PREPARATIVE EXAMPLE 503



Step A:

To a solution of 3-Br adduct (1.1 g, 4.1 mmol) from Preparative Example 142 in THF (40 mL) at 0 °C was added CH_3SNa (0.32 g, 4.53 mmol) in one portion. The heterogenous mixture was stirred for 72 h at rt and the mixture was concentrated under reduced pressure. The crude product was partitioned between water (10 mL) and EtOAc (30 mL) and the layers were separated. The organic layer was washed with brine (1 x 10 mL) and dried (Na_2SO_4). The organic layer was filtered and concentrated under reduced pressure to afford 1.0 g (88%) of a yellow solid. mp 150-152 °C; M+H = 280. This material was taken onto Step B without further purification.

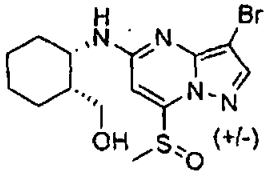
Step B:

To a solution of thiomethyl derivative (1.5 g, 5.37 mmol) from Step A in dioxane/DIPEA (15 mL/4 mL) at rt was added amino alcohol (1.3 g, 8.06 mmol) from Preparative Example 10. The mixture was heated at reflux for 48 h, cooled to rt, and concentrated under reduced pressure. The crude product was purified by flash chromatography using CH_2Cl_2/MeOH (30:1) as eluent to afford 1.8 g of product (90%) as a yellow crystalline solid. mp 167-169 °C; M+H = 373.

Step C:

To a solution of thiomethyl derivative (2.2 g, 5.92 mmol) from Step B in CH_2Cl_2 (20 mL) at 0 °C was added MCPBA (1.53 g, 8.9 mmol) in one portion. The resulting mixture was stirred for 2h at 0 °C whereupon the mixture was diluted with CH_2Cl_2 (20 mL) and sat. aq. $NaHCO_3$ (15 mL). The layers were separated and the organic layer was washed with sat. aq. $NaHCO_3$ (15 mL) and brine (1 x 15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 2.0 g of a brown solid (87%). mp 181-183 °C; M+H = 388.

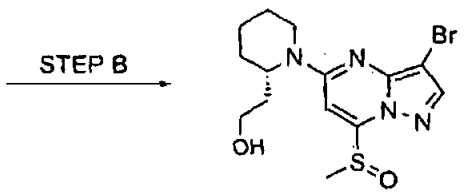
PREPARATIVE EXAMPLE 504



The title compound (racemic) was prepared according to the procedure set forth in Preparative Example 503 except substituting the commercially available *cis*-hydroxymethyl-1-cyclohexylamine hydrochloride in Step B.

PREPARATIVE EXAMPLE 505





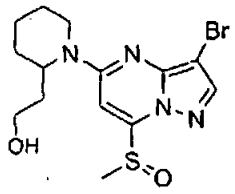
Step A:

Treatment of thiomethyl derivative (2.0 g, 7.2 mmol) from Step A of Preparative Example 503 with (*S*)-piperidine-2-ethanol (1.2 g, 9.3 mmol) from Preparative Example 500 under the identical conditions as described in Step B of Preparative Example 503, 0.90 g (34%) of the title compound was prepared semisolid, mp 173-175 °C. M+H = 372.

Step B:

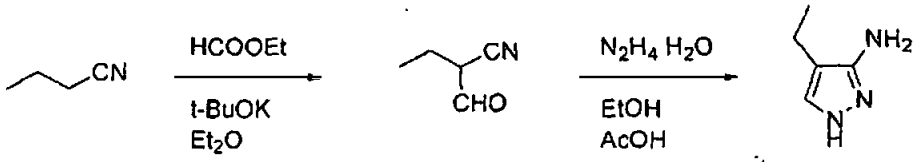
Following the procedure from Step C in Preparative Example 503, the thiomethyl derivative (0.30 g, 0.81 mmol) was treated with MCPBA (0.21 g, 1.2 mmol) to afford 0.31 g (99%) the title compound as a yellow viscous oil. M+H = 388.

PREPARATIVE EXAMPLE 506



The title compound (racemic) was prepared according to the procedure set forth in Preparative Example 505 except substituting the commercially available piperidine-2-ethanol. M+H = 388.

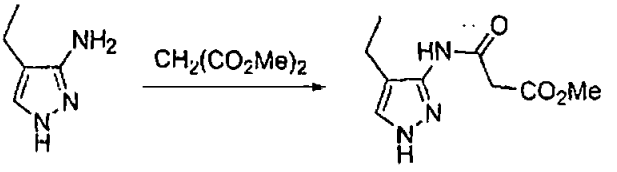
PREPARATIVE EXAMPLE 507



t-BuOK (112.0g, 1.00 mol) was stirred under N_2 in dry Et_2O (3.0 L) in a 5 L flask equipped with an addition funnel. A mixture of butyronitrile (69.0 g, 1.00 mol) and ethylformate (77.7 g, 1.05 mol) was added dropwise during 3 hrs, the reaction mixture was then stirred overnight at room temperature. The mixture was cooled to 0°C, AcOH (57 mL) was added, the mixture was filtered, and the solid was washed with Et_2O (500 mL). The combined filtrates were evaporated at room temperature on a rotovap to give pale yellow oil (95.1g).

The oil was dissolved in dry EtOH (100 mL), 99% hydrazine monohydrate (48 mL) was added, then AcOH (14 mL) was added, and the mixture was refluxed under N_2 overnight. The solvents were evaporated and the resulting oil was chromatographed on silicagel with CH_2Cl_2:7N NH_3 in MeOH. 22.4 g (20%) of 3-amino-4-ethylpyrazole was obtained as clear oil that solidified upon standing.

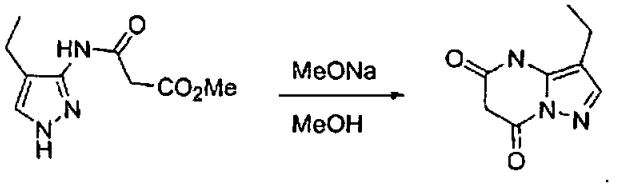
PREPARATIVE EXAMPLE 508



Step A:

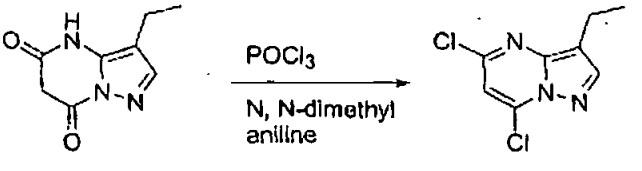
The pyrazole from Preparative Example 507 (9.80g) and dimethylmalonate (45 mL) were stirred and refluxed under N_2 for 3 hrs. The excess of dimethylmalonate was evaporated in a vacuum and the residue was chromatographed with 15:1 CH_2Cl_2:MeOH to yield pale yellow solid (10.6 g, 57%). LCMS: MH^+ = 212.

Step B:



Dry MeOH (200 mL) was added under N_2 to a mixture of the amide from Setp A (11.9g, 56.4 mmol) and sodium methoxide (4.57g, 84.6 mmol). The mixture was stirred and refluxed under N_2 for 5 hrs, cooled to rt, and conc. HCl (20 mL) was added. The solvents were evaporated and the residue was suspended in H_2O (300 mL). The solid was filtered off, washed on filter with 2x300 mL of H_2O, and dried in a vacuum at 100°C. 7.40g (73%) of cream-colored solid was obtained. LCMS: MH^+ = 180.

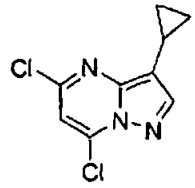
Step C:



$POCl_3$ (100 mL) and N, N-dimethylaniline (20 mL) were added under N_2 to the diketone from Step B (7.70 g), and the mixture was stirred and refluxed for 20 hrs under N_2. Then it was cooled to rt, carefully poured onto 1 L of crushed ice, and extracted with EtOAc (2x500 mL). The extracts were washed with H_2O (500 mL), dried over Na_2SO_4, filtered, and the solvent was evaporated. The

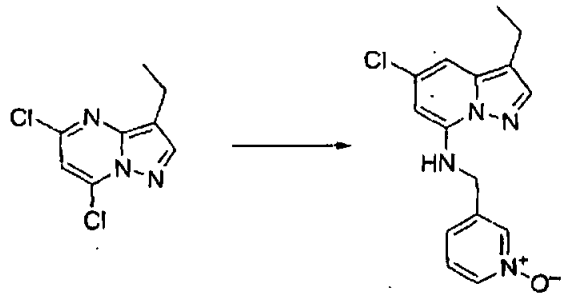
residue was chromatographed with CH_2Cl_2 to yield pale yellow solid (8.20 g, 90%). LCMS: MH^+ = 216.

PREPARATIVE EXAMPLE 508.10



By essentially the same procedure set forth in Preparative Example 508, only substituting the compound from Preparative Example 1, the above compound was prepared. LCMS: MH^+ = 228.

PREPARATIVE EXAMPLE 509

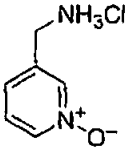
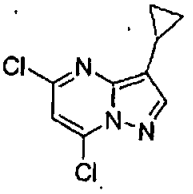
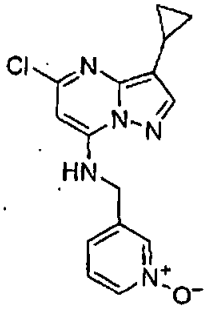
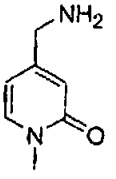
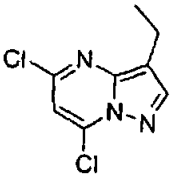
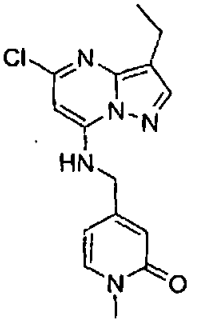
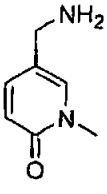
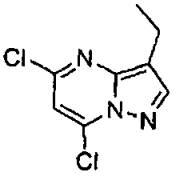
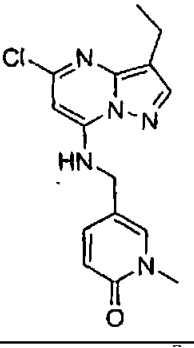
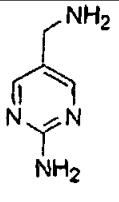
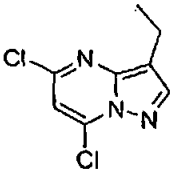
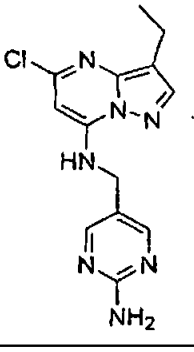


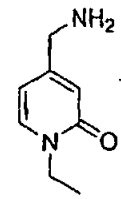
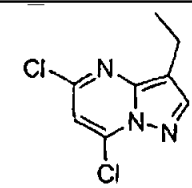
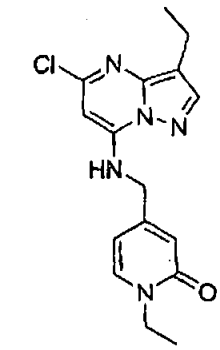
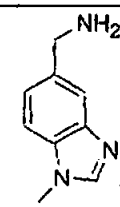
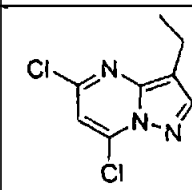
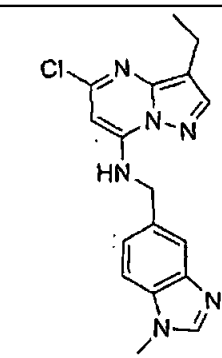
A mixture of the dichloride from Preparative Example 508 (3.13g, 14.5 mmol), the amine.HCl from Preparative Example (3.00g, 18.9 mmol), DIPEA (7.5 mL), and dry NMP (40 mL) plus dry dioxane (40 mL) was stirred at 60°C for 4 days under N_2. The solvents were then distilled off in a vacuum and the residue was chromatographed with 6:1 EtOAc: MeOH and then rechromatographed with 12:1 CH_2Cl_2:MeOH. So obtained solid was suspended in H_2O (100 mL), filtered, washed on filter with H_2O (2x100 mL), and dried in a vacuum. Pale rose solid (2.37g, 54%) was obtained. M+H = 304.

Preparative Examples 510-516

By essentially the same procedure set forth in Preparative Example 509 only substituting the amines in Column 2 of Table 500 and the chlorides shown in Column 3 of Table 500, the compounds shown in Column 4 of Table 500 were prepared.

TABLE 500

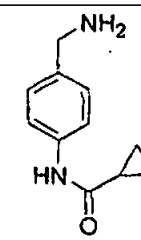
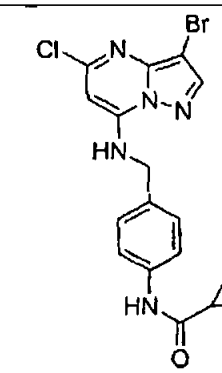
Prep. Ex.	Column 2	Column 3	Column 4	CMPD
510				M+H = 316
512				M+H = 318
513				M+H = 318
514				

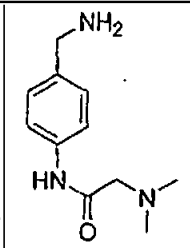
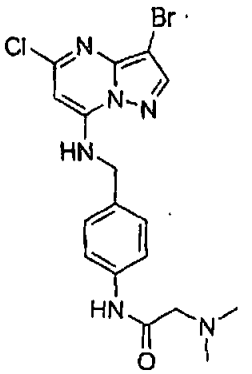
515				M+H = 332
516				

PREPARATIVE EXAMPLE 517:

By essentially the same procedure set forth in Preparative Example 184 only substituting the amines in Column 2 of Table 501, the compounds shown in Column 3 of Table 501 were prepared.

TABLE 501

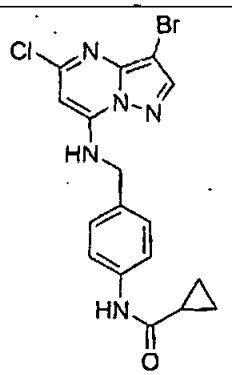
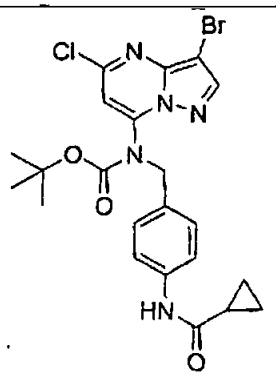
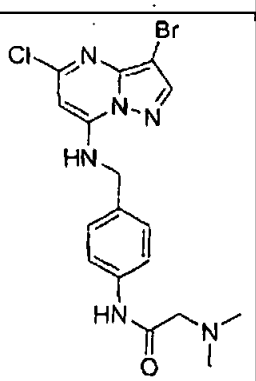
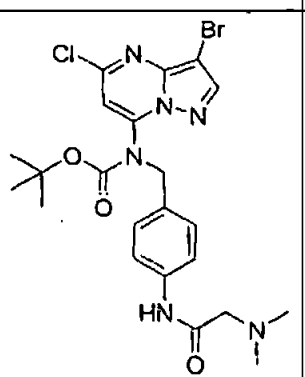
Prep. Ex.	Column 2	Column 3	CMPD
518			M+H= 422.1

519			

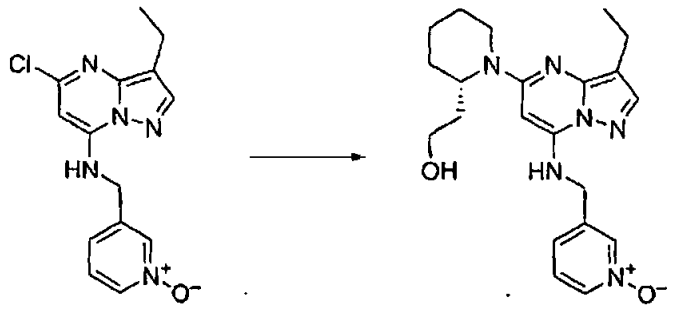
PREPARATIVE EXAMPLE 520-521:

By essentially the same procedure set forth in Preparative Example 192 only substituting the compounds in Column 2 of Table 502, the compounds shown in Column 3 of Table 502 were prepared.

TABLE 502

Prep. Ex.	Column 2	Column 3	CMPD
520			M+H= 522.1
521			M+H= 539.1

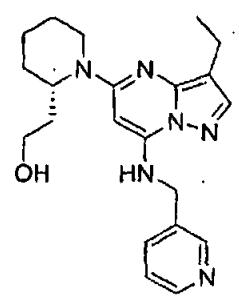
EXAMPLE 1000:



A mixture of the compound prepared in Preparative Example 509 (1.50 g, 4.94 mmol) with the aminoalcohol from Preparative Example 500 (1.91 g, 14.8 mmol) in dry NMP (3 mL) was stirred under N_2 at 160°C for 48 hr. The NMP was distilled off in a vacuum and the residue was chromatographed first with 5:1 EtOAc:MeOH, then the crude product was rechromatographed with 10:1 CH_2Cl_2:MeOH. White solid (460 mg, 24%) was obtained. LCSM: MH^+ = 397; mp = 113-115 °C.

EXAMPLE 1001:

Major side product isolated (540 mg, 29%) was deoxygenated product (LCMS: MH^+ = 381; mp = 49-52 °C:

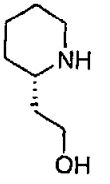
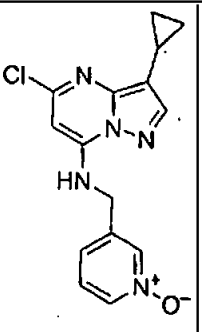
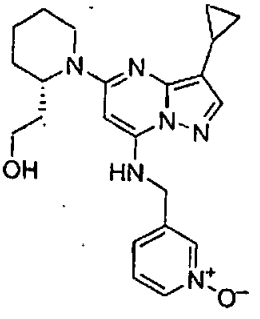
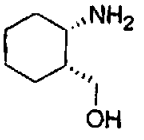
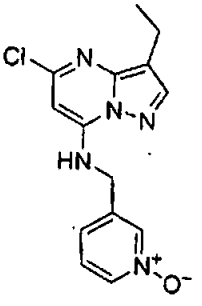
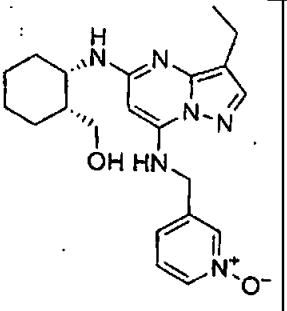
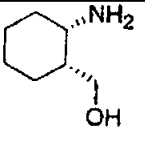
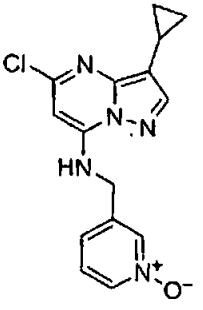
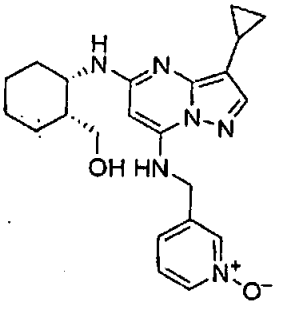
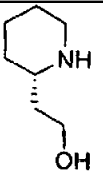
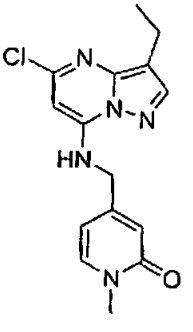
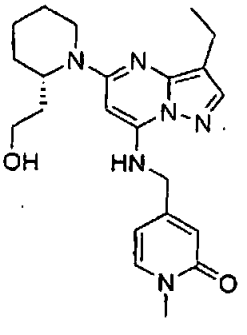


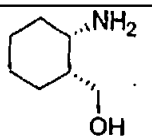
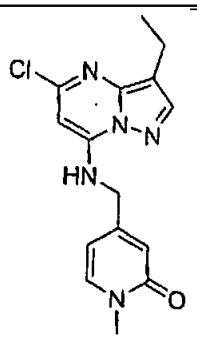
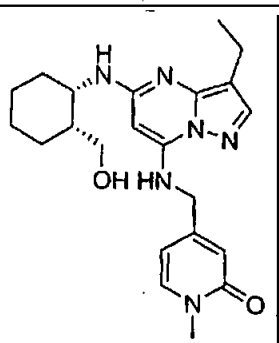
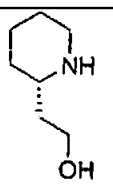
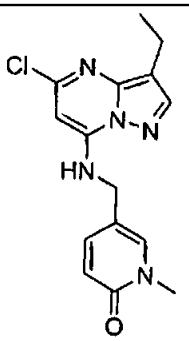
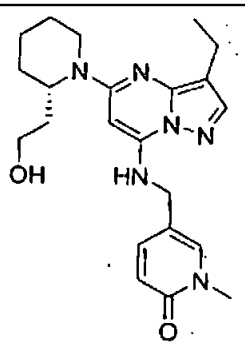
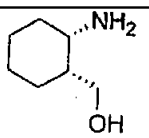
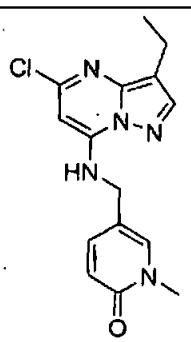
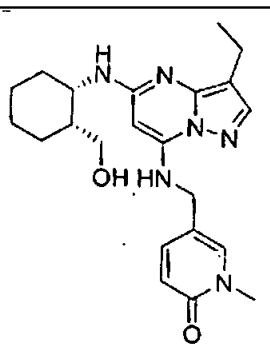
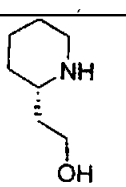
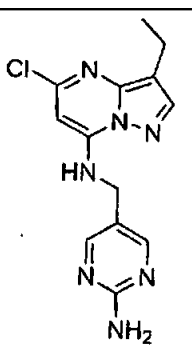
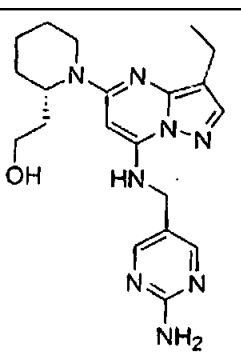
EXAMPLES 1002 – 1014:

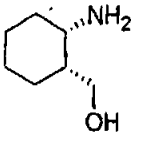
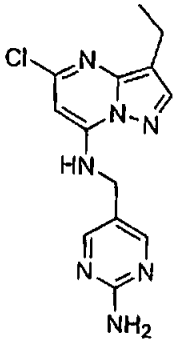
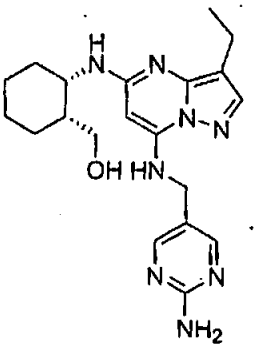
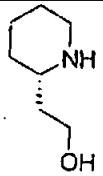
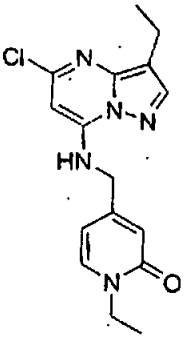
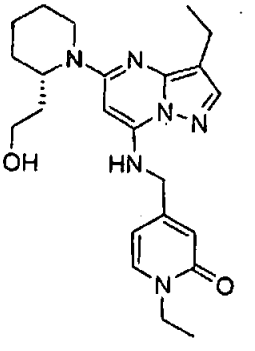
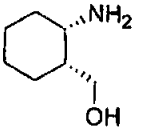
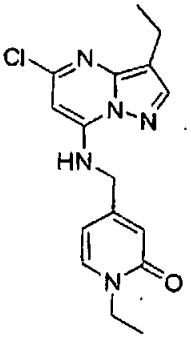
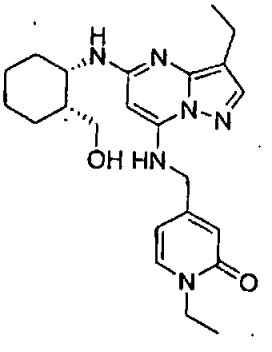
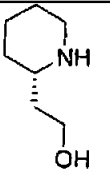
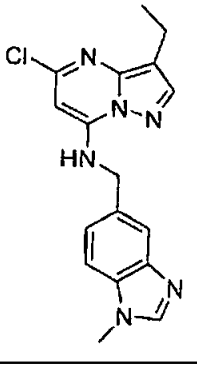
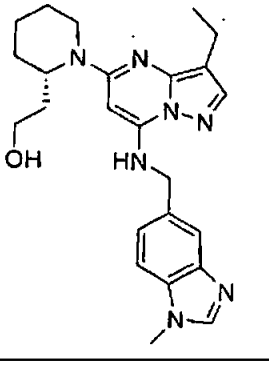
By essentially the same procedure set forth in Example 1000 only substituting the amines in Column 2 of Table 1000 and the chlorides in Column 3 of Table 1000 the compounds in column 4 of Table 1000 were prepared.

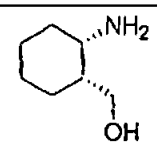
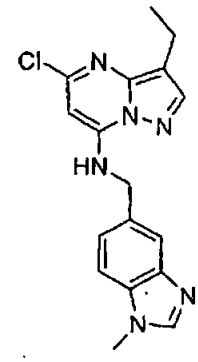
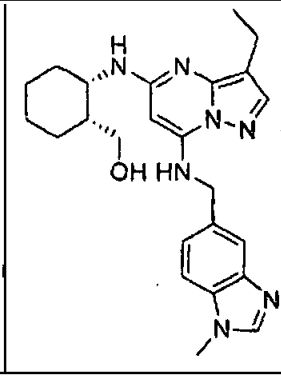
TABLE 1000

Ex.	Column 2	Column 3	Column 4	CMPD

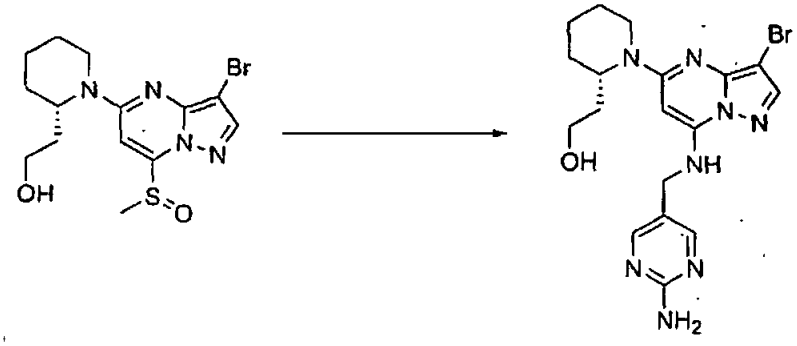
1002				MH^+ = 409; mp = 165-171 °C
1003				MH^+ = 397; mp = 219-221 °C
1004				MH^+ = 409; mp = 138-142 °C
1005				MH^+ = 411; mp = 194-196 °C

1006				MH^+ = 411; mp = 118-120 °C
1007				MH^+ = 411; mp = 85-87 °C
1008				MH^+ = 411; mp = 105-108 °C
1009				MH^+ = 397; mp = 173-177 °C

1010				MH^+ = 397; mp = 169-173 °C
1011				MH^+ = 425
1012				MH^+ = 425; mp = 232-234 °C
1013				

1014				

EXAMPLE 1015:



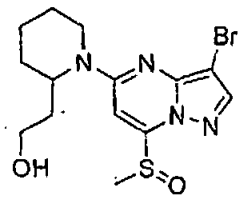
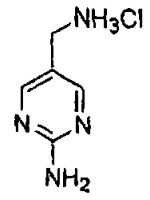
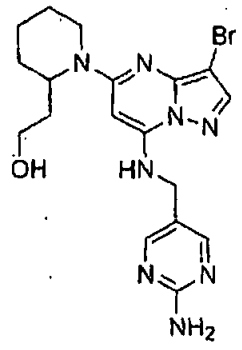
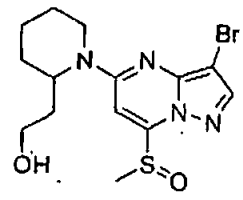
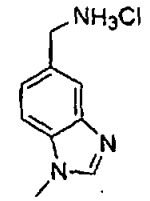
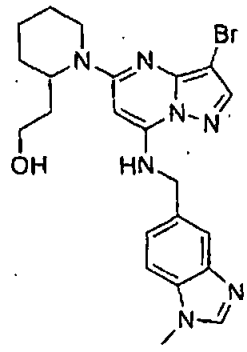
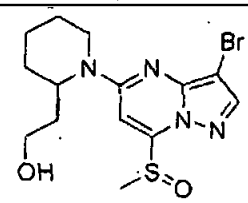
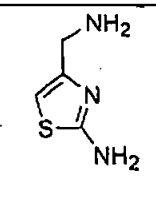
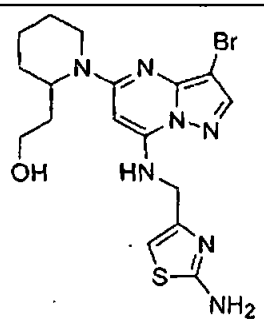
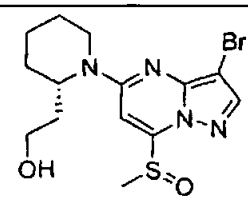
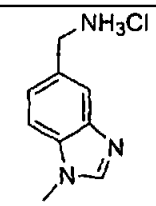
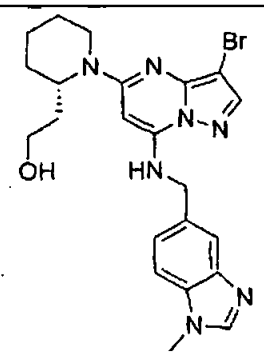
To a solution of sulfoxide from Preparative Example 505 (0.10 g, 0.28 mmol) in *n*-BuOH in a sealed tube was added Et_3N (0.13 mL, 1.0 mmol) followed by the amine dihydrochloride (0.13 g, 0.65 mmol) from Preparative Example 216. The tube was sealed and was heated to 100 °C, cooled to room temperature, and was concentrated under reduced pressure. The crude residue was purified by preparative TLC (6 x 1000 μM) eluting with CH_2Cl_2/MeOH (20:1) to afford 50 mg (40 %) of a pale white solid. mp 182-185 °C; M+H = 446.

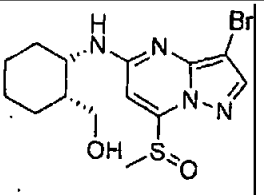
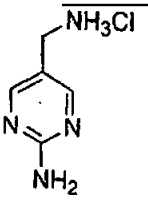
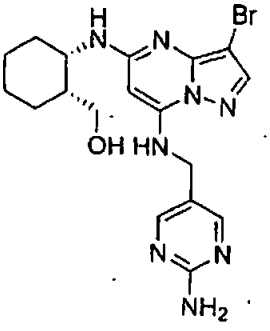
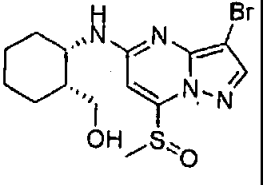
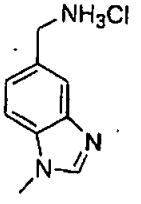
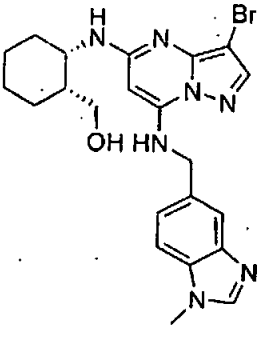
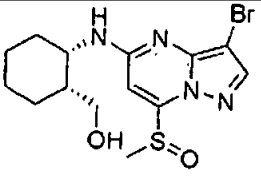
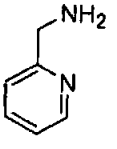
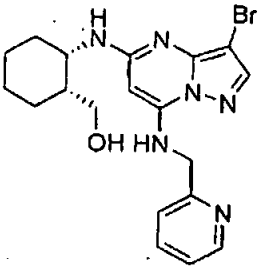
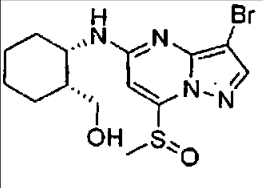
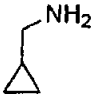
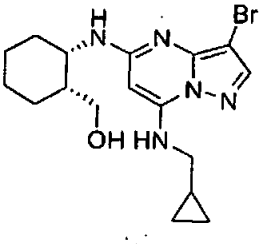
EXAMPLES 1016-1026:

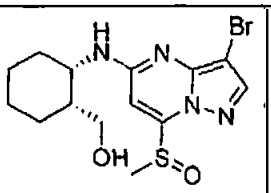
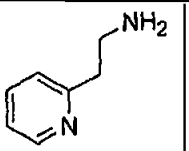
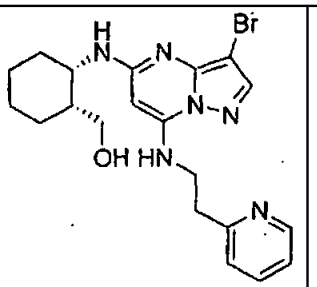
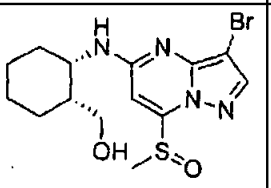
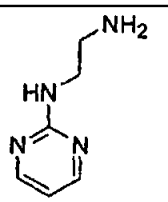
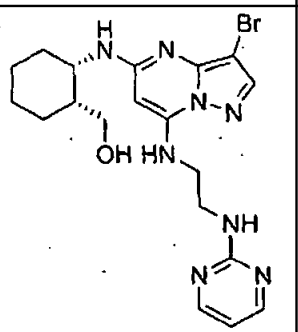
By essentially the same procedure set forth in Example 1015 only substituting the sulfoxide shown in Column 2 of Table 1001 and the amine in Column 3 of Table 1001, the compounds shown in Column 4 of Table 1001 were prepared.

TABLE 1001

Ex.	Column 2	Column 3	Column 4	CMPD

1016				mp = 182-185 °C; M+H = 448
1017				mp = 187-189 °C; M+H = 445
1018				mp = 139-143 °C; M+H = 453
1020				mp = 186-189 °C; M+H = 485

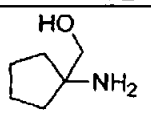
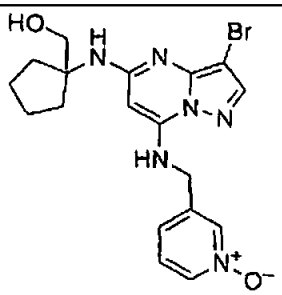
1021				mp = 154-157 °C; M+H = 448
1022				mp = 103-105 °C; M+H = 485
1023	 (±)		 (±)	mp = 203-205 °C; M+H = 432
1024	 (±)		 (±)	mp = 210-212 °C; M+H = 395

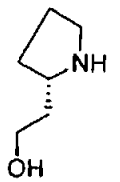
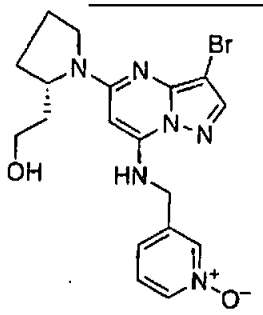
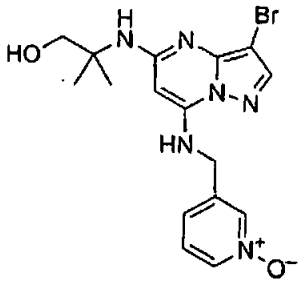
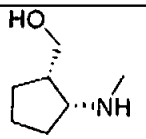
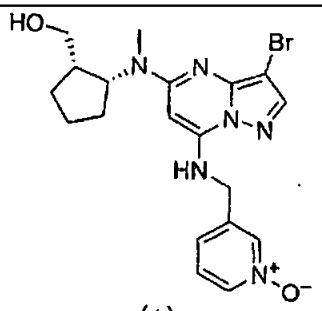
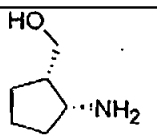
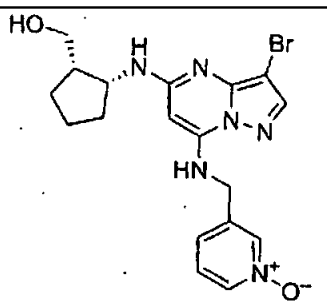
1025	 (±)		 (±)	mp = 82-84 °C; M+H = 446
1026	 (±)		 (±)	mp = 86-90 °C; M+H = 462

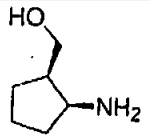
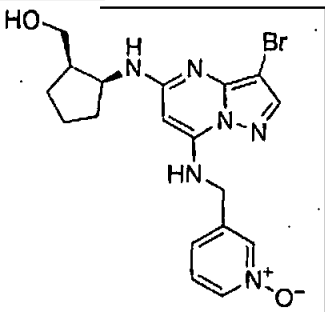
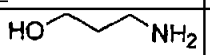
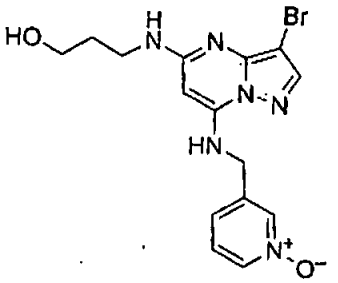
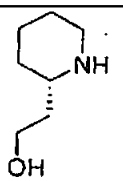
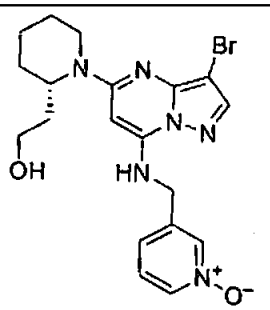
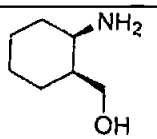
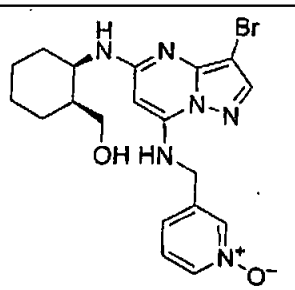
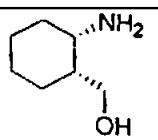
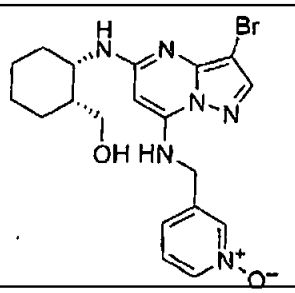
EXAMPLES 1027-1038:

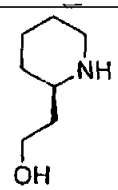
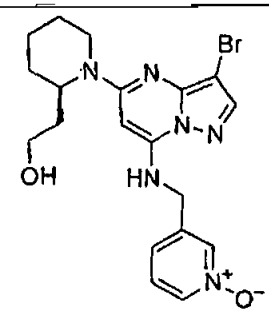
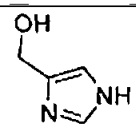
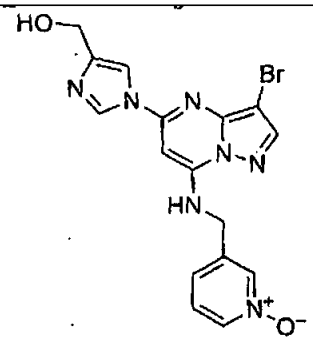
By essentially the same conditions set forth in Example 341, Steps A and B only substituting the amines in Column 2 of Table 1002 and the compound prepared in Preparative Example 193.10, the compounds in Column 4 of Table 1002 were prepared.

TABLE 1002

Ex.	Column 2	Column 4	CMPD
1027			mp = 160-163 °C; M+H = 434

1028			mp = 122-124 °C; M+H = 434
1029			mp = 153-156 °C; M+H = 408
1030	 (±)	 (±)	mp = 170-174 °C; M+H = 448
1031			mp = 166-169 °C; M+H = 434

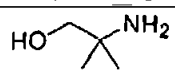
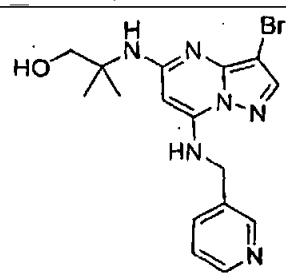
1032			mp = 167-168 °C; M+H = 434
1033			MH^+ = 393
1034			mp = 157-160 °C; M+H = 447
1035			mp = 164-168 °C; M+H = 448
1036			mp = 165-168 °C; M+H = 448

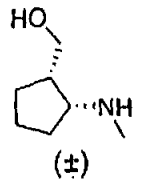
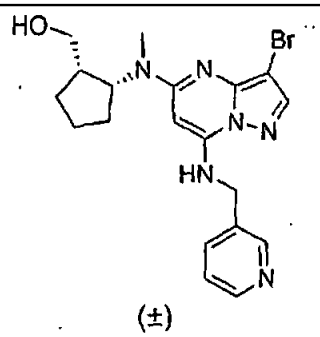
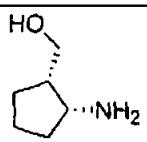
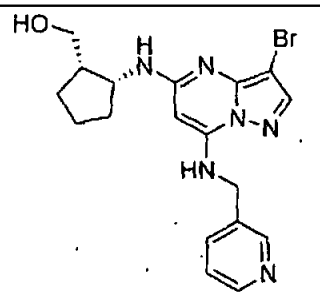
1037			mp = 131-135 °C; M+H = 447
1038			

EXAMPLES 1039-1041:

By essentially the same procedure set forth in Example 340 only substituting the amines in Column 2 of Table 1003, the compounds shown in Column 4 of Table 1003 were prepared.

TABLE 1003

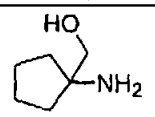
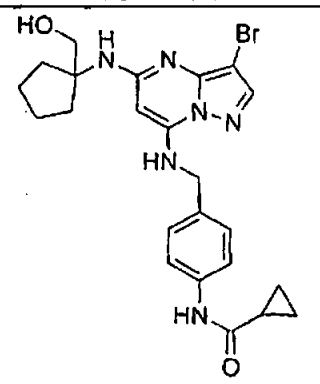
Ex.	Column 2	Column 4	CMPD
1039			mp = 210-212 °C; M+H = 392

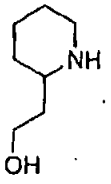
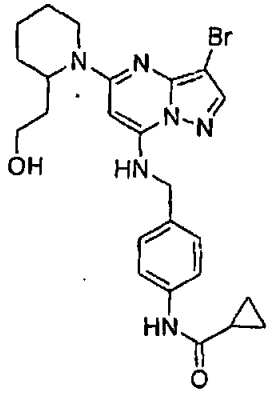
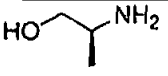
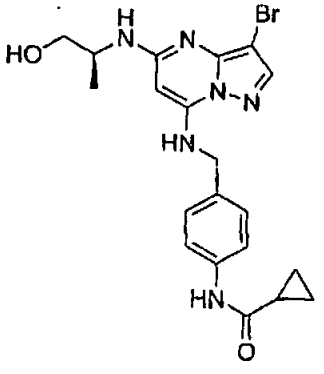
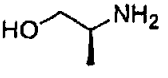
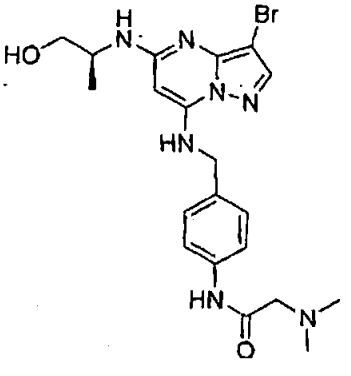
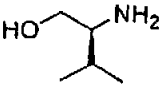
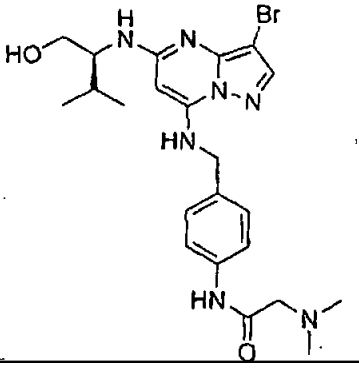
1040			mp = 128-130 °C; M+H = 432
1041			mp = 148-151 °C; M+H = 18

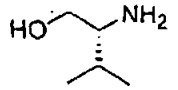
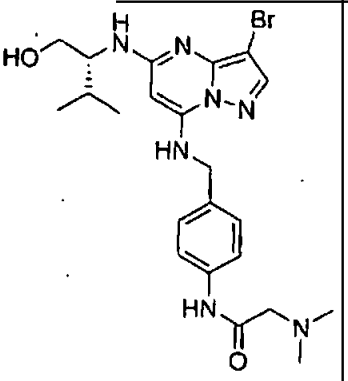
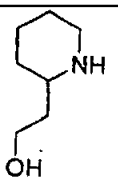
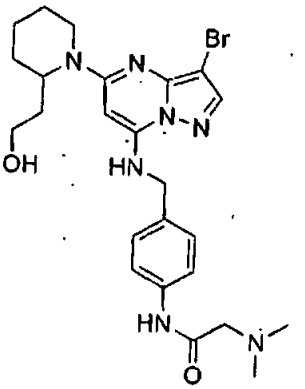
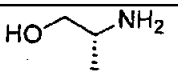
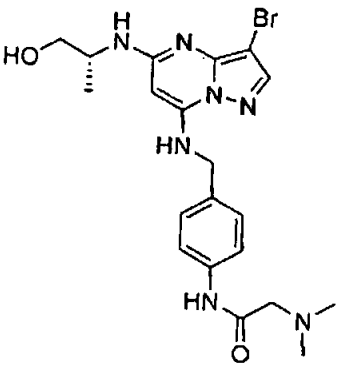
EXAMPLES 1042-1057:

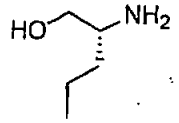
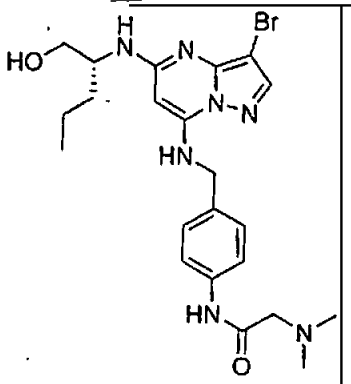
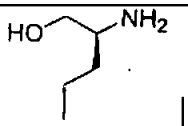
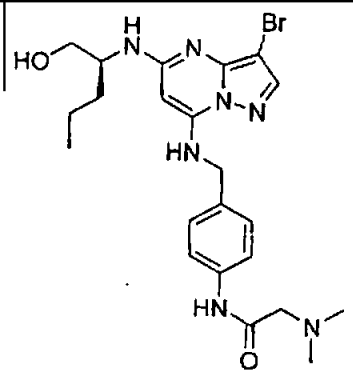
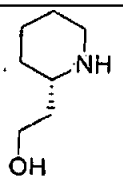
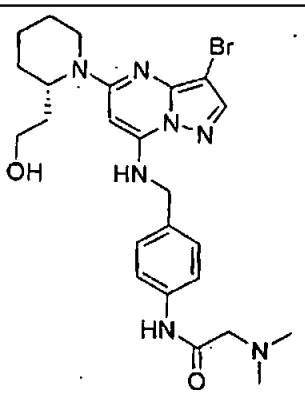
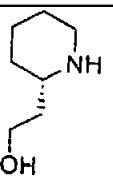
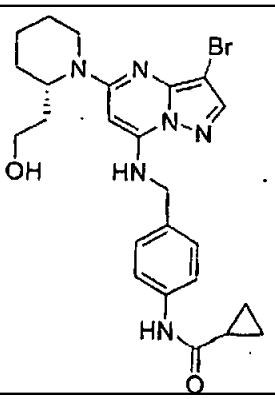
By essentially the same procedure set forth in Example 340 only using the appropriate 5-chloroderivative and substituting the amines in Column 2 of Table 1004, the compounds shown In Column 4 of Table 1004 were prepared.

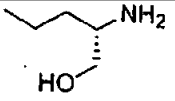
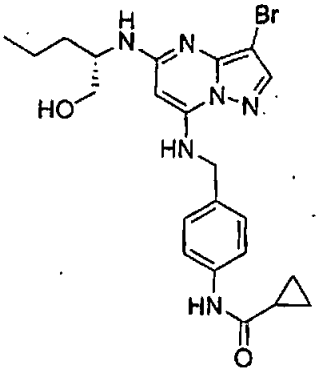
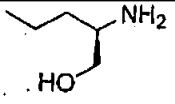
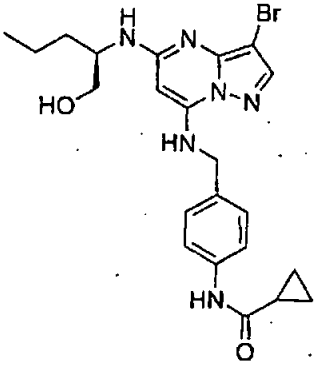
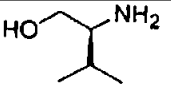
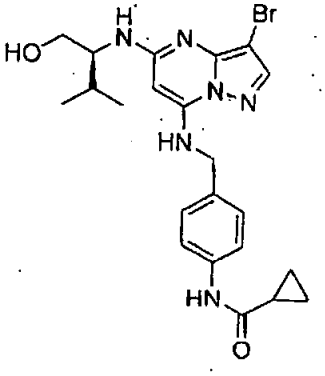
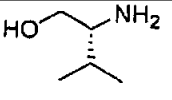
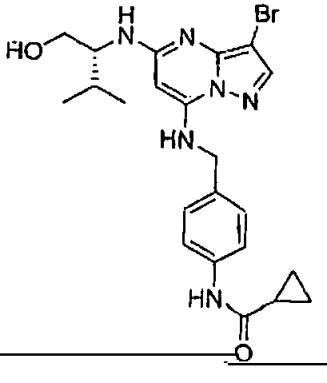
TABLE 1004

Ex.	Column 2	Column 4	CMPD
1042			M+H= 500.3

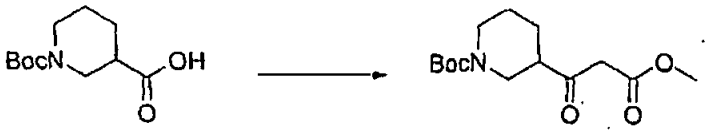
1043			M+H= 514.1
1044			M+H= 460.3
1045			M+H= 477.1
1046			M+H= 505.1

1047			M+H= 505.1
1048			M+H=531.1
1049			M+H= 477.1

1050			M+H= 505.1
1051			M+H= 505.1
1052			M+H= 531.1
1053			M+H= 514.1

1054			M+H= 488.3
1055			M+H= 488.3
1056			M+H= 488.1
1057			M+H= 488.1

PREPARATIVE EXAMPLE 10-K:

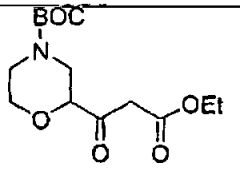
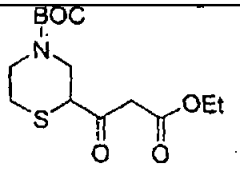
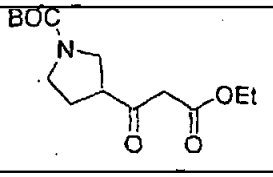


$SOCl_2$ (18.5 mL) was added slowly under N_2 to a stirred mixture of the acid (50.0 g, 218 mmol) and pyridine (44.0 mL) in anhydrous CH_2Cl_2 (60 mL). The mixture was stirred at 25°C for 20 min, then Meldrum's acid (35.0 g, 243 mmol) and DMAP (66.6 g, 546 mmol) were added and the mixture was stirred under N_2 for 1 hr. Then Et_2O (2 L) was added, the mixture was washed with 1 M HCl (3x500 mL), brine (500 mL), and the organic layer was dried over Na_2SO_4, filtered, and the solvent was evaporated. The residue was dissolved in MeOH (580 mL), and the mixture was refluxed for 4 hr. The solvent was evaporated and the residue was purified by column chromatography on silica gel with 10:1 CH_2Cl_2/EtOAc as eluent. Pale yellow oil (26.5 g, 43 %) was obtained.

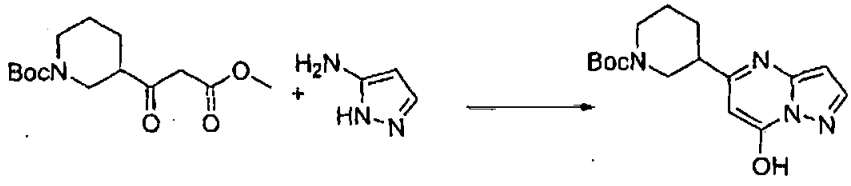
PREPARATIVE EXAMPLES 10-K-40-K:

By essentially same procedure set forth in Preparative Example 10-K, the compounds given in Column 2 of Table 10-K were prepared.

TABLE 10-K

Prep. Ex.	Column 2
20-K	
30-K	
40-K	

PREPARATIVE EXAMPLE 100-K:

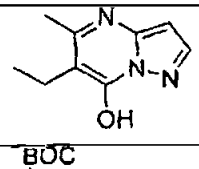
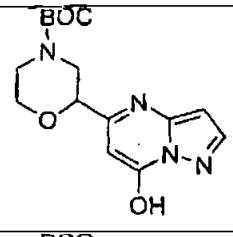
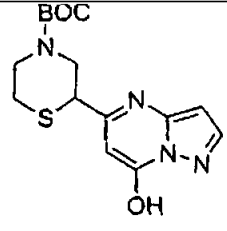


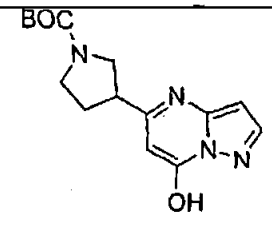
A mixture of the b-ketoester from Preparative Example 10-K (20.0 g, 70.1 mmol) and 3-aminopyrazole (5.40 g, 65.0 mmol) in anhydrous toluene (60 mL). was stirred and refluxed under N_2 for 24 hr. The solvent was evaporated and the residue was purified by column chromatography on silica gel with 20:1 CH_2Cl_2/MeOH as eluent. White solid (15.0 g, 73 %) was obtained. LC-MS: 319 [M+H].

PREPARATIVE EXAMPLE 101-K – 104-K:

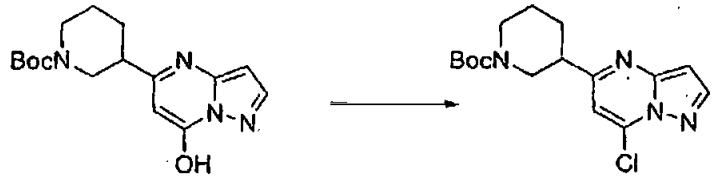
By essentially same procedure set forth in Preparative Example 100-K, combining 3-aminopyrazole with the corresponding β-ketoesters, compounds given in Column 2 of Table 100-K were prepared.

TABLE 100-K

Prep. Ex.	Column 2
101-K	
102-K	
103-K	

104-K	

PREPARATIVE EXAMPLE 200-K:

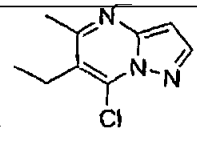
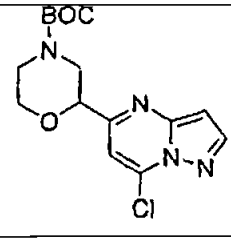


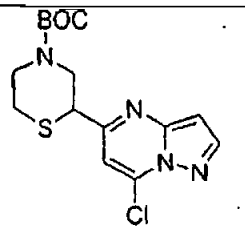
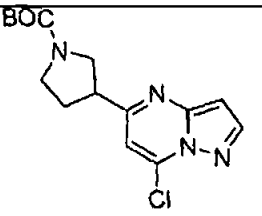
A mixture of the product from Preparative Example 100-K (12.50 g, 39.3 mmol), N,N-dimethylaniline (15.5 mL), and $POCl_3$ (125 mL) was stirred at 25°C for 4 days. Excess of $POCl_3$ was evaporated and the residue was poured into saturated aqueous $NaHCO_3$ (600 mL). The mixture was extracted with CH_2Cl_2 (3x200 mL), the combined extracts were dried over Na_2SO_4, filtered; and the solvent was evaporated. The residue was purified by column chromatography on silica gel with 8:1 CH_2Cl_2/EtOAc as eluent. Pale yellow wax (9.41 g, 71 %) was obtained. LC-MS: 337 [M+].

PREPARATIVE EXAMPLE 201-K – 204-K:

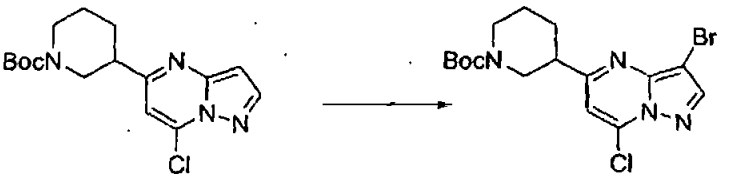
By essentially same procedure set forth in Preparative Example 200-K, compounds given in Column 2 of Table 200-K were prepared.

TABLE 200-K

Prep. Ex.	Column 2
201-K	
202-K	

203-K	
204-K	

PREPARATIVE EXAMPLE 300-K:



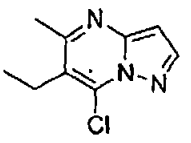
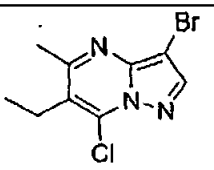
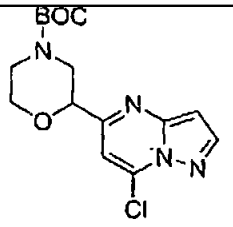
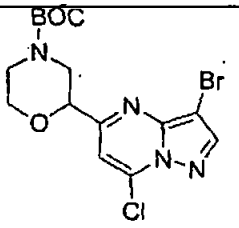
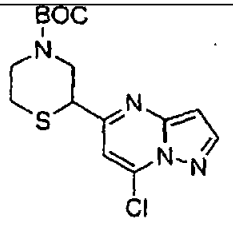
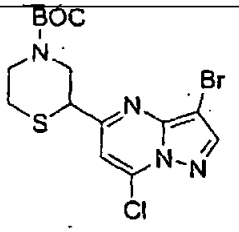
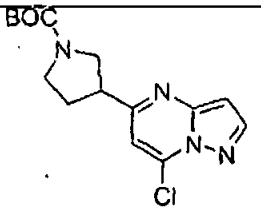
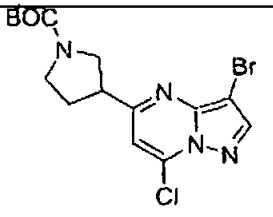
A solution of NBS (4.03 g, 22.7 mmol) in anhydrous CH_3CN (40 mL) was added under N_2 to a stirred solution of the product from Preparative Example 200-K (7.63 g, 22.7 mmol) in anhydrous CH_3CN (60 mL) and CH_2Cl_2 (20 mL). The mixture was stirred for 2 hr, the solvents were evaporated, and the residue was purified by column chromatography on silica gel with 20:1 CH_2Cl_2/EtOAc as eluent. Pale yellow solid foam (9.20 g, 97 %) was obtained. LC-MS: 417 [M+H].

PREPARATIVE EXAMPLE 301-K – 304-K:

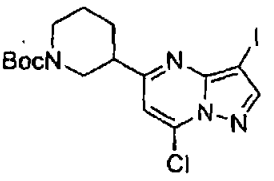
By essentially same procedure set forth in Preparative Example 300-K only substituting the compounds shown in Column 2 of Table 300-K, the compounds given in Column 3 of Table 300-K were prepared.

TABLE 300-K

Prep. Ex.	Column 2	Column 3

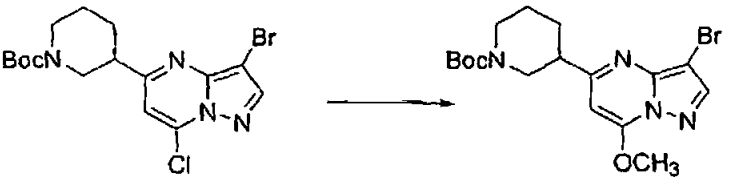
301-K		
302-K		
303-K		
304-K		

PREPARATIVE EXAMPLE 303-K:



By essentially the same procedure set forth in Preparative Example 300-K only substituting N-iodosuccinimide the above compound was prepared.

PREPARATIVE EXAMPLE 400-K:



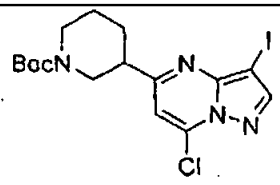
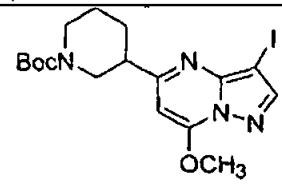
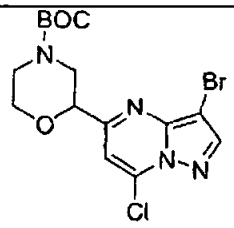
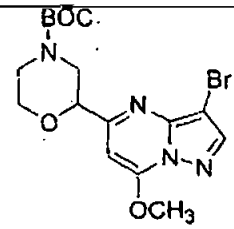
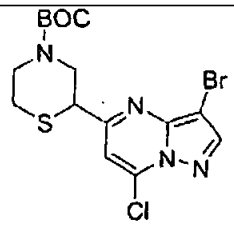
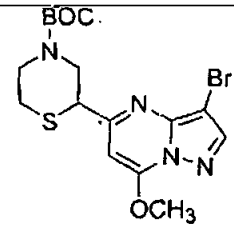
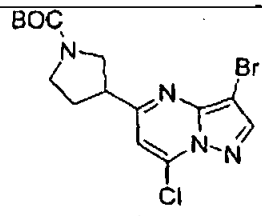
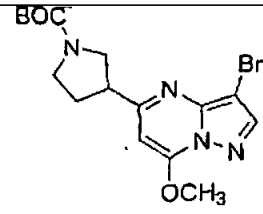
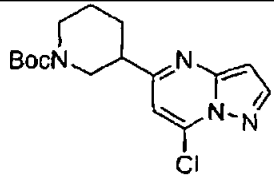
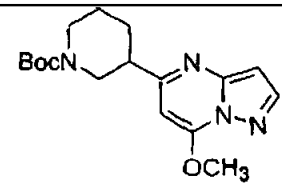
A mixture of the product from Preparative Example 300-K (8.00 g, 19.3 mmol) and MeONa (2.16 g, 40.0 mmol) in anhydrous MeOH (100mL) was stirred for 20 hr. CH_2Cl_2 (200mL) was then added, the mixture was filtered through

Celite, the solvent was evaporated, and the residue was purified by column chromatography on silica gel with 2:1 CH_2Cl_2/EtOAc as eluent. White solid (7.75 g, 98 %) was obtained.

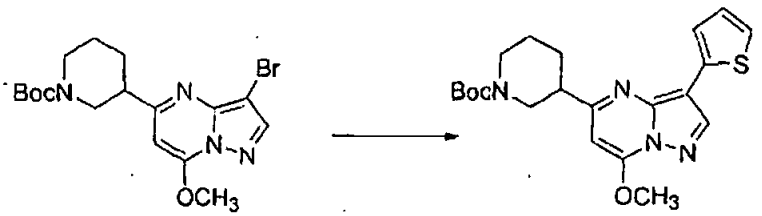
PREPARATIVE EXAMPLES 401-K – 405-K:

By essentially the same procedure set forth in Preparative Example 400-K, only substituting the compound shown in Column 2 of Table 400-K, the compounds shown in Column 3 of Table 400-K were prepared.

TABLE 400-K

Prep. Ex.	Column 2	Column 3
401-K		
402-K		
403-K		
404-K		
405-K		

PREPARATIVE EXAMPLE 500-K:

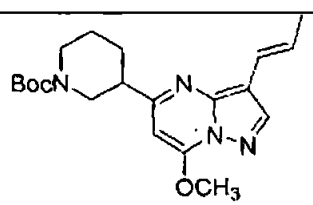
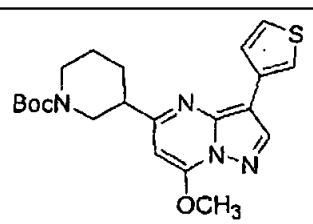


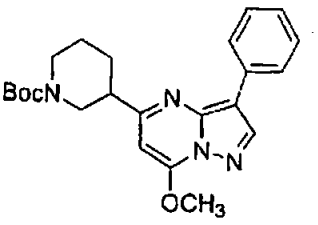
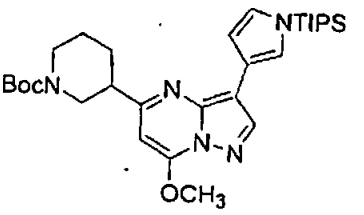
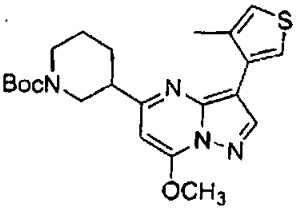
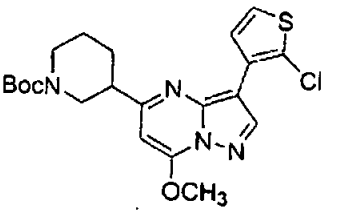
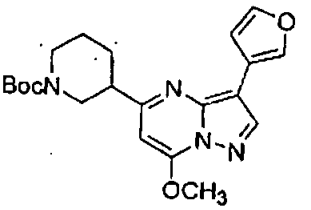
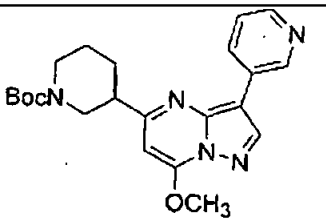
A mixture of the product from Preparative Example 400-K (600 mg, 1.46 mmol), 2-thienylboronic acid (230 mg, 1.80 mmol), $Pd[PPh_3]_4$ (160 mg, 0.14 mmol), and Na_2CO_3 (466 mg, 4.40 mmol) in 1,2-dimethoxyethane (20 mL) and H_2O (4 mL) was stirred and refluxed under N_2 for 20 hr. The solvents were evaporated and the residue was purified by column chromatography on silica gel with 2:1 CH_2Cl_2/EtOAc as eluent. Pale yellow solid (355 mg, 59 %) was obtained. LC-MS: 415 [M+].

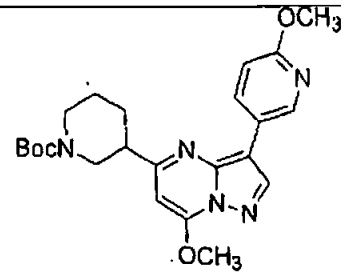
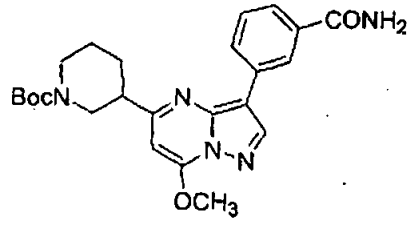
PREPARATIVE EXAMPLES 501-511-K:

By essentially same procedure set forth in Preparative Example 500-K only substituting the appropriate boronic acid, the compounds given in Column 2 of Table 500-K were prepared.

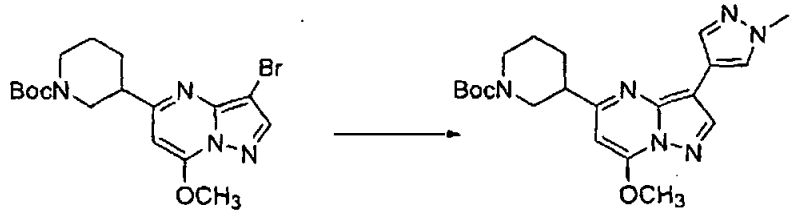
TABLE 500-K

Prep. Ex.	Column 2	Data
501-K		LCMS: MH^+=373
502-K		LCMS: MH^+=415

503-K		LCMS: MH^+=409
504-K		LCMS: MH^+=555
505-K		LCMS: MH^+=429
506-K		
507-K		LCMS: MH^+=399
508-K		LCMS: MH^+=410

510-K		LCMS: MH^+=425
511-K		LCMS: MH^+=452

PREPARATIVE EXAMPLE 520-K:



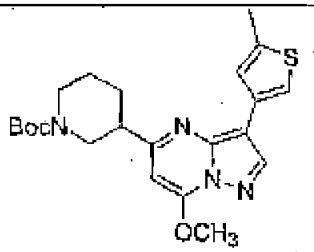
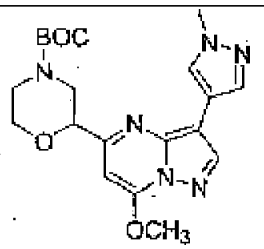
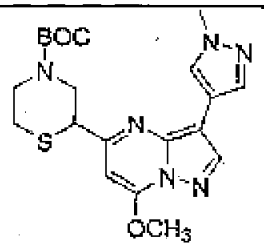
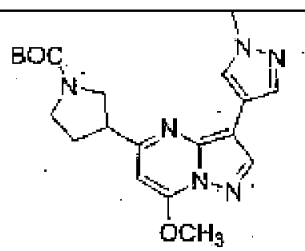
A mixture of the product from Preparative Example 400-K (1.23 g, 3.00 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2yl)1-H-pyrazole (850 mg, 4.00 mmol), $Pd[PPh_3]_4$ (348 mg, 0.30 mmol), and Na_2CO_3 (1.27 g, 12.0 mmol) in 1,2-dimethoxyethane (36 mL) and H_2O (7.5 mL) was stirred and refluxed under N_2 for 20 hr. The solvents were evaporated and the residue was purified by column chromatography on silica gel with 20:1 EtOAc/MeOH as eluent. Pale orange solid (740 mg, 60 %) was obtained. LC-MS: 413 [M+H].

PREPARATIVE EXAMPLE 530-K – 533-K:

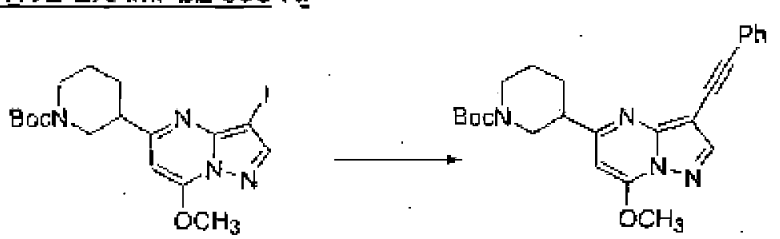
By essentially same procedure set forth in Preparative Example 520-K, the compounds shown in Column 2 of Table 530-K were prepared.

TABLE 530-K

Prep. Ex.	Column 2	Data

530-K		LC-MS: 429 [M+H].
531-K		
532-K		
533-K		

PREPARATIVE EXAMPLE 550-K:



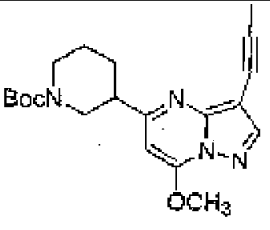
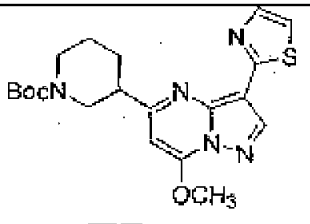
A mixture of the compound from Preparative Example 512-K (230 mg, 0.50 mmol), tributylphenyltin (235 mg, 0.60 mmol), and Pd[PPh3]4 (58 mg, 0.05 mmol) in anhydrous dioxane (5 mL) was stirred under N2 at 90oC for 3 hr. The solvent was evaporated and the residue was purified by column chromatography

on silica gel with 20:1 CH_2Cl_2/EtOAc as eluent. Pale yellow wax (46 mg, 21 %) was obtained. LC-MS: 433 [M+].

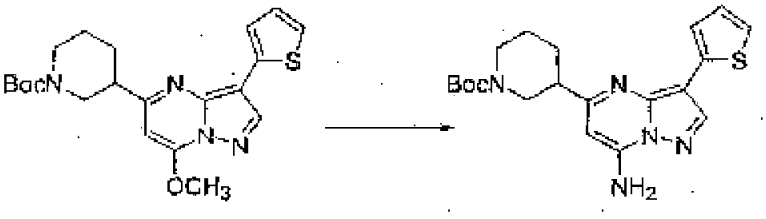
PREPARATIVE EXAMPLES 551-K -552-K:

By essentially same procedure set forth in Preparative Example 550-K, only substituting the appropriate tributyltin reagent, the compounds given in Column 2 of Table 550-K were prepared.

TABLE 550-K

Prep. Ex.	Column 2	Data
551-K		LCMS: MH^+=371
552-K		LCMS: MH^+=416

PREPARATIVE EXAMPLE 600-K:

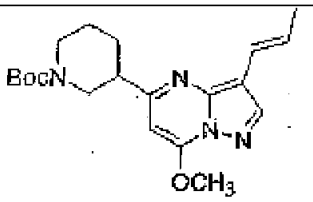
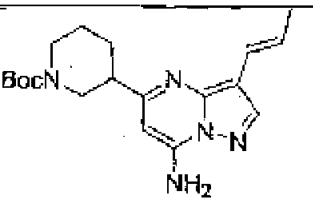
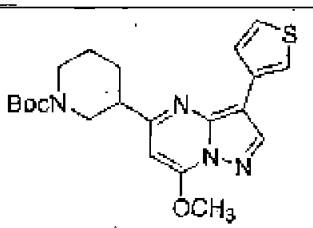
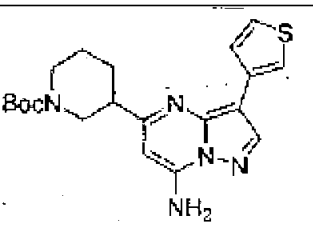
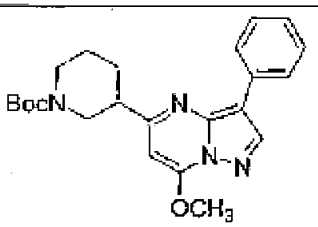
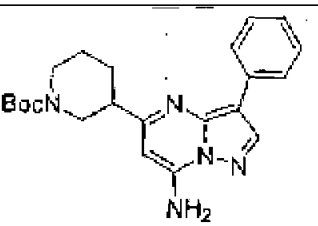
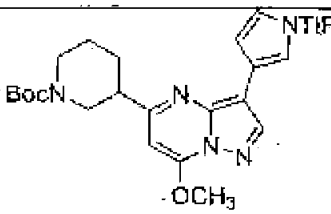
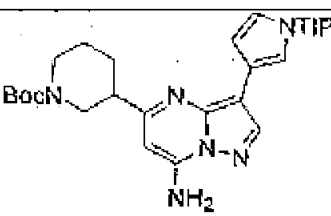
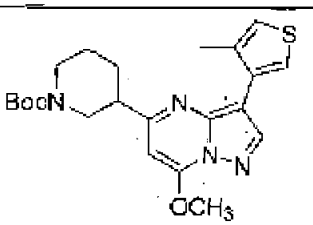
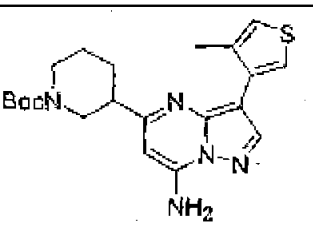


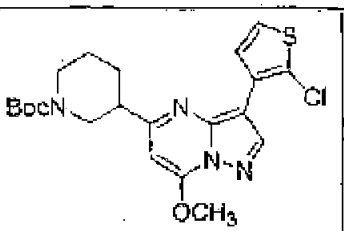
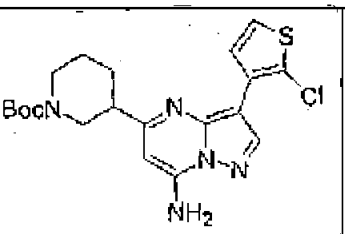
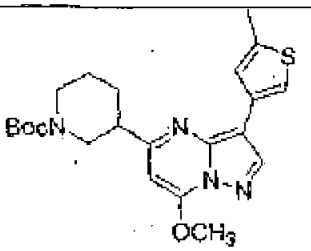
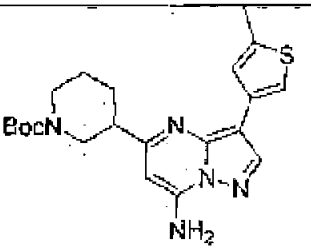
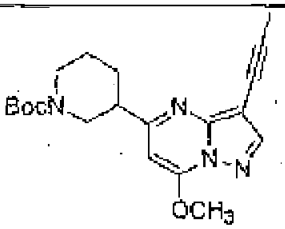
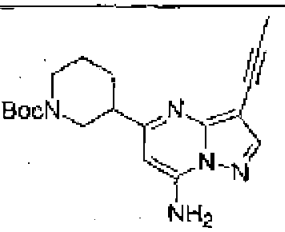
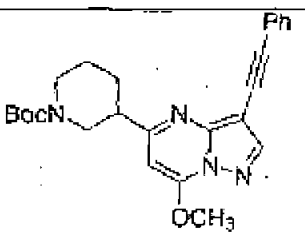
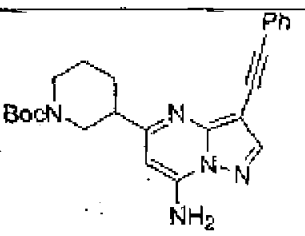
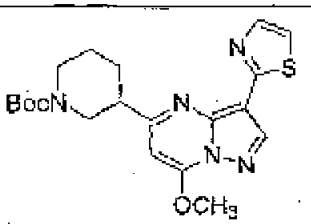
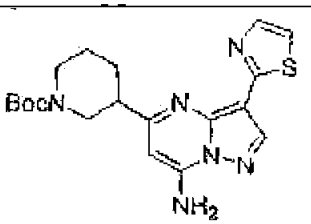
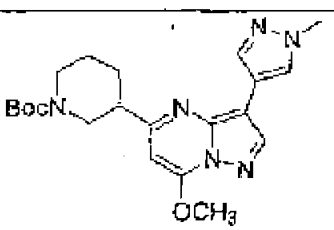
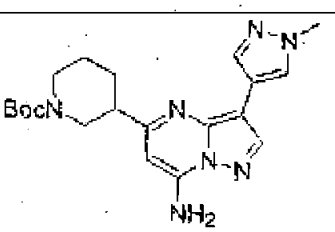
A mixture of the product from Preparative Example 500-K (350 mg, 0.85 mmol), 2.0 M NH_3 in 2-propanol (7.5 mL), and conc. aqueous NH_4OH (0.75 mL) was stirred in a closed pressure vessel at 75°C for 3 days. The solvents were evaporated and the residue was purified by column chromatography on silica gel with 50:1 CH_2Cl_2/MeOH as eluent. Pale yellow solid (143 mg, 42 %) was obtained. LC-MS: 400 [M+].

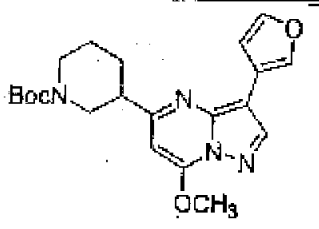
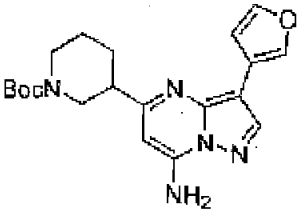
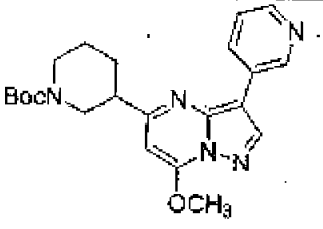
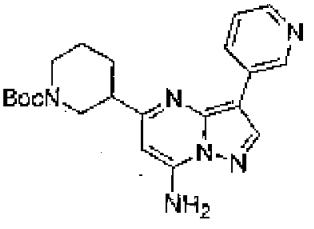
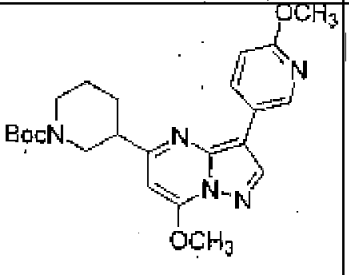
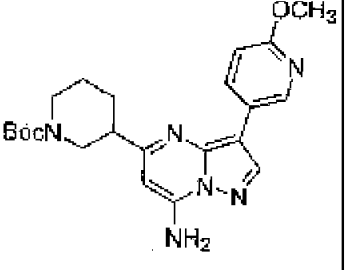
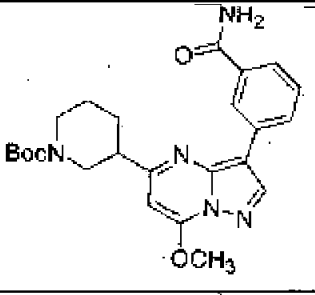
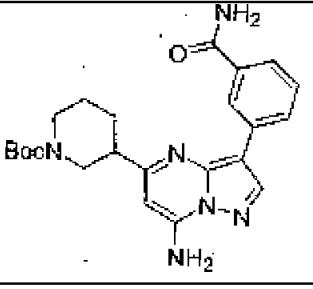
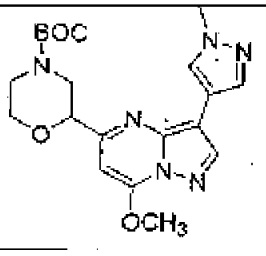
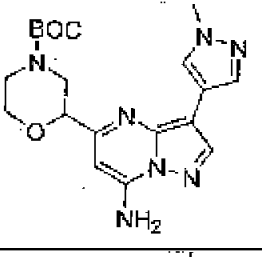
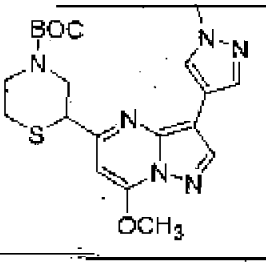
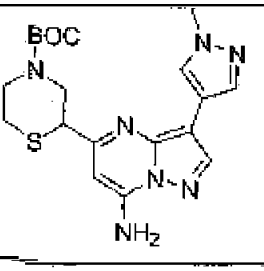
PREPARATIVE EXAMPLE 601-K -615-K:

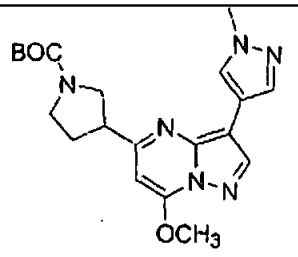
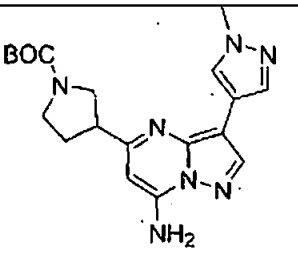
By essentially same procedure set forth in Preparative Example 600-K only substituting the compounds in Column 2 of Table 600-K, the compounds given in Column 3 of Table 600-K were prepared.

TABLE 600-K

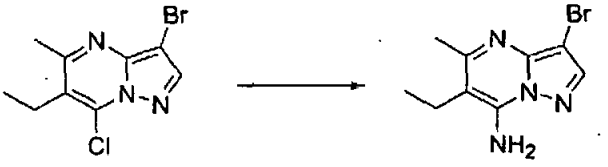
Prep. Ex.	Column 2	Column 3	Data
601-K			LCMS: MH^+=359
602-K			LCMS: MH^+=400
603-K			
604-K			LCMS: MH^+=540
605-K			LCMS: MH^+=414

606-K			LCMS: M^+=434
607-K			LCMS: MH^+=414
608-K			LCMS: MH^+=356
609-K			LCMS: MH^+=418
610-K			LCMS: MH^+=401
611-K			LCMS: MH^+=398

612-K			LCMS: MH^+=384
613-K			LCMS: MH^+=395
614-K			LCMS: MH^+=425
615-K			LCMS: MH^+=437
616-K			
617-K			

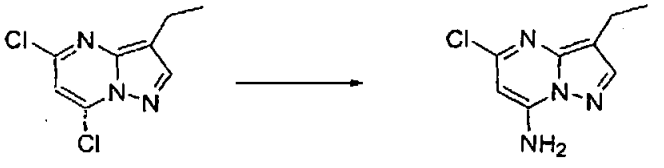
618-K			

PREPARATIVE EXAMPLE 650-K:



A mixture of the product from Preparative Example 201-K (100 mg, 0.37 mmol), 2.0 M NH_3 in 2-propanol (2.0 mL), and conc. aqueous NH_4OH (0.2 mL) was stirred in a closed pressure vessel at 50°C for 2 days. The solvents were evaporated and the residue was purified by column chromatography on silica gel with 30:1 CH_2Cl_2/MeOH as eluent. White solid (38 mg, 41 %) was obtained. LC-MS: 257 [M+2H].

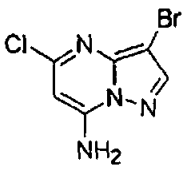
PREPARATIVE EXAMPLE 660-K:



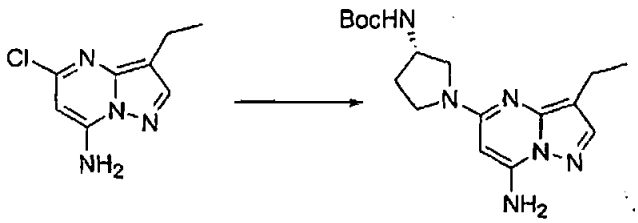
A mixture of the starting material (2.16 g, 10.0 mmol), 2.0 M NH_3 in 2-propanol (50.0 mL), and conc. aqueous NH_4OH (10.0 mL) was stirred in a closed pressure vessel at 50°C for 2 days. The solvents were evaporated, the solid was suspended in H_2O (100 mL), filtered, washed on filter with H_2O (100 mL), and dried in a vacuum at 100°C. Slightly beige solid (1.80 g, 91 %) was obtained.

PREPARATIVE EXAMPLE 661-K:

By essentially same procedure set forth in Preparative Example 660-K, compound given below was prepared.



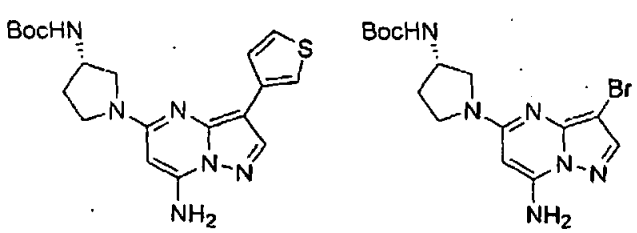
PREPARATIVE EXAMPLE 662-K:



A mixture of the product from Preparative Example 660-K (600 mg, 3.05 mmol), the amine (837 mg,4.50 mmol), and $NaHCO_3$ (756 mg, 9.00 mmol) in anhydrous N-methylpyrrolidone (4 mL) was stirred under N_2 at 140°C for 18 hr. The mixture was cooled to 25oC, CH_2Cl_2 (15 mL) was added and the mixture was filtered. The solvents from the filtrate were distilled off and the residue was purified by column chromatography on silica gel with 2:1 CH_2Cl_2/EtOAc as eluent. White solid (1.01g, 95 %) was obtained.

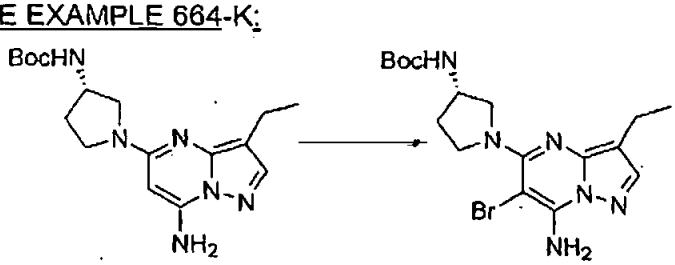
PREPARATIVE EXAMPLE 663-K:

By essentially same procedure set forth in Preparative Example 662-K, compounds given below were prepared.



LC-MS: 401 [M+H].

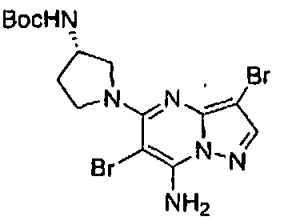
PREPARATIVE EXAMPLE 664-K:



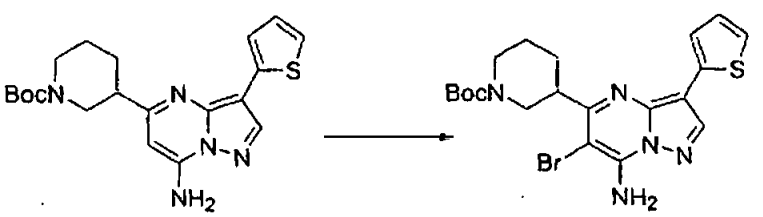
A solution of NBS (142 mg, 0.80 mmol) in anhydrous CH_3CN (5 mL) was added under N_2 to a stirred solution of the product from Preparative Example 662-K (400 mg, 0.90 mmol) in anhydrous CH_3CN (5 mL) and CH_2Cl_2 (5 mL). The mixture was stirred for 18 hr, the solvents were evaporated, and the residue was purified by column chromatography on silica gel with 3:1 CH_2Cl_2/EtOAc as eluent. White solid (330 mg, 67 %) was obtained.

PREPARATIVE EXAMPLE 665-K:

By essentially same procedure set forth in Preparative Example 664-K, compound given below was prepared.



PREPARATIVE EXAMPLE 700-K:



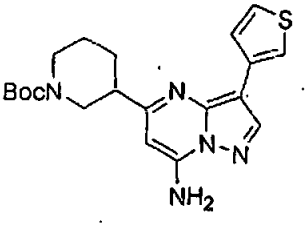
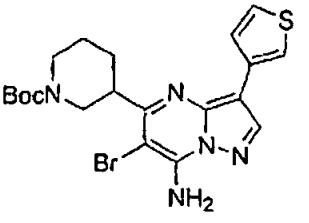
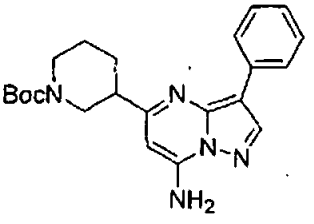
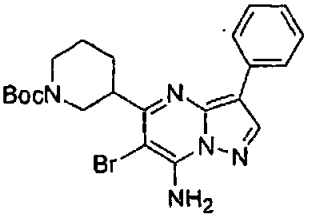
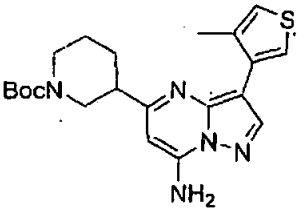
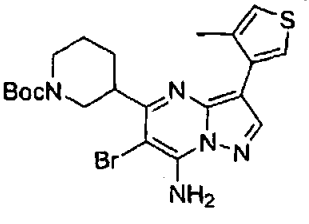
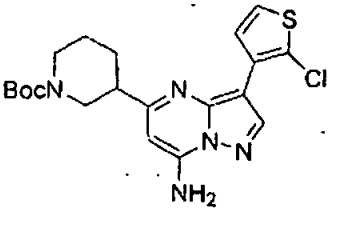
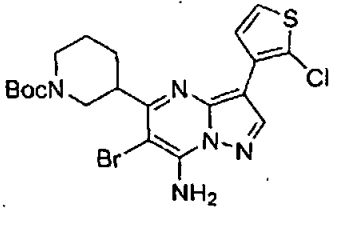
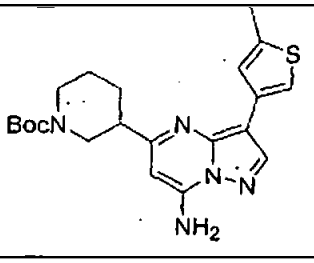
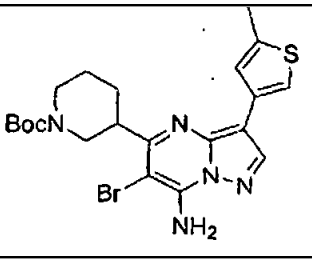
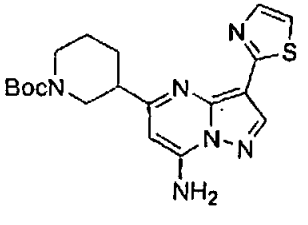
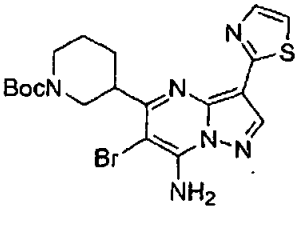
A solution of Br_2 (16 mg) in CH_2Cl_2 (0.5 mL) was added under N_2 to a stirred solution of the product from Preparative Example 600-K (40 mg, 0.10 mmol) in t-$BuNH_2$ (2.0 mL). The mixture was stirred for 1 hr, the solvents were evaporated, and the residue was purified by column chromatography on silica gel with 10:1 CH_2Cl_2/EtOAc as eluent. Off-white solid (18 mg, 38 %) was obtained. LC-MS: 480 [M+H].

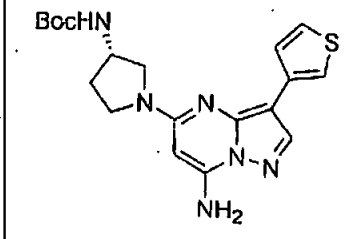
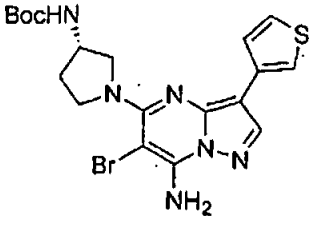
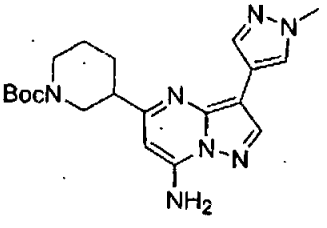
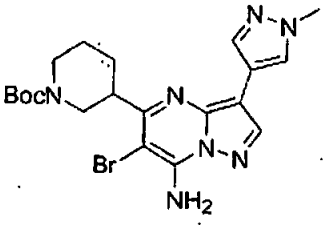
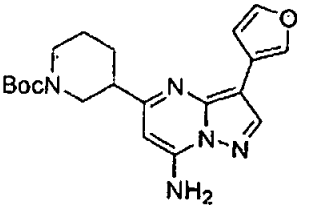
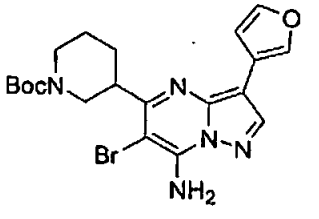
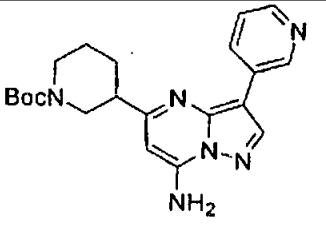
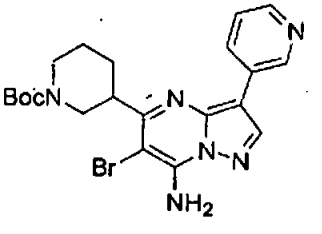
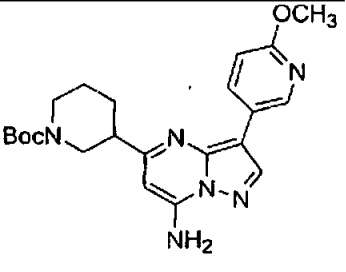
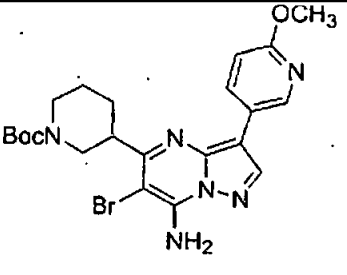
PREPARATIVE EXAMPLE 701-712-K:

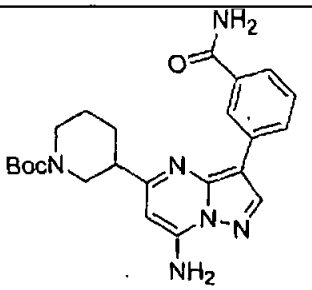
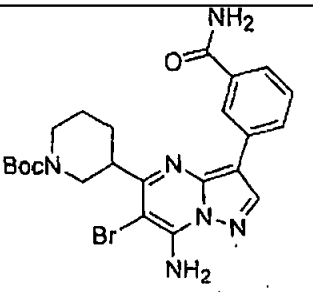
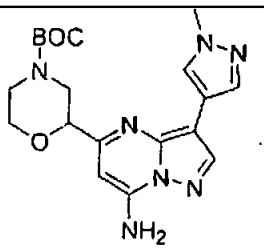
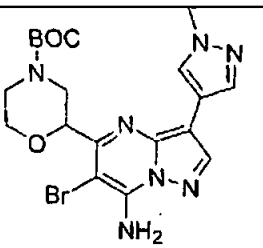
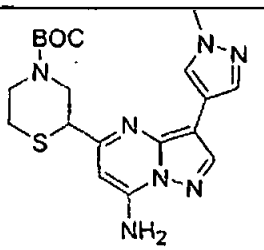
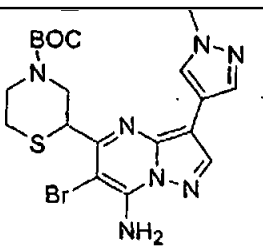
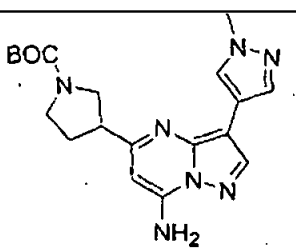
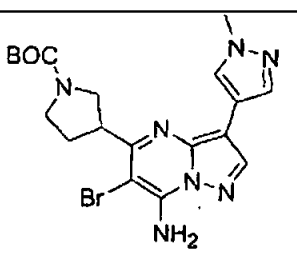
By essentially the same procedure set forth in Preparative Example 700-K only substituting the compounds in Column 2 of Table 700-K, the compounds in Column 3 of Table 700-K were prepared.

TABLE 700-K

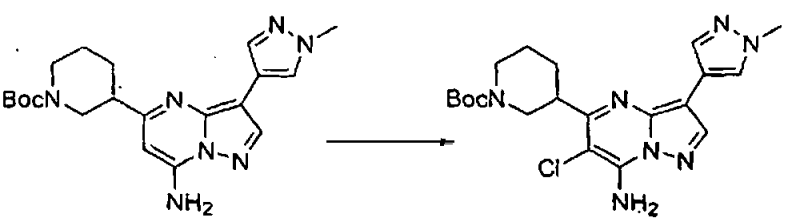
Prep. Ex.	Column 2	Column 3	Data

701-K			LCMS: MH^+=
702-K			
703-K			LCMS: MH^+=
704-K			LCMS: M^+=
705-K			LCMS: MH^+=
706-K			LCMS: MH^+=

707-K			LCMS: M^+=479
708-K			LCMS: M^+=476
709-K			LCMS: M^+=462
710-K			LCMS: M^+=473
711-K			LCMS: M^+ = 503

712-K			LCMS: M^+H = 517
713-K			
714-K			
715-K			

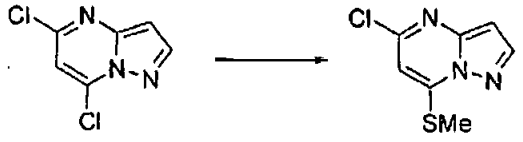
PREPARATIVE EXAMPLE 750-K:



A solution of N-chlorosuccinimide (23 mg, 0.17 mmol) in anhydrous CH_3CN (2 mL) was added under N_2 to a stirred solution of the product from Preparative Example 611-K (73 mg, 0.17 mmol) in anhydrous CH_3CN (2 mL). The mixture was stirred for 24 hr, the solvents were evaporated, and the residue

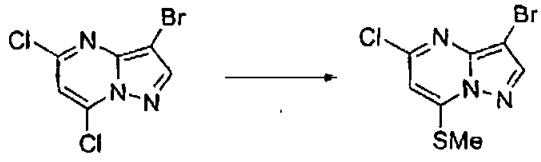
was purified by column chromatography on silica gel with 1:1 CH_2Cl_2/EtOAc as eluent. White solid (54 mg, 68.%) was obtained. LC-MS: 432 [M+].

PREPARATIVE EXAMPLE 800-K:



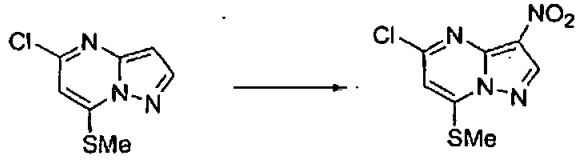
To a solution of dichloride (3.0 g, 16.0 mmol) prepared as described earlier in THF (25 mL) was added NaSMe (1.1 g, 16.0 mmol) in one portion. The resulting mixture was stirred for 12 h at rt and was concentrated under reduced pressure. The crude product was partitioned between EtOAc (150 mL) and H_2O (30 mL) and the layers were separated. The organic layer was washed sequentially with H_2O (2 x 30 mL) and brine (1 x 30 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 3.0 g (94 % yield) of a tan solid. LC-MS: 200.1 [M+H], purity 99%.

PREPARATIVE EXAMPLE 900-K:



Prepared the procedure outlined in Preparative Example 800-K except starting with the dichloride shown above (7.4 g, 27.7 mmol) prepared as described earlier and NaSMe (2.1 g, 30.5 mmol) afforded 7.4 g (96% yield) of the title compound as a light orange solid. LC-MS: 278.1 [M+H], purity 95%.

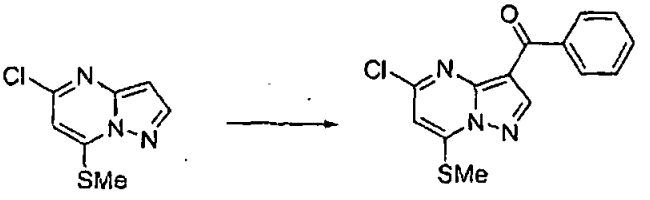
PREPARATIVE EXAMPLE 1000-K:



To a solution of thiomethyl derivative from Preparative Example 800-K (1.5 g, 7.5 mmol) in H_2SO_4 (9 mL) at 0 °C was added 60% HNO_3 (4.5 mL) dropwise. The resulting solution was stirred for 2h at 0 °C and 2h at rt. The reaction mixture was poured into beaker containing ice (~15 g) and the heterogeneous mixture was stirred for 45 min. The resulting ppt was collected

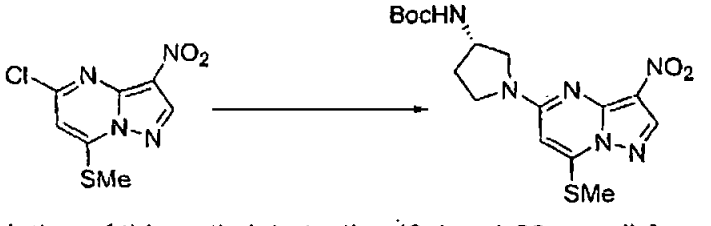
by filtration and was washed sequentially with H_2O (2 x 3 mL) and Et_2O (2 x 3 mL). The ppt was placed under high vacuum to remove trace volatiles to afford 1.1 g (60%) of an orange solid. LC-MS: 245.0 [M+H], purity 90%.

PREPARATIVE EXAMPLE 1100-K:



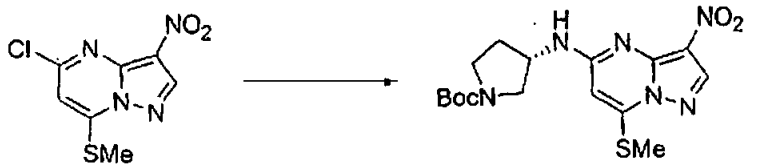
To a solution of thiomethyl derivative (0.20 g, 1.0 mmol) from Preparative Example 800-K in CH_2Cl_2 (5 mL) at 0 °C was added $AlCl_3$ (0.70 g, 5.3 mmol) followed by benzoyl chloride (0.40 mL, 3.5 mmol). The mixture was heated at reflux for 12 h at rt whereupon the mixture was carefully quenched at 0 °C with sat. aq. $NaHCO_3$ (3 mL). CH_2Cl_2 (5 mL) was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, washed with brine (1 x 5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 0.27 g (88% crude yield) of a brown solid. LC-MS: 304.0 [M+H], purity 85%.

PREPARATIVE EXAMPLE 1200-K:



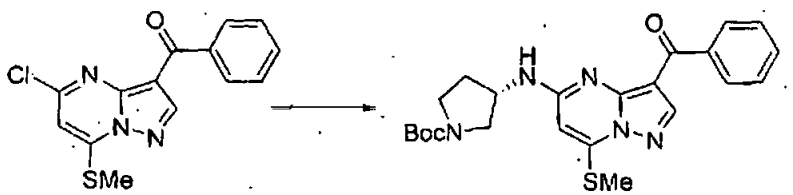
To a solution of thiomethyl derivative (0.4 g, 1.63 mmol) from Preparative Example 1000-K in dioxane/DIPEA (7 ml/2 mL) at room temperature was added (*S*)-(-)-3-(Boc-amino)pyrrolidine (0.36 g, 1.96 mmol) in a single portion. The mixture was stirred at reflux for 12 h and was cooled to rt. The mixture was filtered and washed with CH_2Cl_2 (2 x 2 mL) and Et_2O (2 x 2 mL). The resultant ppt was dried under vacuum to afford 0.57 g (90% yield) of a yellow solid. LC-MS: 395.1 [M+H], purity 90%.

PREPARATIVE EXAMPLE 1300-K:



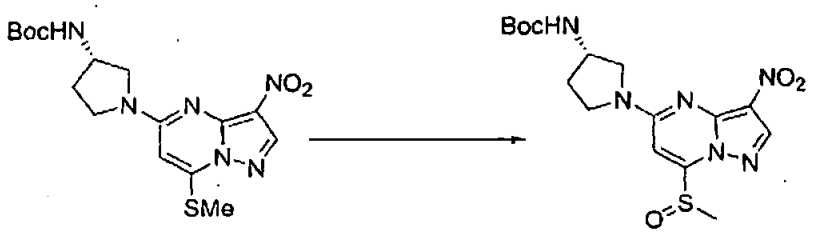
The above compound was prepared according to the procedure outlined in Preparative Example 1200-K utilizing thiomethyl derivative from Preparative Example 1000 (66 mg, 0.27 mmol) and (*S*)-(-)-1-(Boc-amino)pyrrolidine (65 mg, 0.35 mmol) to afford 83 mg (77% yield) of a yellow solid. LC-MS: 395.1 [M+H], purity 99%.

PREPARATIVE EXAMPLE 1400-K:



The title compound was prepared according to the procedure outlined in Preparative Example 1200-K utilizing thiomethyl derivative (0.30 g, 1 mmol) from Preparative Example 1100-K and (*S*)-(-)-1-(Boc-amino)pyrrolidine (0.24 g, 1.3 mmol) to afford 160 mg (35% yield) of a yellow solid. LC-MS: 454.1 [M+H], purity 60%.

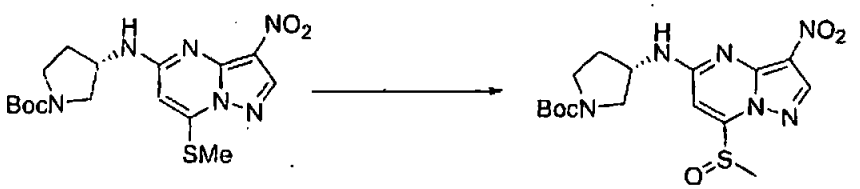
PREPARATIVE EXAMPLE 1500-K:



To a solution of thiomethyl adduct (0.17 g, 0.42 mmol) from Preparative Example 1200-K in CH_2Cl_2 (2 mL) at 0 °C was added MCPBA (0.11 g, 0.63 mmol) in one portion. The mixture was stirred for 2 h at 0 °C and 1 h at rt whereupon an additional portion of MCPBA (54 mg, 0.32 mmol) was added. The mixture was stirred for 2 h at rt where upon CH_2Cl_2 (3 mL) and sat. aq. $NaHCO_3$ (3 mL) were added. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined and washed with brine (1 x 3mL). The organic layer was dried (Na_2SO_4), filtered, and

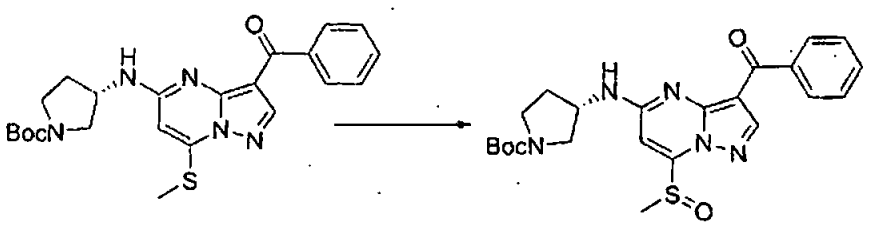
concentrated under reduced pressure to afford 0.17 (98% crude yield) of a yellow solid. This material was used directly without further purification. LC-MS: 411.1 [M+H], purity 85%.

PREPARATIVE EXAMPLE 1600-K:



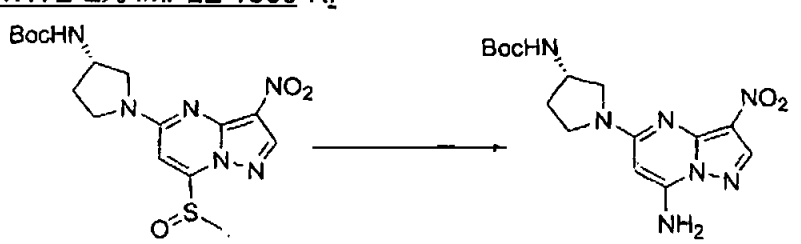
The title compound was prepared according to the procedure outlined in Preparative Example 1500-K utilizing thiomethyl derivative (82 mg, 0.21 mmol) from Preparative Example 1300-K 0 to afford 84 mg (98% yield) of a yellow solid. This material was used directly without further purification. LC-MS: 411.1 [M+H], purity 89%.

PREPARATIVE EXAMPLE 1700:



The title compound was prepared according to the procedure outlined in Preparative Example 1500-K utilizing thiomethyl derivative (0.15 g, 0.33 mmol) from Preparative Example 1400-K to afford 152 mg (98% yield) of a yellow solid. This material was used directly without further purification. LC-MS: 470.1 [M+H], purity 40%.

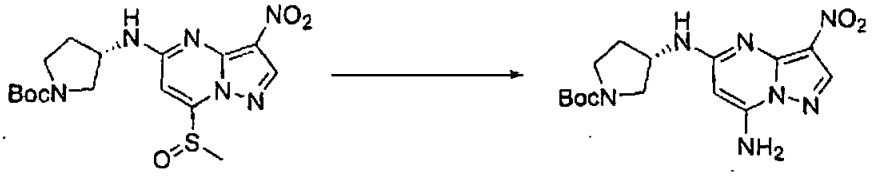
PREPARATIVE EXAMPLE 1800-K:



To a pressure tube charged with a stir bar was added sulfoxide (0.15 g, 0.36 mmol) from Preparative Example 1500-K followed by 2M NH_3 in IPA (4 mL) and conc. NH_4OH (1 mL). The tube was capped and was heated to 85 °C and

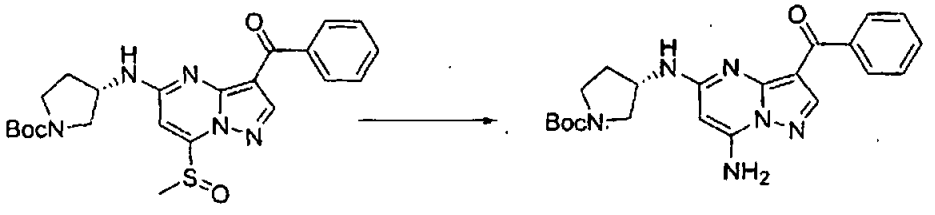
stirred for 14h. The mixture was cooled to room temperature, concentrated under reduced pressure, and placed under high vacuum to remove trace volatiles. The crude product was purified by preparative thin-layer chromatography (4 x 1000 μM) plates using a 20:1 mixture of CH_2Cl_2/MeOH as eluent to afford 105 mg (80% yield) of a yellow/orange solid. LC-MS: 364.2 [M+H], purity 99%.

PREPARATIVE EXAMPLE 1900-K:



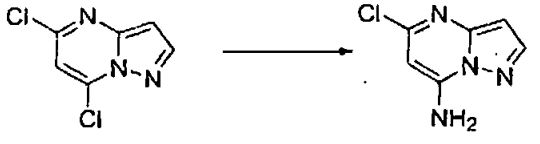
The title compound was prepared according to the procedure outlined in Preparative Example 1800-K utilizing thiomethyl derivative (60 mg, 0.15 mmol) from Preparative Example 1600-K to afford 21 mg (39% yield) of an off-white solid. LC-MS: 364.1 [M+H], purity 90%.

PREPARATIVE EXAMPLE 2000-K:



The title compound was prepared according to the procedure outlined in Preparative Example 1800-K utilizing thiomethyl derivative (140 mg, 0.30 mmol) from Preparative Example 1700-K to afford 30 mg (24% yield) of yellow crystalline solid. LC-MS: 423.1 [M+H], purity 93%.

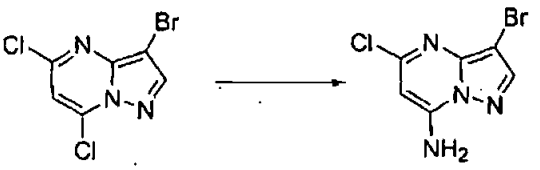
PREPARATIVE EXAMPLE 2100-K:



To a pressure tube charged with dichloride (5 g, 26.7 mmol) and a stir bar was added conc. NH_4OH (110 mL). The tube was sealed and heated to 70 °C. The mixture was stirred for 5 h, cooled to rt, and concentrated to dryness under reduced pressure. The resultant solid was suspended in H_2O (70 mL), filtered,

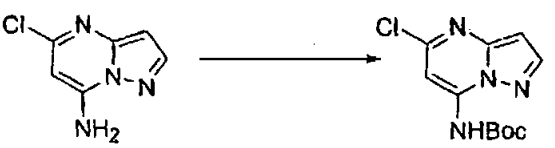
and the solid was washed with Et_2O (100 mL). The crude material was dried under reduced pressure to afford 4.2 g (93% yield) of a yellow solid that was used without purification. LC-MS: 169.0 [M+H], purity 99%.

PREPARATIVE EXAMPLE 2200-K:



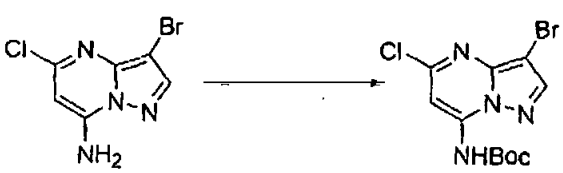
The title compound was prepared according to the procedure outlined in Preparative Example 2100-K except utilizing the 3-bromo derivative (2.0 g, 7.5 mmol) to afford 1.7 g (92% yield) of a white solid. mp >215 °C; LC-MS: 249.0 [M+H], purity 99%.

PREPARATIVE EXAMPLE 2300-K:



To a solution of 7-amino adduct (4.2 g, 24.8 mmol) from Preparative Example 2100-K in CH_2Cl_2 (50 mL) at rt was added Boc_2O (5.9 g, 27.3 mmol) and DMAP (3.3 g, 27.3 mmol). The resulting solution was stirred for 12 h at rt and was diluted with CH_2Cl_2 (50 mL) and sat. aq. $NaHCO_3$ (25 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layers were washed with brine (1 x 30 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude product was purified by 40M Flash Elute using a gradient (1L of CH_2Cl_2 to 2.5L of 1% MeOH (7M NH_3):CH_2Cl_2 to afford 6.3 g (95% yield) of a white solid. LC-MS: 269.0 [M+H], purity 99%.

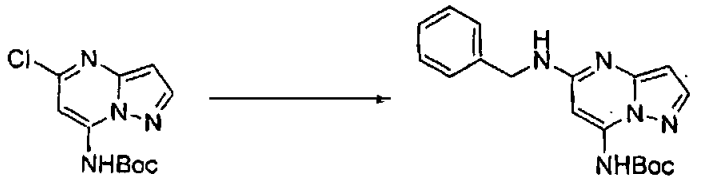
PREPARATIVE EXAMPLE 2400-K:



The title compound was prepared according to the procedure outlined in Preparative Example 2300-K except utilizing the 3-bromo derivative (2.0 g, 8.1

mmol) from Preparative Example 2200-K to afford 2.5 g (89% yield) of a white solid; LC-MS: 349.1 [M+H], purity 95%.

PREPARATIVE EXAMPLE 2500-K:

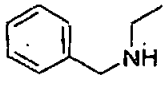
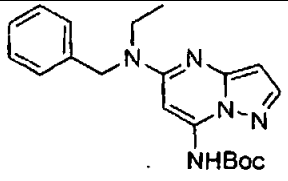
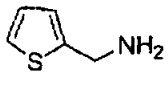
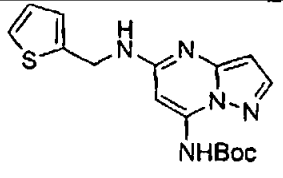


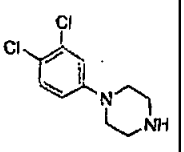
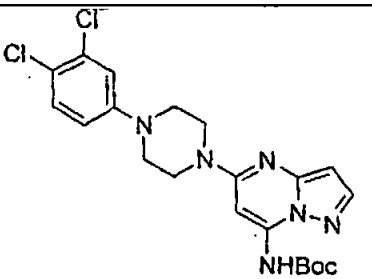
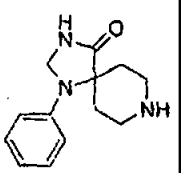
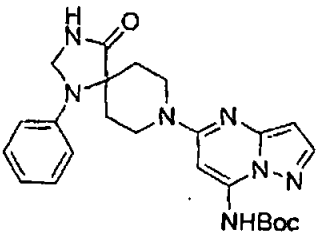
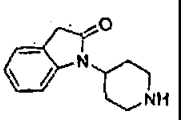
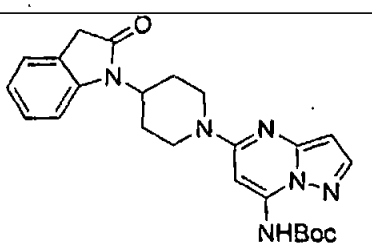
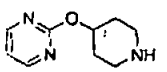
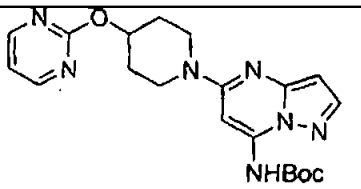
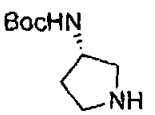
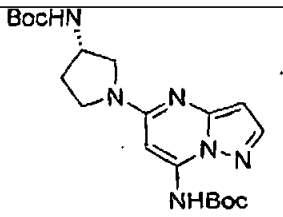
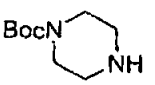
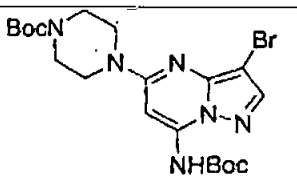
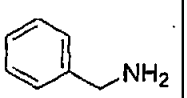
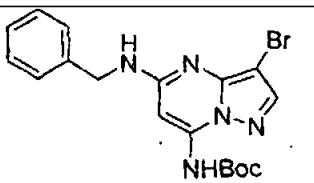
To a solution of Boc derivative (0.10 g, 0.37 mmol) from Preparative Example 2300-K in dioxane/DIPEA (3 ml/0.5 mL) at rt was added benzylamine (61 μL ,0.56 mmol) dropwise. The mixture was stirred at reflux for 12 h, cooled to rt, and concentrated under reduced pressure. The crude product was purified by preparative thin-layer chromatography (4 x 1000 μM plates) using a 30:1 mixture of CH_2Cl_2/MeOH as eluent to afford 65 mg (52% yield) of a yellow solid. LC-MS: 340.1 [M+H], purity 99%.

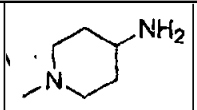
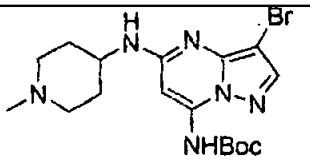
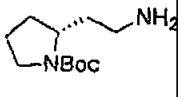
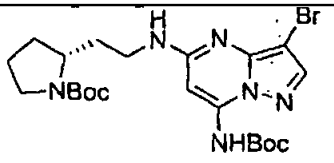
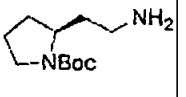
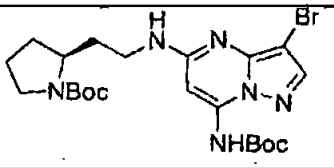
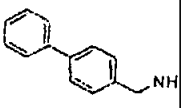
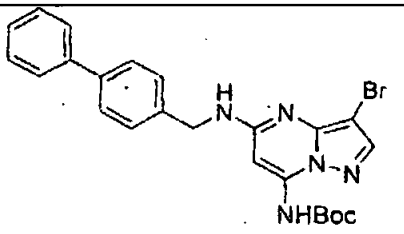
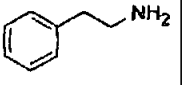
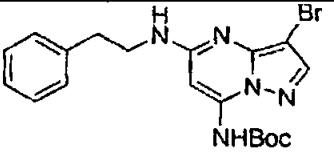
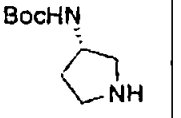
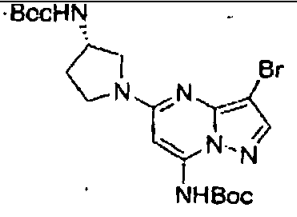
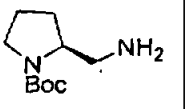
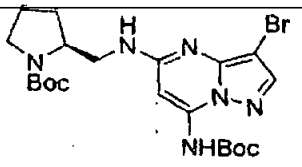
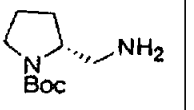
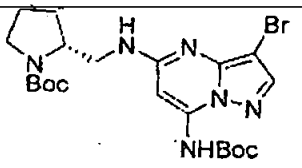
PREPARATIVE EXAMPLES 2501-K -2525-K:

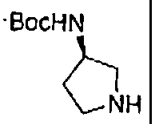
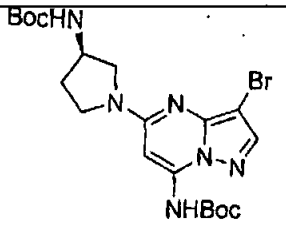
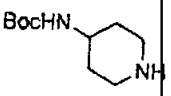
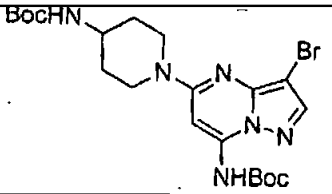
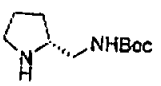
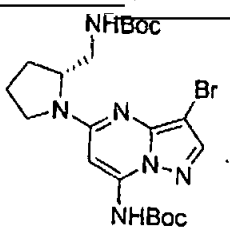
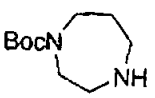
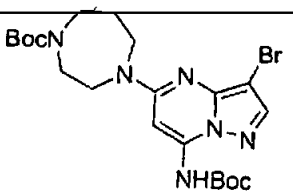
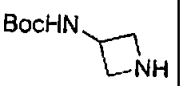
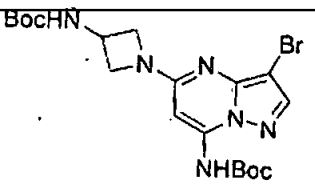
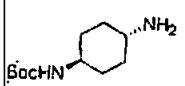
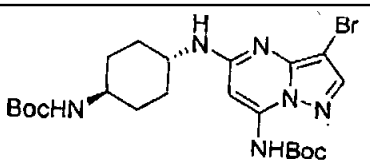
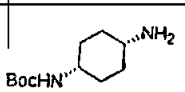
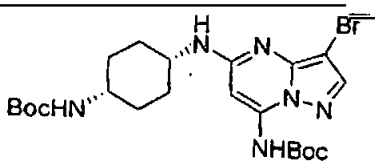
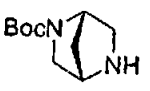
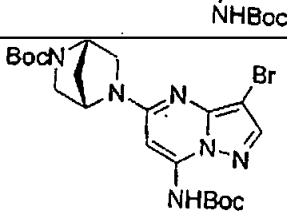
Following the procedure set forth in Preparative Example 2500-K but substituting commercially available amines, the compounds in Column 3 of Table 2500-K.

TABLE 2500-K

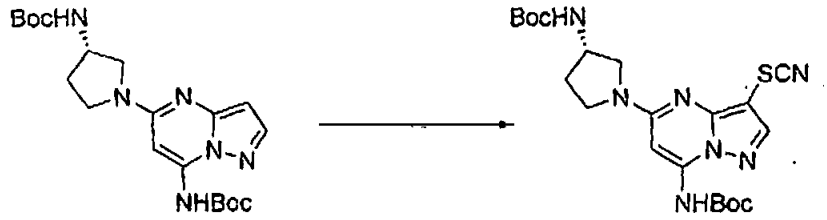
Prep. Ex.	*Column 2*	*Column 3*	1.Yield (%) 2. LC-MS
2501-K			1. 12 2. 368.1
2502-K			1. 30 2. 346.1

2503-K			1. 69 2. 463.1
2504-K			1. 98 2. 464.1
2505-K			1. 46 2. 449.1
2506-K			1. 72 2. 412.1
2507-K			1. 94 2. 419.2
2508-K			1. 90 2. 499.1
2509-K			1. 47 2. 420.1

2510-K			1. 57 2. 427.1
2511-K			1. 85 2. 525.1
2512-K			1. 80 2. 525.1
2513-K			1. 53 2. 494.1
2514-K			1. 49 2. 434.1
2515-K			1. 95 2. 499.1
2516-K			1. 54 2. 513.1
2517-K			1. 84 2. 513.1

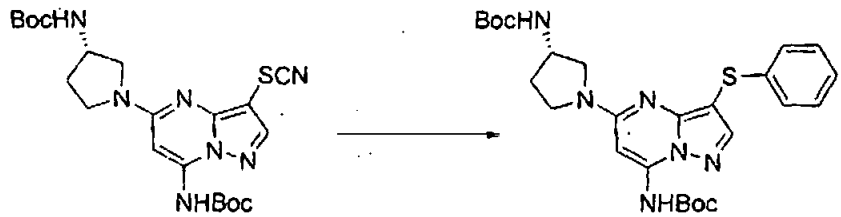
2618-K			1. 79 2. 499.1
2519-K			1. 78 2. 513.1
2520-K			1. 82 2. 513.1
2521-K			1. 92 2. 513.1
2522-K			1. 12 2. 485.3
2523-K			1. 28 2. 525.1
2524-K			1. 30 2. 525.1
2525-K			1. 89 2. 511.3

PREPARATIVE EXAMPLE 2600-K:



To a solution of Boc derivative (0.53 g, 1.27 mmol) from Preparative Example 2507-K in MeOH (4 mL) at 0 °C was added KSCN (0.15 g, 1.52 mmol) followed by Br_2 (75 μL, 1.52 mmol). The mixture was allowed to warm to rt , stir for 12h, and was concentrated under reduced pressure. The crude residue was suspended in EtOAc (7 mL) and sat. aq. $NaHCO_3$ (2 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 7 mL) and the organic layers were combined. The organic layer was washed with brine (1 x 5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography using a 20:1 mixture of CH_2Cl_2/MeOH as eluent to afford 0.37g (65% yield) as a light yellow solid. LCMS: 476.3 [M+H} 99% purity.

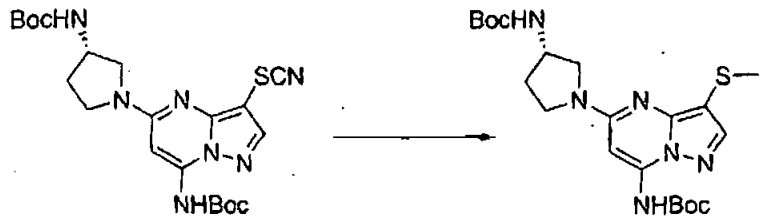
PREPARATIVE EXAMPLE 2700-K:



To a solution of thiocyanate (100 mg, 0.21 mmol) from Preparative Example 2600-K in THF (2 mL) at 0 °C was added $Pd(PPh_3)_4$ (24 mg, 0.021 mmol) followed by dropwise addition of PhMgBr (1.0 M in THF, 1.26 mL). The mixture was stirred for 12 h at rt and was treated with sat. aq NH_4Cl (2 mL) and CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, washed with brine (1 x 3 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by preparative thin-layer chromatography (4 x 1000

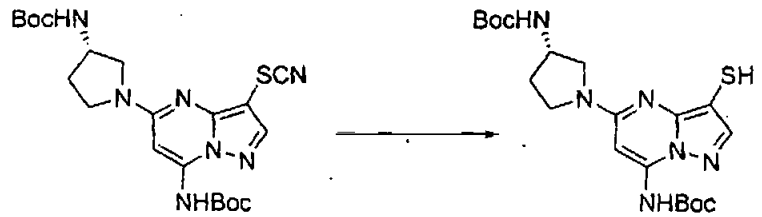
μM plates) using a 3:1 mixture of hexanes/EtOAc as eluent to afford 66 mg (60% yield) of a yellow semisolid. LC-MS: 527.1 [M+H], purity 99%.

PREPARATIVE EXAMPLE 2800-K:



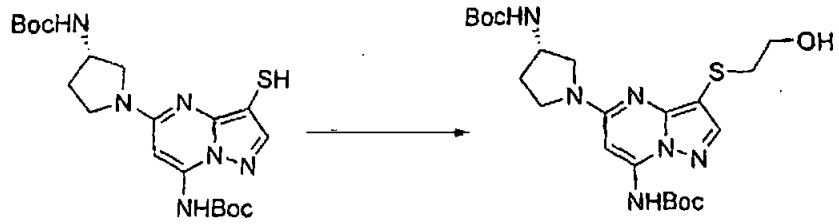
To a solution of thiocyanate (100 mg, 0.21 mmol) from Preparative Example 2600-K in MeOH (1.5 mL) at rt was added PPh_3 (55 mg, 0.21 mmol) in a single portion. The mixture was heated to reflux, stirred for 12 h, cooled and concentrated under reduced pressure. The crude product was purified by preparative thin-layer chromatography (4 x 1000 μM plates) using a 3:1 mixture of hexanes/EtOAc as eluent to afford 66 mg (68% yield) of a white solid. LC-MS: 465.3 [M+H], purity 99%.

PREPARATIVE EXAMPLE 2900-K:



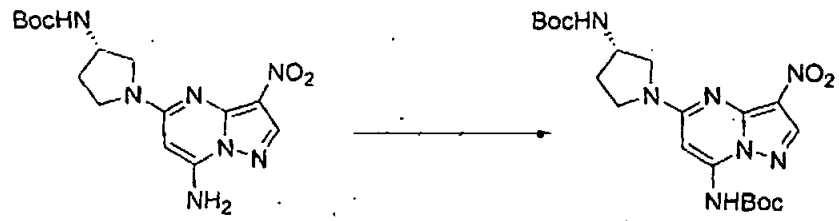
To a solution of thiocyanate (0.15 g, 0.32 mmol) from Preparative Example 2600-K in EtOH (2.5 mL) at rt was added a 0.1 M soln. of KH_2PO_4 (0.1 mL) followed by DTT (0.19 g, 1.26 mmol). The resulting mixture was stirred for 12 h at rt and was concentrated under reduced pressure. The resulting semisolid was dissolved in CH_2Cl_2 (5 mL) and was washed sequentially with H_2O (3 x 2 mL) and brine (3 x 2 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 0.13 g (90% crude yield) of a light yellow semisolid. This material was taken on crude without purification.

PREPARATIVE EXAMPLE 3000-K:



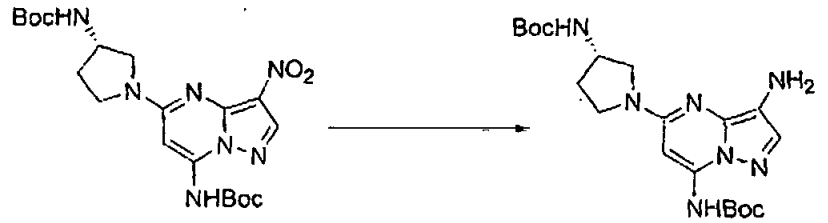
To a solution of the crude sulfhydryl derivative (80 mg, 0.18 mmol) from Preparative Example 2900-K in DMF (1.5 mL) at 0 °C was added K_2CO_3 (73 mg, 0.53 mmol) followed by bromoethanol (37 μL, 0.53 mmol). The resulting mixture was stirred for 72 h at rt where upon the mixture was diluted with EtOAc (5 mL) and water (2 mL). The layers were separated and the organic layer was washed with H_2O (3 x 2 mL) and brine (3 x 2 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford a yellow semisolid. The crude product was purified by preparative thin-layer chromatography (4 x 1000 μM plates) using a 1:1 mixture of hexanes/EtOAc as eluent to afford 37 mg (41% yield) of a light brown semisolid. LC-MS: 495.1 [M+H], purity 99%.

PREPARATIVE EXAMPLE 3100-K:



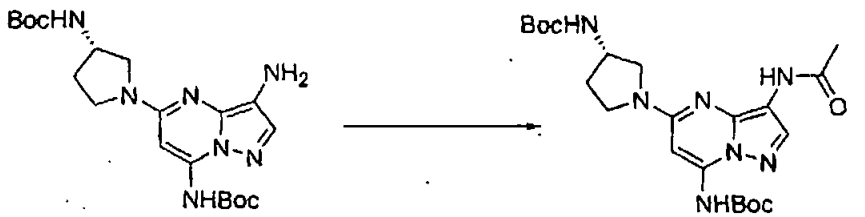
The title compound was prepared according to the procedure outlined in Preparative Example 2300-K except utilizing the 3-nitro derivative (0.20 g, 0.55 mmol) from Preparative Example 1800-K to afford 0.25 g (97% yield) of a yellow semisolid. LC-MS: 464.3 [M+H], purity 99%.

PREPARATIVE EXAMPLE 3200-K:



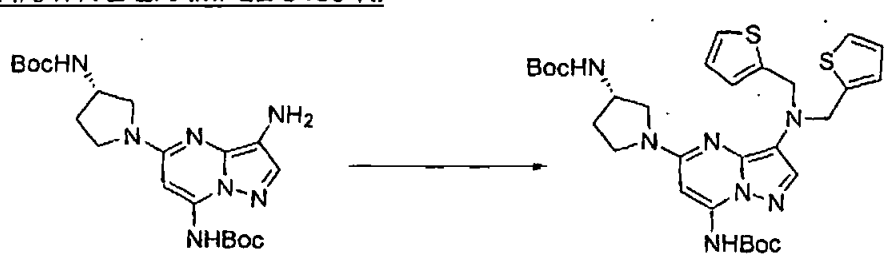
To a solution of 3-nitro adduct (70 mg, 0.15 mmol) from Preparative Example 3100-K in MeOH (2 mL) at rt was added Pd/C (10%, 25 mg dry). The mixture was stirred under H_2 (1 atm) for 12h whereupon the mixture was filtered thru a pad of Celite. The pad was washed generously with MeOH (2 x 4 mL) and the filtrate was concentrated under reduced pressure to afford 64 mg (98% yield) of a pink solid. LC-MS: 434.1 [M+H], purity 90%.

PREPARATIVE EXAMPLE 3300-K:



To a solution of 3-amino adduct (60 mg, 0.14 mmol) from Preparative Example 3200-K in CH_2Cl_2 (3 mL) at 0 °C was added Et_3N (29 μL, 0.21 mmol) followed by AcCl (12 μL, 0.17 mmol). The resulting mixture was stirred at rt for 12 h and was diluted with brine (3 mL) and CH_2Cl_2 (3 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 3 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by preparative thin-layer chromatography (2 x 1000 μM plates) using a 20:1 mixture of CH_2Cl_2/MeOH as eluent to afford 65 mg (68% yield) of a pink semisolid. LC-MS: 476.1 [M+H], purity 99%.

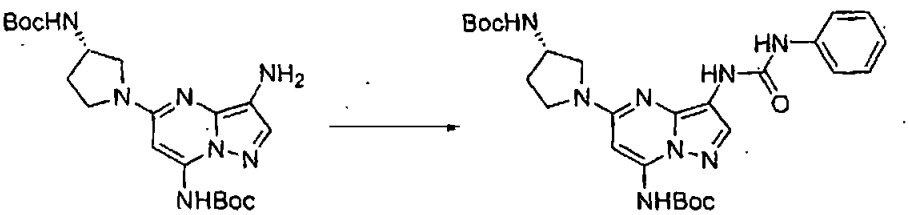
PREPARATIVE EXAMPLE 3400-K:



To a solution of 3-amino adduct (69 mg, 0.16 mmol) from Preparative Example 3200-K in CH_2Cl_2 (1 mL)/AcOH (0.1 mL) at 0 °C was added 2-thiophenecarboxaldehyde (18 μL, 0.19 mmol) followed by $NaB(OAc)_3H$ (41 mg, 0.19 mmol). The resulting mixture was stirred at rt for 12 h and was diluted with

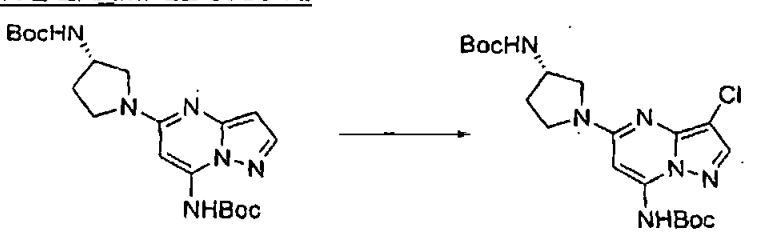
1N NaOH (1 mL) and CH_2Cl_2 (3 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 3 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by preparative thin-layer chromatography (2 x 1000 μM plates) using a 30:1 mixture of CH_2Cl_2/MeOH as eluent to afford 97 mg (96% yield) of a brown/orange oil. LC-MS: 626.1 [M+H], purity 96%.

PREPARATIVE EXAMPLE 3500-K:



To a solution of 3-amino adduct (90 mg, 0.21 mmol) from Preparative Example 3200-K in CH_2Cl_2 (1.5 mL) at 0 °C was added Et_3N (32 μL, 0.31 mmol) followed by PhNCO (27 μL, 0.25 mmol). The resulting mixture was stirred at rt for 12 h and was diluted with sat. aq. $NaHCO_3$ (2 mL) and CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 3 mL). The organic layers were combined, washed with brine (1 x 3 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by preparative thin-layer chromatography (2 x 1000 μM plates) using a 20:1 mixture of CH_2Cl_2/MeOH as eluent to afford 110 mg (95% yield) of a white solid. LC-MS: 553.1 [M+H], purity 99%.

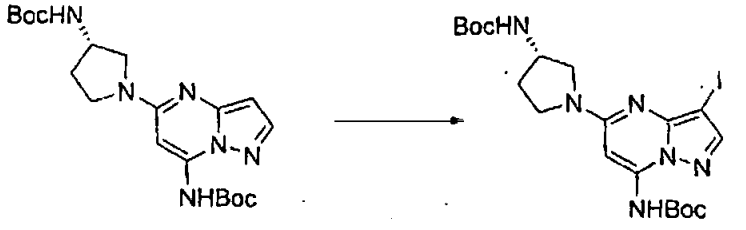
PREPARATIVE EXAMPLE 3600-K:



To a solution of 3-H adduct (0.15 g, 0.36 mmol) from Preparative Example 2507-K in CH_3CN (2 mL) at 0 °C was added NCS (48 mg, 0.36 mmol) in a single portion. The mixture was stirred for 3h at 0 °C whereupon the mixture was concentrated under reduced pressure. The crude product was purified by preparative thin-layer chromatography (4 x 1000 μM plates) using a 2:1 mixture

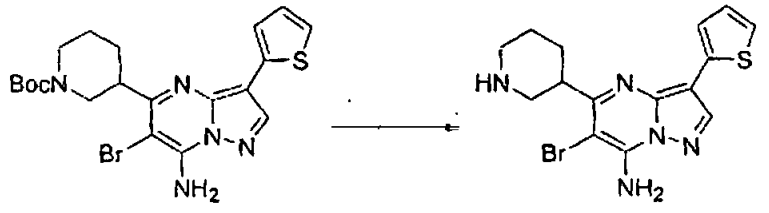
of hexanes/EtOAc as eluent to afford 0.16 g (98% yield) of a light yellow semisolid. LC-MS: 453.1 [M+H], purity 83%.

PREPARATIVE EXAMPLE 3700-K:



The title compound was prepared according to the procedure outlined in Preparative Example 3600-K utilizing the 3-H derivative (0.20 g, 0.55 mmol) from Preparative Example 2507-K and NIS (0.13 g, 0.60 mmol) to afford 0.25 g (97% yield) of a yellow semisolid. LC-MS: 464.3 [M+H], purity 99%.

EXAMPLE 100-K:



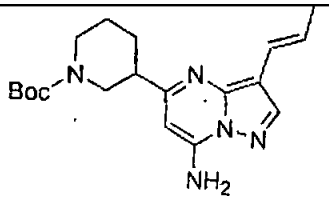
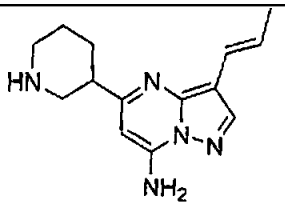
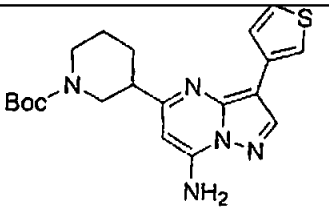
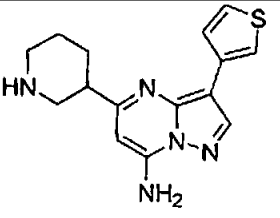
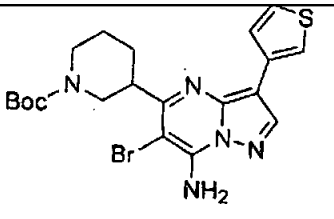
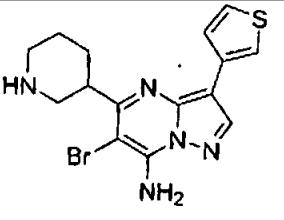
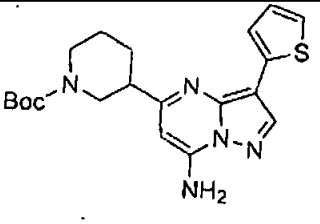
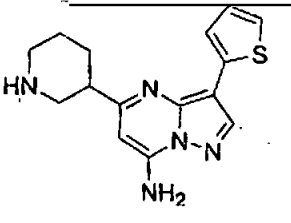
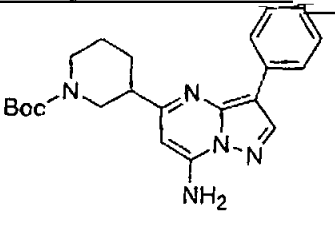
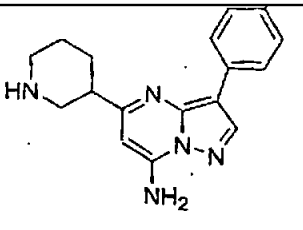
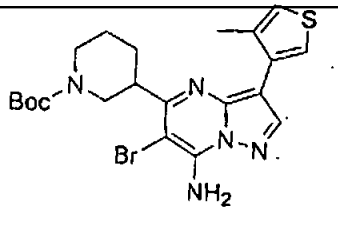
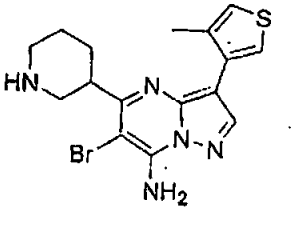
TFA (0.3 mL) was added under N_2 to a stirred solution of the product from Preparative Example 700-K (18 mg, 0.04 mmol) in CH_2Cl_2 (1.5 mL). The mixture was stirred for 1 hr, the solvent was evaporated, and the residue was mixed with solid Na_2CO_3 (100 mg) and 10:1 CH_2Cl_2/MeOH (2.0 mL). The mixture was stirred under N_2 for 10 min, the solution was withdrawn and loaded onto a silica gel preparative TLC plate, which was then developed with 10:1 CH_2Cl_2/7N NH_3 in MeOH. Pale yellow solid (5 mg, 35%) was obtained. LC-MS: 380 [M+H]. Mp = 106-109°C. SCH 773943

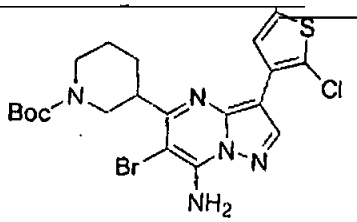
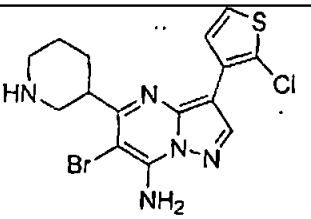
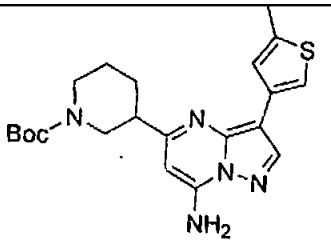
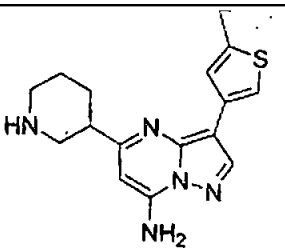
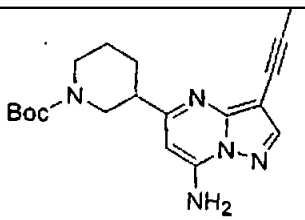
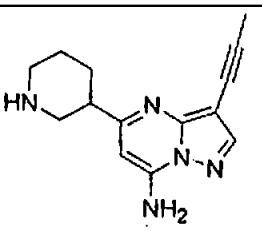
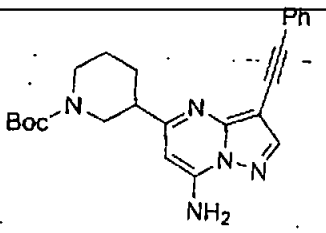
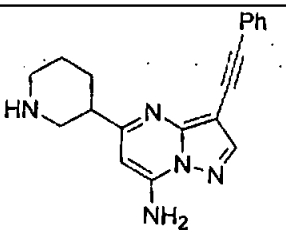
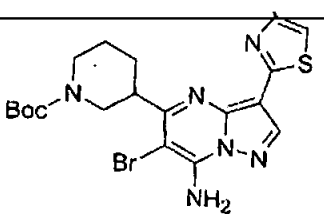
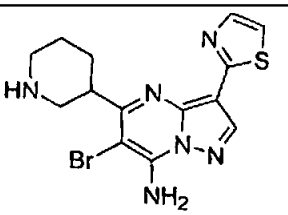
EXAMPLES 101-K -123-K:

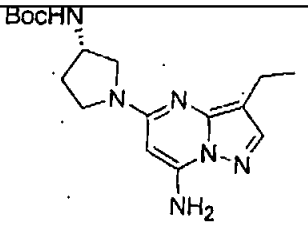
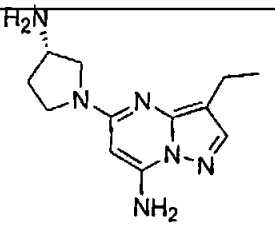
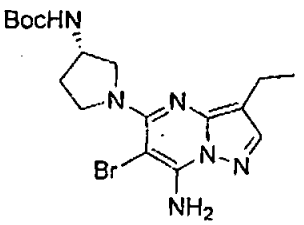
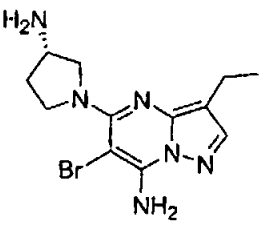
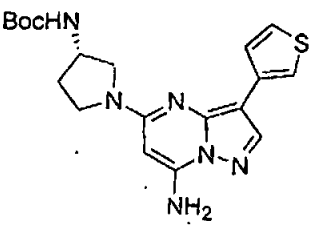
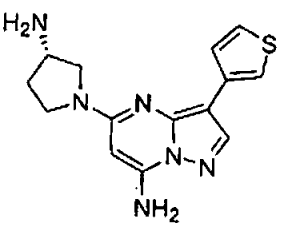
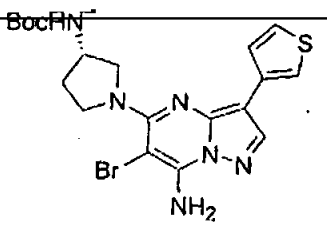
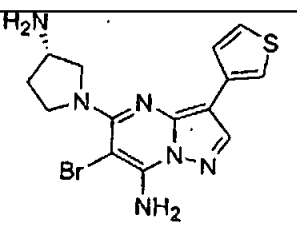
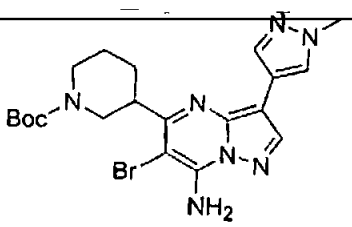
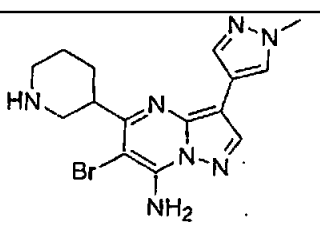
By essentially the same procedure set forth in Example 100-K only substituting the compounds shown in Column 2 of Table 800-K, the compounds shown in Column 3 of Table 800-K were prepared.

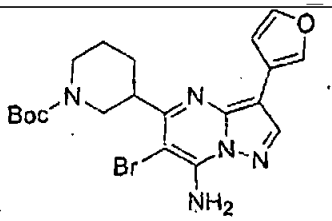
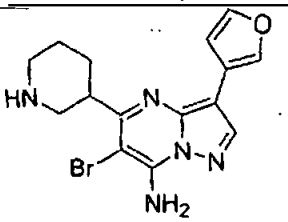
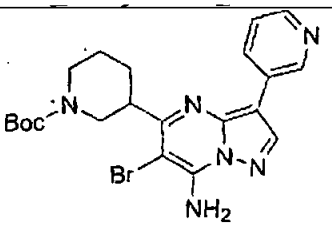
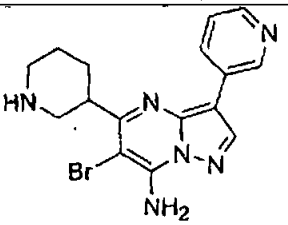
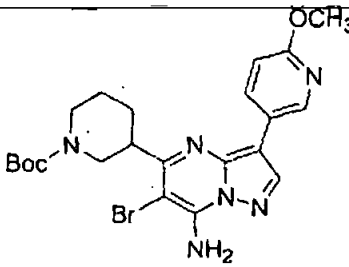
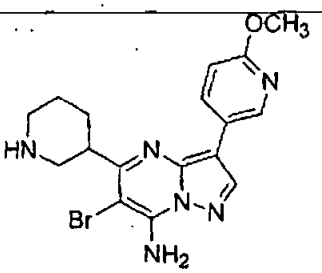
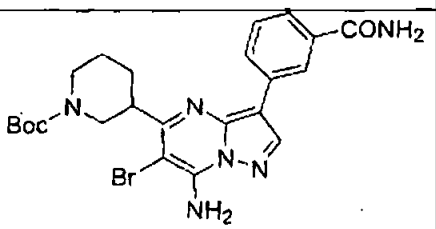
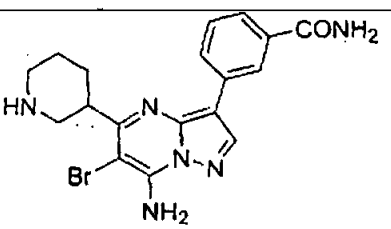
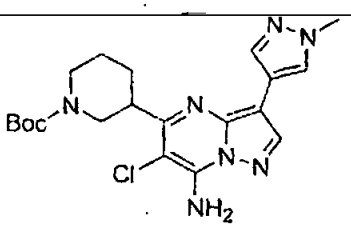
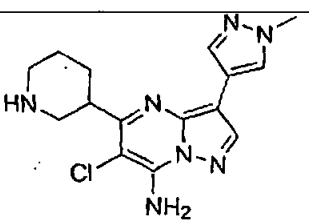
TABLE 800-K

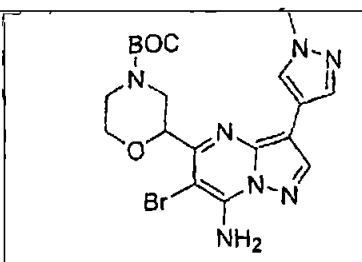
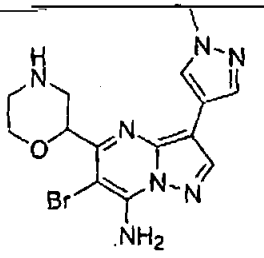
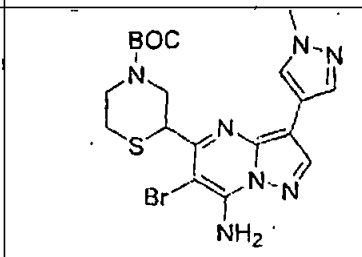
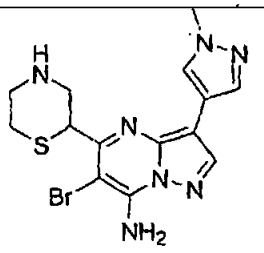
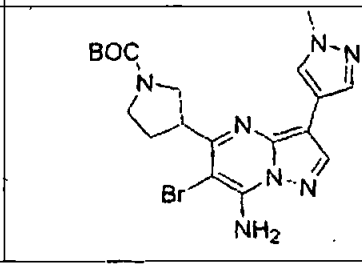
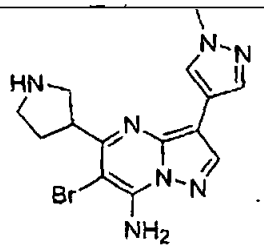
Ex.	Column 2	Column 2	Data

101 -K			LCMS: MH^+=258 mp = 200-202°C
102 -K			LCMS: MH^+=300 mp = 104-106°C
103 -K			LCMS: MH^+=380
104 -K			LCMS: MH^+=300 mp = 191-193°C
105 -K			
106 -K			mp = 157-159°C

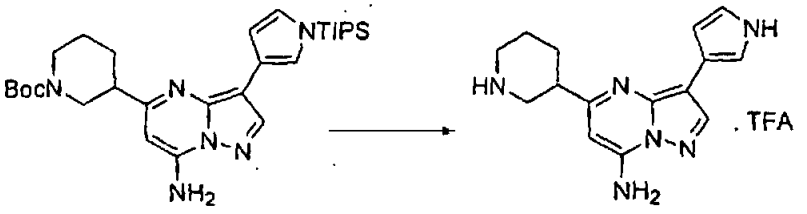
107 -K			LCMS: MH^+=414 mp = 96-99°C
108 -K			LCMS: $M2H^+$=394
109 -K			LCMS: MH^+=256 wax
110 -K			LCMS: MH^+=318 wax
111 -K			LCMS: M^+=379 mp = 247-249°C

112 -K			LCMS: MH^+=247 mp = 148-150°C
113 -K			LCMS: MH^+=327 mp = 114-116°C
114 -K			LCMS: MH^+=301 mp = 227-229°C
115 -K			LCMS: MH^+=379 mp = 156-158°C
118 -K			LCMS: M^+=376 mp = 95-98°C

119 -K			LCMS: M^+=362 mp = 161-163°C.
120 -K			LCMS: M^+=373 mp = 220-222°C
121 -K			LCMS: M^+=403 mp = 95-98°C
122 -K			LCMS: M^+=415 mp = 90-93°C
123 -K			LCMS: M^+=332 mp = 200-203°C.

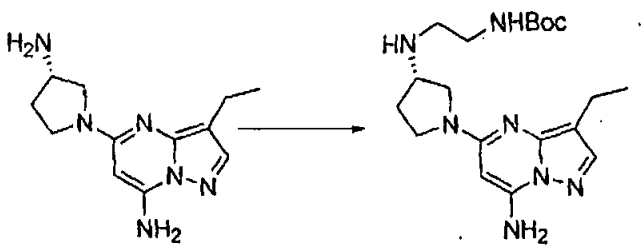
124 -K			
125 -K			
126 -K			

EXAMPLE 200-K:



TFA (0.5 mL) was added under N_2 to a stirred solution of the product from Preparative Example 604-K (30 mg, 0.056 mmol) in CH_2Cl_2 (1.0 mL). The mixture was stirred for 4 hr, the solvent was evaporated, and the residue was mixed with solid NaHCO3 (200 mg) and 4:1 CH_2Cl_2/MeOH (5 mL). The mixture was stirred under N_2 for 30 min, additional CH2Cl2 (5 mL) was then added, the mixture was filtered through Celite, and the solvent was evaporated. Pale brown wax (31 mg) was obtained. LC-MS: 284 [M+2H].

EXAMPLE 300-K:

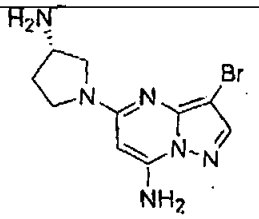
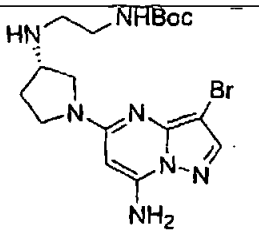
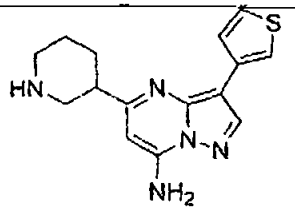
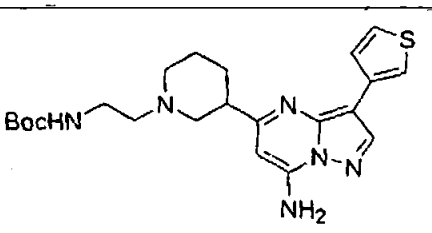


A mixture of the product from Example 112-K (70 mg, 0.29 mmol) and tert-butyl N-(2-oxoethyl)carbamate (45 mg,0.29 mmol) in anhydrous CH_2Cl_2 (2 mL) was stirred under N_2 at 25°C for 1 hr. Then $NaBH(OAc)_3$ (106 mg, 0.50 mmol) was added, the mixture was stirred for 1 hr, and then quenched with MeOH (2 mL). The solvents were evaporated and the residue was purified by column chromatography on silica gel with 20:1 CH_2Cl_2/ 7 N NH_3 in MeOH as eluent. White solid (84 mg, 76 %) was obtained. LC-MS: 390 [M+H]. Mp = 75-78°C.

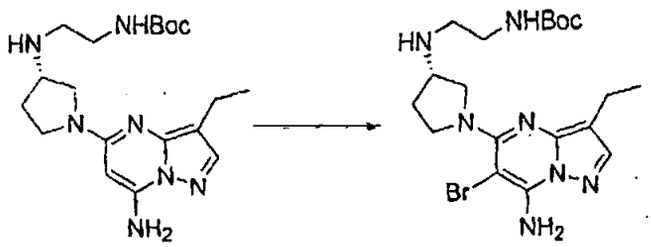
EXAMPLE 401-K - 402-K:

By essentially same procedure set forth in Example 300-K only substituting the compounds shown in Column 2 of Table 900-K, the compounds shown in Column of Table 900-K were prepared.

TABLE 900-K

Ex.	Column 2	Column 3	Data
401 -K			white solid LC-MS: 440 [M+].
402 -K			pale yellow wax . LC-MS: 443 [M+H].

EXAMPLE 500-K:

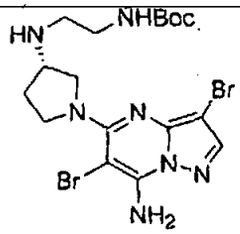
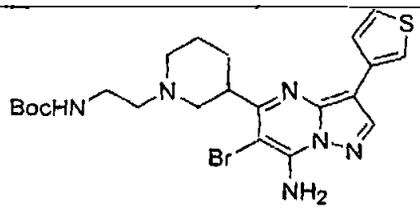


A solution of NBS (23 mg, 0.13 mmol) in anhydrous CH_3CN (1.0 mL) was added under N_2 to a stirred solution of the product from Example 300-K (50 mg, 0.13 mmol) in anhydrous CH_3CN (2.0 mL) and CH_2Cl_2 (1.0 mL). The mixture was stirred for 20 hr, the solvents were evaporated, and the residue was purified by column chromatography on silica gel with 20:1 CH_2Cl_2/MeOH as eluent. White solid (38 mg, 63 %) was obtained. LC-MS: 468 [M+]. Mp = 150-152°C.

EXAMPLE 500-K - 502-K:

By essentially same procedure set forth in Example 500-K, compounds shown in Column 2 of Table 930-K were prepared.

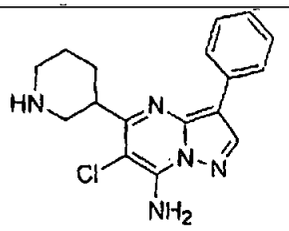
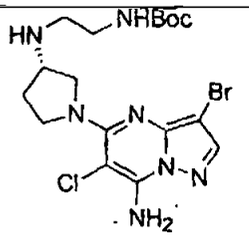
TABLE 930-K

Ex.	Column 2	Data
501-K		colorless solid. LC-MS: 520 [M+H].
502-K		pale yellow wax LC-MS: 523 [M+H]. SCH 785438

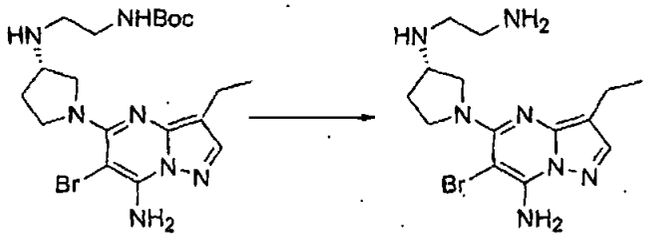
EXAMPLE 701-K - 702-K:

By essentially same procedure set forth in Example 500-K only substituting N-chlorosuccinimide, compounds shown in Column 2 of Table 940-K were prepared.

TABLE 940-K

Ex.	Column 2	Data
701 -K		LCMS: M^+= mp =
702 -K		white solid. LC-MS: 476 [M+H].

EXAMPLE 800-K:

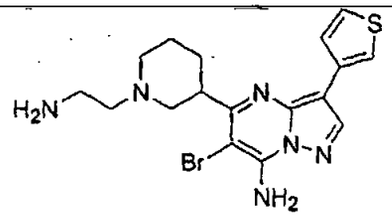
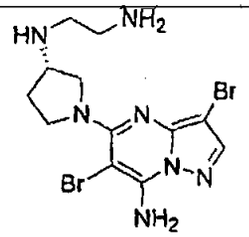
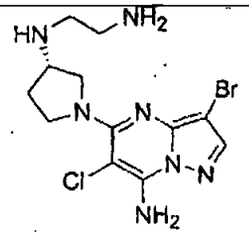


TFA (0.4 mL) was added under N_2 to a stirred solution of the product from Example 500-K (30 mg, 0.064 mmol) in CH_2Cl_2 (2.0 mL). The mixture was stirred for 1 hr, the solvent was evaporated, and the residue was mixed with solid Na_2CO_3 (200 mg) and 10:1 CH_2Cl_2/MeOH (2.0 mL). The mixture was stirred under N_2 for 10 min, the solution was withdrawn and loaded onto a silica gel preparative TLC plate, which was then developed with 10:1 CH_2Cl_2/7N NH_3 in MeOH. White solid (10 mg, 42%) was obtained. LC-MS: 368 [M+]. Mp = 132-135°C.

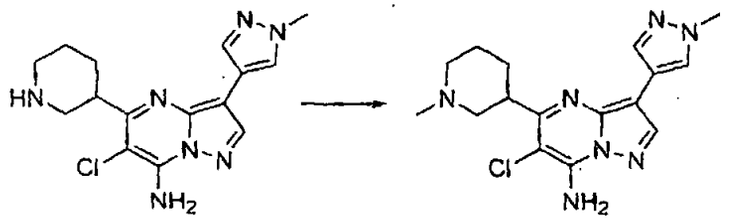
EXAMPLES 801-K - 803-K:

By essentially same procedure set forth in Example 800-K, compounds shown in Column 2 of Table 950-K were prepared:

TABLE 950-K

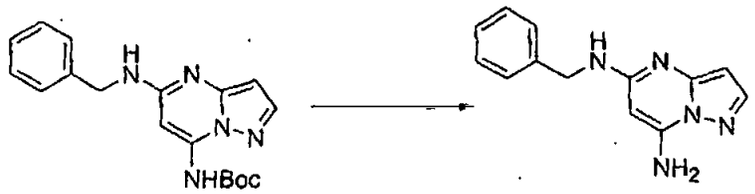
Ex.	Column 2	Data
801 -K		pale yellow solid LC-MS: 421 [M+H]. Mp = 148-150°C.
802 -K		white solid LC-MS: 420 [M+H]. Mp = 92-95°C.
803 -K		pale yellow solid. LC-MS: 376 [M+H]. Mp = 138-140°C.

EXAMPLE 900-K:



A solution of 37% HCHO (0.002 mL) in H_2O (0.02 mL) was added under N2 to a stirred solution of the product from Preparative Example 823-K (9 mg, 0.027 mmol) in anhydrous THF (1 mL) an MeOH (0.3 mL) and then the mixture was stirred under N_2 at 25°C for 5 hr. Then $NaBH(OAc)_3$ (8 mg, 0.038 mmol) was added and the mixture was stirred for 1 hr. The solvents were evaporated and the residue was purified by preparative TLC on silica gel with 10:1 CH_2Cl_2/ 7 N NH_3 in MeOH as eluent. White solid 8 mg, 85 %) was obtained. LC-MS: 346 [M+]. Mp = 92-95°C.

PREPARATIVE EXAMPLE 3800-K:

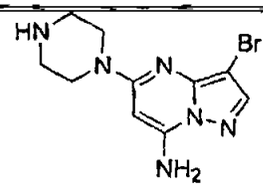


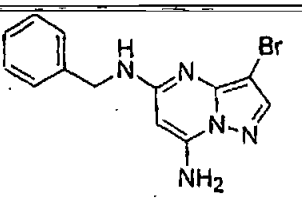
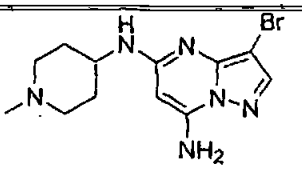
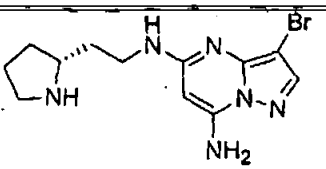
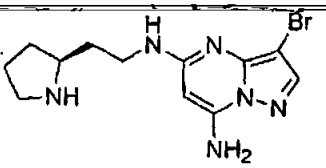
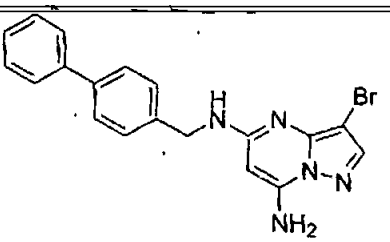
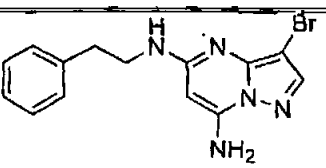
To a mixture of 7-amino adduct (65 mg, 0.19 mmol) from Preparative Example 2500-K in CH_2Cl_2 (2 mL) at 0 °C was added TFA (1 mL) dropwise. The resulting mixture was stirred for 12 h at rt and was concentrated under reduced pressure. The crude material was partitioned between EtOAc (5 mL) and sat. aq. Na_2CO_3 (2 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL) and the organic layers were combined. The organic layer was washed with brine (1 x 3 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by preparative thin-layer chromatography (4 x 1000 μM plates) using a 20:1 mixture of CH_2Cl_2/MeOH (7M NH_3) as eluent to afford 41 mg (89% yield) as a brown solid. mp 111-113 °C; LC-MS: 240.0 [M+H], purity 98%.

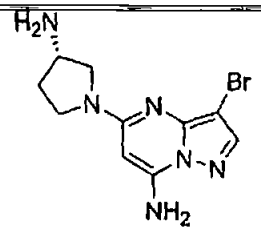
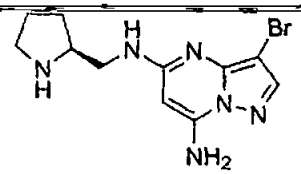
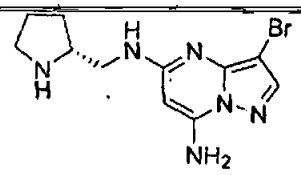
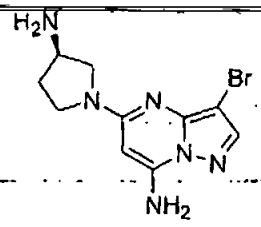
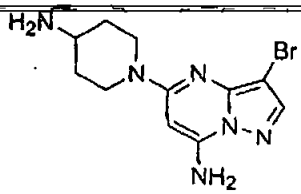
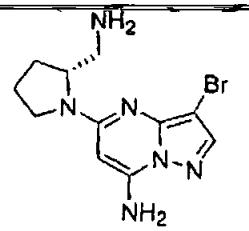
EXAMPLES 1000-1025-K:

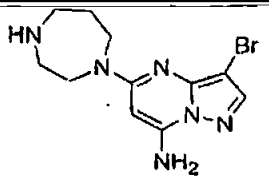
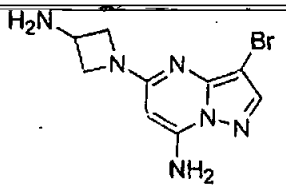
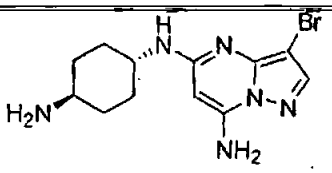
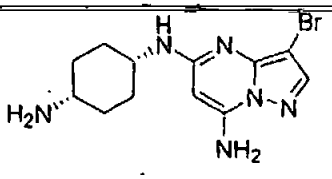
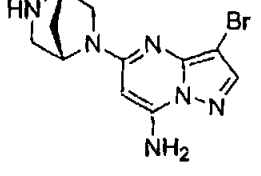
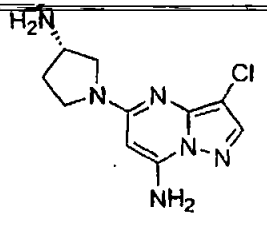
By essentially the same procedure set forth in Preparative Example 3800-K but utilizing the appropriate Boc derivatives, the compounds in Column 2 of Table 1000-K were prepared.

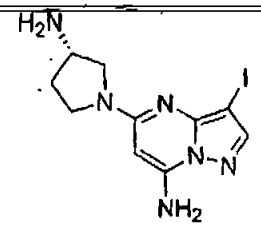
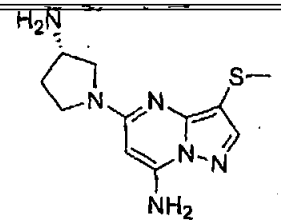
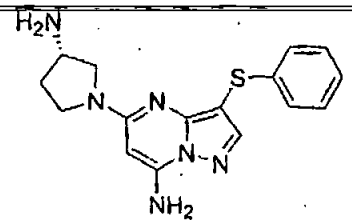
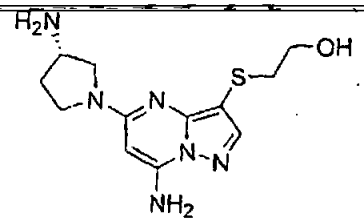
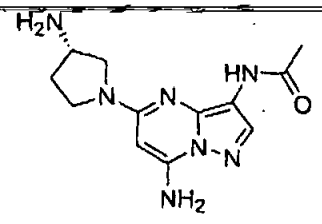
TABLE 1000-K

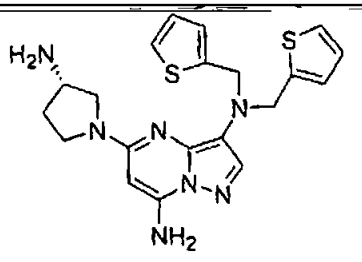
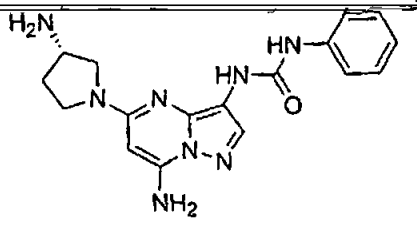
Ex.	*Column 2*	1.Yield (%) 2. LC-MS 3. mp
1000-K		1. 10 2. 297.1 3. 138-141

1001-K		1. 95 2. 320.1 3. 115-117
1002-K		1. 70 2. 327.1 3. 110-113
1003-K		1. 26 2. 325.1 3. 114-117
1004-K		1. 46 2. 325.1 3. 105-107
1005-K		1. 81 2. 394.1 3. 166-168
1006-K		1. 90 2. 334.1 3. 43-45

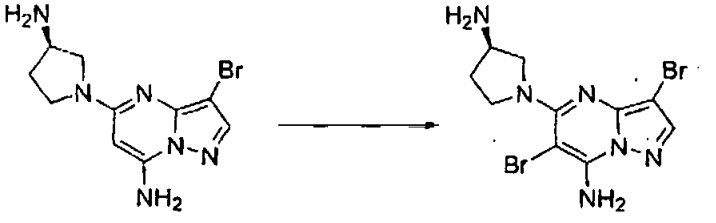
1007-K		1. 45 2. 299.1 3. 115-117
1008-K		1. 73 2. 313.1 3. 131-133
1009-K		1. 62 2. 313.1 3. 130-134
1010-K		1. 88 2. 299.1 3. 114-117
1011-K		1. 67 2. 313.1 3. 169-171
1012-K		1. 36 2. 313.1 3. 90-93

1013-K		1. 89 2. 313.1 3. 154-156
1014-K		1. 30 2. 285.3
1015-K		1. 83 2. 325.1 3. 115-117
1016-K		1. 80 2. 325.1 3. 105-107
1017-K		1. 64 2. 311.1 3. 98-102
1018-K		1. 79 2. 253.1 3. 188-190

1019-K		1. 20 2. 345.2 3. 127-129
1020-K		1. 70 2. 265.1 3. 120-122
1021-K		1. 87 2. 327.1 3. xxx-xxx
1022-K		1. 21 2. 295.1 3. xxx-xxx
1023-K		1. 17 2. 276.1

1024-K		1. 21 2. 295.1 3. xxx-xxx
1025-K		1. 20 2. 353.2 3. >200

EXAMPLE 1100-K:

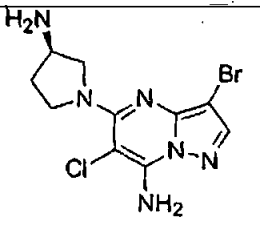
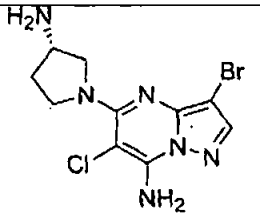
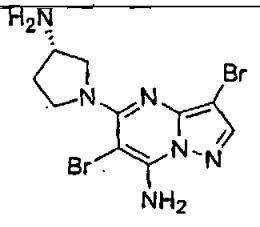
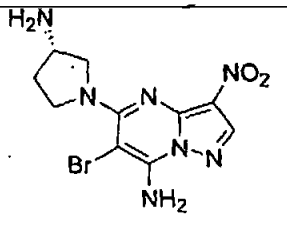
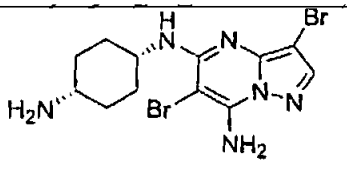


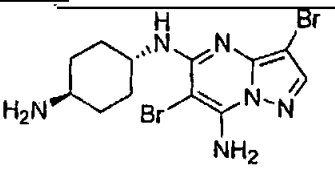
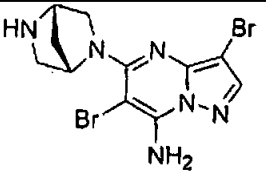
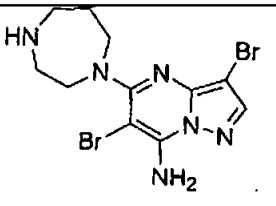
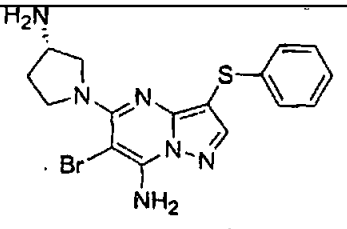
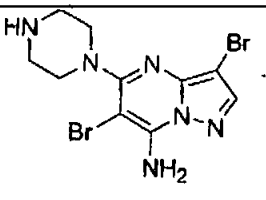
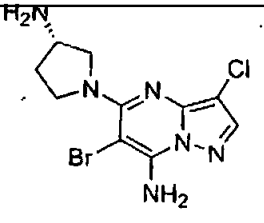
To a solution of 7-amino adduct (20 mg, 0.067 mmol) from Example 1010-K in CH_3CN at 0 °C was added NBS (12 mg, 0.067 mmol) in a single portion. The mixture was stirred for 2 hours at rt and was concentrated under reduced pressure. The crude product was purified by preparative thin-layer chromatography (2 x 1000 μM plates) using a 10:1 mixture of CH_2Cl_2/MeOH(7M NH_3) as eluent to afford 20 mg (79% yield) as a light orange solid. mp 159-161 °C. LC-MS: 377.1 [M+H], purity 99%.

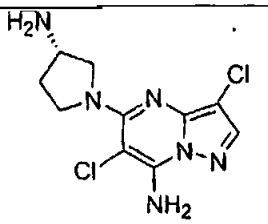
EXAMPLES 1101-K - 1112-K:

Following the procedure set forth in Example 1100-K and utilizing either NBS, NCS, or NIS the compounds in Column 3 of Table 1100-K were prepared.

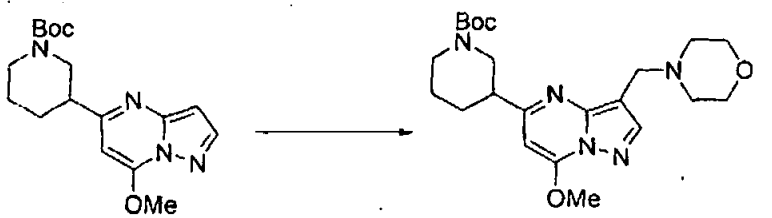
TABLE 1100-K

Prep. Ex.	*Column 2*	*Column 3*	1.Yield (%) 2. LC-MS 3. mp (°C)
1101-K	NCS		1. 41 2. 333.2 3. 123-125
1102-K	NCS		1. 64 2. 333.2 3. 122-125
1103-K	NBS		1. 66 2. 377.2 3. 159-161
1104-K	NBS		1. 38 2. 344.1 3. xxx-xxx
1105-K	NBS		1. 89 2. 403.1 3. 66-68

1106-K	NBS		1. 90 2. 403.1 3. 170-172
1107-K	NBS		1. 53 2. 389.1 3. xxx-xxx
1108-K	NBS		1. 48 2. 391.1 3. 142-144
1109-K	NBS		1. 59 2. 407.2 3. 156-158
1110-K	NBS		1. 75 2. 375.1 3. 134-136
1111-K	NBS		1. 63 2. 333.1 3. 153-155

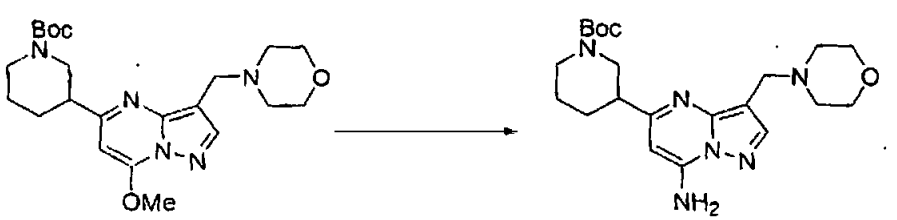
1112-K	NCS		1. 15 2. 287.1 3. >200

PREPARATIVE EXAMPLE 3900-K:



To a solution of 7-methoxy adduct (0.10 g, 0.30 mmol) from Preparative Example 402-K in AcOH at rt was added morpholine (29 μL, 0.33 mmol) followed by 40% formaldehyde in H_2O (1 mL). The resulting mixture was stirred at rt for 12h whereupon the mixture was concentrated under reduced pressure. The crude semisolid was partitioned between CH_2Cl_2 (5 mL) and sat. aq. $NaHCO_3$ (3 mL) and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL) and the organic layers were combined. The organic layer was washed with brine (1 x 3 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 0.11 g (84% crude yield) of a light yellow semisolid. LC-MS: 432.1 [M+H], purity 94%.

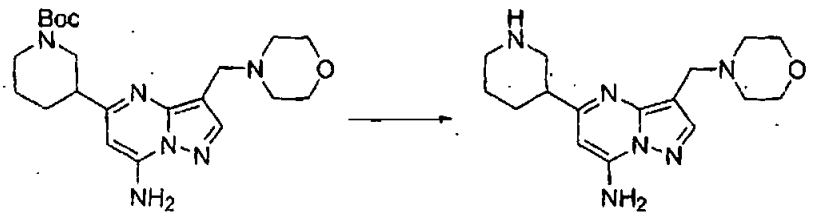
PREPARATIVE EXAMPLE 4000-K:



To a pressure tube charged with a stir bar was added 7-methoxy (96 mg, 0.22 mmol) from Preparative Example 3900-K followed by 2M NH_3 in IPA (2 mL) and conc. NH_4OH (2 mL). The tube was capped and was heated to 85 °C and stirred for 14h. The mixture was cooled to rt, concentrated under reduced pressure, and placed under high vacuum to remove trace volatiles. The crude product was purified by preparative thin-layer chromatography (4 x 1000 μM)

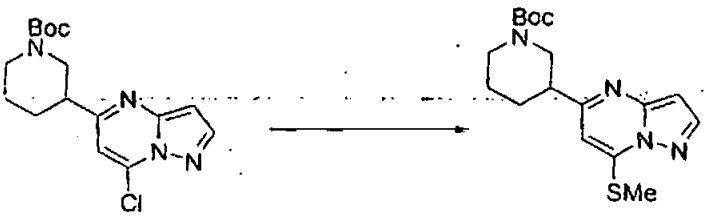
plates using a 10:1 mixture of CH_2Cl_2/MeOH as eluent to afford 40 mg (43% yield) of a yellow semisolid. LC-MS: 417.1 [M+H], purity 89%.

EXAMPLE 1200-K:



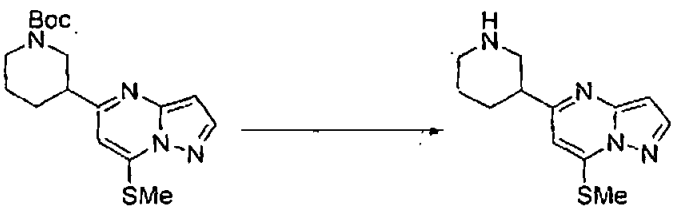
To a mixture of 7-amino adduct (40 mg, 0.096 mmol) from Preparative Example 4000-K was added 4N HCl/dioxane (3 mL) dropwise. The resulting mixture was stirred for 12 h at rt and was concentrated under reduced pressure. The crude material was taken up in CH_2Cl_2 (5 mL) and was concentrated under reduced pressure and this procedure was repeated 3x. The resulting solid was triturated with Et2O (3 x 3 m) and was concentrated under reduced pressure to afford 26 mg (75 % yield) of a light yellow solid. mp 190-193 °C; LC-MS: 317.1 [M+H], purity >90%.

PREPARATIVE EXAMPLE 4100-K:



The title compound was prepared from 7-chloro adduct (2.6 g, 7.7 mmol) from Preparative Example 200-K and NaSMe (0.65 g, 9.3 mmol) according to the procedure outlined in Preparative Example 1 to afford 2.6 g (98% yield) of a pale white solid. LC-MS: 349.1 [M+H], purity. 98%.

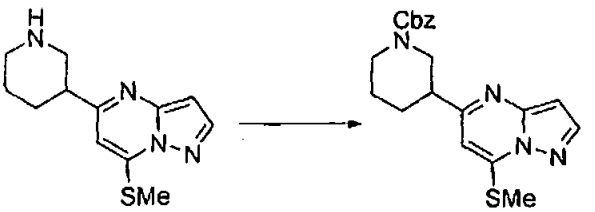
PREPARATIVE EXAMPLE 4200-K:



The above compound was prepared from 7-thiomethyl adduct (1.1 g, 3.1 mmol) from Preparative Example 4100-K according to the procedure outlined in

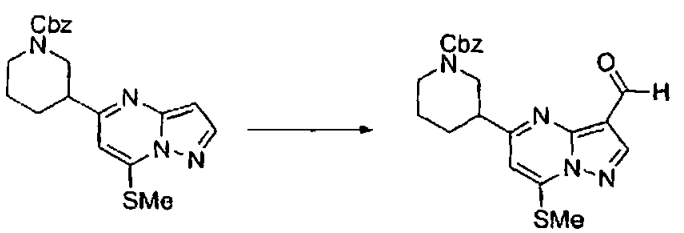
Example 1 to afford 0.70 g (90% yield) of a yellow semisolid. LC-MS: 249.1 [M+H], purity 98%.

PREPARATIVE EXAMPLE 4300-K:



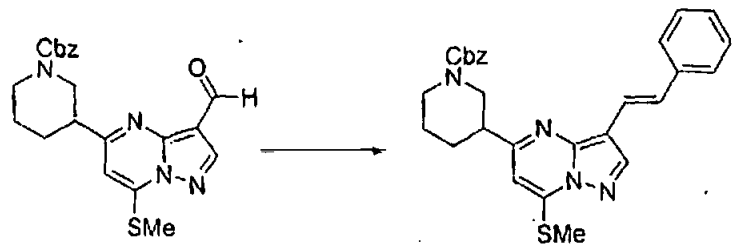
To a solution of thiomethyl adduct (1.3 g, 3.13 mmol) from Preparative Example 4200-K in CH_2Cl_2 (20 mL) at 0 °C was added Et_3N (0.65 mL, 4.7 mmol) followed by CbzCl (0.48 mL, 3.4 mmol). The resulting mixture was stirred for 12h at rt and the mixture was diluted CH_2Cl_2 (15 mL) and sat. aq. $NaHCO_3$ (5 mL) and 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 5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using CH_2Cl_2 as eluent to afford 0.96 g (80% yield) of a yellow oil. LC-MS: 383.1 [M+H], purity 91%.

PREPARATIVE EXAMPLE 4400-K:



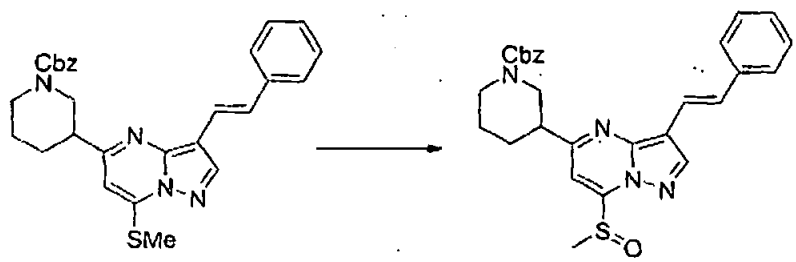
To a solution of 7-thiomethyl adduct (0.29 g, 0.75 mmol) from Preparative Example 4300-K in DMF (3 ml) at 0 °C was added $POCl_3$ (0.10 mL, 1.1 mmol). The resulting mixture was allowed to warm to rt and stir for 12h. The mixture was cooled to 0 oC and was treated with ice water (2 ml) and CH_2Cl_2 (5 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, washed with brine (1 x 5 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 0.28 g (91% yield) of a yellow solid. LC-MS: 433.2 [M+H], purity 84%.

PREPARATIVE EXAMPLE 4500-K:



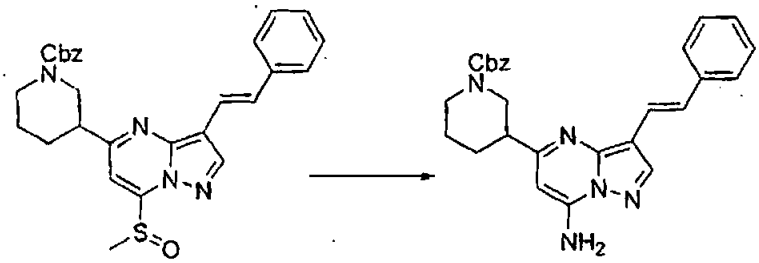
To a mixture of benzyltriphenyphosphonium bromide (0.64 g, 1.48 mmol) and NaH (59 mg, 1.48 mmol) in dry THF (3 mL) at rt was added thiomethyl adduct (0.21 g, 0.50 mmol) from Preparative Example 4400-K. The mixture was heated at reflux for 12h, cooled to rt, and diluted with CH_2Cl_2 (5 mL) and brine (2 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, 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 by preparative thin-layer chromatography (2 x 1000 μM plates) using a 1:1 mixture of hexanes/EtOAc as eluent to afford 100 mg (42% yield) as a light orange solid.

PREPARATIVE EXAMPLE 4600-K:



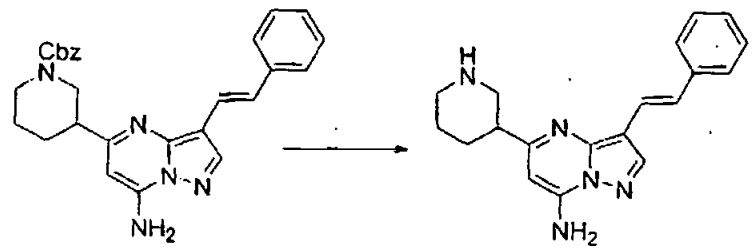
The title compound was prepared from 7-thiomethyl adduct (0.10 g, 0.21 mmol) from Preparative Example 4500-K according to the procedure outlined in Preparative Example 1500-K to afford 0.11 g (quantitative yield) of a yellow solid. LC-MS: 501.3 [M+H], purity 63%.

PREPARATIVE EXAMPLE 4700-K:



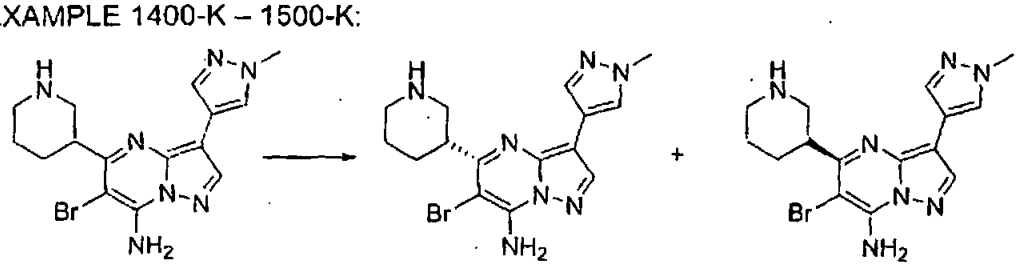
The title compound was prepared from 7-sulfoxide adduct (0.11 g, 0.21 mmol) from Preparative Example 4600-K according to the procedure outlined in Preparative Example 1800-K to afford 83 mg (40% yield) of a yellow solid. LC-MS: 454.1 [M+H], purity 90%.

EXAMPLE 1300-K:



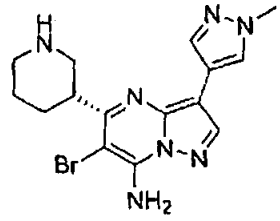
To a solution of 7-amino adduct (38 mg, 0.083 mmol) from Preparative Example 4700-K in CH_3CN (3 mL) at 0 °C was added TMSI (0.12 mL, 0.83 mmol) dropwise. The mixture was stirred for 12h at rt whereupon 1N NaOH (2 mL) was added. The mixture was extracted with EtOAc (5 x 5 mL) and the organic layers were combined. The organic layer was washed with brine (1 x 3 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude product was purified by preparative thin-layer chromatography (2 x 1000 μM plates) using a 10:1 mixture of CH_2Cl_2/MeOH(7M NH_3) as eluent to afford 15 mg (56% yield) as a light yellow solid. mp 144-146 °C. LCMS: 319.4 [M+H} 90% purity.

EXAMPLE 1400-K – 1500-K:

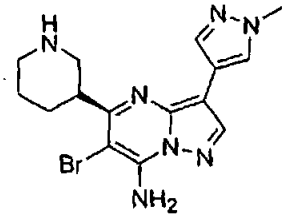


The compound prepared in Example 118-K was separated into individual enantiomers by semi-preparative HPLC using a ChiralPak OD column (flow rate = 9 mL/min) and a gradient of 85 : 15 hexanes : isopropanol with 0.2% diethylamine to 75 : 25 hexanes : isopropanol solution with 0.2% diethylamine as eluent.

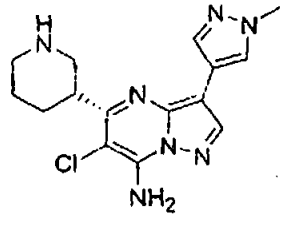
Example 1400-K (first eluting isomer, (R)): LCMS: M^+ = 376.



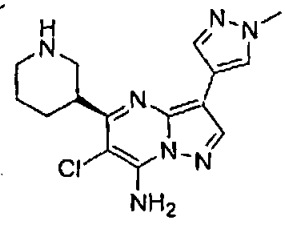
Example 1500-K (second eluting isomer, (S)): M^+ = LCMS: 376:



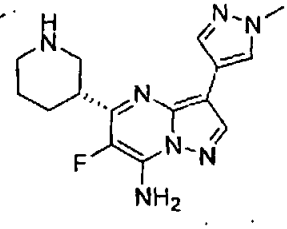
Example 1600K-, Example 1700-K, Example 1800-K and Example 1900-K: By a similar procedure, the following compounds can also be prepared:



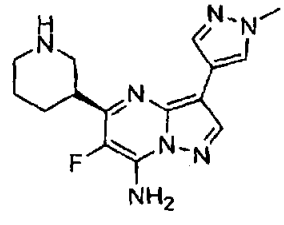
1600-K



1700-K



1800-K



1900-K

ASSAY:

BACULOVIRUS CONSTRUCTIONS: Cyclins A and E were cloned into pFASTBAC (Invitrogen) by PCR, with the addition of a GluTAG sequence

(EYMPME) at the amino-terminal end to allow purification on anti-GluTAG affinity columns. The expressed proteins were approximately 46kDa (cyclin E) and 50kDa (cyclin A) in size. CDK2 was also cloned into pFASTBAC by PCR, with the addition of a haemaglutinin epitope tag at the carboxy-terminal end (YDVPDYAS). The expressed protein was approximately 34kDa in size.

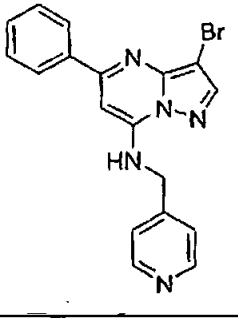
ENZYME PRODUCTION: Recombinant baculoviruses expressing cyclins A, E and CDK2 were infected into SF9 cells at a multiplicity of infection (MOI) of 5, for 48 hrs. Cells were harvested by centrifugation at 1000 RPM for 10 minutes. Cyclin-containing (E or A) pellets were combined with CDK2 containing cell pellets and lysed on ice for 30 minutes in five times the pellet volume of lysis buffer containing 50mM Tris pH 8.0, 0.5% NP40, 1mM DTT and protease/phosphatase inhibitors (Roche Diagnostics GmbH, Mannheim, Germany). Mixtures were stirred for 30-60 minutes to promote cyclin-CDK2 complex formation. Mixed lysates were then spun down at 15000 RPM for 10 minutes and the supernatant retained. 5ml of anti-GluTAG beads (for one liter of SF9 cells) were then used to capture cyclin-CDK2 complexes. Bound beads were washed three times in lysis buffer. Proteins were competitively eluted with lysis buffer containing 100-200ug/mL of the GluTAG peptide. Eluate was dialyzed overnight in 2 liters of kinase buffer containing 50mM Tris pH 8.0, 1mM DTT, 10mM MgCl2, 100uM sodium orthovanadate and 20% glycerol. Enzyme was stored in aliquots at -70°C.

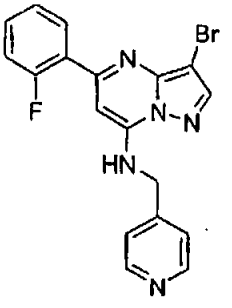
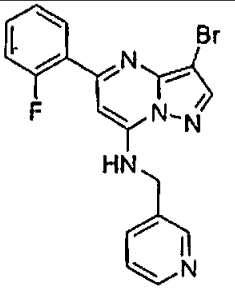
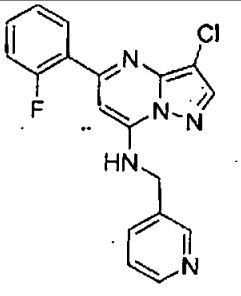
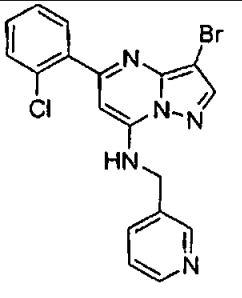
IN VITRO KINASE ASSAY: CDK2 kinase assays (either cyclin A or E-dependent) were performed in low protein binding 96-well plates (Corning Inc, Corning, New York). Enzyme was diluted to a final concentration of 50 μg/ml in kinase buffer containing 50mM Tris pH 8.0, 10mM $MgCl_2$, 1mM DTT, and 0.1mM sodium orthovanadate. The substrate used in these reactions was a biotinylated peptide derived from Histone H1 (from Amersham, UK). The substrate was thawed on ice and diluted to 2 μM in kinase buffer. Compounds were diluted in 10%DMSO to desirable concentrations. For each kinase reaction, 20 μl of the 50 μg/ml enzyme solution (1 μg of enzyme) and 20 μl of the 1 μM substrate solution

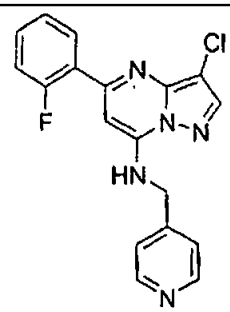
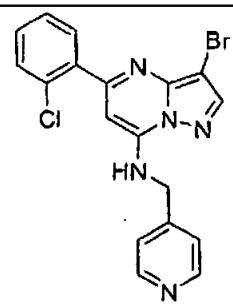
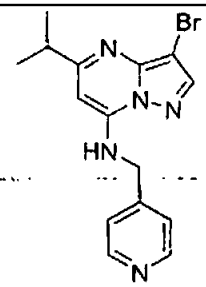
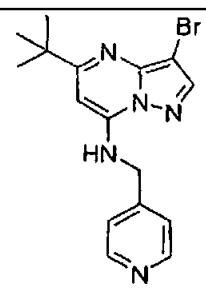
were mixed, then combined with 10 µl of diluted compound in each well for testing. The kinase reaction was started by addition of 50 µl of **4** µM ATP and **1** µCi of 33P-ATP (from Amersham, UK). The reaction was allowed to run for 1 hour at room temperature. The reaction was stopped by adding 200 µl of stop buffer containing 0.1% Triton X-100, 1mM ATP, 5mM EDTA, and 5 mg/ml streptavidine coated SPA beads (from Amersham, UK) for 15 minutes. The SPA beads were then captured onto a 96-well GF/B filter plate (Packard/Perkin Elmer Life Sciences) using a Filtermate universal harvester (Packard/Perkin Elmer Life Sciences.). Non-specific signals were eliminated by washing the beads twice with 2M NaCl then twice with 2 M NaCl with 1% phosphoric acid. The radioactive signal was then measured using a TopCount 96 well liquid scintillation counter (from Packard/Perkin Elmer Life Sciences).

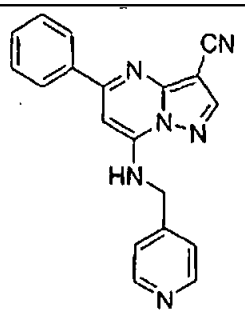
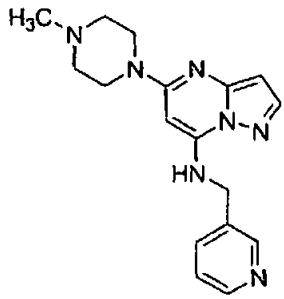
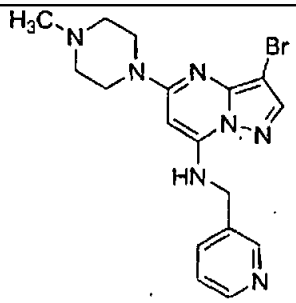
IC_{50} DETERMINATION: Dose-response curves were plotted from inhibition data generated, each in duplicate, from 8 point serial dilutions of inhibitory compounds. Concentration of compound was plotted against % kinase activity, calculated by CPM of treated samples divided by CPM of untreated samples. To generate IC_{50} values, the dose-response curves were then fitted to a standard sigmoidal curve and IC_{50} values were derived by nonlinear regression analysis. The thus-obtained IC_{50} values for the compounds of the invention are shown in **Table 87**. These kinase activities were generated by using cyclin A or cyclin E using the above-described assay.

Table 87

CMPD	Example	IC_{50} (µM)
	1	0.020 0.029

	3	0.032 0.024
	4	0.011
	5	0.021
	8	0.003

	6	0.064 0.029
	7	0.01 0.006
	10	0.042
	12	0.17

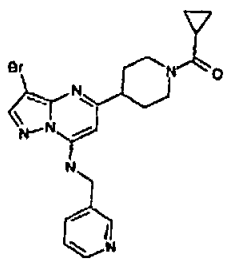
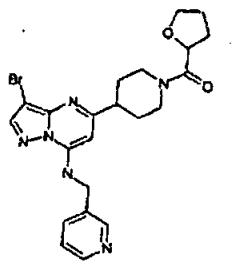
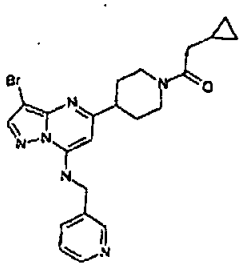
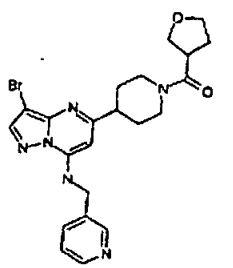
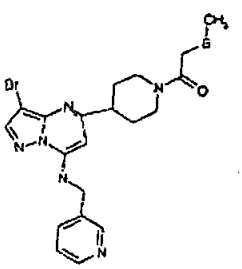
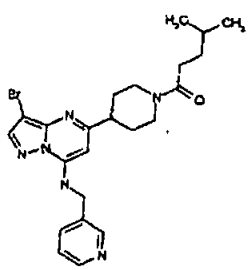
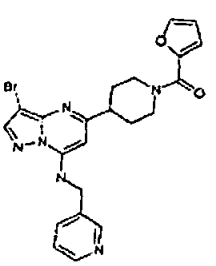
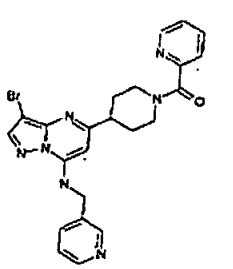
	16	0.62
	1	5.6
	3	0.14

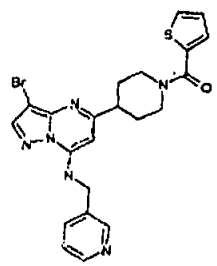
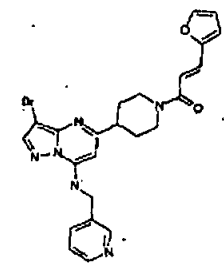
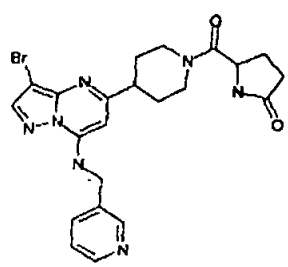
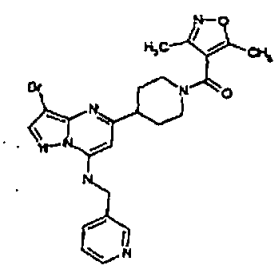
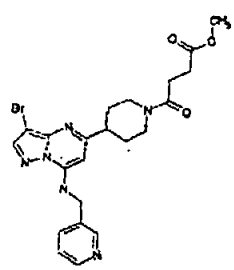
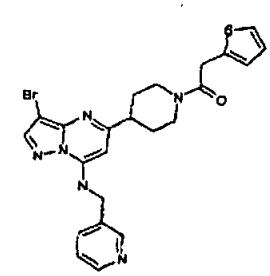
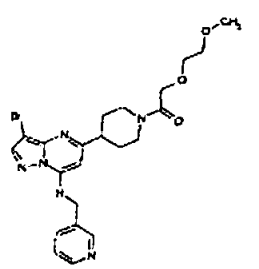
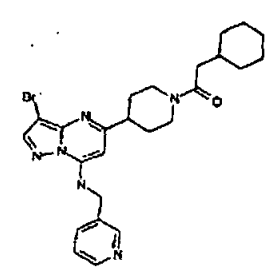
As demonstrated above by the assay values, the compounds of the present invention exhibit excellent CDK inhibitory properties.

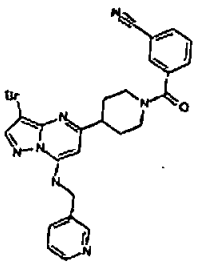
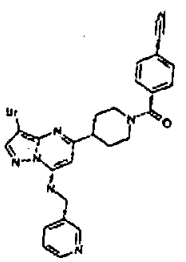
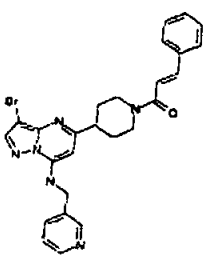
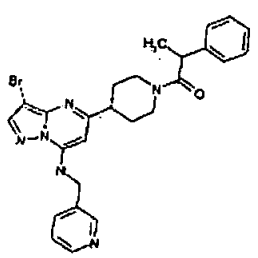
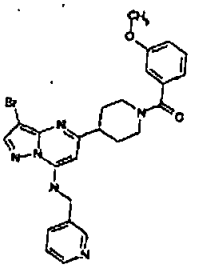
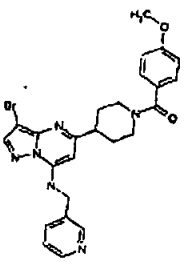
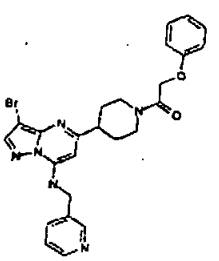
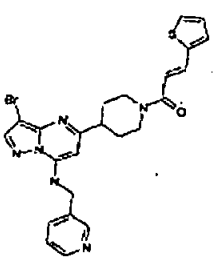
While the present invention has been described with in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

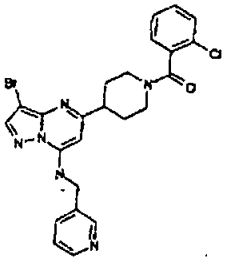
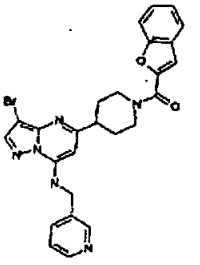
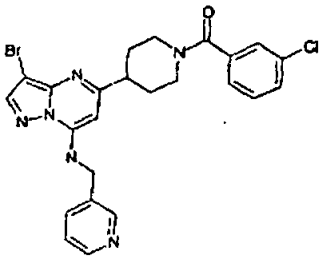
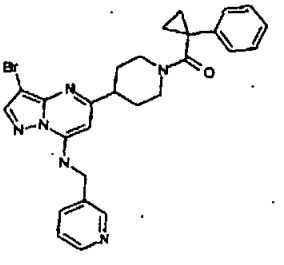
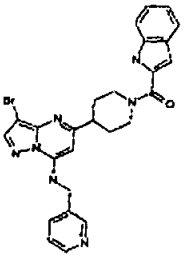
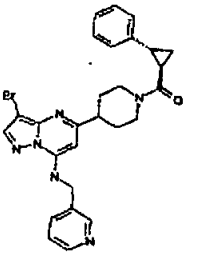
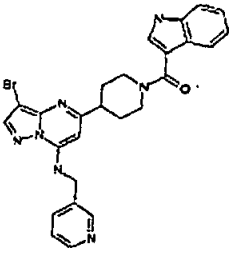
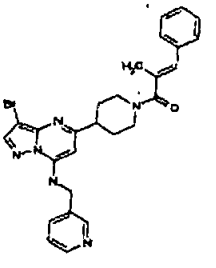
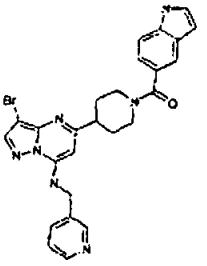
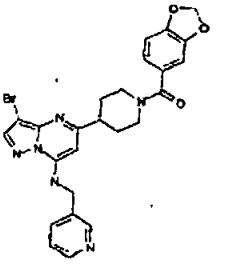
445

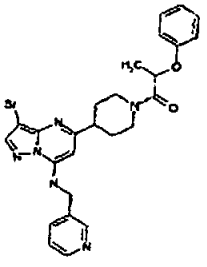
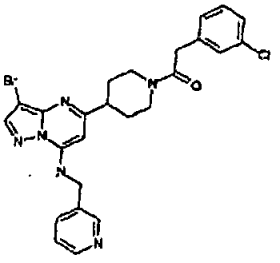
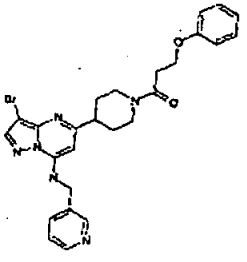
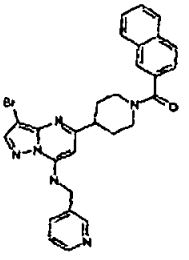
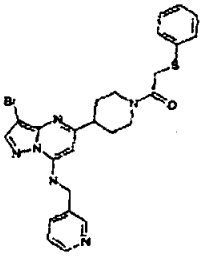
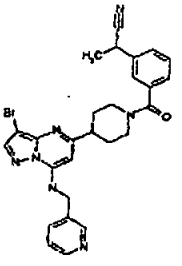
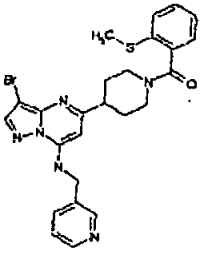
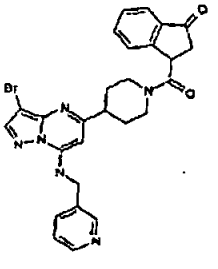
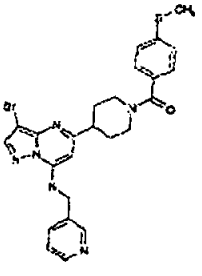
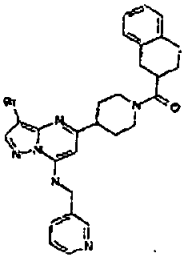
TABLE 43

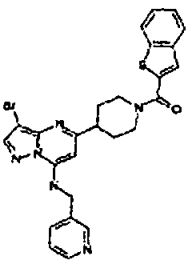
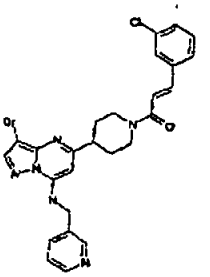
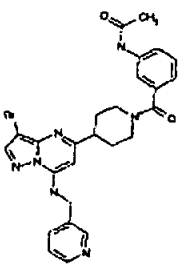
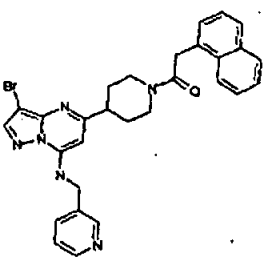
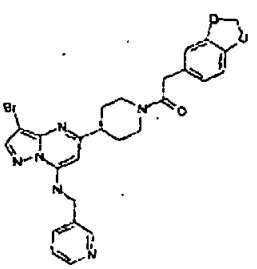
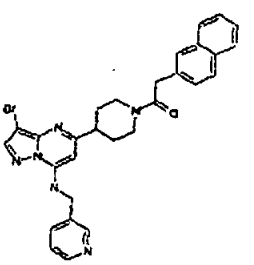
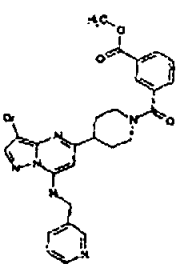
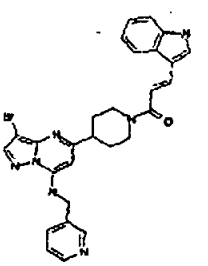
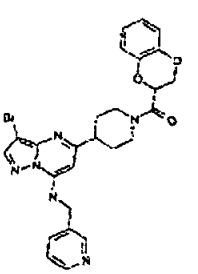
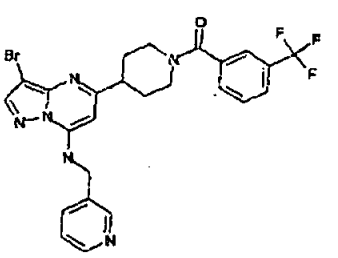
Ex.	Compound	m/z	Ex.	Compound	m/z
4301		457.25	4305		487.27
4302		471.26	4306		487.27
4303		477.26	4307		487.27
4304		483.27	4308		494.27

Ex.	Product	m/z	Ex.	Product	m/z
4309		499.27	4313		509.28
4310		500.27	4314		512.28
4311		503.28	4315		513.28
4312		505.28	4316		513.28

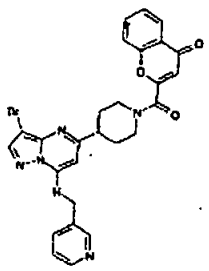
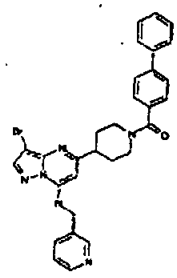
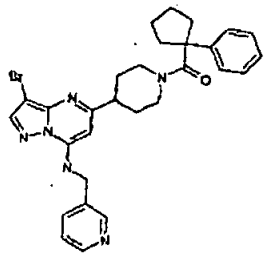
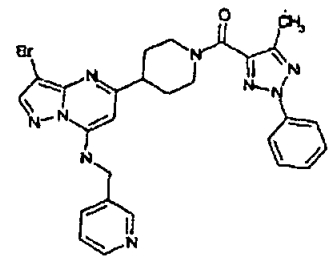
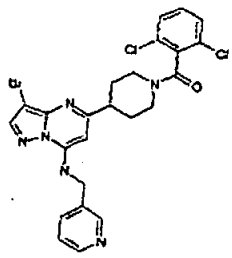
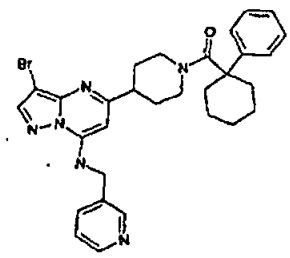
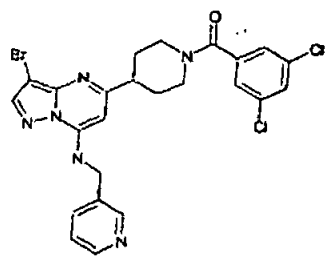
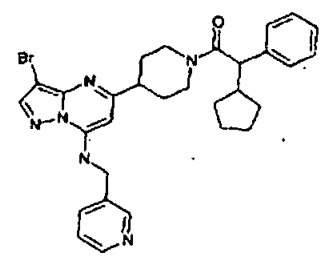
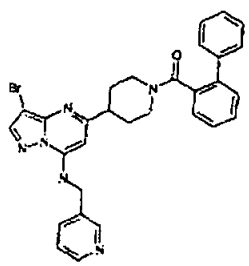
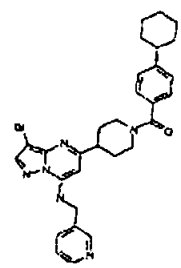
Ex.	Product	m/z
4317		518.28
4318		518.28
4319		519.29
4320		521.29
4321		523.29
4322		523.29
4323		523.29
4324		525.29

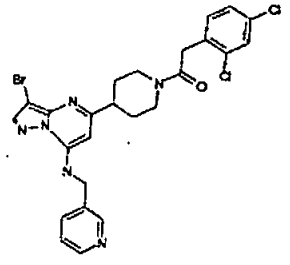
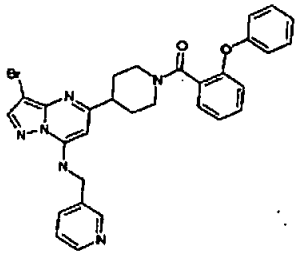
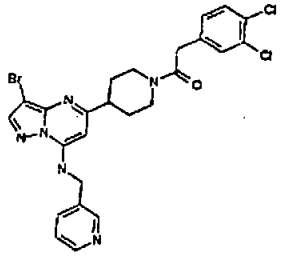
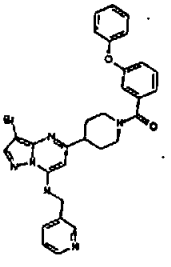
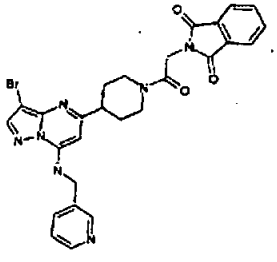
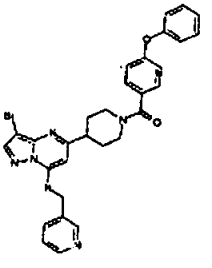
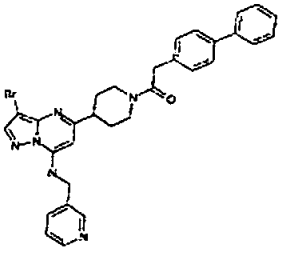
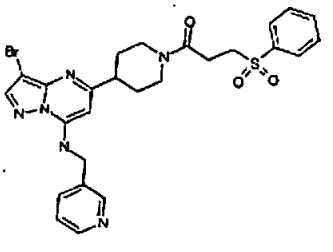
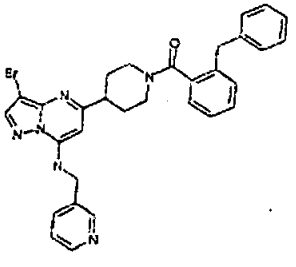
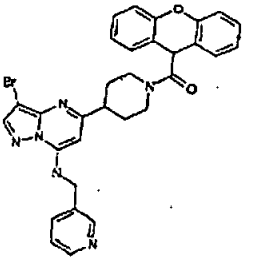
Product	1.Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4325 2. 527.29		1. 4330 2. 533.29
	1. 4326 2. 527.29		4331
	1. 4327 2. 532.29		1. 4332 2. 533.29
	1. 4328 2. 532.29		1. 4333 2. 533.29
	1. 4329 2. 532.29		1. 4334 2. 537.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4335 2.537.3		1. 4340 2. 541.3
	1.4336 2. 537.3		1. 4341 2. 543.3
	1. 4337 2. 539.3		1. 4342 2. 546.3
	1. 4338 2. 539.3		1. 4343 2. 547.3
	1. 4339 2. 539.3		1. 4344 2. 547.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4345 2. 549.3		1. 4350 2. 553.3
	1. 4346 2. 550.3		1. 4351 2. 557.31
	1. 4347 2. 551.3		1. 4352 2. 557.31
	1. 4348 2. 551.3		1. 4353 2. 558.31
	1. 4349 2. 551.3		1. 4354 2. 561.31

451

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4355 2. 561.31		1. 4360 2. 569.31
	1. 4356 2. 561.31		1. 4361 2. 574.32
	1. 4357 2. 561.31		1. 4362 2. 573.32
	1. 4358 2. 561.31		1. 4363 2. 573.32
	1. 4359 2. 569.31		1. 4364 2. 575.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4365 2. 575.32		1. 43700 2. 585.32
	1. 43666 2. 575.32		1. 4371 2. 583.32
	1. 4367 2. 574.32		1. 4372 2. 585.32
	1. 43688 2. 583.32		1. 4373 2. 585.32
	1. 4369 2. 583.32		1. 4374 2. 597.33

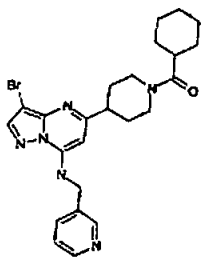
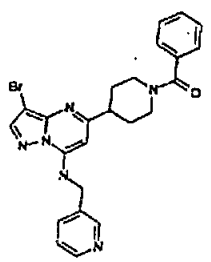
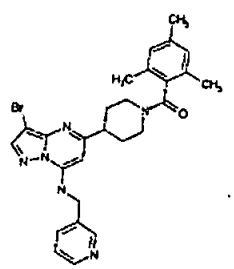
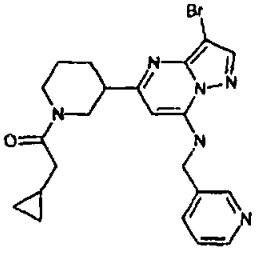
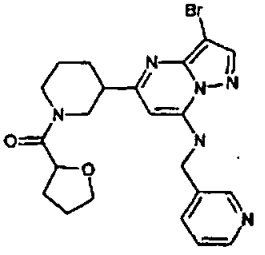
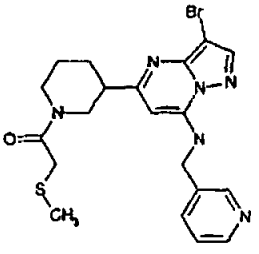
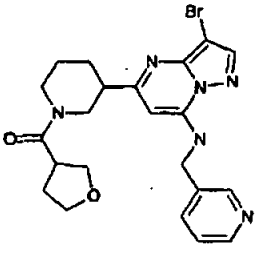
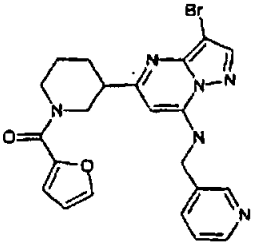
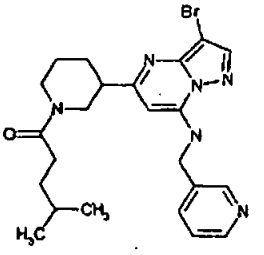
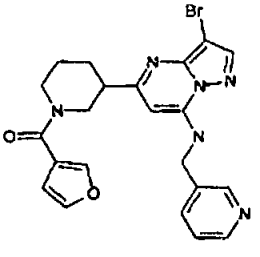
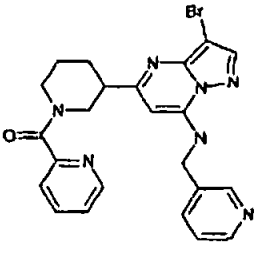
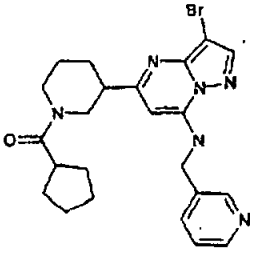
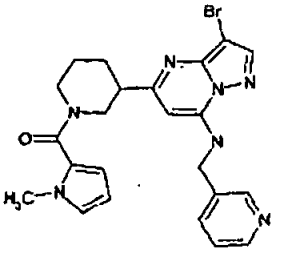
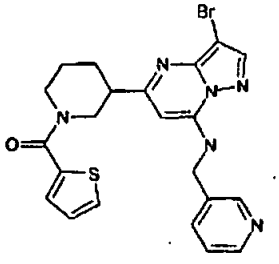
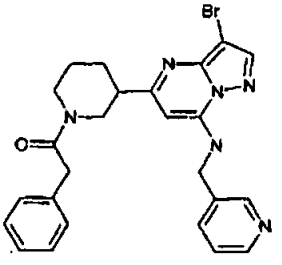
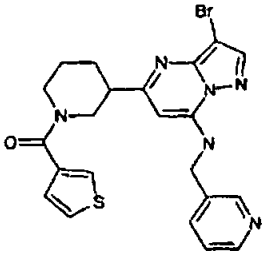
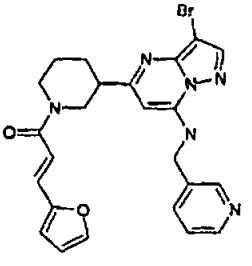
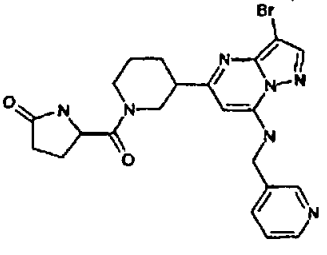
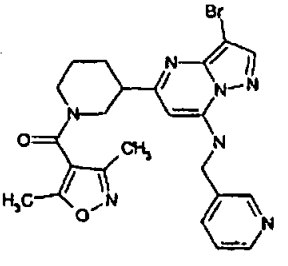
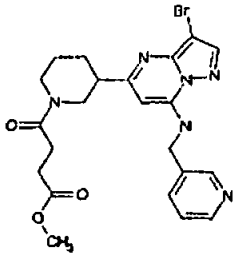
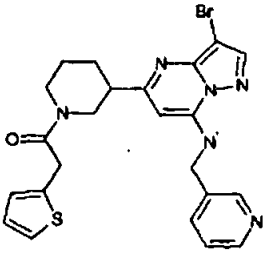
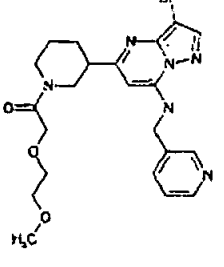
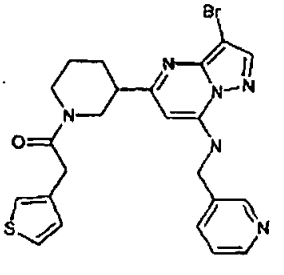
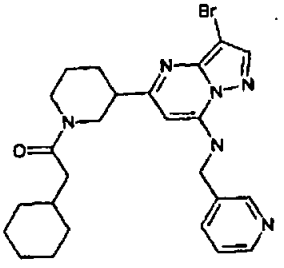
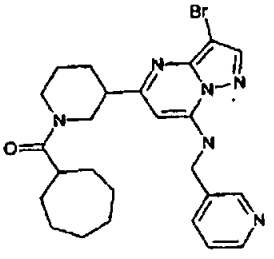
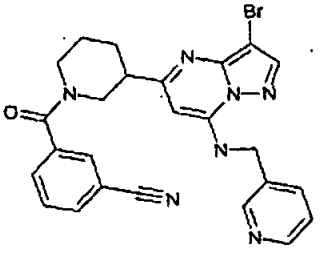
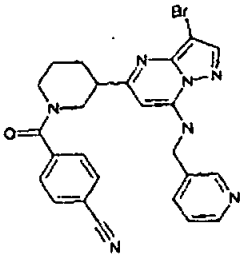
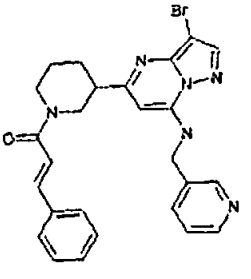
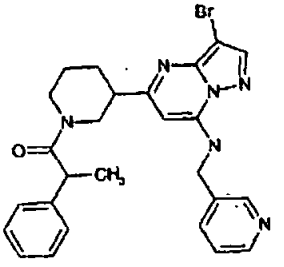
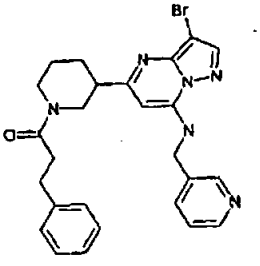
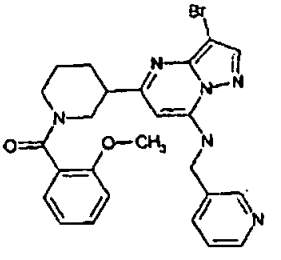
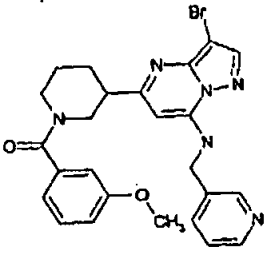
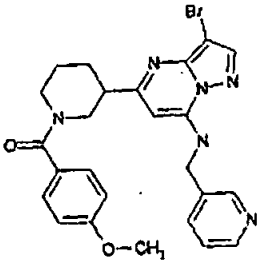
Product	1. Ex. 2. m/z
	1. 4375 2. 499.27
	1. 4376 2. 493.27
	1. 4377 2. 535.29

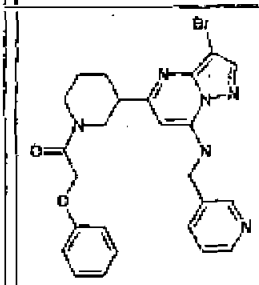
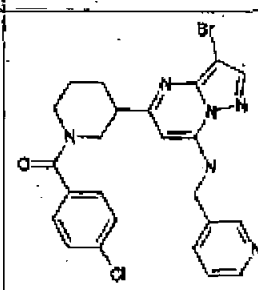
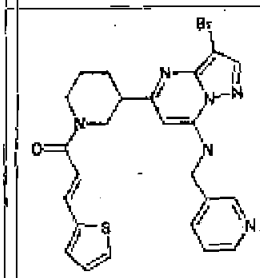
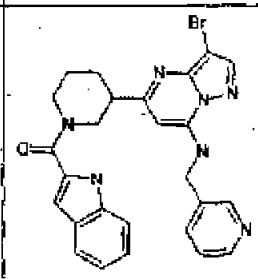
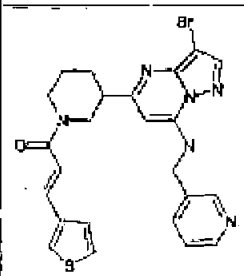
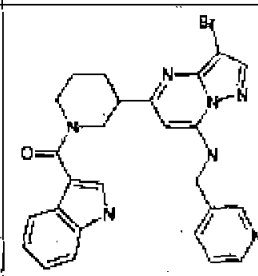
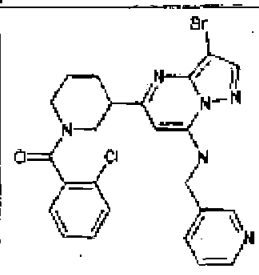
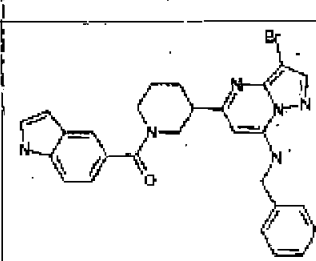
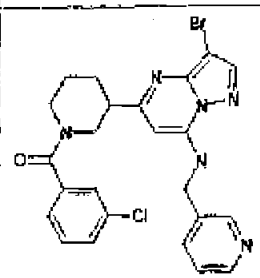
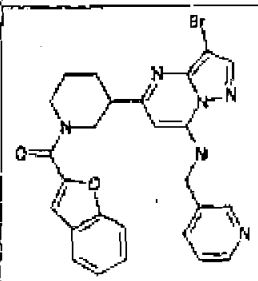
TABLE 44

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4401 2. 471.3		1. 4408 2. 487.27
	1. 4402 2. 475.26		1. 4407 2. 487.27
	1. 4403 2. 483.27		1. 4408 2. 487.27
	1. 4404 2. 481.26		1. 4409 2. 494.3
	1. 4405 2. 485.27		1. 4410 2. 496.27

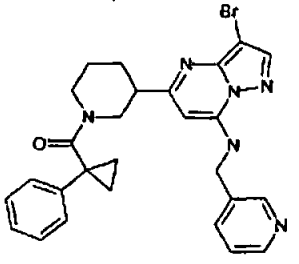
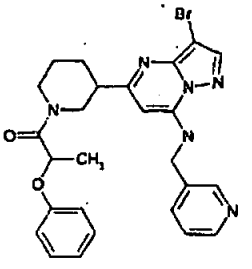
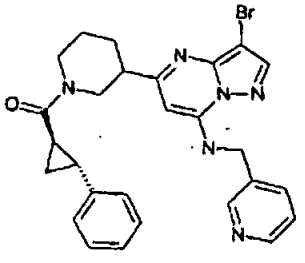
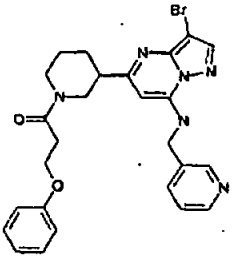
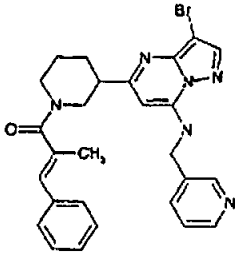
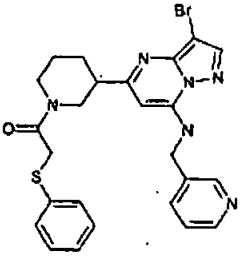
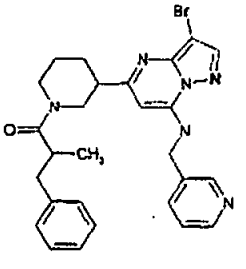
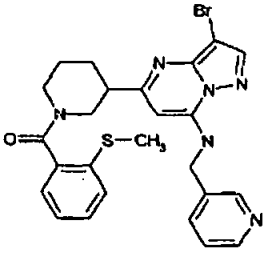
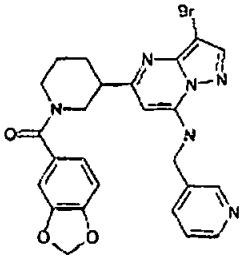
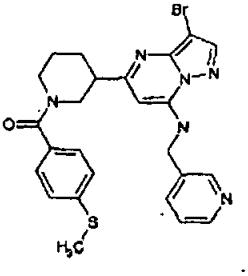
Product	1. Ex 2. m/z	Product	1. Ex. 2. m/z
	1. 4411 2. 499.27		1. 4416 2. 507.28
	2. 4412 2. 499.27		1. 4417 2. 509.3
	1. 4413 2. 500.27		1. 4418 2. 512.28
	1. 4414 2. 503.28		1. 4419 2. 513.28
	1. 4415 2. 505.28		1. 4420 2. 513.28

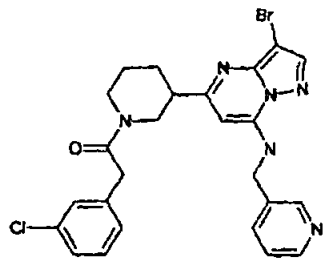
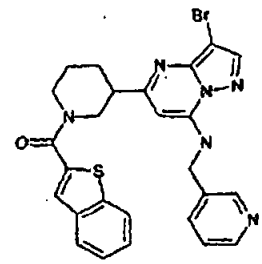
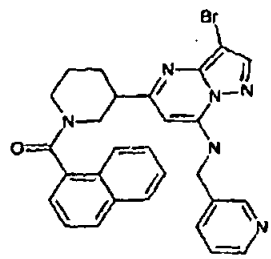
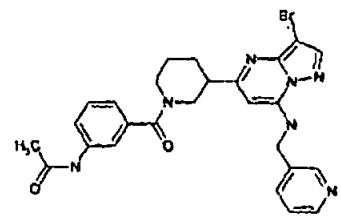
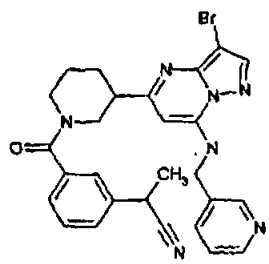
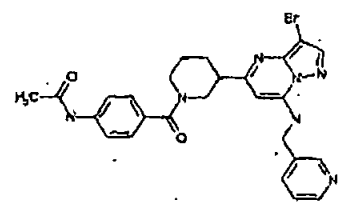
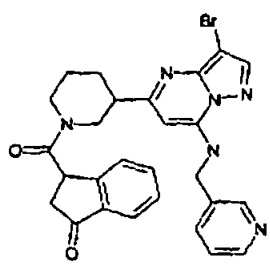
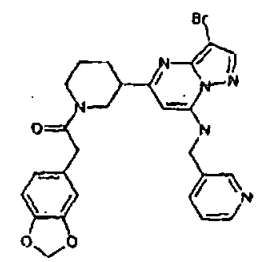
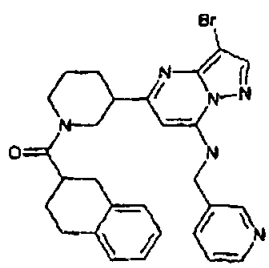
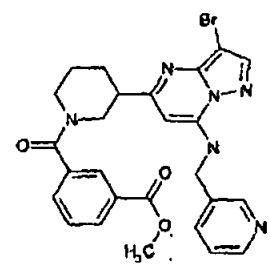
Product	1. x. 2. m/z
	1. 4421 2. 513.28
	1. 4422 2. 513.28
	1. 4423 2. 518.28
	1. 4424 2. 518.28
	1. 4425 2. 519.3

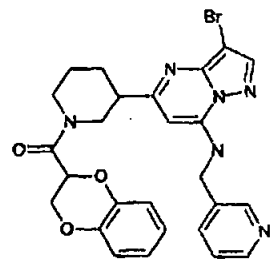
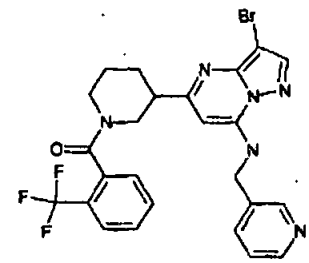
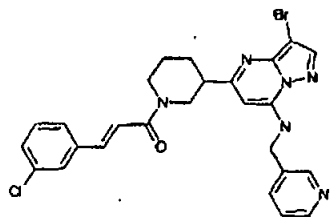
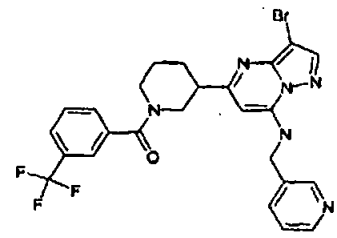
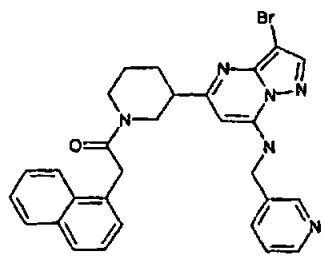
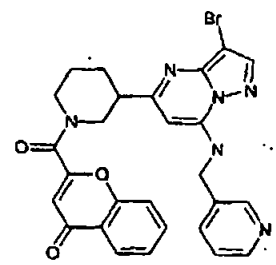
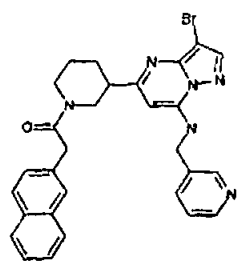
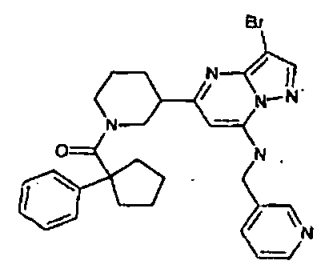
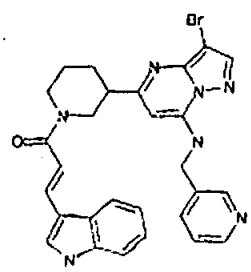
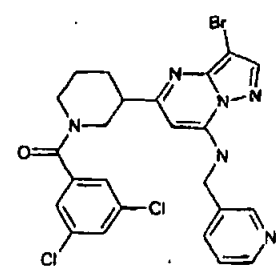
Product	1. Ex. 2. m/z
	1. 4426 2. 521.29
	1. 4428 2. 521.29
	1. 4428 2. 523.29
	1. 4429 2. 523.29
	1. 4430 2.523.29

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4431 2. 523.29		1. 4436 2. 527.29
	1. 4432 2. 525.29		1. 4437 2. 532.29
	1. 4433 2. 525.3		1. 4438 2. 532.29
	1. 4434 2. 527.29		1. 4439 2. 532.29
	1. 4435 2. 527.29		1. 4440 2. 531.29

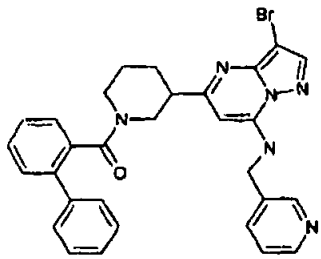
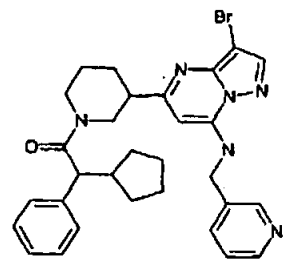
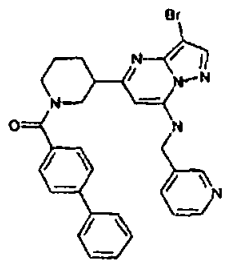
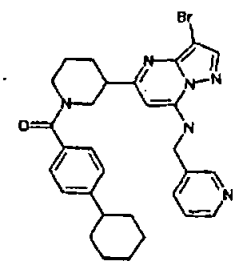
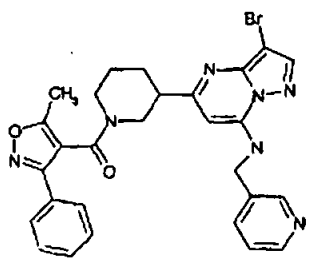
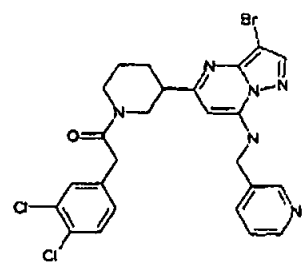
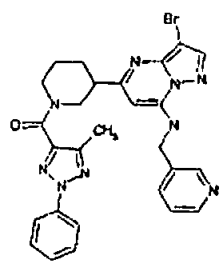
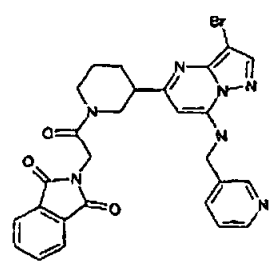
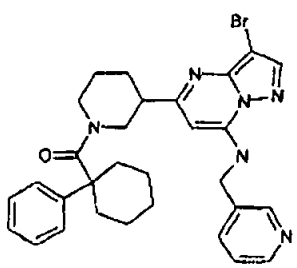
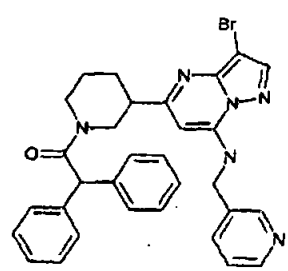
456

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4441 2. 533.3		1. 4446 2. 537.3
	1. 4442 2. 531.29		1. 4447 2. 537.3
	1. 4443 2. 533.29		1. 4448 2. 539.3
	1. 4444 2. 535.29		1. 4449 2.539.3
	1. 4445 2. 537.3		1. 4450 2.539.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4451 2. 541.3		1. 4456 2. 549.3
	1. 4451 2. 543.3		1. 4457 2. 550.3
	1. 4453 2. 546.3		1. 4458 2. 550.3
	1. 4454 2.547.3		1. 4459 2. 551.3
	1. 4455 2.547.3		1. 4460 2. 551.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4461 2. 549.3		1. 4466 2. 561.31
	1. 4462 2. 553.3		1. 4467 2. 561.31
	1. 4463 2. 557.3		1. 4468 2. 561.31
	1. 4464 2. 557.31		1. 4469 2. 561.31
	1. 4465 2. 558.31		1. 4470 2. 562.3

458

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4471 2. 569.31		1. 4476 2.572.31
	1. 4472 2. 569.31		1. 4477 2. 573.32
	1. 4473 2. 572.31		1. 4478 2. 574.32
	1. 4474 2. 572.31		1. 4479 2. 576.32
	1. 4475 2. 575.32		1. 4480 2. 583.32

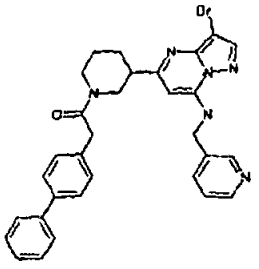
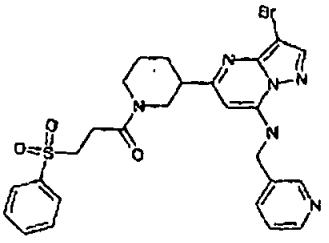
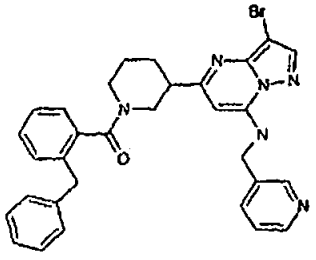
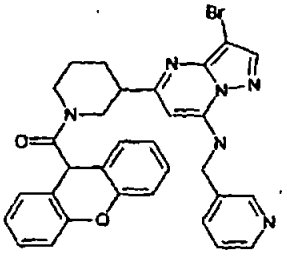
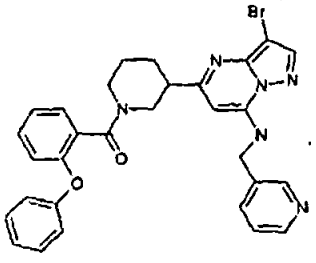
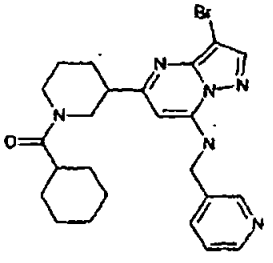
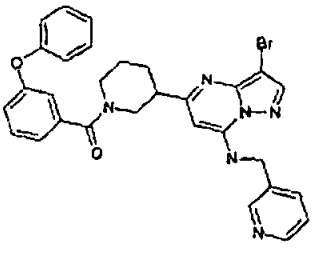
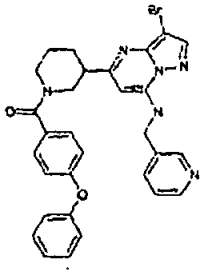
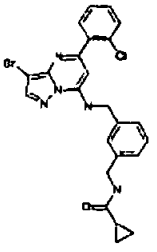
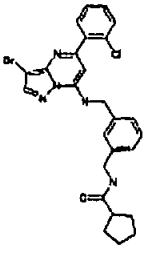
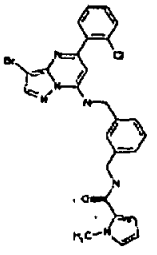
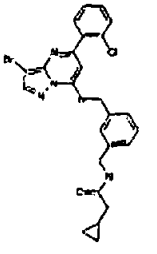
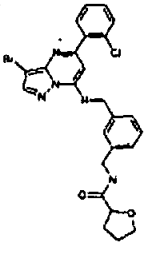
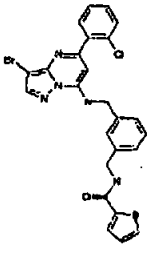
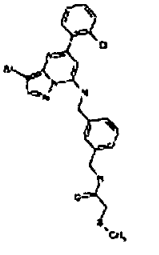
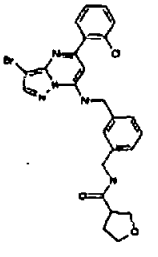
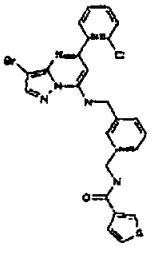
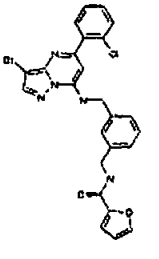
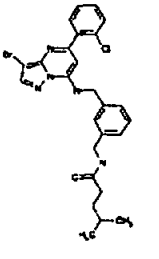
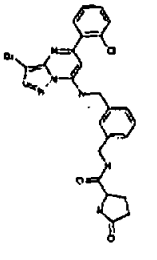
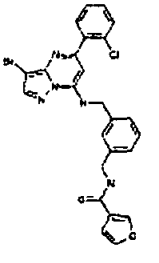
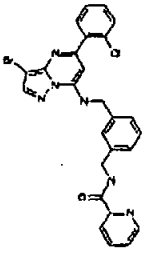
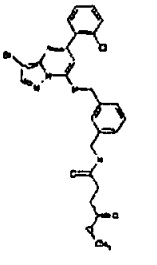
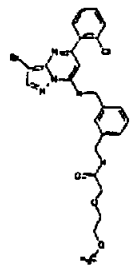
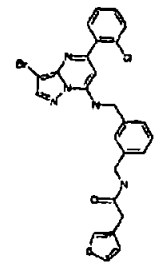
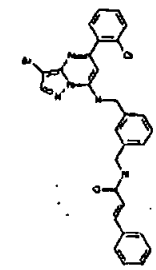
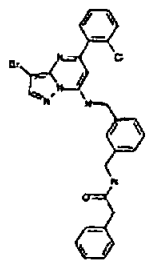
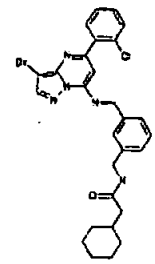
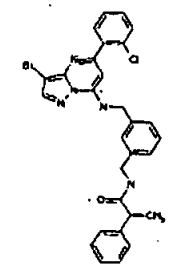
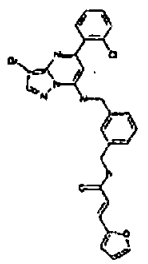
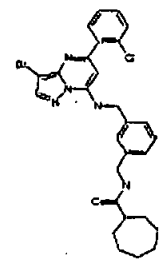
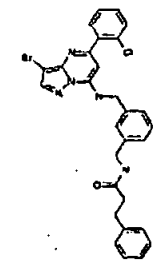
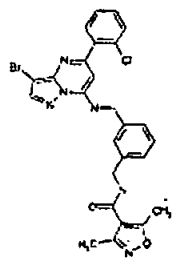
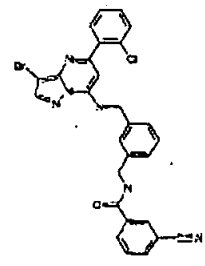
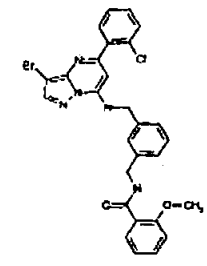
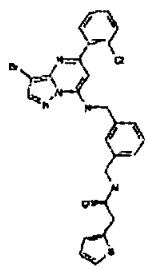
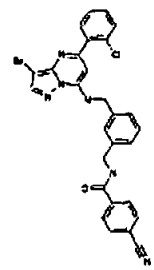
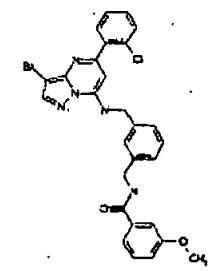
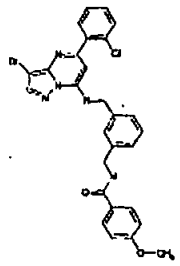
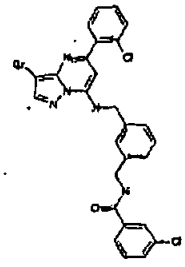
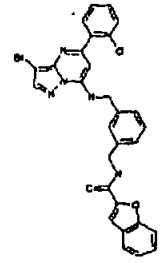
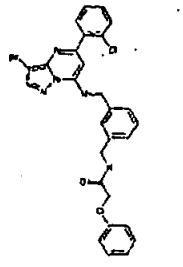
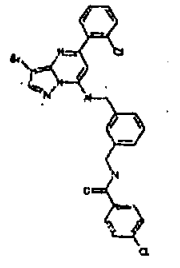
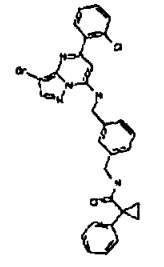
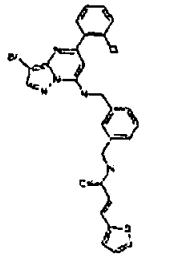
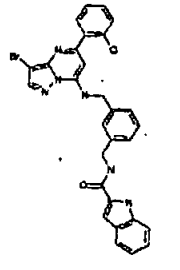
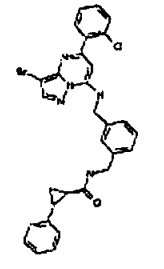
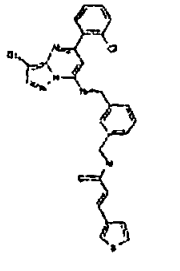
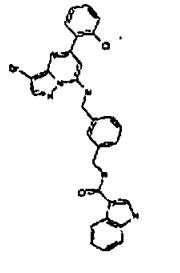
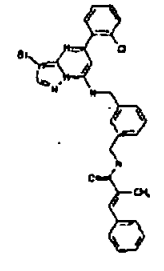
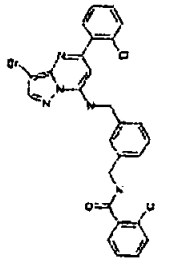
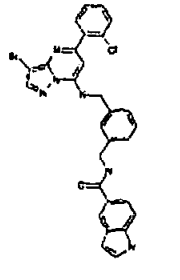
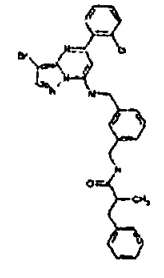
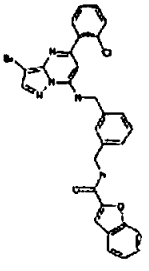
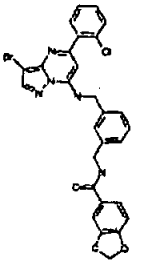
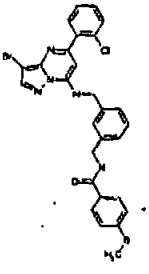
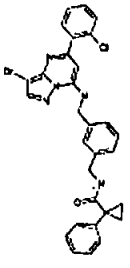
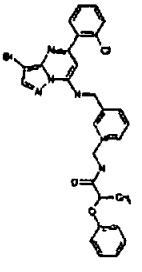
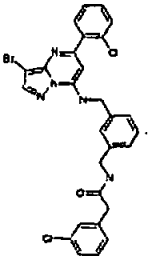
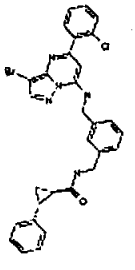
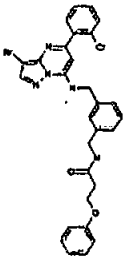
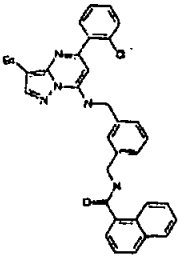
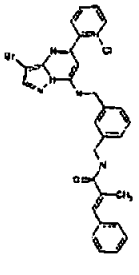
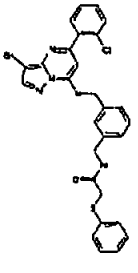
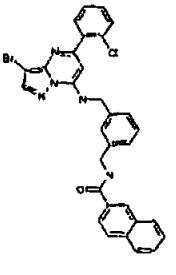
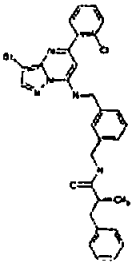
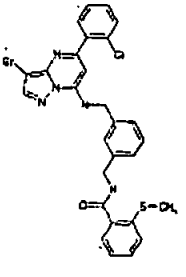
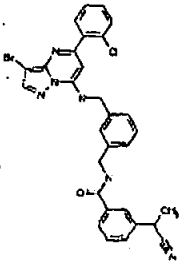
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4481 2. 583.32		1. 4486 2. 585.32
	1. 4482 2. 583.32		1. 4487 2. 597.33
	1. 4483 2. 585.32		1. 4488 2. 499.27
	1. 4484 2. 585.32		
	1. 4485 2. 585.3		

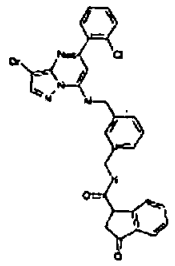
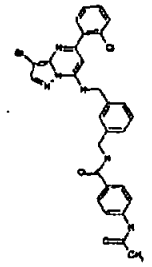
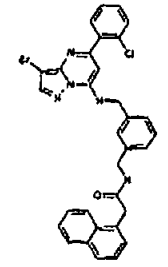
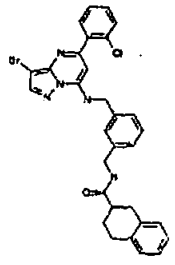
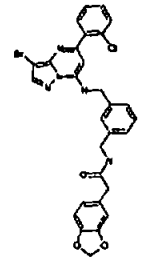
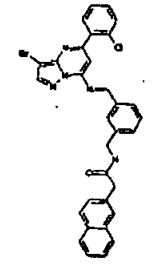
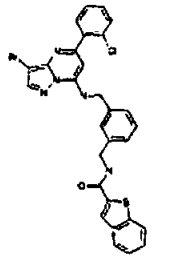
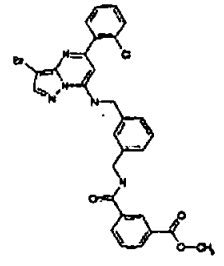
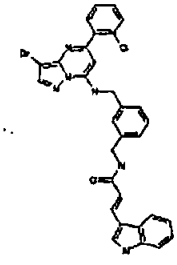
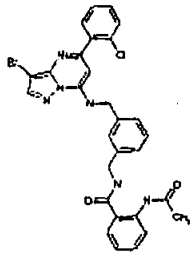
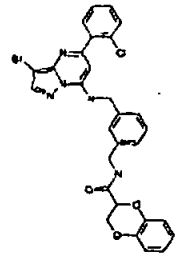
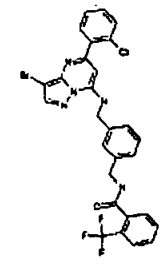
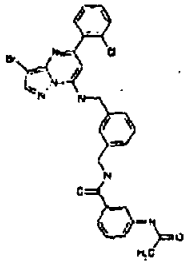
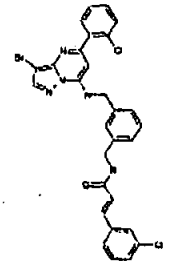
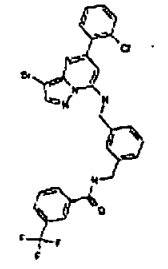
TABLE 45

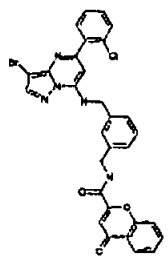
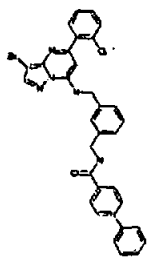
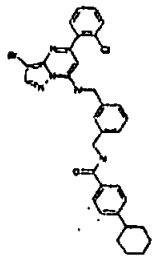
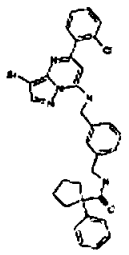
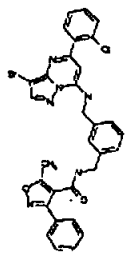
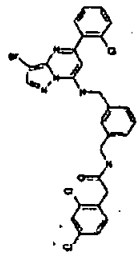
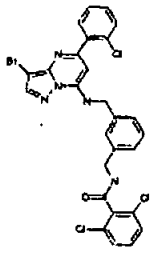
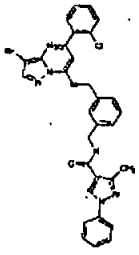
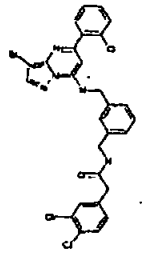
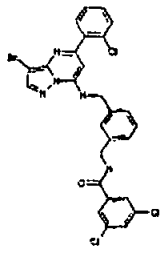
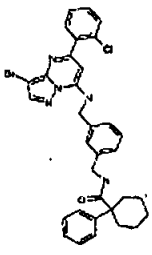
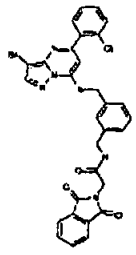
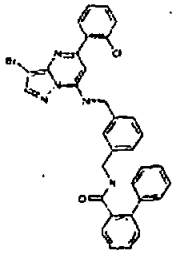
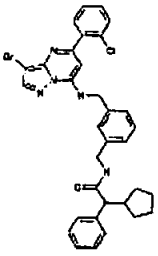
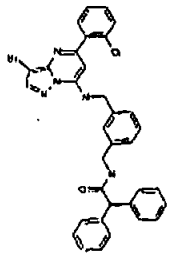
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4501 2. 512.28		1. 4506 2. 540.3		1. 4511 2. 551.3
	1. 4502 2. 526.29		1. 4507 2. 542.3		1. 4512 2. 554.3
	1. 4503 2. 532.29		1. 4508 2. 542.3		1. 4513 2. 554.3
	1. 4504 2. 538.3		1. 4509 2. 542.3		1. 4514. 2. 555.31
	1. 4505 2. 538.3		1. 4510 2. 549.3		1. 4515 2. 558.31

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4516 2. 560.31		1. 4521 2. 568.31		1. 4526 2. 574.32
	1. 4517 2. 562.31		1. 4522 2. 568.31		1. 4527 2. 576.32
	1. 4518 2. 564.31		1. 4523 2. 568.31		1. 4528 2. 576.32
	1. 4519 2. 567.31		1. 4524 2. 573.32		1. 4529 2. 578.32
	1. 4520 2. 568.31		1. 4525 2. 573.32		1. 4530 2. 578.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4531 2. 578.32		1. 4536 2. 582.32		1. 4541 2. 588.32
	1. 4532 2. 578.32		1. 4537 2. 582.32		1. 4542 2. 588.32
	1. 4533 2. 580.32		1. 4538 2. 587.32		1. 4543 2. 588.32
	1. 4534 2. 580.32		1. 4539 2. 587.32		1. 4544 2. 588.32
	1. 4535 2. 582.32		1. 4540 2. 587.32		1. 4545 2. 590.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4546 2. 588.32		1. 4551 2. 592.33		1. 4556 2. 593.33
	1. 4547 2. 588.32		1. 4552 2. 592.33		1. 4557 2. 596.33
	1. 4548 2. 588.32		1. 4553 2. 592.33		1. 4558 2. 596.33
	1. 4549 2. 588.32		1. 4554 2. 594.33		1. 4559 2. 598.33
	1. 4550 2. 590.32		1. 4555 2. 594.33		1. 4560 2. 601.33

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. E 2. m
	1. 4561 2. 602.33		1. 4665 2. 605.33		1. 457 612.3
	1. 4562 2. 602.33		1. 4567 2. 606.33		1. 4572 612.3
	1. 4563 2. 604.33		1. 4568 2. 606.33		1. 4573 613.34
	1. 4564 2. 603.3		1. 4569 2. 606.33		1. 4574 616.34
	1. 4565 2. 605.33		1. 4570 2. 608.33		1. 4575 2 616.34

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4576 2. 616.34		1. 4581 2. 624.34		1. 4586 2. 630.35
	1. 4577 2. 616.34		1. 4582 2. 629.35		1. 4587 2. 630.35
	1. 4578 2. 616.34		1. 4583 2. 629.35		1. 4588 2. 630.35
	1. 4579 2. 616.34		1. 4584 2. 630.35		1. 4589 2. 631.35
	1. 4580 2. 624.34		1. 4585 2. 630.35		1. 4590 2. 638.35

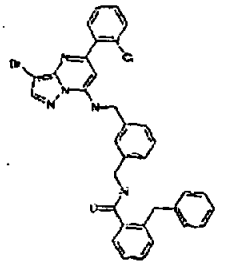
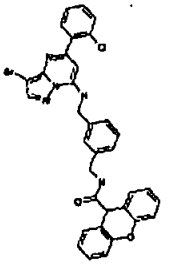
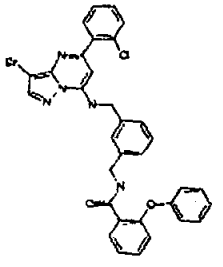
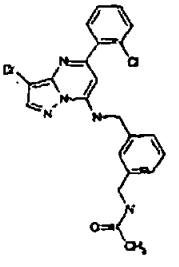
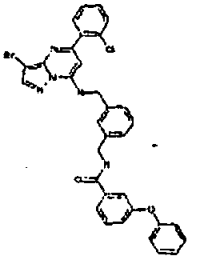
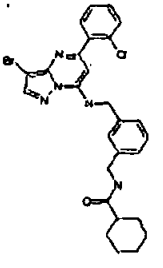
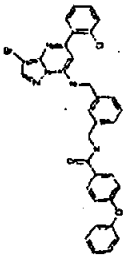
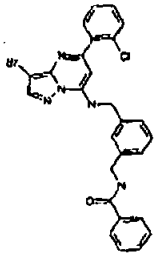
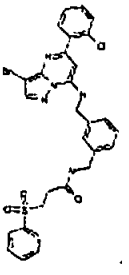
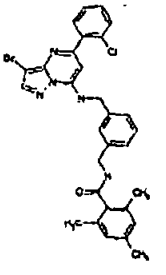
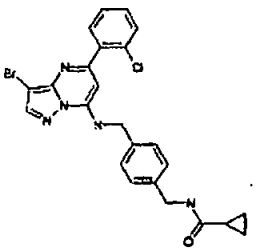
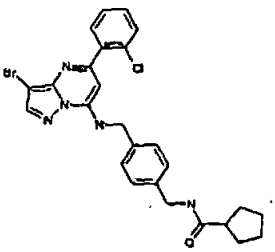
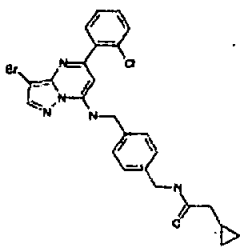
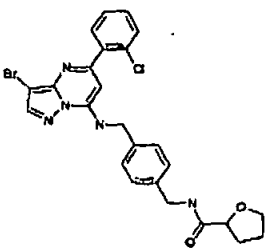
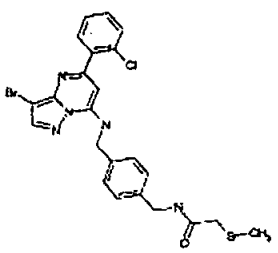
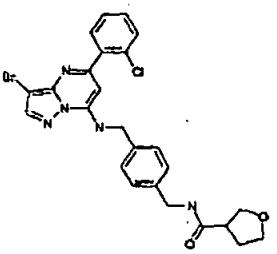
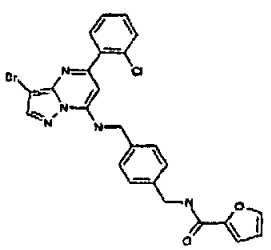
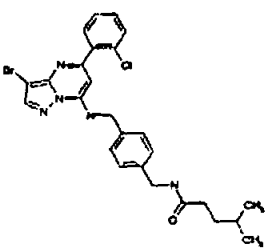
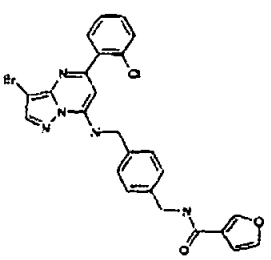
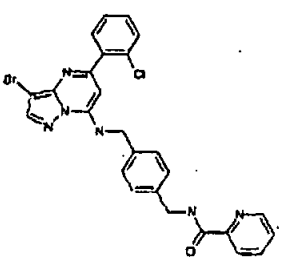
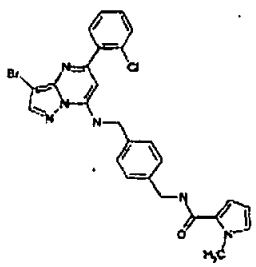
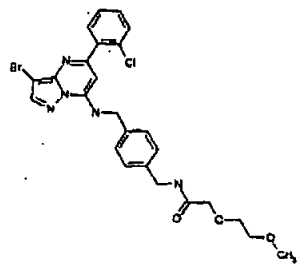
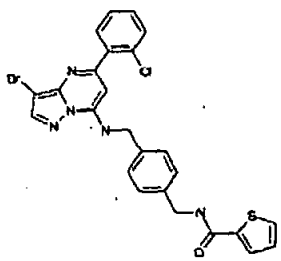
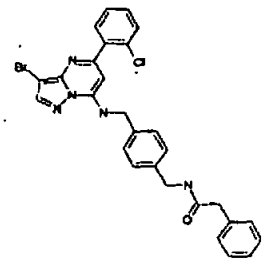
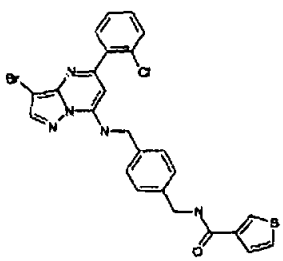
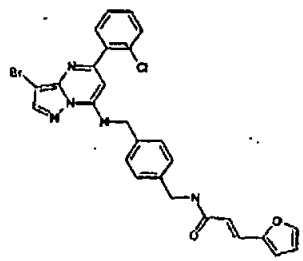
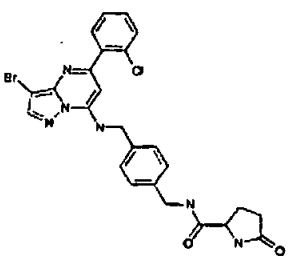
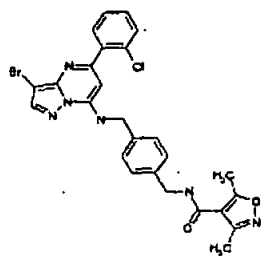
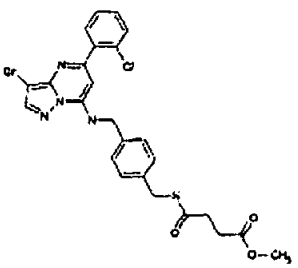
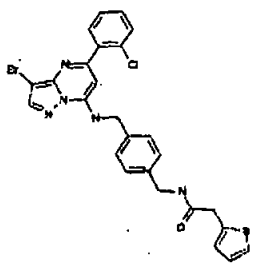
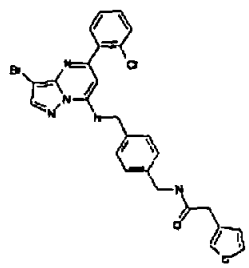
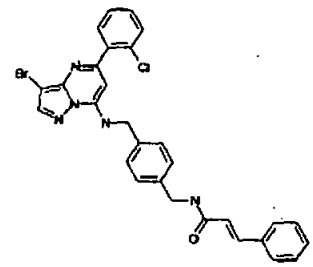
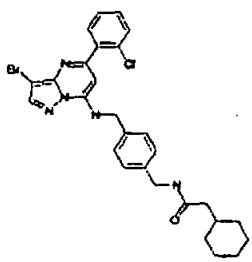
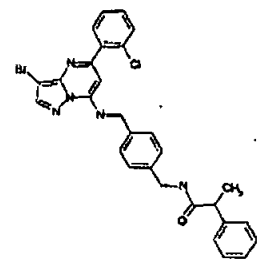
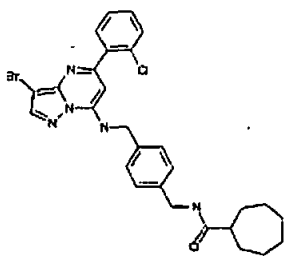
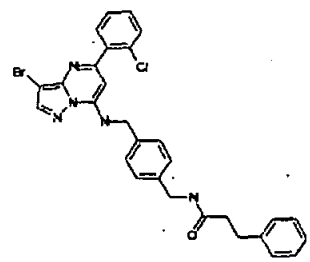
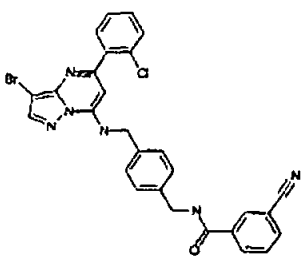
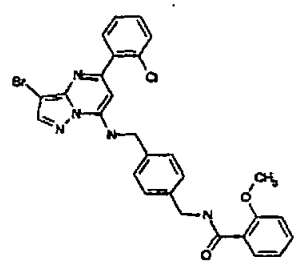
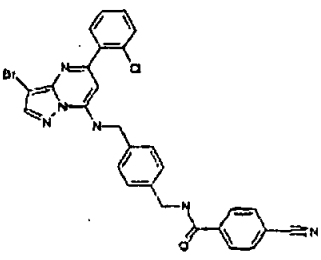
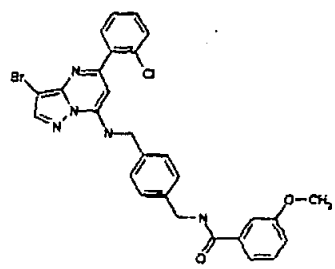
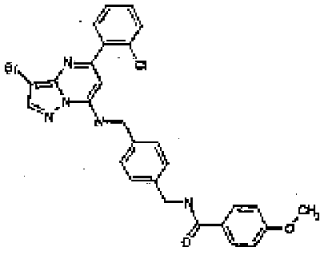
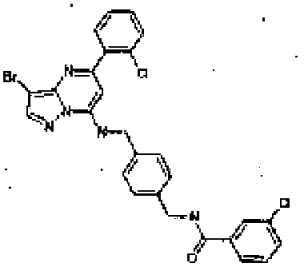
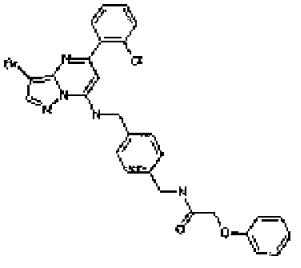
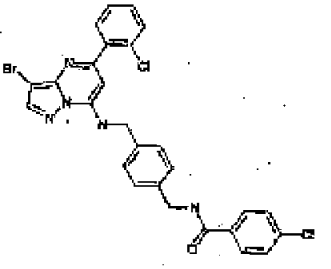
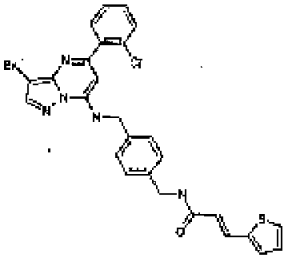
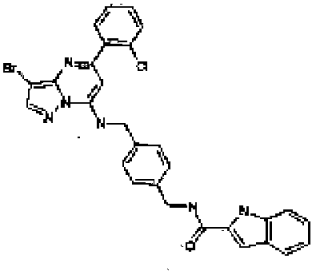
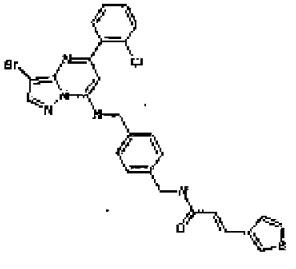
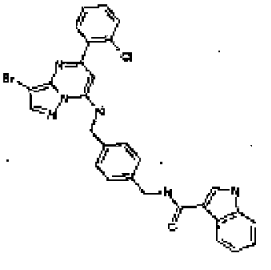
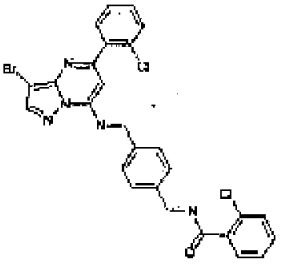
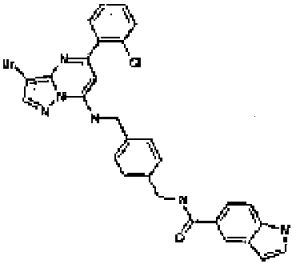
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4591 2. 638.35		1. 4596 2. 652.36
	1. 4592 2. 640.35		1. 4597 2. 486.27
	1. 4593 2. 640.35		1. 4598 2. 554.3
	1. 4594 2. 640.35		1. 4599 2. 548.3
	1. 4595 2. 640.35		1. 46100 2.

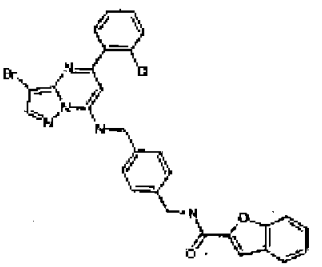
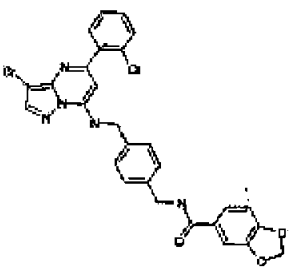
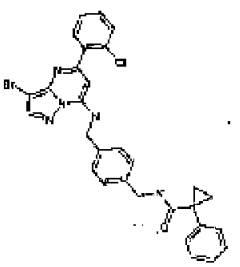
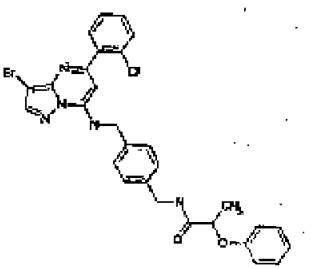
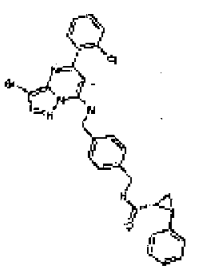
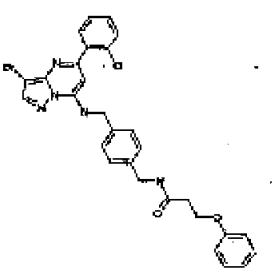
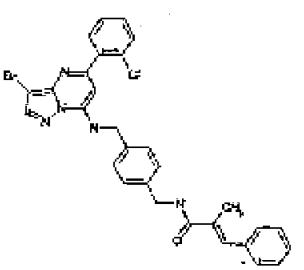
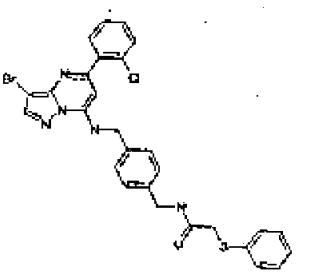
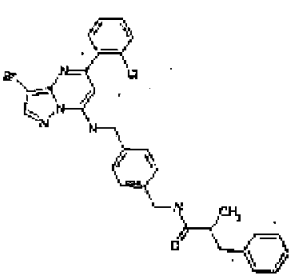
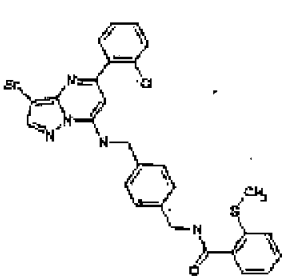
TABLE 46

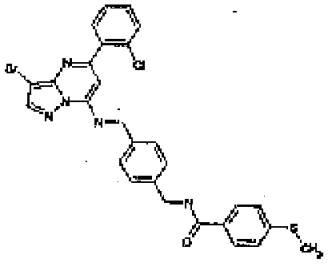
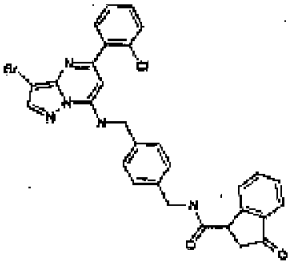
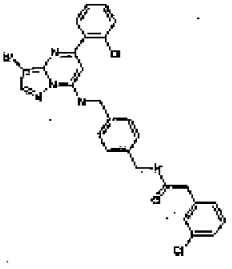
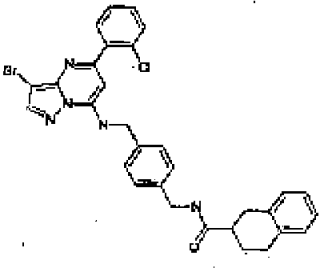
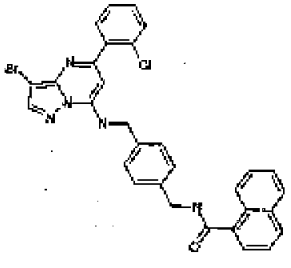
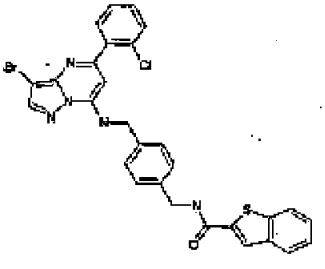
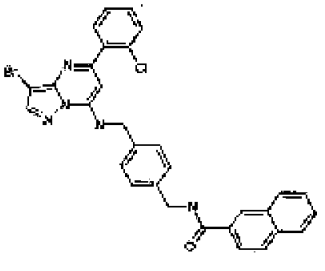
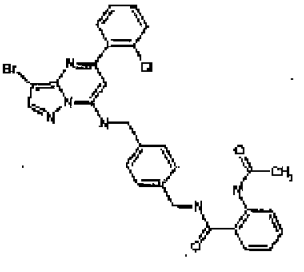
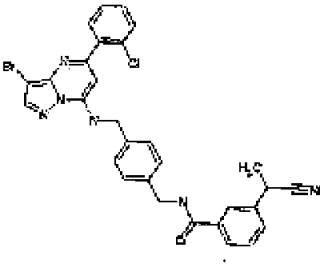
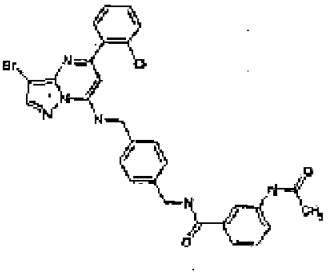
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4601 2. 512.28		1. 4606 2. 540.3
	1. 4602 2. 526.29		1. 4607 2. 542.3
	1. 4603 2. 532.29		1. 4608 2. 542.3
	1. 4604 2. 538.3		1. 4609 2. 542.3
	1. 4605 2. 536.3		1. 4610 2. 547.3

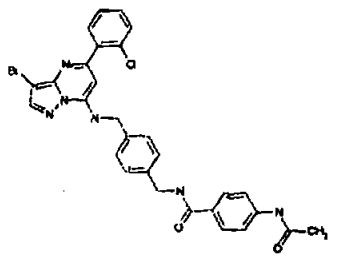
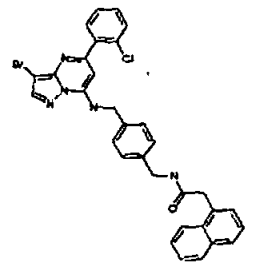
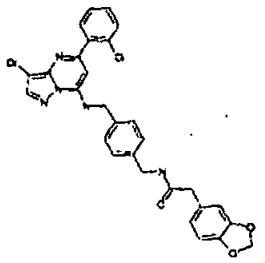
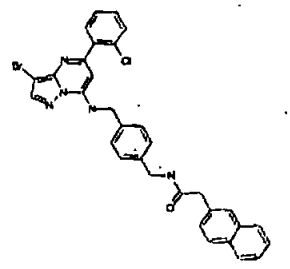
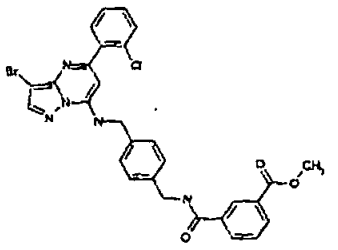
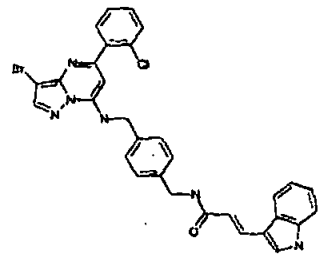
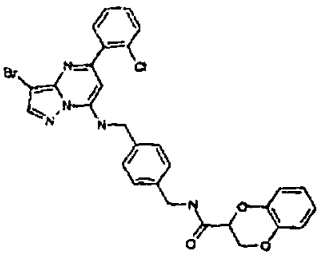
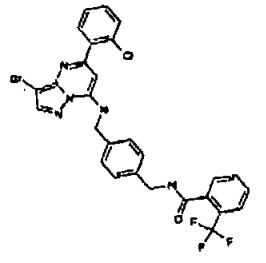
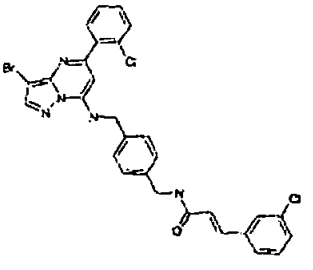
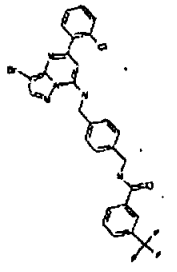
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4611 2. 551.3		1. 4616 2. 560.31
	1. 4612 2. 552.3		1. 4617 2. 562.31
	1. 4613 2. 552.3		1. 4618 2. 562.3
	1. 4614 2. 555.31		1. 4619 2. 567.31
	1. 4615 2. 558.31		1. 4620 2. 568.31

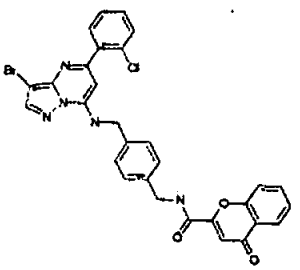
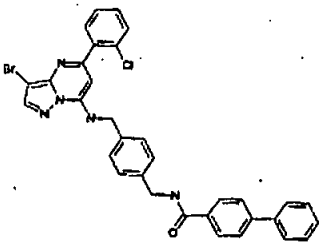
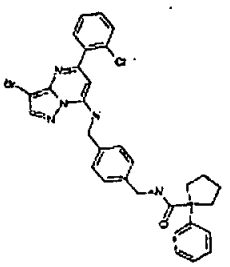
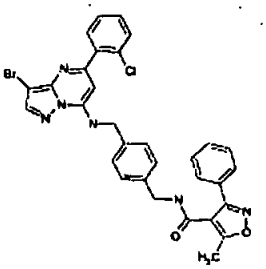
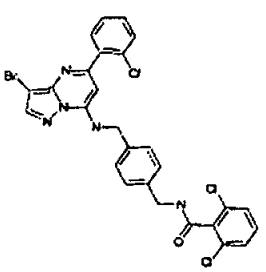
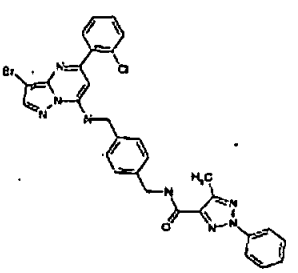
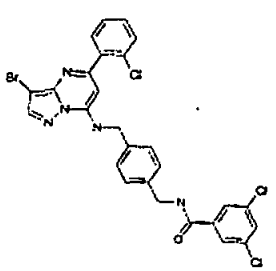
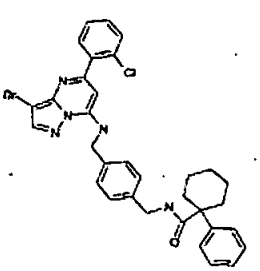
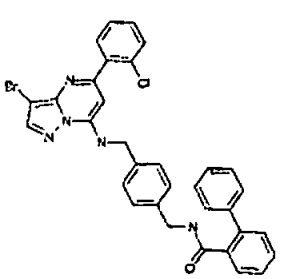
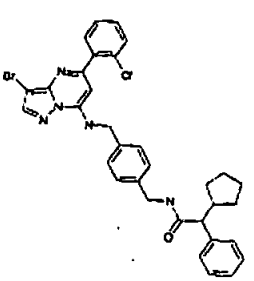
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4621 2. 568.31		1. 4626 2. 574.32
	1. 4622 2. 568.31		1. 4627 2. 576.32
	1. 4623 2. 568.31		1. 4628 2. 576.32
	1. 4624 2. 573.32		1. 4629 2. 578.32
	1. 4625 2. 573.32		1. 4630 2. 578.32

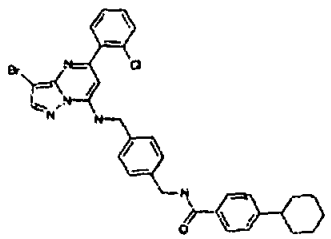
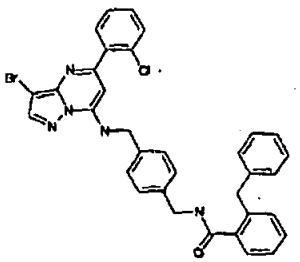
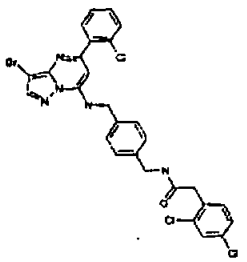
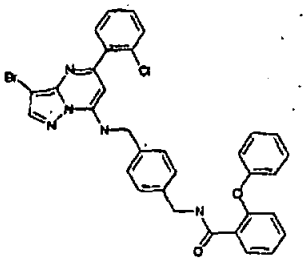
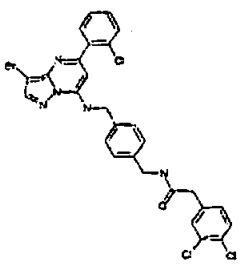
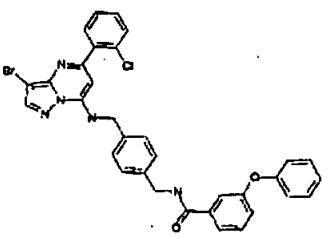
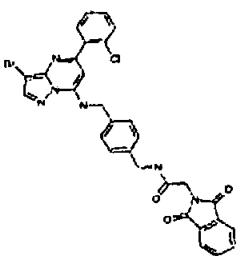
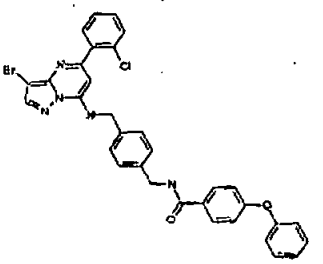
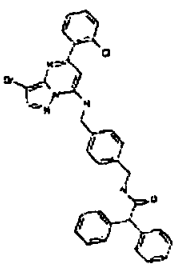
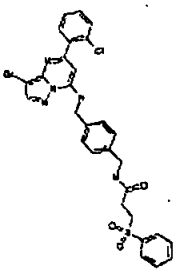
Product	1. Ex. 2, m/x	Product	1. Ex. 2, m/z
	1. 4631 2. 578.32		1. 4636 2. 582.32
	1. 4632 2. 578.32		1. 4637 2. 582.32
	1. 4633 2. 580.32		1. 4638 2. 587.32
	1. 4634 2. 580.32		1. 4639 2. 585.3
	1. 4635 2. 582.32		1. 4640 2. 585.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4641 2. 588.32		1. 4646 2. 592.33
	1. 4642 2. 588.32		1. 4647 2. 592.33
	1. 4643 2. 588.32		1. 4648 2. 592.33
	1. 4644 2,. 588.32		1. 4649 2.
	1. 4645 2. 590.32		1. 4650 2. 594.33

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4651 2. 594.33		1. 4656 2. 602.33
	1. 4652 2. 596.33		1. 4657 2. 602.33
	1. 4653 2. 596.3		1. 4658 2. 604.33
	1. 4654 2. 598.33		1. 4659 2. 603.3
	1. 4655 2. 601.33		1. 4660 2. 605.33

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4661 2. 605.33		1. 4666 2. 612.34
	1. 4662 2. 606.33		1. 4667 2. 612.34
	1. 4663 2. 606.33		1. 4668 2. 613.34
	1. 4664 2. 606.33		1. 4669 2. 616.34
	1. 4665 2. 608.33		1. 4670 2. 616.34

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4671 2. 616.34		1. 4676 2. 624.34
	1. 4672 2. 616.34		1. 4677 2. 629.35
	1. 4673 2. 616.34		1. 4678 2. 629.35
	1. 4674 2. 616.34		1. 4679 2. 630.35
	1. 4675 2. 624.34		1. 4680 2. 630.35

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4681 2. 630.35		1. 4686 2. 638.35
	1. 4682 2. 630.35		1. 4687 2. 640.35
	1. 4683 2. 630.35		1. 4688 2. 640.35
	1. 4684 2. 631.35		4689 2.
	1. 4685 2. 638.35		1. 4690 2. 640.35

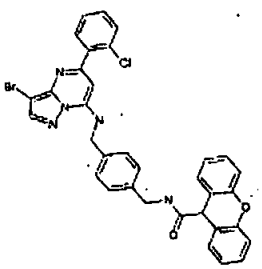
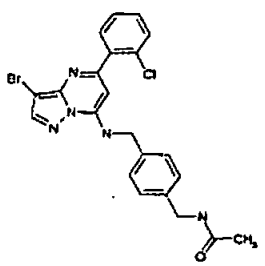
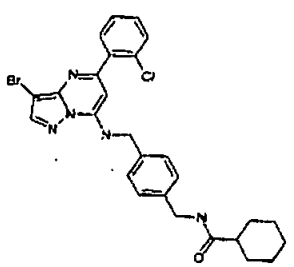
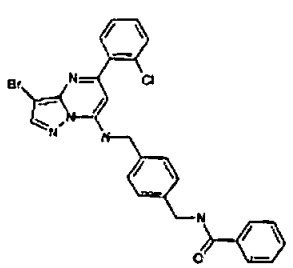
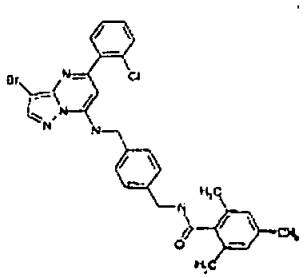
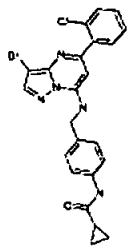
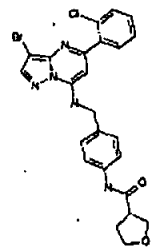
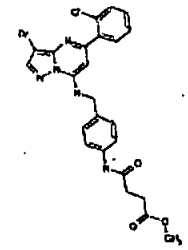
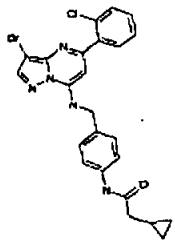
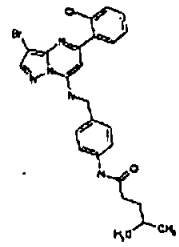
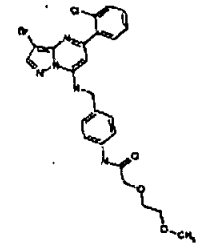
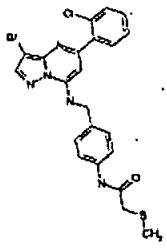
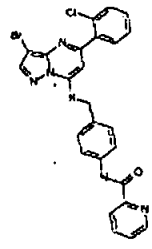
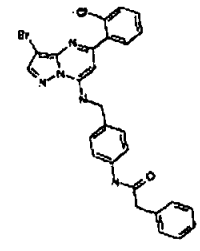
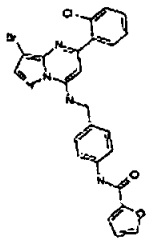
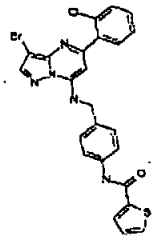
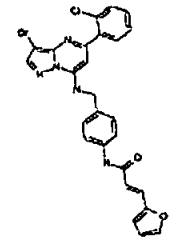
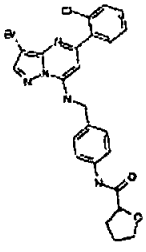
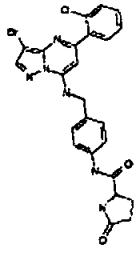
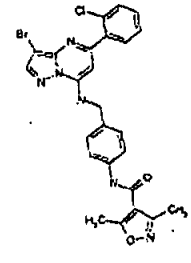
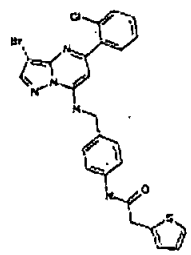
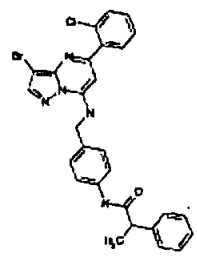
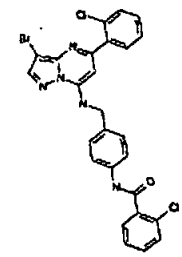
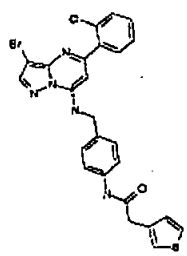
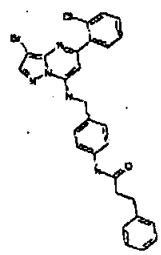
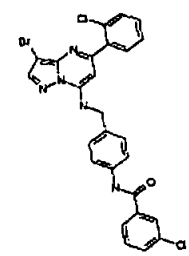
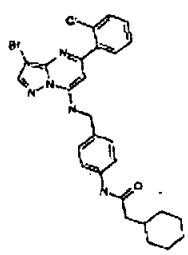
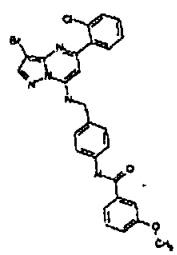
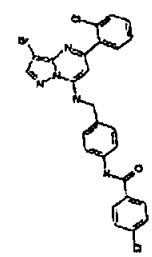
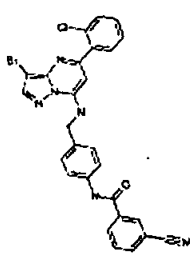
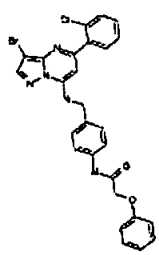
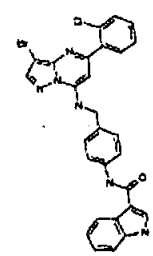
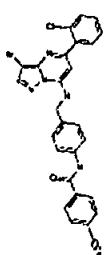
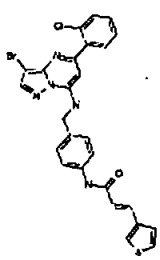
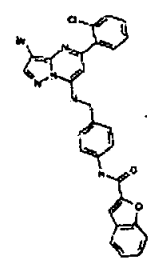
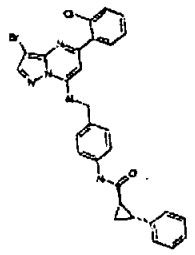
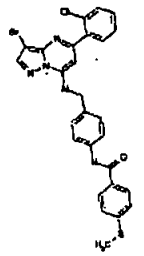
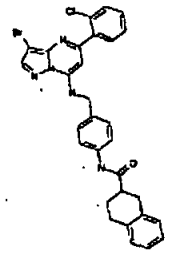
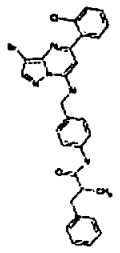
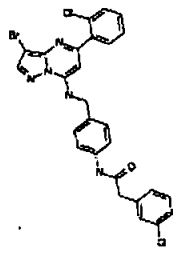
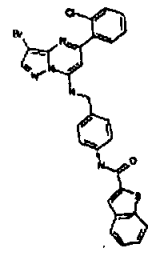
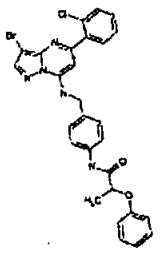
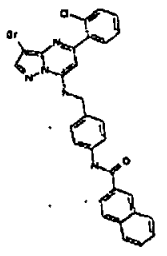
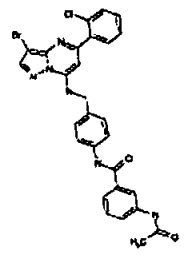
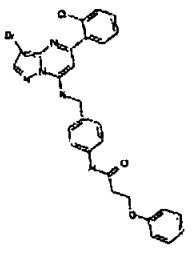
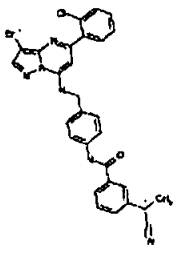
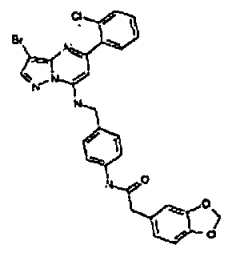
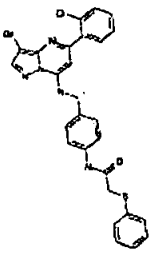
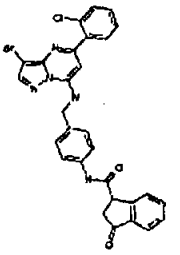
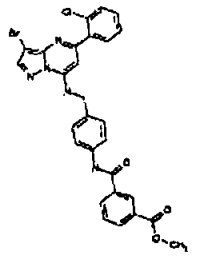
Product	1. Ex. 2. m/z
	1. 4691 2. 652.36
	1. 4692 2. 484.3
	1. 4693 2. 554.3
	1. 4694 2. 548.3
	1. 4695 2. 590.32

TABLE 47

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4701 2. 498.27		1. 4706 2. 528.29		1. 4711 2. 544.3
	1. 4702 2. 512.28		1. 4707 2. 528.29		1. 4712 2. 546.3
	1. 4703 2. 518.28		1. 4708 2. 535.29		1. 4713 2. 548.3
	1. 4704 2. 524.29		1. 4709 2. 540.3		1. 4714 2. 550.3
	1. 4705 2. 528.29		1. 4710 2. 541.3		1. 4715 2. 553.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4716 2. 554.3		1. 4721 2. 562.31		1. 4726 2. 568.31
	1. 4717 2. 554.3		1. 4722 2. 562.31		1. 4727 2. 568.31
	1. 4718 2. 554.3		1. 4723. 2 564.31		1. 4728 2. 568.31
	1. 4719 2. 559.31		1. 4724 2. 564.31		1. 4729 2. 573.32
	1. 4720 2. 559.31		1. 4725 2. 566.31		1. 4730 2. 574.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4731 2. 574.32		1. 4736 2. 580.32		1. 4741 2. 588.32
	1. 4732 2. 576.32		1. 4737 2. 582.32		1. 4742 2. 590.32
	1. 4733 2. 578.32		1. 4738 2. 584.32		1. 4743 2. 591.33
	1. 4734 2. 578.32		1. 4739 2. 585.32		1. 4744 2. 592.33
	1. 4735 2. 580.32		1. 4740 2. 588.32		1. 4745 2. 592.33

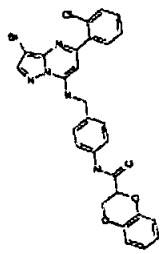
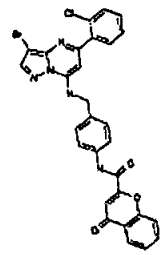
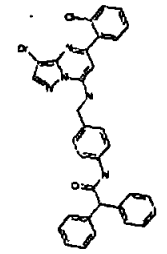
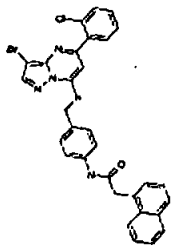
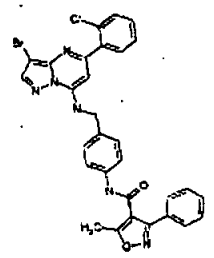
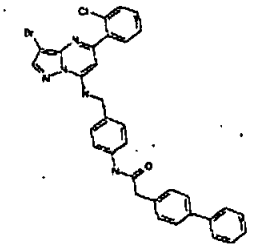
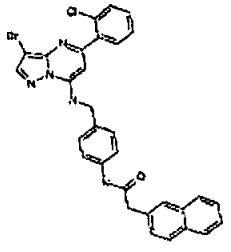
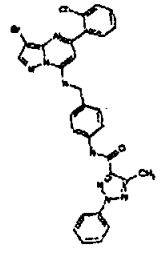
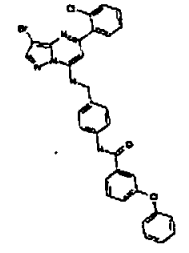
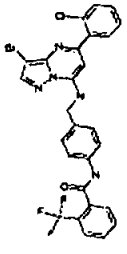
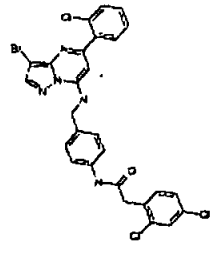
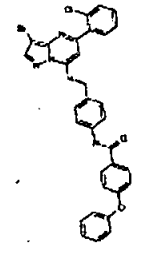
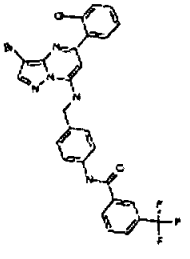
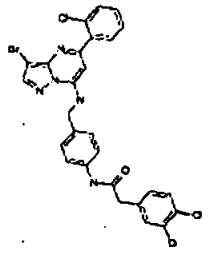
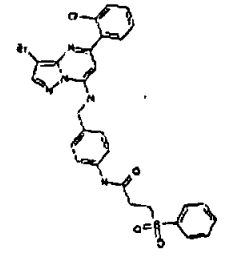
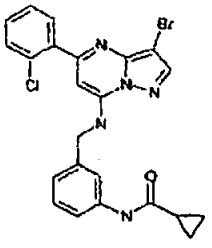
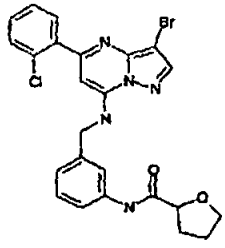
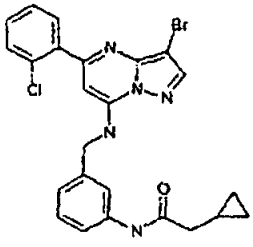
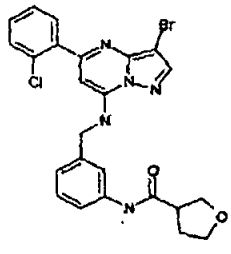
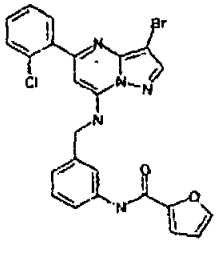
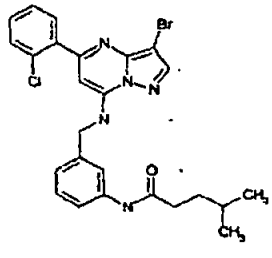
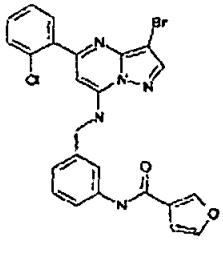
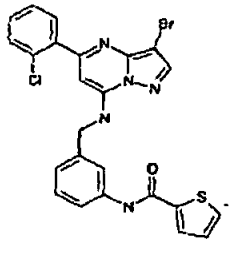
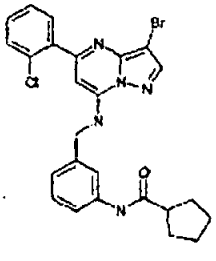
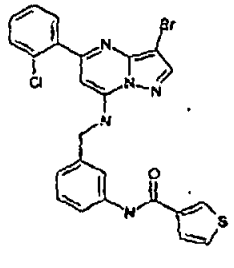
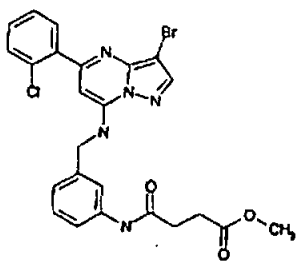
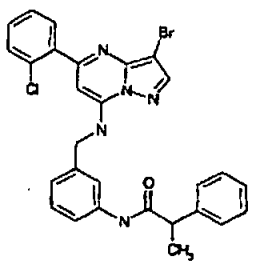
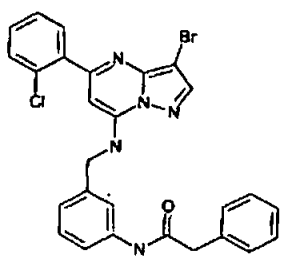
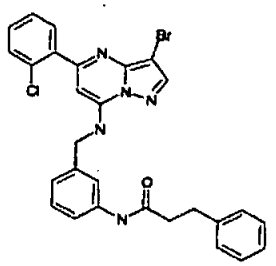
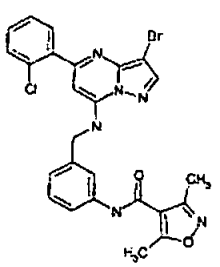
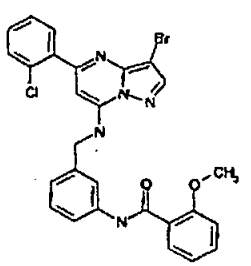
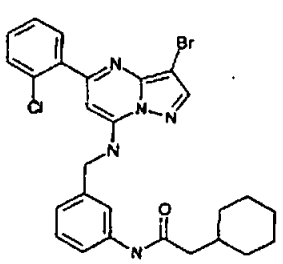
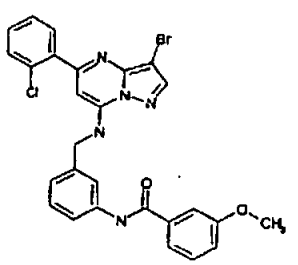
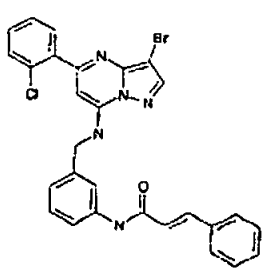
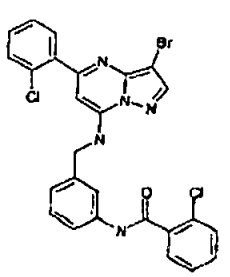
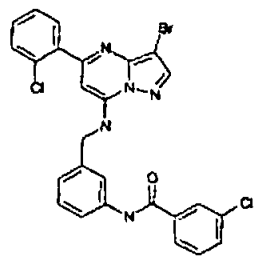
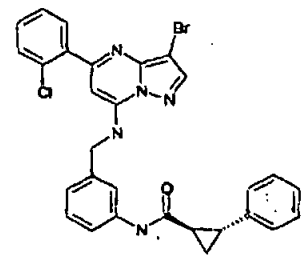
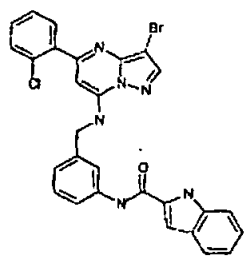
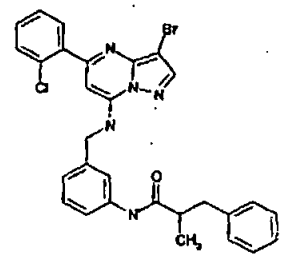
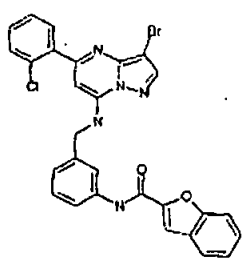
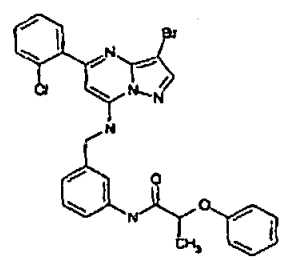
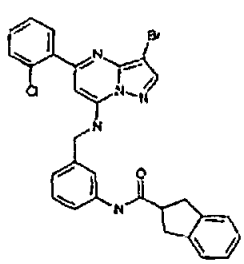
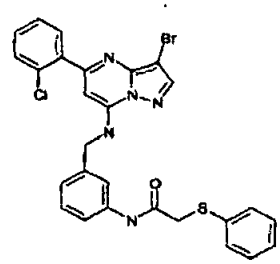
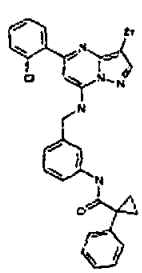
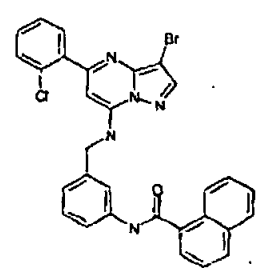
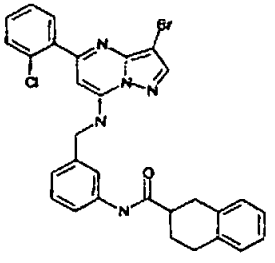
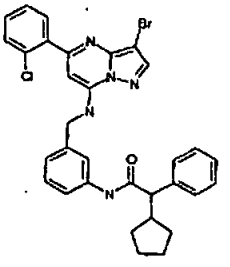
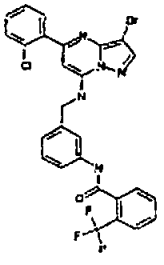
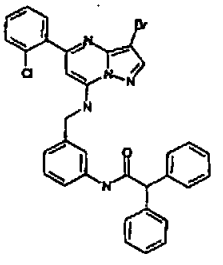
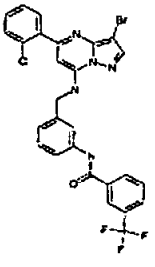
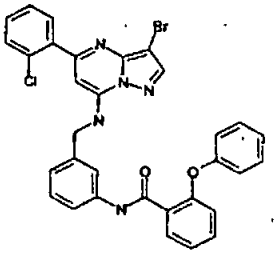
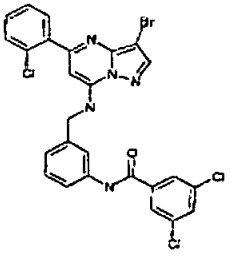
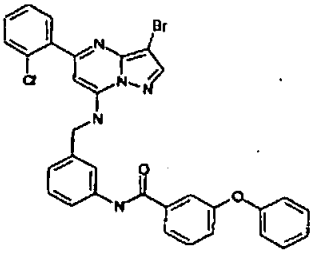
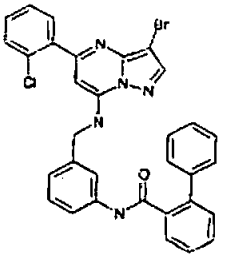
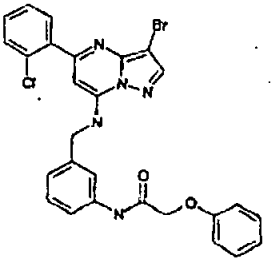
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4746 2. 592.33		1. 4751 2. 602.33		1. 4756 2. 624.34
	1. 4747 2. 598.33		1. 4752 2. 615.34		1. 4757 2. 624.34
	1. 4748 2. 598.33		1. 4753 2. 615.34		1. 4758 2. 626.34
	1. 4749 2. 602.33		1. 4754 2. 616.34		1. 4759 2. 624.34
	1. 4750 2. 602.33		1. 4755 2. 616.34		1. 4760 2. 626.34

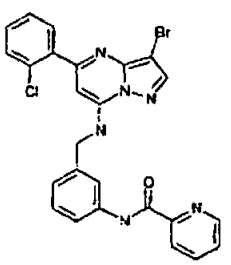
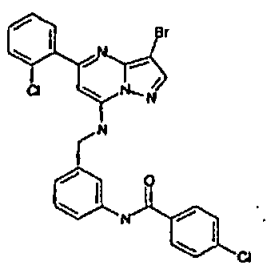
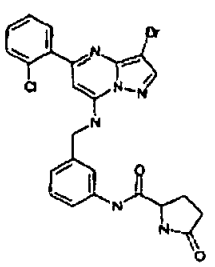
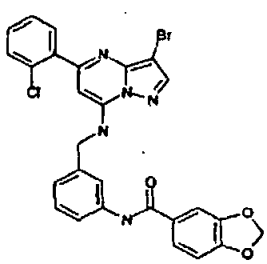
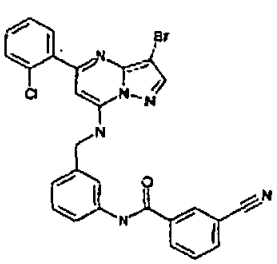
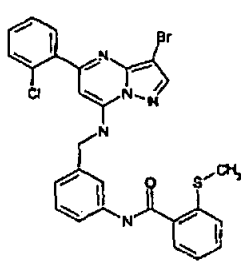
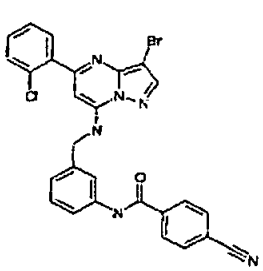
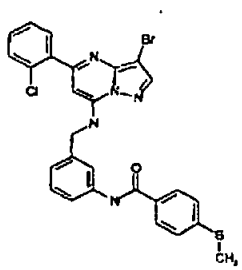
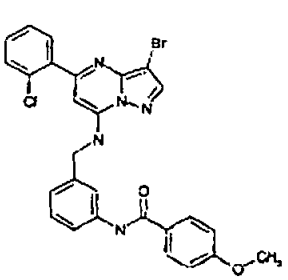
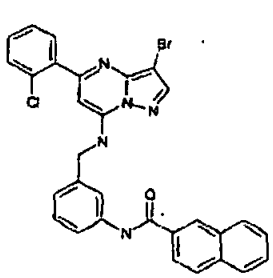
TABLE 48

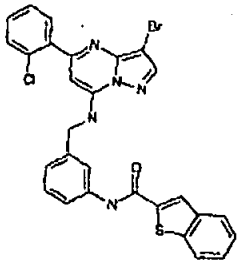
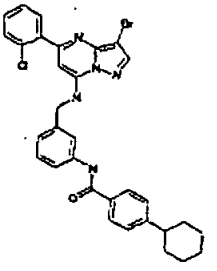
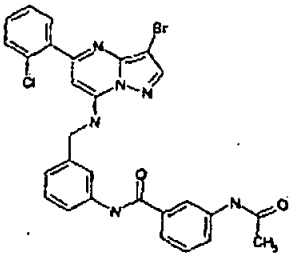
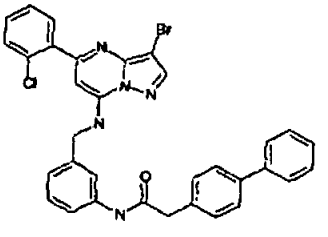
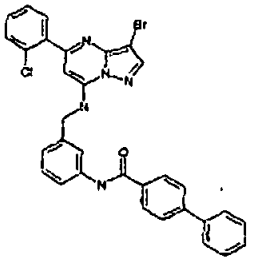
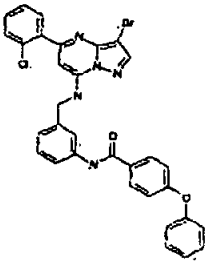
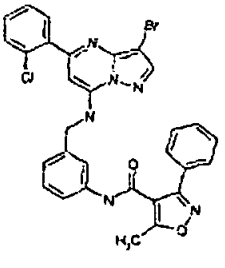
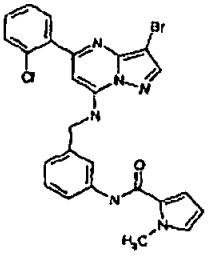
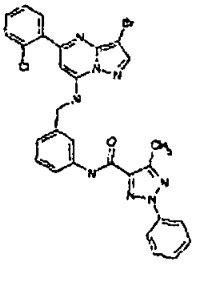
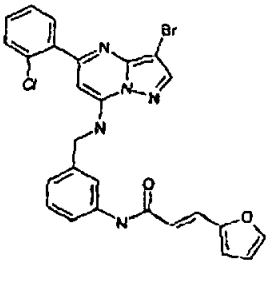
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4801 2. 498.27		1.4806 2. 528.29
	1. 4802 2. 512.28		1.. 4807 2. 528.29
	1. 4803 2. 524.29		1. 4808 2. 528.29
	1. 4804 2. 524.29		1. 4809 2. 540.3
	1. 4805 2. 526.29		1. 4810 2. 540.3

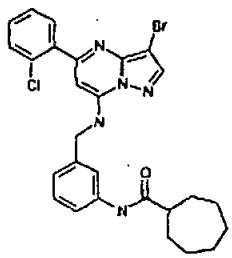
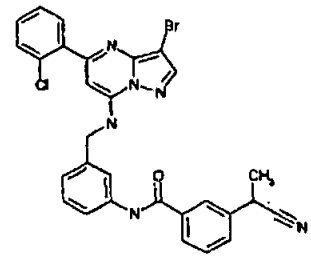
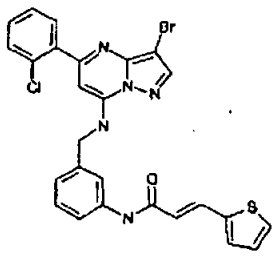
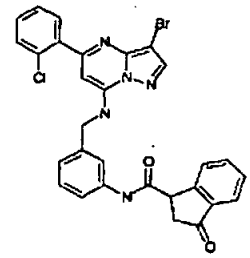
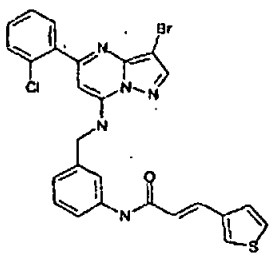
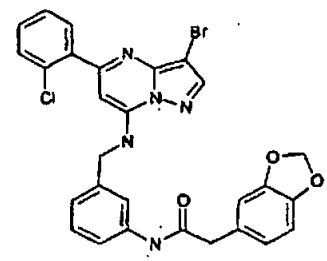
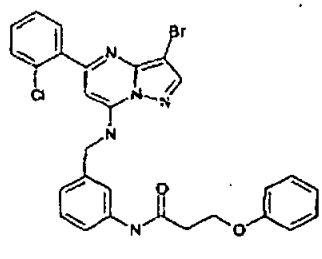
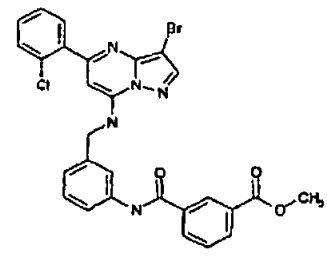
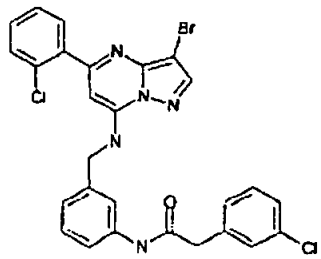
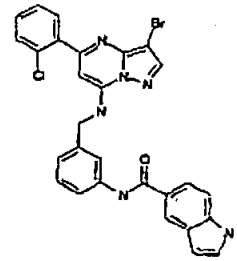
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4811 2. 544.3		1. 4816 2. 562.31
	1. 4812 2. 548.3		1. 4817 2. 562.31
	1. 4813 2. 553.3		1. 4818 2. 564.31
	1. 4814 2. 554.3		1. 4819 2. 564.31
	1. 4815 2. 560.31		1. 4820 2. 568.31

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4821 2. 568.31		1. 4826 2. 574.32
	1. 4822 2. 573.32		1. 4828 2. 576.32
	1. 4821 2. 574.32		1. 4829 2. 578.32
	1. 4824 2. 574.32		1. 4829 2. 580.32
	1. 4825 2. 574.32		1. 4830 2. 584.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4831 2. 588.32		1. 4836 2. 616.34
	1. 4832 2. 602.33		1. 4837 2. 624.34
	1. 4833 2. 602.33		1. 4838 2. 626.34
	1. 4834 2. 602.33		1. 4839 2. 626.34
	1. 4835 2. 610.34		1. 4840 2. 564.31

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4841 2. 535.29		1. 4846 2. 568.31
	1. 4842 2. 541.3		1. 4847 2. 578.32
	1. 4843 2. 559.31		1. 4848 2. 580.32
	1. 4844 2. 559.31		1. 4849 2. 580.32
	1. 4845 2. 564.31		1. 4850 2. 584.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4851 2. 590.32		1. 4856 2. 616.34
	1. 4852 2. 591.33		1. 4857 2. 624.34
	1. 4853 2. 610.34		1. 4858 2. 626.34
	1. 4854 2. 615.34		1. 4859 2. 537.3
	1. 4855 2. 615.34		1. 4860 2. 550.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4861 2. 554.3		1. 4866 2. 587.32
	1. 4862 2. 566.31		1. 4867 2. 588.32
	1. 4863 2. 566.31		1. 4868 2. 592.33
	1. 4864 2. 578.32		1. 4869 2. 592.33
	1. 4865 2. 582.32		1. 4870 2. 573.32

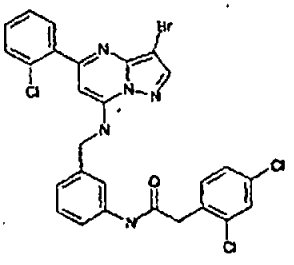
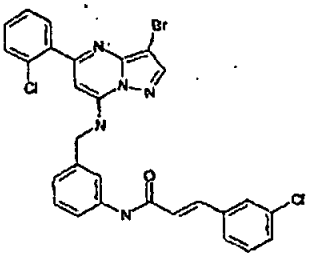
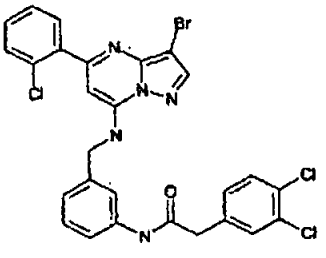
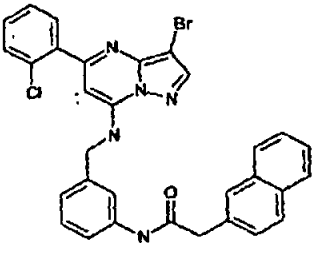
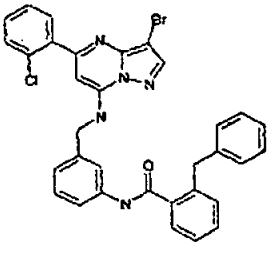
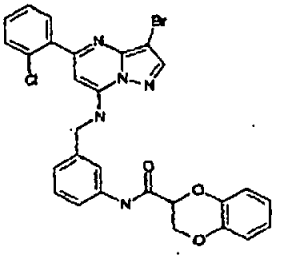
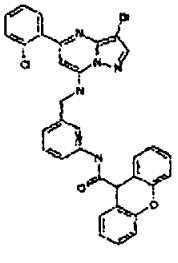
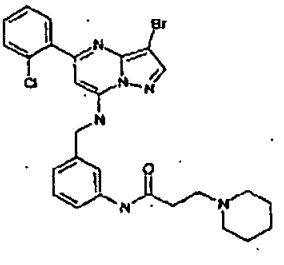
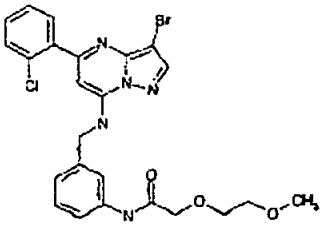
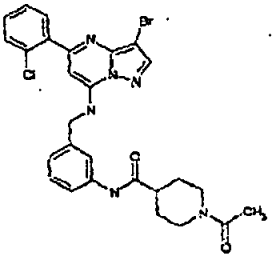
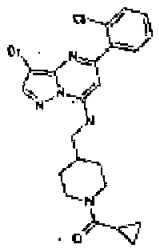
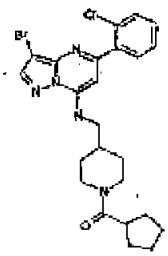
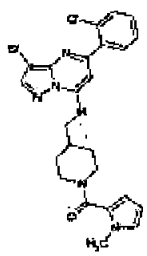
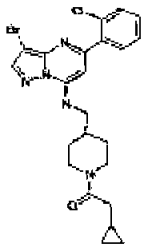
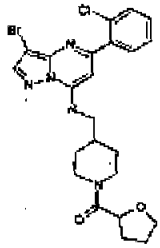
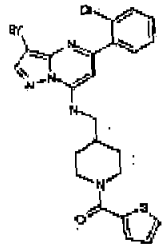
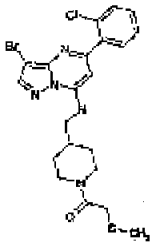
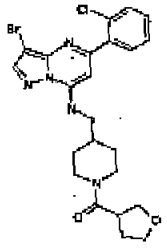
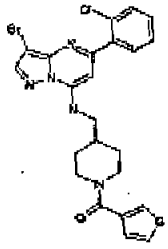
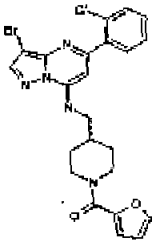
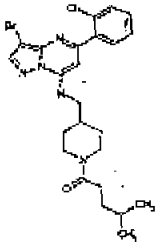
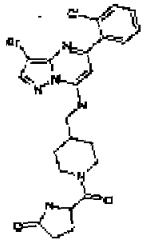
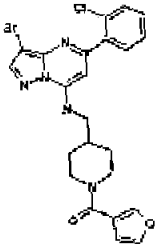
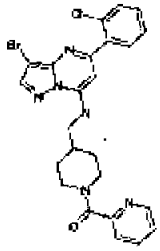
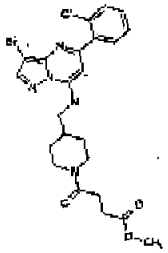
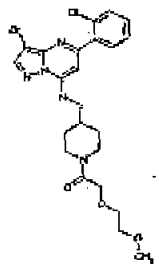
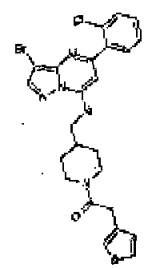
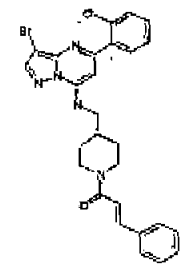
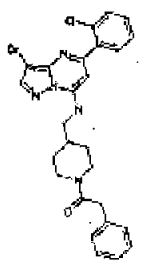
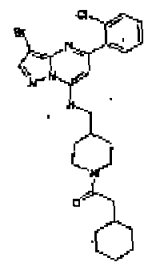
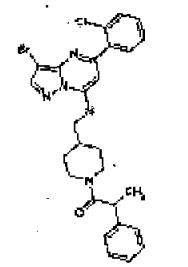
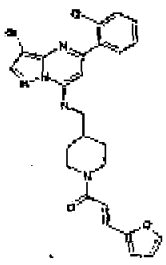
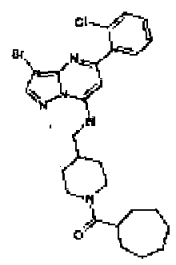
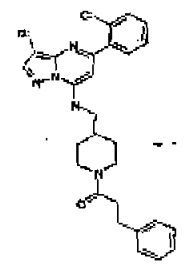
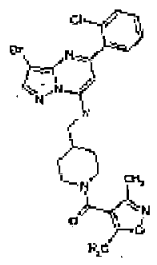
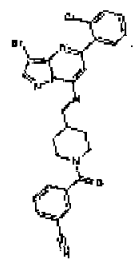
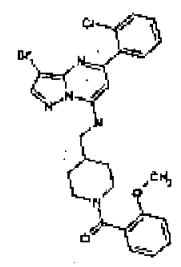
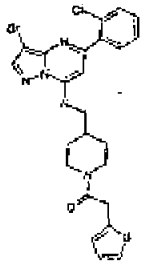
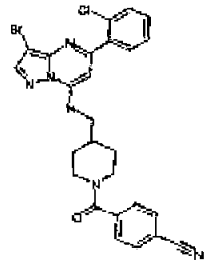
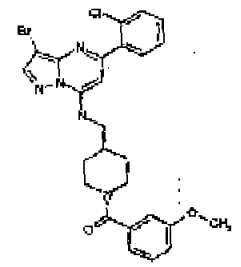
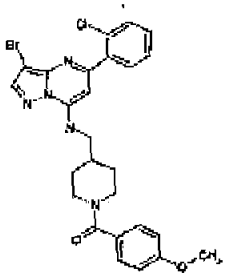
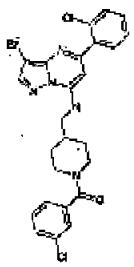
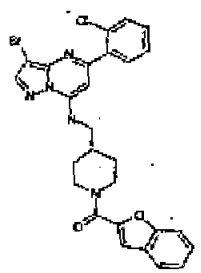
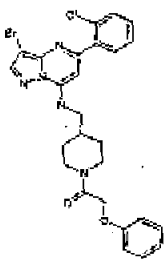
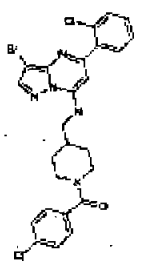
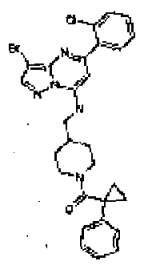
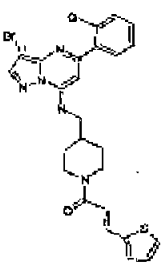
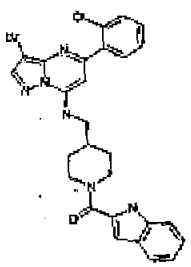
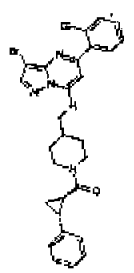
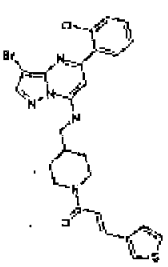
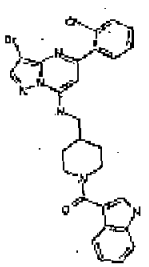
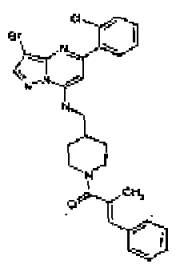
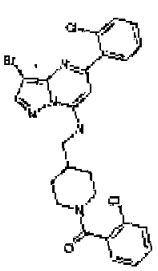
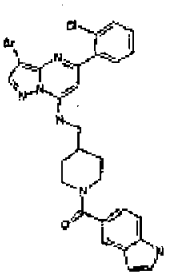
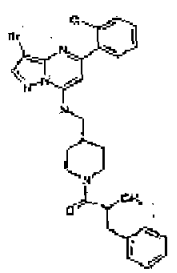
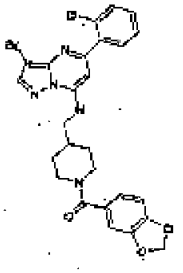
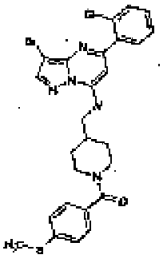
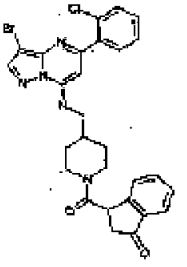
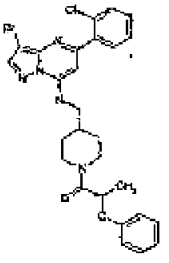
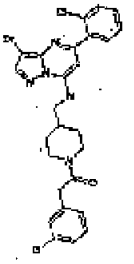
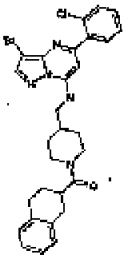
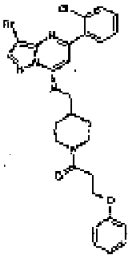
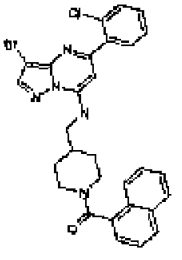
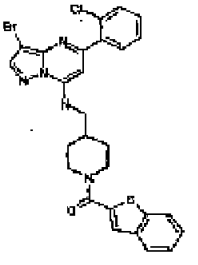
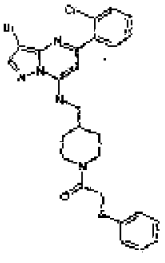
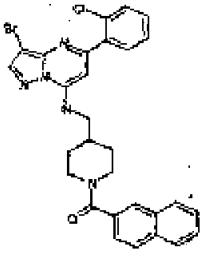
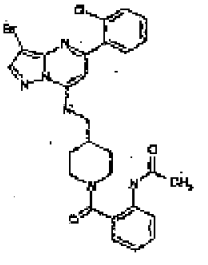
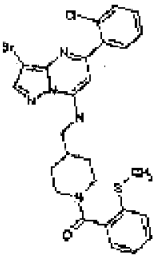
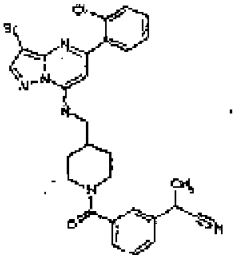
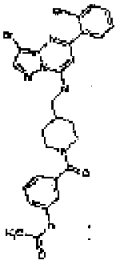
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4871 2. 616.34		1. 4876 2. 594.33
	1. 4872 2. 616.34		1. 4877 2. 598.33
	1. 4873 2. 624.34		1. 4878 2. 592.33
	1. 4874 2. 638.35		1. 4879 2. 569.31
	1. 4875 2. 546.3		1. 4880 2. 583.32

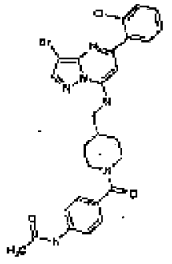
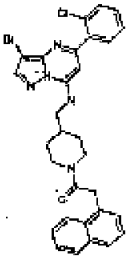
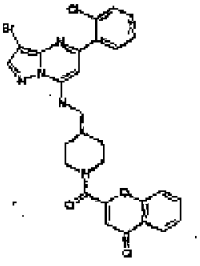
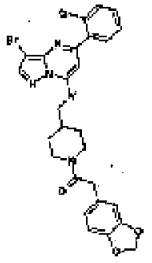
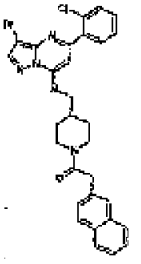
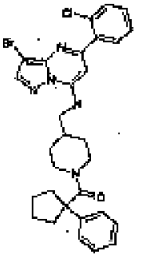
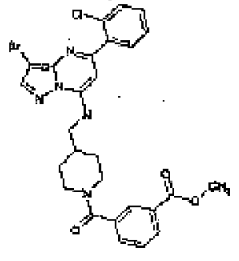
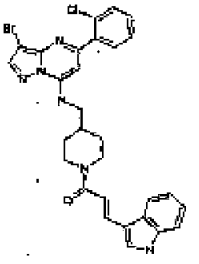
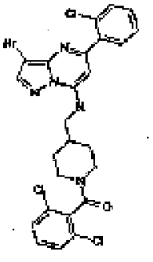
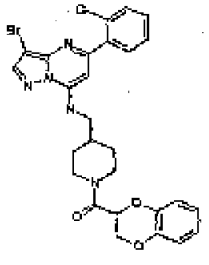
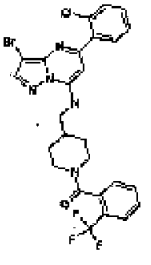
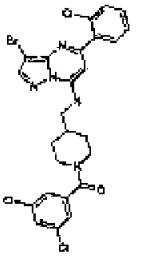
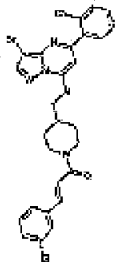
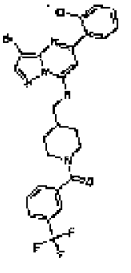
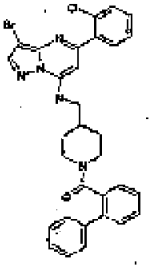
TABLE 49

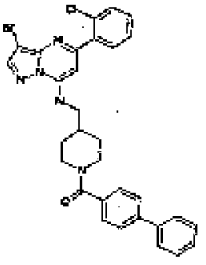
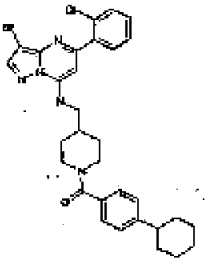
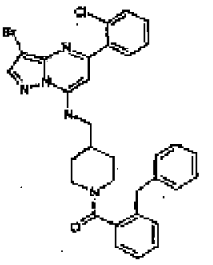
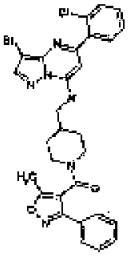
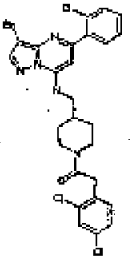
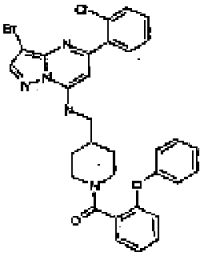
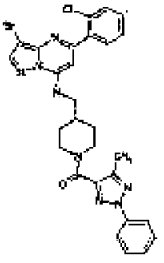
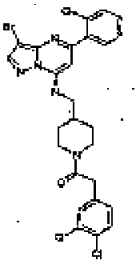
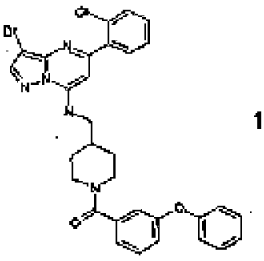
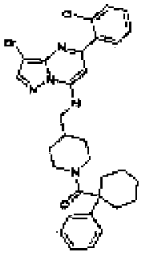
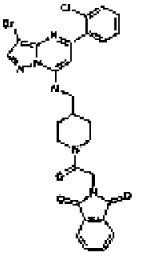
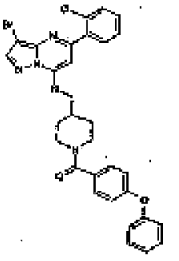
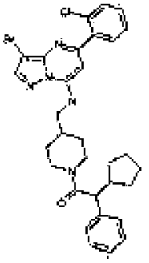
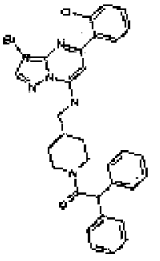
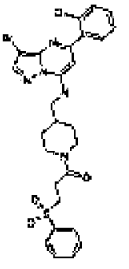
Product	1. Ex. 2, m/z	Product	1. Ex. 2. m/z	Product	1. Ex, 2. m/z
	1. 4901 2. 490.27		1. 4906 2. 518.28		1. 4911 2. 529.29
	1. 4902 2. 504.28		1. 4907 2. 520.29		1. 4912 2. 532.29
	1. 4903 2. 510.28		1. 4908 2. 520.29		1. 4913 2. 532.29
	1. 4904 2. 516.28		1. 4909 2. 520.29		1. 4914 2. 533.29
	1. 4905 2. 516.28		1. 4910 2. 527.29		1. 4915 2. 536.29

Product	1. Ex. 2, m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4916 2. 538.3		1. 4921 2. 546.3		1. 4926 2 552.3
	1. 4917 2 .540.3		1. 4922 2. 546.3		1. 4927 2. 554.3
	1. 4918 2. 542.3		1. 4923 2. 546.3		1. 4928 2. 554.3
	1. 4919 2. 545.3		1. 4924 2. 551.3		1. 4929 2. 556.31
	1. 4920 2. 548.3		1. 4925 2. 551.3		1. 4930 2. 556.31

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4931 2. 556.31		1. 4936 2. 560.31		1. 4941 2. 566.31
	1. 4932 2. 556.31		1. 4937 2. 560.31		1. 4942 2. 566.31
	1. 4933 2. 558.31		1. 4938 2. 565.31		1. 4943 2. 566.31
	1. 4934 3. 558.31		1. 4939 2. 565.3		1. 4944 2. 568.31
	1. 4935 2. 560.31		1. 4940 2. 565.31		1. 4945 2. 568.31

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. m/z
	1. 4946 2. 570.31		1. 4951 2. 571.31		1. 4956 580.3
	1. 4947 2. 570.31		1. 4952 2. 574.32		1. 4957 2 580.32
	1. 4948 2. 570.31		1. 4953 2. 576.32		1. 4958 2. 582.32
	1. 4949 2. 572.31		1. 4954 2. 576.32		1. 4959 2. 583.32
	1. 4950 2. 572.31		. 4955 2. 579.32		1. 4960 2. 583.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. E m
	1. 4961 2. 583.32		1. 4966 2. 590.32		1. 49 594
	1. 4962 2. 584.32		1. 4967 2. 590.32		1. 497 594.3
	1. 4963 2. 584.32		1. 4968 2. 591.3		1. 4973 594.33
	1. 4964 2. 584.32		1. 4969 2. 594.33		1. 4974 2 594.33
	1. 4965 2. 586.32		1. 4970 2. 594.33		1. 4975 2. 602.33

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4976 2. 602.33		1. 4981 2. 608.33		1. 4986 2. 616.34
	1. 4977 2. 607.33		1. 4982 2. 608.33		1. 4987 2. 618.34
	1. 4978 2. 607.33		1. 4983 2. 608.33		1. 4988 2. 618.34
	1. 4979 2. 605.33		1. 4984 2. 609.33		1. 4989 2. 618.34
	1. 4980 2. 608.33		1. 4985 2. 616.34		1. 4990 2. 618.34

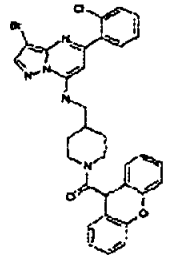
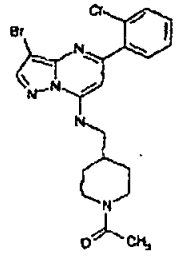
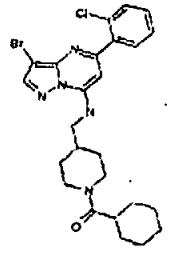
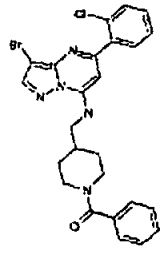
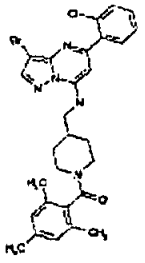
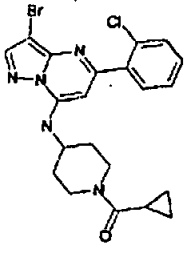
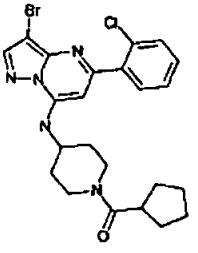
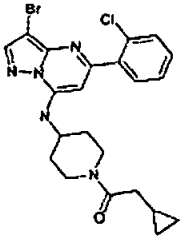
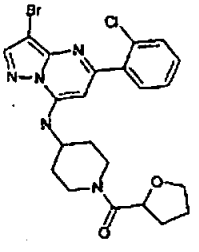
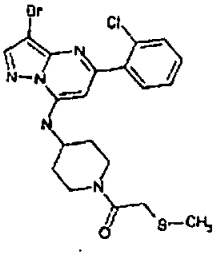
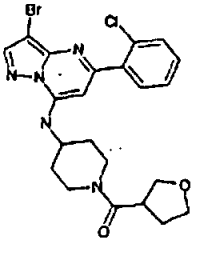
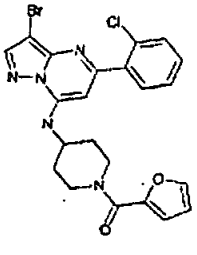
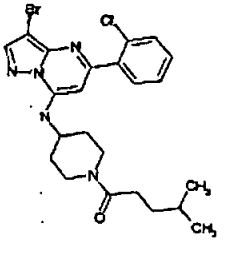
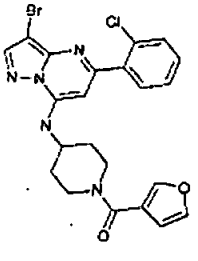
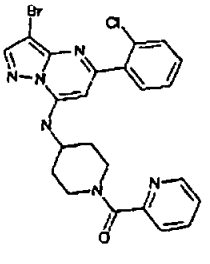
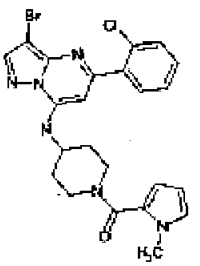
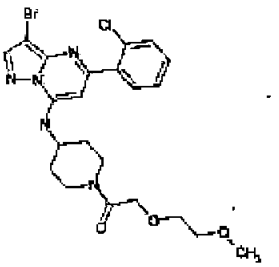
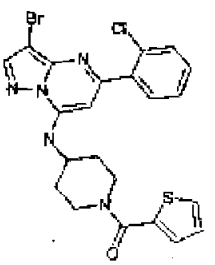
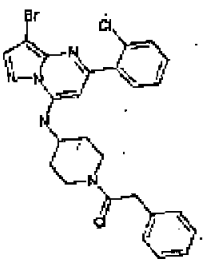
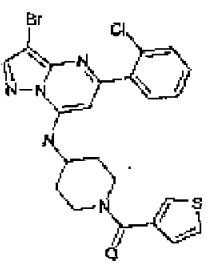
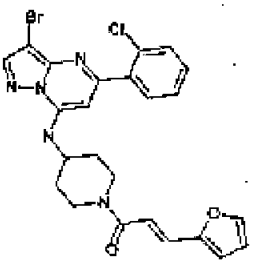
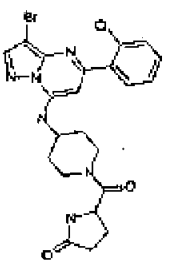
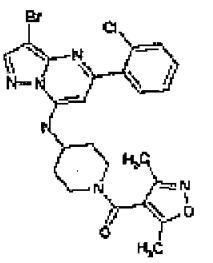
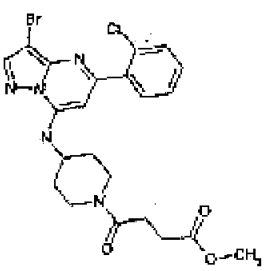
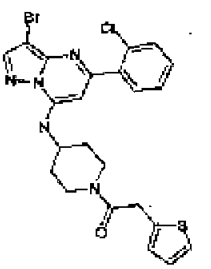
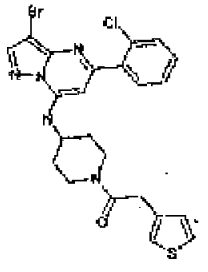
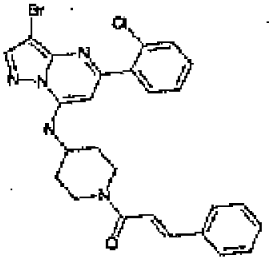
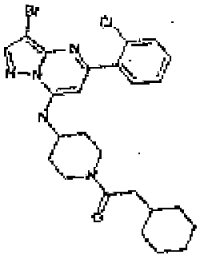
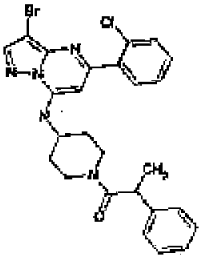
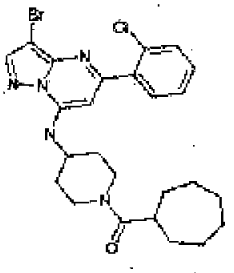
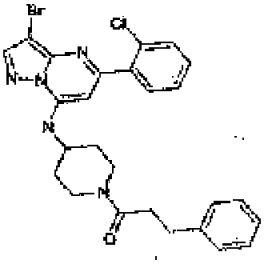
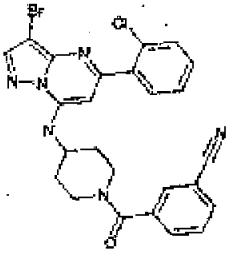
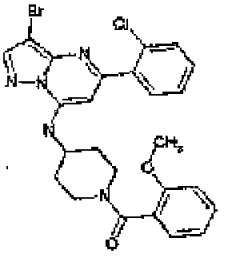
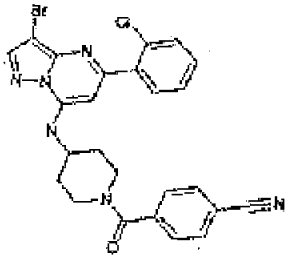
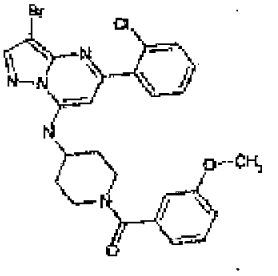
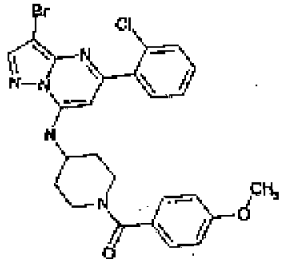
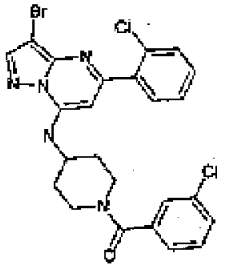
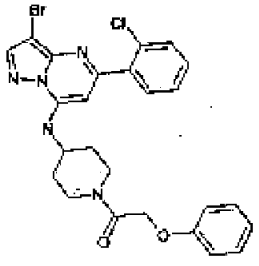
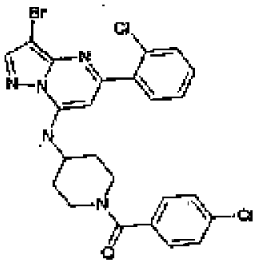
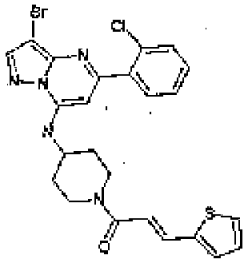
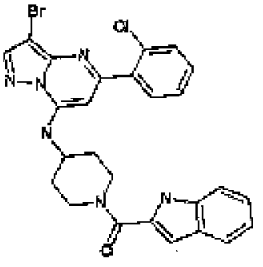
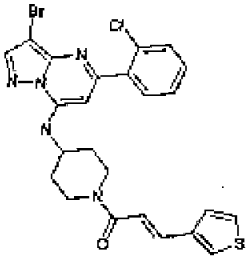
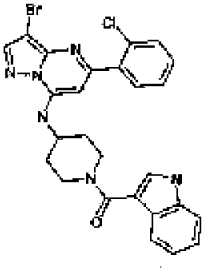
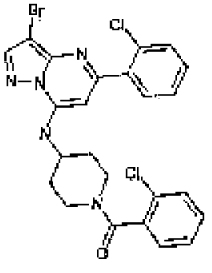
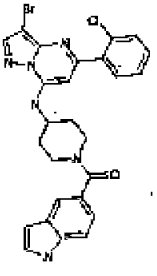
Product	1. Ex. 2. m/z
	1. 4991 2. 630.35
	1. 4992 2. 464.26
	1. 4993 2. 532.29
	1. 4994 2. 526.29
	1. 4995 2. 568.31

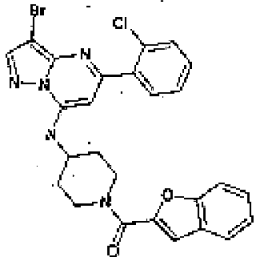
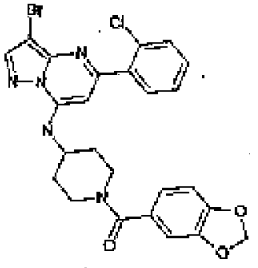
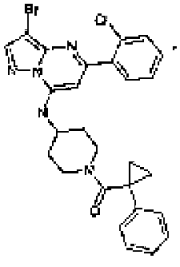
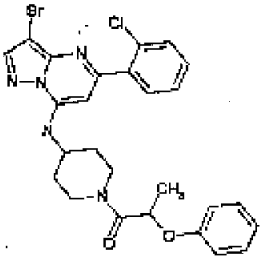
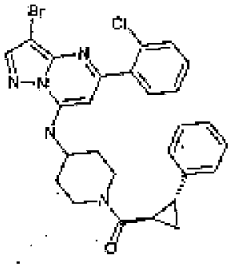
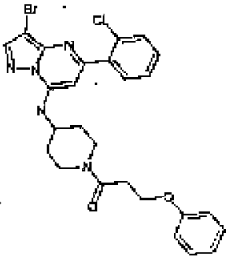
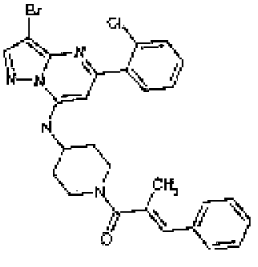
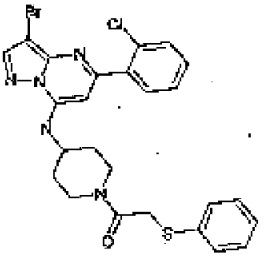
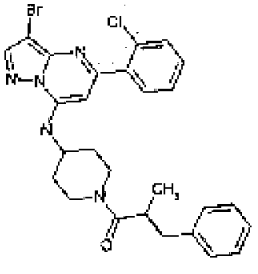
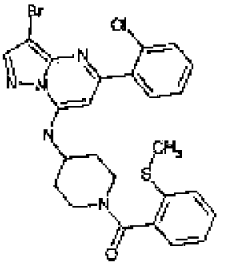
TABLE 50

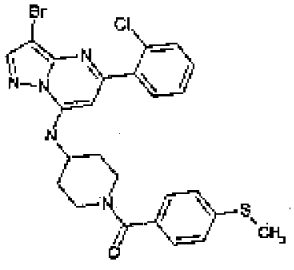
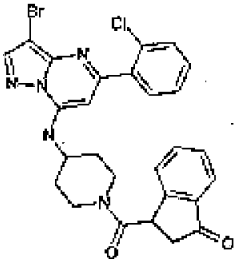
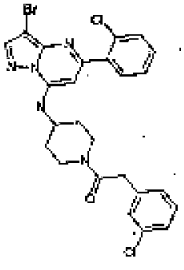
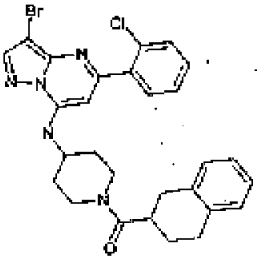
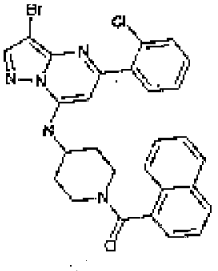
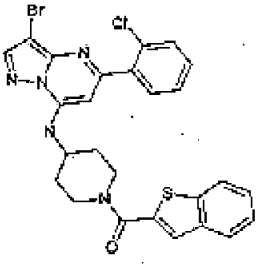
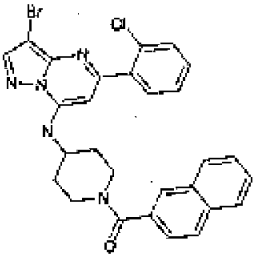
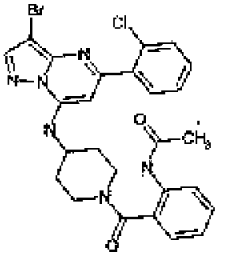
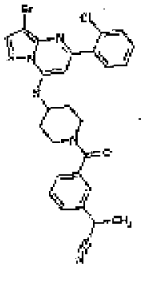
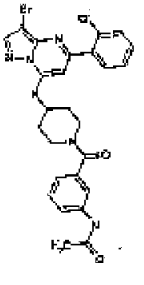
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5001 2.476.26		1. 5006 2. 504.28
	1. 5002 2. 490.27		1. 5007 2. 506.28
	1. 5003 2. 496.27		1. 5008 2. 506.28
	1. 5004 2. 502.28		1. 5009 2. 506.28
	1. 5005 2. 502.28		1. 5010 2. 513.28

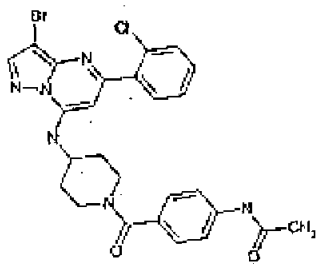
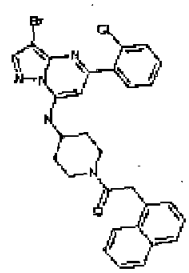
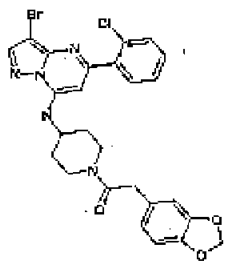
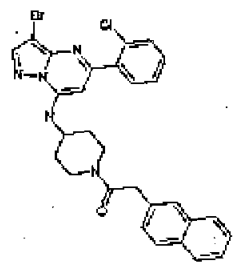
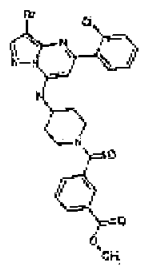
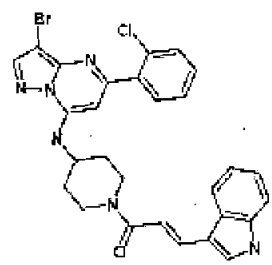
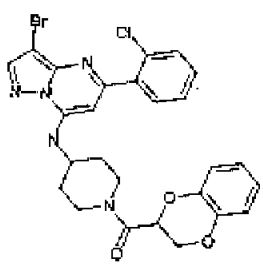
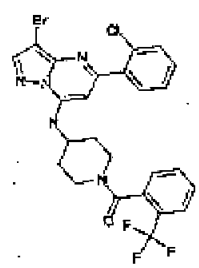
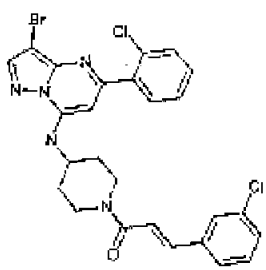
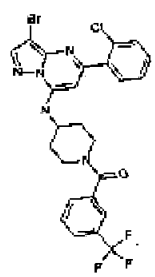
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5011 2. 515.26		1. 5016 2. 524.29
	1. 5012 2. 518.28		1. 5017 2. 526.29
	1. 5013 2. 518.28		1. 5018 2. 528.29
	1. 5014 2. 519.29		1. 5019 2. 531.29
	1. 5015 2. 522.29		1. 5020 2. 532.29

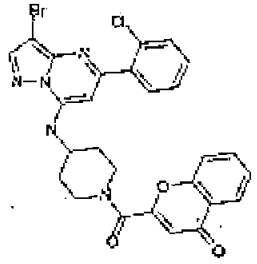
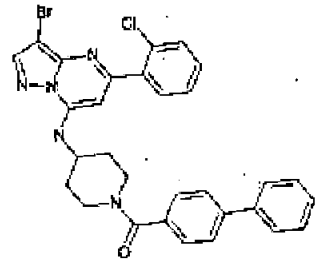
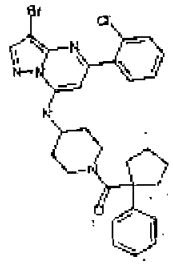
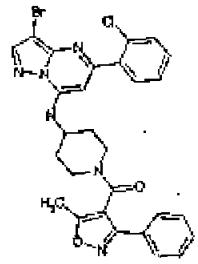
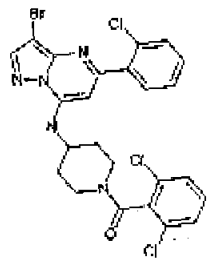
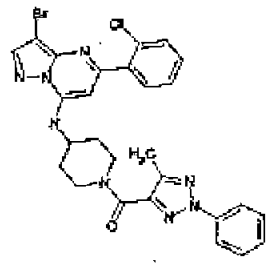
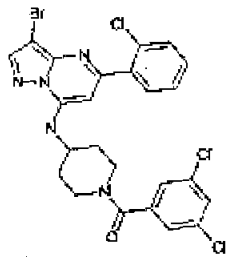
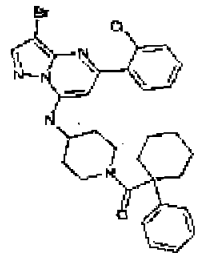
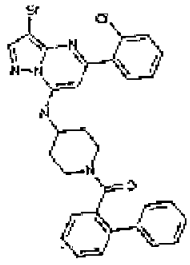
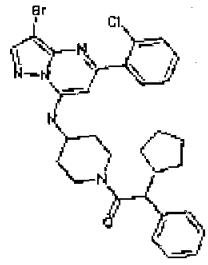
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5021 2. 532.29		1. 5026 2. 538.3
	1. 5022 2. 532.29		1. 5027 2. 540.3
	1. 5023 2. 532.29		1. 5028 2. 540.3
	1. 5024 2. 537.3		1. 5029 2. 542.3
	1. 5025 2. 537.3		1. 5030 2. 542.3

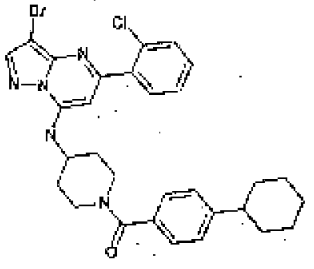
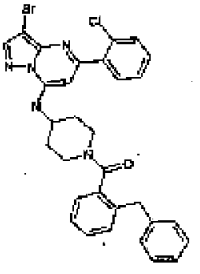
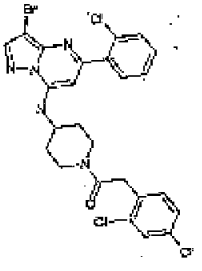
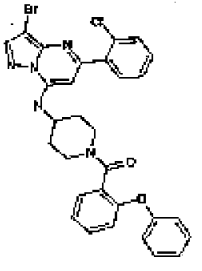
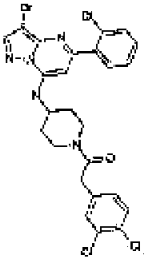
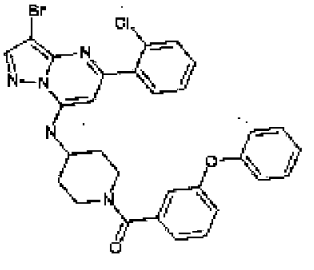
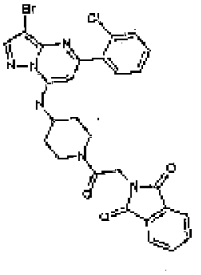
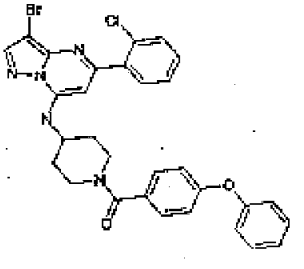
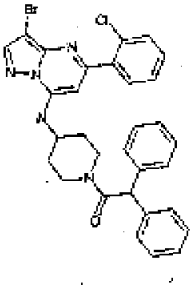
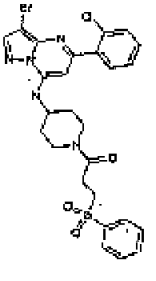
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5031 2. 542.3		1. 5036 2. 546.3
	1. 5032 2. 542.3		1. 5037 2 .546.3
	1. 5033 2. 544.3		1. 5038 2. 551.3
	1. 5034 2. 544.3		1. 5039 2. 551.3
	1. 5035 2 .546.3		1. 5040

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5041 2. 552.3		1. 5046 2. 556.31
	1. 5042 2. 552.3		1. 5047 2. 556.31
	1. 5043 2. 552.3		1. 5048 2. 556.31
	1. 5044 2. 552.3		1. 5049 2. 558.31
	1. 5045 2. 554.3		1. 5050 2. 558.31

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5051 2. 558.31		1. 5056 2. 566.31
	1. 5052 2. 560.31		1. 5057 2. 566.31
	1. 5053 2. 562.31		1. 5058 2. 568.31
	1. 5054 2. 562.31		1. 5059 2. 569.31
	1. 5055 2. 565.31		1. 5060 2. 569.31

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5061		1. 5066 2. 576.32
	1. 5062 2. 570.31		1. 5067 2. 576.32
	1. 5063 2. 570.31		1. 5068 2. 577.32
	1. 5064 2. 570.31		1. 5069 2. 580.32
	1. 5065 572.31		1. 5070 2. 580.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5071 2. 580.32		1 5076 2. 588.32
	1. 5072 2. 580.32		1. 5077 2. 593.33
	1 5073 2. 580.32		1 5078 2. 593.33
	1 5074 2. 580.32		1. 5079 2. 594.33
	1 5075 2. 588.32		1. 5080 2. 594.33

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5081 2. 594.33		1. 5086 2. 602.33
	1. 5082 2. 594.33		1.5087 2. 604.33
	1. 5083 2. 594.33		1. 5088 2. 604.33
	1. 5084 2. 595.33		1. 5089 2. 604.33
	1.5085 2. 602.33		1. 5090 2. 604.33

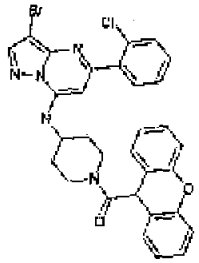
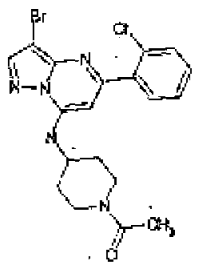
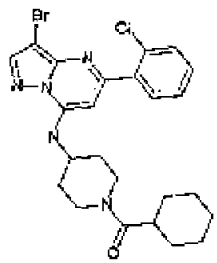
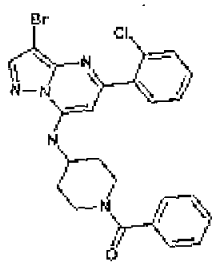
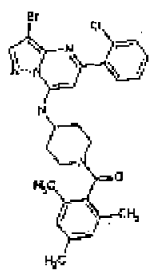
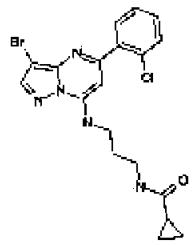
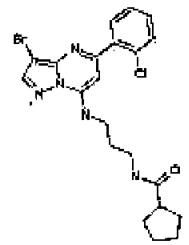
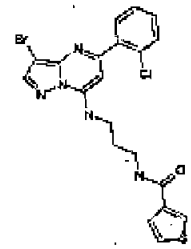
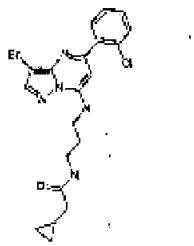
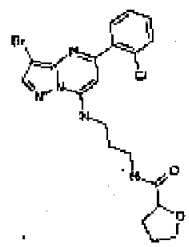
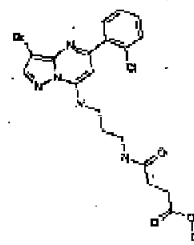
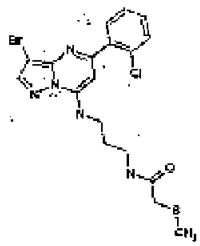
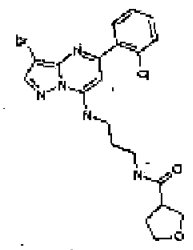
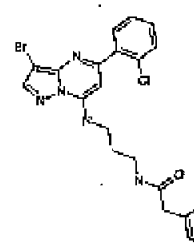
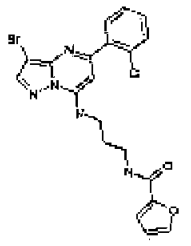
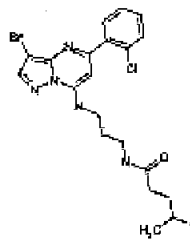
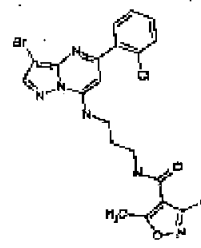
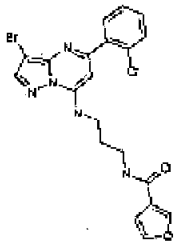
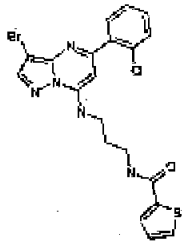
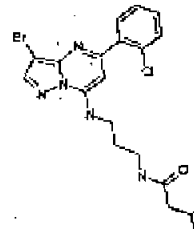
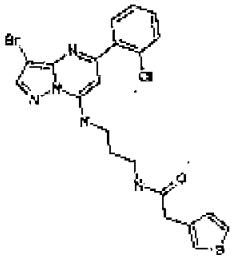
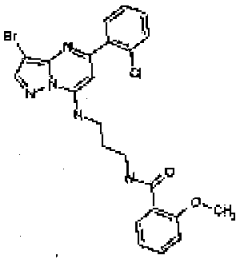
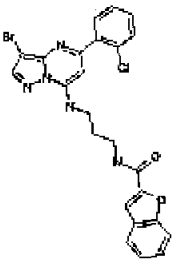
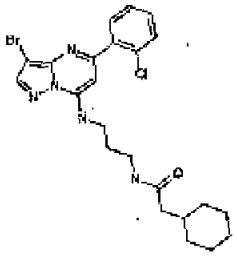
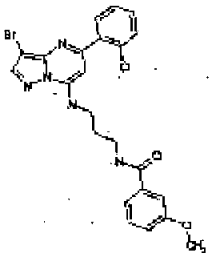
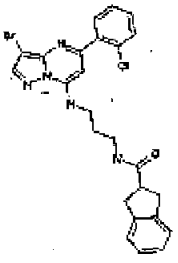
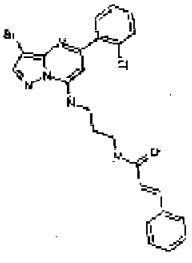
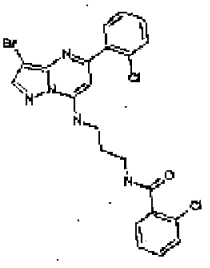
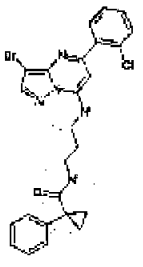
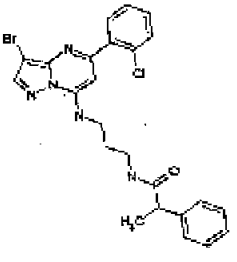
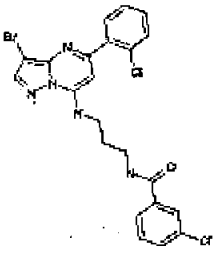
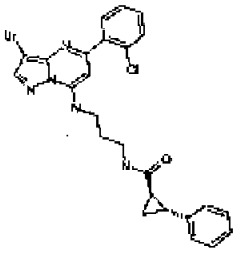
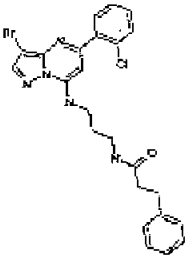
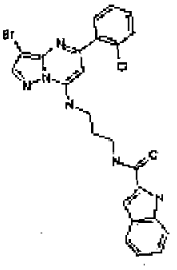
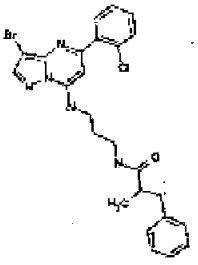
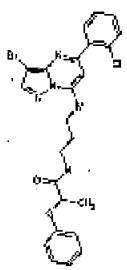
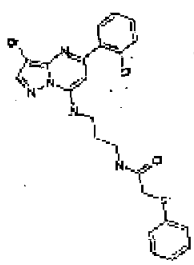
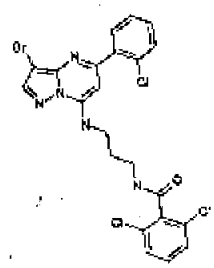
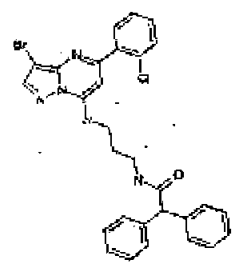
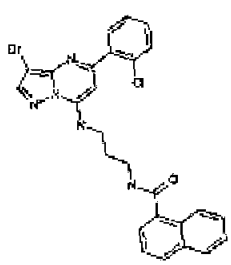
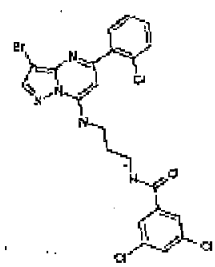
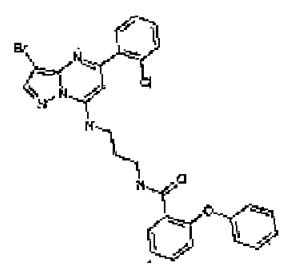
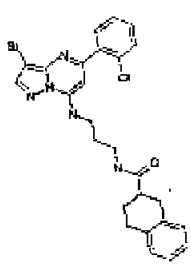
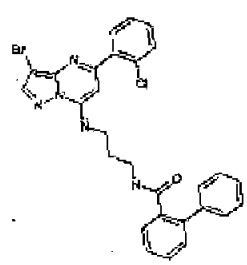
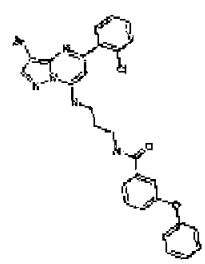
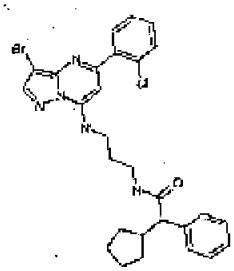
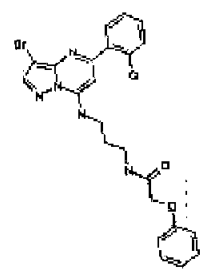
Product	1. Ex. 2. m/z
	1. 5091 2. 616.34
	1. 5092 2. 450.25
	1. 5093 2. 518.28
	1. 5094 2. 512.28
	1. 5095 2.554.3

TABLE 51

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5101 2. 448.8		1. 5106 2. 476.8		1. 5111 2. 490.8
	1. 5102 2. 462.8		1. 5107 2. 478.8		1. 5112 2. 494.8
	1. 5103 2. 468.8		1. 5108 2. 478.8		1. 5113 2. 498.8
	1. 5104 2. 474.7		1. 5109 2. 478.8		1. 5114 2. 503.8
	1. 5105 2. 474.7		1. 5110 2. 490.8		1. 5115 2. 504.8

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5116 2. 504.8		1. 5121 2. 514.8		1. 5126 2. 524.8
	1. 5117 2. 504.9		1. 5122 2. 514.8		1. 5127 2. 524.9
	1. 5118 2. 510.8		1. 5123 2. 519.2		1. 5128 2 . 524.9
	1. 5119 2. 512.8		1. 5124 2. 519.2		1. 5129 2. 524.9
	1. 5120 2. 512.8		1. 5125 2. 523.8		1. 5130 2. 526.9

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5131 2. 528.8		1. 5136 2. 552.8		1. 5141 2. 567.8
	1. 5132 2. 530.9		1. 5137 2. 553.7		1. 5142 2. 574.9
	1. 5133 2. 534.8		1. 5138 2. 553.7		1. 5143 2. 576.9
	1. 5134 2. 538.9		1. 5139 2. 560.9		1. 5144 2. 576.9
	1. 5135 2. 552.8		1. 5140 2. 566.9		1. 5145 2. 514.8

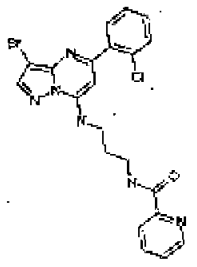
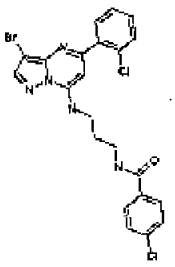
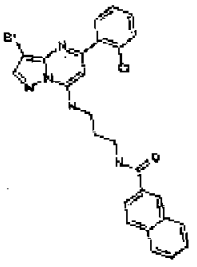
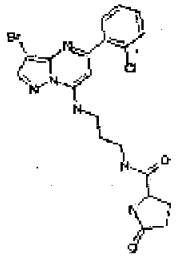
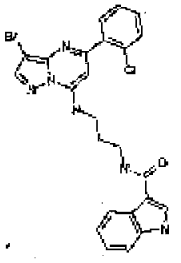
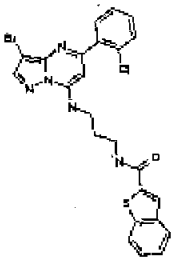
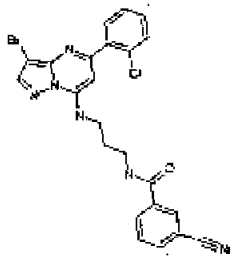
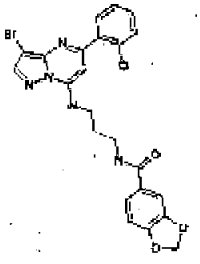
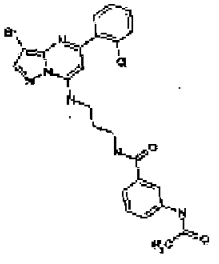
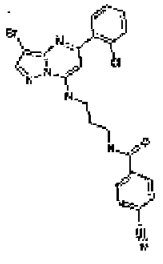
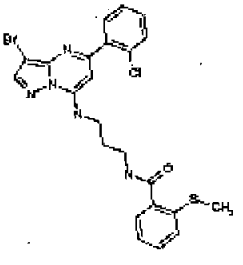
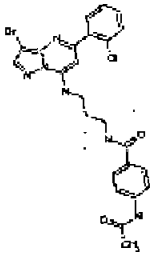
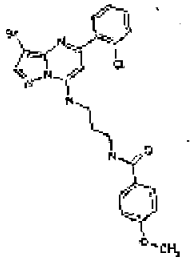
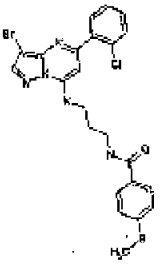
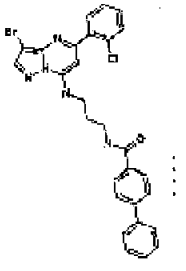
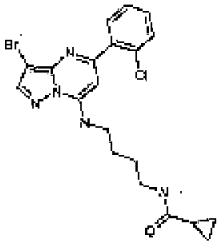
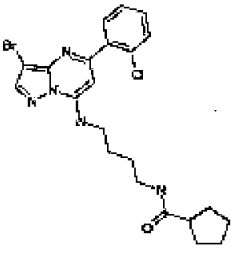
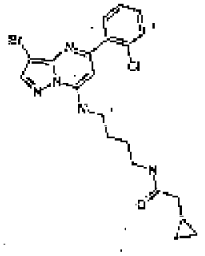
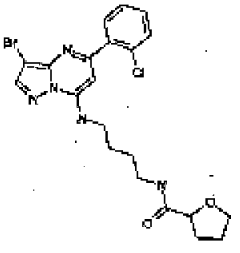
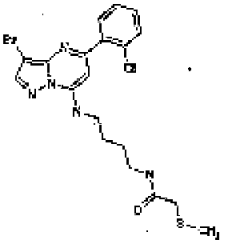
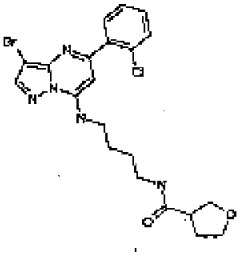
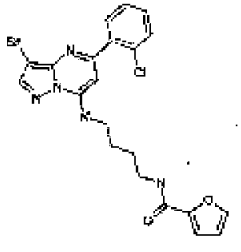
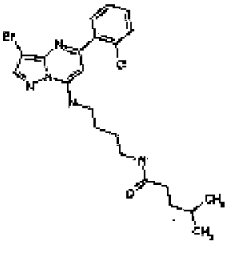
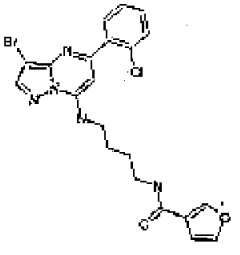
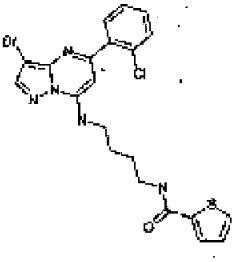
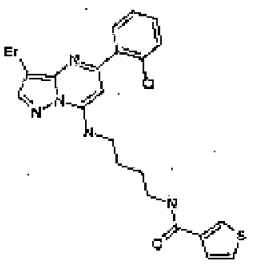
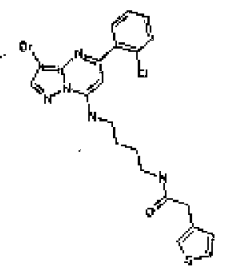
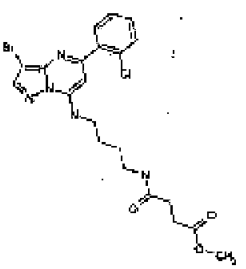
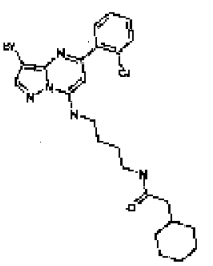
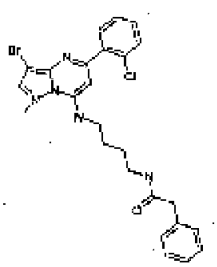
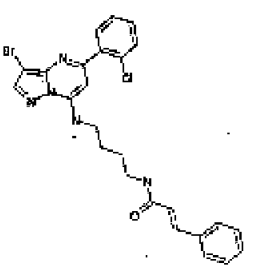
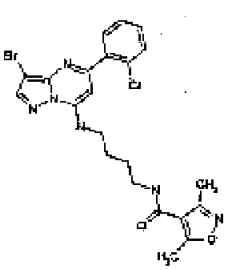
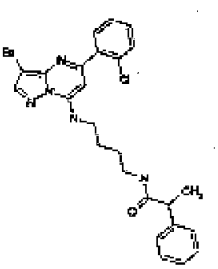
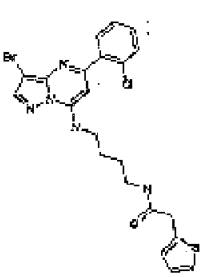
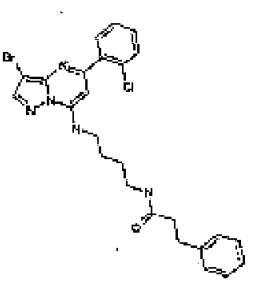
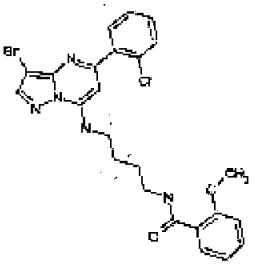
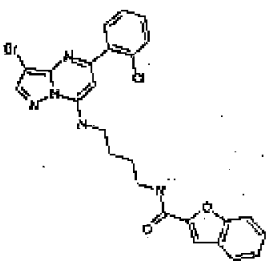
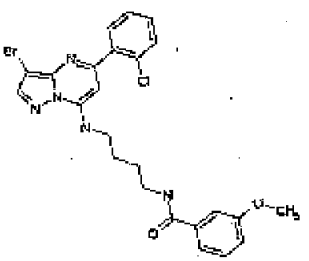
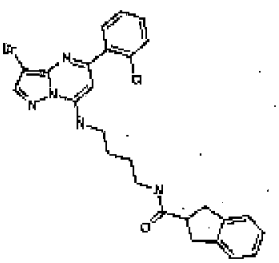
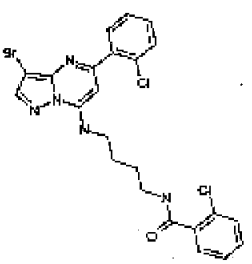
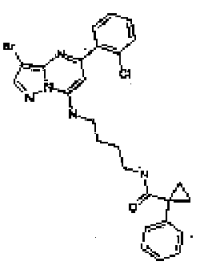
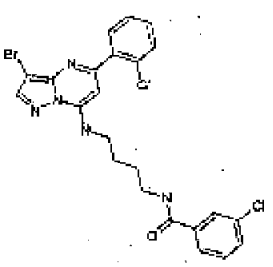
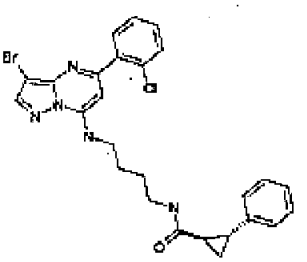
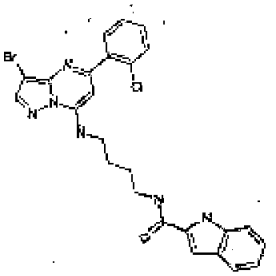
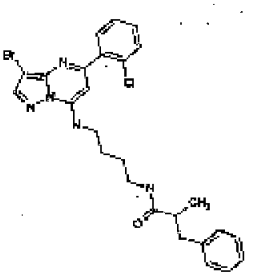
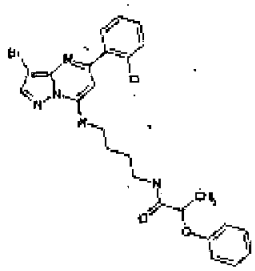
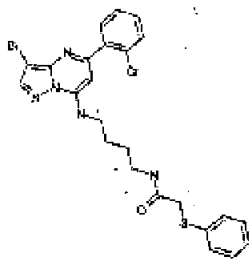
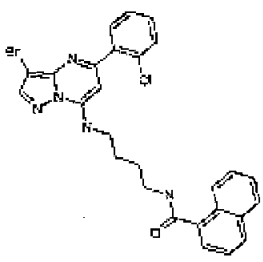
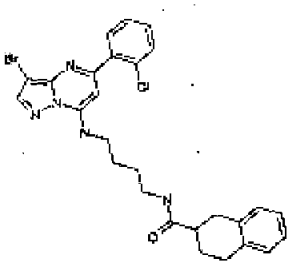
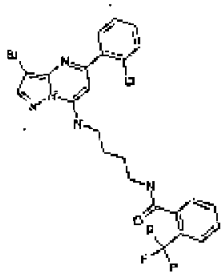
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5146 2. 485.8		1. 5151 2. 519.2		1. 5156 2. 534.8
	1. 5147 2. 491.8		1. 5152 2. 523.8		1. 5157 2. 540.9
	1. 5148 2. 509.8		1. 5153 2. 528.8		1. 5158 2. 541.8
	1. 5149 2. 509.8		1. 5154 2. 530.9		1. 5159 2. 541.8
	1. 5150 2. 514.8		1. 5155 2. 530.9		1. 5160 2. 560.9

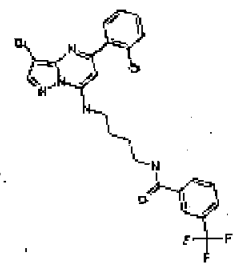
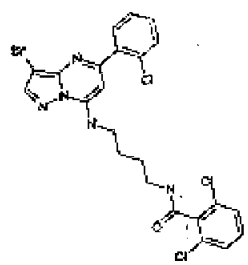
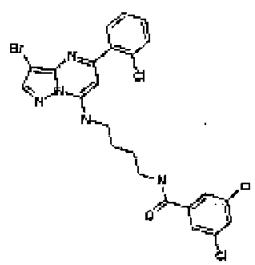
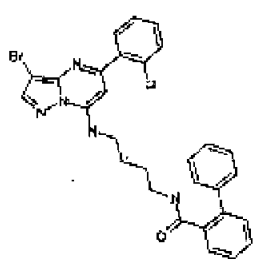
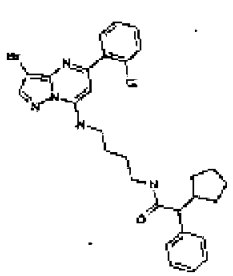
TABLE 52

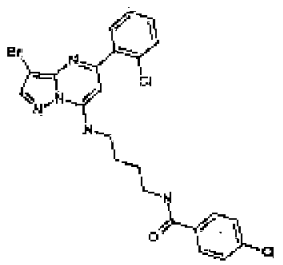
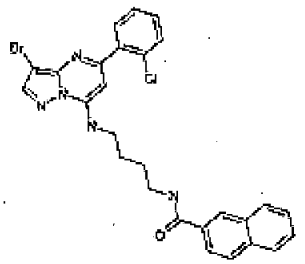
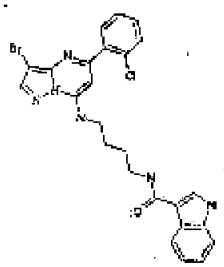
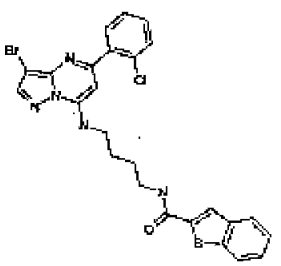
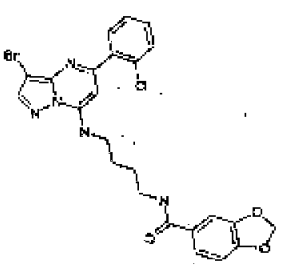
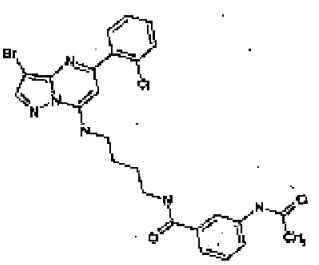
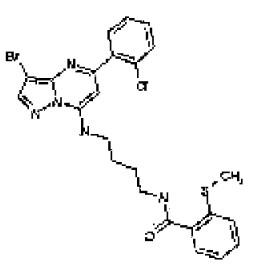
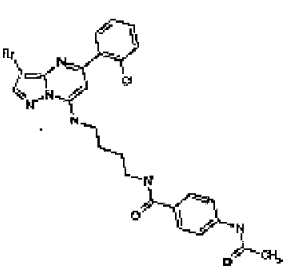
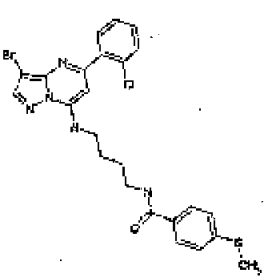
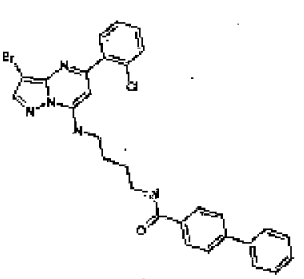
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5201 2. 462.8		1. 5206 2. 490.8
	1. 5202 2. 476.8		1. 5207 2. 492.8
	1. 5203 2. 482.8		1. 5208 2. 492.8
	1. 5204 2. 488.8		1. 52009 2. 492.9
	1. 5205 2. 468.8		1. 5210 2. 504.8

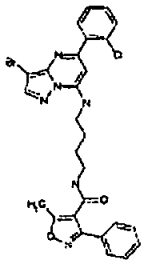
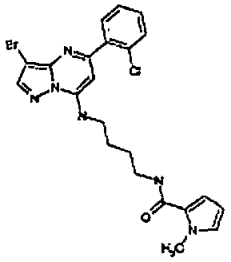
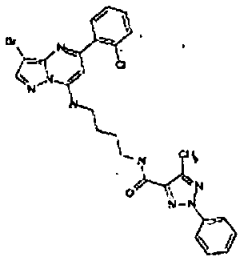
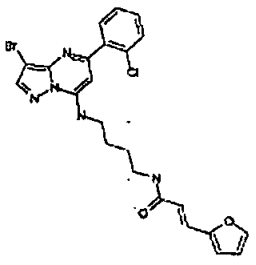
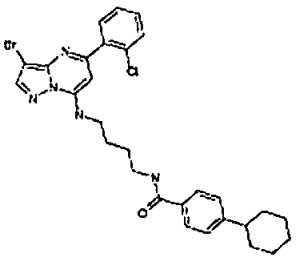
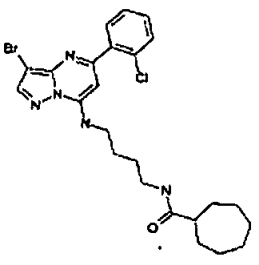
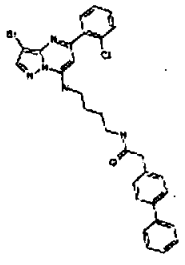
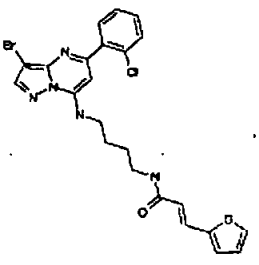
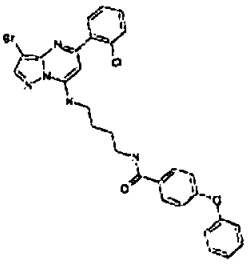
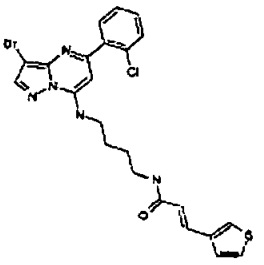
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5211 2. 504.8		1. 5216 2. 518.9
	2. 5212 2. 508.8		1. 5217 2. 518.9
	1. 5213 2. 512.8		1. 5218 2. 524.9
	1. 5214 2. 517.8		1. 5219 2. 526.9
	1. 5215 2. 518.9		1. 5220 2. 526.9

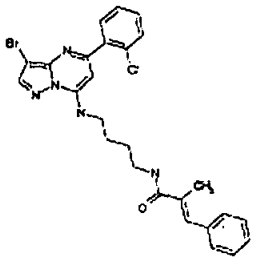
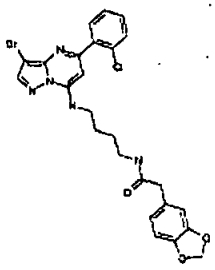
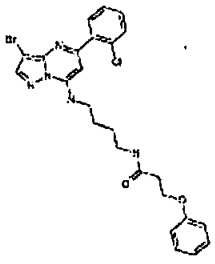
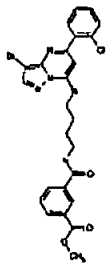
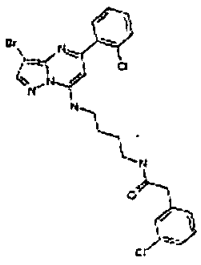
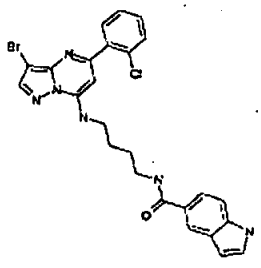
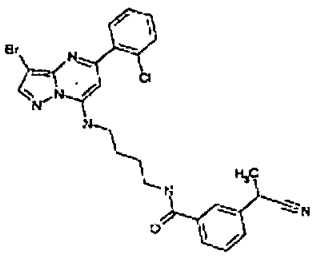
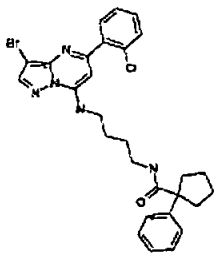
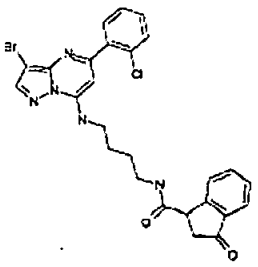
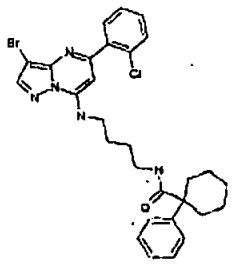
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5221 2. 528.8		1. 5226 2. 536.8
	1. 5222 2. 528.8		1. 5227 2. 538.9
	1. 5223 2. 533.3		1. 5228 2. 536.9
	1. 5224 2. 533.3		1. 5229 2. 536.9
	1. 5225 2. 537.9		1. 5230 2. 540.9

Product	1. Ex. 2. m/z
	1. 5231 2. 542.9
	1. 5232 2. 544.9
	1. 5233 2. 548.9
	1. 5234 2. 552.9
	1. 5235 2. 566.8

Product	1. Ex. 2. m/z
	1. 5236 2. 566.8
	1. 5237 2. 567.7
	1. 5238 2. 567.7
	1. 5239 2. 574.9
	1. 5240 2. 581

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5241 2. 533.3		1. 5246 2. 548.9
	1. 5242 2. 537.9		1. 5247 2. 554.9
	1. 5243 2. 542.8		1. 5248 2. 555.9
	1. 5244 2. 544.9		1. 5249 2. 555.9
	1. 5245 2. 544.9		1. 5250 2. 574.9

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5251 2. 579.9		1. 5256 2. 501.8
	1. 5252 2. 579.9		1. 5257 2. 514.8
	1. 5253 2. 581		1. 5258 2. 518.9
	1. 5254 2. 588.9		1. 5259 2. 530.9
	1. 5255 2. 590.9		1. 5260 2. 530.9

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5261 2. 538.9		1. 5266 2. 556.9
	1. 5262 2. 542.9		1. 5267 2. 556.9
	1. 5263 2. 547.3		1. 5268 2. 537.9
	1. 5264 2. 551.9		1. 5269 2. 566.9
	1. 5265 2. 552.9		1. 5270 2. 581

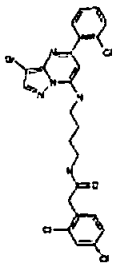
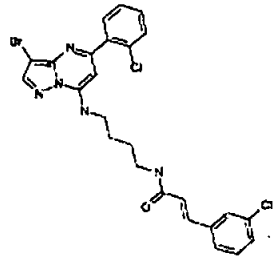
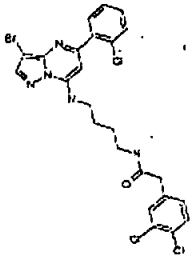
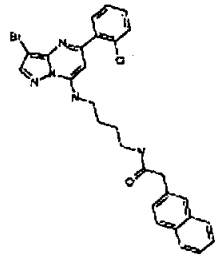
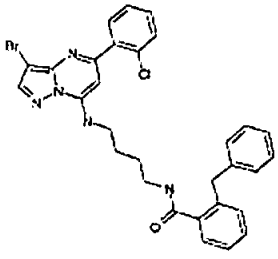
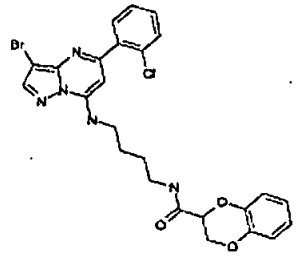
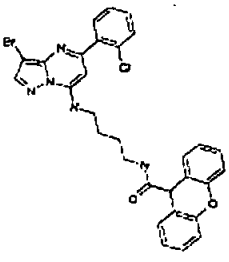
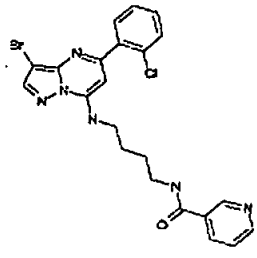
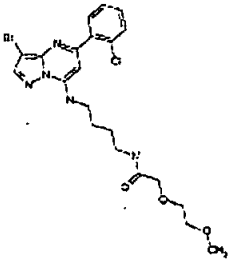
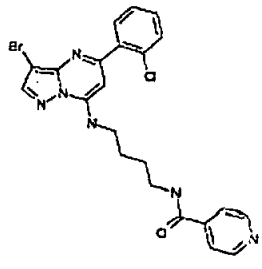
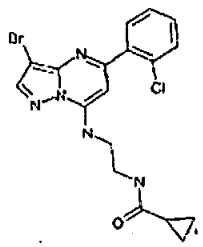
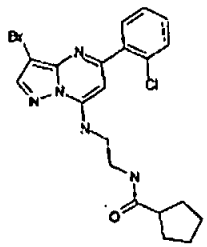
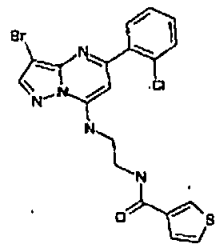
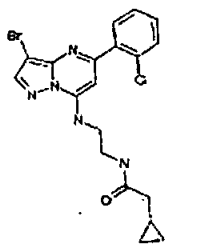
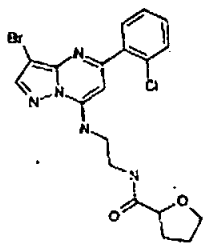
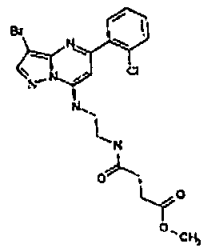
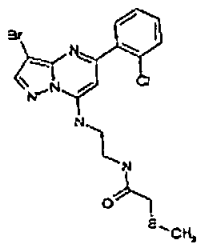
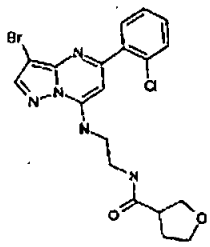
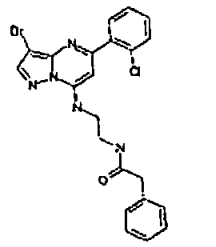
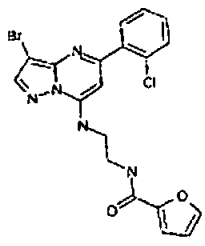
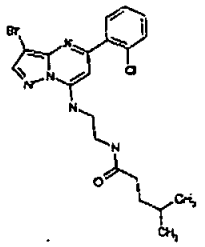
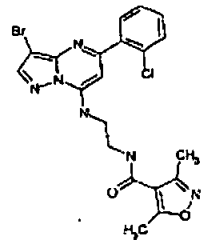
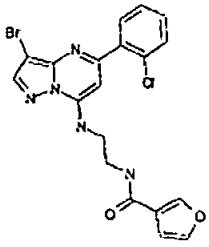
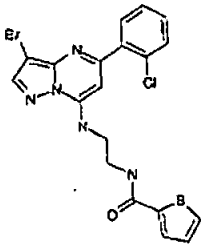
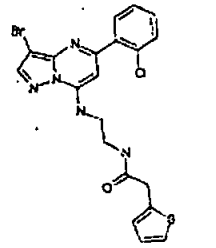
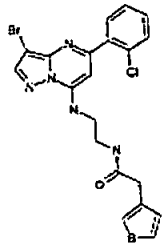
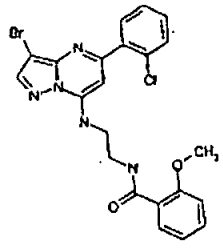
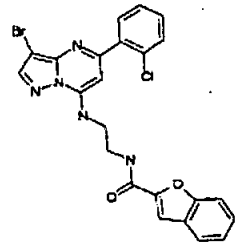
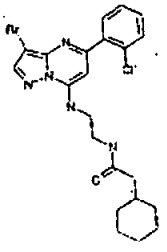
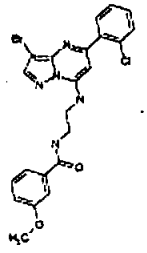
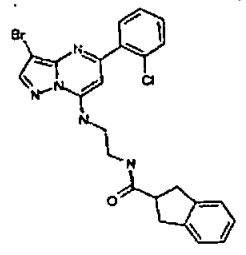
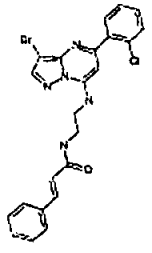
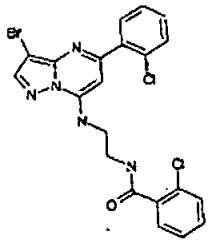
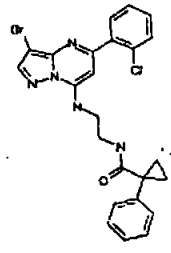
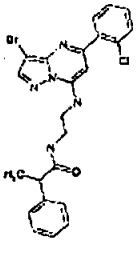
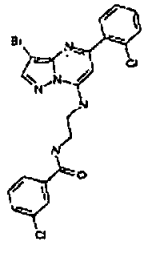
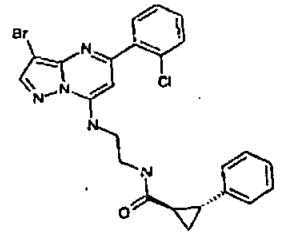
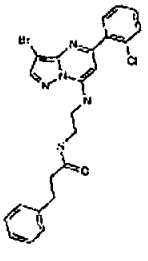
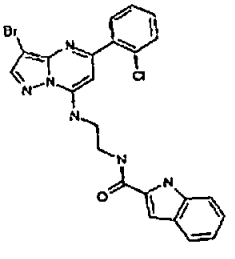
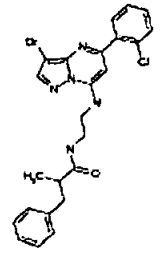
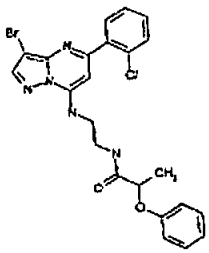
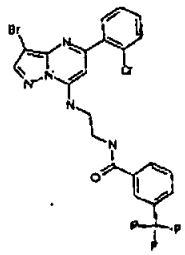
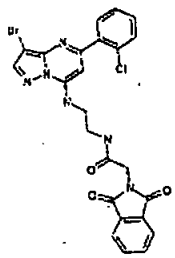
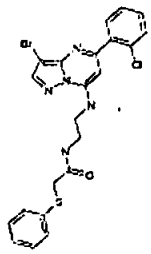
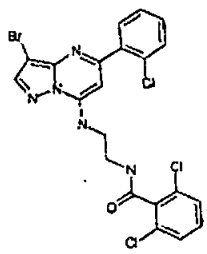
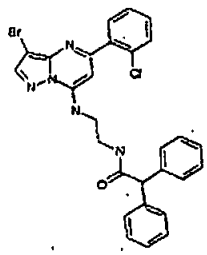
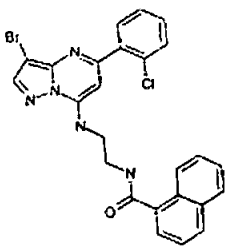
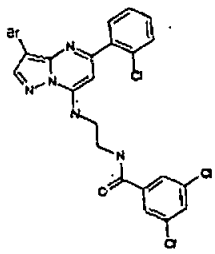
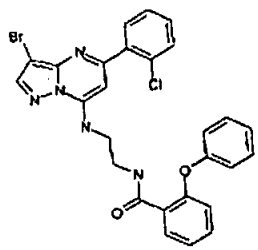
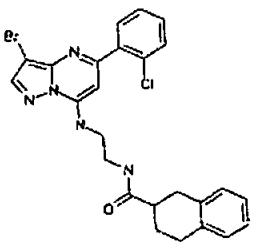
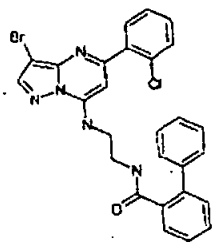
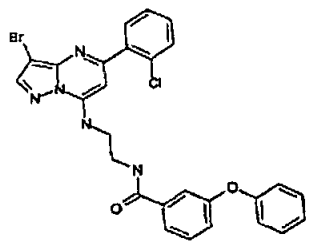
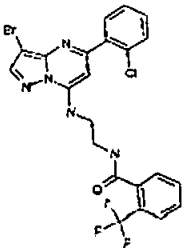
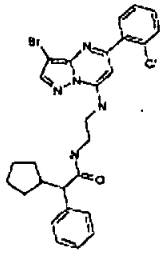
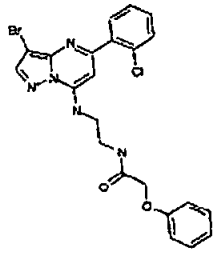
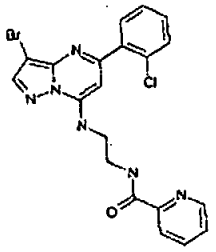
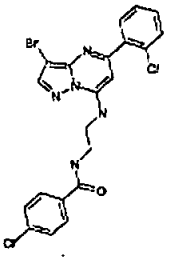
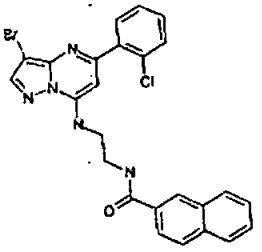
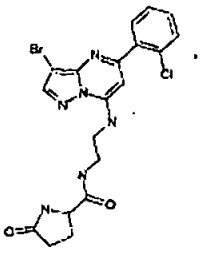
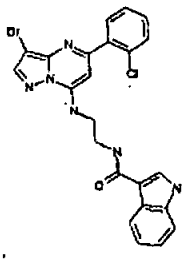
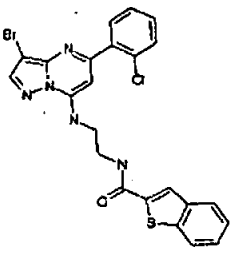
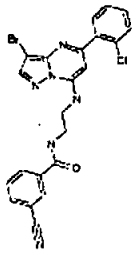
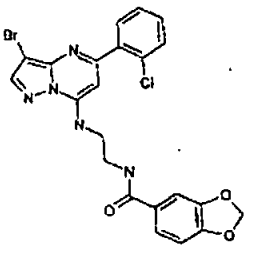
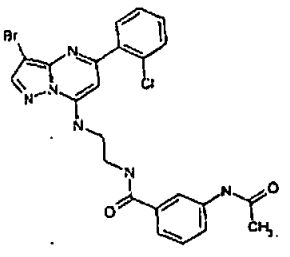
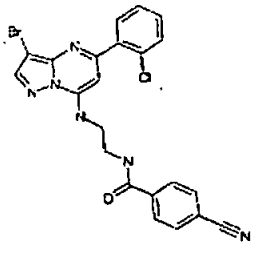
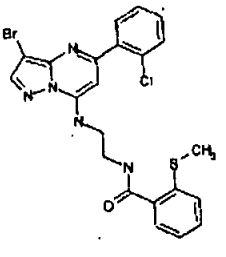
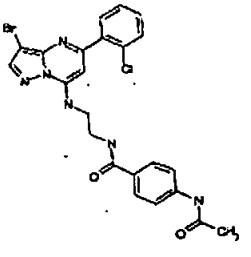
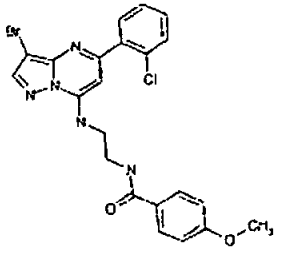
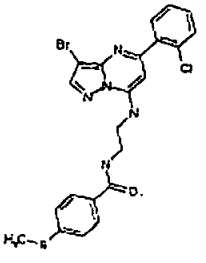
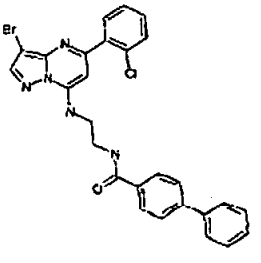
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5271 2. 581.7		1. 5276 2. 559.3
	1. 5272 2. 581.7		1. 5277 2. 562.9
	1. 5273 2. 588.9		1. 5278 2. 556.9
	1. 5274 2. 602.9		1. 5279 2. 499.8
	1. 5275 2. 510.8		1. 5280 2. 499.8

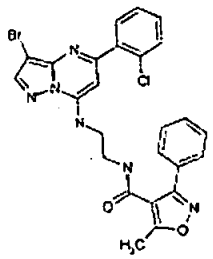
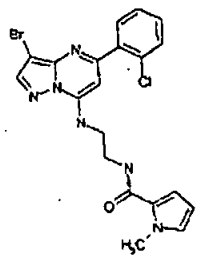
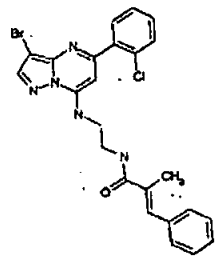
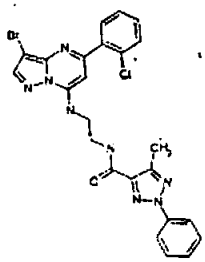
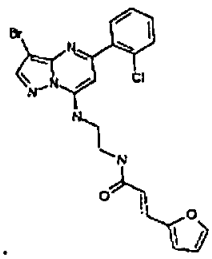
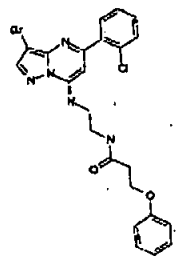
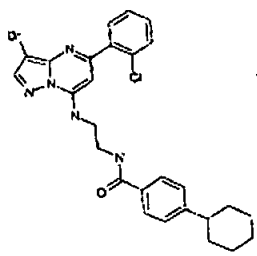
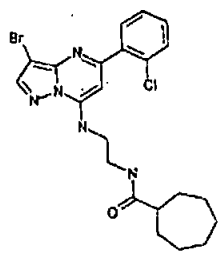
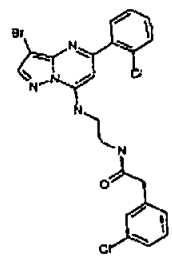
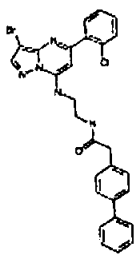
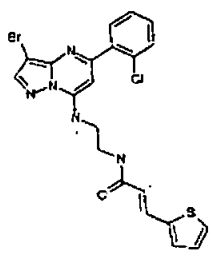
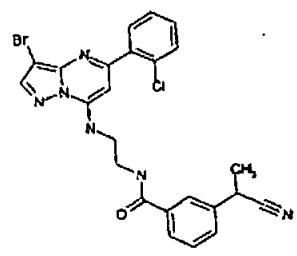
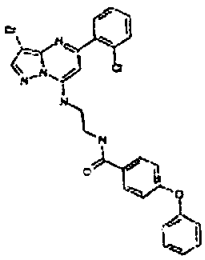
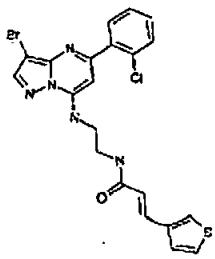
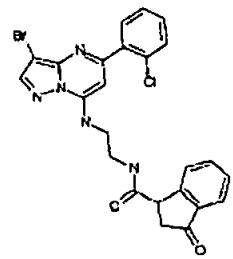
TABLE 53

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5301 2. 434.7		1. 5306 2. 462.8		1. 5311 2. 476.8
	1. 5302 2. 448.8		1. 5307 2. 464.8		1. 5312 2. 480.8
	1. 5303 2. 454.8		1. 5308 2. 464.8		1. 5313 2. 484.8
	1. 5304 2. 460.7		1. 5309 2. 464.8		1. 5314 2. 489.8
	1. 5305 2. 460.7		1. 5310 2. 476.8		1. 5315 2. 490.8

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5316 2. 490.8		1. 5321 2. 500.8		1. 5326 2. 510.8
	1. 5317 2. 490.8		1. 5322 2. 500.8		1. 5327 2. 510.8
	1. 5318 2. 496.8		1. 5323 2. 505.2		1. 5328 2. 510.8
	1. 5319 2. 498.8		1. 5324 2. 505.2		1. 5329 2. 510.8
	1. 5320 2. 498.8		1. 5325 2. 509.8		1. 5330 2. 512.8

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5331 2. 514.8		1. 5336 2. 538.8		1. 5341 2 553.8
	1. 5332 2. 516.9		1. 5337 2. 539.6		1. 5342 2 560.9
	1. 5333 2. 520.8		1. 5338 2. 539.6		1. 5343 2. 562.9
	1. 5334 2. 524.9		1. 5339 2. 546.9		1. 5344 2. 562.9
	1. 5335 2. 538.8		1.5340 2. 552.9		1. 5345 2. 500.8

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5346 2. 471.7		1. 5351 2. 505.2		1. 5356 2. 520.8
	1. 5347 2. 477.8		1. 5352 2. 509.8		1. 5357 2. 526.8
	1. 5348 2. 495.8		1. 5353 2. 514.8		1. 5358 2. 527.8
	1. 5349 2. 495.8		1. 5355 2. 516.9		1. 5359 2. 527.8
	5350 2. 500.8		1. 5356 2. 516.9		1. 5360 2. 546.9

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5361 2. 551.8		1. 5366 2. 473.8		1. 5371 2.510.8
	1. 5362 2. 551.8		1. 5367 2. 486.8		1. 5372 2 514.8
	1. 5363 2. 552.9		1. 5368 2. 490.8		1. 5373 2 519.2
	1. 5364 2. 560.9		1. 5369 2. 502.8		1. 5374 2 523.8
	1. 5365 2. 562.9		1. 5370 2. 502.8		1. 5375 2 524.8

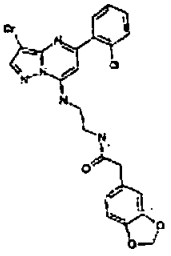
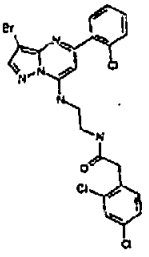
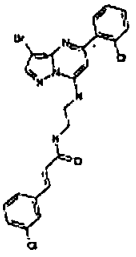
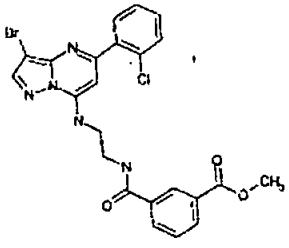
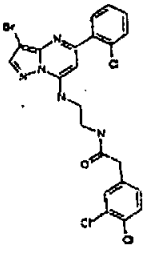
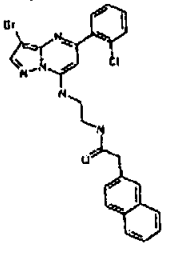
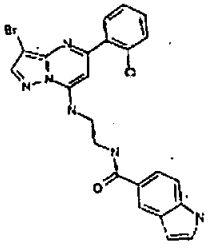
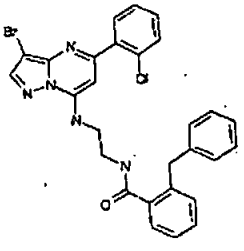
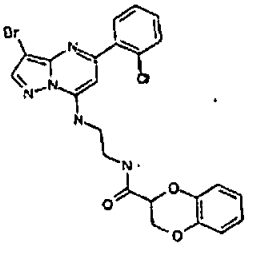
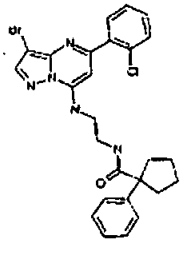
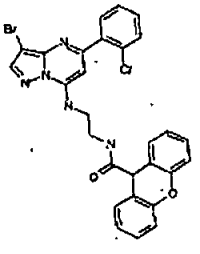
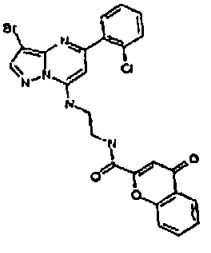
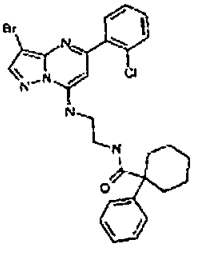
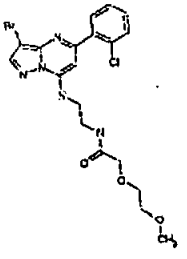
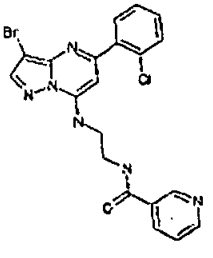
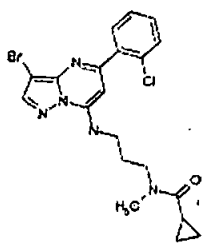
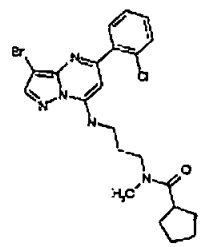
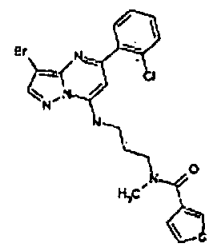
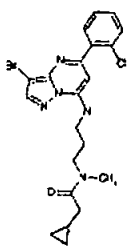
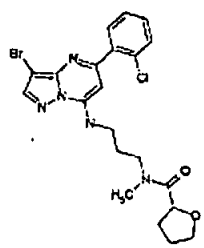
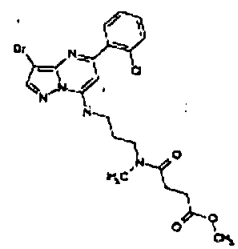
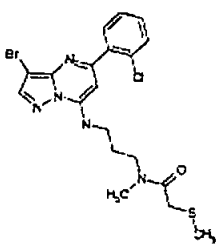
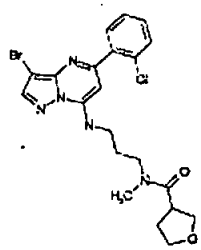
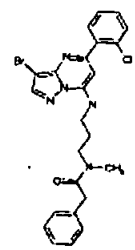
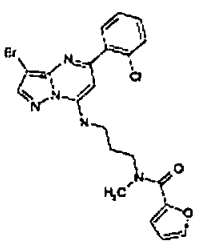
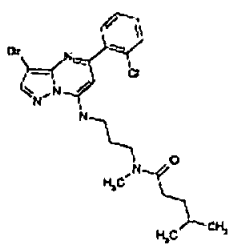
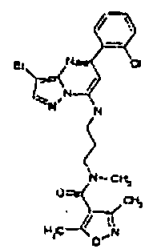
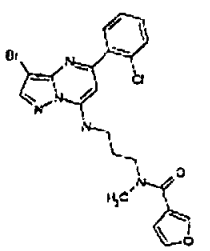
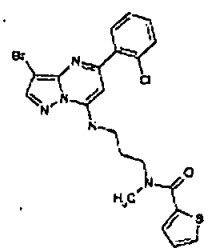
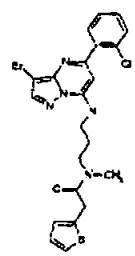
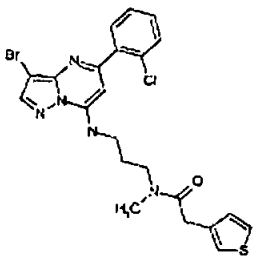
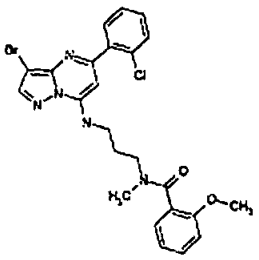
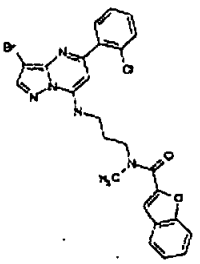
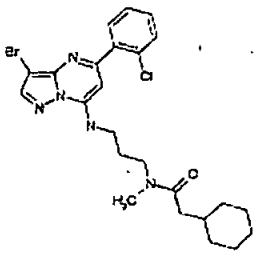
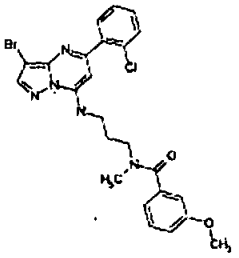
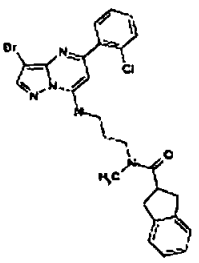
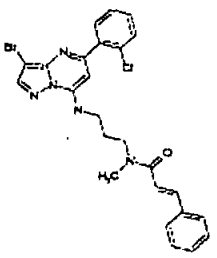
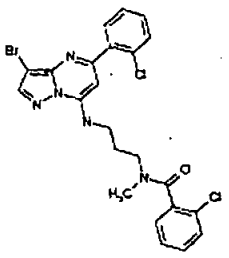
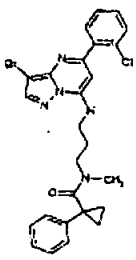
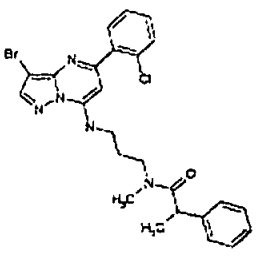
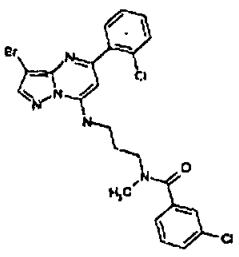
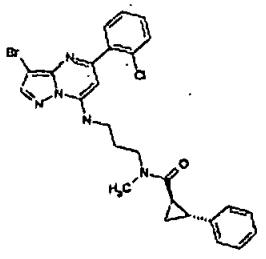
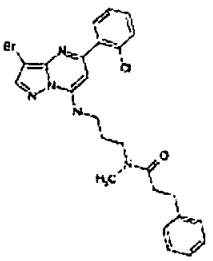
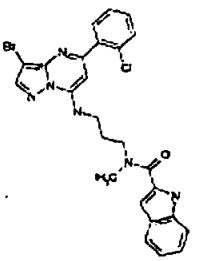
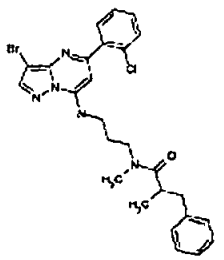
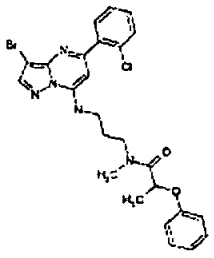
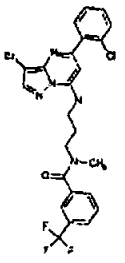
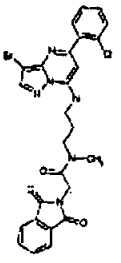
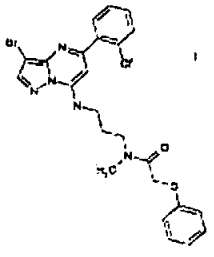
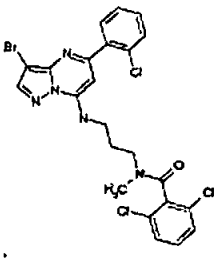
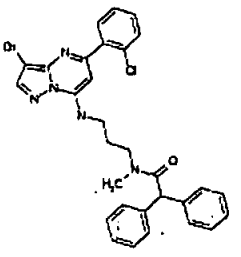
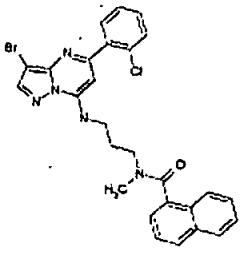
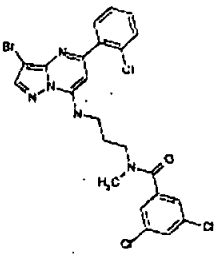
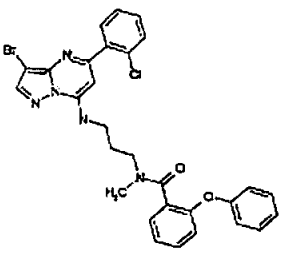
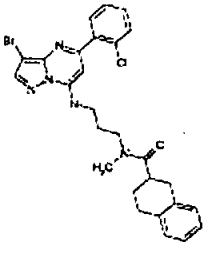
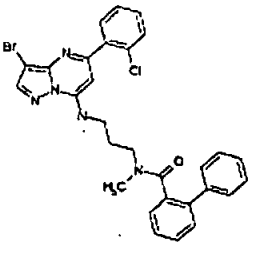
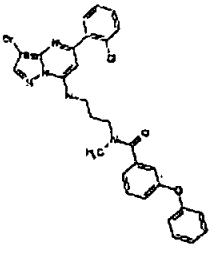
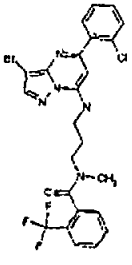
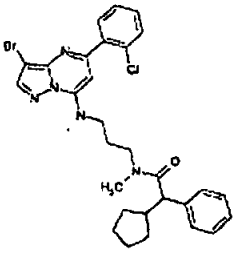
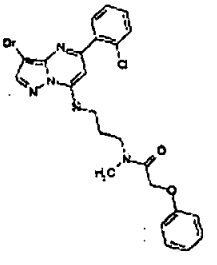
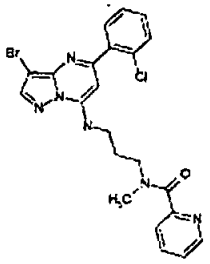
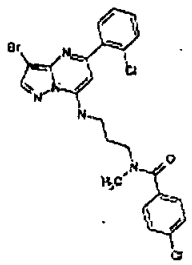
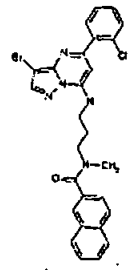
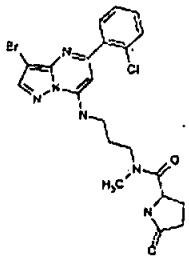
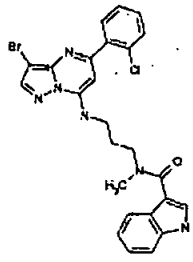
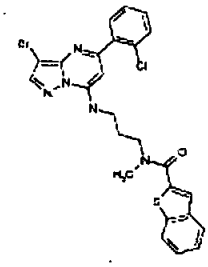
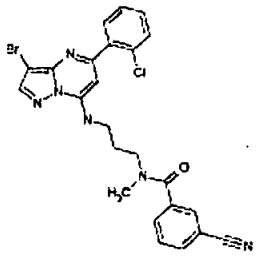
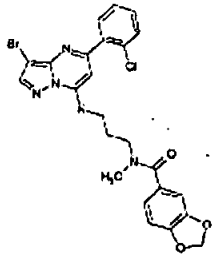
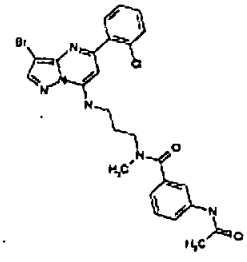
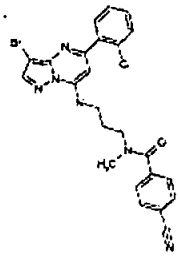
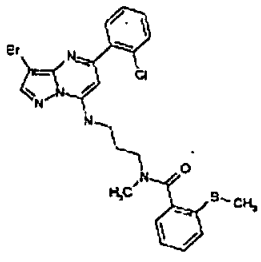
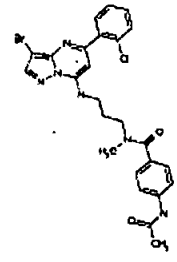
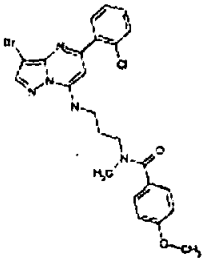
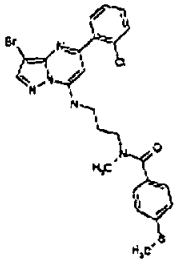
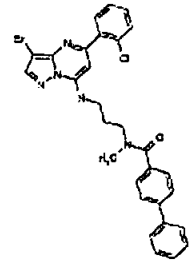
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2 m/z
	1. 5376 2. 528.8		1. 5381 2. 553.7		1. 5386 2 531.2
	1. 5377 2. 528.8		1. 5382 2. 553.7		1. 5387 2 534.8
	1. 5378 2. 509.8		1. 5383 2. 560.9		1. 5388 2 528.8
	1. 5379 2. 538.9		1. 5384 2. 574.9		1. 5389 2. 538.8
	1. 5380 2. 552.9		1. 5385 2. 482.8		1. 5390 2. 471.7

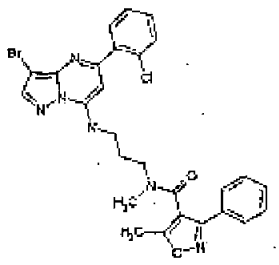
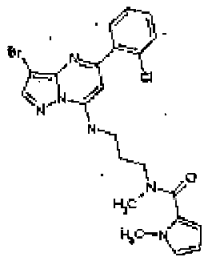
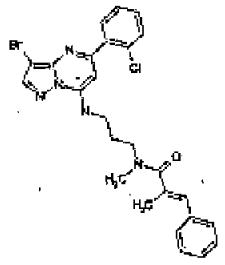
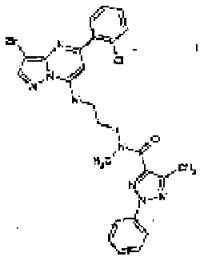
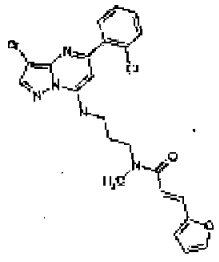
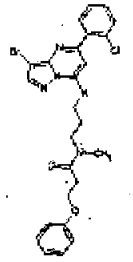
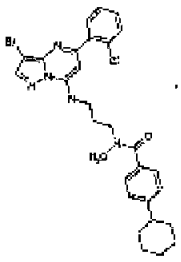
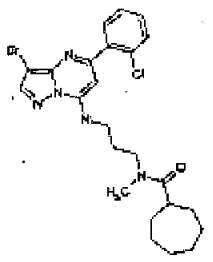
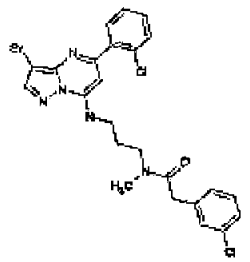
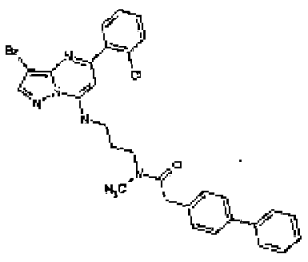
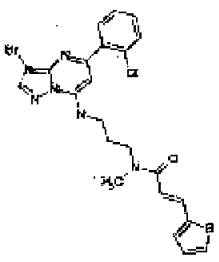
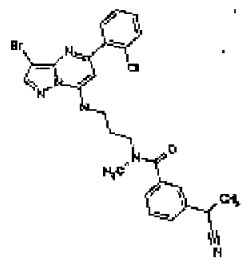
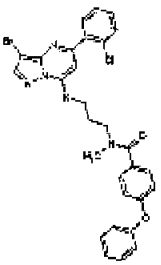
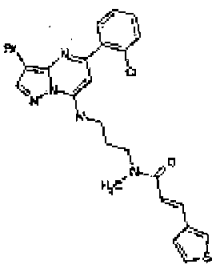
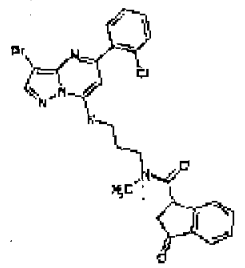
TABLE 54

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5401 2. 463.3		1. 5406 2. 491.3		1. 5411 2. 505.3
	1. 5402 2. 477.3		1. 5407 2. 493.3		1. 5412 2. 509.3
	1. 5403 2. 483.3		1. 5408 2. 493.3		1. 5413 2. 513.3
	1. 5404 2. 489.3		1. 5409 2. 493.3		1. 5414 2. 518.3
	1. 5405 2. 489.3		1. 5410 2. 505.3		1. 5415 2. 519.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5416 2. 519.3		1. 5121 2. 529.3		1. 5426 2. 539.3
	1. 5417 2. 519.3		1. 5422 2. 529.3		1. 5427 2. 539.3
	1. 5418 2. 525.3		1. 5423 2. 533.3		1. 5428 2. 539.3
	1. 5419 2. 527.3		1. 5424 2. 533.3		1. 5429 2. 539.3
	1. 5420 2. 527.3		1. 5425 2. 538.3		1. 5430 2. 541.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2 m/z
	1. 5431 2. 543.3		1. 5436 2. 567.3		1. 5441 : 582.3
	1. 5432 2. 545.3		1. 5437 2. 567.3		1. 5442 2 589.3
	1. 5433 2. 549.3		1. 5438 2. 567.3		1. 5443 2 591.3
	1. 5434 2. 553.3		1. 5439 2. 575.3		1. 5444 2. 591.3
	1. 5435 2. 567.3		1. 5440 2. 581.3		1. 5445 2. 529.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5446 2. 500.3		1. 5451 2. 533.3		1. 5456 2. 549.3
	1. 5447 2. 830.5		1. 54525 2. 719.4		1. 5457 2. 555.3
	1. 5448 2. 524.3		1. 5453 2. 543.3		1. 5458 2. 556.3
	1. 5449 2. 524.3		1. 5454 2. 545.3		1.5459 2. 556.3
	1. 5450 2. 529.3		1. 5455 2. 545.3		1. 5460 2. 575.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5461 2. 580.3		1. 5466 2. 502.3		1. 5471 2 539.3
	1. 5462 2. 580.3		1. 5467 2. 515.3		1. 5472 2 543.3
	1. 5463 2. 581.3		1. 5468 2. 519.3		1. 5473 2 547.3
	1. 5464 2. 589.3		1. 5469 2. 531.3		1. 5474 2. 552.3
	1. 5465 2. 591.3		1. 5470 2. 531.3		1. 5475 2. 553.3

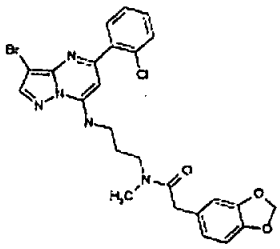
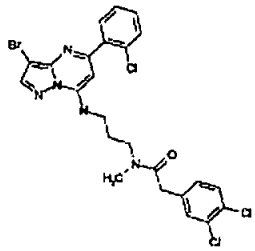
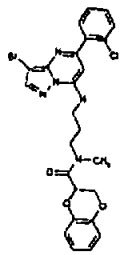
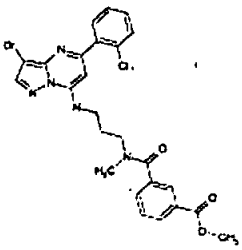
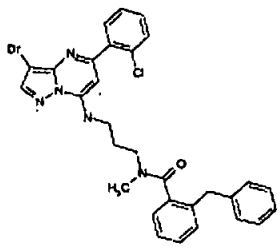
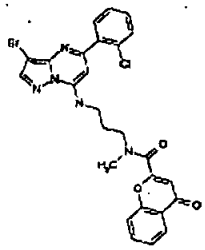
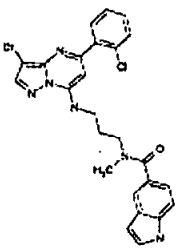
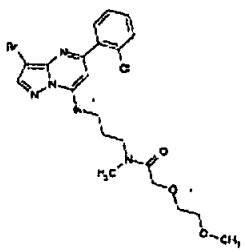
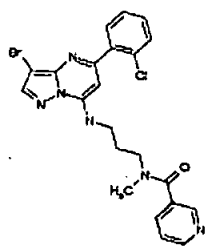
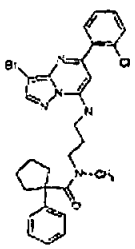
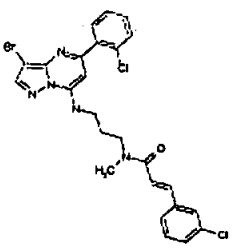
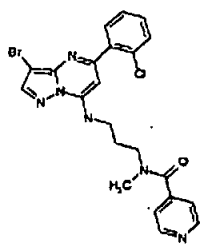
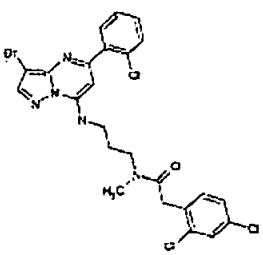
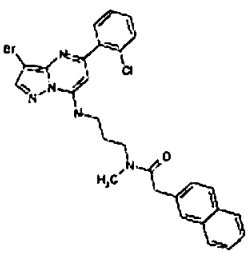
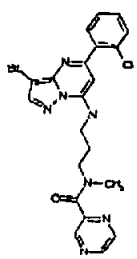
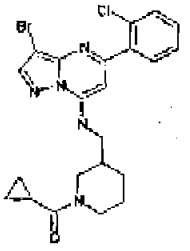
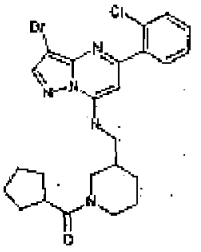
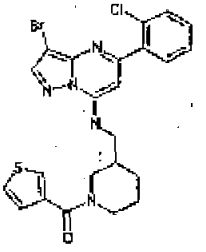
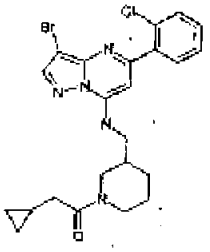
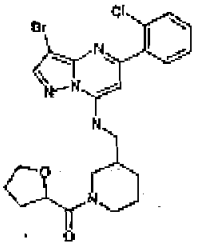
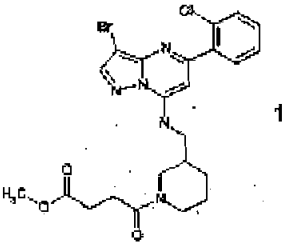
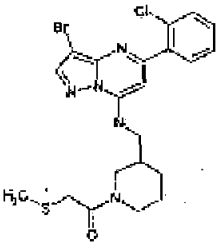
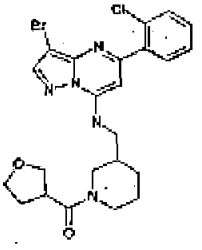
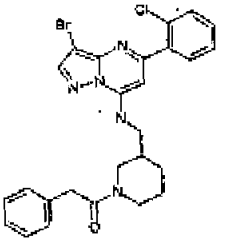
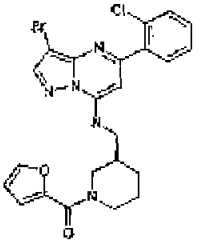
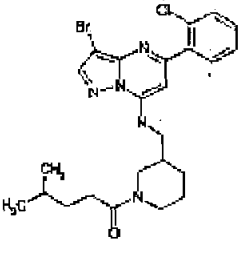
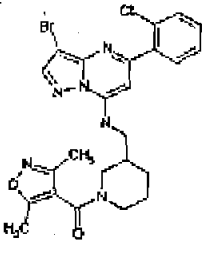
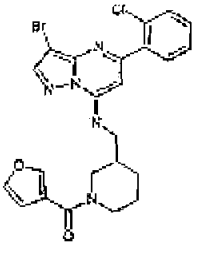
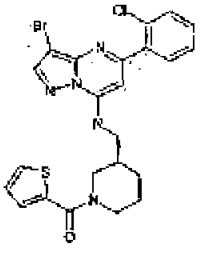
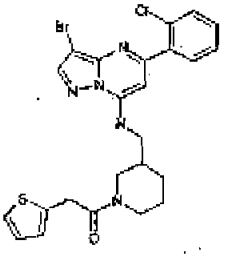
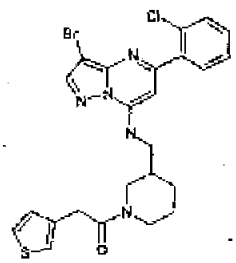
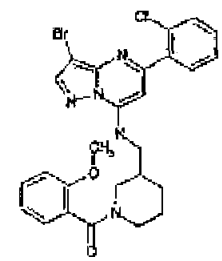
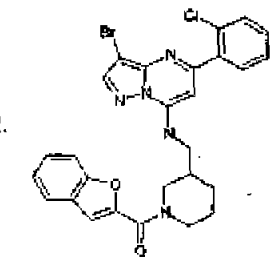
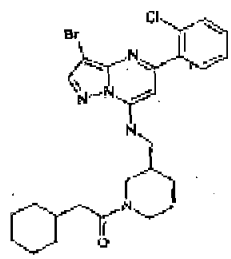
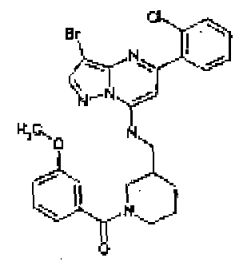
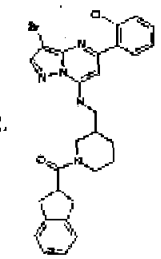
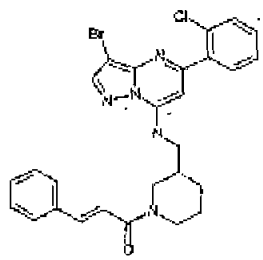
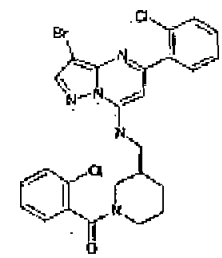
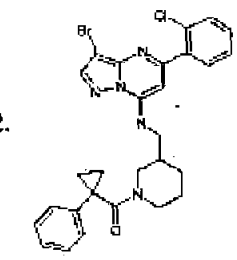
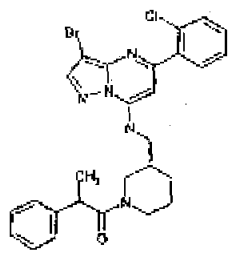
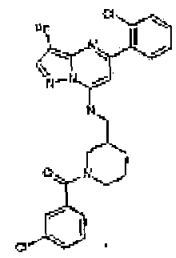
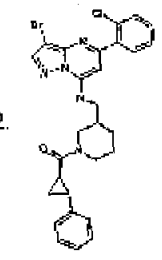
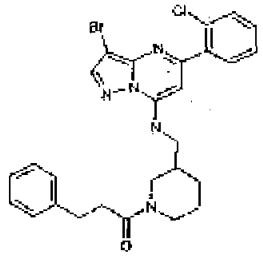
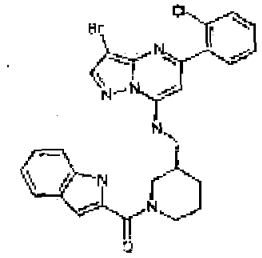
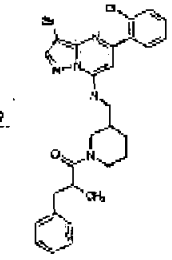
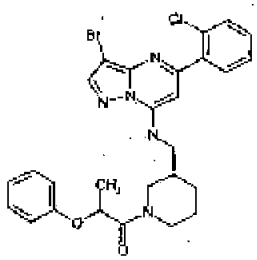
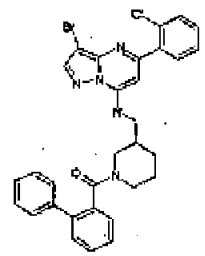
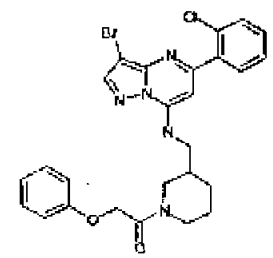
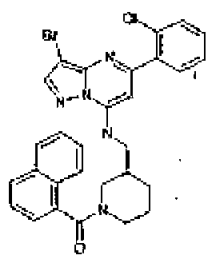
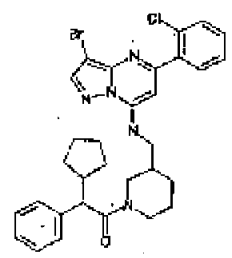
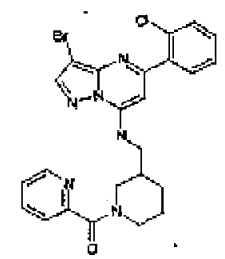
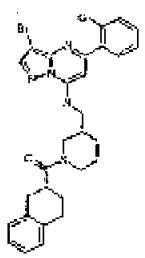
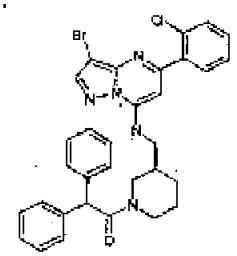
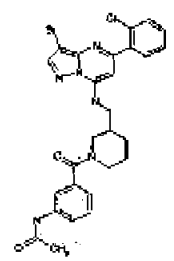
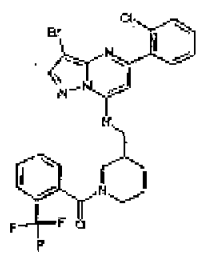
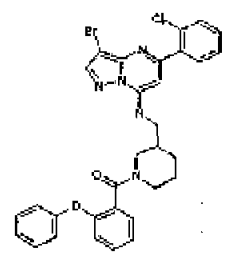
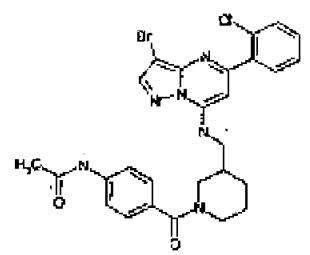
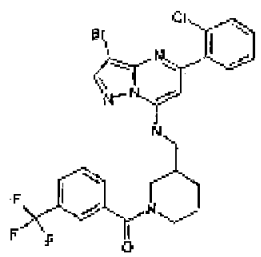
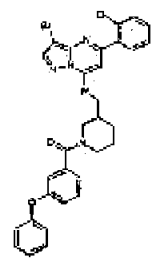
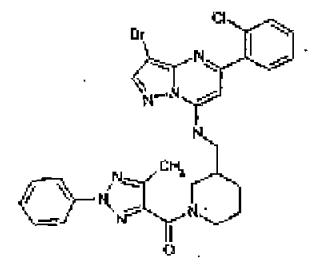
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5476 2. 557.3		1. 5481 2. 581.3		. 5486 2.
	1. 5477 2. 557.3		1. 5482 2. 589.3		1. 5487 2. 891.5
	1. 5478 2. 538.3		1. 5483 2. 511.3		1. 5488 2. 500.3
	1. 5479 2. 567.3		1. 5484 2. 559.3		1. 5489 2. 500.3
	1. 5480 2. 581.3		1. 5485 2. 563.3		1. 5490 2. 501.3

TABLE55

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5501 2. 488.81		1. 5506 2. 516.87		1. 5511 2. 530.87
	1. 5502 2. 502.84		1. 5507 2. 518.84		1. 5512 2. 534.84
	1. 5503 2. 508.87		1. 5508 2. 518.84		1. 5513 2. 538.87
	1. 5504 2. 514.81		1. 5509 2. 518.88		1. 5514 2. 543.85
	1. 5505 2. 514.81		1. 5510 2. 530.87		1. 5515 2. 544.9

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5516 2. 544.9		1. 5521 2. 554.87		1. 5526 2. 564.87
	1. 5517 2. 544.92		1. 5522 2. 554.87		1. 5527 2. 564.91
	1. 5518 2. 550.89		1. 5523 2. 559.29		1. 5528 2. 564.91
	1. 5519 2. 552.9		1. 5524 2. 559.29		1. 5529 2. 564.91
	1. 5520 2. 552.9		1. 5525 2. 563.88		1. 5530 2. 566.93

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5531 2. 568.9		1. 5536 2. 600.95		1. 5541
	1. 5532 2. 574.91		1. 5537 2. 606.99		1. 5542 2 525.83
	1. 5533 2. 578.94		1. 5538 2. 614.97		1. 5543 2. 581.9
	1. 5534 2. 592.85		1. 5539 2. 618.95		1. 5544 2. 581.9
	1. 5535 2. 592.85		1. 5540 2. 616.95		1. 5545 2. 605.92

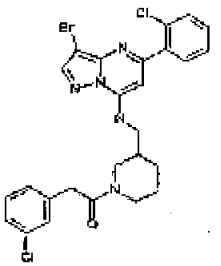
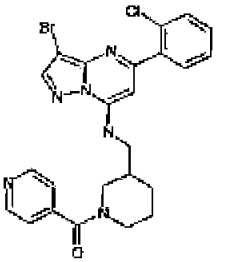
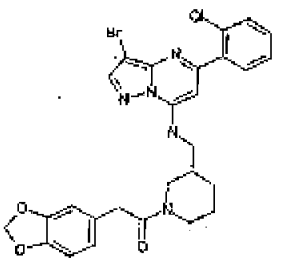
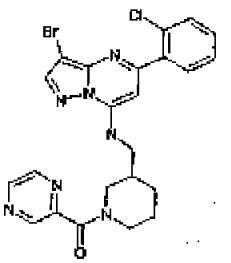
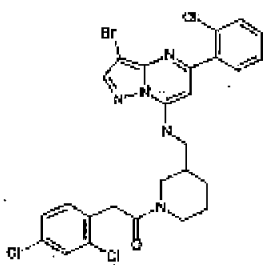
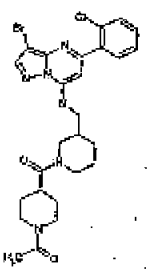
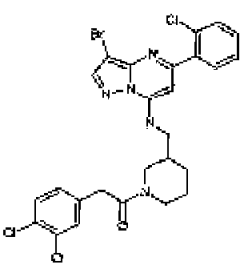
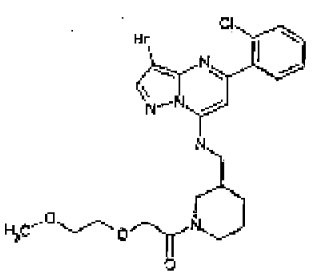
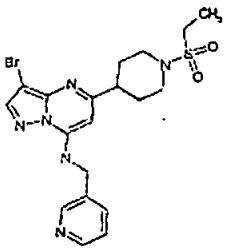
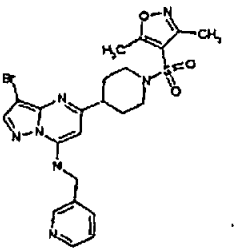
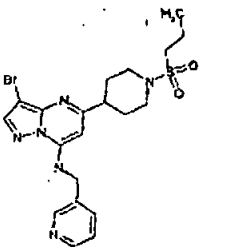
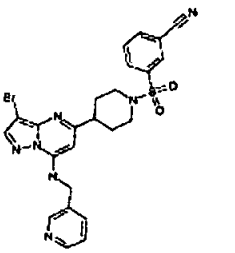
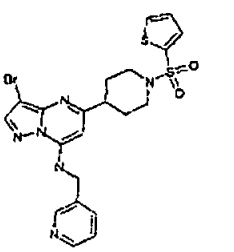
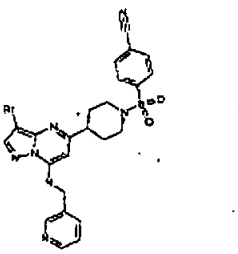
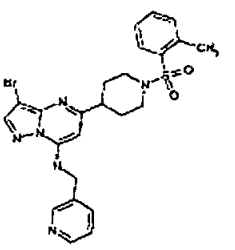
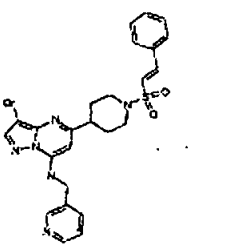
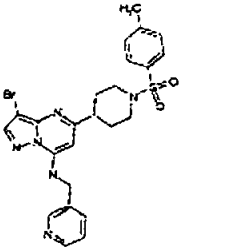
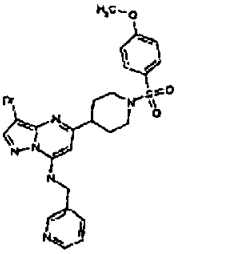
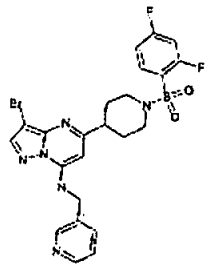
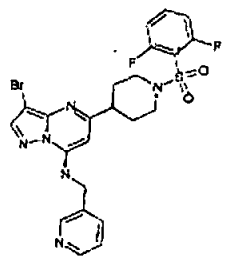
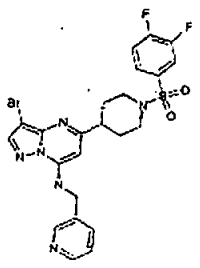
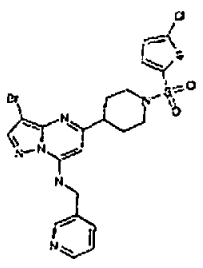
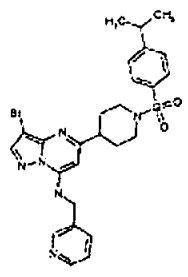
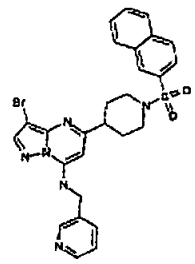
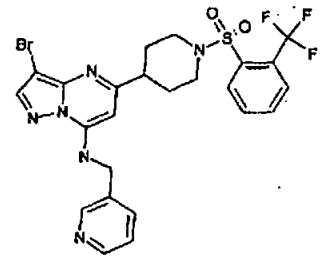
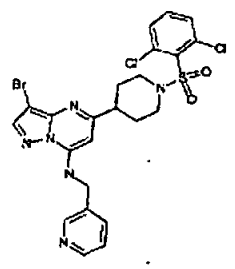
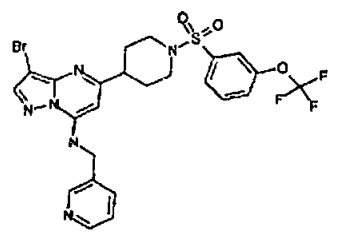
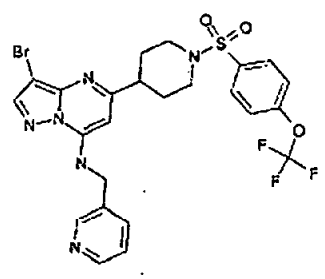
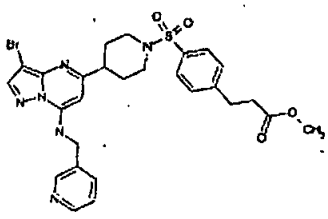
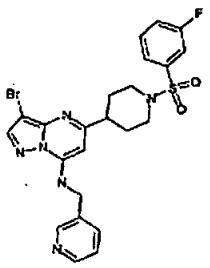
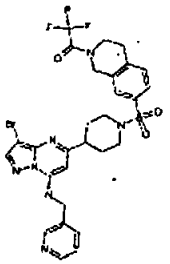
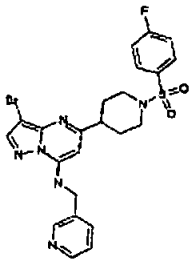
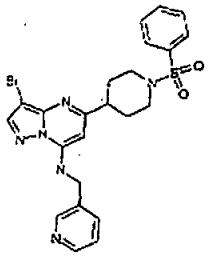
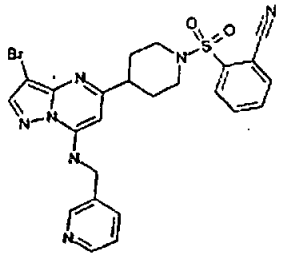
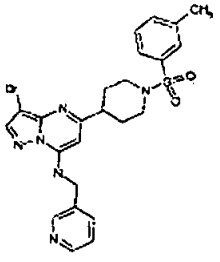
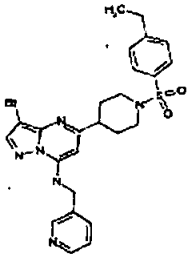
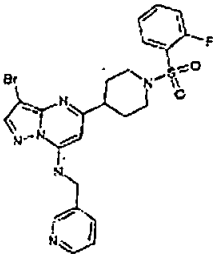
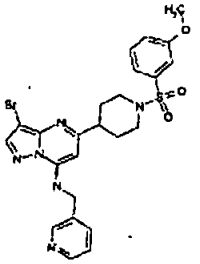
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5546 2. 573.32		1. 5551 2. 525.83
	1. 5547 2. 582.88		1. 5552 2. 526.82
	1. 5548 2. 607.76		1. 5553 2. 573.92
	1. 5549 2. 607.76		
	1. 5550 2. 536.86		

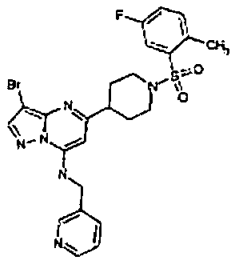
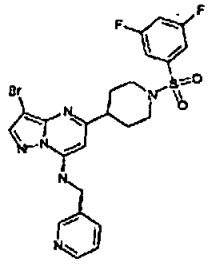
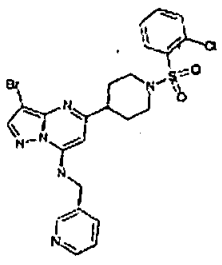
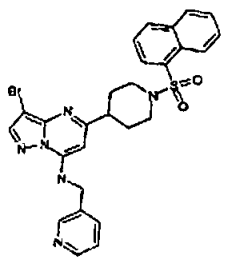
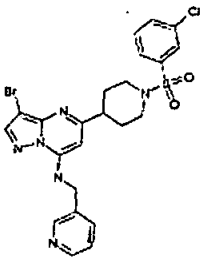
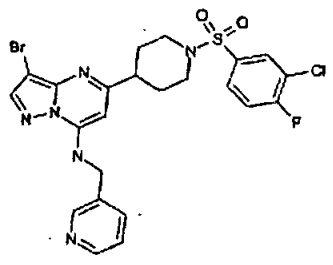
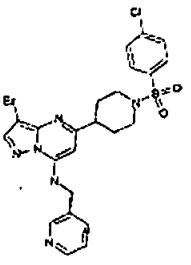
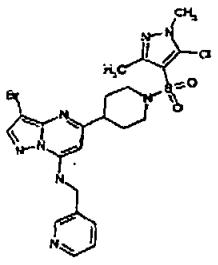
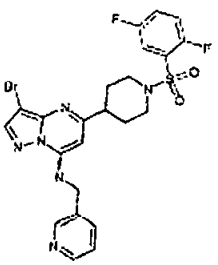
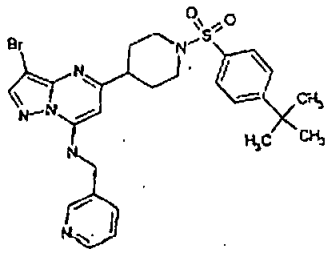
TABLE 56

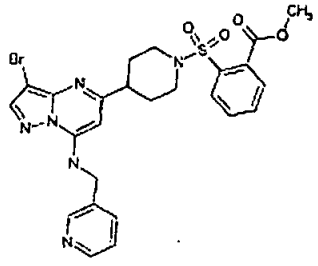
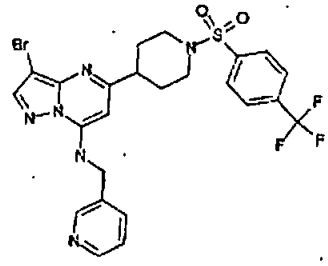
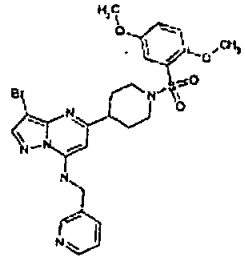
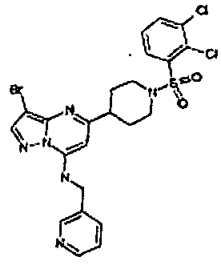
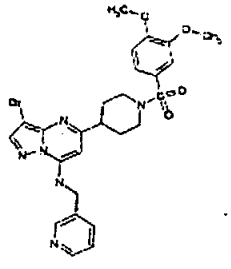
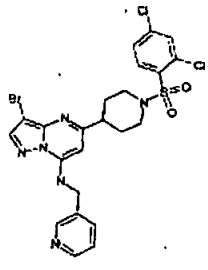
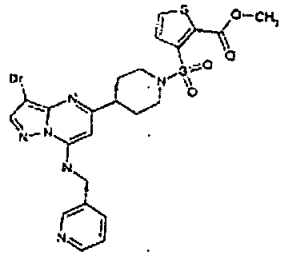
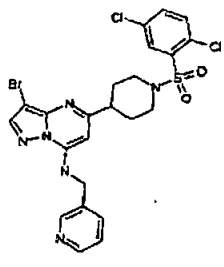
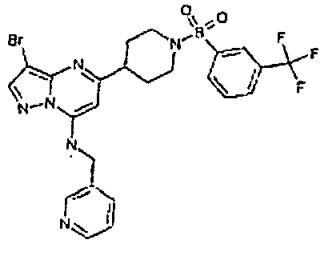
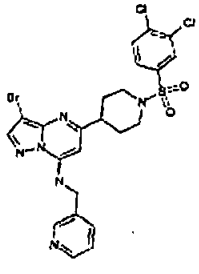
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5601 2. 481.26		1. 5606 2. 548.3
	1. 5602 2. 495.27		1. 5607 2. 554.3
	1. 5603 2. 535.29		1. 5608 2. 554.3
	1. 5604 2. 543.3		1. 5609 2. 555.31
	1. 5605 2. 543.3		1. 5610 2. 559.31

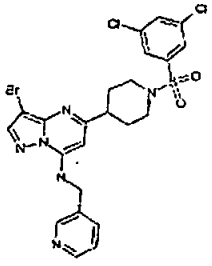
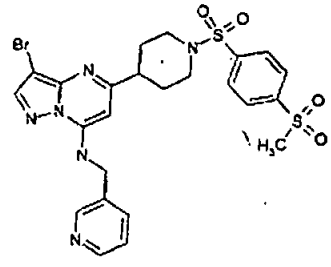
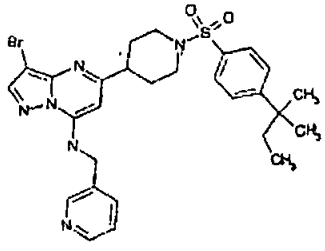
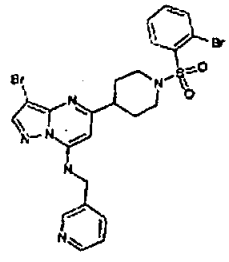
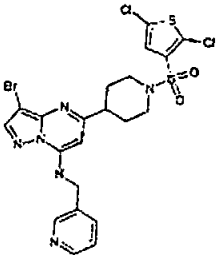
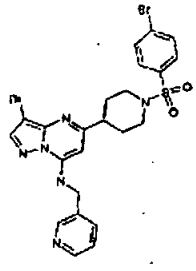
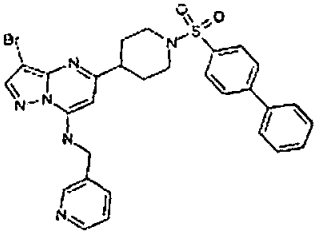
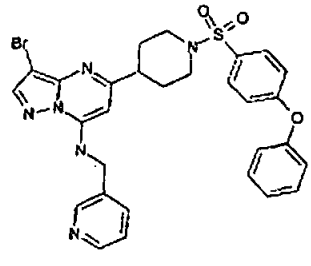
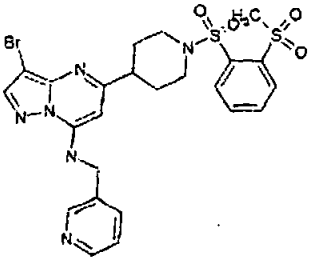
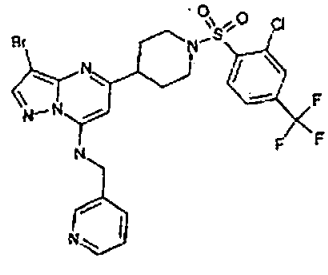
Product	1. Ex. 2. m/z
	1. 5611 2. 565.31
	1. 5612 2. 565.31
	1. 5613 2. 565.31
	1. 5614 2. 569.31
	1. 5615 2. 571.31

Product	1. Ex. 2. m/z
	1 .5616 2. 579.32
	1. 5617
	1. 5618
	1. 5619
	1. 5620

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5621 2. 615.34		1. 5626 2. 547.3
	2. 5622 2. 680.37		1. 5627 2. 547.3
	1. 5623 2. 529.29		1. 5628 2. 554.3
	1. 5624 2. 543.3		1. 5629 2. 555.31
	1. 5625 2. 547.3		1. 5630 2. 559.31

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5631 2. 561.31		1. 5636 2. 565.31
	1. 5632 2. 563.31		1. 5637 2. 579.32
	1. 5633 2. 563.31		1. 5638 2. 581.32
	1. 5634 2. 563.31		1. 5639 2. 581.32
	1. 5635 2. 563.31		1. 5640 2. 585.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5641 2. 587.32		1. 5646.
	1. 5642 2. 589.32		1. 5647 2. 597.33
	1. 5643 2. 589.32		1. 5648 2. 597.33
	1. 5644 2. 593.33		1. 5649 2. 597.33
	1. 5645 2. 597.33		1. 5650 2. 597.33

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5651 2. 597.33		1. 5656 2. 607.33
	1. 5652 2. 599.33		1. 5657 2. 607.33
	1. 5653 2. 603.33		1. 5658 2. 607.33
	1. 5654 2. 605.33		1. 5659 2. 621.34
	1. 5655 2. 607.33		1. 5660 2. 631.35

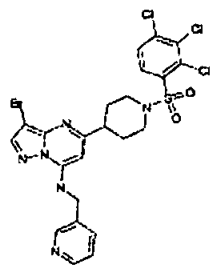
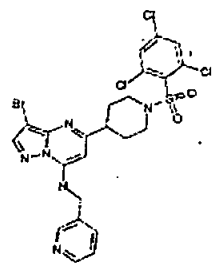
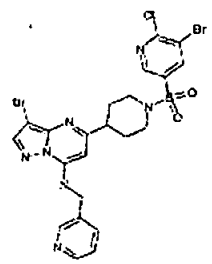
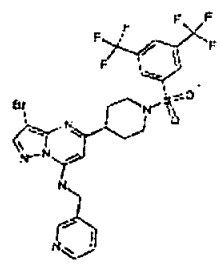
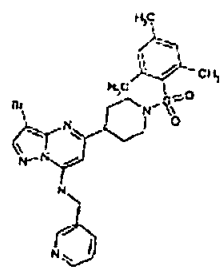
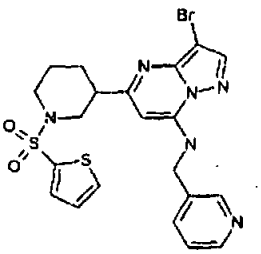
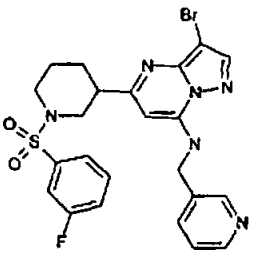
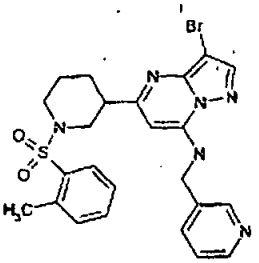
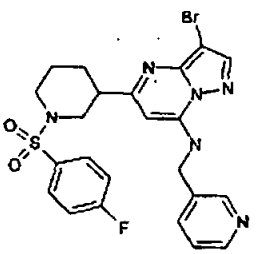
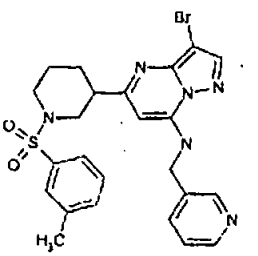
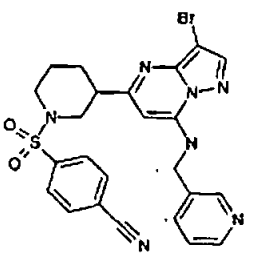
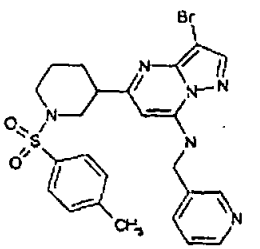
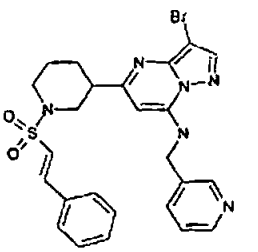
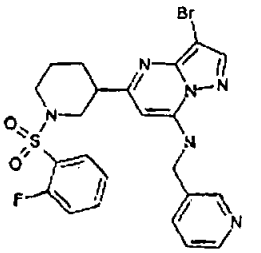
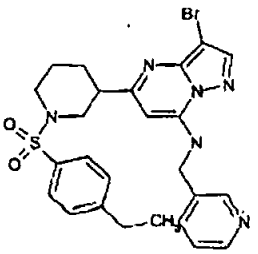
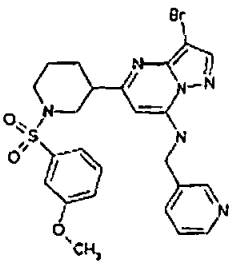
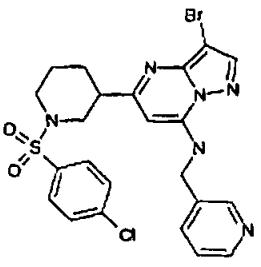
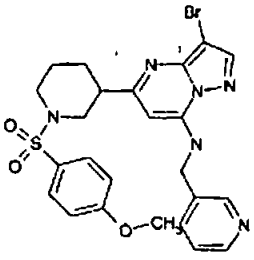
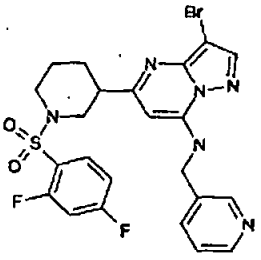
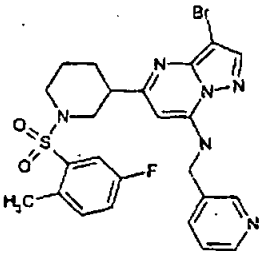
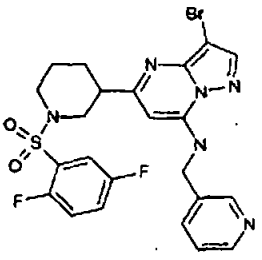
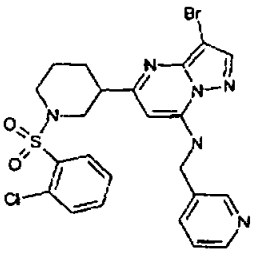
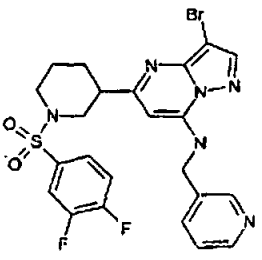
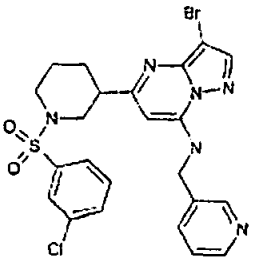
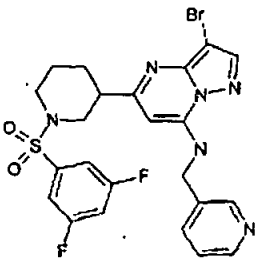
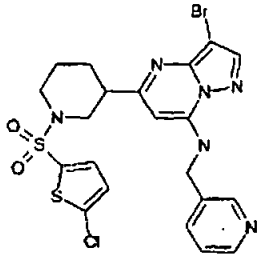
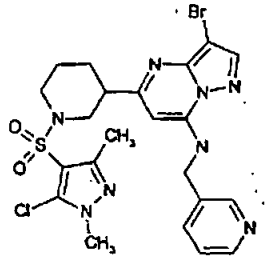
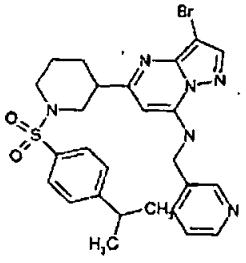
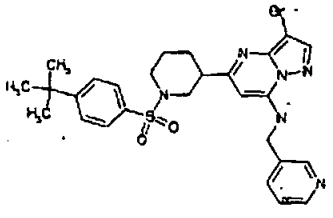
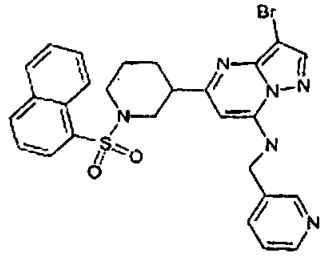
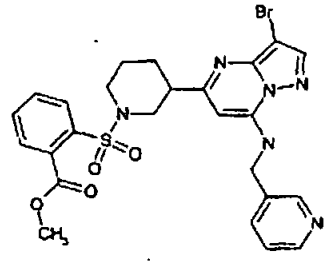
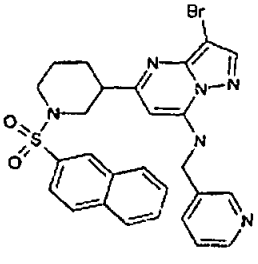
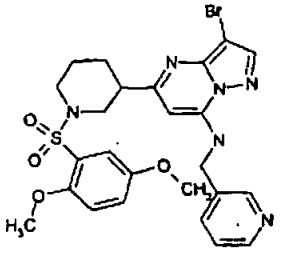
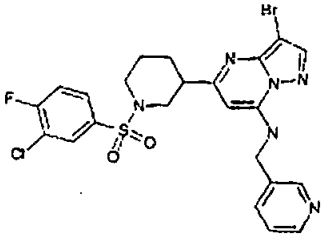
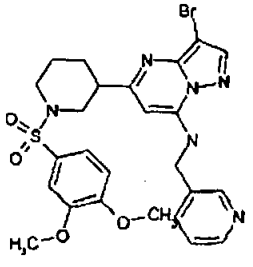
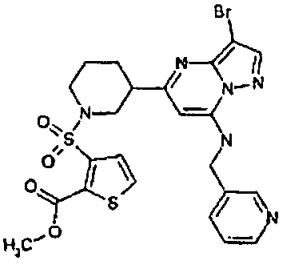
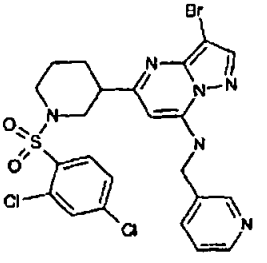
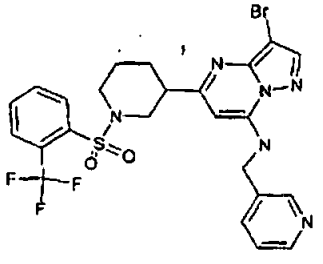
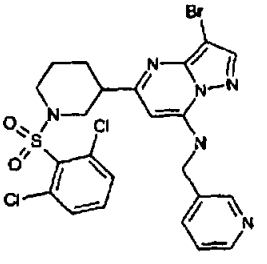
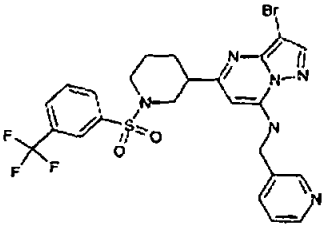
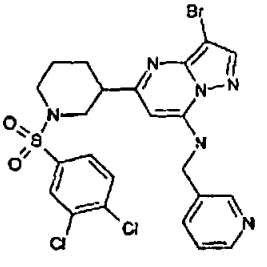
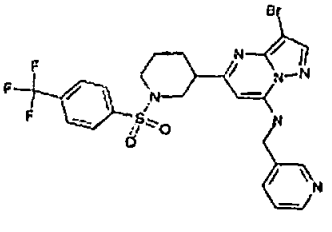
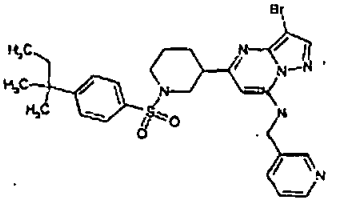
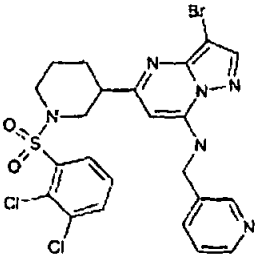
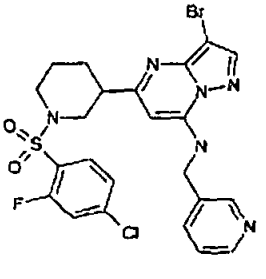
Product	1. Ex. 2. m/z
	1. 5661 2. 631.35
	1. 5662 2. 631.35
	1. 5663 2. 642.35
	1. 5664 2. 665.37
	1. 5665 2. 571.31

TABLE 57

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5701 2. 535.29		1. 5706 2. 547.3
	1. 5702 2. 540.3		1. 5707 2. 547.3
	1. 5703 2. 543.3		1. 5708 2. 554.3
	1. 5704 2. 543.3		1. 5709 2. 555.31
	1. 5705 2. 547.3		1. 5710 2. 555.31

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5711 2. 559.31		1. 5716 2. 563.31
	1. 5712 2. 559.31		1. 5717 2. 565.31
	1. 5713 2. 561.31		1. 5718 2. 565.31
	1. 5714 2. 562.31		1. 5719 2. 565.31
	1. 5715 2. 563.31		1. 5720 2. 565.31

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5721 2. 569.31		1. 5726 2. 581.32
	1. 5722 2. 571.31		1. 5727 2. 585.32
	1. 5723 2. 579.32		1. 5728 2. 587.32
	1. 5724 2. 579.32		1. 5729 2. 589.32
	1. 5725 2. 581.32		1. 5730 2. 589.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5731 2. 591.33		1. 5736 2. 597.33
	1. 5732 2. 597.33		1. 5737 2. 597.33
	1. 5733 2. 595.33		1. 5738 2. 596.33
	1. 5734 2. 597.33		1. 5739 2. 597.33
	1. 5735 2. 597.33		1. 5740 2. 581.32

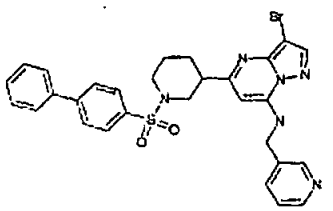
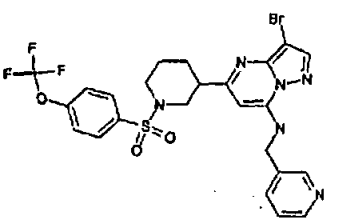
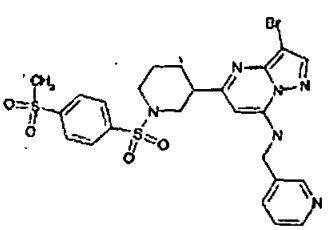
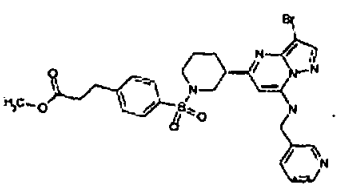
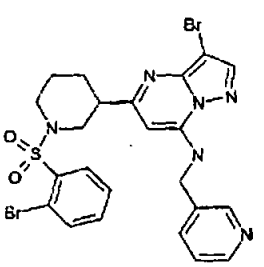
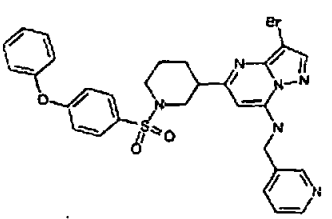
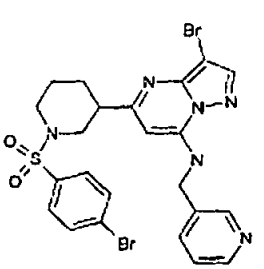
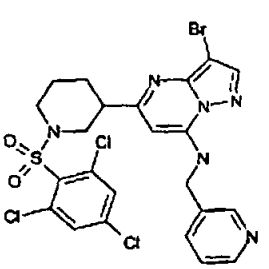
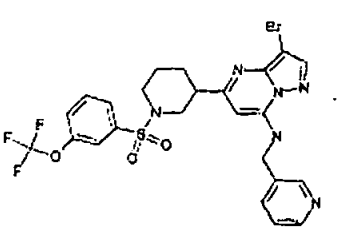
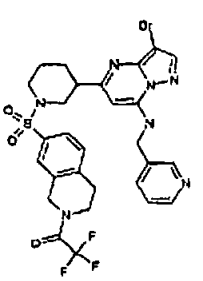
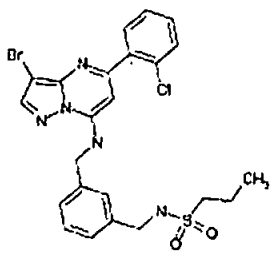
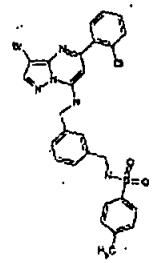
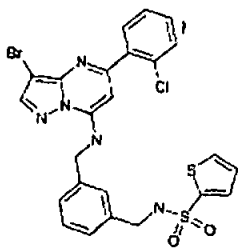
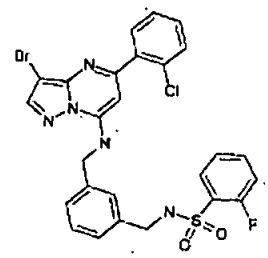
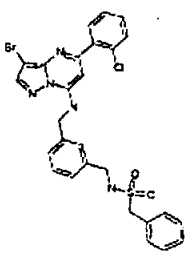
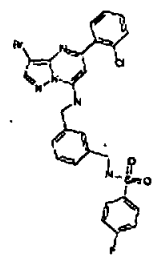
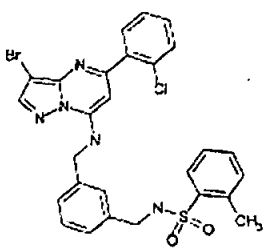
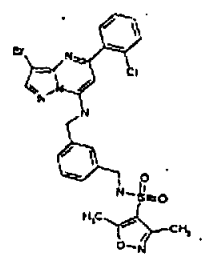
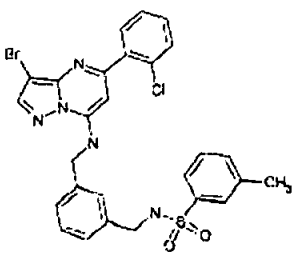
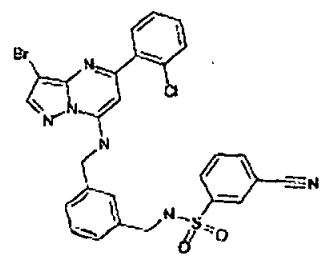
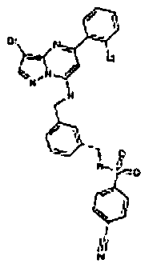
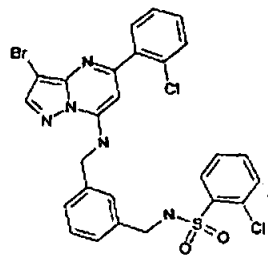
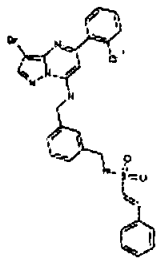
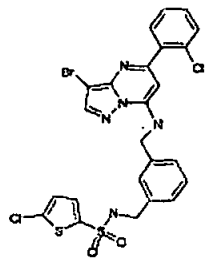
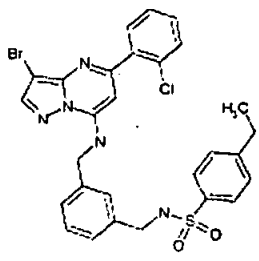
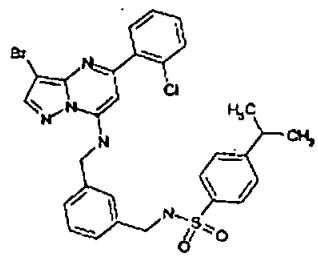
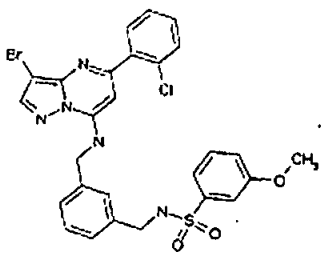
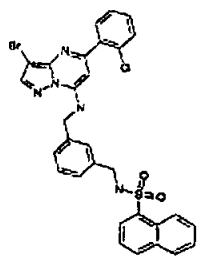
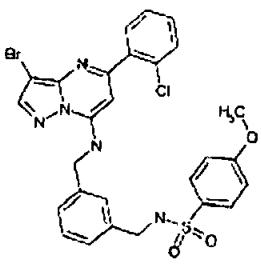
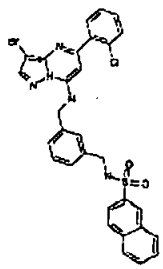
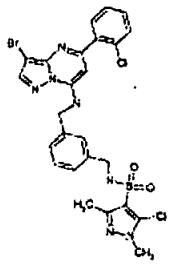
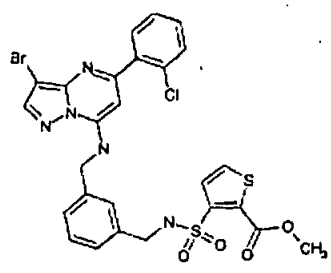
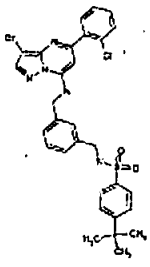
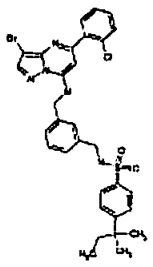
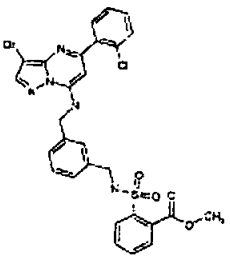
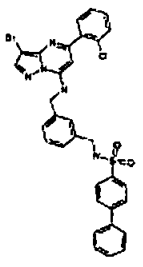
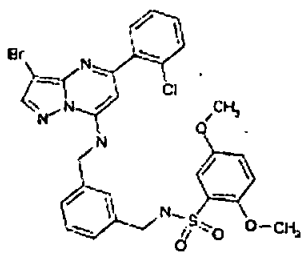
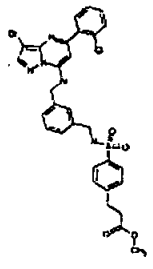
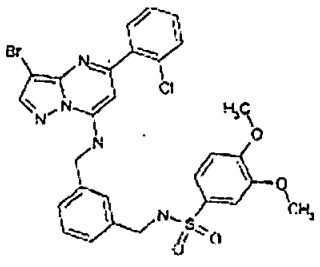
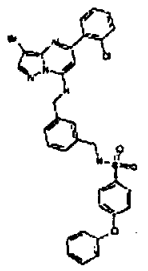
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5741 2. 605.33		1. 5746 2. 613.34
	1. 5742 2. 607.33		1. 5747 2. 615.34
	1. 5743 2. 607.33		1. 5748 2. 621.34
	1. 5744 2. 607.33		1. 5749 2. 631.35
	1. 57454 2. 613.34		1. 5750 2. 680.37

TABLE 58

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5801 2. 550.3		1. 5806 2. 598.33
	1. 5802 2. 590.32		10 5807 2. 602.33
	1. 5803 2. 598.33		1. 5808 2. 602.33
	1. 5804 2. 598.33		1. 5809 2. 603.33
	1. 5805 2. 598.33		1. 5810 2. 609.33

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1..5811 2. 609.33		1. 5816 2. 618.34
	1. 5812 2. 610.34		1. 5817 2. 624.34
	1. 5813 2. 612.34		1. 5818 2. 626.34
	1. 5814 2. 614.34		1. 5819 2. 634.35
	1. 5815 2. 614.34		1. 5820 2. 632.35

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5821 2. 636.35		1. 5826 2. 648.36
	1. 5822 2. 640.35		1. 5827 2. 654.36
	1. 5823 2. 642.35		1. 5828 2. 660.36
	1. 5824 2. 644.35		1. 5829 2. 670.37
	1. 5825 2. 644.35		1. 5830 2. 676.37

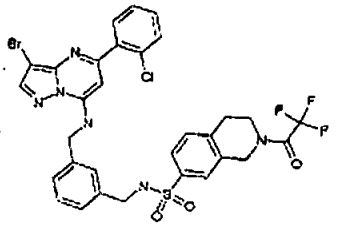
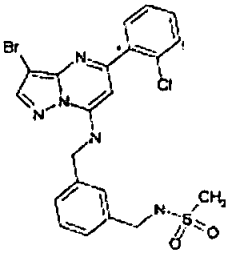
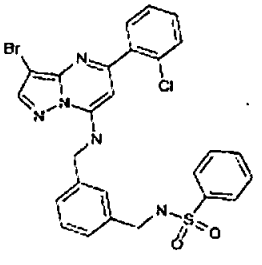
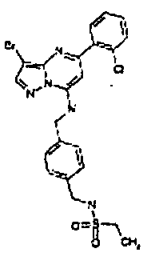
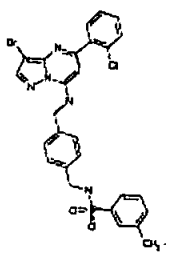
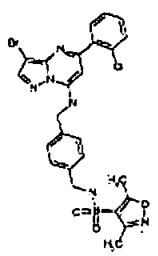
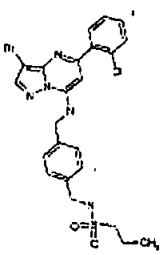
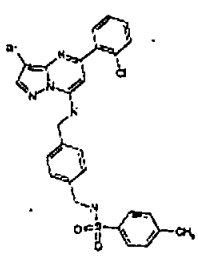
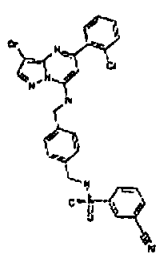
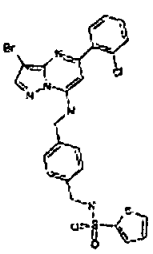
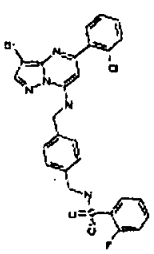
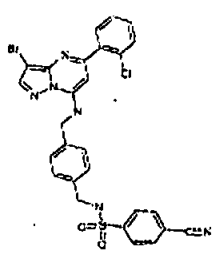
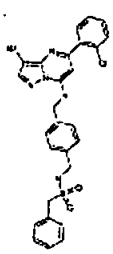
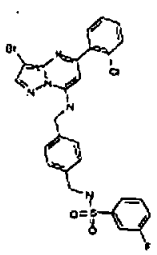
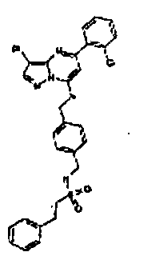
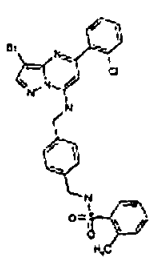
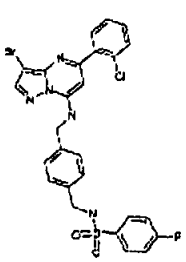
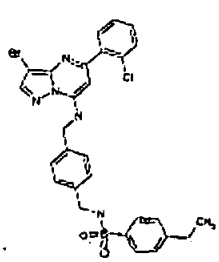
Product	1. Ex. 2. m/z
	1. 5831 2. 735.4
	1. 5832 2. 522.29
	1. 5833 2. 584.32

TABLE 59

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5901 2. 536.29		1. 5906 2. 598.33		1. 5911 2. 603.33
	1. 5902 2. 550.3		1. 5907 2. 598.33		1. 5912 2. 609.33
	1. 5903 2. 590.32		1. 5908 2. 602.33		1. 5913 2. 609.33
	1. 5904 2. 598.33		1. 5909 2. 602.33		1. 5914 2. 610.34
	1. 5905 2. 598.33		1. 5910 2. 602.33		1. 5915 2. 612.34

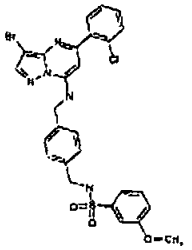
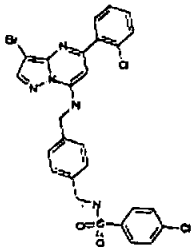
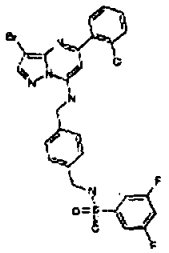
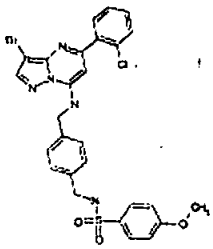
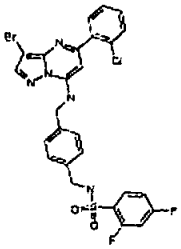
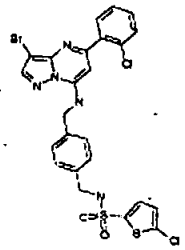
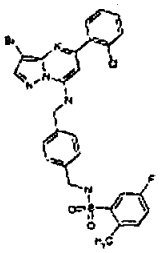
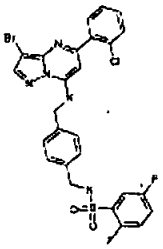
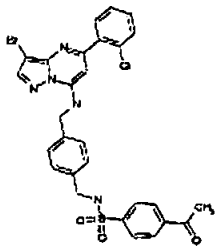
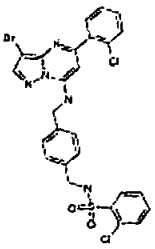
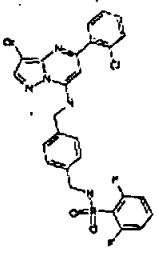
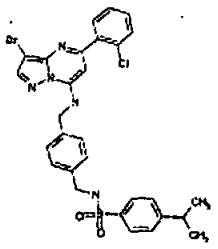
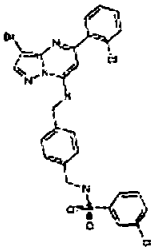
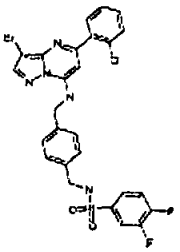
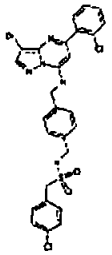
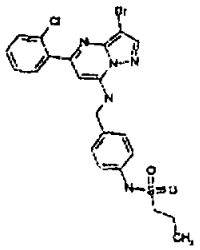
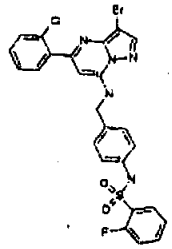
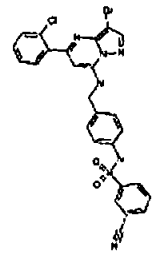
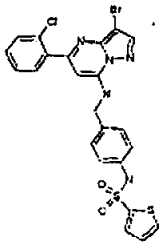
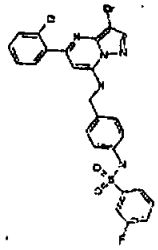
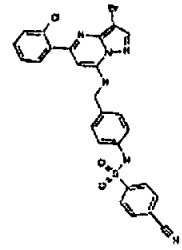
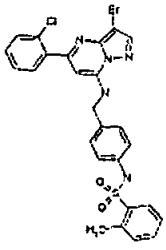
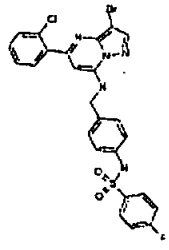
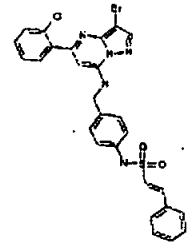
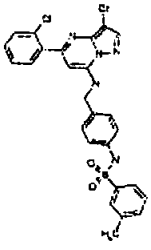
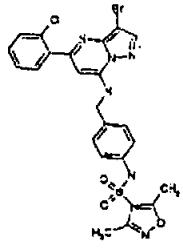
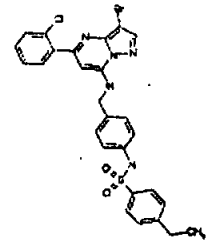
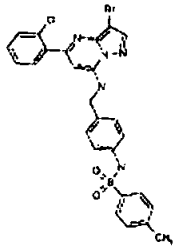
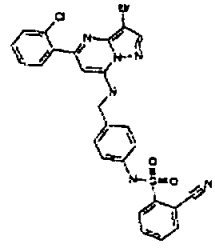
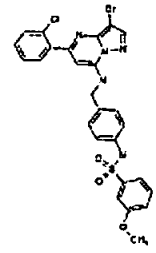
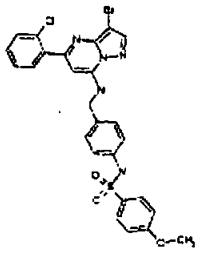
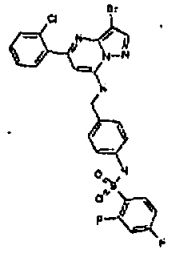
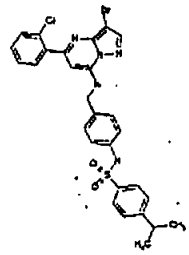
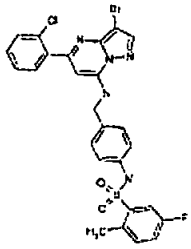
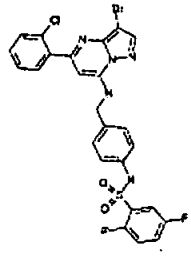
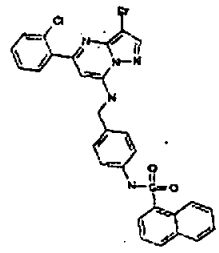
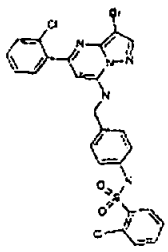
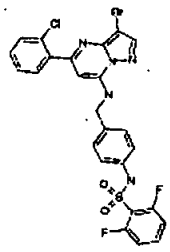
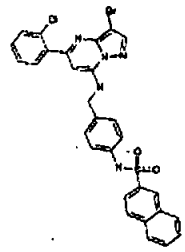
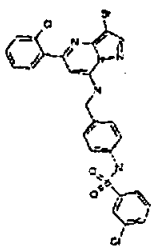
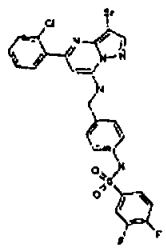
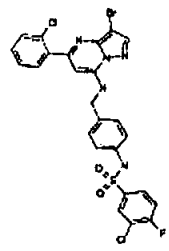
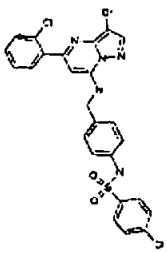
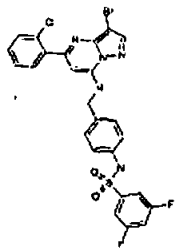
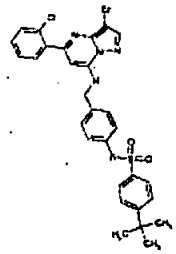
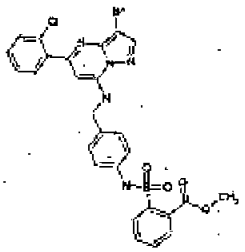
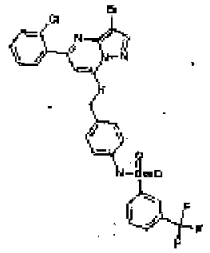
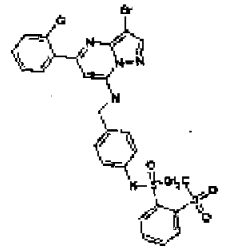
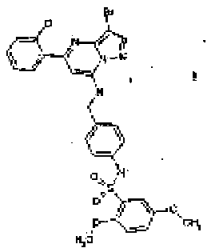
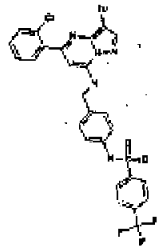
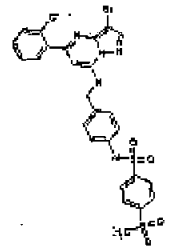
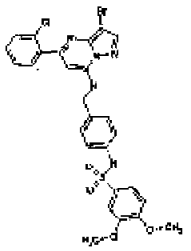
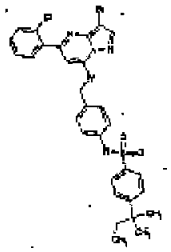
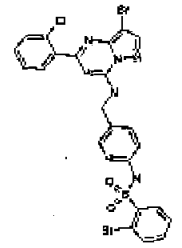
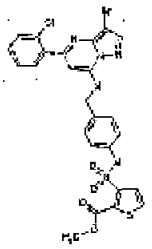
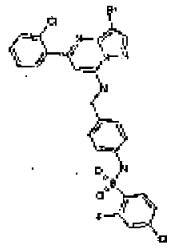
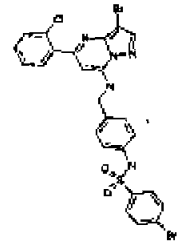
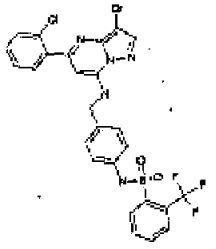
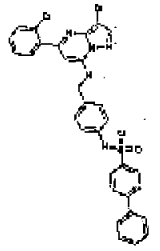
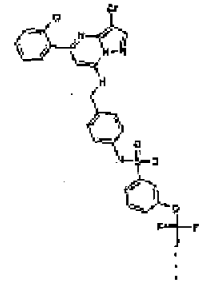
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5916 2. 614.34		1. 5921 2. 618.34		1. 5926 2. 620.34
	1. 5917 2. 614.34		1. 5922 2. 620.34		1. 5927 2. 624.34
	1. 5918 2. 616.34		1. 5923 2. 620.34		1. 5928 2. 626.34
	1. 5919 2. 618.34		1. 5924 2. 620.34		1. 5929 2. 626.34
	1. 5920 2. 618.34		1. 5925 2. 620.34		1. 5930 2. 632.35

TABLE60

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6001 2. 536.29		1. 6006 2. 588.32		1. 6011 2. 595.33
	1. 6002 2. 576.32		1. 6007 2. 588.32		1. 6012 2. 595.33
	1. 6003 2. 584.32		1. 6008 2. 588.32		1. 6013 2. 596.33
	1. 6004 2. 584.32		1. 6009 2. 589.32		1. 6014 2. 598.33
	1. 6005 2. 584.32		1. 6010 2. 595.33		1. 6015 2. 600.33

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6016 2. 600.33		1. 6021 2. 606.33		1. 6026 2. 612.34
	1. 6017 2. 602.33		1. 6022 2. 606.33		1. 6027 2. 620.34
	1. 6018 2. 604.33		1. 6023 2. 606.33		1. 6028 2. 620.34
	1. 6019 2. 604.33		1. 6024 2. 606.33		1. 6029 2. 622.34
	1. 6020 2. 604.33		1. 6025 2. 606.33		1. 6030 2. 626.34

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6031 2. 628.35		1. 6036 2. 638.35		1. 6041 2. 648.36
	1. 6032 2. 630.35		1. 6037 2. 638.35		1. 60425 2. 648.36
	1. 6033 2. 630.35		1. 6038 2. 638.35		1. 6043 2. 648.36
	1. 6034 2. 634.35		1. 6039 2. 622.34		1. 6044 2. 648.36
	1. 6035 2. 638.35		1. 6040 2. 646.36		1. 6045 2. 654.36

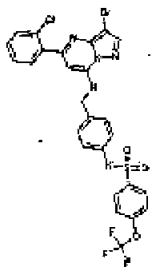
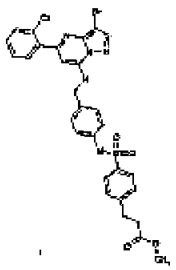
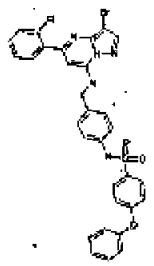
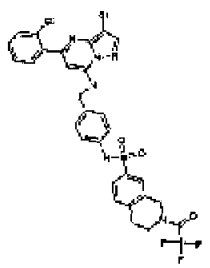
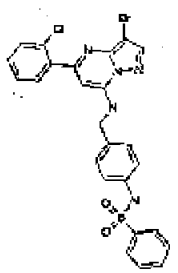
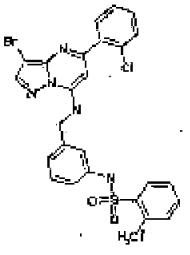
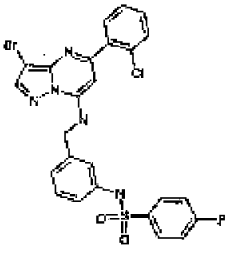
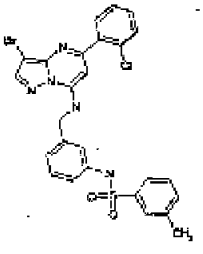
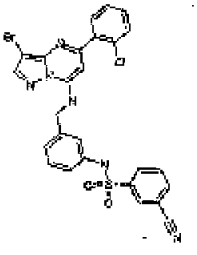
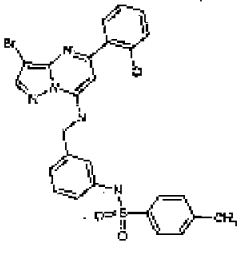
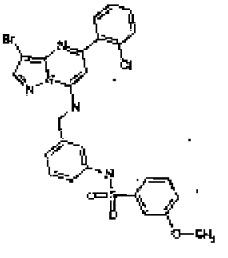
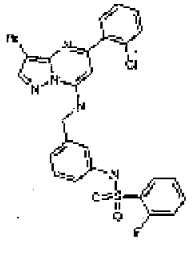
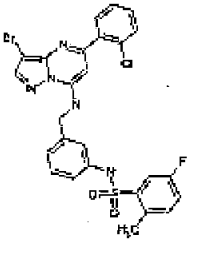
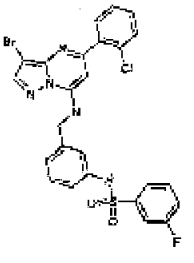
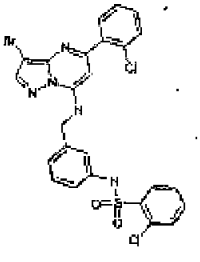
Product	1. Ex. 2, m/z
	1. 6046 2. 654.36
	1. 6047 2. 656.36
	1. 6048 2. 662.36
	1. 6049 2. 721.4
	1. 6050 2. 570.31

TABLE 61

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6101 2. 584.32		1. 6106 2. 588.32
	1. 6102 2. 584.32		1. 6107 2. 595.33
	1. 6103 2. 584.32		1. 6108 2. 600.33
	1. 6104 2. 588.32		1. 6109 2. 602.33
	1. 6105 2. 588.32		1. 6110 2. 604.33

5

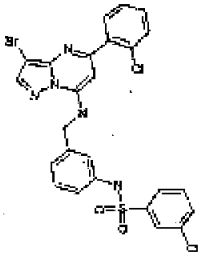
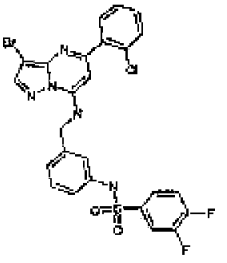
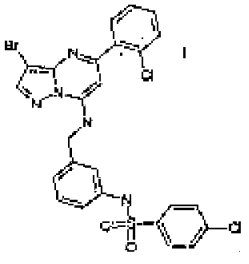
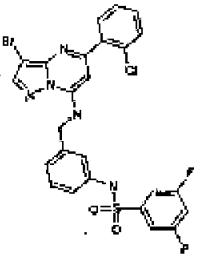
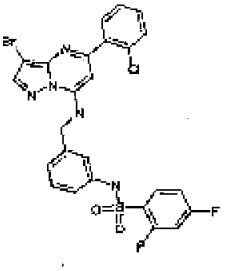
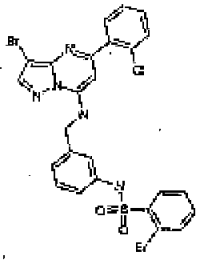
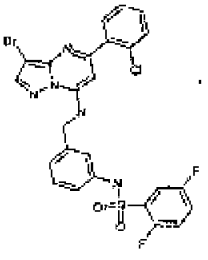
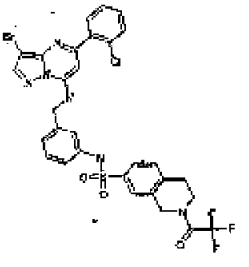
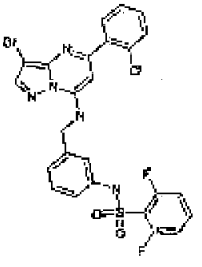
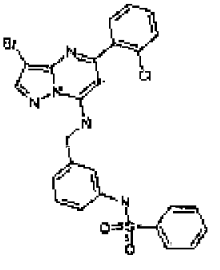
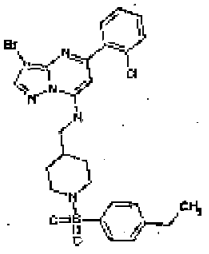
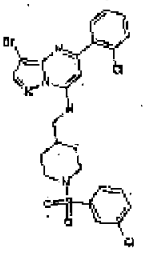
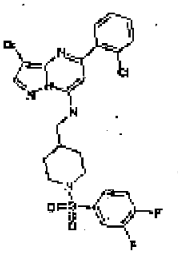
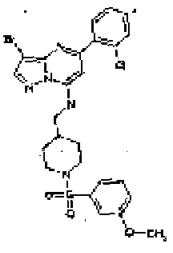
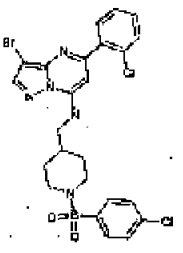
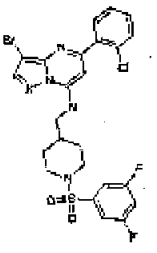
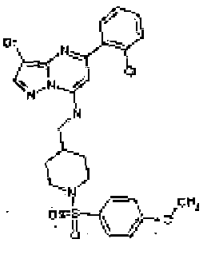
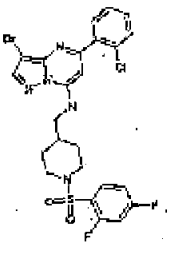
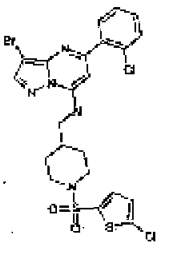
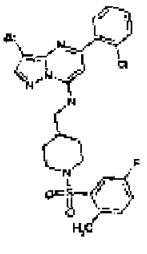
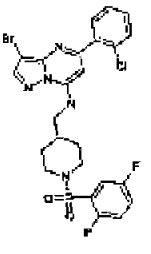
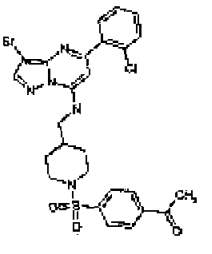
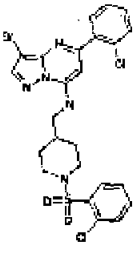
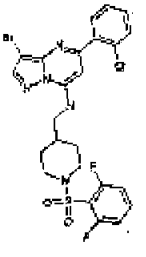
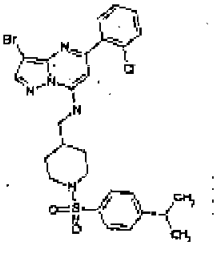
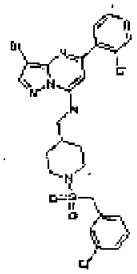
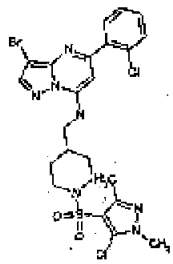
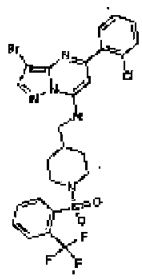
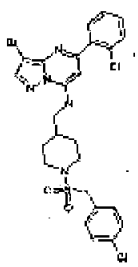
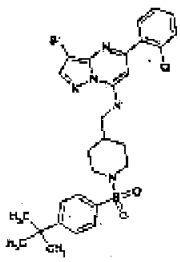
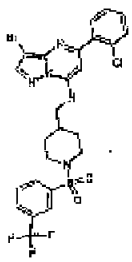
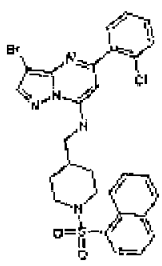
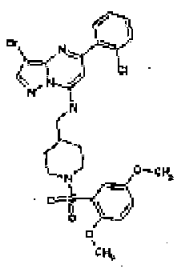
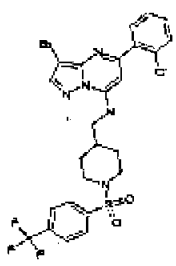
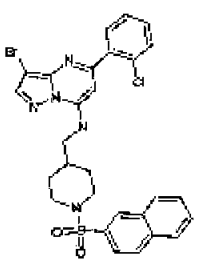
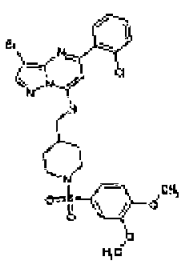
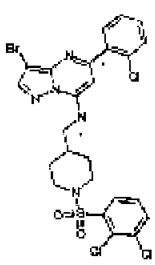
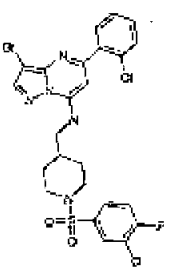
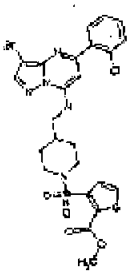
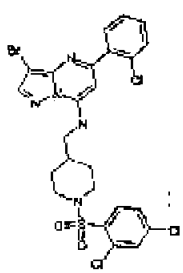
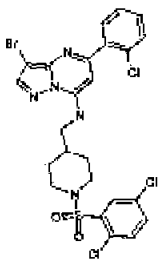
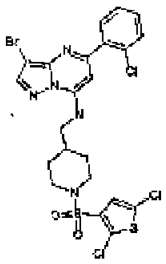
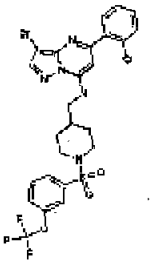
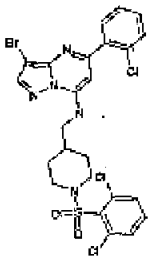
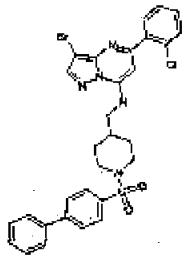
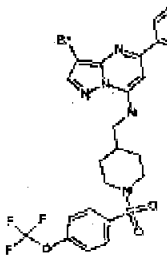
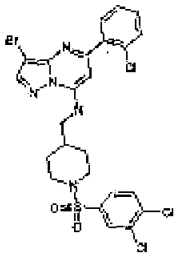
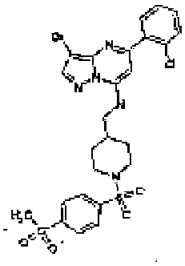
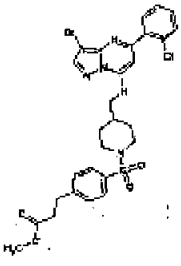
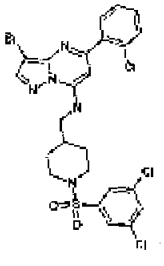
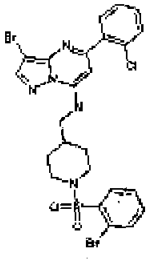
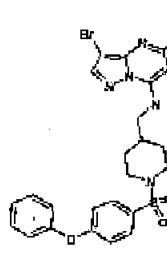
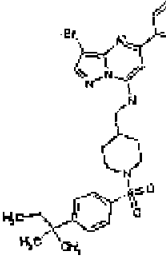
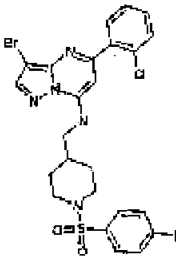
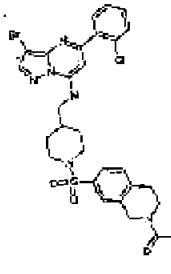
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6111 2. 604.33		1. 6116 2. 606.33
	1. 6112 2. 604.33		1. 6117 2. 606.33
	1. 6113 2. 606.33		1. 6118 2. 648.38
	1. 6114 2. 606.33		1. 6119 2. 721.4
	1. 6115 2. 606.33		1. 6120 2. 570.31

TABLE62 Error! Objects cannot be created from editing field codes.

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6216 2. 690.32		1. 6221 2. 596.33		1. 6226 2. 598.33
	1. 6217 2. 592.33		1. 6222 2. 596.33		1. 6227 2. 596.33
	1. 6218 2. 592.33		1. 6223 2. 598.33		1. 6228 2. 602.33
	1. 6219 2. 592.33		1. 6224 2. 596.33		1. 6229 2. 604.33
	1. 6220 2. 594.33		1. 6225 2. 598.33		1. 6230 2. 604.33

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6231 2. 610.34		1. 6236 2. 614.34		1. 6241 2. 630.35
	1. 6232 2. 610.34		1. 6237 2. 618.34		1. 6242 2.
	1. 6233 2. 612.34		1. 6238 2. 622.34		1. 6243 2. 630.35
	1. 6234 2. 612.34		1. 6239 2. 622.34		1. 6244 2. 630.35
	1. 6235 2. 614.34		1. 6240 2. 626.34		1. 6245 2. 630.35

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1 .6246 2. 630.35		1 .6251 2. 636.35		1. 6256 2. 646.36
	1. 6247 2. 630.35		1.0 6252 2. 636.35		1. 6257 2. 646.36
	1. 6248 2. 630.35		1. 6253 2. 640.35		1. 6258 2. 648.36
	1. 6249 2. 630.35		1. 6254 2. 640.35		1. 6259 2. 654.36
	1 .6250 2. 632.35		1. 6255 2. 638.35		1. 6260 2. 713.39

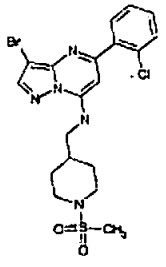
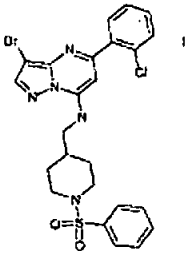
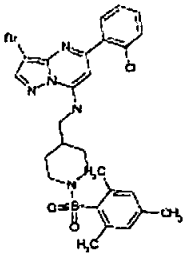
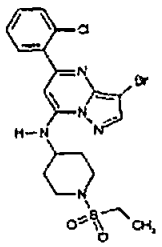
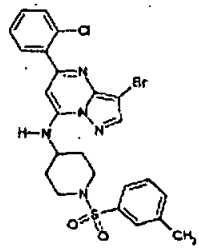
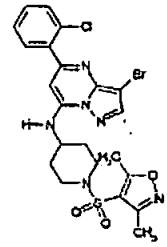
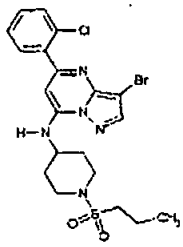
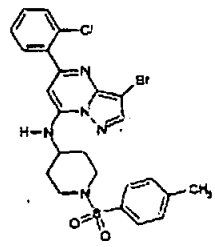
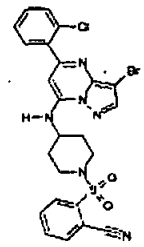
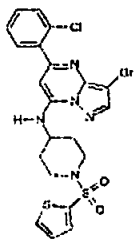
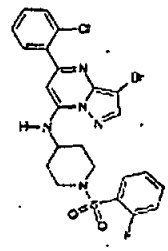
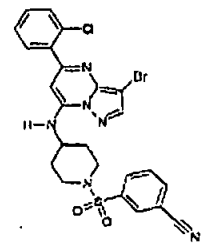
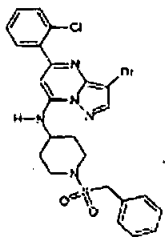
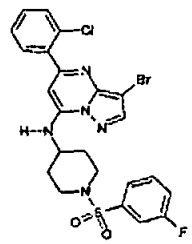
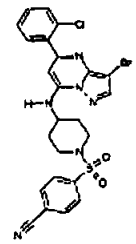
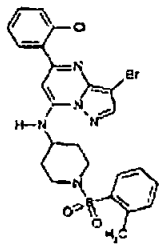
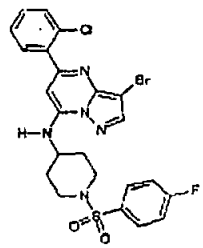
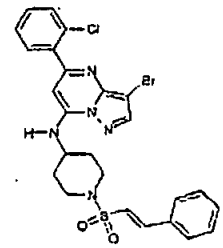
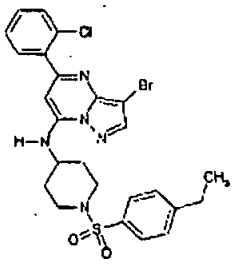
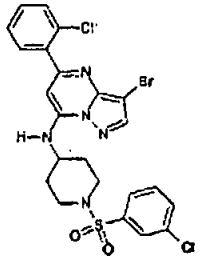
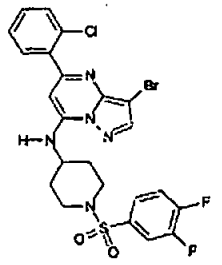
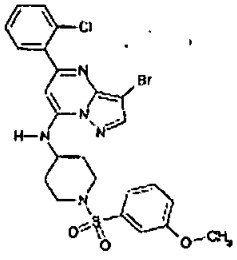
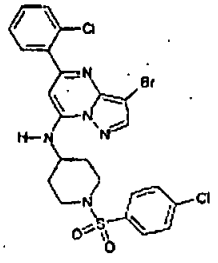
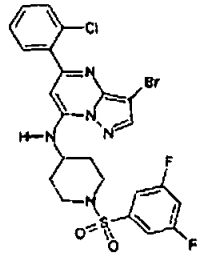
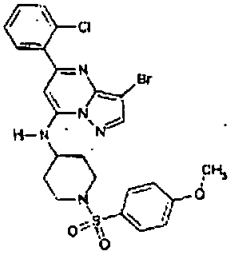
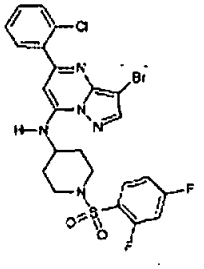
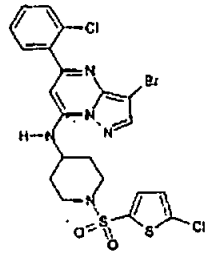
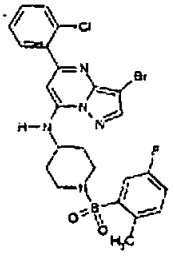
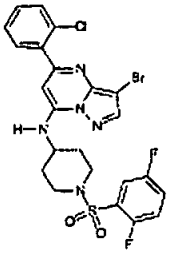
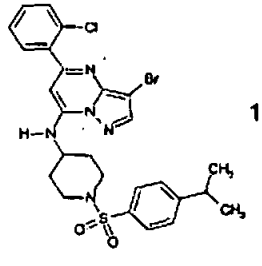
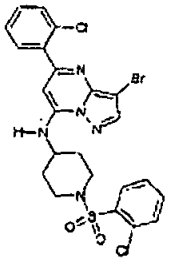
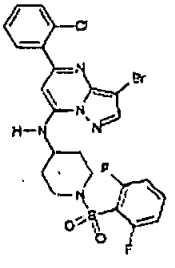
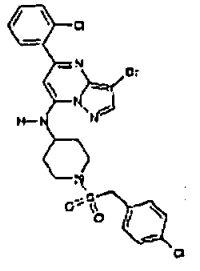
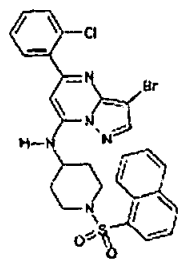
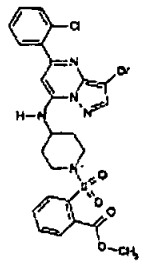
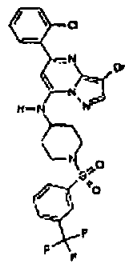
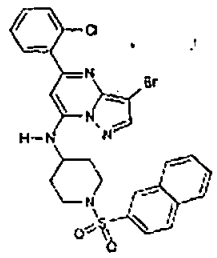
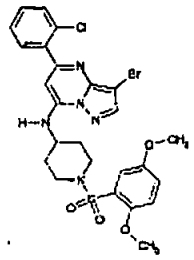
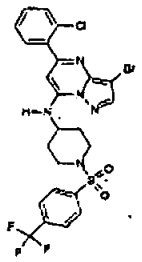
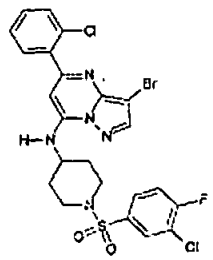
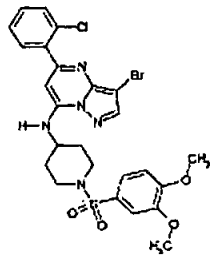
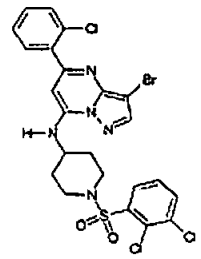
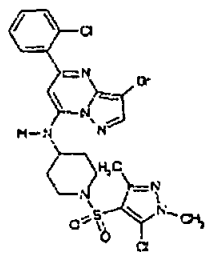
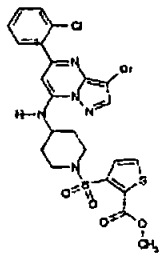
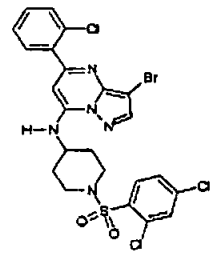
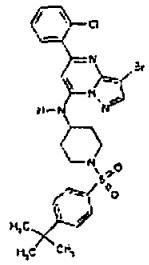
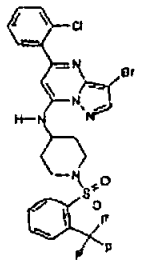
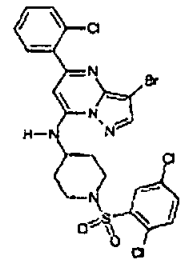
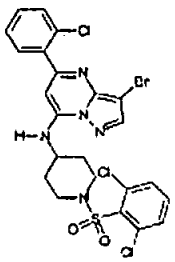
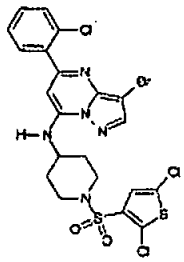
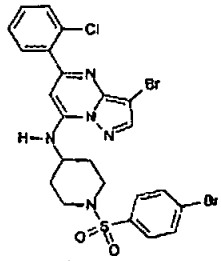
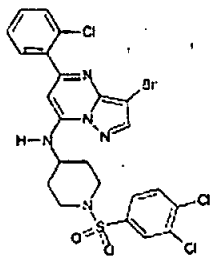
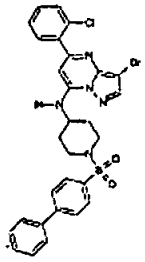
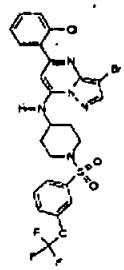
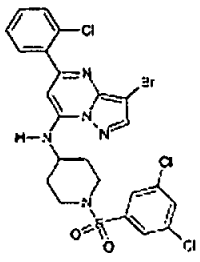
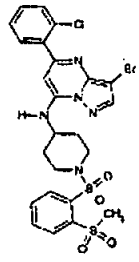
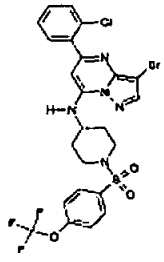
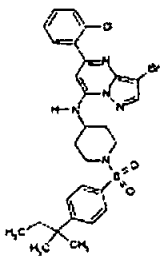
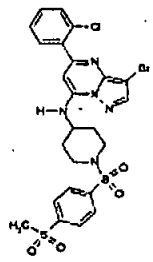
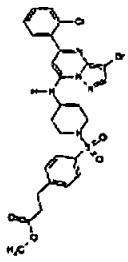
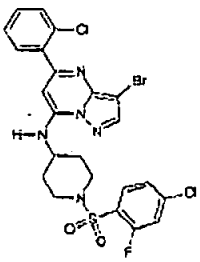
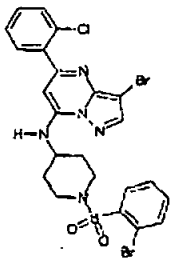
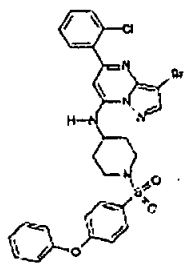
Product	1. Ex. 2. m/z
	1. 6261 2. 500.27
	1. 6262 2. 562.31
	1. 6263 2. 604.33

TABLE 63

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6301 2. 500.27		1. 6306 2. 562.31		1. 6311 2. 567.31
	1. 6302 2. 514.28		1. 6307 2. 562.31		1. 6312 2. 573.32
	1. 6303 2. 554.3		1. 6308 2. 566.31		1. 6313 2. 573.32
	1. 6304 2. 562.31		1. 6309 2. 566.31		1. 6314 2. 573.32
	1. 6305 2. 562.31		1. 6310 2. 566.31		1. 6315 2. 574.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6316 2. 576.32		1. 6321 2. 582.32		1. 6326 2. 584.32
	1. 6317 2. 578.32		1. 6322 2. 582.32		1. 6327 2. 584.32
	1. 6318 2. 578.32		1. 6323 2. 584.32		1. 6328 2. 588.32
	1. 6319 2. 580.32		1. 6324 2. 582.32		1. 6329 2. 590.32
	1. 6320 2. 582.32		1. 6325 2. 584.32		1. 6330 2. 596.33

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6331 2. 598.33		1. 6336 2. 606.33		1. 6341 2. 616.34
	1. 6332 2. 598.33		1. 6337.2. 608.33		1. 6342 2. 616.34
	1. 6333 2. 600.33		1. 6338 2. 608.33		1. 6343 2. 616.34
	1. 6334 2. 600.33		1. 6339 2. 612.34		1.6344 2. 616.34
	1. 6335 2. 604.33		1. 6340 2. 616.34		1. 6345 2. 616.34

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6346 2. 616.34		1. 6351 2. 622.34		1. 6356 2. 626.34
	1. 6347 2. 616.34		1. 6352 2. 624.34		1. 6357 2. 632.35
	1. 6348 2. 616.34		1. 6353 2. 626.34		1. 6358 2. 632.35
	1. 6349 2. 618.34		1. 6354 2. 626.34		1. 6359 2. 634.35
	1. 6350 2. 600.33		1. 6355 2. 626.34		1. 6360 2. 640.35

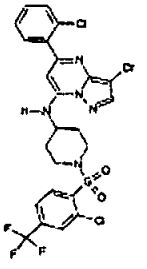
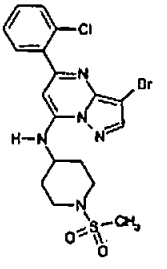
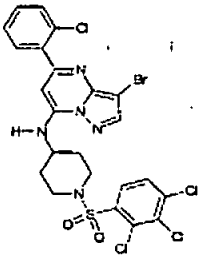
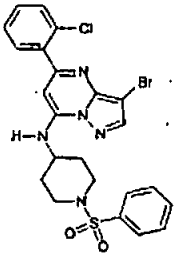
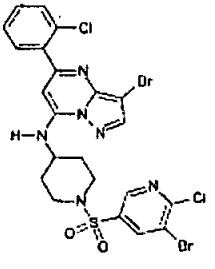
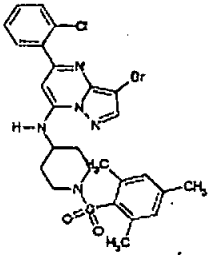
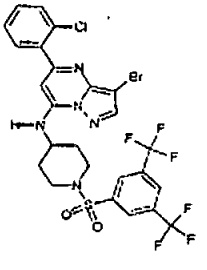
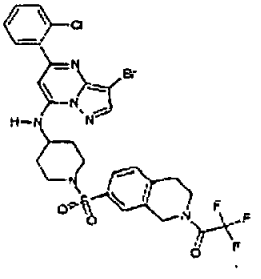
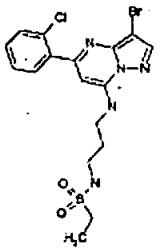
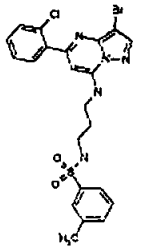
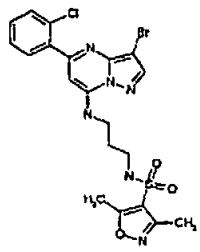
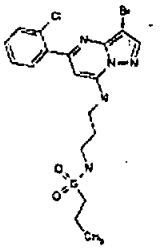
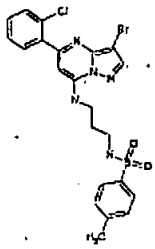
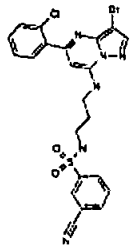
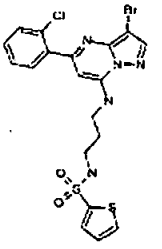
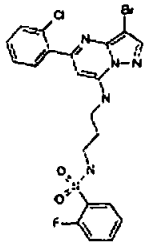
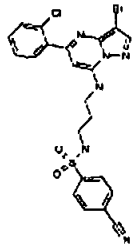
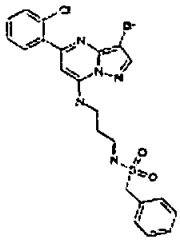
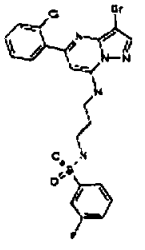
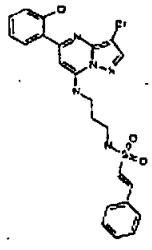
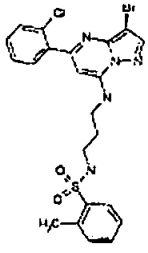
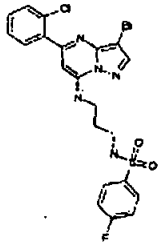
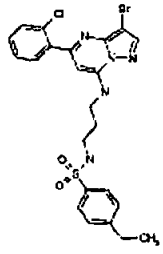
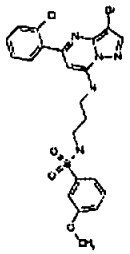
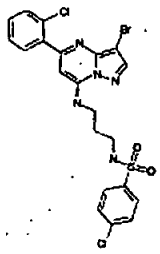
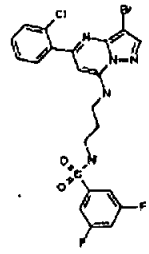
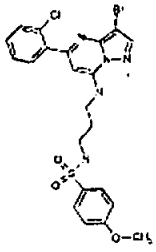
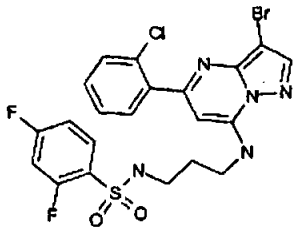
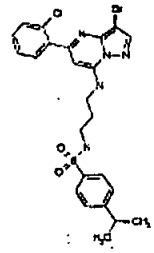
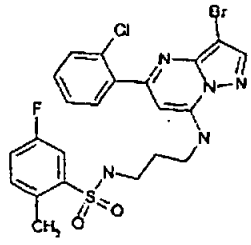
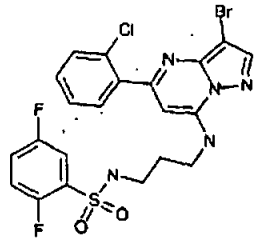
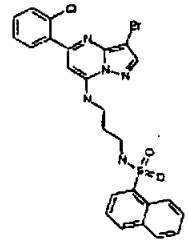
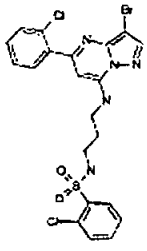
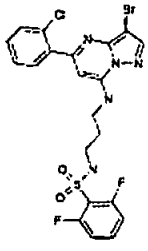
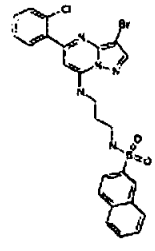
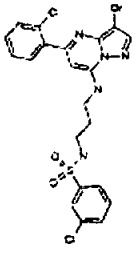
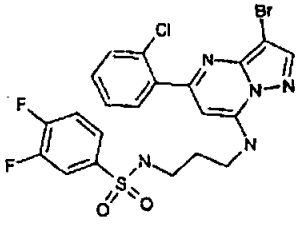
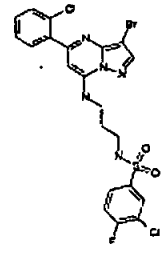
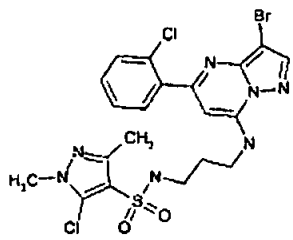
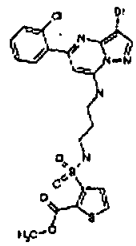
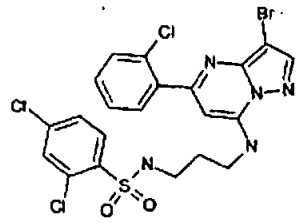
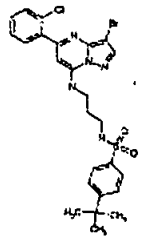
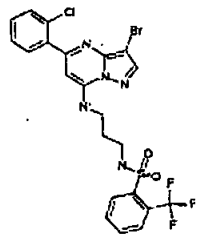
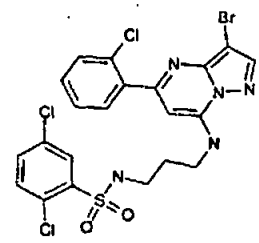
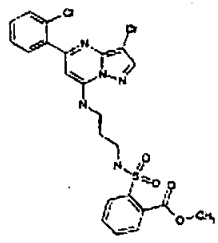
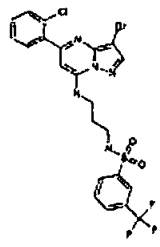
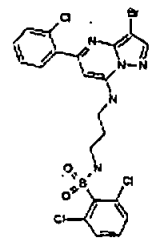
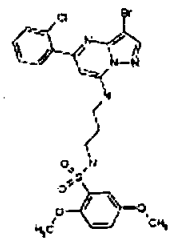
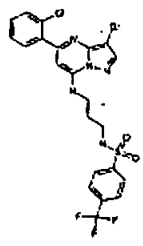
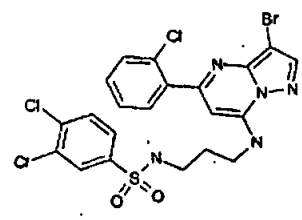
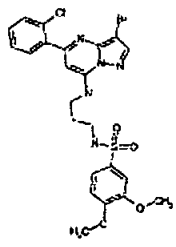
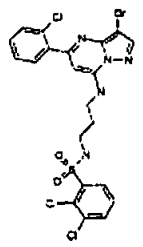
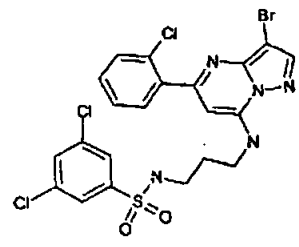
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6361 2. 650.36		1. 6366 2. 486.27
	1. 6362 2. 650.36		1. 6367 2. 548.3
	1. 6363 2. 661.36		1. 6368 2. 590.32
	1. 6364 2. 684.38		
	1. 6365 2. 699.38		

TABLE 64

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6401 2. 474.26		1. 6406 2. 536.29		1. 6411 2. 541.3
	1. 6402 2. 488.27		1. 6407 2. 536.29		1. 6412 2. 547.3
	1. 6403 2. 528.29		1. 6408 2. 540.3		1. 6413 2. 547.3
	1. 6404 2. 536.29		1. 6409 2. 540.3		1. 6414 2. 548.3
	1. 6405 2. 536.29		1. 6410 2. 540.3		1. 6415 2. 550.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6416 2. 552.3		1. 6421 2. 556.31		1. 6426 2 558.31
	1. 6417 2. 552.3		1. 6122 2. 558.31		1. 6427 2 564.31
	1. 6418 2. 554.3		1. 6423 2. 558.31		1. 6428 2. 572.31
	1. 6419 2. 556.31		1. 6424 2. 558.31		1. 6429 2. 572.31
	1. 6420 2. 556.31		1. 6425 2. 558.31		1. 6430 2. 574.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2 m/z
	1. 6431 2. 574.32		1. 6436 2. 586.32		1. 6441 590.32
	1. 6432 2. 578.32		1. 6437 2. 590.32		1. 6442 590.32
	1. 6433 2. 580.32		1. 6438 2. 590.32		1. 6443 2 590.32
	1. 6434 2. 582.32		1. 6439 2. 590.32		1. 6444 2 590.32
	1. 6435 2. 582.32		1. 6440 2. 589.32		1. 6445 2 590.32

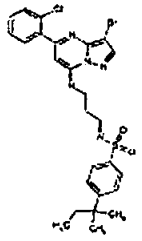
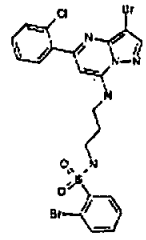
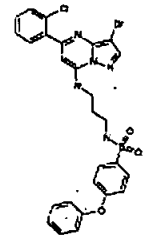
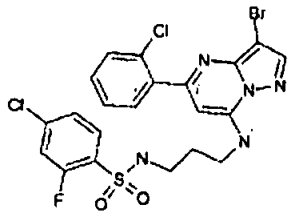
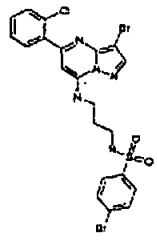
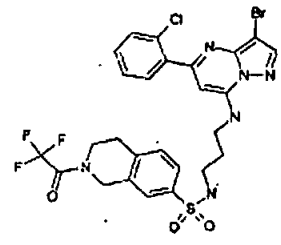
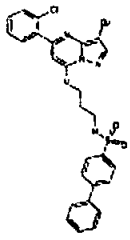
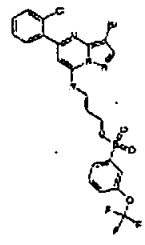
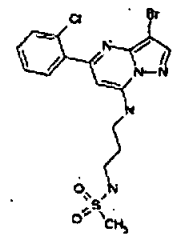
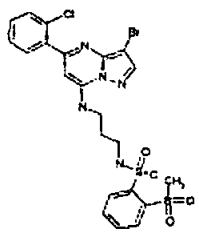
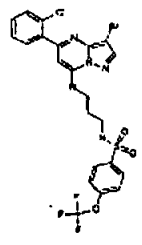
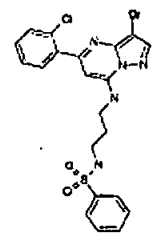
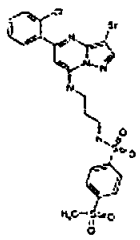
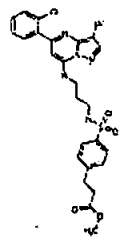
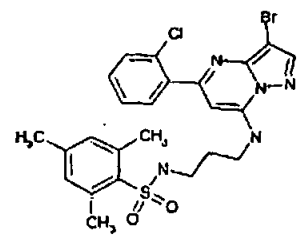
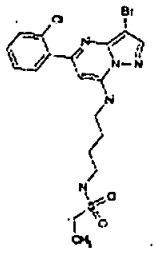
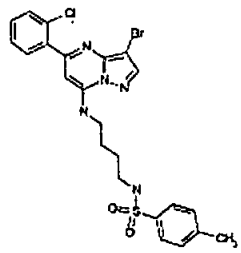
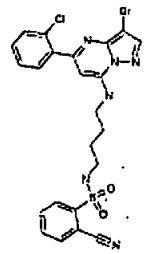
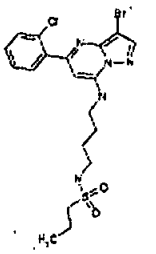
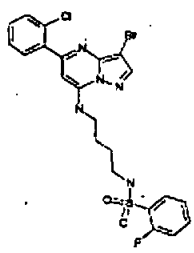
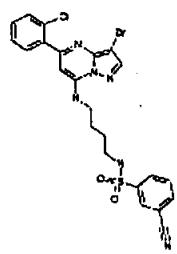
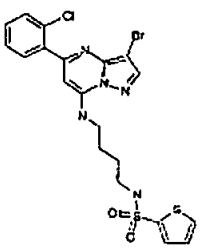
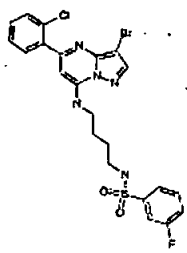
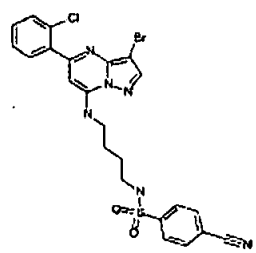
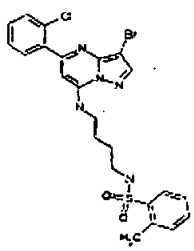
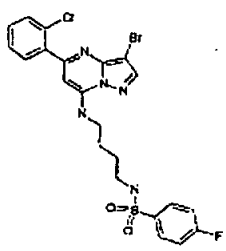
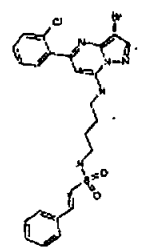
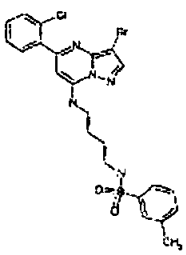
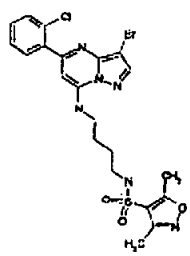
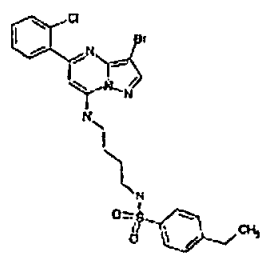
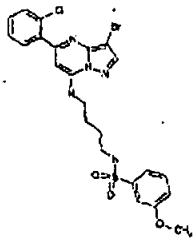
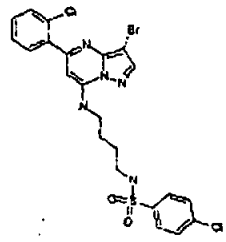
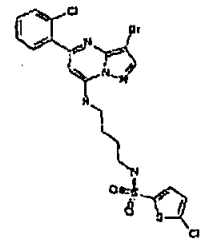
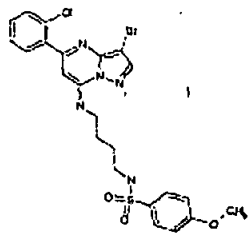
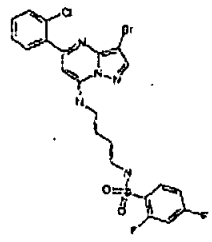
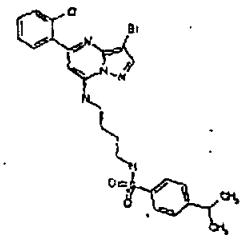
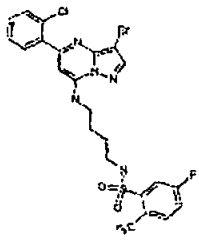
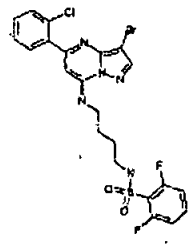
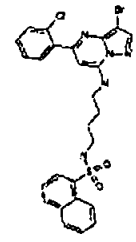
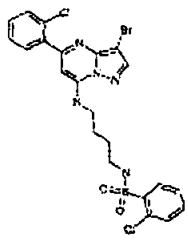
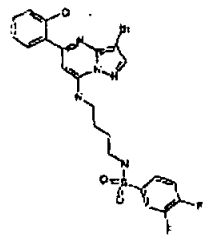
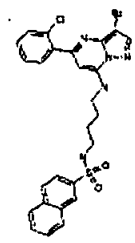
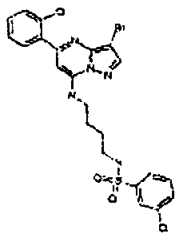
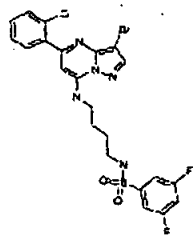
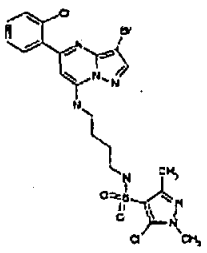
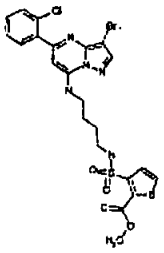
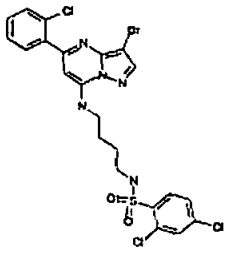
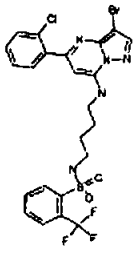
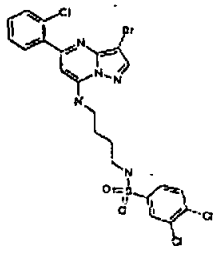
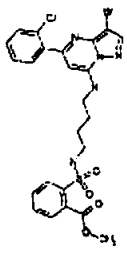
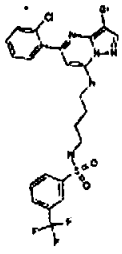
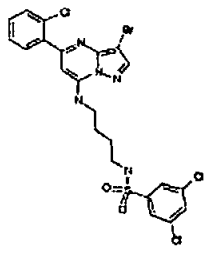
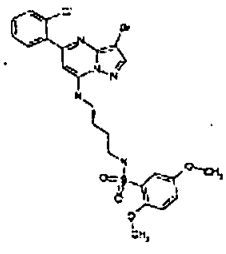
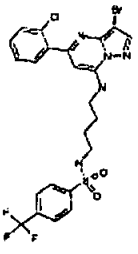
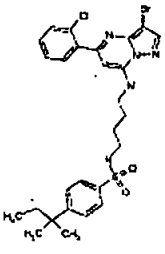
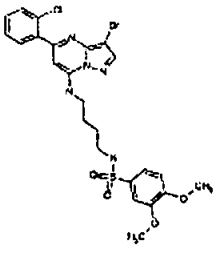
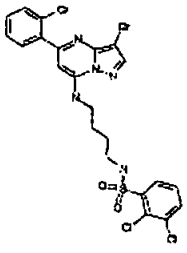
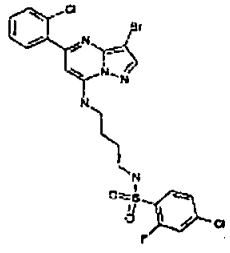
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2 m/z
	1. 6446 2. 592.33		1. 6451 2. 600.33		1. 6456 : 614.34
	1. 6447 2. 574.32		1. 6452 2. 600.33		1. 6447 2 673.37
	1. 6448 2. 598.33		1. 6453 2. 606.33		1. 6458 2 460.25
	1. 6449 2. 600.33		1. 6454 2. 606.33		6459 2.
	1. 6450 2. 600.33		1. 6455 2. 608.33		1. 6460 2. 564.31

TABLE 65

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6501 2. 488.27		1. 6506 2. 550.3		1. 6511 2. 581.31
	1. 6502 2. 502.28		1. 6507 2. 554.3		1. 6512 2. 561.31
	1. 6503 2. 542.3		1. 6508 2. 554.3		1. 6213 2. 561.31
	1. 6504 2. 550.3		1. 6509 2. 554.3		1. 6514 2. 562.31
	1. 6505 2. 550.3		1. 6510 2. 555.31		1. 6515 2. 564.31

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6516 2. 566.31		1. 6521 2. 570.31		1. 6526 2. 576.32
	1. 6517 2. 566.31		1. 6522 2. 572.31		1. 6527 2. 578.32
	1. 6518 2. 568.31		1. 6523 2. 572.31		1. 6528 2. 586.32
	1. 6519 2. 570.31		1. 6524 2. 572.31		1. 6529 2. 586.32
	1. 6520 2. 570.31		1. 6525 2. 572.31		1. 6530 2. 588.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6531 2. 588.32		1. 6536 2. 600.33		1. 6541 2. 604.33
	1. 6532 2. 592.33		1. 6537 2. 604.33		1. 6542 2. 604.33
	1. 6533 2. 594.33		1. 6538 2. 604.33		1. 6543 2. 604.33
	1. 6534 2. 596.33		1. 6539 2. 604.33		1. 6544 2. 606.33
	1. 6535 2. 596.33		1. 6540 2. 604.33		1. 6545 2. 588.32

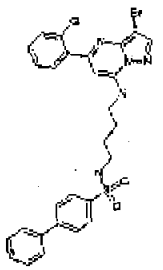
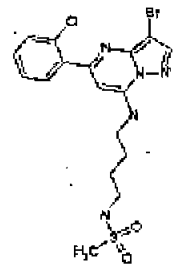
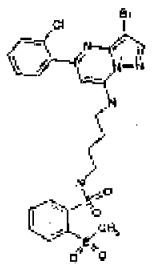
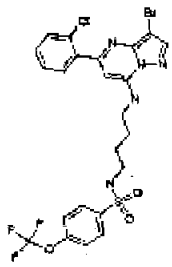
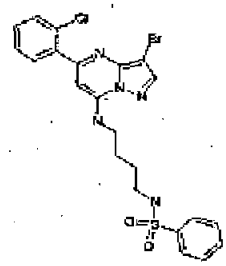
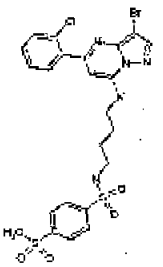
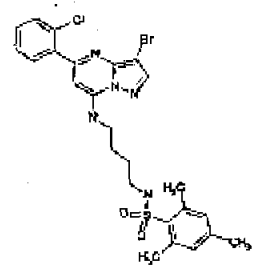
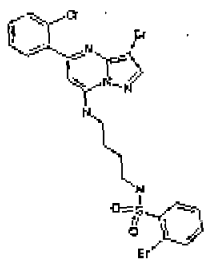
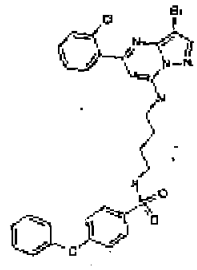
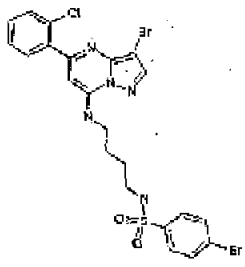
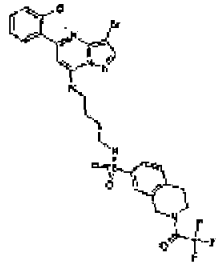
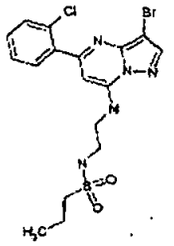
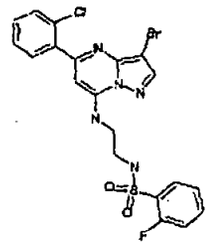
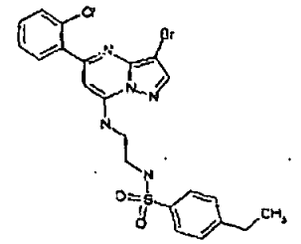
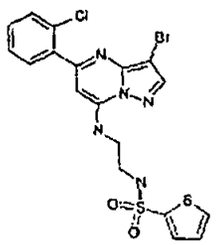
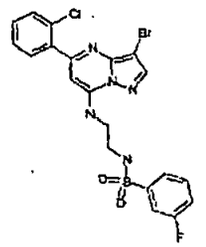
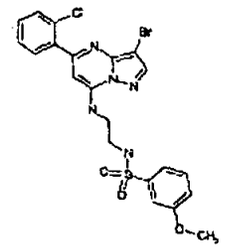
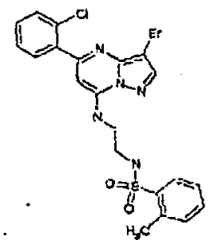
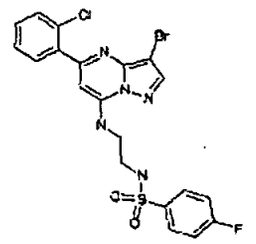
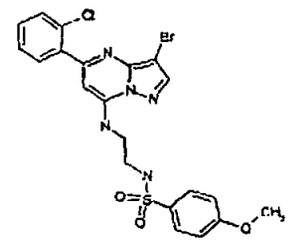
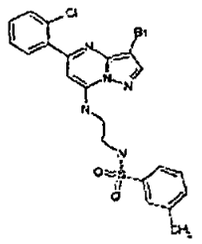
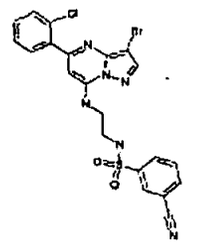
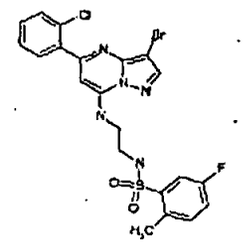
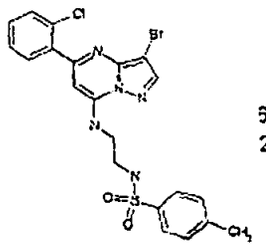
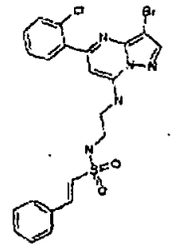
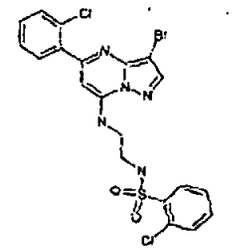
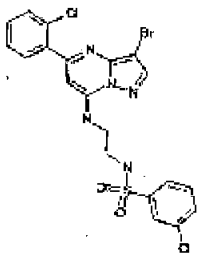
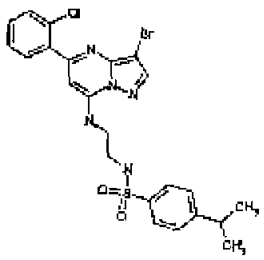
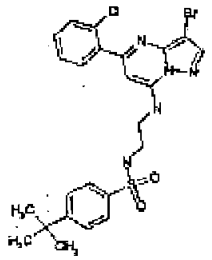
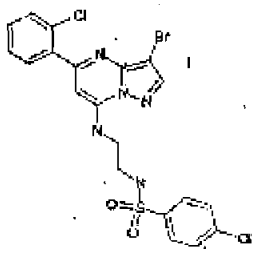
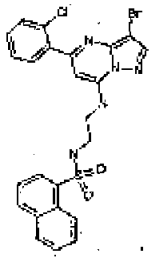
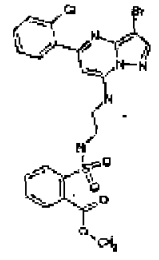
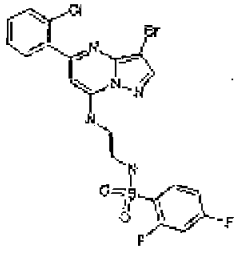
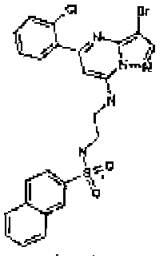
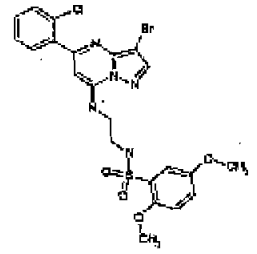
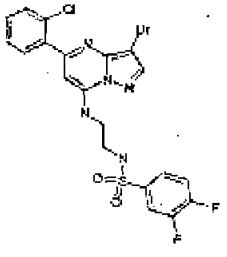
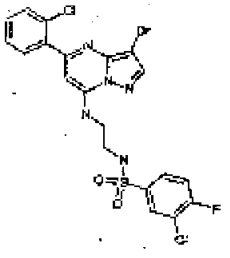
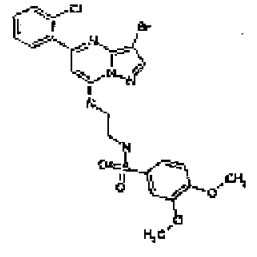
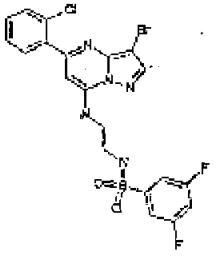
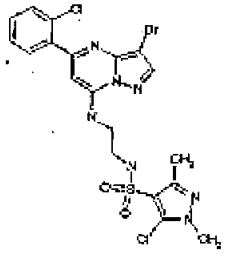
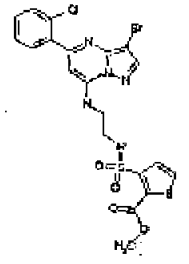
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6546 2. 612.34		1. 6551 2. 620.34		1. 6556 2. 474.26
	1. 6547 2. 614.34		1. 6552 2. 620.34		1. 6557 2. 536.29
	1. 6548 2. 614.34		1. 6553 2. 622.34		1. 6558 2. 578.32
	1. 6549 2. 614.34		1. 6554 2. 626.35		
	1. 6550 2. 614.34		1. 6555 2. 687.38		

TABLE 67

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. m/z
	1. 6701 2. 474.26		1. 6706 2. 526.29		1. 6711 536.2
	1. 6702 2. 514.28		1. 6707 2. 526.29		1. 6712. 538.3
	1. 6703 2. 522.29		1. 6708 2. 526.29		1. 6713 2 538.3
	1. 6704 2. 522.29		1. 6709 2. 533.29		1. 6714 2.
	6705 2. 22.29		1. 6710 2. 534.29		1. 6715 2. 542.3

5

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6716 2. 542.3		1. 6721 2. 550.3		1. 6726 2 564.31
	1. 6717 2. 542.3		1. 6722 2. 558.31		1. 6727 2. 566.31
	1. 6718 2. 544.3		1. 6723 2. 558.31		1. 6728 2. 568.31
	1. 6719 2. 544.3		1. 6724 2. 560.31		1. 6729 2. 568.31
	1. 6720 2. 544.3		1. 6725 2. 560.31		1. 6730 2. 572.31

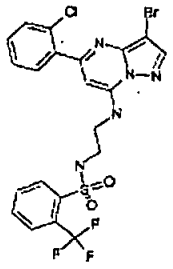
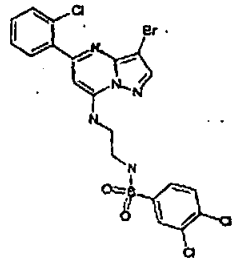
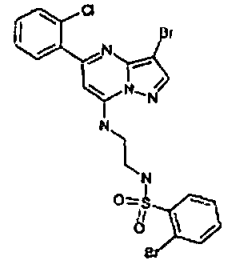
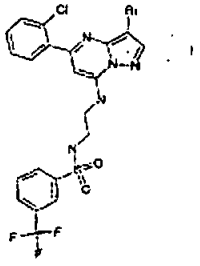
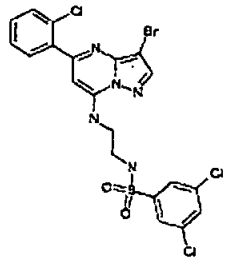
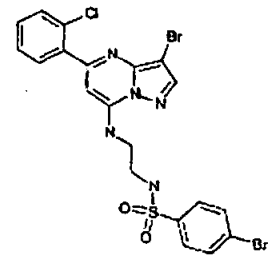
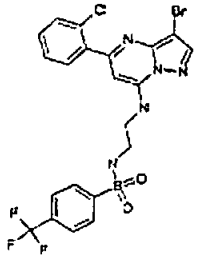
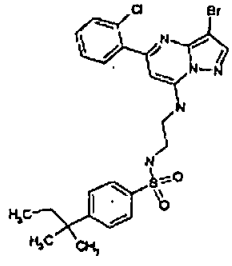
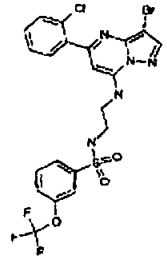
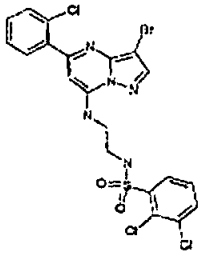
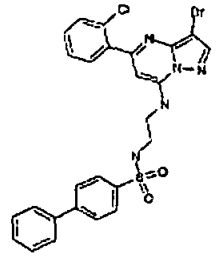
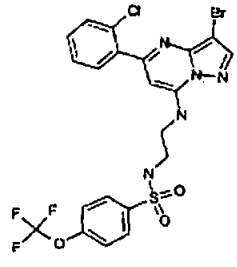
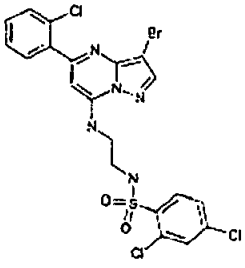
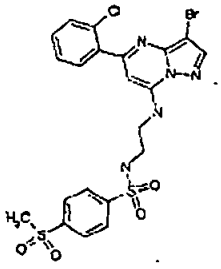
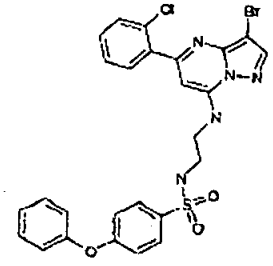
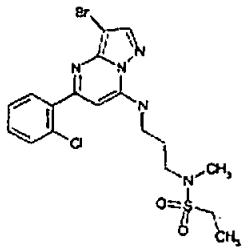
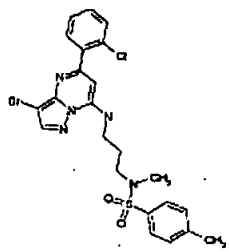
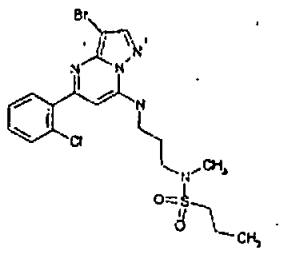
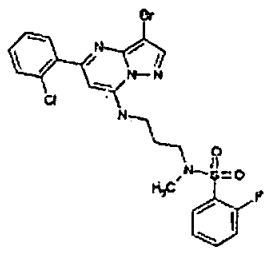
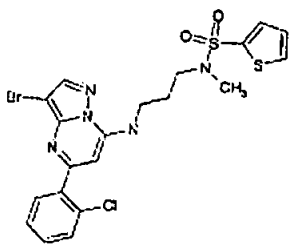
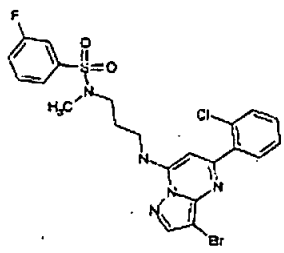
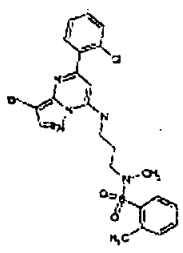
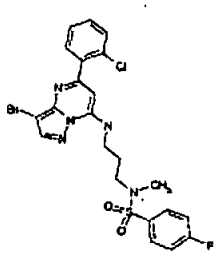
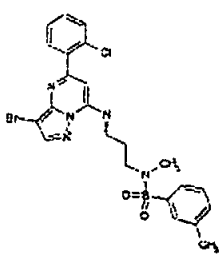
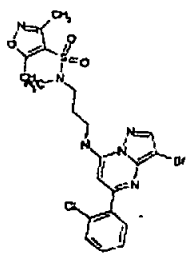
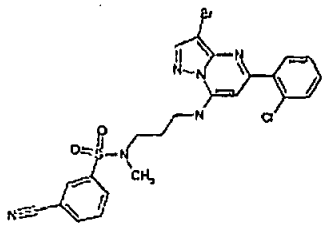
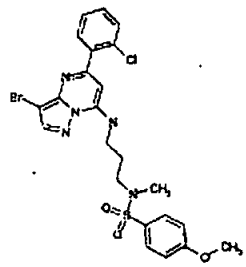
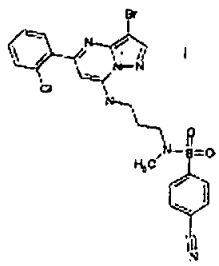
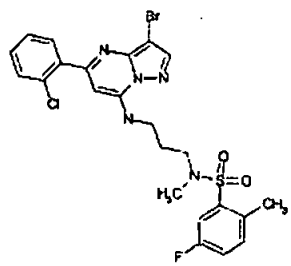
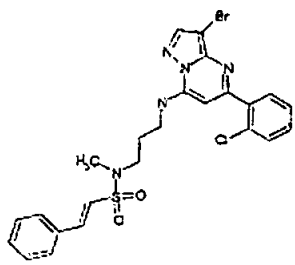
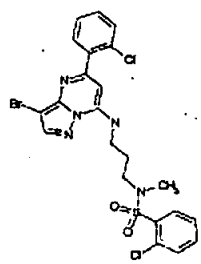
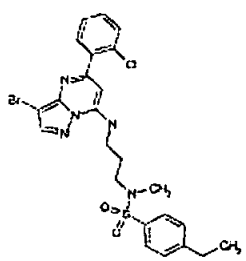
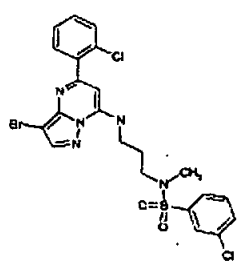
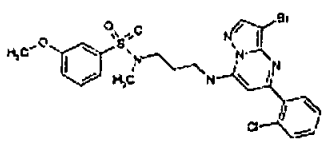
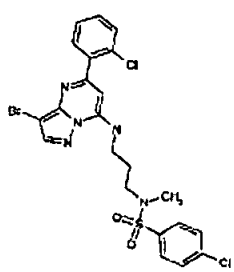
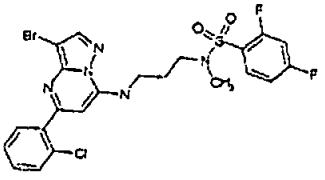
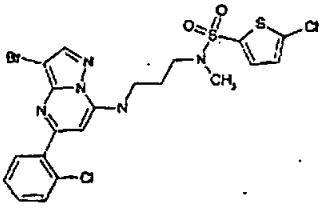
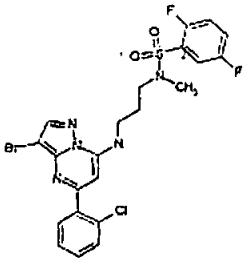
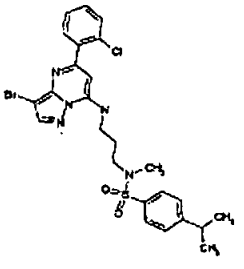
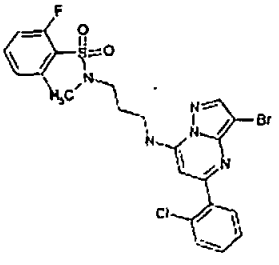
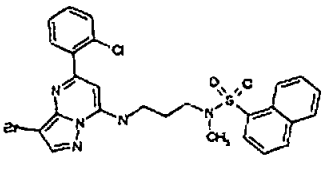
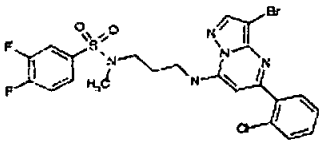
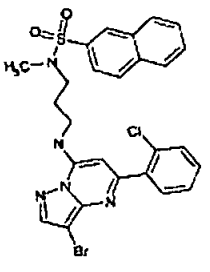
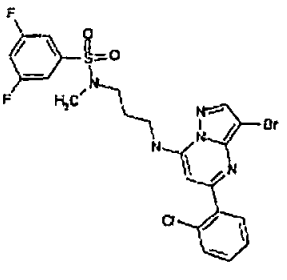
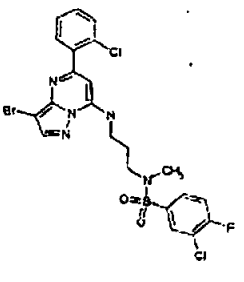
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6731 2. 576.32		1. 6736 2. 576.32		1. 6741 2 586.32
	1. 6732 2. 576.32		1. 6737 2. 576.32		1. 6742 2 586.32
	1. 6733 2. 576.32		1. 6738 2. 576.32		1. 6743 2. 592.33
	1. 6734 2. 576.32		1. 6739 2. 584.32		1. 6744 2. 592.33
	1. 6735 2. 576.32		1. 6740 2. 586.32		1. 6745 2. 600.33

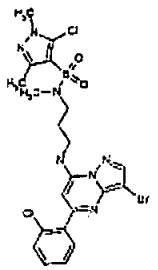
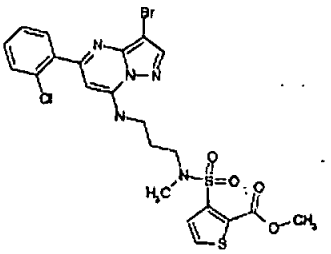
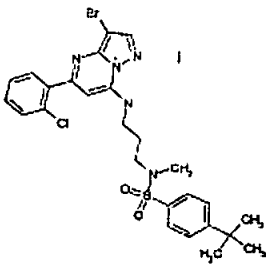
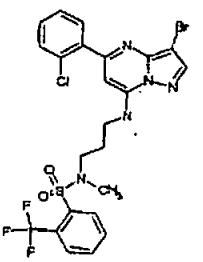
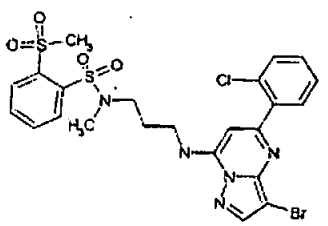
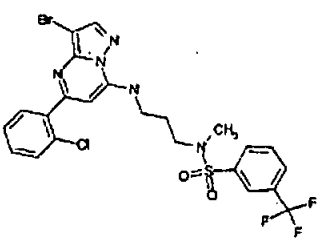
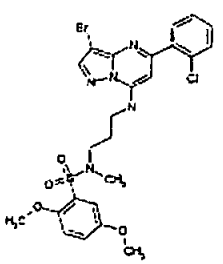
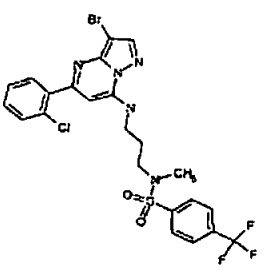
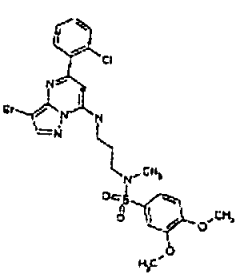
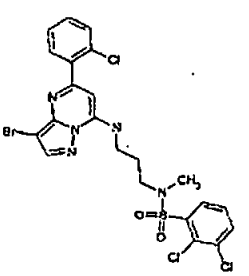
TABLE 68

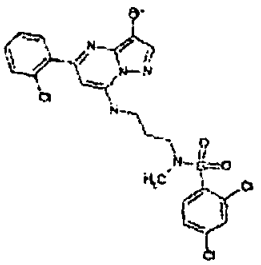
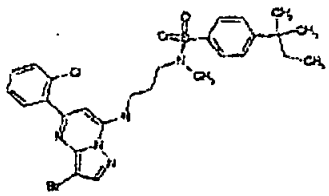
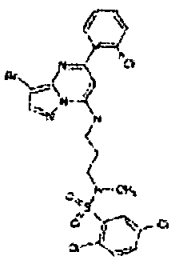
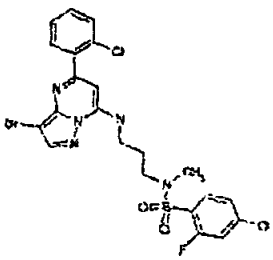
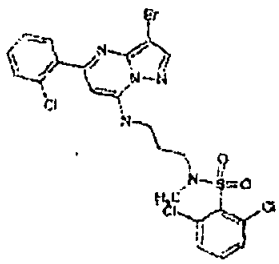
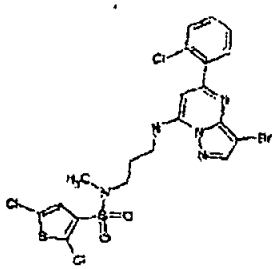
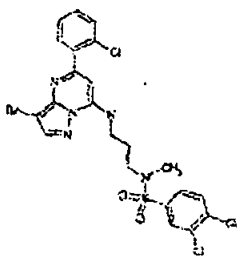
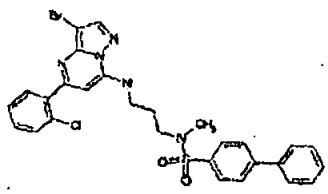
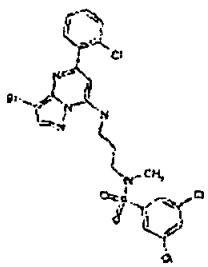
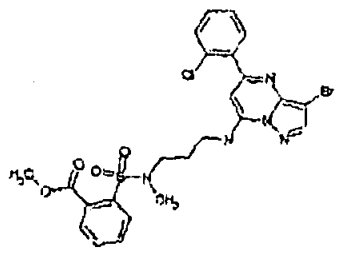
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6801 2. 488.27		1. 6806 2. 550.3
	1. 6802 2. 502.28		1. 6807 2. 554.3
	1. 6803 2. 542.3		1. 6808 2. 554.3
	1. 6804 2. 550.3		1. 6809 2. 554.3
	1. 68058 2. 550.3		1. 6810 2. 555.31

Error! Objects cannot be created from editing field codes.

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6811 2. 561.31		1. 6816 2. 566.31
	1. 6812 2. 561.31		1. 6817 2. 568.31
	1. 6813 2. 562.31		1. 6818 2. 570.31
	1. 6814 2. 564.31		1. 6819 2. 570.31
	1. 6815 2. 566.31		1. 6820 2. 570.31

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6821 2. 571.31		1. 6826 2. 576.32
	1. 6822 2. 572.31		1. 6827 2. 578.32
	1. 6823 2. 572.31		1. 6828 2. 586.32
	1. 6824 2. 572.31		1. 6829 2. 586.32
	1. 6825 2. 572.31		1. 6830 2. 588.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6831 2. 588.32		1. 6836 2. 600.33
	1. 6832 2. 592.33		1. 6837 2. 602.33
	1. 6833 2. 614.34		1. 6838 2. 604.33
	1. 6834 2. 596.33		1. 6839 2. 604.33
	1. 6835 2. 596.33		1. 6840 2. 604.33

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6841 2. 604.33		1. 6846 2. 606.33
	1. 6842 2. 604.33		1. 6847 2. 588.32
	1. 6843 2. 605.33		1. 6848 2. 610.34
	1. 6844 2. 604.33		1. 6849 2. 612.34
	1. 6845 2. 604.33		

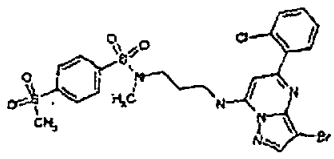
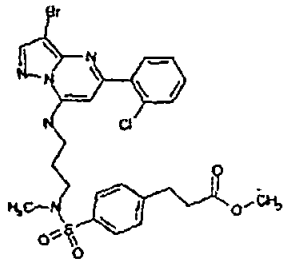
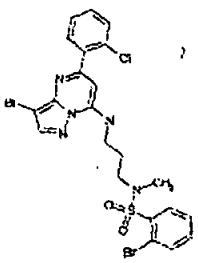
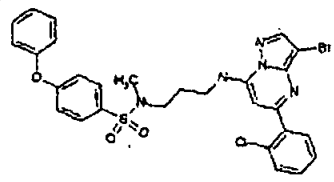
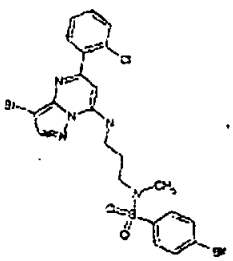
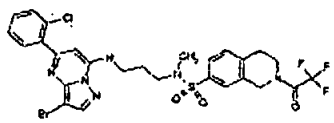
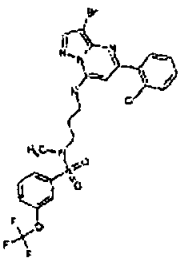
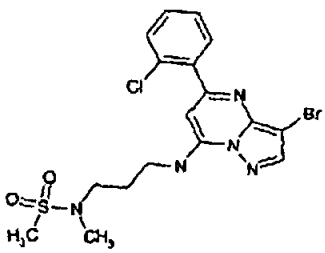
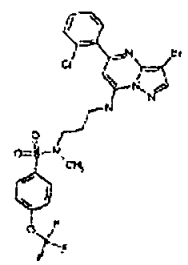
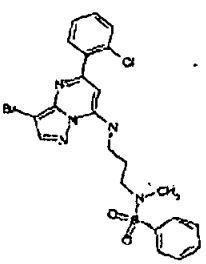
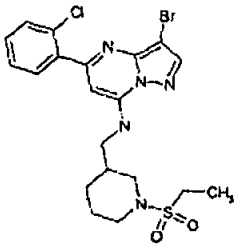
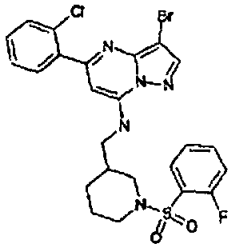
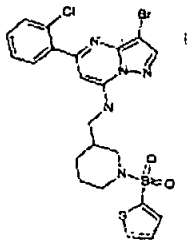
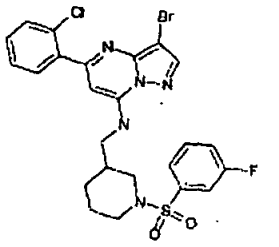
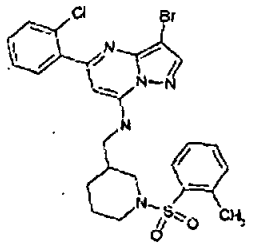
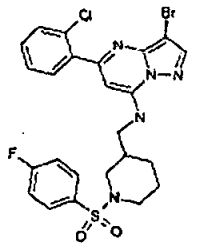
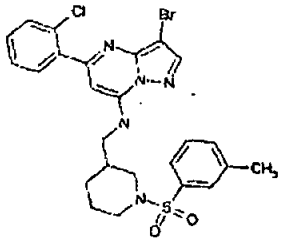
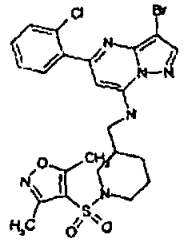
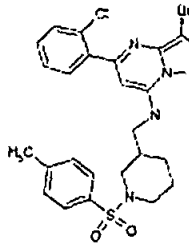
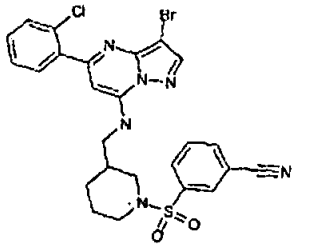
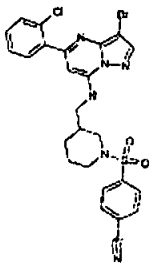
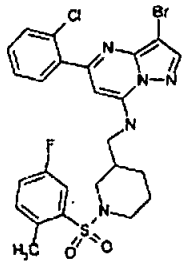
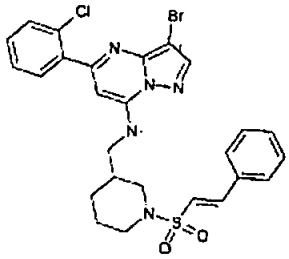
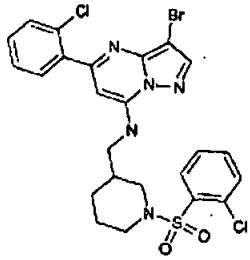
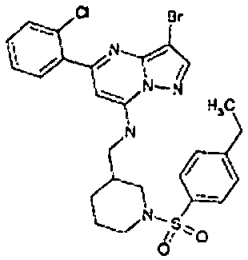
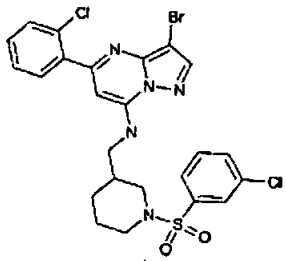
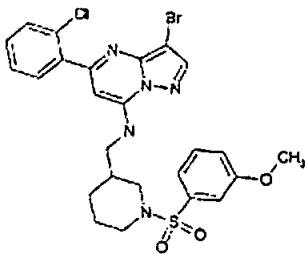
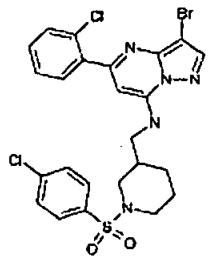
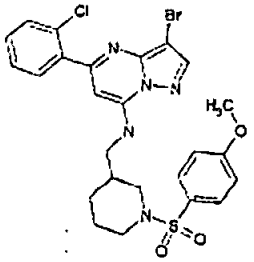
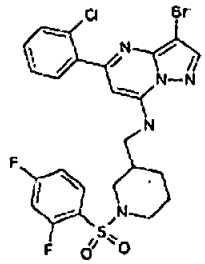
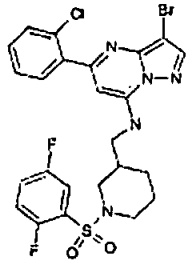
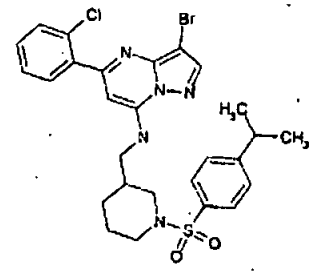
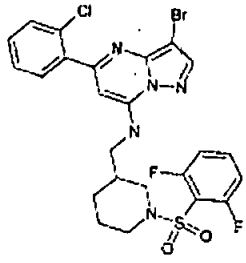
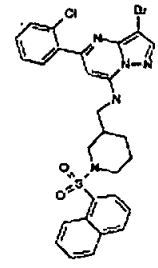
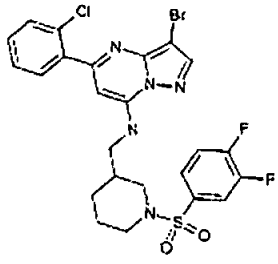
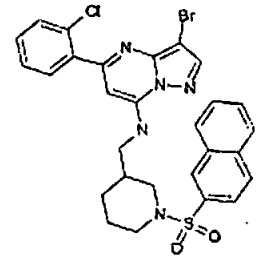
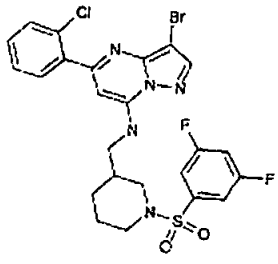
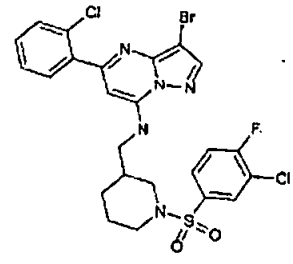
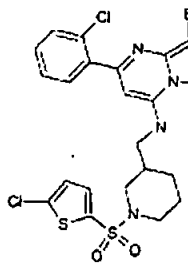
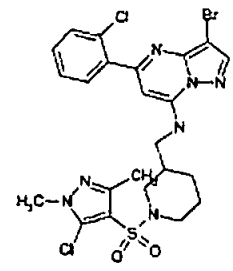
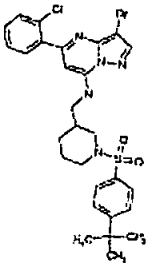
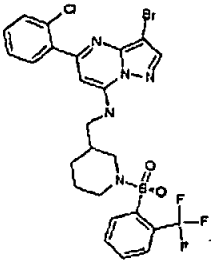
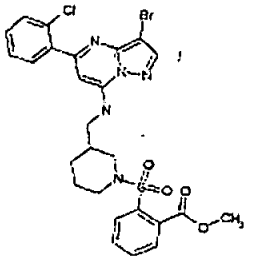
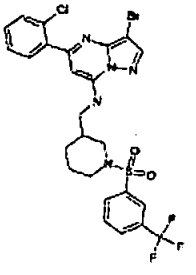
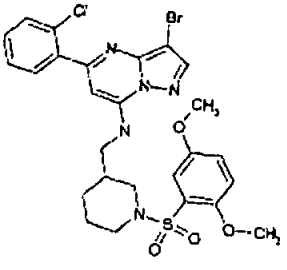
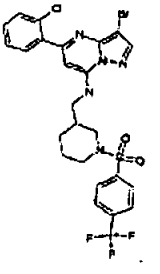
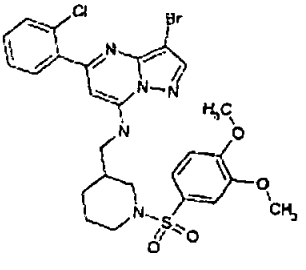
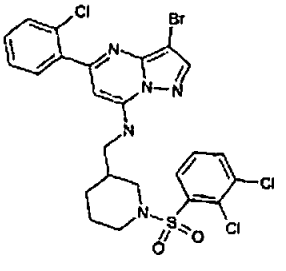
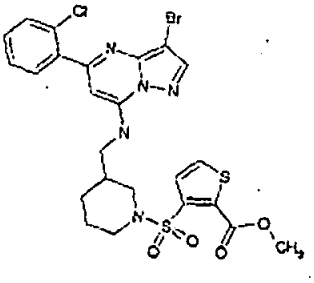
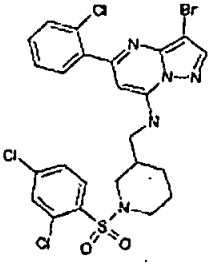
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6851 2. 614.34		1. 6856 2. 620.34
	1. 6852 2. 614.34		1. 6858 2. 628.35
	1. 6853 2. 614.34		1. 6857 2. 687.38
	1. 6854 2. 620.34		1. 6859 2. 474.26
	1. 6855 2. 620.34		1. 6860 2. 536.29

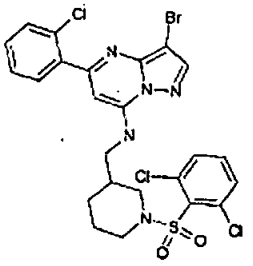
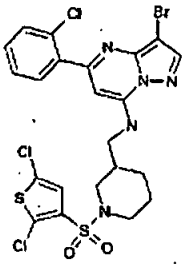
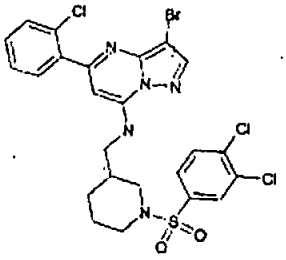
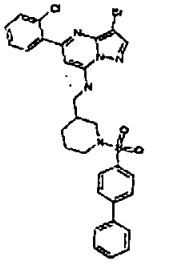
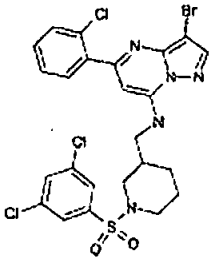
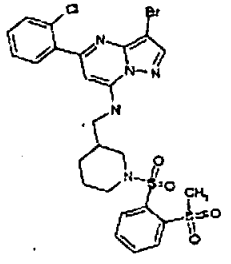
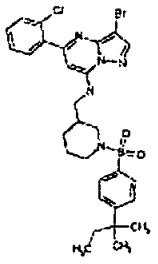
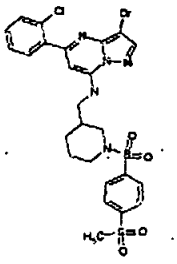
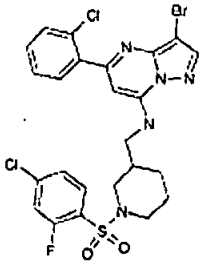
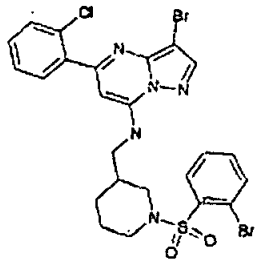
TABLE 69

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6901 2. 514.28		1. 6906 2. 580.32
	1. 6902 2. 568.31		1. 6907 2. 580.32
	1. 6903 2. 576.32		1. 6908 2. 580.32
	1. 6904 2. 576.32		1. 6909 2. 581.32
	1. 6905 2. 576.32		1. 6910 2. 587.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6911 2. 587.32		1. 6916 2. 594.33
	1. 6912 2. 588.32		1. 6917 2. 596.33
	1. 6913 2. 590.32		1. 6918 2. 596.33
	1. 6914 2. 592.33		1. 6919 2. 596.33
	1. 6915 2. 592.33		1. 6920 2. 598.33

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6921 2. 598.33		1. 6926 2. 604.33
	1. 6922 2. 598.33		1. 6927 2. 612.34
	1. 6923 2. 598.33		1. 6928 2. 612.34
	1. 6924 2. 598.33		1. 6929 2. 614.34
	1. 6925 2. 602.33		1. 6930 2. 614.34

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6931 2. 618.34		1. 6936 2. 630.35
	1. 6932 2. 620.34		1. 6937 2. 630.35
	1..6933 2. 622.34		1. 6938 2. 630.35
	1. 6934 2. 622.34		1. 6939 2. 630.35
	1. 6935 2. 626.34		1. 6940 2. 630.35

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6941 2. 630.35		1. 6946 2. 636.35
	1. 6942 2. 630.35		1. 6947 2. 638.35
	1. 6943 2. 630.35		1. 6948 2. 640.35
	1. 6944 2. 632.35		1. 6949 2. 640.35
	1. 6945 2. 614.34		1. 6950 2. 640.35

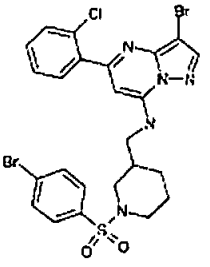
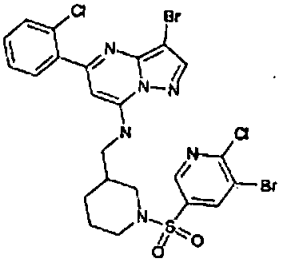
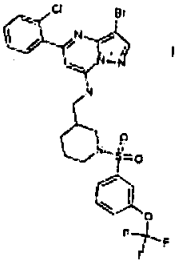
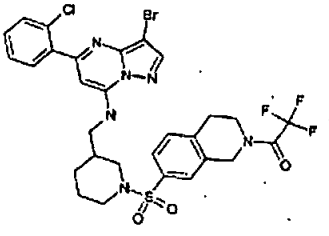
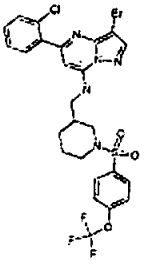
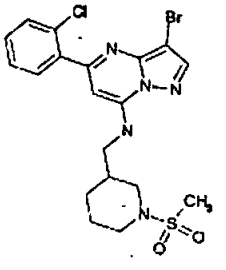
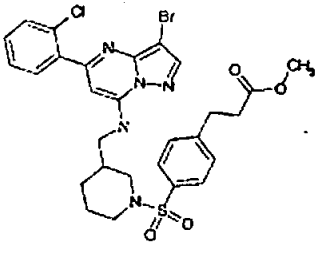
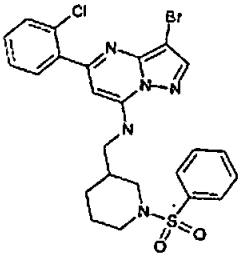
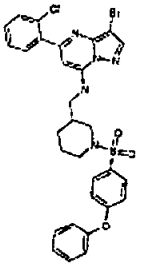
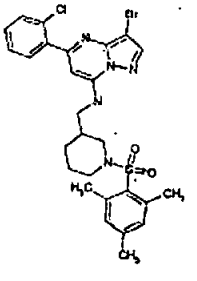
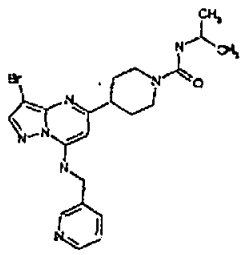
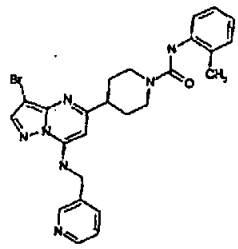
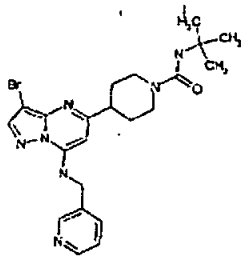
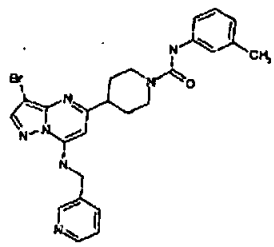
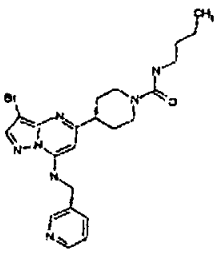
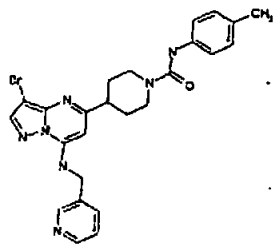
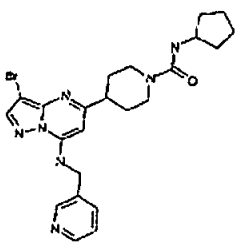
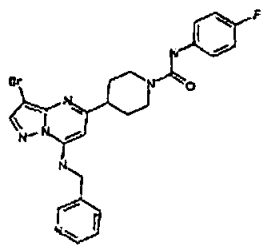
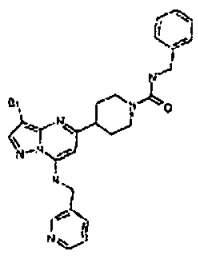
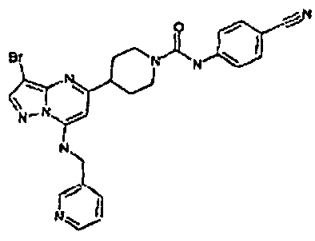
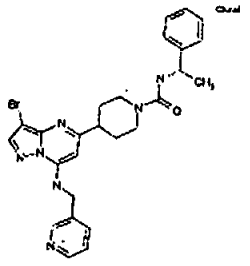
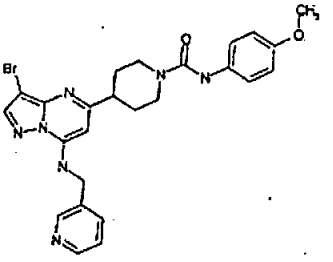
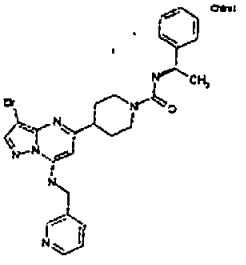
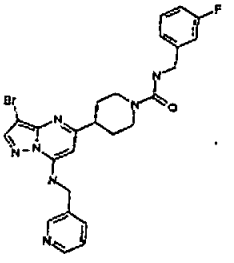
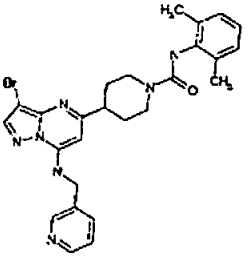
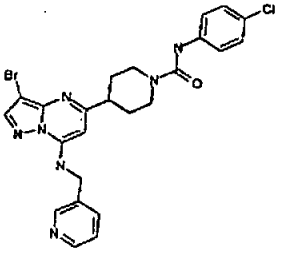
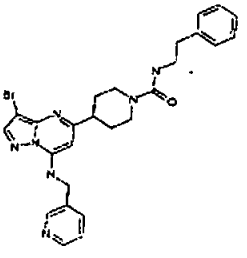
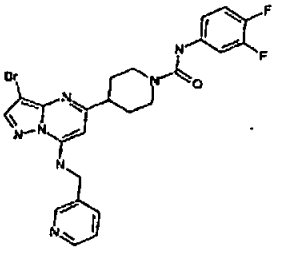
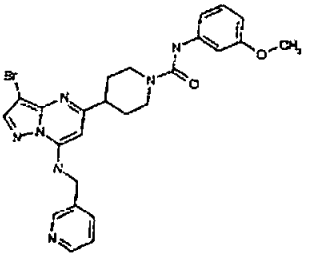
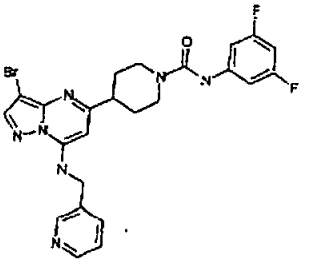
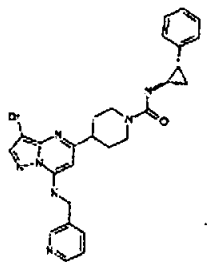
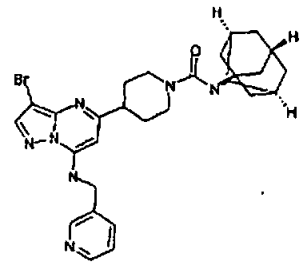
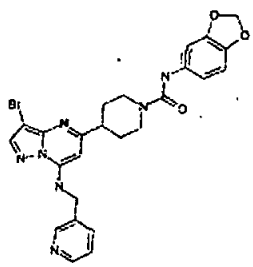
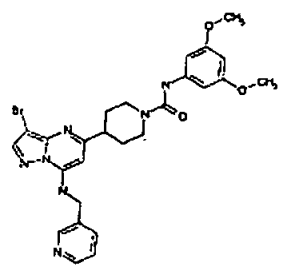
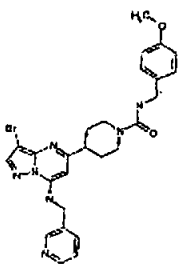
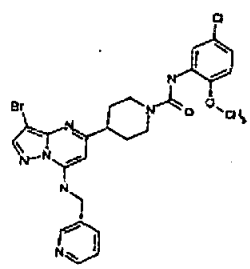
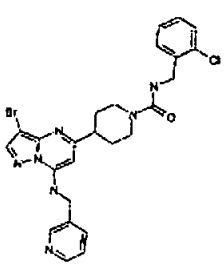
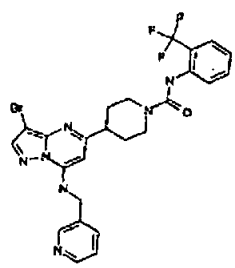
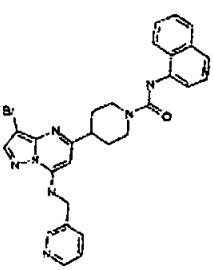
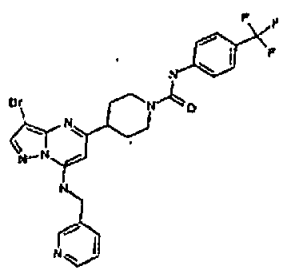
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6951 2. 640.35		1. 6956 2. 675.23
	1. 6952 2. 646.36		1. 6957 2. 713.39
	1. 6953 2. 646.36		1. 6958 2. 500.27
	1. 6954 2. 648.36		1. 6959 2. 562.31
	1. 6955 2. 654.36		1. 6960 2. 604.33

TABLE 70

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7001 2. 472.26		1. 7006 2. 522.29
	1. 7002 2. 488.27		1. 7007 2. 520.29
	1. 7003 2. 488.27		1. 7008 2. 520.29
	1. 7004 2. 500.27		1. 7009 2. 526.29
	1. 7005 2. 520.29		1. 7010 2. 533.29

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7011 2. 536.29		1. 7016 2. 538.3
	1. 7012 2. 536.29		1. 7017 2. 540.3
	1. 7013 2. 536.29		1. 7018 2. 542.3
	1. 7014 2. 536.29		1. 7019 2. 544.3
	1. 7015 2. 536.29		1. 7020 2. 544.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7021 2. 548.3		1. 7026 2. 566.31
	1. 7022 2. 552.3		1. 7027 2. 568.31
	1. 7023 2. 552.3		1. 7028 2. 572.31
	1. 7024 2. 556.31		1. 7029 2. 576.32
	1. 7025 2. 558.31		1. 7030 2. 576.32

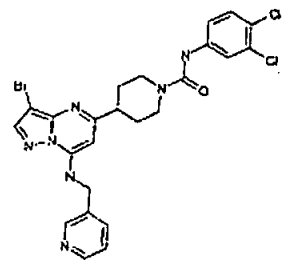
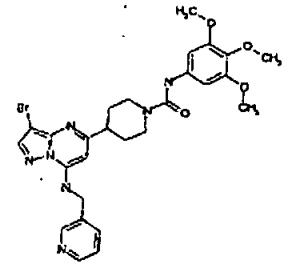
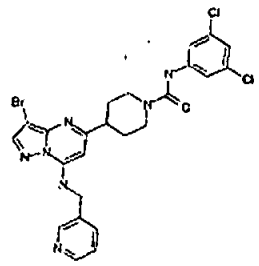
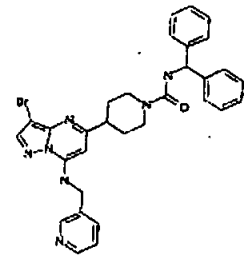
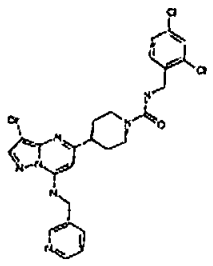
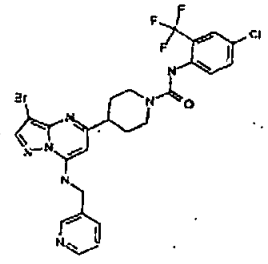
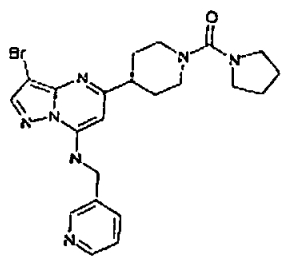
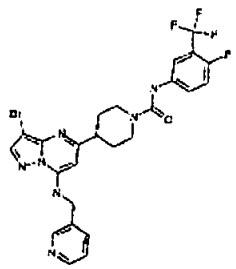
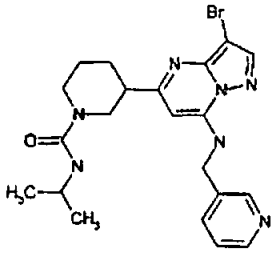
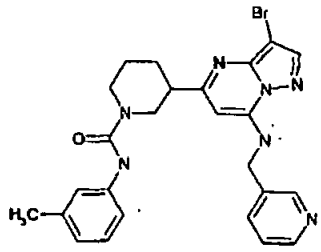
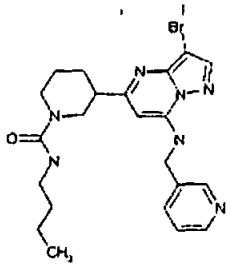
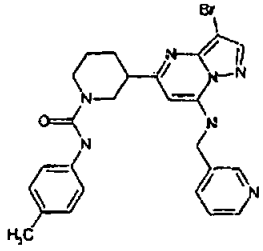
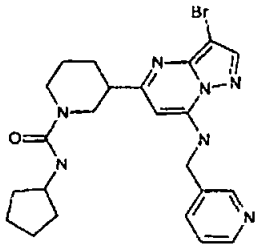
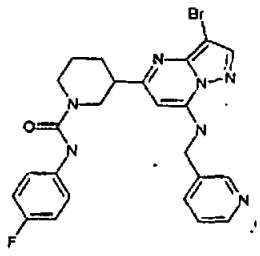
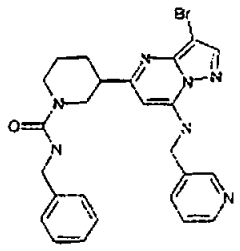
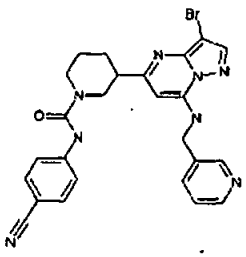
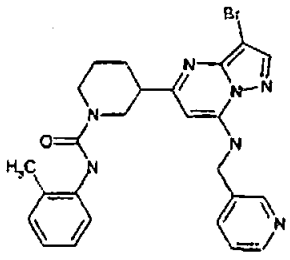
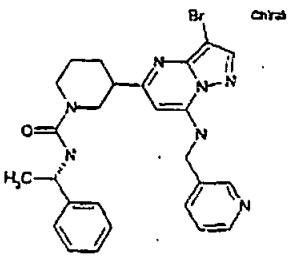
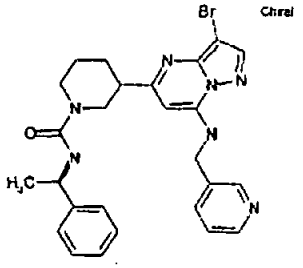
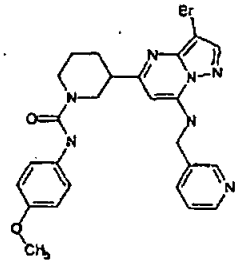
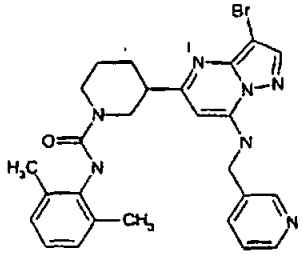
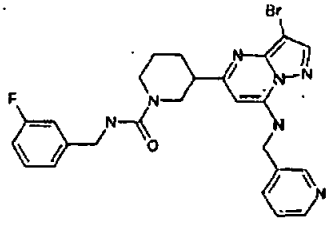
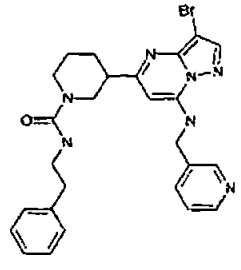
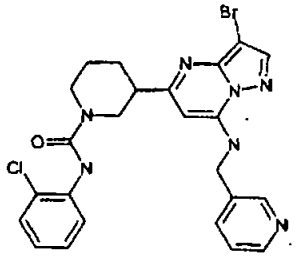
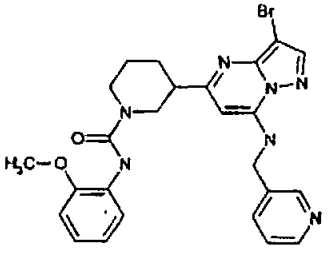
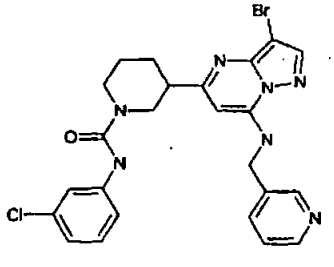
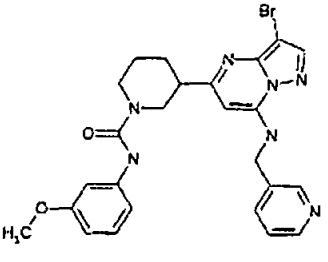
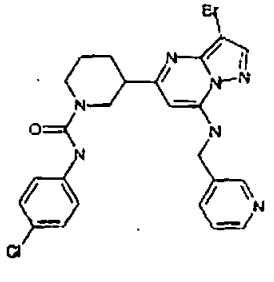
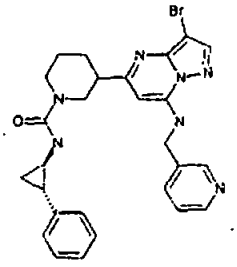
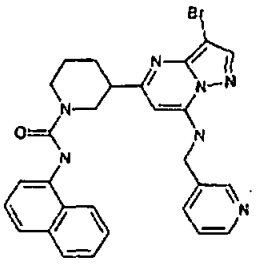
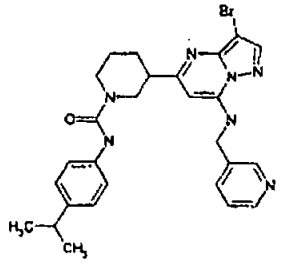
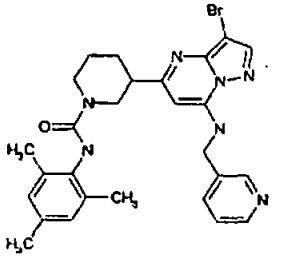
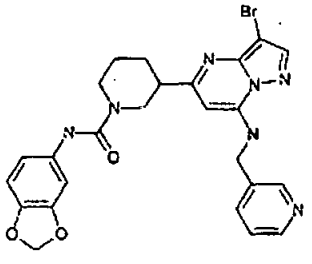
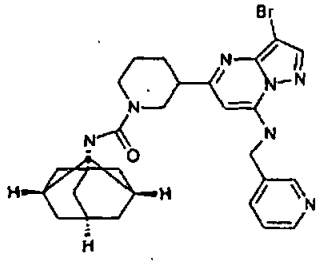
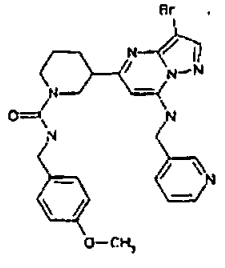
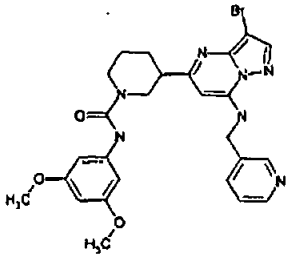
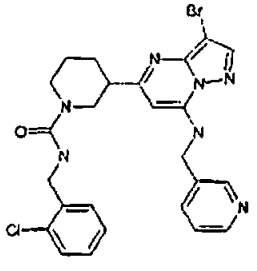
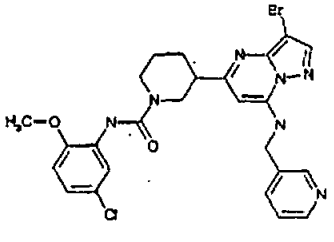
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7031 2. 576.32		1. 7036 2. 598.33
	1. 7032 2. 576.32		1. 7037 2. 598.33
	1. 7033 2. 590.32		1. 7038 2. 610.34
	1. 7034 2. 486.27		
	1. 7035 2. 594.33		

TABLE 71

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1 . 7101 2. 474.26		1. 7106 2. 522.29
	1. 7102 2. 488.27		1. 7107 2. 522.29
	1. 7103 2. 500.27		1. 7108 2. 526.3
	1. 7104 2. 522.29		1. 7109 2. 533.29
	1. 7105 2. 522.29		1. 7110 2. 536.29

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7111 2. 536.29		1. 7116 2. 538.3
	1. 7112 2. 536.29		1. 7117 2. 540.3
	1. 7113 2. 536.29		1. 7118 2. 542.3
	1. 7114 2. 536.29		1. 7119 2. 542.3
	1. 7115 2. 536.3		1. 7120 2. 542.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7121 2. 546.3		1. 7126 2. 558.31
	1. 7122 2. 550.3		1. 7127 2. 550.3
	1. 7123 2. 552.3		1. 7128 2. 566.31
	1. 7124 2. 552.3		1. 7129 2. 565.31
	1. 7125 2. 556.31		1. 7130 2. 572.31

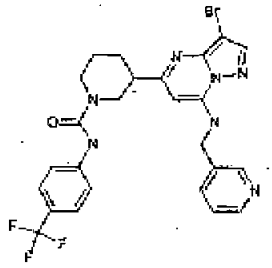
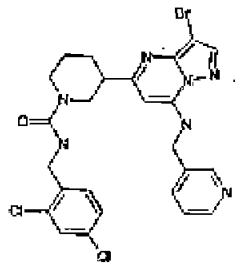
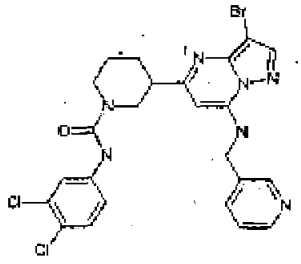
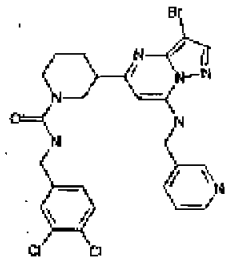
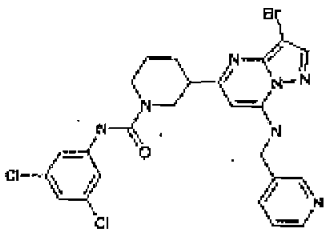
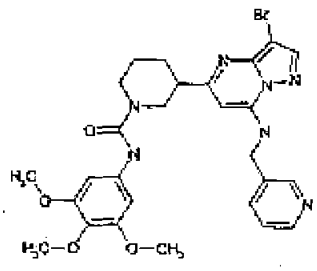
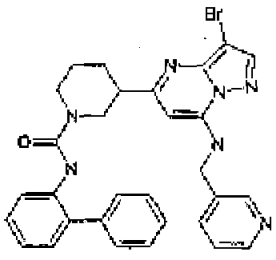
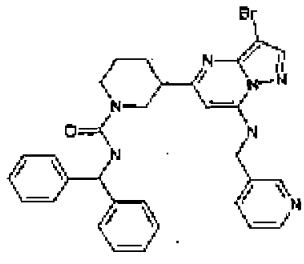
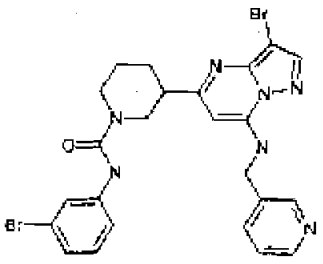
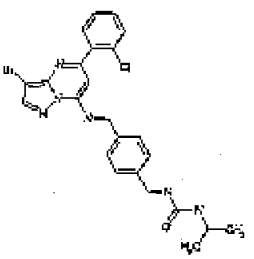
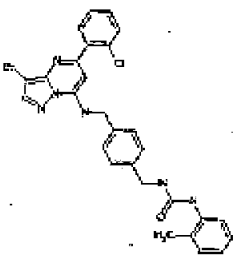
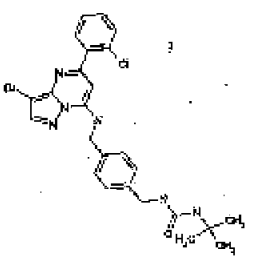
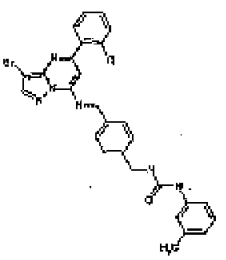
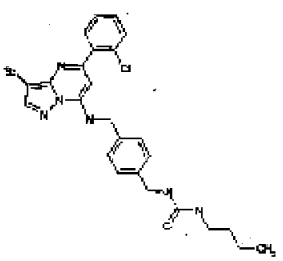
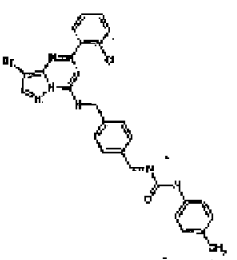
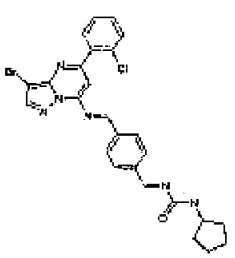
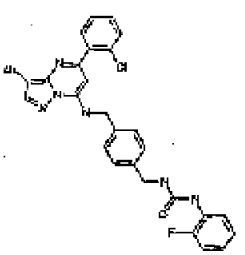
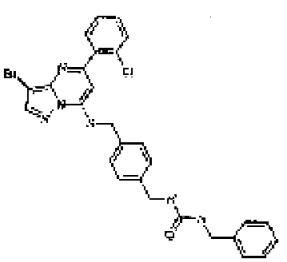
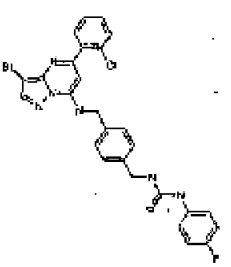
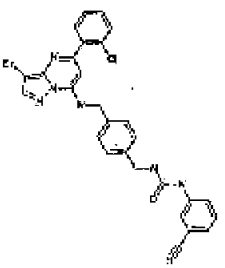
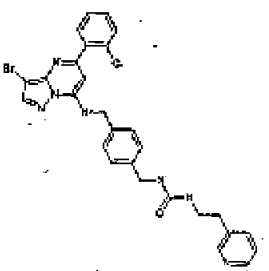
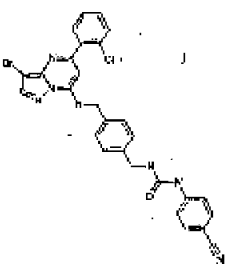
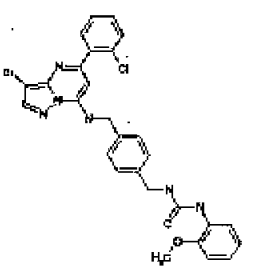
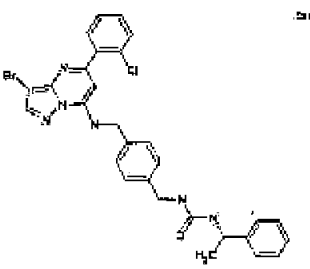
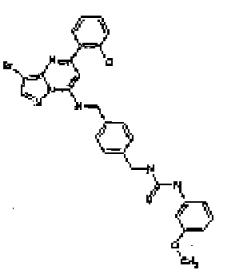
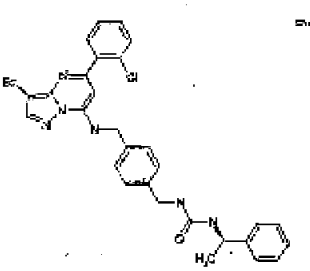
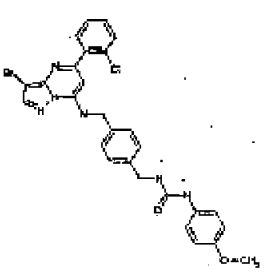
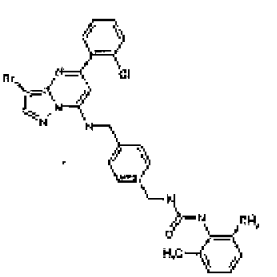
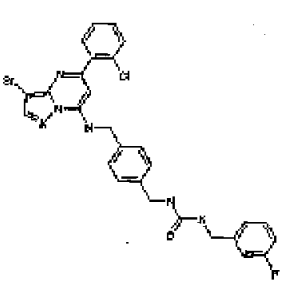
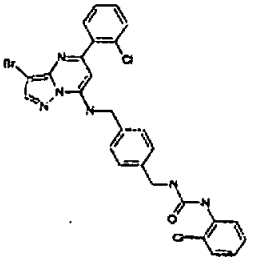
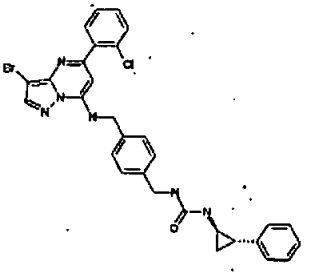
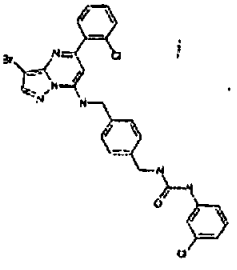
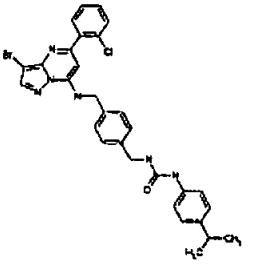
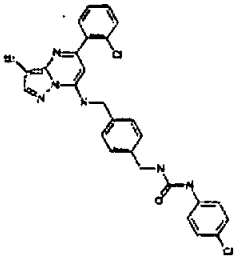
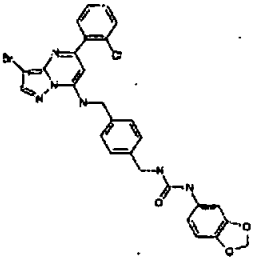
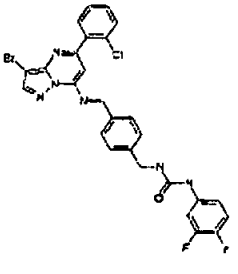
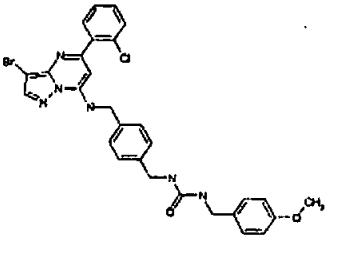
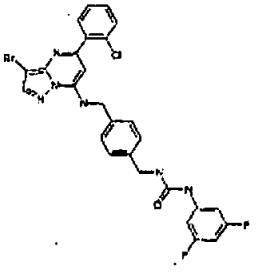
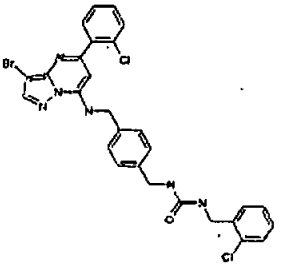
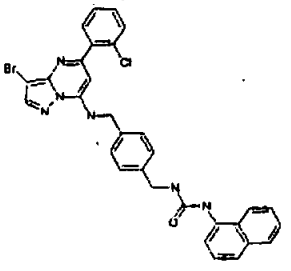
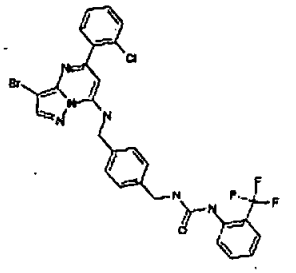
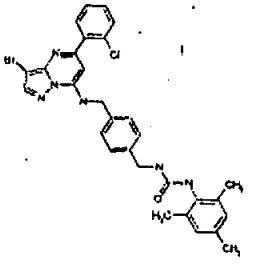
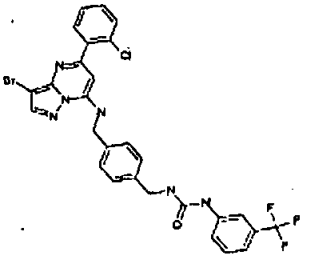
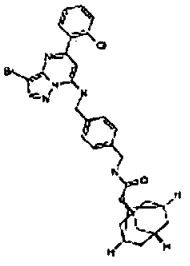
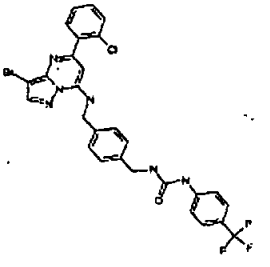
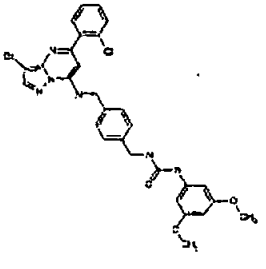
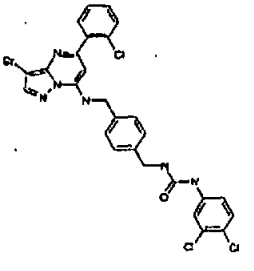
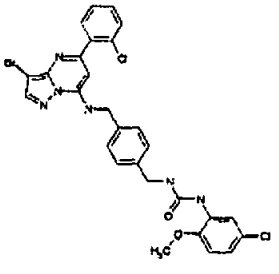
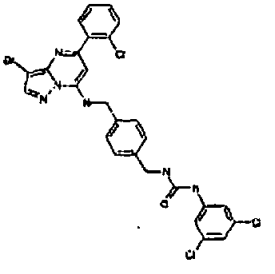
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7131 2. 576.32		1. 7136 2. 590.32
	1. 7132 2. 576.32		1. 7137 2. 590.32
	1. 7133 2. 576.32		1. 7138 2. 598.33
	1. 7134 2. 584.32		1. 7139 2. 598.33
	1. 7135 2. 585.3		

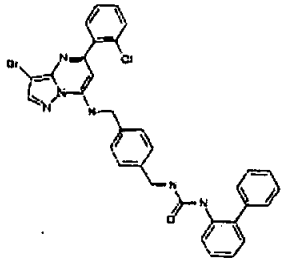
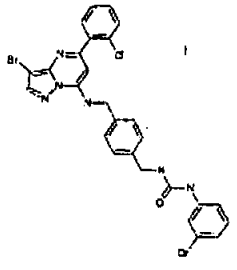
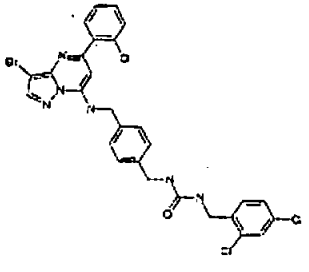
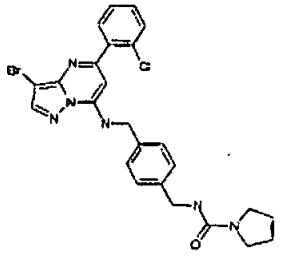
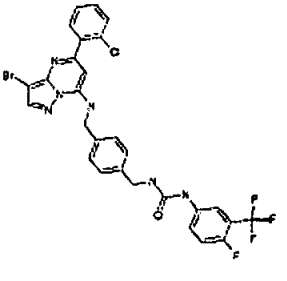
TABLE 72

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7201 2. 529.29		1. 7206 2. 577.32
	1. 7202 2. 543.3		1. 7207 2. 577.32
	1. 7203 2. 543.3		1. 7208 2. 577.32
	1. 7204 2. 555.31		1. 7209 2. 581.32
	1. 7205 2. 577.32		1. 7210 2. 581.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7211 2. 588.32		1. 7216 2. 591.33
	1. 7212 2. 588.32		1. 7217 2. 593.33
	1. 7213 2. 591.33		1. 7218 2. 593.33
	1. 7214 2. 591.33		1. 7219 2. 593.33
	1. 7215 2. 591.33		1. 7220 2. 595.33

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7221 2. 597.33		1. 7226 2. 603.33
	1. 7222 2. 597.33		1. 7227 2. 603.33
	1. 7223 2. 597.33		1. 7228 2. 607.33
	1. 7224 2. 599.33		1. 7229 2. 607.14
	1. 7225 2. 599.33		1. 7230 2. 611.34

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7231 2. 613.34		1. 7236 2. 631.35
	1. 7232 2. 605.33		1. 7237 2. 631.35
	1. 7233 2. 621.34		1. 7238 2. 631.35
	1. 7234 2. 623.34		1. 7239 2. 631.35
	1. 7235 2. 627.34		1. 7240 2. 631.35

Product	1. Ex. 2. m/z
	1. 7241 2. 639.35
	1. 7242 2. 641.35
	1. 7243 2. 645.35
	1. 7244 2. 541.3
	1. 7245 2. 649.36

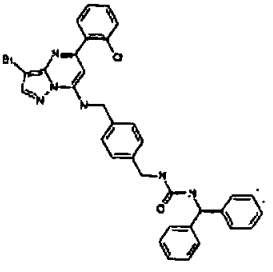
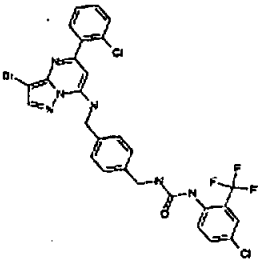
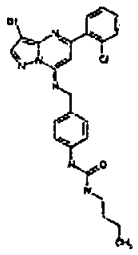
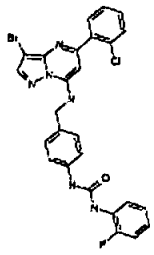
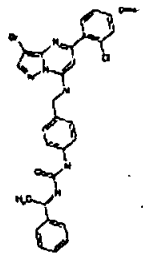
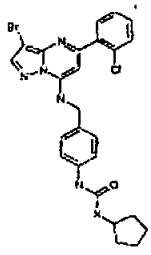
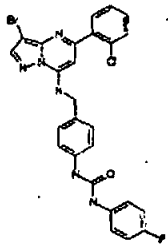
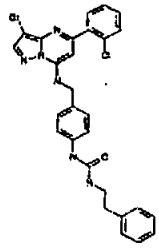
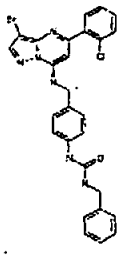
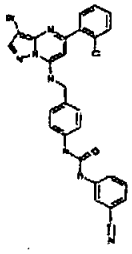
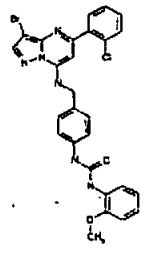
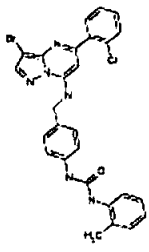
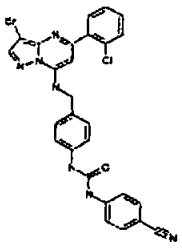
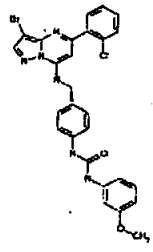
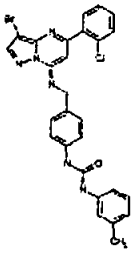
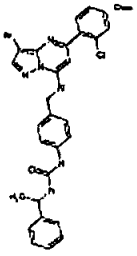
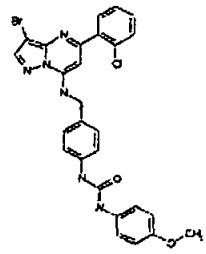
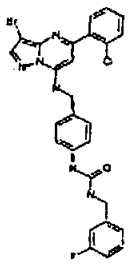
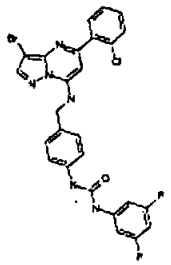
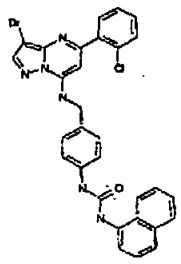
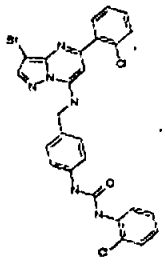
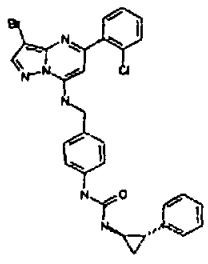
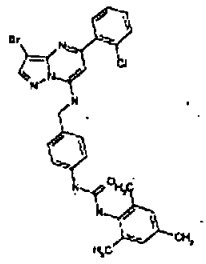
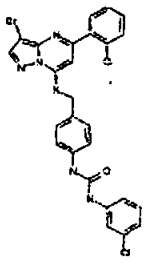
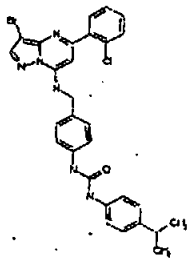
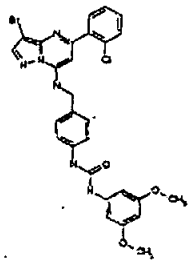
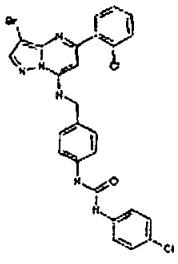
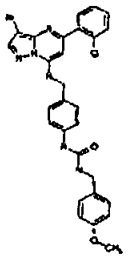
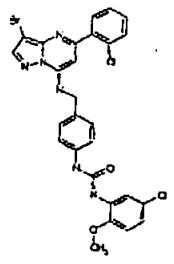
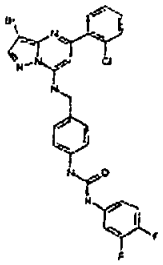
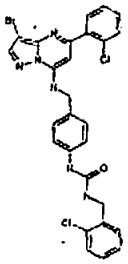
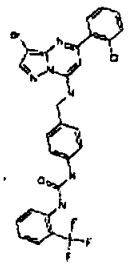
Product	1. Ex. 2. m/z
	1. 7246 2. 653.36
	1. 7247 2. 665.37

TABLE 73

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7301 2. 529.29		1. 7306 2. 567.31		1. 7311 2. 577.32
	1. 7302 2. 541.3		1. 7307 2. 567.31		1. 7312 2. 577.32
	1. 7303 2. 563.13		1. 7308 2. 574.32		1. 7313 2. 579.32
	1. 7304 2. 563.31		1. 7309 2. 574.32		1. 7314 2. 579.32
	1. 7305 2. 563.31		1. 7310 2. 577.32		1. 7315 2. 579.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7316 2. 581.32		1. 7321 2. 585.32		1. 7326 2. 599.33
	1. 7317 2. 583.32		1. 7322 2. 589.32		1. 7327 2. 591.33
	1. 7318 2. 583.32		1. 7323 2. 591.33		1. 7328
	1. 7319 2. 583.32		1. 7324 2. 593.33		1.7329 2. 613.34
	1. 7320 2. 585.32		1. 7325 2. 597.33		1. 7330 2. 617.34

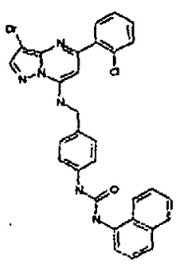
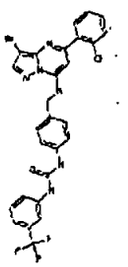
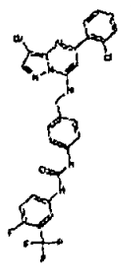
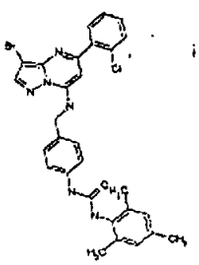
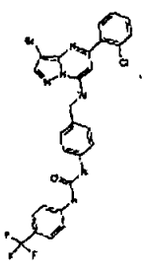
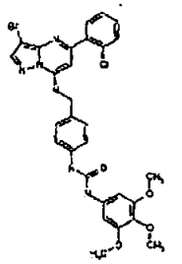
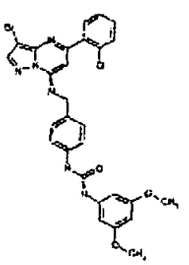
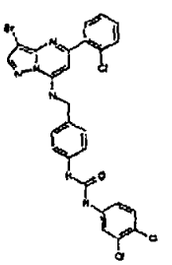
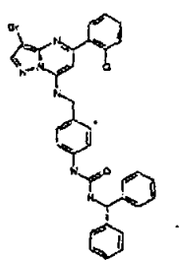
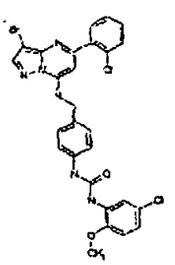
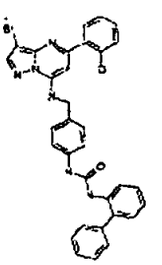
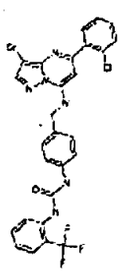
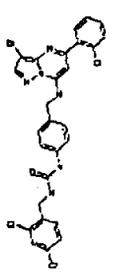
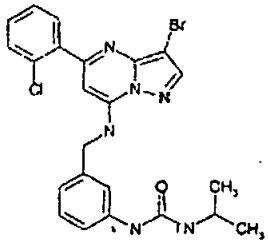
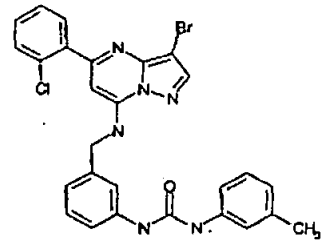
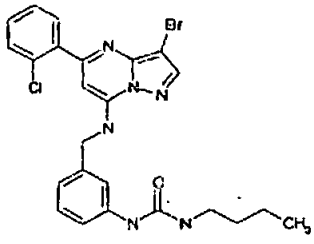
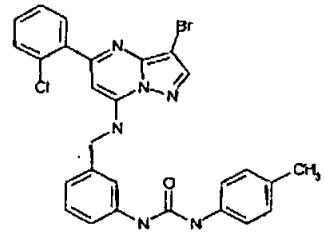
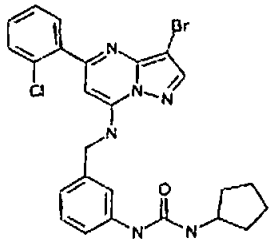
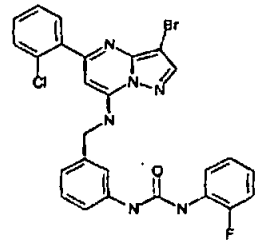
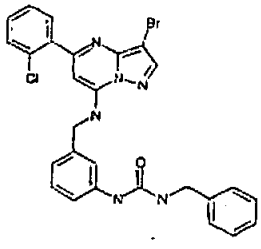
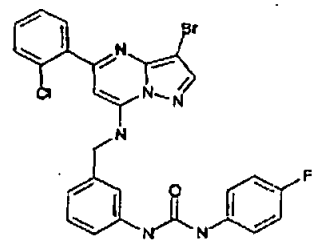
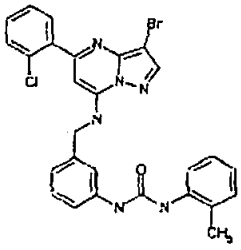
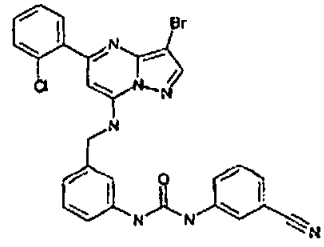
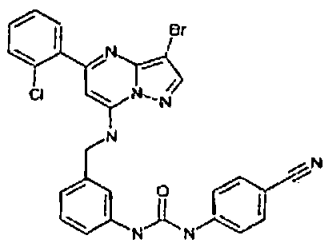
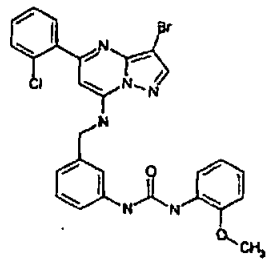
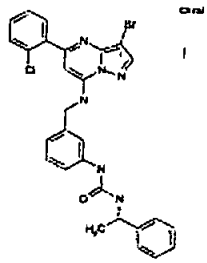
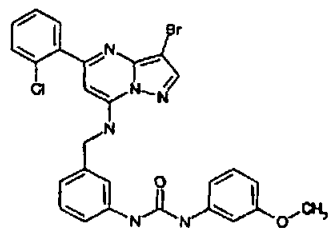
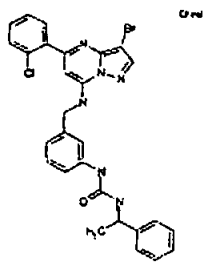
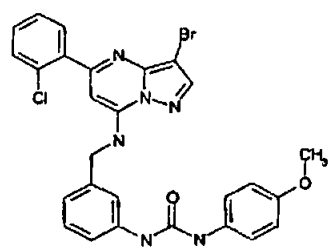
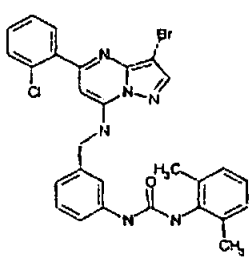
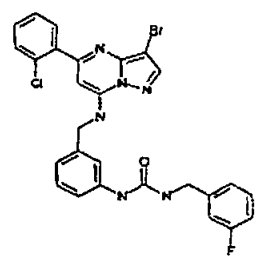
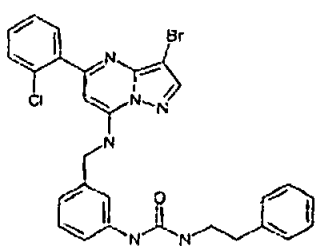
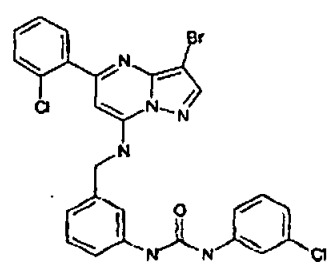
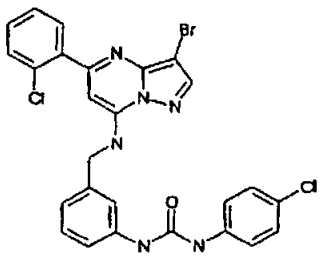
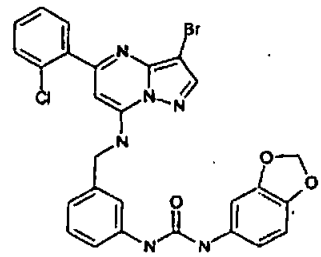
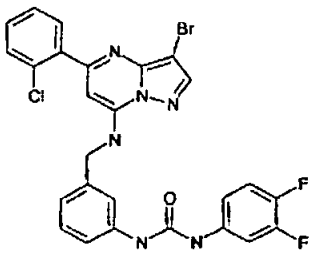
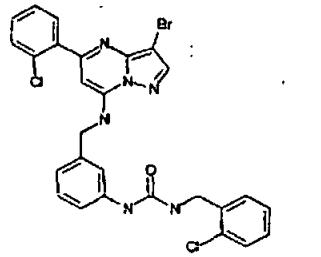
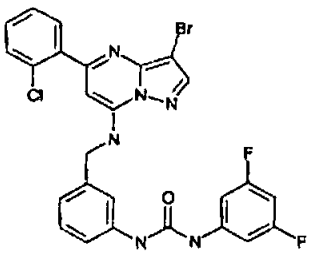
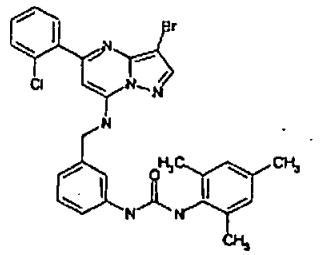
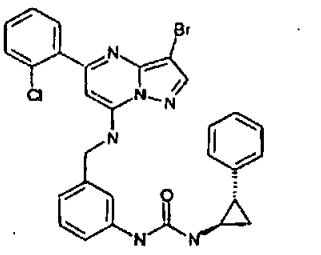
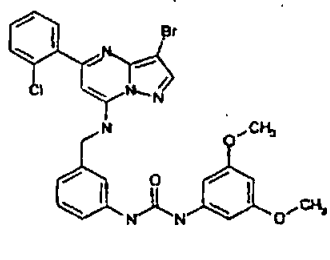
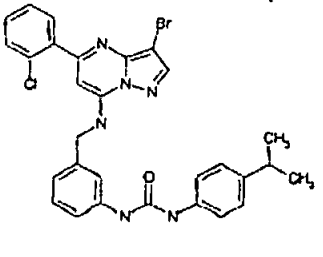
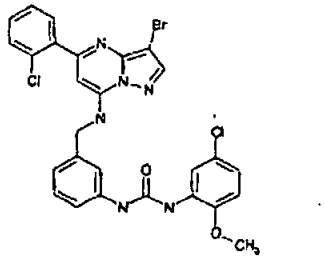
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7331 2. 599.33		1. 7336 2. 617.34		1. 73412. 635.35
	1. 7332 2. 591.33		1. 7337 2. 617.34		1. 7342 2. 639.35
	1. 7333 2. 609.33		1. 7338 2. 617.34		1. 7343 2. 639.35
	1. 7334 2. 613.34		1. 7339 2. 625.34		
	1. 7335 2. 617.34		1. 7340 2. 631.35		

TABLE 74

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7401 2. 515.28		1. 7406 2. 563.31
	1. 7402 2. 529.29		1. 7407 2. 563.31
	1. 7403 2. 541.3.		1. 7408 2. 567.31
	1. 7404 2. 563.13		1. 7409 2. 567.31
	1. 7405 2. 563.31		1. 7410 2. 574.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7411 2. 574.32		1. 7416 2. 579.32
	1. 7412 2. 577.14		1. 741 7 2. 579.32
	1. 7413 2. 577.32		1. 7418 2. 579.32
	1. 7414 2. 577.32		1. 7419 2. 581.32
	1. 7415 2. 577.32		1. 7420 2. 583.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7421 2. 583.32		1. 7426 2. 593.33
	1. 7422 2. 585.32		1. 7427 2. 597.33
	1. 7423 2. 585.32		1. 7428 2. 591.33
	1. 7424 2. 589.32		1. 7429 2. 609.33
	1. 7425 2. 591.33		1. 7430 2. 613.34

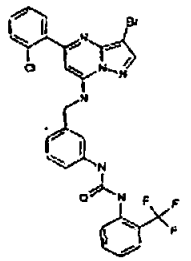
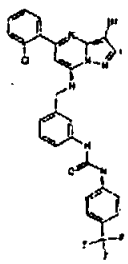
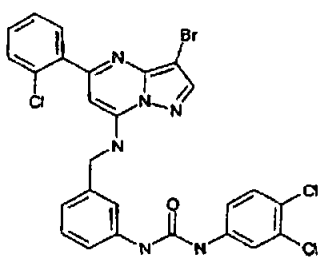
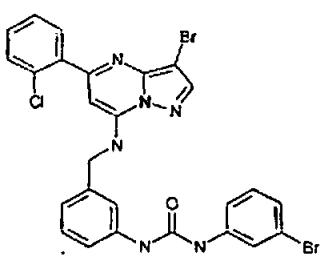
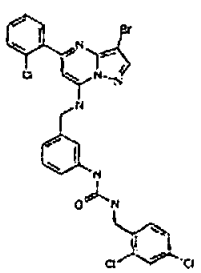
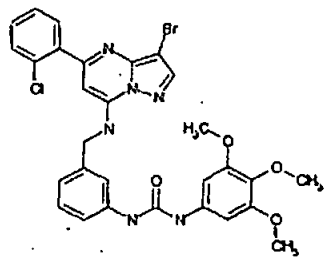
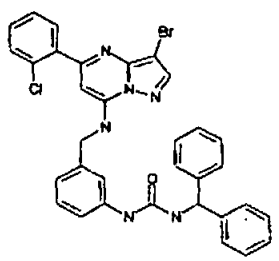
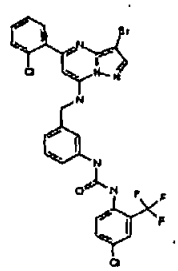
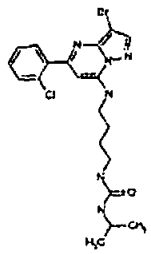
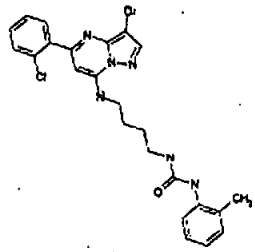
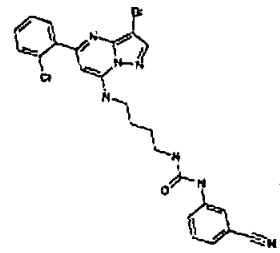
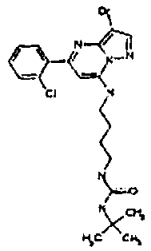
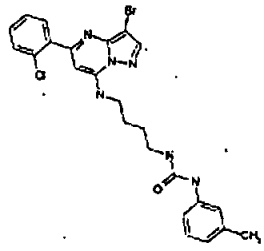
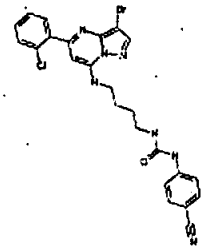
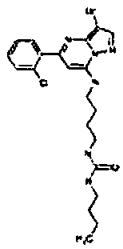
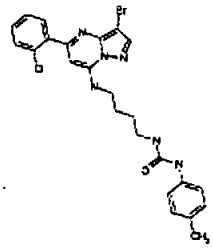
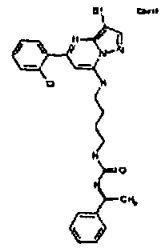
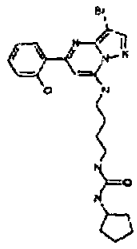
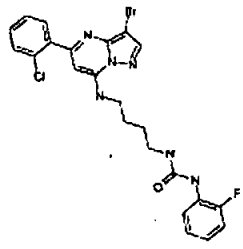
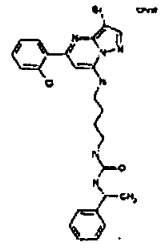
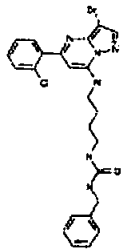
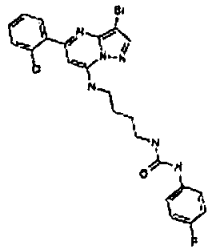
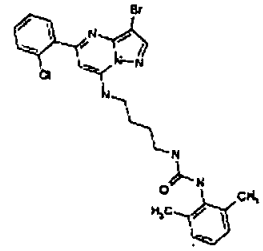
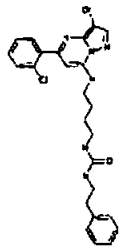
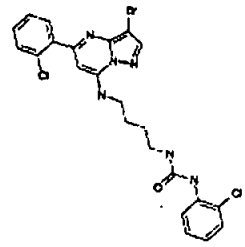
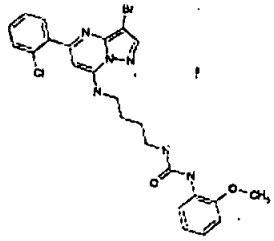
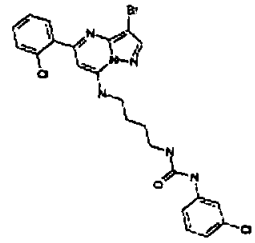
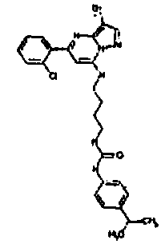
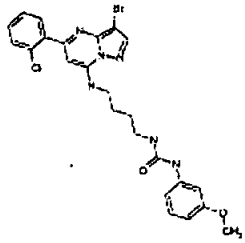
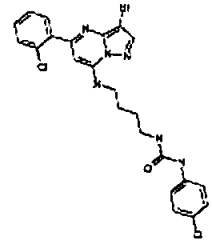
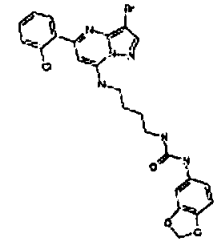
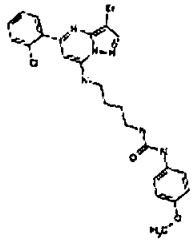
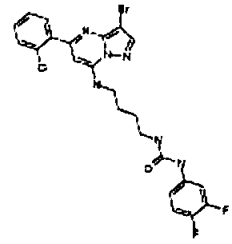
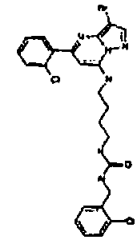
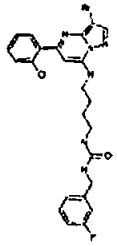
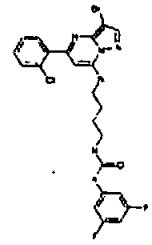
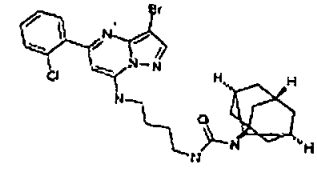
Product	1. Ex. 2. m/z
	1. 7431 2. 617.34
	1. 7432 2. 617.34
	1. 7433 2. 617.34
	1. 7434 2. 627.34
	1. 7435 2. 631.35
	1. 7436 2. 639.35
	1. 7437 2. 639.35
	1. 7438 2. 651.36

TABLE75

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7501 2. 481.26		1. 7506 2. 529.29		1. 7511 2. 540.3
	1. 7502 2. 495.27		1. 7507 2. 529.29		1. 7512 2. 540.3
	1. 7503 2. 495.27		1. 7508 2. 529.29		1. 7513 2. 543.3
	1. 7504 2. 507.28		1. 7509 2. 533.29		1. 7514 2. 543.3
	1. 7505 2. 529.29		1. 7510 2. 533.29		1. 7515 2. 543.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7516 2. 543.3		1. 7521 2. 549.3		1. 7526 2 555.31
	1. 7517 2. 545.3		1. 7522 2. 549.3		1. 7527 2 557.31
	1. 7518 2. 545.3		1. 7523 2. 549.3		1. 7528 2 559.31
	1. 7519 2. 545.3		1. 7524 2. 551.3		1. 7529 2 560.31
	1. 7520 2. 547.3		1. 7525 2. 551.3		1. 7530 2 573.32

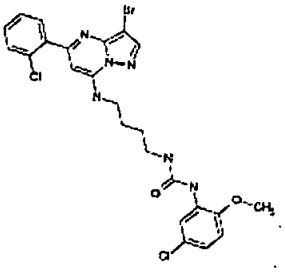
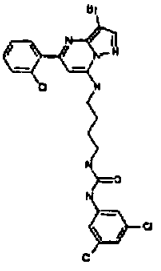
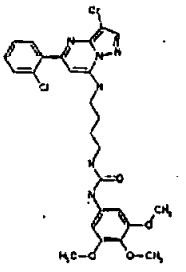
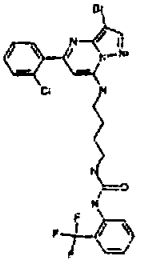
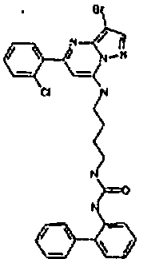
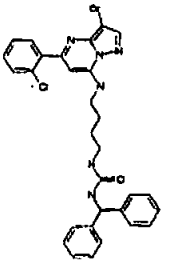
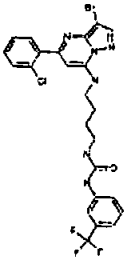
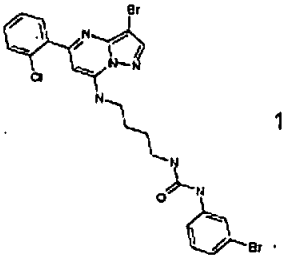
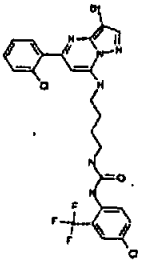
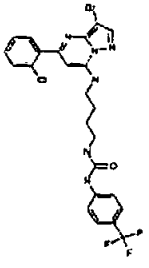
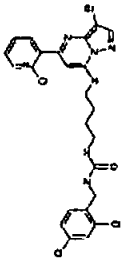
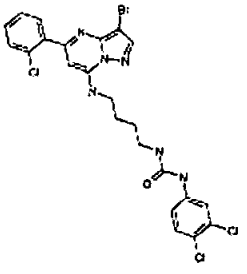
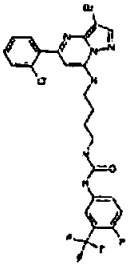
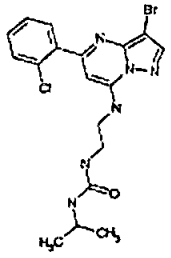
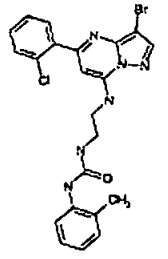
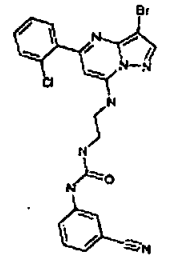
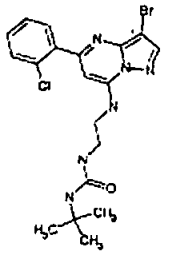
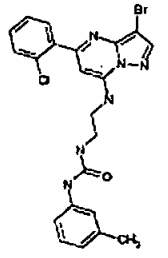
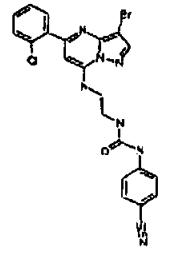
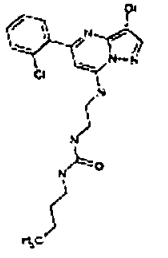
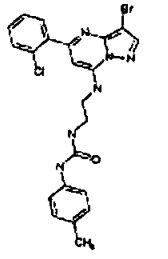
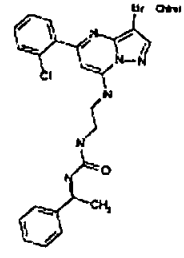
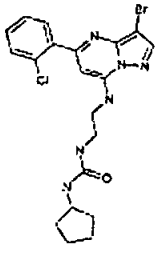
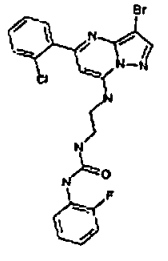
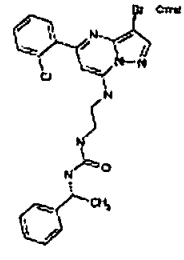
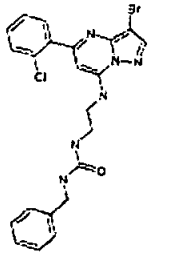
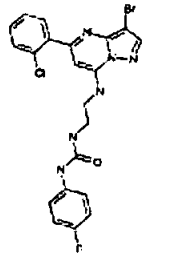
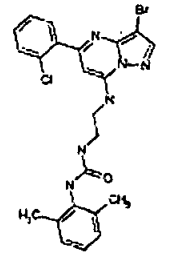
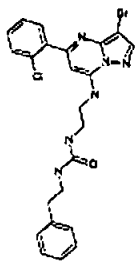
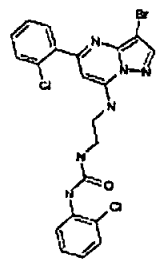
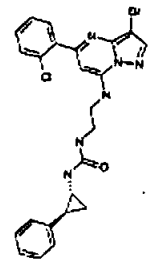
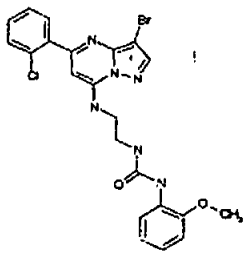
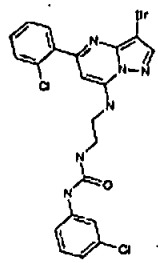
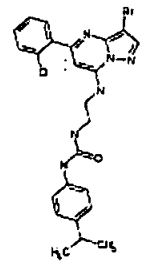
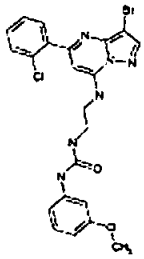
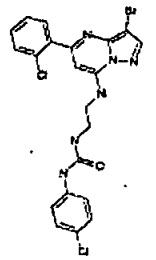
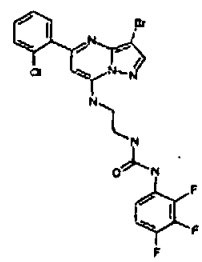
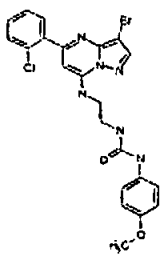
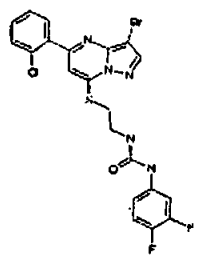
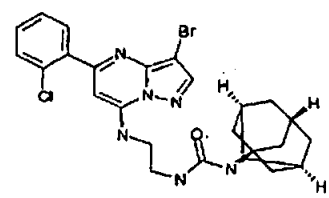
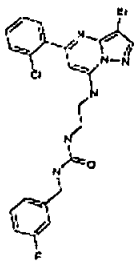
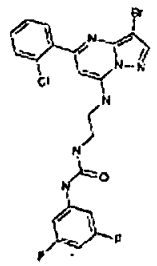
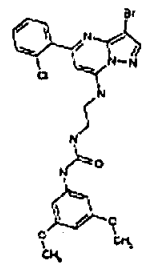
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7531 2. 579.32		1. 7536 2. 583.32		1. 7541 2. 605.33
	1. 7532 2. 583.32		1. 7537 2. 591.33		1. 7542 2. 605.33
	1. 7533 2. 583.32		1. 7538 2. 593.33		1. 7543 2. 614.34
	1. 7534 2. 583.32		1. 7539 2. 597.33		
	1. 7535 2. 583.32		1. 7540 2. 601.33		

TABLE 76

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7601 2. 453.25		1. 7606 2. 501.28		1. 7611 2. 512.28
	1. 7602 2. 467.26		1. 7607 2. 501.28		1. 7612 2. 512.28
	1. 7603 2. 467.26		1. 7608 2.501.28		1. 7613 2. 515.28
	1. 7604 2. 479.26		1. 7609 2. 505.28		1. 7614 2. 515.28
	1. 7605 2. 501.28		1. 7610 2. 505.28		1. 7615 2. 515.28

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 761 6 2. 515.28		1. 7621 2. 521.29		1. 7626 2. 527.29
	1. 7617 2. 517.28		1. 7622 2. 521.29		1. 7627 2. 529.29
	1. 7618 2. 517.28		1. 7623 2. 521.29		1. 7628 2. 541.3
	1. 7619 2. 517.28		1. 7624 2. 523.29		1. 7629 2. 545.3
	1. 7620 2. 519.29		1. 7625 2. 523.29		1. 7630 2. 547.3

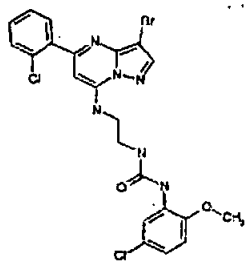
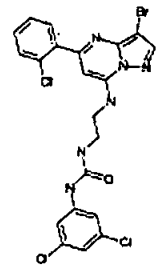
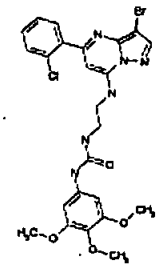
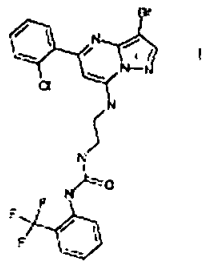
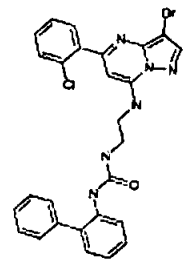
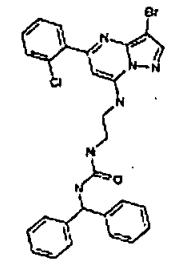
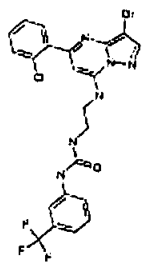
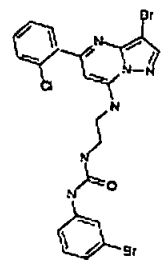
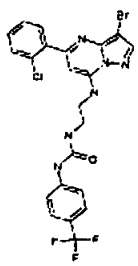
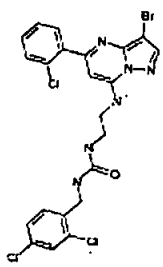
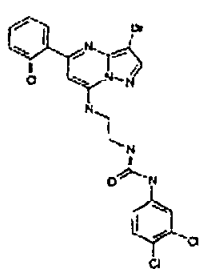
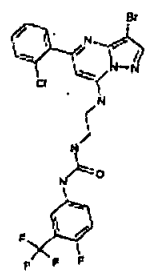
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7631 2. 551.3		1. 7636 2. 555.31		1. 7641 2. 577.32
	1. 7632 2. 555.31		1. 7637 2. 563.31		1. 7642 2. 577.32
	1. 7633 2. 555.31		1. 7638 2. 565.31		
	1. 7634 2. 555.31		1. 7639 2. 569.31		
	1. 7635 2. 555.31		1. 7640 2. 573.32		

TABLE 77

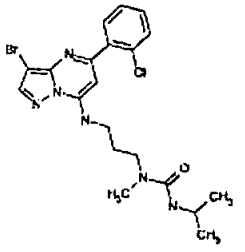
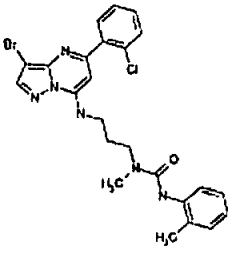
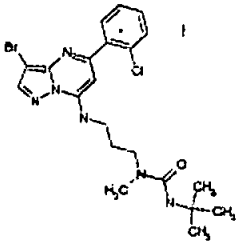
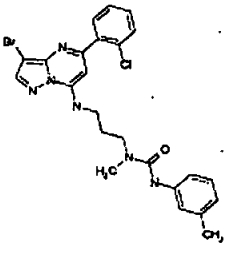
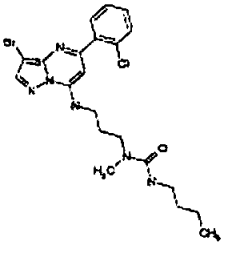
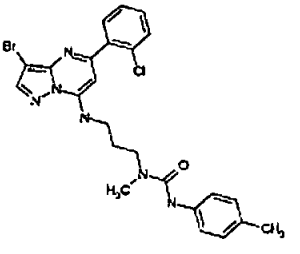
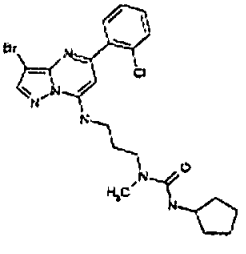
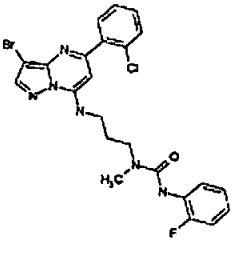
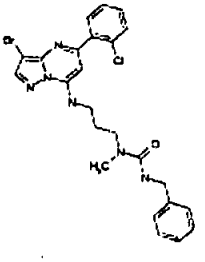
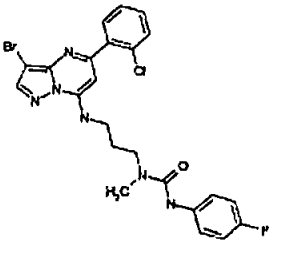
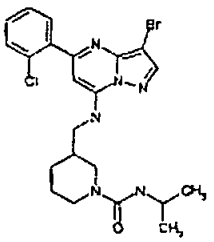
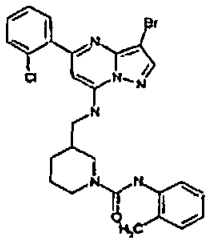
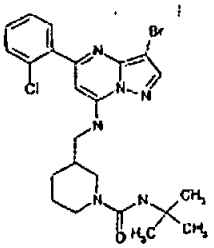
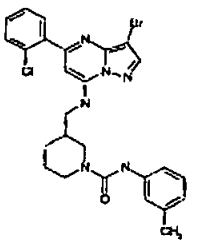
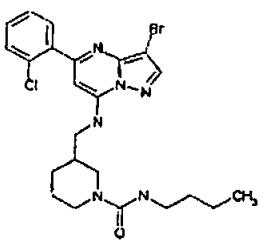
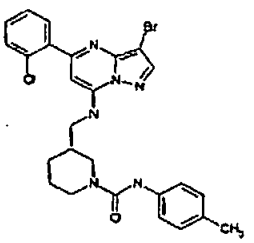
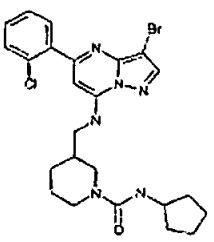
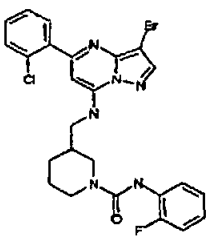
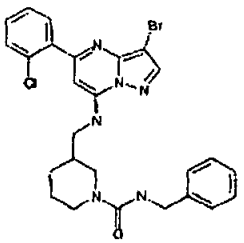
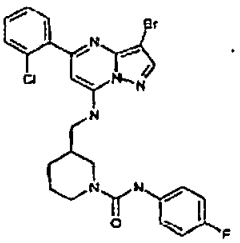
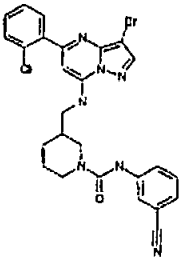
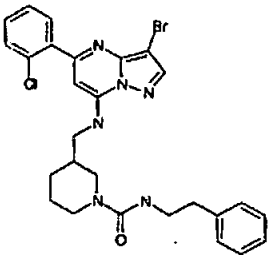
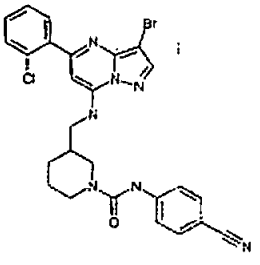
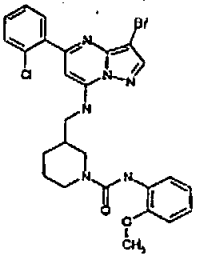
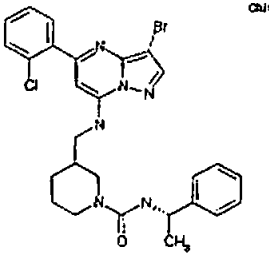
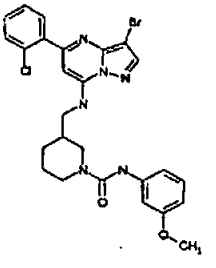
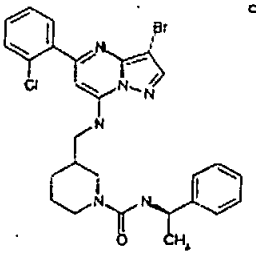
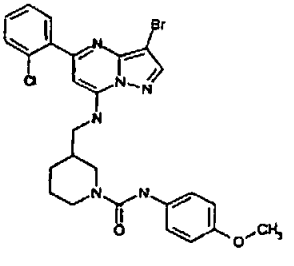
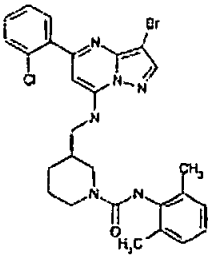
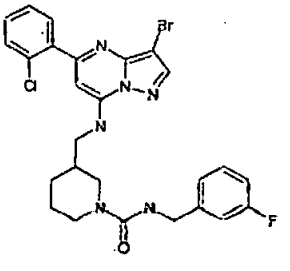
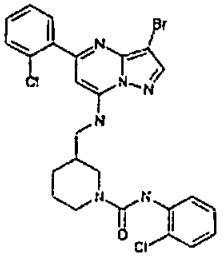
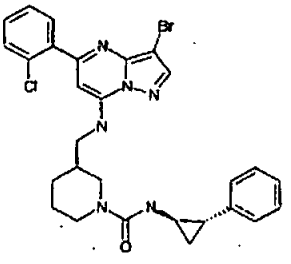
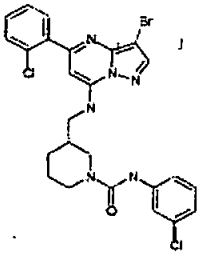
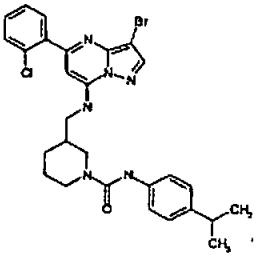
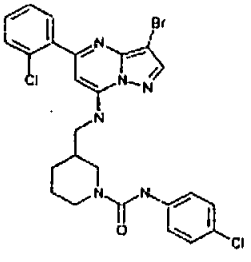
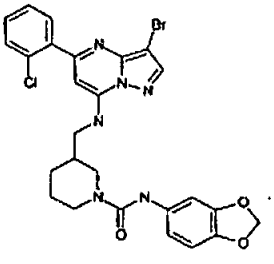
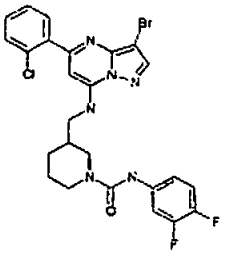
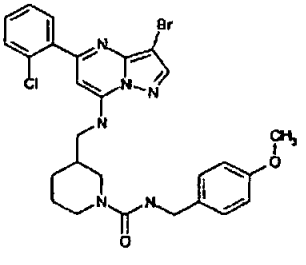
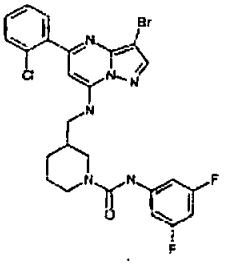
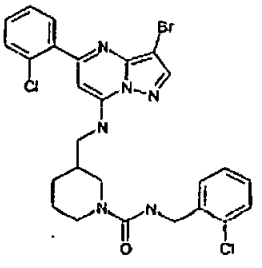
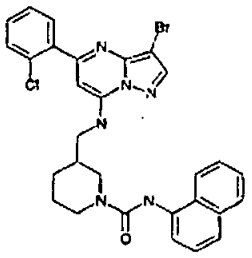
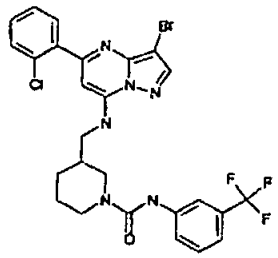
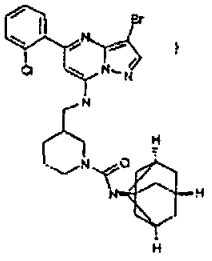
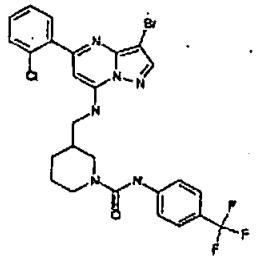
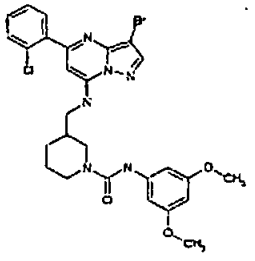
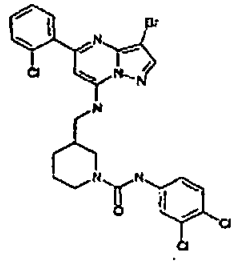
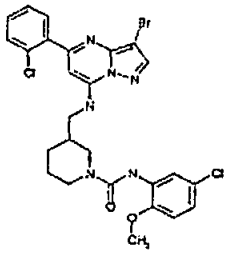
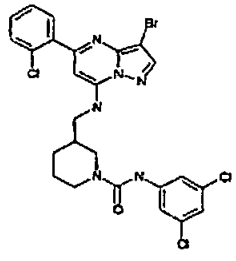
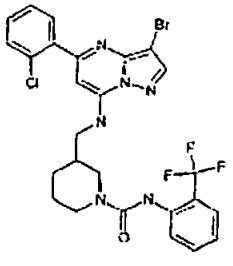
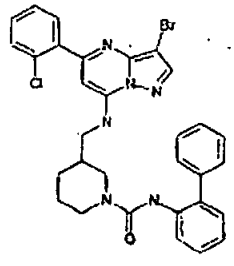
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7701 2. 481.26		1. 7706 2. 529.29
	1. 7702 2. 495.27		1. 7707 2. 529.29
	1. 7703 2. 495.27		1. 7708 2. 529.29
	1. 7704 2. 507.28		1. 7709 2. 533.29
	1. 7705 2. 529.29		1. 7710 2. 533.29

TABLE 78

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7801 2. 507.28		1. 7806 2. 555.31
	1. 7802 2. 521.29		1. 7807 2. 555.31
	1. 7803 2. 521.29		1. 7808 2. 555.31
	1. 7804 2. 533.29		1. 7809 2. 559.31
	1. 7805 2. 555.31		1. 7810 2. 559.31

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7811 2. 566.31		1. 7816 2. 569.31
	1. 7812 2. 566.31		1. 7817 2. 571.31
	1. 7813 2. 569.31		1. 7818 2. 571.31
	1. 7814 2. 569.31		1. 7819 2. 571.31
	1. 7815 2. 569.31		1. 7820 2. 573.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7821 2. 575.32		1. 7826 2. 581.32
	1. 7822 2. 575.32		1. 7827 2. 583.32
	1. 7823 2. 575.32		1. 7828 2. 585.32
	1. 7824 2. 577.32		1. 7829 2. 585.32
	1. 7825 2. 577.32		1. 7830 2. 589.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7831 2. 591.33		1. 7836 2. 609.33
	1. 7832 2. 599.33		1. 7837 2. 609.33
	1. 7833 2. 601.33		1. 7838 2. 609.33
	1. 7834 2. 605.33		1. 7839 2. 609.33
	1. 7835 2. 609.33		1. 7840 2. 617.34

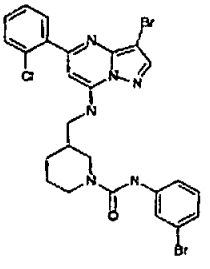
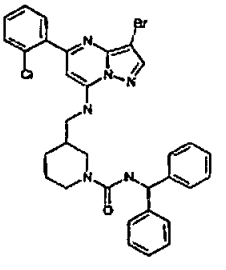
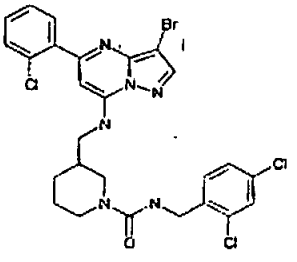
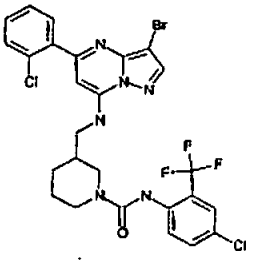
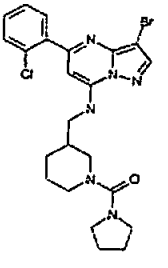
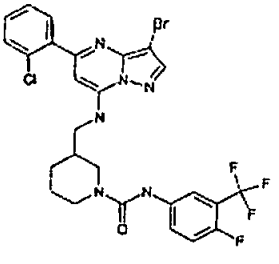
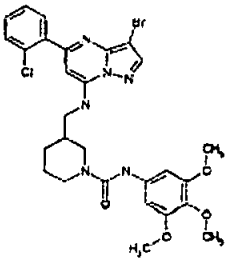
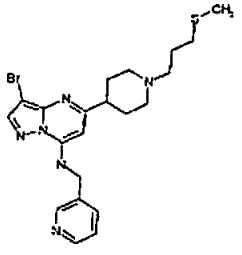
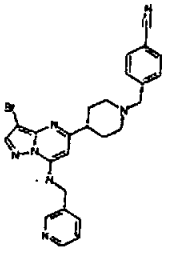
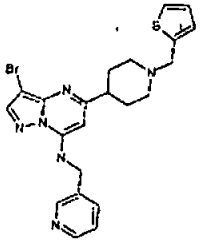
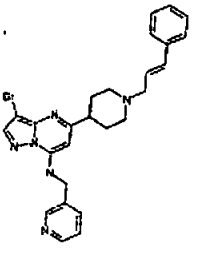
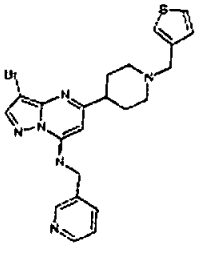
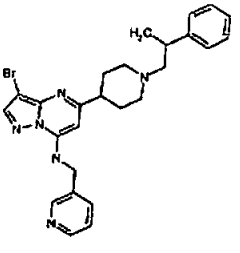
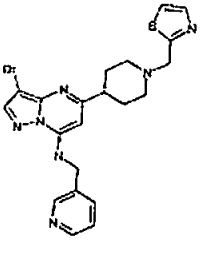
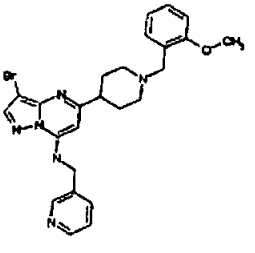
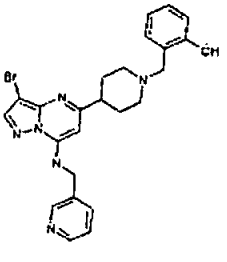
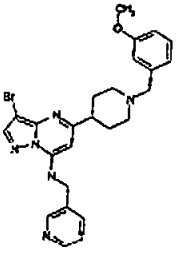
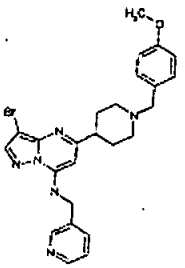
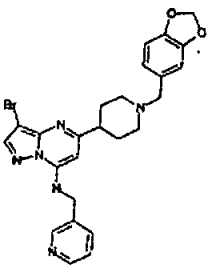
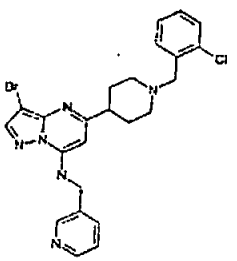
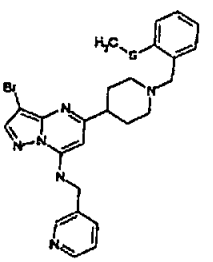
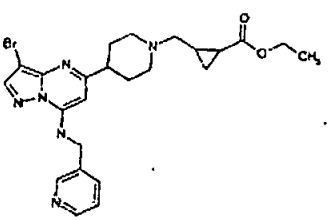
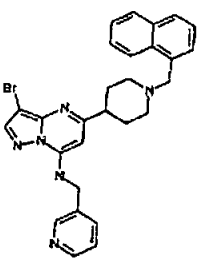
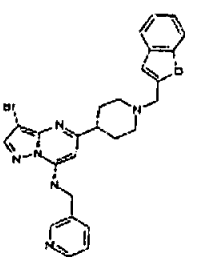
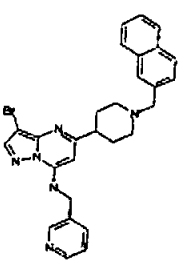
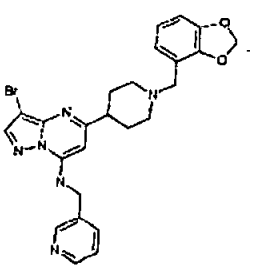
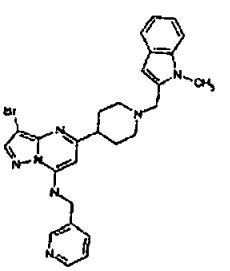
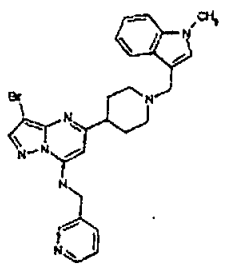
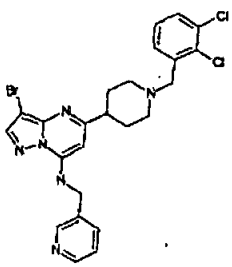
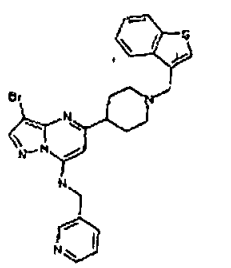
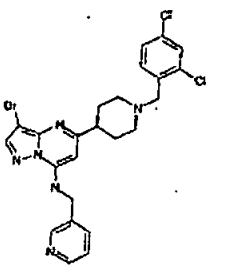
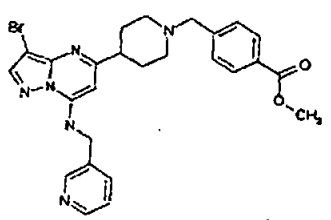
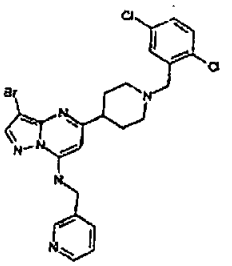
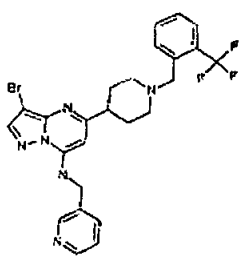
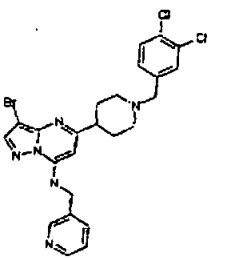
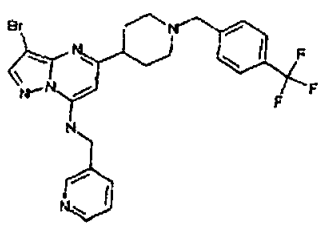
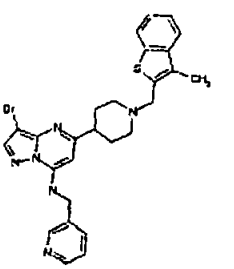
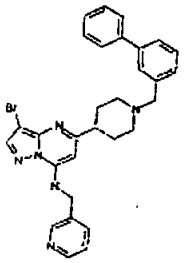
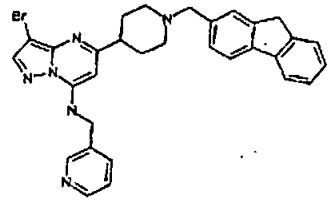
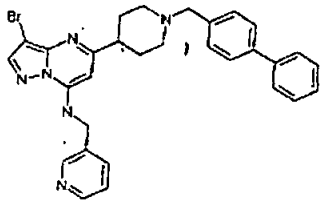
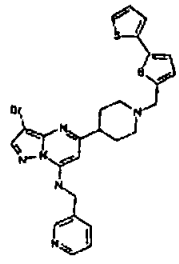
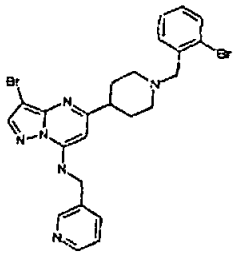
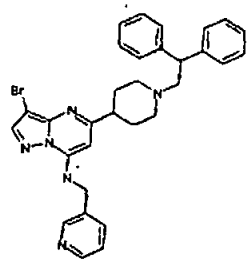
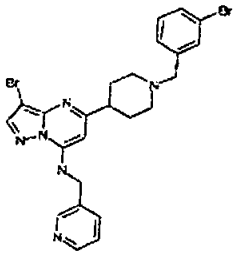
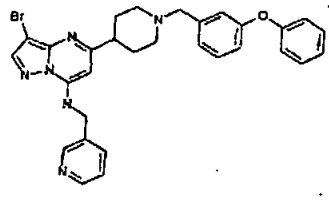
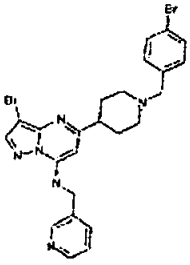
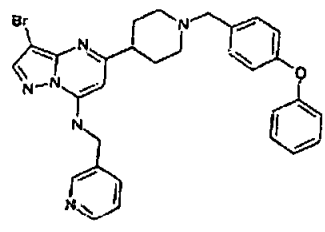
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7841 2. 619.34		1. 7846 2. 631.35
	1. 7842 2. 623.34		1. 7847 2. 643.35
	1. 7843 2. 519.29		
	1. 7844 2. 627.34		
	1. 7845 2. 631.35		

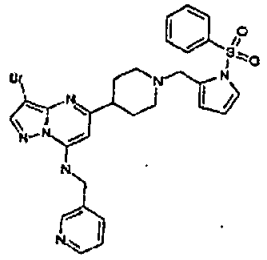
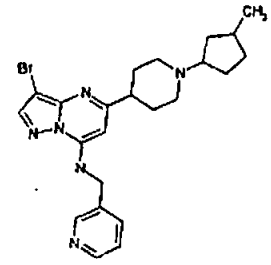
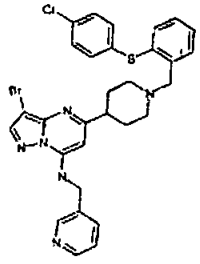
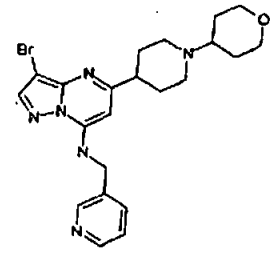
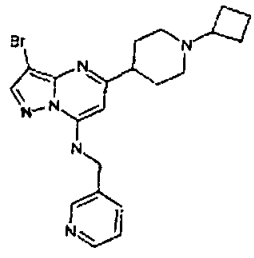
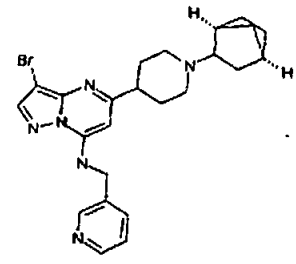
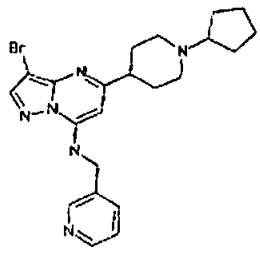
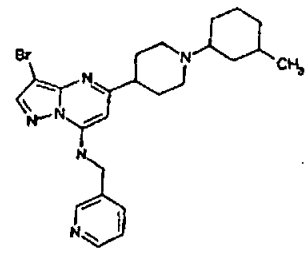
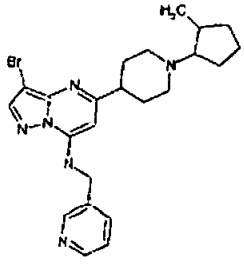
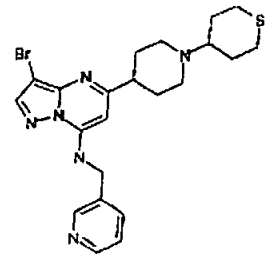
TABLE 79

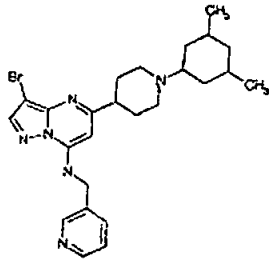
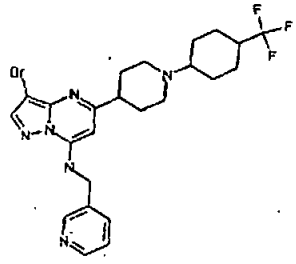
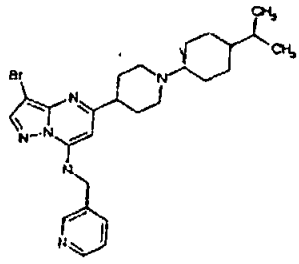
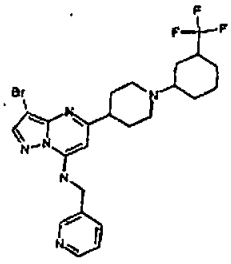
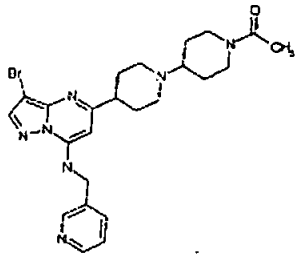
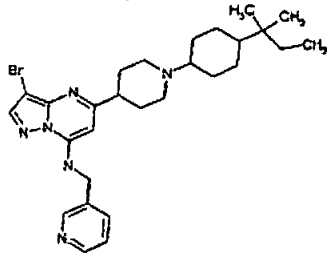
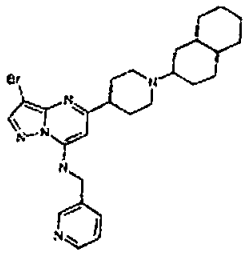
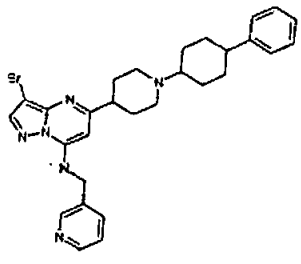
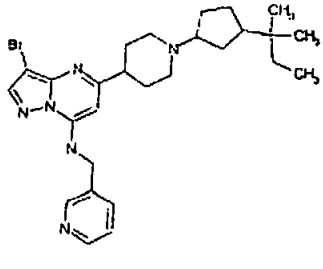
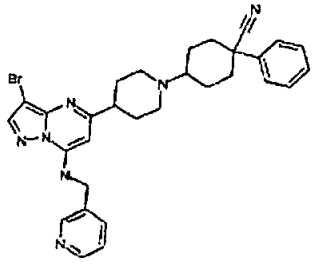
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7901 2. 477.26		1. 7906 2. 504.28
	1. 7902 2. 485.27		1. 7907 2. 505.28
	1. 7903 2. 485.27		1. 7908 2. 507.28
	1. 7904 2. 486.27		1. 7909 2. 509.28
	1. 7905 2. 495.27		1. 7910 2. 509.28

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7911 2. 509.28		1. 7916 2. 523.29
	1. 7912 2. 513.28		1. 7917 2. 525.29
	1. 7913 2. 515.28		1. 7918 2. 529.29
	1. 7914 2. 519.29		1. 7919 2. 529.29
	1. 7915 2. 523.29		1. 7920 2. 530.29

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7921 2. 530.29		1. 7926 2. 547.3
	1. 7922 2. 535.29		1. 7927 2. 547.3
	1. 7923 2. 537.3		1. 7928 2. 547.3
	1. 7924 2. 547.3		1. 7929 2. 547.3
	1. 7925 2. 547.3		1. 7930 2. 549.3

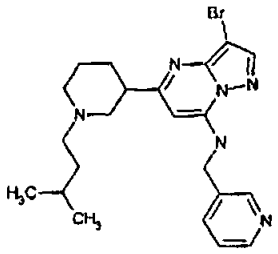
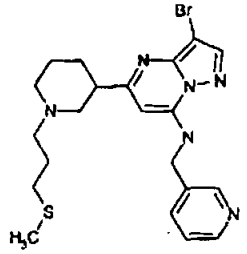
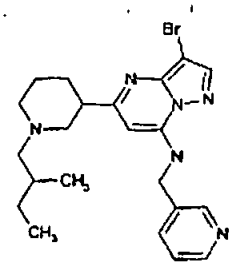
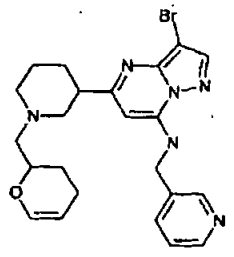
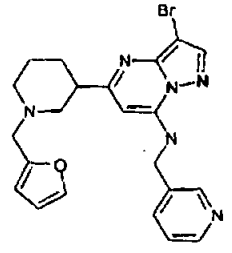
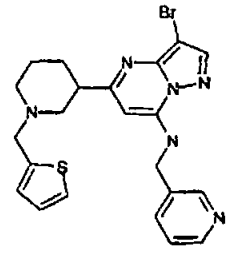
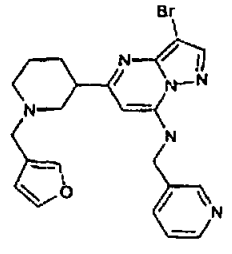
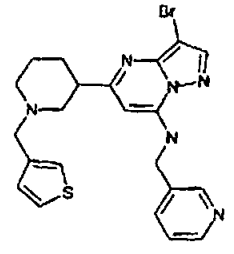
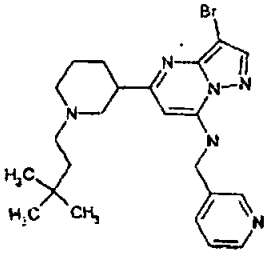
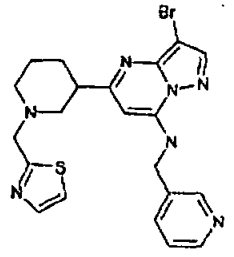
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7931 2. 555.31		1. 7936 2. 567.31
	1. 7932 2. 555.31		1. 7937 2. 567.31
	1. 7933 2. 557.31		1. 7938 2. 569.31
	1. 7934 2. 557.31		1. 7939 2. 571.31
	1. 7935 2. 557.31		1. 7940 2. 571.31

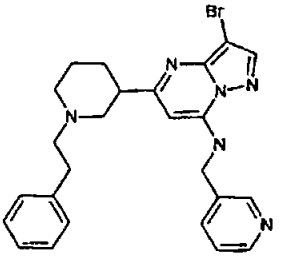
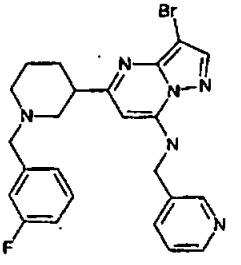
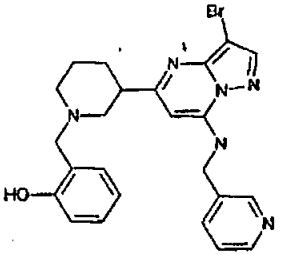
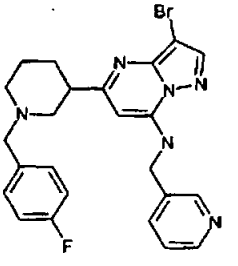
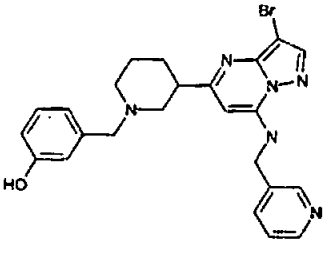
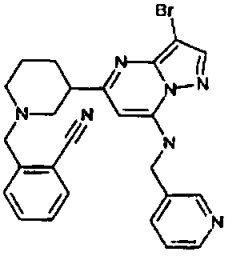
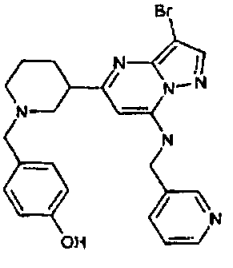
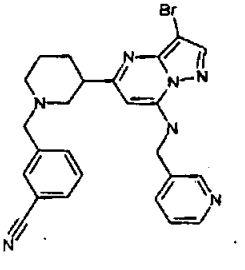
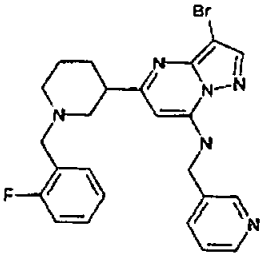
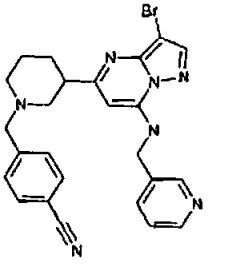
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7941 2. 608.33		1. 7946 2. 471.26
	1. 7942 2. 621.34		1. 7947 2. 473.26
	1. 7943 2. 443.24		1. 7948 2. 483.27
	1. 7944 2. 457.25		1. 7949 2. 485.27
	1. 7945 2. 471.26		1. 7950 2. 489.27

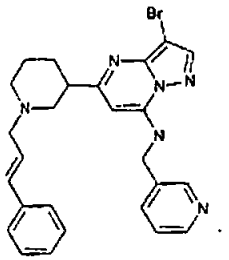
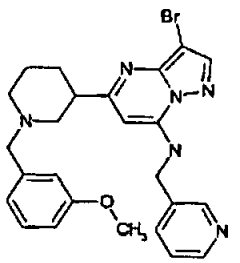
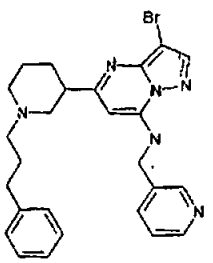
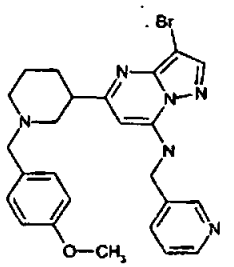
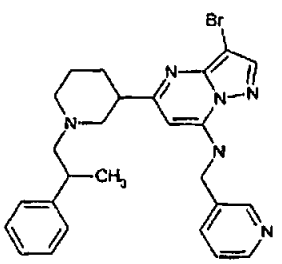
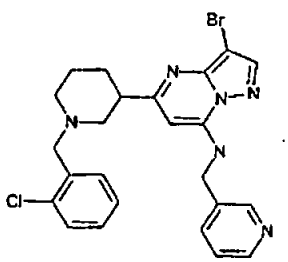
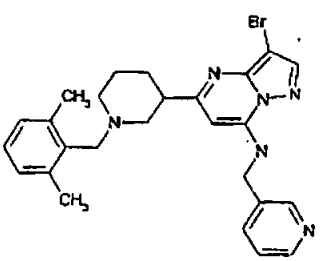
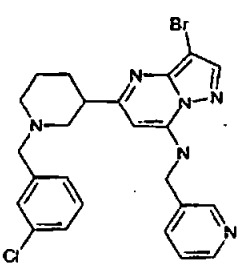
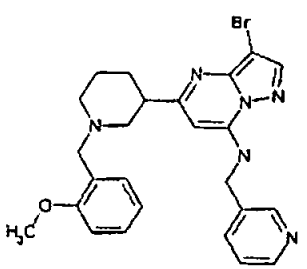
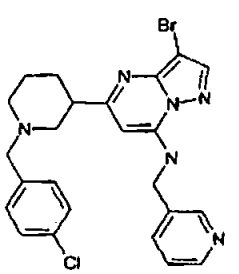
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7951 2. 499.27		1. 7956 2. 536.29
	1. 7952 2. 513.28		1. 7957 2. 539.3
	1. 7953 2. 514.28		1. 7958 2. 541.3
	1. 7954 2. 525.29		1. 7959 2. 547.3
	1. 7955 2. 525.29		1. 7960 2. 572.31

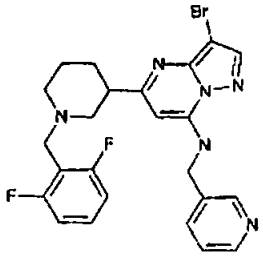
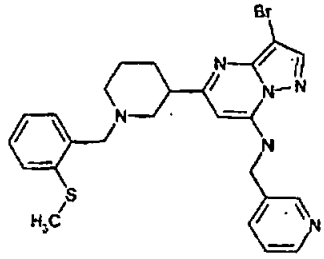
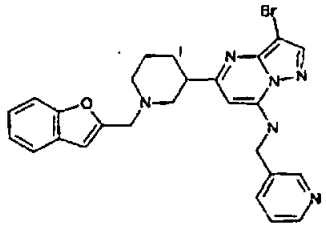
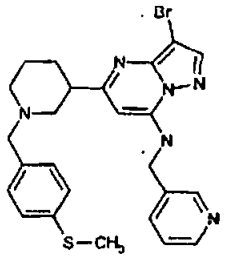
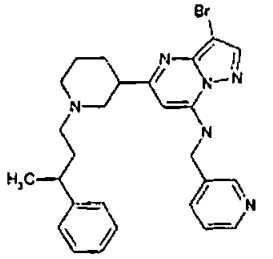
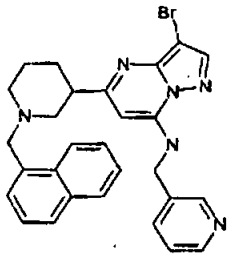
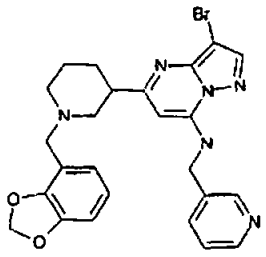
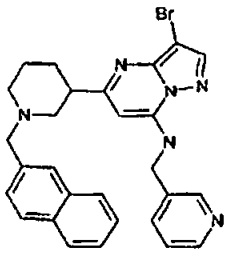
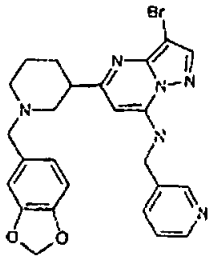
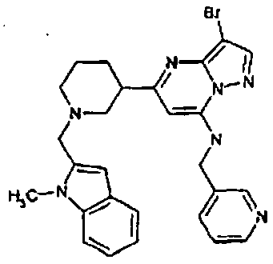
629

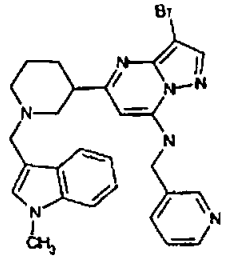
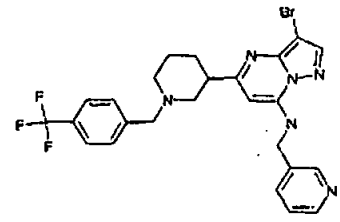
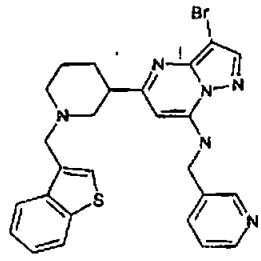
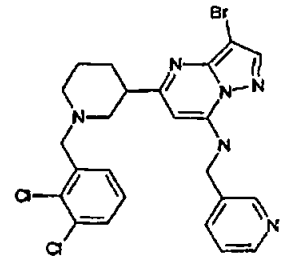
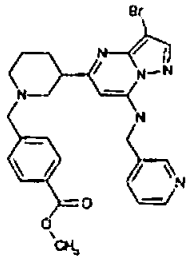
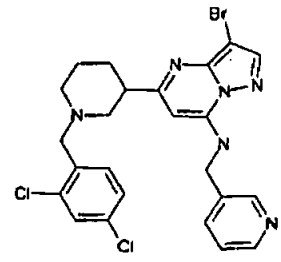
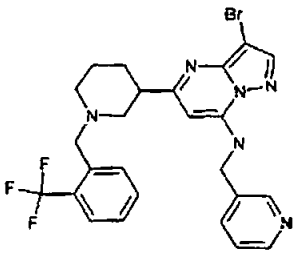
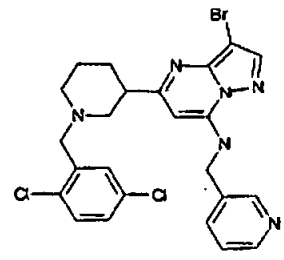
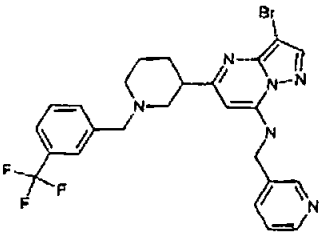
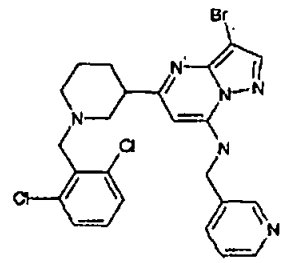
TABLE 80

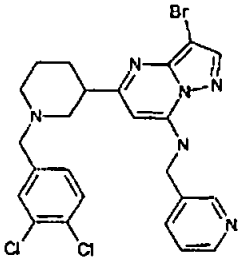
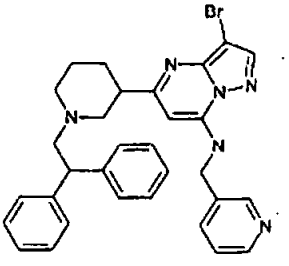
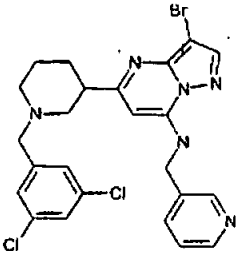
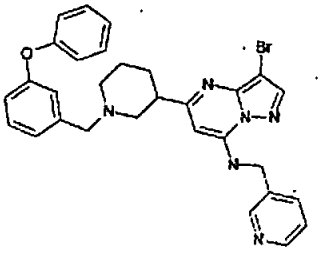
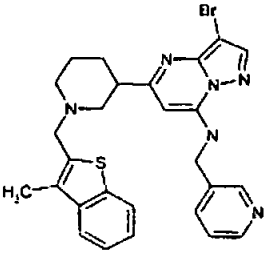
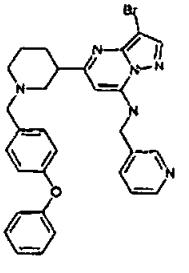
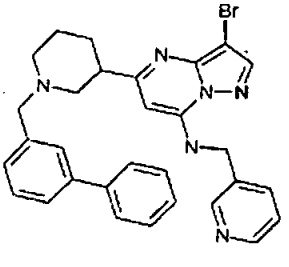
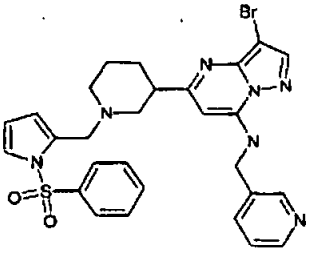
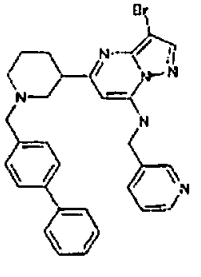
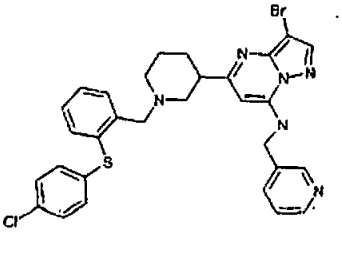
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8001 2. 459.25		1. 8006 2. 477.26
	1.8002 2. 459.25		1. 8007 2 485.27
	1. 8003 2. 469.26		1. 8008 2. 485.27
	1. 8004 2. 469.26		1. 8009 2. 485.27
	1. 8005 2. 473.26		1. 8010 2. 486.27

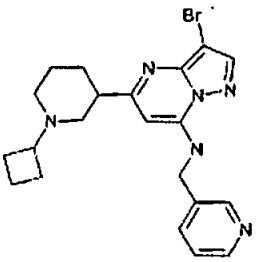
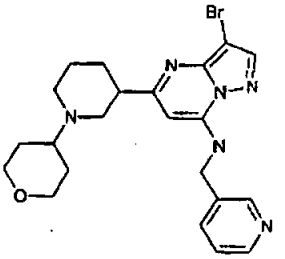
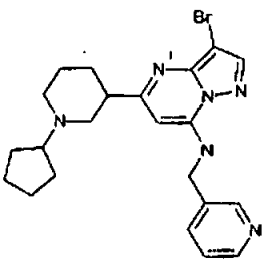
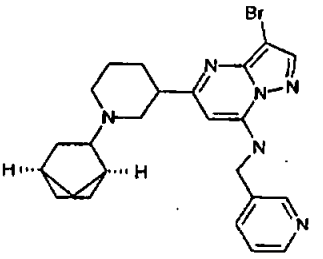
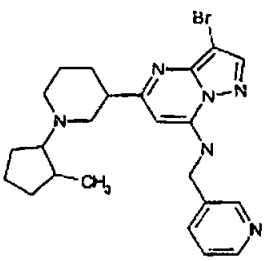
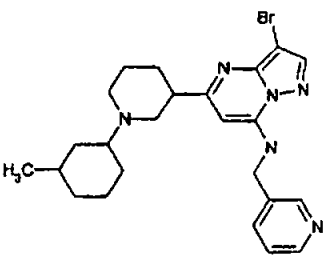
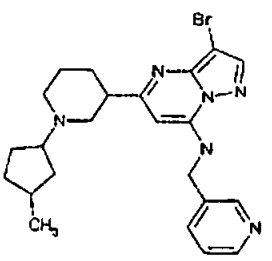
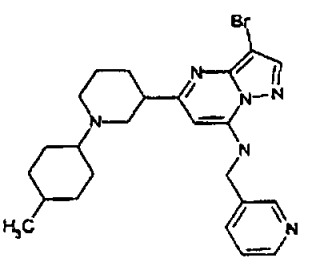
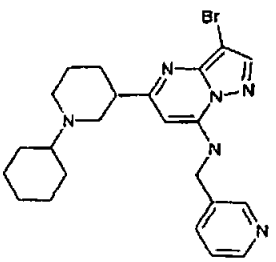
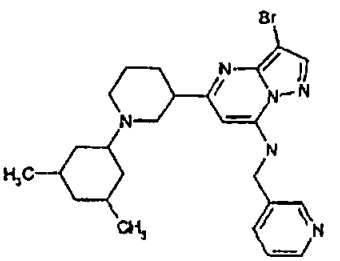
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8011 2. 493.27		1. 8016 2. 495.27
	1. 8012 2. 495.27		1. 8017 2. 495.27
	1. 8013 2. 495.27		1. 8018 2. 502.28
	1. 8014 2. 495.27		1. 8019 2. 502.28
	1. 8015 2. 495.27		1. 8020 2. 502.28

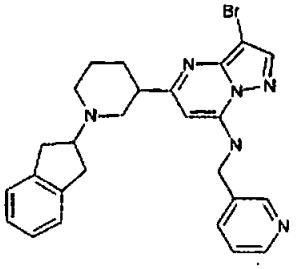
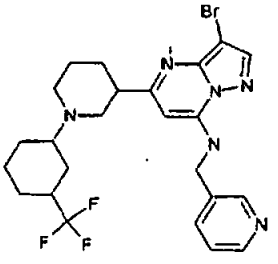
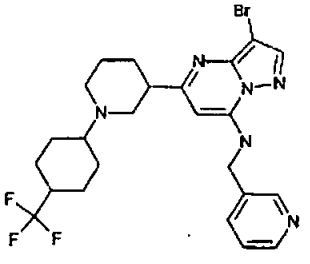
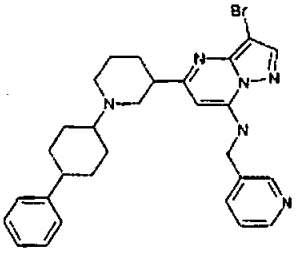
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8021 2. 505.28		1. 8026 2. 509.28
	1. 8022 2. 505.28		1. 8027 2. 509.28
	1. 8023 2. 507.28		1. 8028 2. 513.28
	1. 8024 2. 507.28		1. 8029 2. 513.28
	1. 8025 2. 507.28		1. 8030 2. 513.28

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8031 2. 515.28		1. 8036 2. 523.29
	1. 8032 2. 519.29		1. 8037 2. 525.29
	1. 8033 2. 521.29		1. 8038 2. 529.29
	1. 8034 2. 523.29		1. 8039 2. 529.29
	1. 8035 2. 523.29		1. 8040 2. 530.29

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8041 2. 530.29		1. 8046 2. 547.3
	1. 8042 2. 535.29		1. 8047 2. 544.3
	1. 8043 2. 537.3		1. 8048 2. 547.3
	1. 8044 2. 547.3		1. 8049 2. 547.3
	1. 8045 2. 547.3		1. 8050 2. 547.3

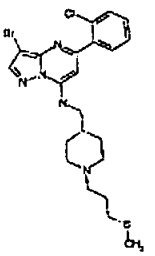
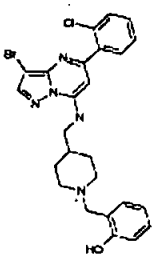
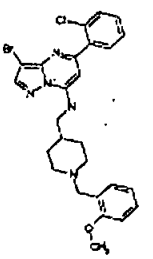
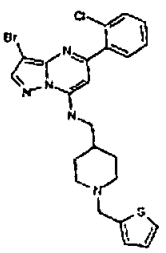
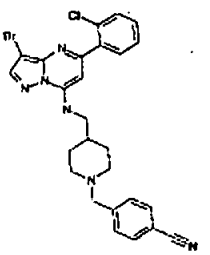
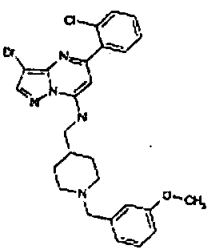
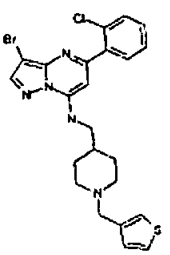
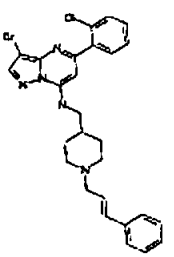
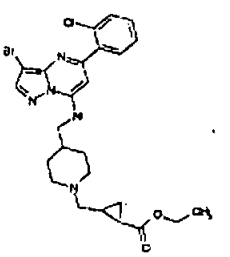
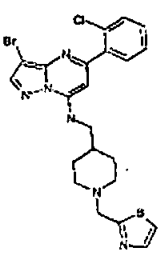
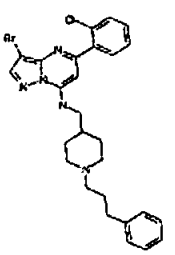
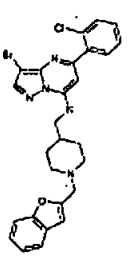
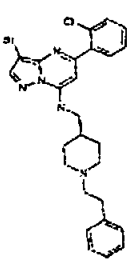
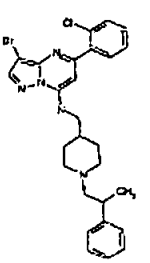
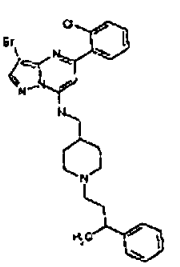
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8051 2. 548.3		1. 8056 2. 569.31
	1. 8052 2. 548.3		1. 8057 2. 569.31
	1. 8053 2. 547.3		1. 8058 2. 571.31
	1. 8054 2. 555.31		1. 8059 2. 608.33
	1. 8055 2. 553.3		1. 8060 2. 621.34

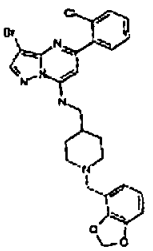
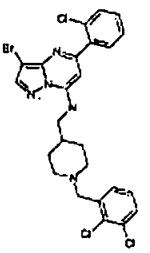
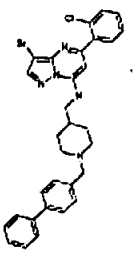
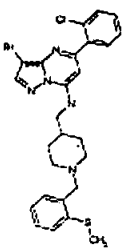
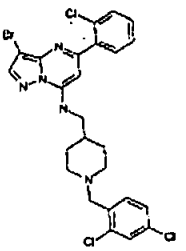
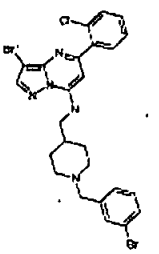
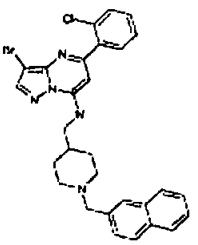
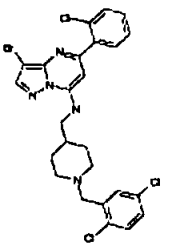
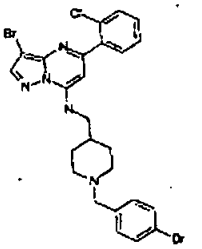
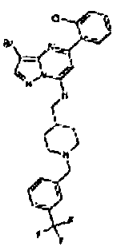
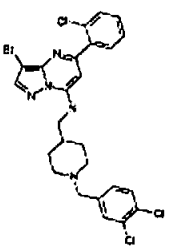
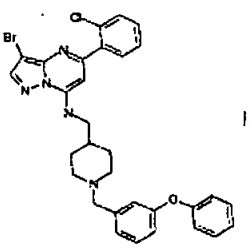
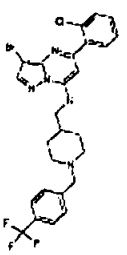
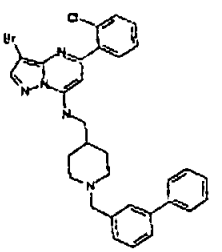
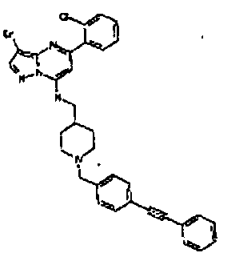
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8061 2. 443.24		1. 8066 2. 473.26
	1. 8062 2. 457.25		1. 8067 2. 483.27
	1. 8063 2. 471.26		1. 8068 2. 485.27
	1. 8064 2. 471.26		1. 8069 2. 483.27
	1. 8065 2. 469.26		1. 8070 2. 499.27

Product	1. Ex. 2. m/z
	1. 8071 2. 505.2 8
	1. 8072 2. 537.3
	1. 8073 2. 537.3
	1. 8074 2. 547.3

637

TABLE81

Product	1. Ex. 2. m/zz	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z.
	1. 8101 2. 510.28		1. 8106 2. 528.29		1. 8111 2. 542.3
	1. 8102 2. 518.28		1. 8107 2. 537.3		1. 8112 2. 542.3
	1. 8103 2. 518.28		1. 8108 2. 538.3		1. 8113 2. 548.3
	1. 8104 2. 519.29		1. 8109 2. 540.3		1. 8114 2. 552.3
	1. 8105 2. 526.29		1. 8110 2. 540.3		1. 8115 2. 554.3

Product	1. Ex. 2: m/zz	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8116 2. 556.31		1. 8121 2. 580.32		1. 8126 2. 588.32
	1. 8117 2. 558.31		1. 8122 2. 580.32		1. 8127 2. 590.32
	1. 8118 2. 562.31		1. 8123 2. 580.32		1. 8128 2. 590.32
	1. 8119 2. 580.32		1. 8125 2. 580.32		I. 8129 2. 604.33
	1. 8120 2. 580.32		1. 8126 2. 588.32		1. 8130 2. 612.34

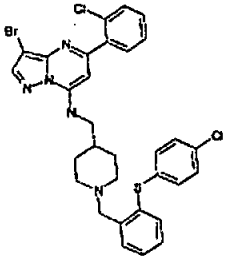
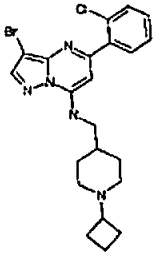
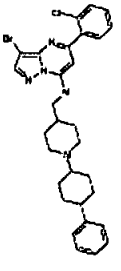
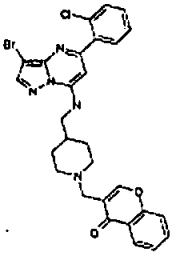
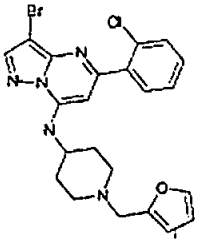
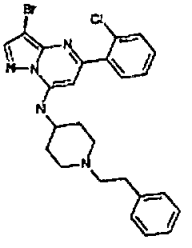
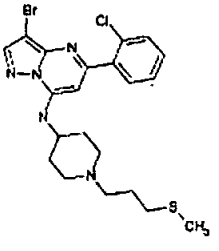
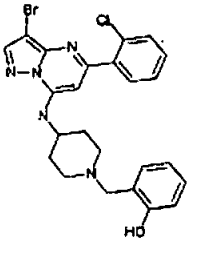
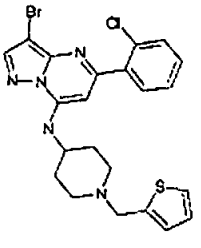
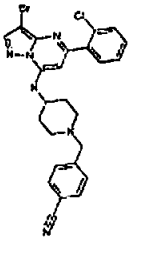
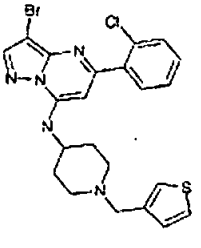
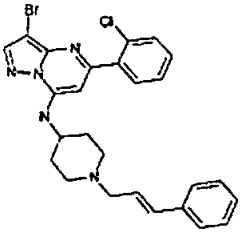
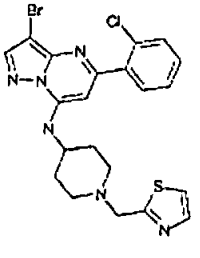
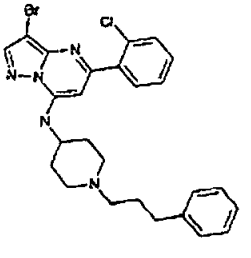
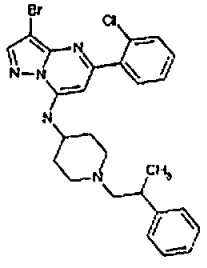
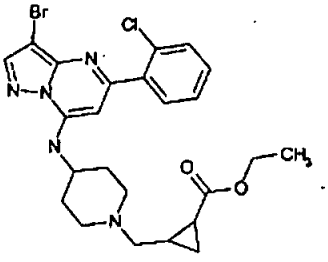
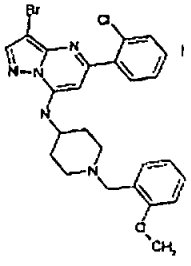
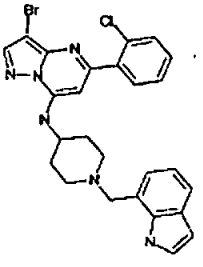
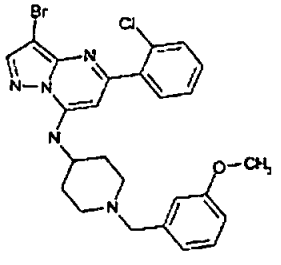
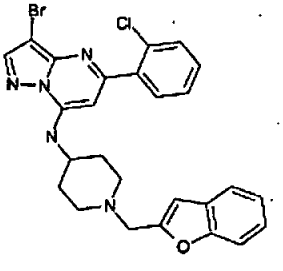
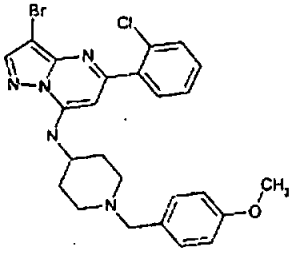
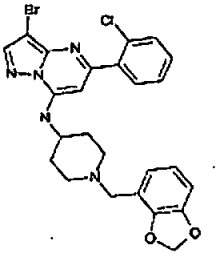
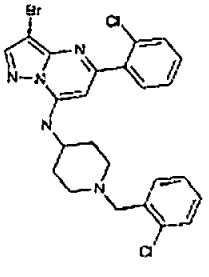
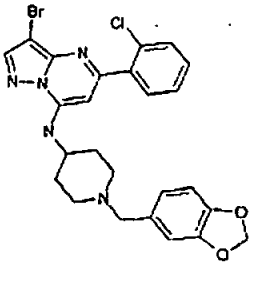
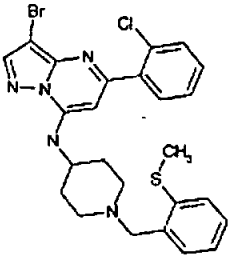
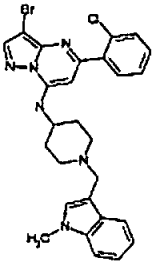
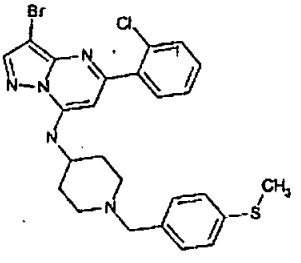
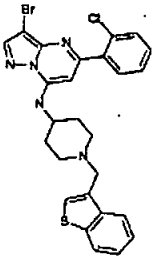
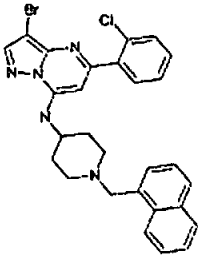
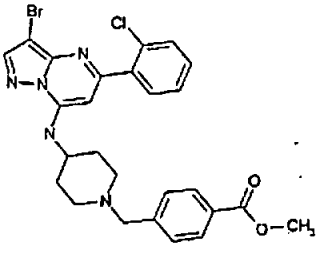
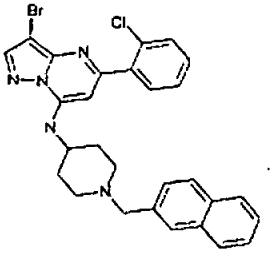
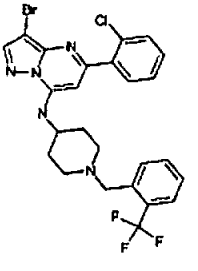
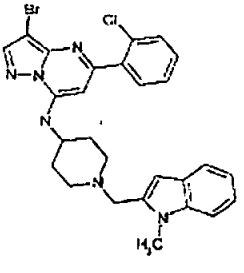
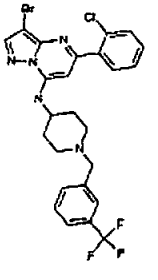
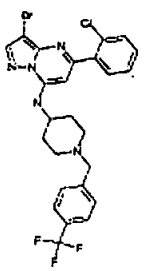
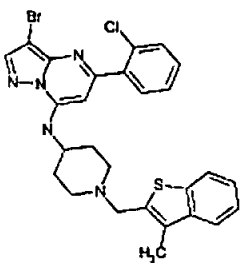
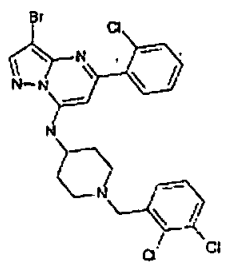
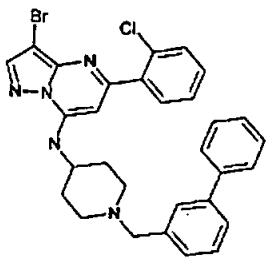
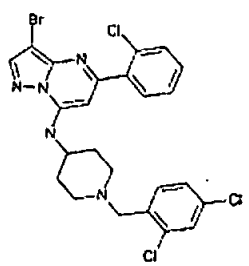
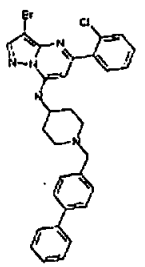
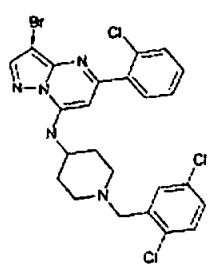
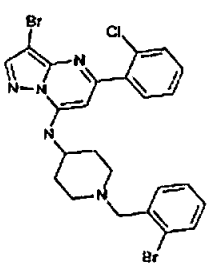
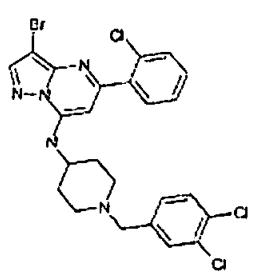
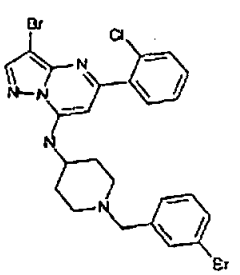
Product	1. Ex. 2. m/z
	1. 8131 2. 654.36
	1. 8132 2. 476.26
	1. 8133 2. 580.32
	1. 8134 2. 580.32

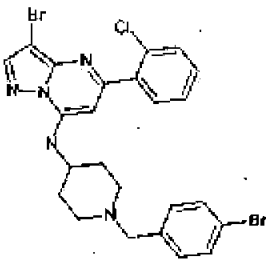
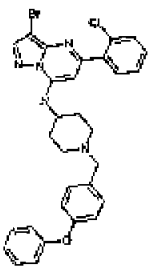
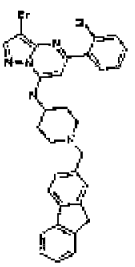
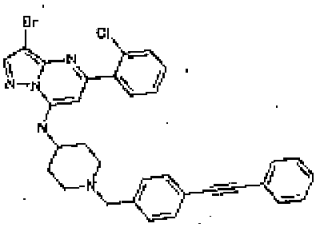
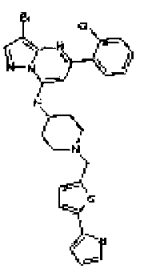
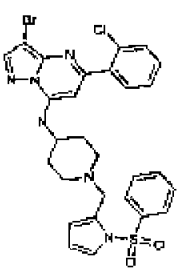
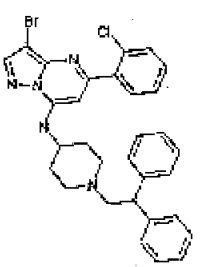
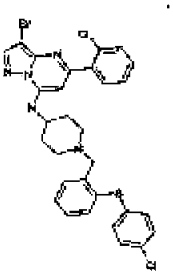
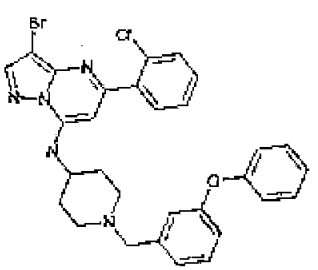
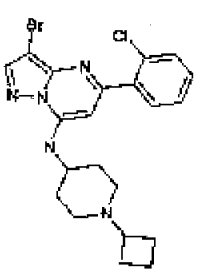
TABLE 82

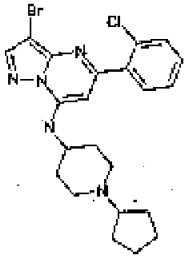
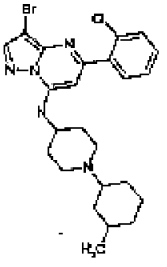
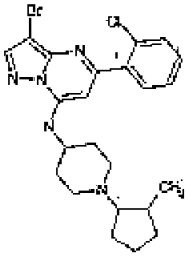
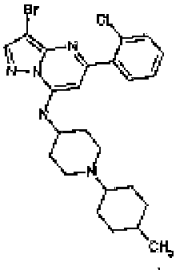
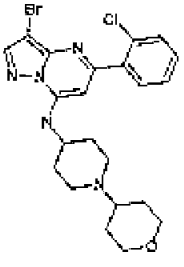
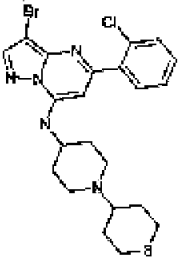
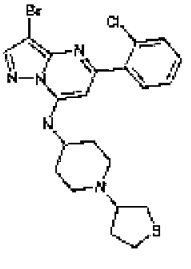
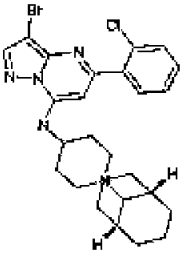
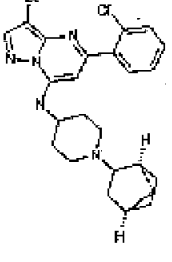
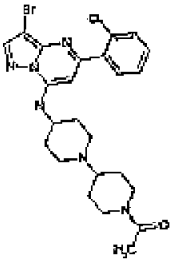
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8201 2. 488.27		1. 8206 2. 512.28
	1. 8202 2. 496.27		1. 8207 2. 514.28
	1. 8203 2. 504.28		1. 8208 2. 523.29
	1. 8204 2. 504.28		1. 8209 2. 524.29
	1. 8205 2. 505.28		1. 8210 2. 526.29

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8211 2. 526.29		1. 8216 2. 534.29
	1. 8212 2. 528.29		1. 8217 2. 537.3
	1. 8213 2. 528.29		1. 8218 2. 538.3
	1. 8214 2. 528.29		1. 8219 2. 542.3
	1. 8215 2. 532.29		1. 8220 2. 542.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8221 2. 544.3		1. 8226 2. 551.3
	1. 8222 2. 544.3		1. 8227 2. 554.3
	1. 8223 2. 548.3		1. 8228 2. 556.31
	1. 8224 2. 548.3		1. 8229 2. 566.31
	1. 8225 2. 551.3		1. 8230 2. 566.31

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8231 2. 566.31		1. 8236 2. 568.31
	1. 8232 2. 566.31		1. 8237 2. 574.32
	1. 8233 2. 566.31		1. 8238 2. 574.32
	1. 8243 2. 566.31		1. 8239 2. 576.32
	1. 8235 2. 566.31		1. 8240 2. 576.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8241 2. 576.32		1. 8246 2. 590.32
	1. 8242 2. 588.32		1. 8247 2. 598.33
	1. 8243 2. 586.32		1. 8248 2. 627.34
	1. 8244 2. 588.32		1. 8249 2. 640.36
	1. 8245 2. 590.32		1. 8250 2. 462.25

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8251 2. 476.26		1. 8256 2. 504.28
	1. 8252 2. 490.27		1. 8257 2. 504.28
	1. 8253 2. 492.27		1. 8258 2. 508.28
	1. 8254 2. 492.27		1. 8259 2. 530.29
	1. 8255 2. 502.28		1. 8260 2. 533.29

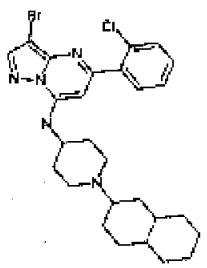
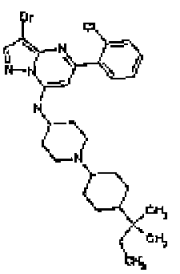
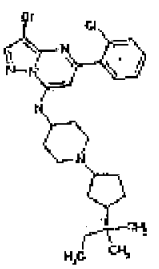
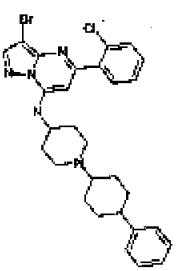
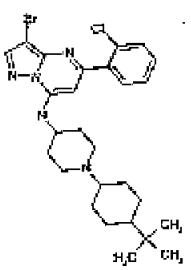
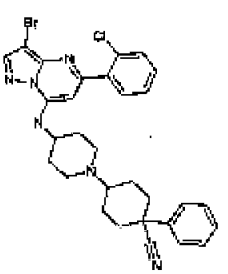
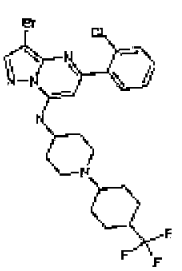
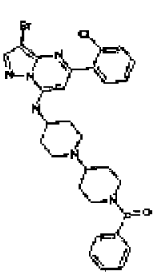
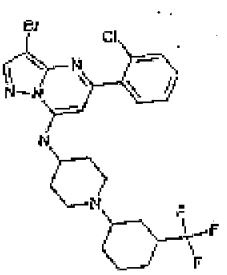
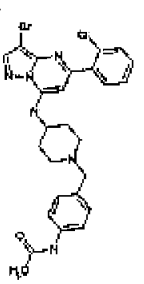
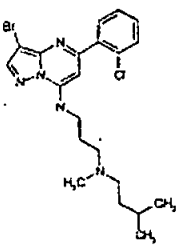
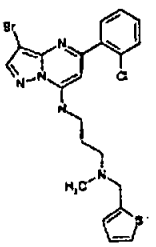
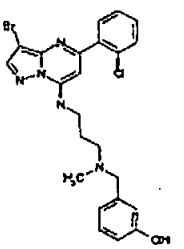
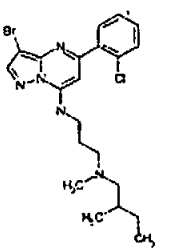
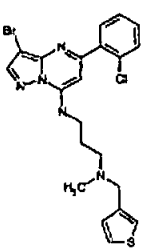
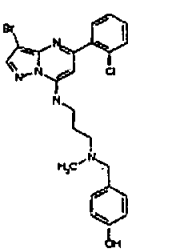
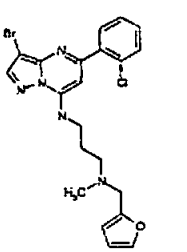
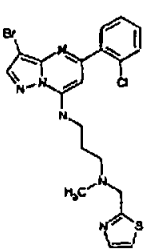
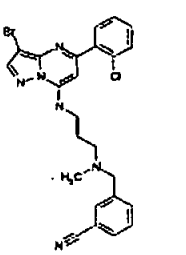
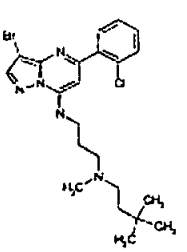
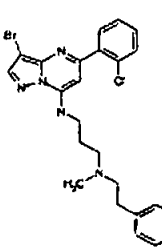
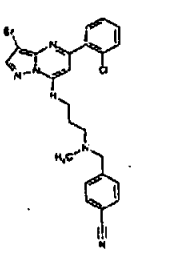
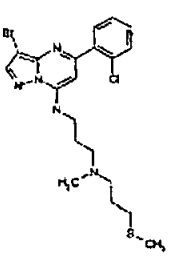
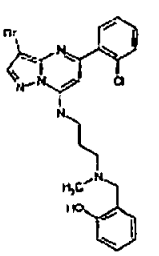
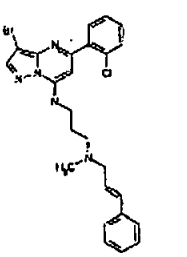
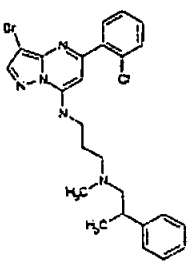
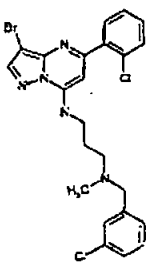
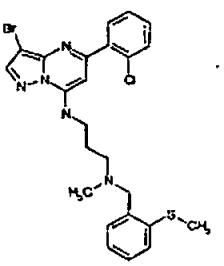
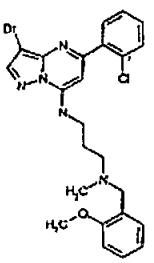
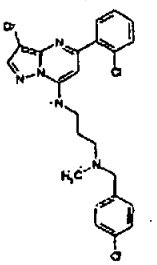
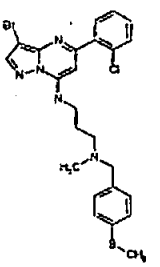
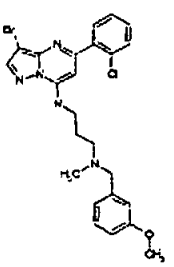
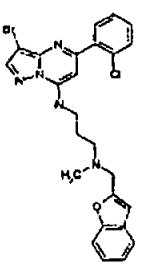
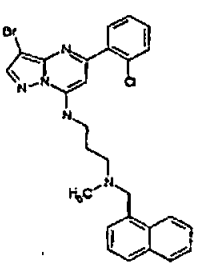
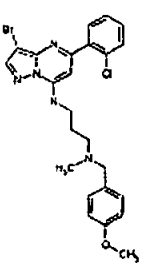
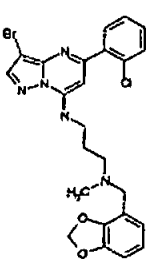
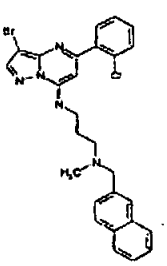
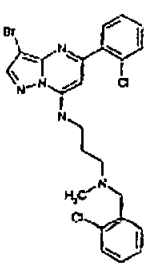
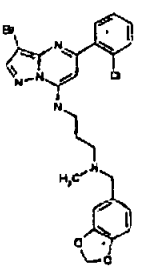
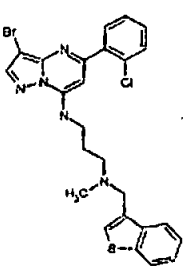
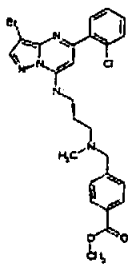
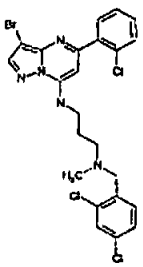
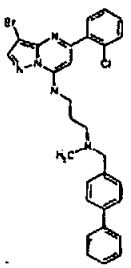
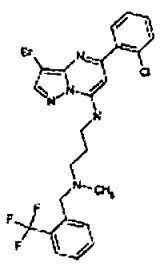
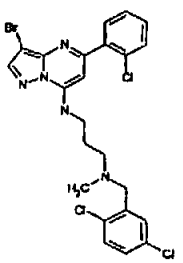
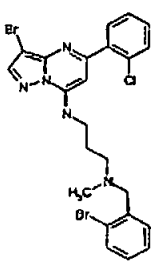
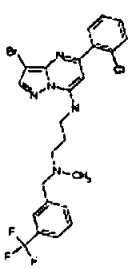
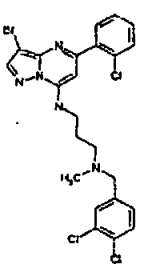
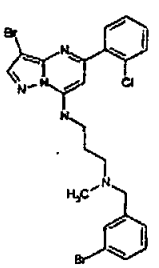
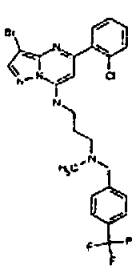
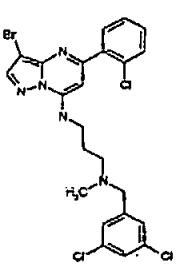
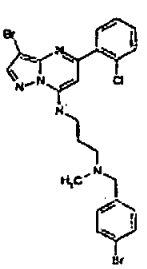
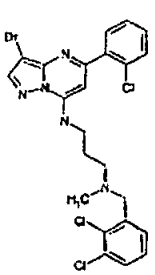
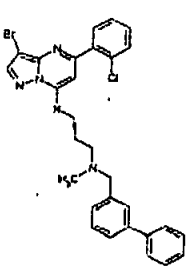
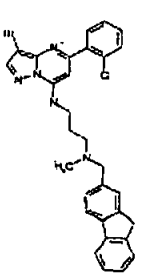
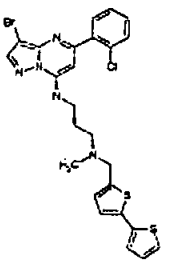
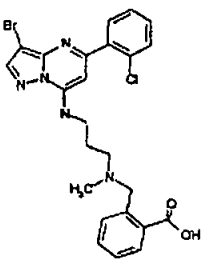
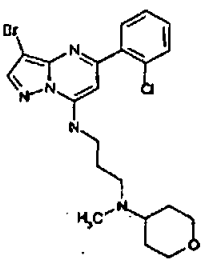
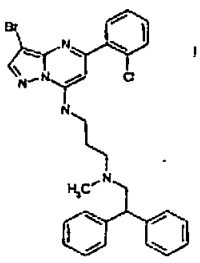
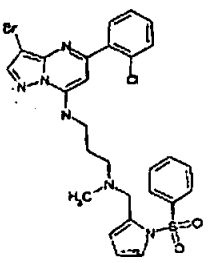
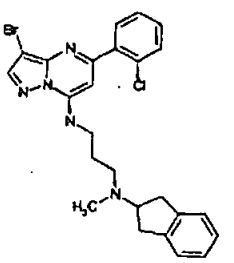
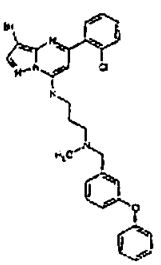
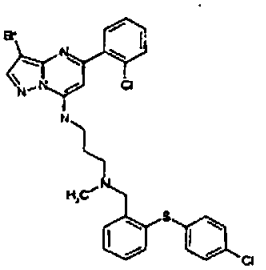
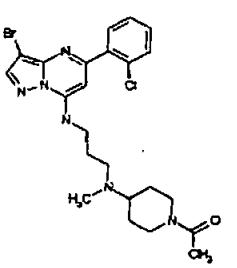
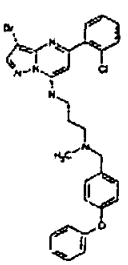
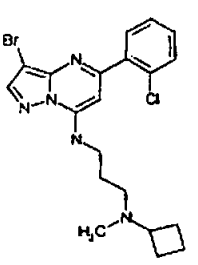
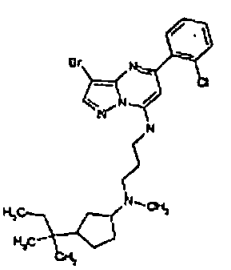
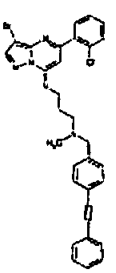
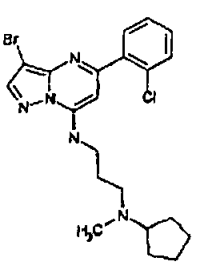
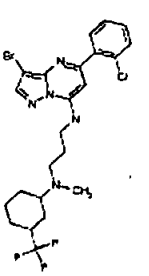
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8261 2. 544.3		1. 8266 2. 560.31
	1. 8262 2. 546.3		1. 8267 2. 566.31
	1. 8263 2. 546.3		1. 8268 2. 591.33
	1. 8264 2. 558.31		1. 8269 2. 595.33
	1. 8265 2. 558.31		1. 8270 2. 555.31

TABLE 83

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8301 2. 465.882		1. 8306 2. 491.79		1. 8311 2. 501.825
	1. 8302 2. 465.885		1. 8307 2. 491.792		1. 8312 2. 501.833
	1. 8303 2. 475.827		1. 8308 2. 492.787		1. 8313 2. 510.822
	1. 8304 2. 479.89		1. 8309 2. 499.846		1. 8314 2. 510.821
	1. 8305 2. 483.829		1. 8310 2. 501.826		1. 8315 2. 511.841

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8316 2. 513.855		1. 8321 2. 519.783		1. 8326 2. 531.804
	1. 8317 2. 515.832		1. 8322 2. 519.781		1. 8327 2. 531.812
	1. 8318 2. 515.832		1. 8323 2. 525.813		1. 8328 2. 535.83
	1. 8319 2. 515.837		1. 8324 2. 529.806		1. 8329 2. 535.831
	1. 8320 2. 519.782		1. 8325 2. 529.81		1. 8330 2. 541.788

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex: 2. m/z
	1. 8331 2. 543.821		1. 8336 2. 554.727		1. 8341 2. 561.838
	1. 8332 2. 553.797		1. 8337 2. 554.738		1. 8342 2. 564.714
	1. 8333 2. 553.796		1. 8338 2. 554.738		1. 8343 2. 564.704
	1. 8334 2. 553.795		1. 8339 2. 554.727		1. 8344 2. 564.72
	1. 8335 2. 554.73		1. 8340 2. 561.836		1. 8345 2. 573.823

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8346 2. 573.735		1. 8351 2. 529.808		1. 8356 2. 479.856
	1. 8347 2. 575.839		1. 8352 2. 614.763		1. 8357 2. 511.842
	1. 8348 2. 577.818		1. 8353 2. 628.727		1. 8358 2. 520.859
	1. 8349 2. 577.814		1. 8354 2. 449.857		1. 8359 2. 533.903
	1. 9350 2. 585.818		1. 8355 2. 463.867		1. 8360 2. 545.823

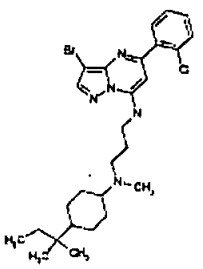
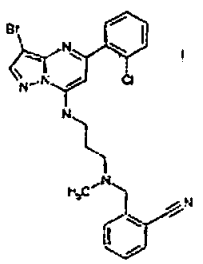
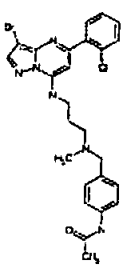
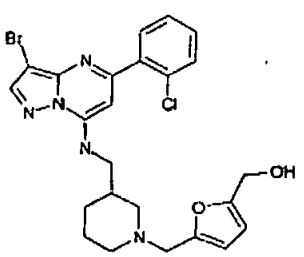
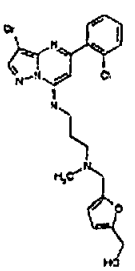
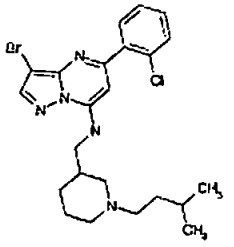
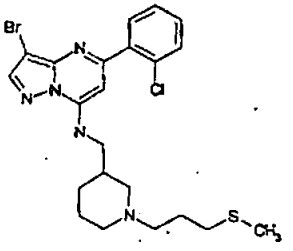
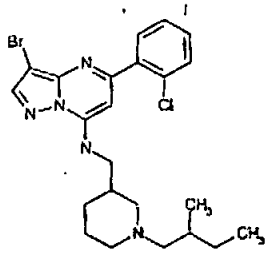
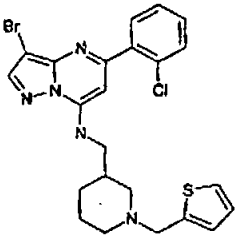
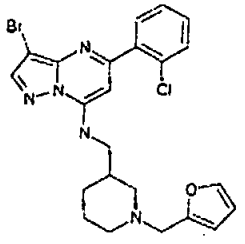
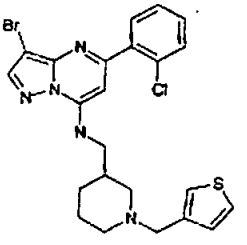
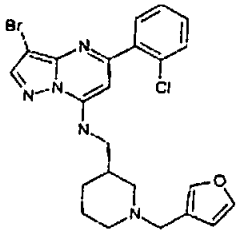
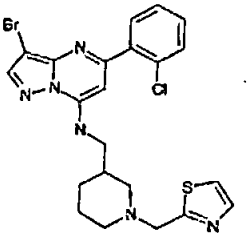
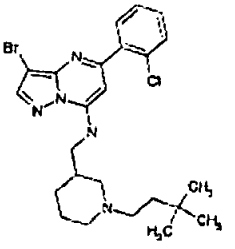
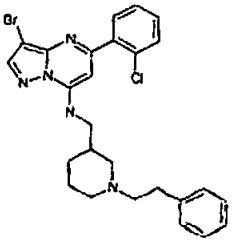
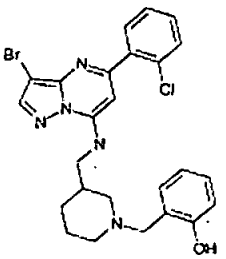
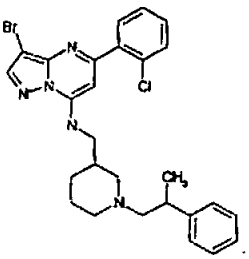
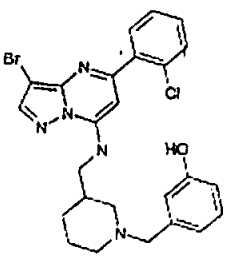
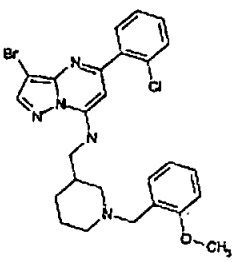
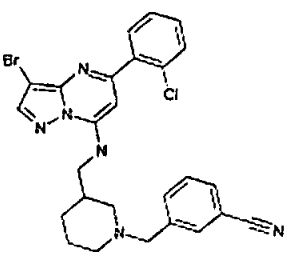
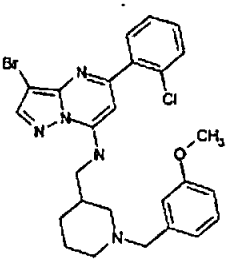
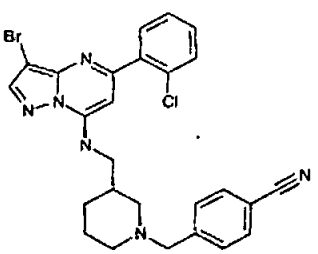
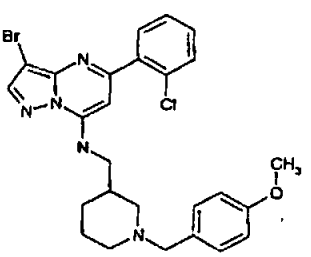
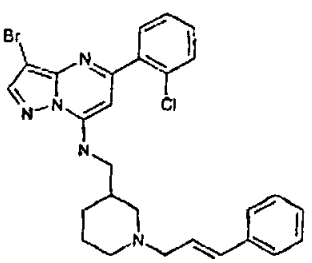
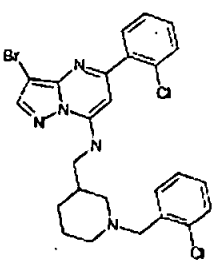
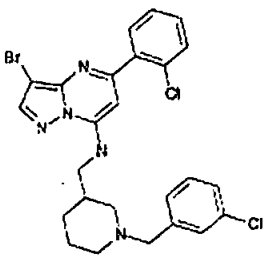
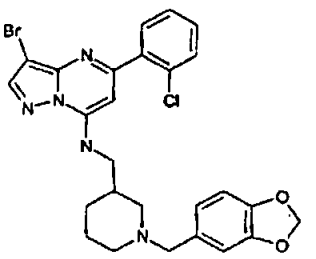
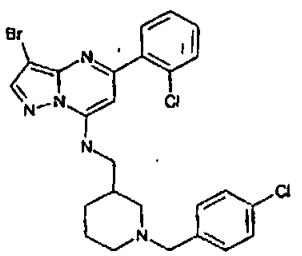
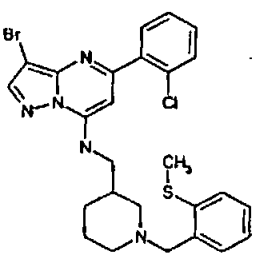
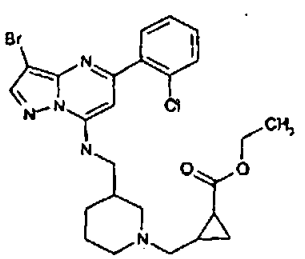
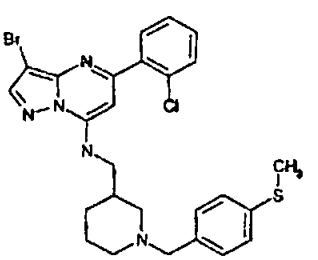
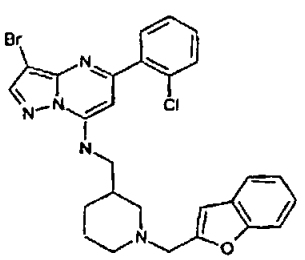
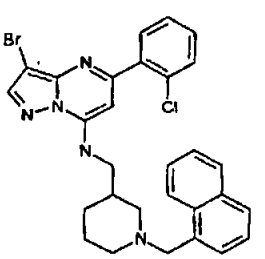
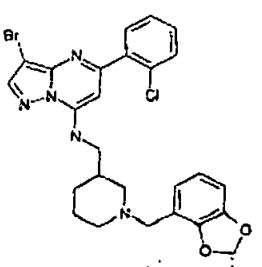
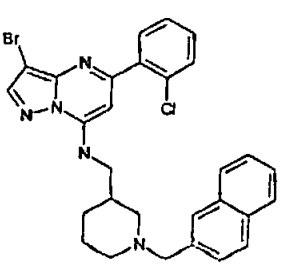
Product	1. Ex. 2. m/z
	1. 8361 2. 547.909
	1. 8362 2. 510.817
	1. 8363 2. 542.833
	1. 8364 2. 573.815
	1. 8365 2. 547.798

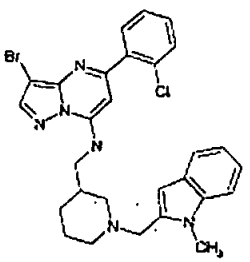
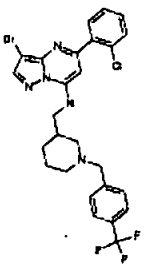
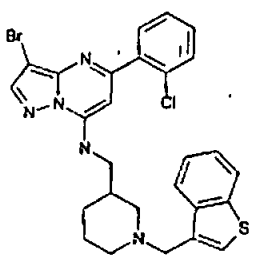
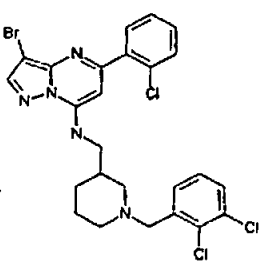
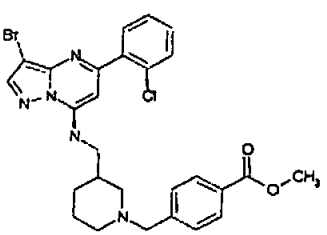
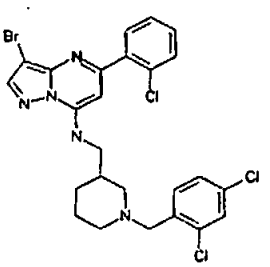
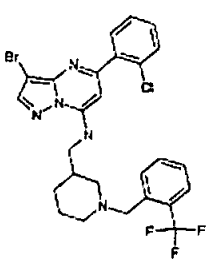
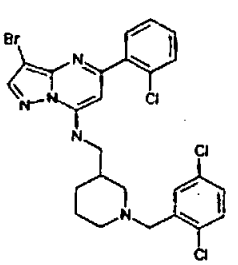
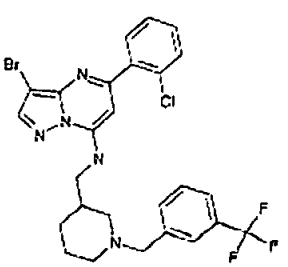
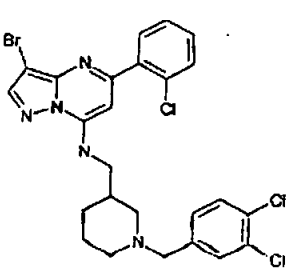
TABLE 84

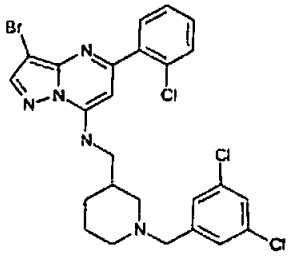
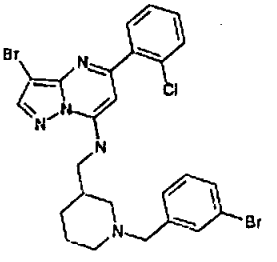
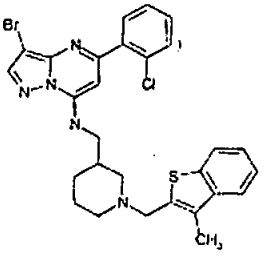
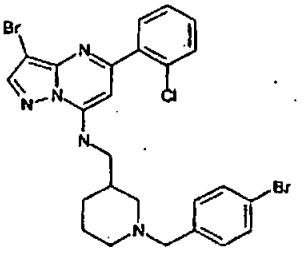
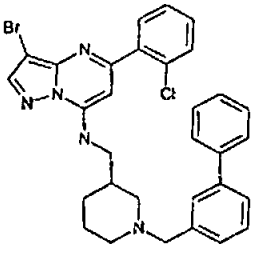
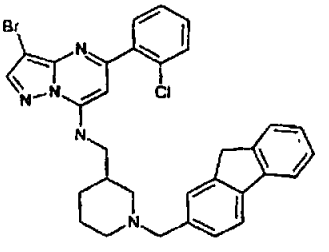
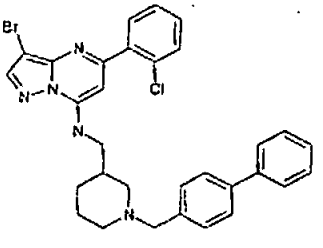
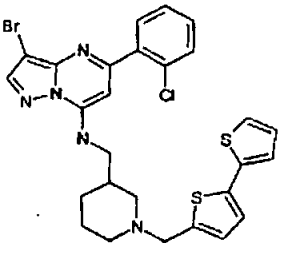
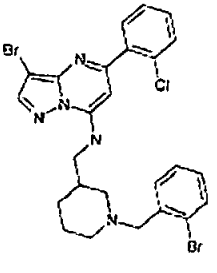
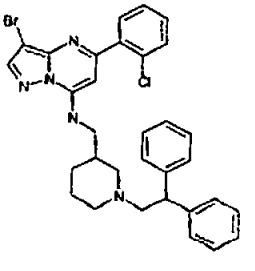
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8401 2. 491.883		1. 8406 2. 509.829
	1. 8402 2. 491.883		1. 8407 2. 517.795
	1. 8403 2. 501.823		1. 8408 2. 517.799
	1. 8404 2. 501.827		1. 8409 2. 518.796
	1. 8405 2. 505.89		1. 8410 2. 525.851

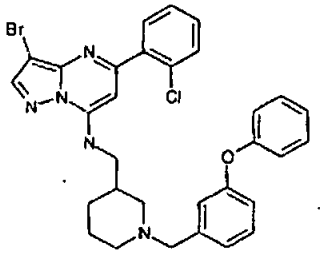
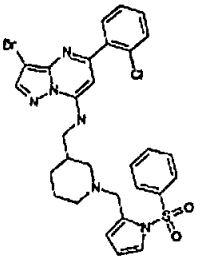
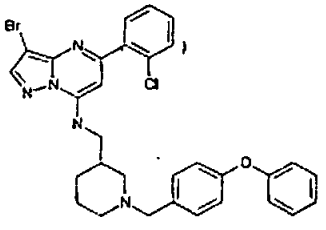
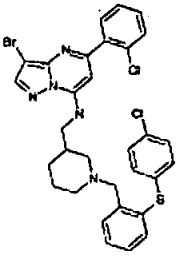
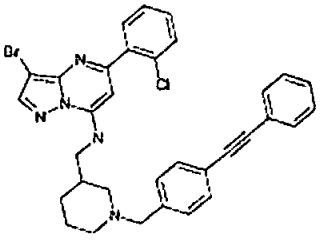
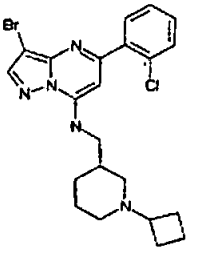
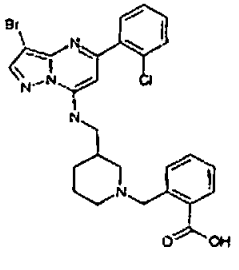
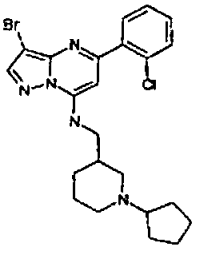
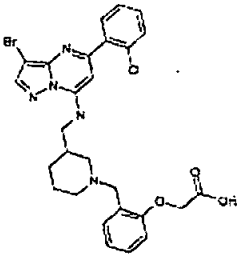
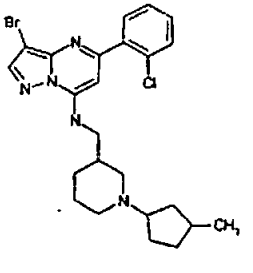
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8411 2. 527.831		1. 8416 2. 539.859
	1. 8412 2. 527.833		1. 8417 2. 541.84
	1. 8413 2. 536.833		1. 8418 2. 541.843
	1. 8414 2. 536.829		1. 8419 2. 541.843
	1. 8415 2. 537.845		1. 8420 2. 546.786

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8421 2. 546.792		1. 8426 2. 555.817
	1. 8422 2. 546.79		1. 8427 2. 557.81
	1. 8423 2. 547.854		1. 8428 2. 557.813
	1. 8424 2. 551.826		1. 8429 2. 561.839
	1. 8425 2. 555.819		1. 8430 2. 561.833

Error! Objects cannot be created from editing field codes.

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8431 2. 564.841		1. 8436 2. 579.794
	1. 8432 2. 567.795		1. 8437 2. 580.738
	1. 8433 2. 569.823		1. 8438 2. 580.732
	1. 8434 2. 579.797		1. 8439 2. 580.733
	1. 8435 2. 579.796		1. 8440 2. 580.734

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8441 2. 580.726		1. 8446 2. 590.726
	1. 8442 2. 581.805		1. 8447 2. 590.724
	1. 8443 2. 587.844		1. 8448 2. 599.834
	1. 8444 2. 587.835		1. 8449 2. 599.749
	1. 8445 2. 590.723		1. 8450 2. 601.854

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8451 2. 603.831		1. 8456 2. 640.779
	1. 8452 2. 603.83		1. 8457 2. 654.746
	1. 8453 2. 611.83		1. 8458 2. 475.871
	1. 8454 2. 555.824		1. 8459 2. 489.879
	1. 8455 2. 585.817		1. 8460 2. 503.885

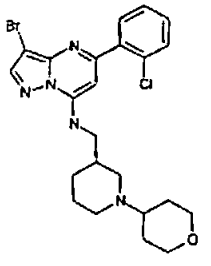
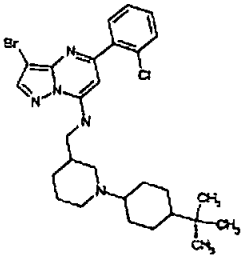
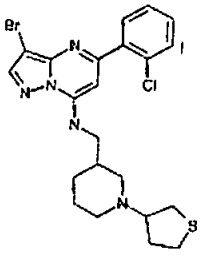
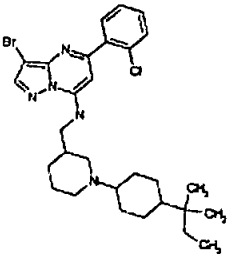
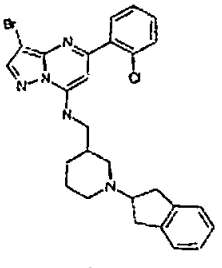
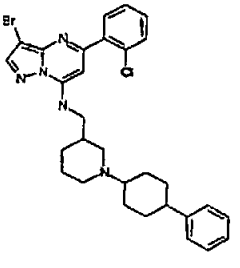
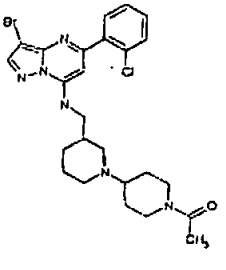
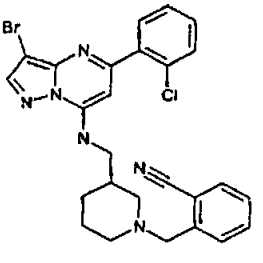
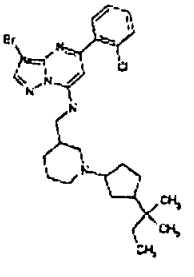
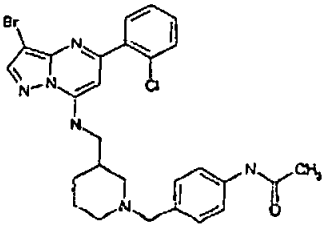
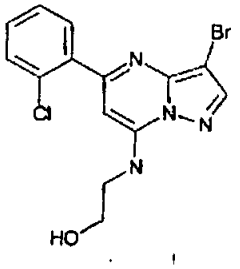
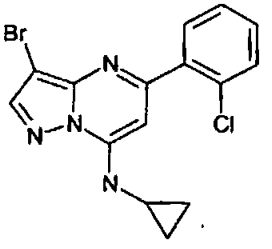
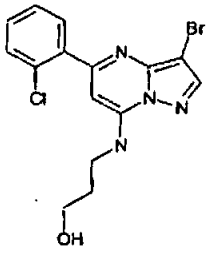
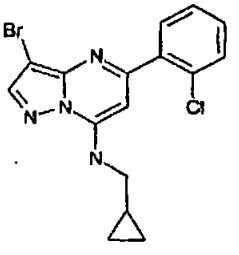
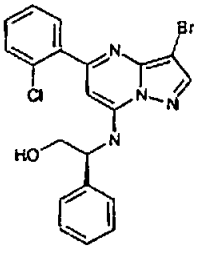
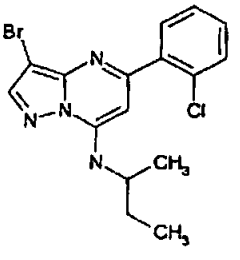
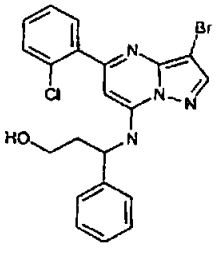
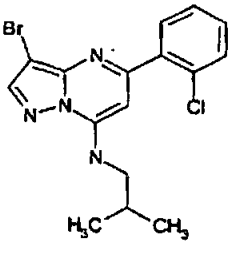
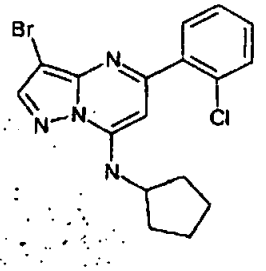
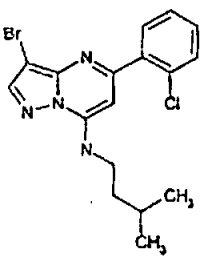
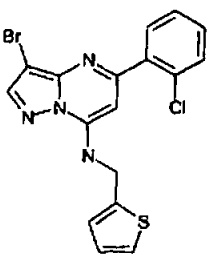
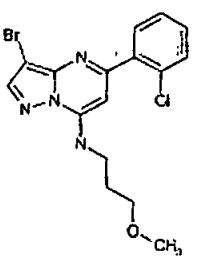
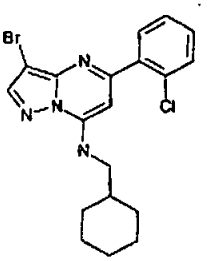
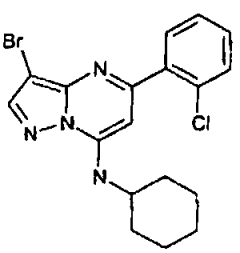
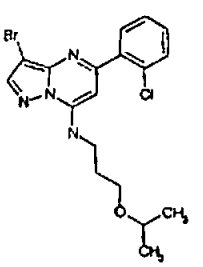
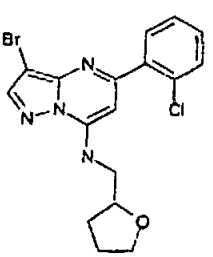
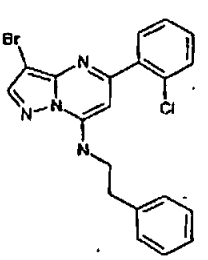
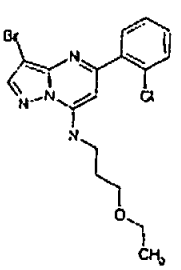
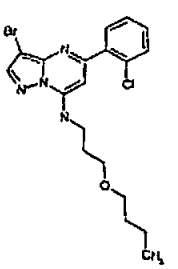
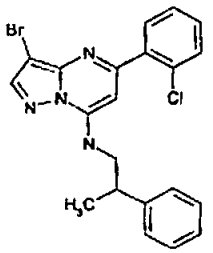
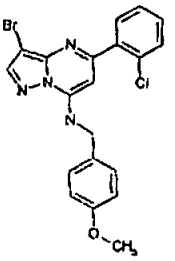
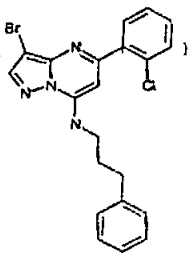
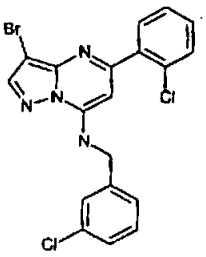
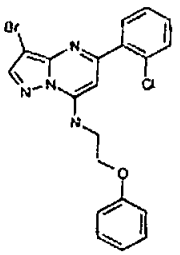
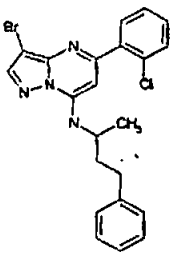
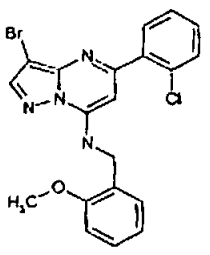
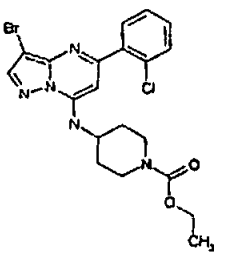
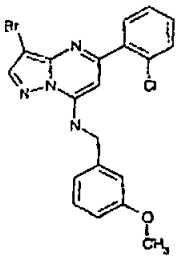
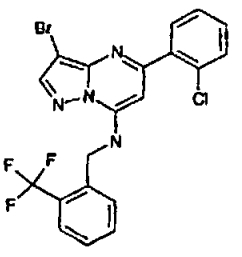
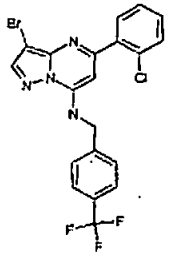
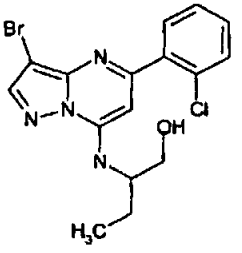
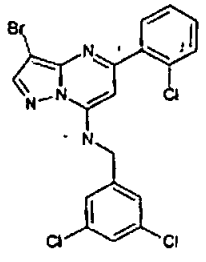
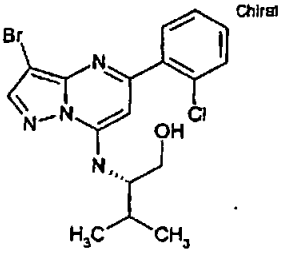
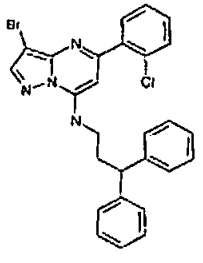
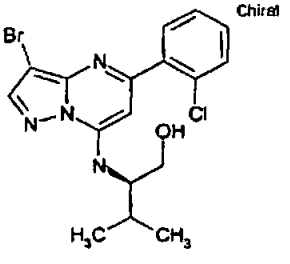
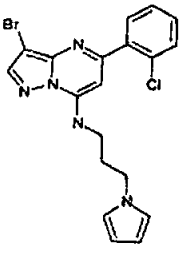
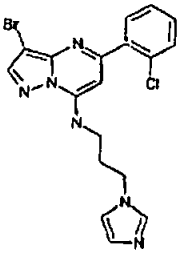
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8461 2. 505.866		1. 8466 2. 559.919
	1. 8462 2. 507.828		1. 8467 2. 573.925
	1. 8463 2. 537.859		1. 8468 2. 579.876
	1. 8464 2. 546.877		1. 8469 2. 536.831
	1. 8465 2. 559.921		1. 8470 2. 568.843

TABLE 85

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1.8501 2. 367.2		1. 8506 2. 443.1
	1. 8502 2. 381.2		1. 8507 2. 323.1
	1. 8503 2. 443.2		1. 8508 2. 365.2
	1. 8504 2. 457.3		1. 8509 2. 379.21
			1. 8510 2. 381.21

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8511 2. 381.21		1. 8516 2. 409.22
	1. 8512 2. 393.22		1. 8517 2. 411.23
	1. 8513 2. 395.22		1. 8518 2. 421.23
	1. 8514 2. 397.22		1. 8519 2. 421.23
	1. 8515 2. 407.22		1. 8520 2. 425.23

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8521 2. 429.24		1. 8526 2. 445.24
	1. 8522 2. 439.24		1. 8527 2 .444.24
	1. 8523 2. 443.24		1. 8528 2. 444.24
	1. 8524 2. 443.24		1. 8529 2. 446.25
	1. 8525 2. 445.24		1. 8530 2. 457.25

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8531 2. 480.26		1. 8536 2. 431.24
	1. 8532 2. 483.27	 Chiral	1. 8537 2. 429.24
	1. 8533 2. 483.27	 Chiral	1. 8538 2. 397.22
			1. 8539 2. 411.23
			1. 8540 2. 411.23

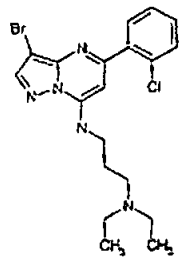
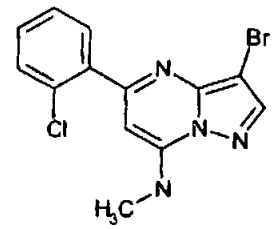
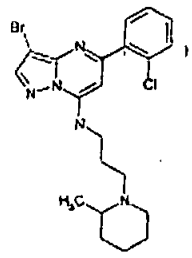
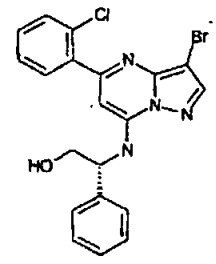
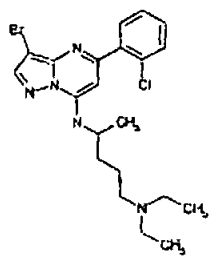
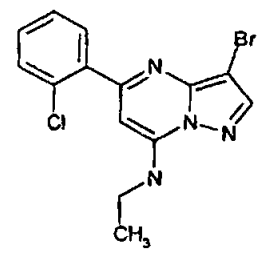
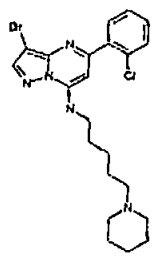
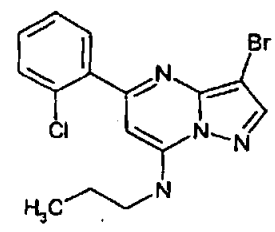
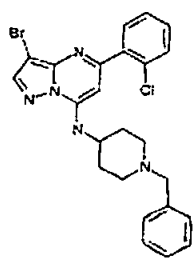
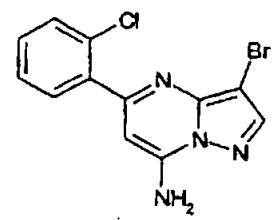
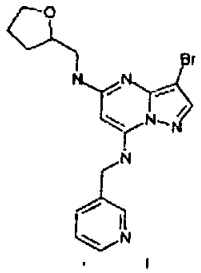
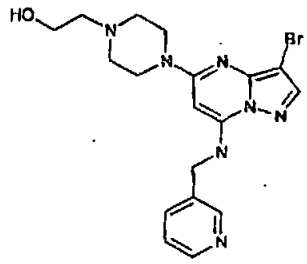
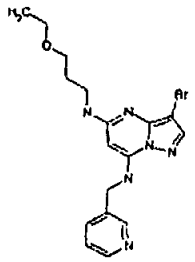
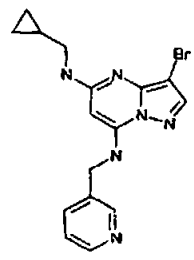
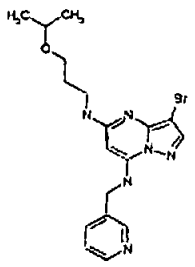
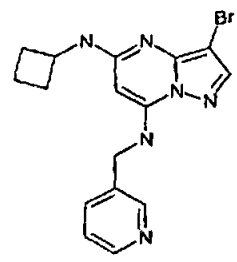
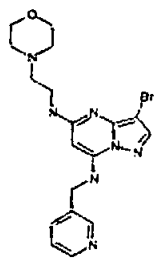
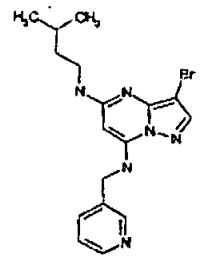
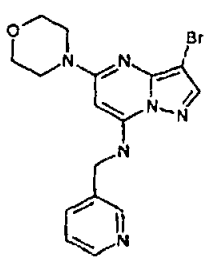
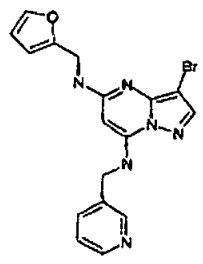
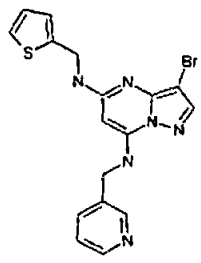
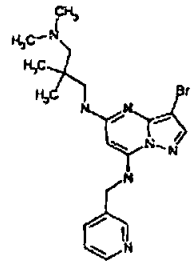
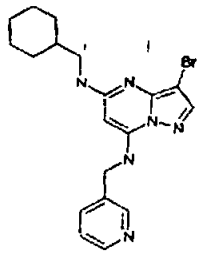
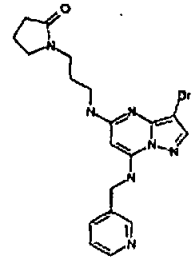
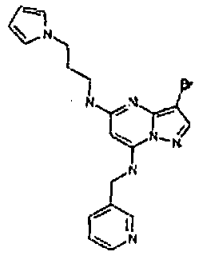
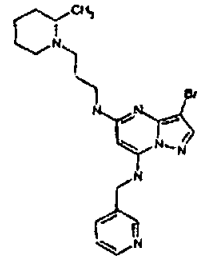
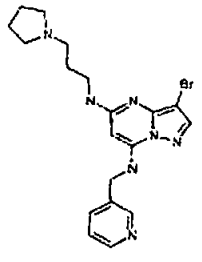
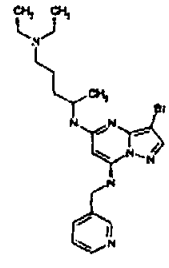
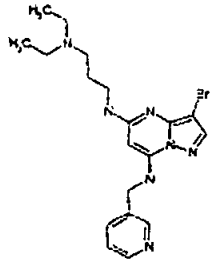
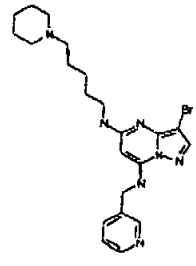
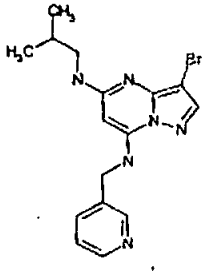
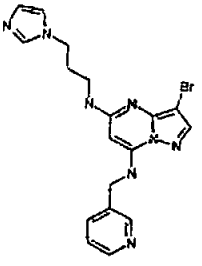
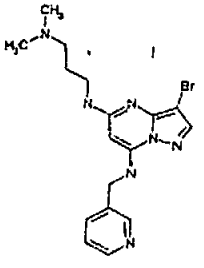
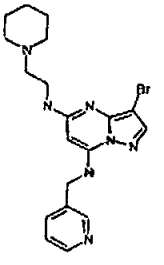
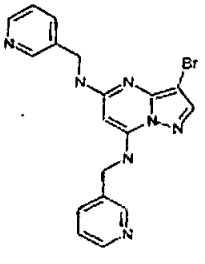
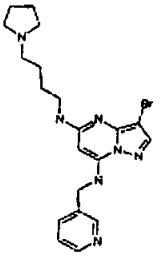
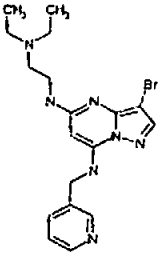
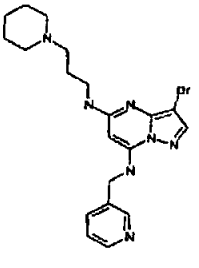
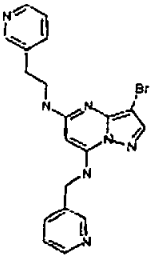
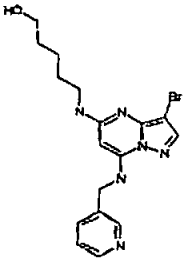
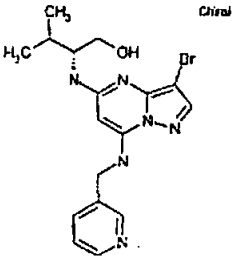
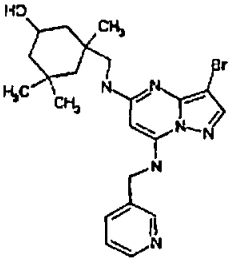
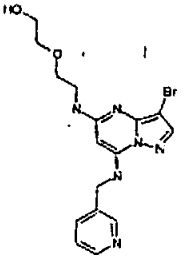
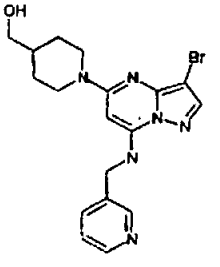
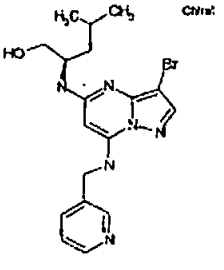
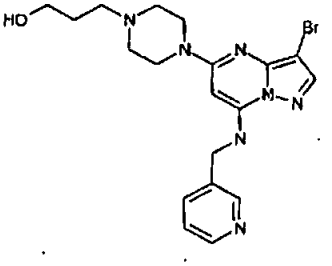
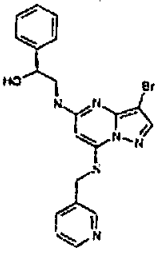
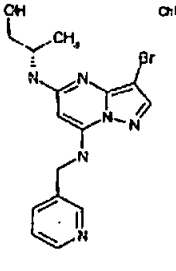
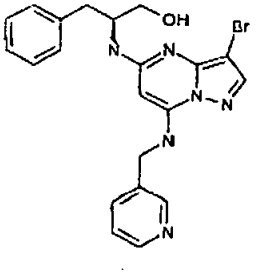
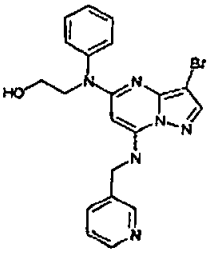
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8541 2. 432.24		1. 8547 2. 478.26
	1. 8542 2. 433.24		1. 8548 2. 498.27
	1. 8543 2. 438.24		1. 8549 2. 365.1
	1. 8545 2. 464.26		1. 8549 2. 337.1
	1. 8546 2. 466.26		1. 8550 2. 351.1

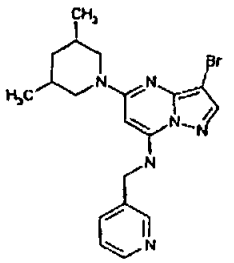
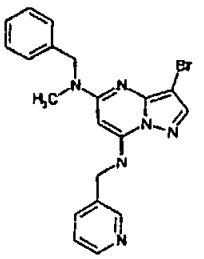
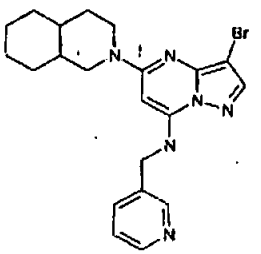
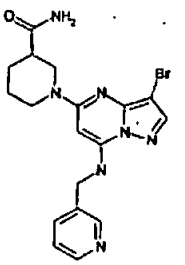
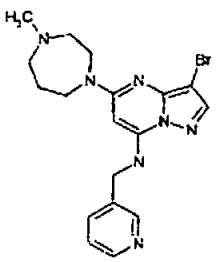
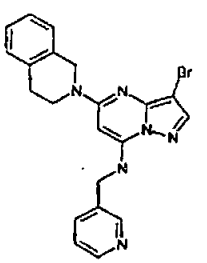
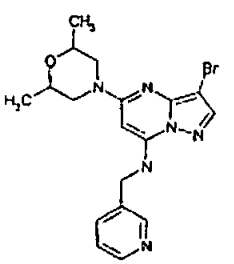
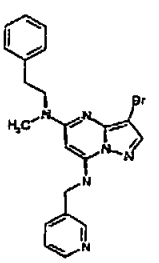
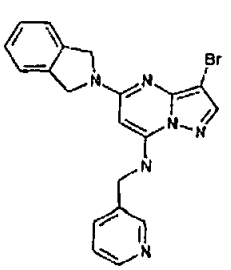
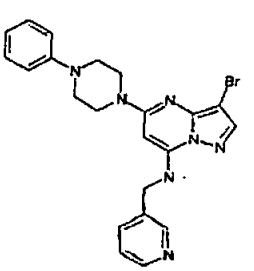
TABLE 86

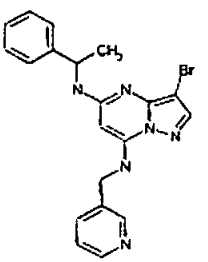
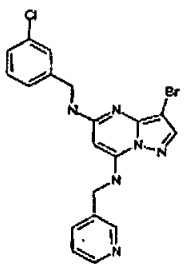
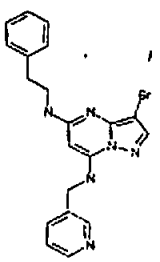
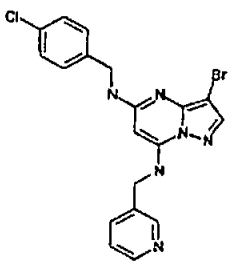
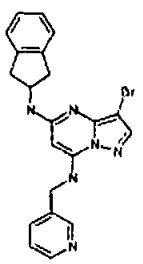
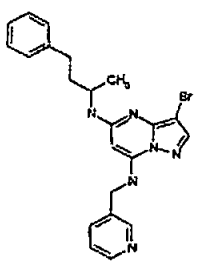
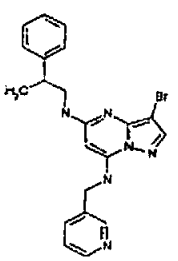
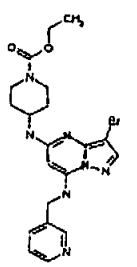
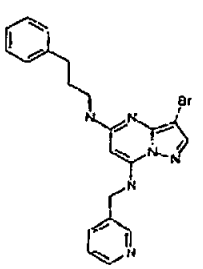
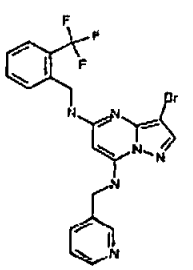
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8601 2. 403.22		1. 8606 2. 434.24
	1. 8602 2. 407.22		1. 8607 2. 375.21
	1. 8603 2. 421.23		1. 8608 2. 375.21
	1. 8604 2. 434.24		1. 8609 2. 391.22
	1. 8605 2. 391.22		1. 8610 2. 399.22

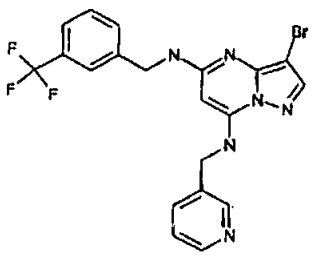
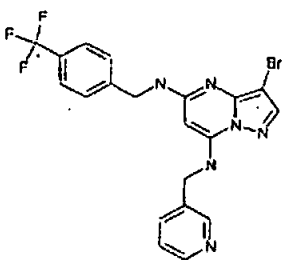
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8611 2. 417.23		1. 8616 2. 434.24
	1. 8612 2. 415.23		1. 8617 2. 446.25
	1. 8613 2. 428.24		1. 8618 2. 460.25
	1. 8614 2. 430.24		1. 8619 2. 459.25
	1. 8615 2. 434.24		1. 8620 2. 474.26

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8621 2. 377.21		1. 8626 2. 427.23
	1. 8622 2. 406.22		1. 8627 2. 431.24
	1. 8623 2. 412.23		1. 8628 2. 446.25
	1. 8624 2. 420.23		1. 8629 2. 446.25
	1. 8625 2. 426.23		1. 8630 2. 407.2

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8631 2. 407.2		1. 8636 2. 475.3
	1. 8632 2. 409.2		1. 8637 2. 419.2
	1. 8633 2. 421.2		1. 8638 2. 448.2
	1. 8634 2. 439.2		1. 8639 2. 379.2
	1. 8635 2. 455.3		1. 8640 2. 437.2

Product	1. Ex. 2. m/z	Product	1. Ex: 2. m/z
	1. 8641 2. 415.23		1. 8646 2. 423.23
	1. 8642 2. 443.24		1. 8647 2. 430.24
	1. 8643 2. 416.23		1. 8648 2. 437.24
	1. 8644 2. 417.23		1. 8649.2. 439.24
	1. 8645 2. 423.23		1. 8650 2. 466.26

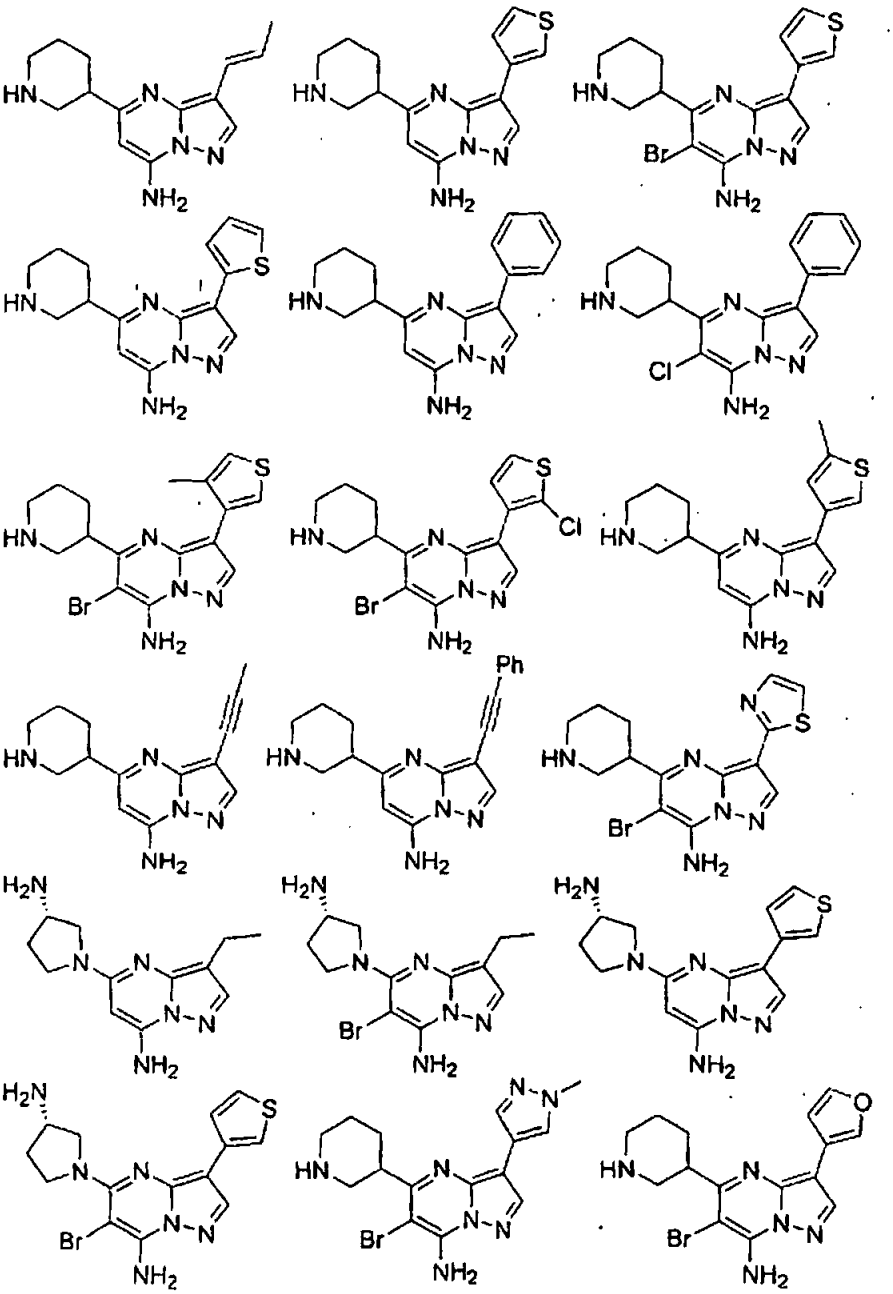
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8651 2. 423.23		1. 8656 2. 445.24
	1. 8652 2. 425.23		1. 8657 2. 445.24
	1. 8653 2. 437.24		1. 8658 2. 451.25
	1. 8654 2. 437.24		1. 8659 2. 476.26
	1. 8655 2. 437.24		1. 8660 2. 479.26

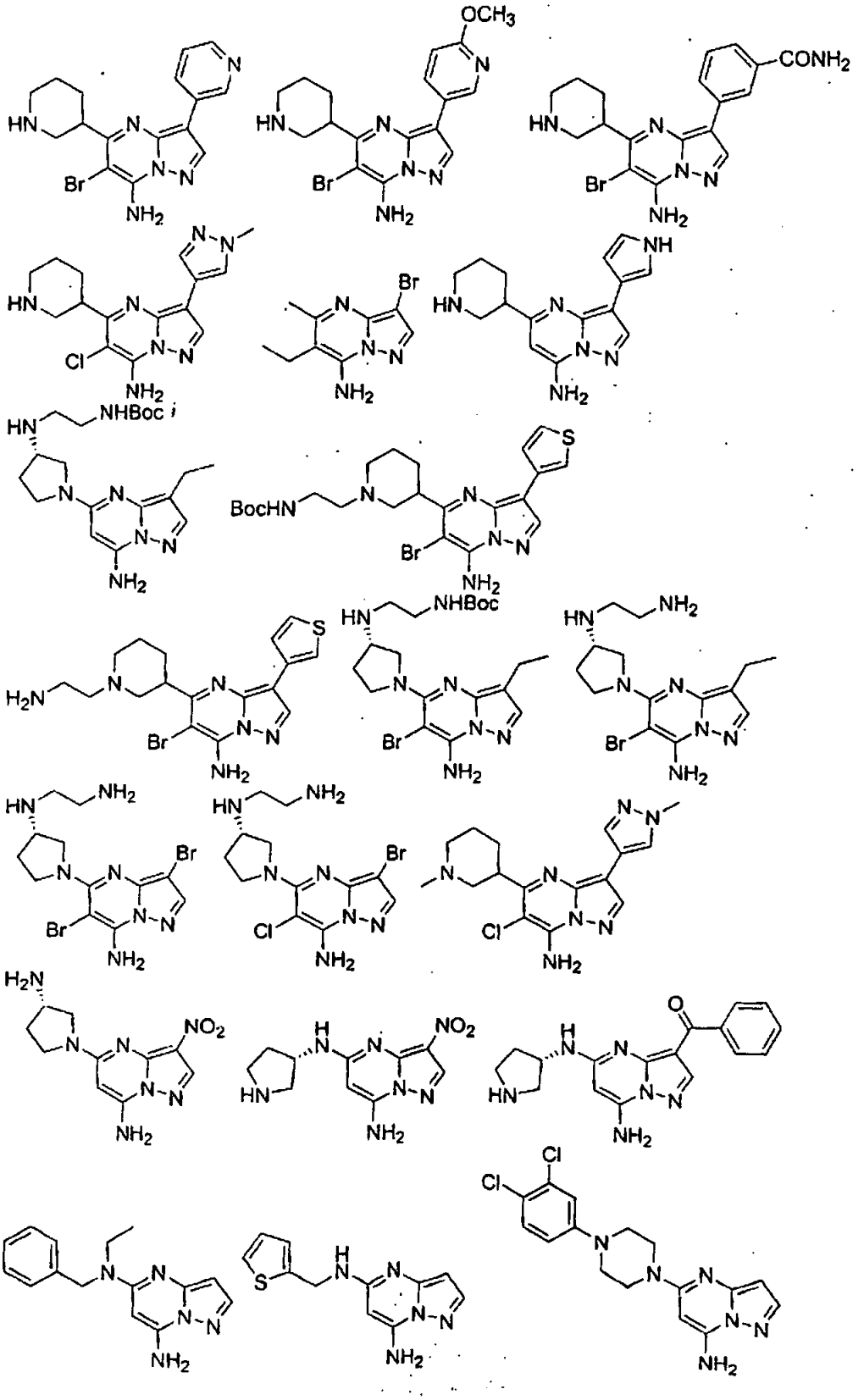
Product	1. Ex. 2. m/z
	1. 8661 2. 477.26
	1. 8662 2. 479.26

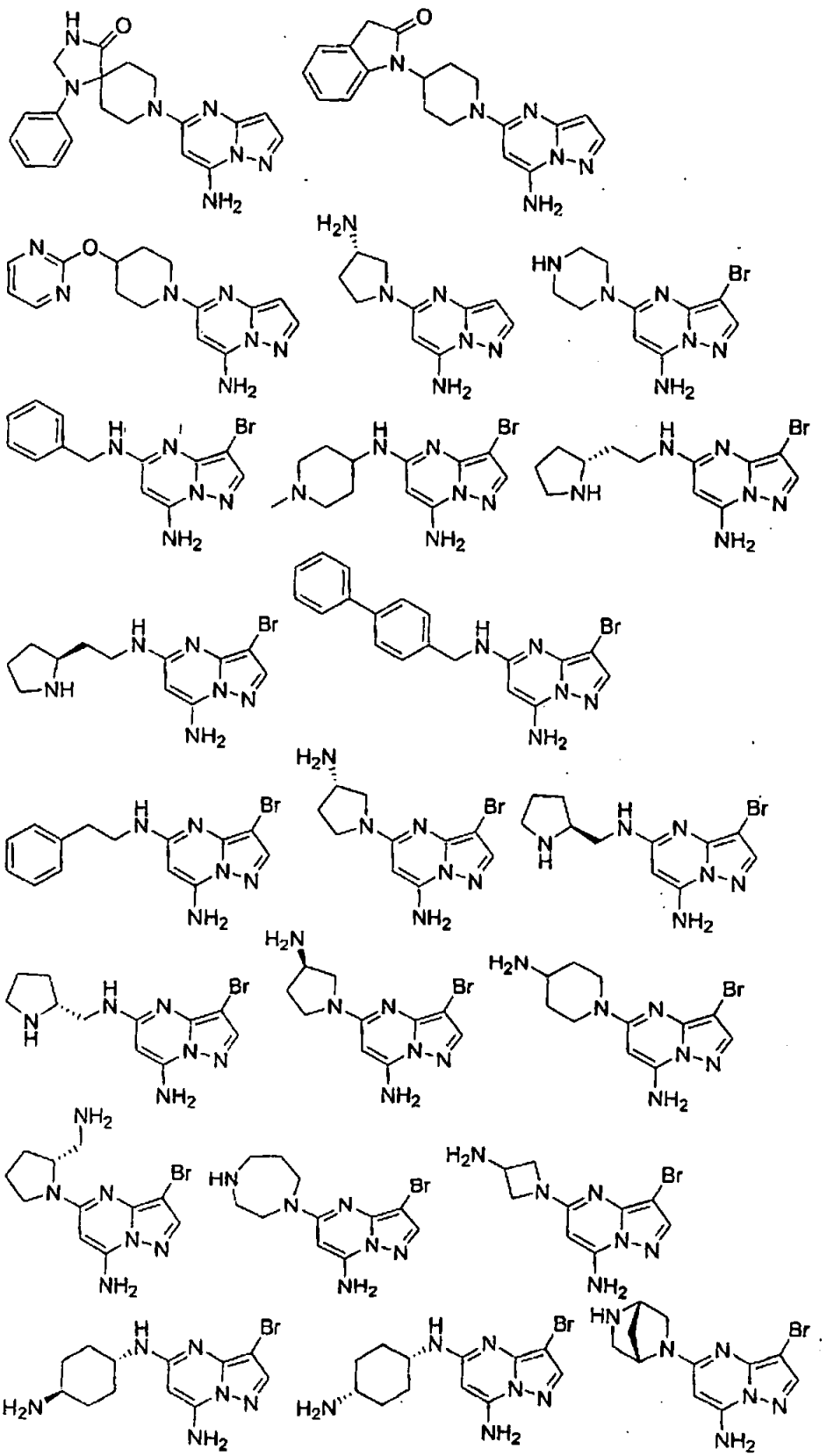
CLAIMS

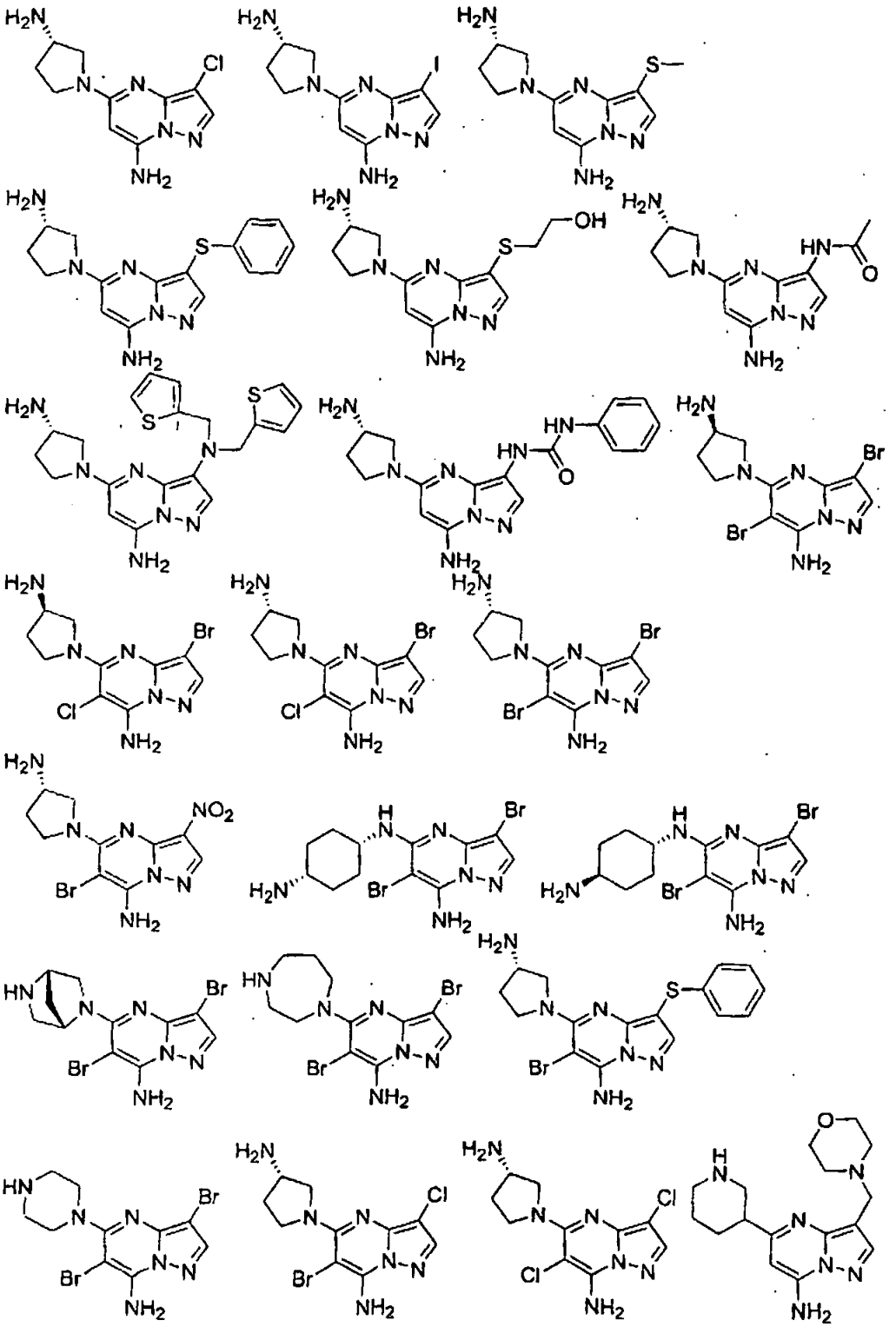
What is claimed is:

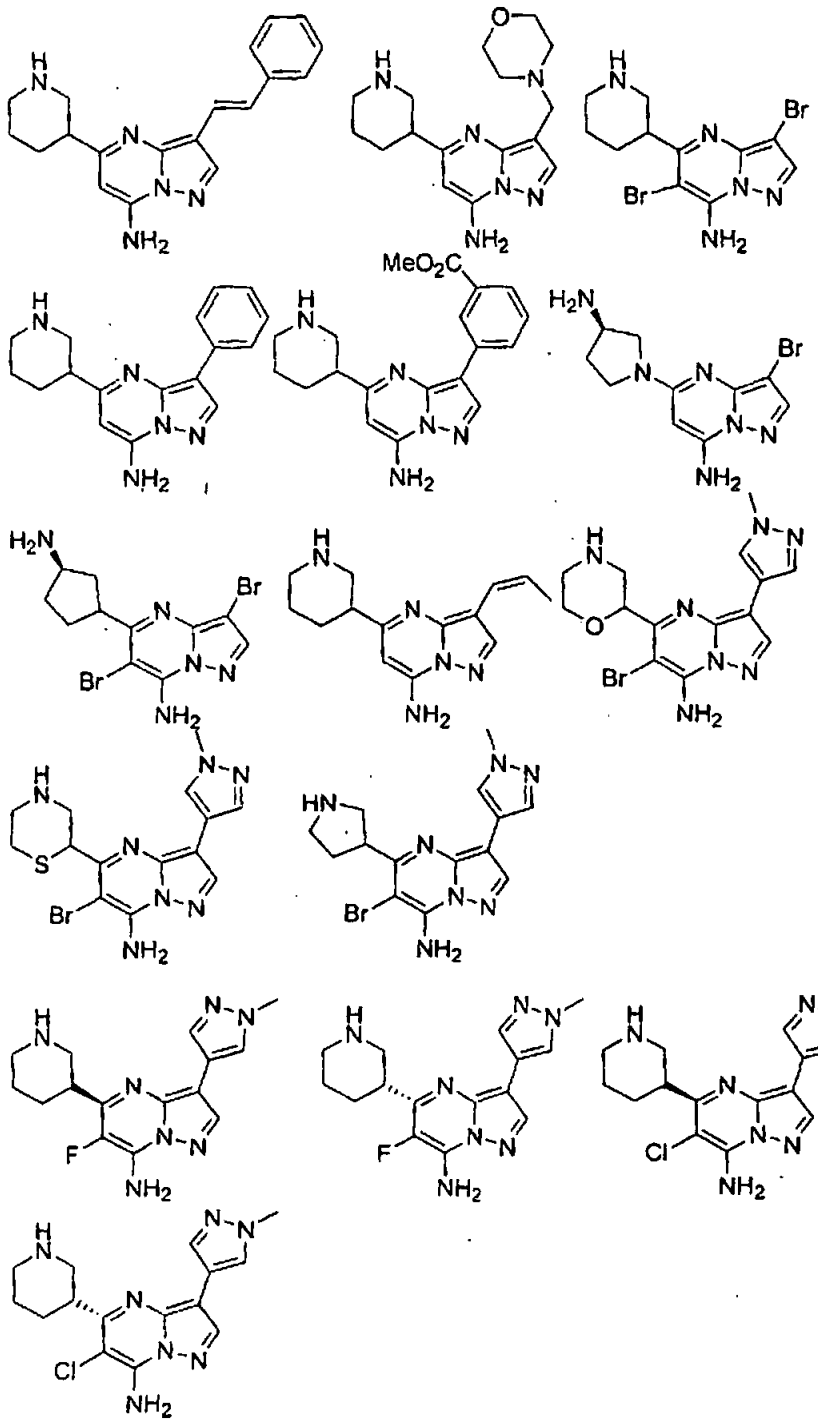
1. A compound selected from the group consisting of the compounds of the formula:











and

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

2. A method of inhibiting one or more cyclin dependent kinases in a patient, comprising administering a therapeutically effective amount of at least

one compound of claim 1, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, to said patient.

3. A method of treating one or more diseases associated with a kinase in a patient, comprising administering a therapeutically effective amount of at least one compound of claim 1, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, to said patient.

4. The method of claim 3, wherein said kinase is a cyclin dependent kinase.

5. The method of claim 4, wherein said cyclin dependent kinase is CDK1, CDK2 or CDK9.

6. The method of claim 5, wherein said kinase is CDK2.

7. The method of claim 3, wherein said kinase is mitogen activated protein kinase (MAPK/ERK).

8. The method of claim 3, wherein said kinase is glycogen synthase kinase 3 (GSK3beta).

9. The method of claim 3, wherein said disease is selected from the group consisting of:

cancer of the bladder, breast, colon, kidney, liver, lung, small cell lung cancer, non-small cell lung cancer, head and neck, esophagus, 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;

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

fibrosarcoma, rhabdomyosarcoma;

head and neck, mantle cell lymphoma, myeloma;

astrocytoma, neuroblastoma, glioma and schwannomas;

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

10. A method of treating one or more diseases associated with cyclin dependent kinase in a mammal, comprising administering to said mammal

an amount of a first compound, which is a compound of claim 1, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof; and

an amount of at least one second compound, said second compound being an anti-cancer agent;

wherein the amounts of the first compound and said second compound result in a therapeutic effect.

11. The method of claim 10, further comprising radiation therapy.

12. The method of claim 10, wherein said anti-cancer agent is selected from the group consisting of a cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, methoxtrexate, temozolomide, cyclophosphamide, SCH 66336, R115777, L778,123, BMS 214662, Iressa, Tarceva, antibodies to EGFR, Gleevec, Intron, ara-C, adriamycin, cytoxan, gemcitabine, Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, oxaliplatin, leucovirin, ELOXATIN™, Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17α-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrazole, Letrazole, Capecitabine, Reloxafine, Droloxafine, Hexamethylmelamine, Avastin, herceptin, Bexxar, Velcade, Zevalin, Trisenox, Xeloda, Vinorelbine,

Porfimer, Erbitux, Liposomal, Thiotepa, Altretamine, Melphalan, Trastuzumab, Lerozole, Fulvestrant, Exemestane, Fulvestrant, Ifosfomide, Rituximab, C225, and Campath.

13. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of claim 1, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, in combination with at least one pharmaceutically acceptable carrier.

14. The pharmaceutical composition of claim 13, additionally comprising one or more anti-cancer agents selected from the group consisting of a cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, methoxtrexate, temozolomide, cyclophosphamide, SCH 66336, R115777, L778,123, BMS 214662, Iressa, Tarceva, antibodies to EGFR, Gleevec, intron, ara-C, adriamycin, cytoxan, gemcitabine, Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, oxaliplatin, leucovirin, ELOXATIN™, Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin, Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17α-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrazole, Letrazole, Capecitabine, Reloxafine, Droloxafine, Hexamethylmelamine, Avastin, herceptin, Bexxar, Velcade, Zevalin, Trisenox, Xeloda, Vinorelbine, Porfimer, Erbitux, Liposomal, Thiotepa, Altretamine, Melphalan, Trastuzumab, Lerozole, Fulvestrant, Exemestane, Fulvestrant, Ifosfomide, Rituximab, C225, and Campath.

15. A method of inhibiting one or more cyclin dependent kinases in a patient, comprising administering a therapeutically effective amount of the pharmaceutical composition of claim 13 to said patient.

16. A method of treating one or more diseases associated with cyclin dependent kinase, comprising administering to a mammal in need of such treatment

an amount of a first compound, which is a compound of claim 1 or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof; and

an amount of temozolomide;

wherein the amounts of the first compound and said temozolomide result in a therapeutic effect.

17. The method of claim 16, further comprising radiation therapy.

18. A pharmaceutical composition comprising (i) a therapeutically effective amount of a compound of claim 1 or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, and (ii) temozolomide.

19. A method of inhibiting one or more kinases, comprising administering the pharmaceutical composition of claim 18.

20. The method of claim 19 wherein said kinase is a cyclin dependent kinase.

21. A method of treating one or more diseases associated with a kinase, comprising administering the pharmaceutical composition of claim 18.

22. A method of treating a cancer, comprising administering the pharmaceutical composition of claim 18.

23. A method of treating a cancer, comprising administering a therapeutically effective amount of at least one compound of claim 1.

24. The method of claim 23, wherein said cancer is selected from the group consisting of:

cancer of the bladder, breast, colon, kidney, liver, lung, small cell lung cancer, non-small cell lung cancer, head and neck, esophagus, 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;

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

fibrosarcoma, rhabdomyosarcoma;

head and neck, mantle cell lymphoma, myeloma;

astrocytoma, neuroblastoma, glioma and schwannomas;

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

25. A method of treating a cancer, comprising administering to a mammal in need of such treatment

an amount of a first compound, which is a compound of claim 1, or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof; and

an amount of at least one second compound, said second compound being an anti-cancer agent;

wherein the amounts of the first compound and said second compound result in a therapeutic effect.

26. The method of claim 25, further comprising radiation therapy.

27. The method of claim 25, wherein said anti-cancer agent is selected from the group consisting of a cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, methoxtrexate, temozolomide, cyclophosphamide, SCH 66336, R115777, L778,123, BMS 214662, Iressa, Tarceva, antibodies to EGFR, Gleevec, intron, ara-C, adriamycin, cytoxan, gemcitabine, Uracil mustard, Chlormethine, Ifosfamide, Melphalan, Chlorambucil, Pipobroman, Triethylenemelamine, Triethylenethiophosphoramine, Busulfan, Carmustine, Lomustine, Streptozocin, Dacarbazine, Floxuridine, Cytarabine, 6-Mercaptopurine, 6-Thioguanine, Fludarabine phosphate, oxaliplatin, leucovirin, ELOXATIN™, Pentostatine, Vinblastine, Vincristine, Vindesine, Bleomycin, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mithramycin,

Deoxycoformycin, Mitomycin-C, L-Asparaginase, Teniposide 17α-Ethinylestradiol, Diethylstilbestrol, Testosterone, Prednisone, Fluoxymesterone, Dromostanolone propionate, Testolactone, Megestrolacetate, Methylprednisolone, Methyltestosterone, Prednisolone, Triamcinolone, Chlorotrianisene, Hydroxyprogesterone, Aminoglutethimide, Estramustine, Medroxyprogesteroneacetate, Leuprolide, Flutamide, Toremifene, goserelin, Cisplatin, Carboplatin, Hydroxyurea, Amsacrine, Procarbazine, Mitotane, Mitoxantrone, Levamisole, Navelbene, Anastrazole, Letrazole, Capecitabine, Reloxafine, Droloxafine, Hexamethylmelamine, Avastin, herceptin, Bexxar, Velcade, Zevalin, Trisenox, Xeloda, Vinorelbine, Porfimer, Erbitux, Liposomal, Thiotepa, Altretamine, Melphalan, Trastuzumab, Lerozole, Fulvestrant, Exemestane, Fulvestrant, Ifosfomide, Rituximab, C225, and Campath.

28. A method of treating a cancer, comprising administering (i) a therapeutically effective amount of at least one compound of claim 1 or a pharmaceutically acceptable salt, solvate, ester or prodrug thereof, and (ii) temozolomide.

NUEVAS PIRAZOLOPIRIMIDINAS COMO INHIBIDORES DE QUINASA DEPENDIENTES DE CICLINA

Referencia a Solicitudes Relacionadas

Esta solicitud es una continuación en parte de la solicitud de patente Norteamericana, Acta Nº 10/776.988, presentada el 11 de febrero de 2004 (que fue publicada como US2004/0209878 el 21 de octubre de 2004), que es una continuación en parte de la solicitud de patente Norteamericana Acta Nº 10/654.546 presentada el 3 de septiembre de 2003, que reivindica prioridad de las solicitudes de patentes Norteamericanas provisionales Actas Nº 60/408.027 presentada el 4 de septiembre de 2002 y de la 60/421.959 presentada el 29 de octubre de 2002.

Campo de la invención

La presente invención se refiere a compuestos pirazolo[1,5-a]pirimidina útiles como inhibidores de proteinquinasas (tales como por ejemplo los inhibidores de las quinasas dependientes de ciclina, proteinquinasas activadas por mitógeno (MAPK/ERK), glicógenos sintasa quinasa 3(GSK3beta) y similares), composiciones farmacéuticas que contienen los compuestos, y métodos de tratamiento en los que se usan los compuestos y composiciones para tratar enfermedades tales como, por ejemplo, cáncer, inflamación, artritis, enfermedades virales, enfermedades neurodegenerativas tales como enfermedad de Alzheimer, enfermedades cardiovasculares y enfermedades fúngicas. Esta solicitud reivindica el beneficio de la prioridad de las solicitudes de patentes provisionales Norteamericanas Acta Nº 60/408.027 presentadas el 4 de septiembre de 2002 y Acta Nº 60/421.959 presentada el 29 de octubre de 2002.

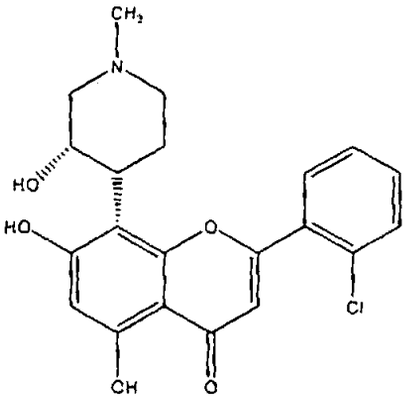
215.132

Antecedentes de la Invención

Los inhibidores de proteinquinasa incluyen quinasas tales como, por ejemplo, los inhibidores de las quinasas dependientes de ciclina (CDKs), proteinquinasas activadas por mitógeno (MAPK/ERK), glicógeno sintasa quinasa 3 (GSK3beta), y similares. Los inhibidores de proteinquinasas han sido descritos, por

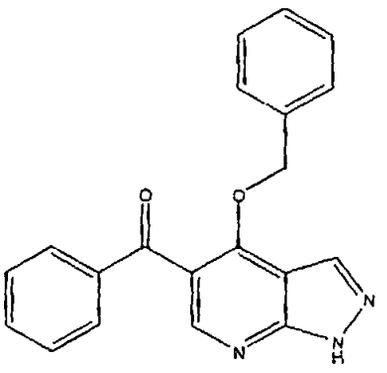
ejemplo, por M. Hale *et* al en WO02/22610 A1 y por Y. Mettey *et* al en *J. Med. Chem.*, (2003) 46 222-236. Las quinasas dependientes de ciclina son proteinquinasas de serina/treonina, que son la fuerza impulsora de la proliferación de células y del ciclo celular. Las CDK's individuales, tales como, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6 y CDK7, CDK8, CDK9 y similares, desempeñan distintas funciones en el progreso del ciclo celular y pueden clasificarse como enzimas de fase G1, S, o G2M. La proliferación descontrolada es una característica de las células cancerosas, y la mala regulación de la función CDK ocurre con alta frecuencia en muchos tumores sólidos importantes. La CDK2 y CDK4 son particularmente interesantes debido a que sus actividades están frecuentemente mal reguladas en una amplia variedad de cánceres humanos. La actividad de la CDK2 es necesaria para progresar a través de la fase G1 a la fase S del ciclo celular, y la CDK2 es uno de los componentes principales del checkpoint (punto de control) G1. Los checkpoints sirven para mantener la secuencia de eventos del ciclo celular apropiada y para permitir que la célula responda a las agresiones o a las señales proliferativas, mientras que la pérdida de control del checkpoint apropiado en las células cancerosas contribuye a la oncogenia. La vía de CDK2 influencia la oncogenia a nivel de la función supresora de tumores (por ejemplo, p52, RB, y p27), y la activación oncogénica (ciclina E). Muchos informes han demostrado que tanto el coactivador, la ciclina E, como el inhibidor, p27, de CDK2 están híper o bien subexpresados, respectivamente, en cáncer de mama, colon, cáncer pulmonar de células no pequeñas, gástrico, de próstata, de vesícula, linfoma no Hodgkins, de ovario y otros cánceres. Se ha demostrado que su expresión alterada está correlacionada con un aumento de los niveles de actividad de la CDK2 y con una baja supervivencia general. Esta observación convierte a la CDK2 y sus vías reguladoras en objetivos obligatorios para los años venideros, una cantidad de pequeñas moléculas orgánicas competitivas de 5'-trifosfato de adenosina (ATP) así como también péptidos han sido mencionados en la literatura como inhibidores de CDK para el tratamiento potencial de cánceres. Patente Norteamericana 6.413.974, col. 1, línea 23- col. 15, línea 10 ofrece una buena descripción de las varias CDKs y su relación con varios tipos de cáncer.

Los inhibidores de CDK son conocidos. Por ejemplo, flavopiridol (Fórmula I) es un inhibidor de CDK no selectivo que está actualmente sometido a pruebas clínicas en humanos, A. M. Sanderowicz *et al*, *J. Clin. Oncol.* (1998) 16, 2986-2999.



Fórmula I

Otros inhibidores conocidos de las CDKs incluyen, por ejemplo, olomoucina (J. Vesely *et al*, *Eur. J. Biochem.*, (1994) 224, 771-786) y roscovitina (I. Meijer *et al*, *Eur. J. Biochem.*, (1997) 243, 527-536). La U.S. 6.107.305 describe ciertos compuestos pirazolo[3,4-b] piridina como inhibidores de CDK. Un compuesto ilustrativo de la patente '305 tiene la Fórmula II:



Fórmula II

K. S. Kim *et al*, *J. Med. Chem.* 45 (2002) 3905-3927 y WO 02/10162 describen ciertos compuestos aminotiazol como inhibidores de CDK.

Las pirazolopirimidinas son conocidas. Por ejemplo, WO92/18504, WO02/50079, WO95/35298, WO02/40485, EP94304104.6, EP0628559 (equivalente a las Patentes Norteamericanas 5.602.136, 5.602.137 y 5.571.813),

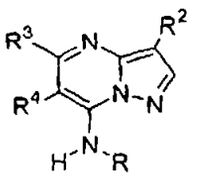
U.S. 6.383.790, *Chem. Farm. Bull.*, (1999) 47 928, *J. Med. Chem.*, (1977) 20, 296, *J. Med. Chem.*, (1976) 19 517 and *Chem. Farm. Bull., (1962)* 10 620 describen varias pirazolopirimidinas. Otras publicaciones de interés son: WO 03/101993 (publicada el 11 de diciembre de 2003), WO 03/091256 (publicada el 6 de noviembre de 2003), y DE 10223917 (publicada el 11 de diciembre de 2003).

Existe una necesidad de nuevos compuestos, formulaciones, tratamientos y terapias para tratar enfermedades y desórdenes asociados con CDKs. Por lo tanto, es un objeto de esta invención proveer compuestos útiles en el tratamiento o prevención o mejoramiento de dichas enfermedades y desórdenes.

Compendio de la Invención

En sus muchas realizaciones, la presente invención provee una nueva clase de compuestos pirazolo[1,5-a]pirimidina como inhibidores de las quinasas dependientes de ciclina, métodos de preparación de dichos compuestos, composiciones farmacéuticas que comprenden uno o más de dichos compuestos, métodos de preparación de formulaciones farmacéuticas que comprenden uno o más de dichos compuestos, y métodos de tratamiento, prevención, inhibición o mejoramiento de una o más enfermedades asociadas con las CDKs usando dichos compuestos o composiciones farmacéuticas.

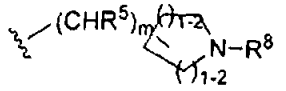
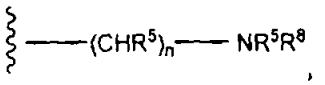
En un aspecto, la presente solicitud describe un compuesto, o sales o solvatos de dicho compuesto farmacéuticamente aceptables, donde dicho compuesto tiene la estructura general que se muestra en la Fórmula III:

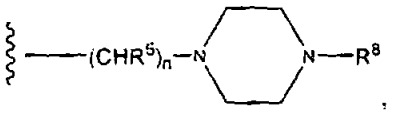
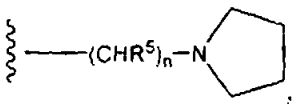
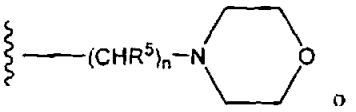


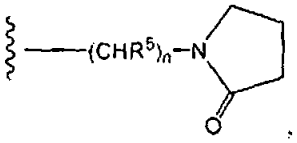
Fórmula III

en la cual:

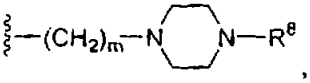
R es H, alquilo, alquenilo, alquinilo, arilalquilo, arilalquenilo, cicloalquilo, cicloalquilalquilo, alquenilalquilo, alquinilalquilo, heterociclilo, heterociclilalquilo, heteroarilalquilo (incluyendo N-óxido de dicho heteroarilo), $-(CHR^5)_n$-arilo,

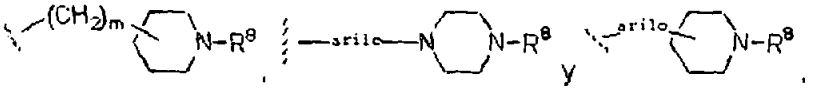
-$(CHR^5)_n$-heteroarilo,  



donde cada uno de dichos alquilo, alquenilo, alquinilo, arilo, cicloalquilo, heterociclilo, y heteroarilo pueden estar no sustituidos u opcionalmente sustituidos con una o más porciones que pueden ser iguales o diferentes, donde cada porción está independientemente seleccionada del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, heterociclilalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^{10}$, $-C(R^4R^5)_p-R^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^{10}$, $-SO_3H$, $-SR^{10}$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^{10}$;

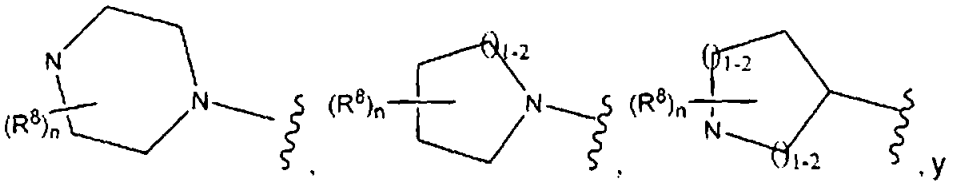
R^2 está seleccionado del grupo que consiste H, R^9, alquilo, alquenilo, alquinilo, CF_3, heterociclilo, heterociclilalquilo, halógeno, haloalquilo, arilo, arilalquilo, heteroarilalquilo, alquinilalquilo, cicloalquilo, heteroarilo, alquilo sustituido con 1-6 grupos R^9 que pueden ser iguales o diferentes y que están independientemente seleccionados de la lista de R^9 que se muestra a continuación, arilo sustituido con 1-3 grupos arilo o heteroarilo que pueden ser iguales o diferentes y que están independientemente seleccionados de grupos fenilo, piridilo, tiofenilo, furanilo y tiazolo, arilo fusionado con un grupo arilo o heteroarilo, heteroarilo sustituido con 1-3 grupos arilo o heteroarilo que pueden ser iguales o diferentes y que están independientemente seleccionados de grupos fenilo, piridilo, tiofenilo, furanilo y tiazolo, heteroarilo fusionado con un grupo arilo o heteroarilo, 



6282

donde uno o más del arilo y/o uno o más del heteroarilo en las definiciones previamente mencionadas para R^2 puede estar no sustituido u opcionalmente sustituido con una o más porciones que pueden ser iguales o diferentes, donde cada porción está independientemente seleccionada del grupo que consiste en halógeno, -CN, $-OR^5$, $-SR^5$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-NR^5R^6$, $-C(O)NR^5R^6$, CF_3, alquilo, arilo y OCF_3;

R^3 está seleccionado del grupo que consiste en H, halógeno, $-NR^5R^6$, $-OR^6$, $-SR^6$, $-C(O)N(R^5R^6)$, alquilo, alquinilo, cicloalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heteroarilo y heteroarilalquilo,



donde cada uno de dichos alquilo, cicloalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heteroarilo y heteroarilalquilo para R^3 y las porciones heterociclilo cuyas estructuras se muestran inmediatamente en lo que antecede para R^3, pueden estar no sustituidas u opcionalmente independientemente sustituidas con una o más porciones que pueden ser iguales o diferentes, donde cada porción está independientemente seleccionado del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-(CR^4R^5)_pOR^5$, $-OR^5$, $-NR^5R^6$, $-(CR^4R^5)_pNR^5R^6$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$, $-N(R^5)C(R^4R^5)_nN(R^5R^6)$ y $-N(R^5)C(O)NR^5R^6$, con la condición de que ningún carbón adyacente a un átomo de nitrógeno en un anillo heterociclilo sea portador de una porción – OR^5;

R^4 es H, halo o alquilo;

R^5 es H, alquilo, arilo, heteroarilo, arilalquilo o cicloalquilo;

688

R^6 está seleccionado del grupo que consiste en H, Boc, alquilo, alquenilo, arilo, arilalquilo, arilalquenilo, cicloalquilo, heterociclilo, heterociclilalquilo, heteroarilo, y heteroarilalquilo, donde cada uno de dichos alquilo, arilo, arilalquilo, cicloalquilo, heterociclilo, heterociclilalquilo, heteroarilo, y heteroarilalquilo pueden estar no sustituidos u opcionalmente sustituidos con una o más porciones que pueden ser iguales o diferentes, donde cada porción está independientemente seleccionadas del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, heterociclilalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^{10}$, $-C(R^4R^5)_p-R^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^{10}$, $-SO_3H$, $-SR^{10}$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^{10}$;

R^{10} está seleccionado del grupo que consiste en H, alquilo, arilo, arilalquilo, cicloalquilo, heterociclilo, heterociclilalquilo, heteroarilo, y heteroarilalquilo, donde cada uno de dichos alquilo, arilo, arilalquilo, cicloalquilo, heterociclilo, heterociclilalquilo, heteroarilo, y heteroarilalquilo pueden estar no sustituidos u opcionalmente sustituidos con una o más porciones que pueden ser iguales o diferentes, donde cada porción está independientemente seleccionada del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, heterociclilalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^4R^5$, $-C(R^4R^5)_p-R^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)NR^4R^5$, $-C(O)R^5$, $-SO_3H$, $-SR^5$, $-S(O_2)R^7$, $-S(O_2)NR^4R^5$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^4R^5$;

u opcionalmente (i) R^5 y R^{10} en la porción $-NR^5R^{10}$, o (ii) R^5 y R^6 en la porción $-NR^5R^6$, pueden estar unidos conjuntamente para formar una porción cicloalquilo o heterociclilo, donde cada porción cicloalquilo o heterociclilo está no sustituida o está independientemente opcionalmente sustituida con uno o más grupos R^9;

R^7 está seleccionado del grupo que consiste en alquilo, cicloalquilo, arilo, arilalquenilo, heteroarilo, arilalquilo, heteroarilalquilo, heteroarilalquenilo, y heterociclilo, donde cada uno de dichos alquilo, cicloalquilo, heteroarilalquilo, arilo, heteroarilo y arilalquilo pueden estar no sustituidos u opcionalmente independientemente sustituidos con una o más porciones que pueden ser iguales o diferentes, donde cada porción está independientemente seleccionada del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$,

$-NR^5R^{10}$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^{10}$, $-C(O)R^5$, $-SR^{10}$, $-S(O_2)R^{10}$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^{10}$, $-N(R^5)C(O)R^{10}$ y $-N(R^5)C(O)NR^5R^{10}$;

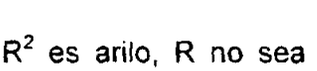
R^8 está seleccionado del grupo que consiste en R^6, $-OR^6$, $-C(O)NR^5R^{10}$, $-S(O_2)NR^5R^{10}$, $-C(O)R^7$, $-C(=N-CN)-NH_2$, $-C(=NH)-NHR^5$, heterociclilo, y $-S(O_2)R^7$;

R^9 está seleccionado del grupo que consiste en halógeno, $-CN$, $-NR^5R^{10}$, $-SCN$, $-NO_2$, $-C(O)R^5$, $-C(O_2)R^6$, $-C(O)NR^5R^{10}$, $-OR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$and $-N(R^5)C(O)NR^5R^{10}$;

m es 0 a 4;

n es 1 a 4; y

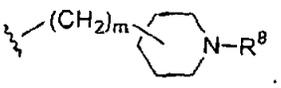
p es 1 a 4,

con la condición de que cuando R^2 es fenilo, R^3 no sea alquilo, alquinilo o halógeno, y que cuando R^2 es arilo, R no sea  , y como condición adicional de que cuando R es arilalquilo, entonces cualquier heteroarilo sustituyente en el arilo de dicho arilalquilo contiene por lo menos tres heteroátomos.

Los compuestos de Fórmula III pueden ser útiles como inhibidores de proteinquinasa y pueden ser útiles en el tratamiento y prevención de enfermedades proliferativas, por ejemplo, cáncer, inflamación y artritis. También pueden ser útiles en el tratamiento de enfermedades neurodegenerativas tales como la enfermedad de Alzheimer, enfermedades cardiovasculares, enfermedades virales y enfermedades fúngicas.

Descripción Detallada

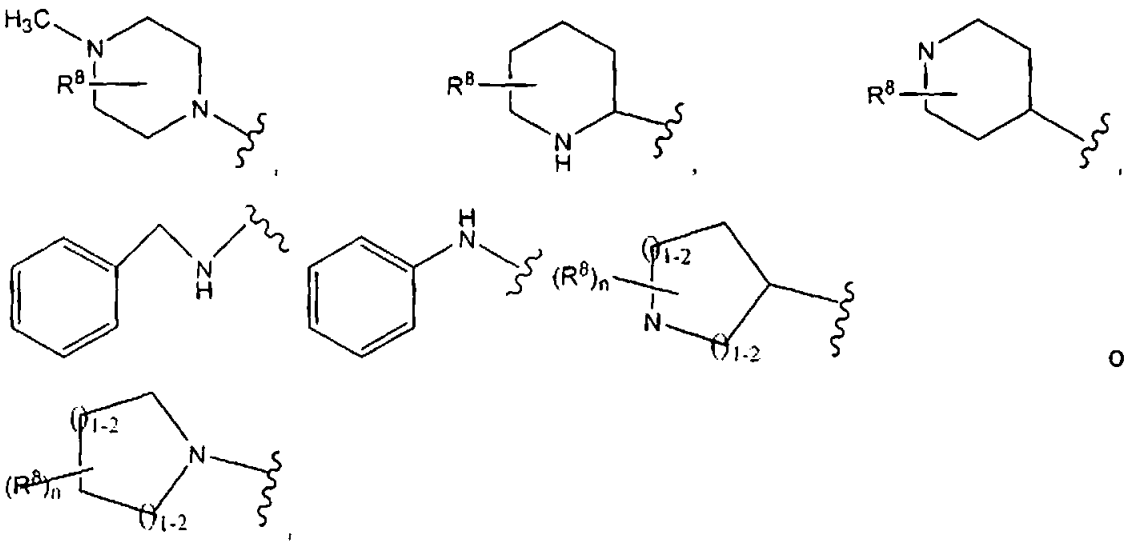
En una realización, la presente invención describe compuestos pirazolo[1,5-a]pirimidina que están representados por la Fórmula estructural III, o una sal o solvato de éstos farmacéuticamente aceptable donde varias porciones son tal como se han descrito anteriormente.

En otra realización, R es $-(CHR^5)_n$-arilo, $-(CHR^5)_n$-heteroarilo, $-(CHR^5)_n$-heteroarilo (con dicho heteroarilo sustituido con un heteroarilo adicional, igual o diferente), $-(CHR^5)_n$-heterociclilo (con dicho heterociclilo sustituido con un heterociclilo adicional, igual o diferente), o  .

690

En otra realización, R^2 es halógeno, CF_3, CN, alquilo inferior, alquilo sustituido con $-OR^6$, alquinilo, arilo, heteroarilo o heterociclilo.

En otra realización, R^3 es H, alquilo inferior, arilo, heteroarilo, cicloalquilo, $-NR^5R^6$,



donde dichos alquilo, arilo, heteroarilo, cicloalquilo y las estructuras heterociclilo que se muestran inmediatamente en lo que antecede para R^3, están opcionalmente sustituidas con una o más porciones que pueden ser iguales o diferentes, donde cada porción está independientemente seleccionado del grupo que consiste en halógeno, CF_3, OCF_3, alquilo inferior, CN, $-C(O)R^5$, $-S(O_2)R^5$, $-C(=NH)-NH_2$, $-C(=CN)-NH_2$, hidroxialquilo, alcoxicarbonilo, $-SR^5$, y OR^5, con la condición de que ningún carbono adyacente a un átomo de nitrógeno en un anillo heterociclilo sea portador de una porción $-OR^5$.

En otra realización, R^4 es H o alquilo inferior.

En otra realización, R^5 es H, alquilo inferior o cicloalquilo.

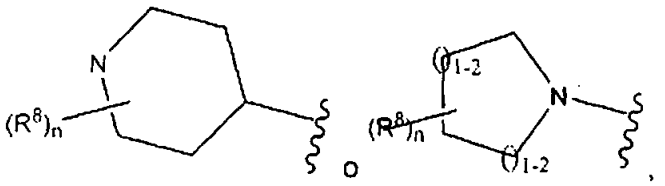
En otra realización, n es 1 a 2.

En una realización adicional, R es $-(CHR^5)_n$-arilo, $-(CHR^5)_n$-heteroarilo.

En una realización adicional, R^2 es halógeno, CF_3, CN, alquilo inferior, alquinilo, o alquilo sustituido con $-OR^6$.

En una realización adicional, R^2 es alquilo inferior, alquinilo o Br.

En una realización adicional, R^3 es H, alquilo inferior, arilo,



en las cuales dicho alquilo, arilo y las porciones heterociclilo que se muestran inmediatamente en lo que antecede para R^3 están opcionalmente sustituidas con una o más porciones que pueden ser iguales o diferentes, y cada porción está independientemente seleccionada del grupo que consiste en halógeno, CF_3, alquilo inferior, hidroxialquilo, alcoxi, $-S(O_2)R^5$, y CN.

En una realización adicional, R^4 es H.

En una realización adicional, R^5 es H, etilo, ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo.

En una realización adicional, R^6 es alquilo o hidroxialquilo.

En una realización adicional, n es 1.

En una realización adicional, p es 1 o 2.

En otra realización, R es H.

En otra realización, R^2 es halógeno.

En otra realización, R^2 es tiofeno, furano, piridina, pirazol, alquiltio o ariltio, donde cada uno de dichos alquilo y arilo de R^2 pueden estar independientemente no sustituidos o sustituidos tal como se definió anteriormente.

En otra realización, R^2 es tiofeno, furano, piridina o pirazol.

En otra realización, R^2 es una amida que puede estar no sustituida o sustituida tal como se definió anteriormente.

En otra realización, R^2 es una urea, que puede estar no sustituida o sustituida tal como se definió anteriormente.

En otra realización, R^2 es un alquenilo.

En otra realización, R^2 es un alquinilo.

En otra realización, R3 es $-NR^5R^6$.

En otra realización, R^4 es H.

En otra realización, R^4 es alquilo inferior no sustituido.

En otra realización, R^4 es alquilo sustituido con $-OR^6$.

En otra realización, R^4 es halo.

692

En otra realización, R^4 es -F, -Cl o -Br.

En otra realización, tanto R^2 como R^4 son halógeno.

En otra realización, tanto R^2 como R^4 son halo y R es H.

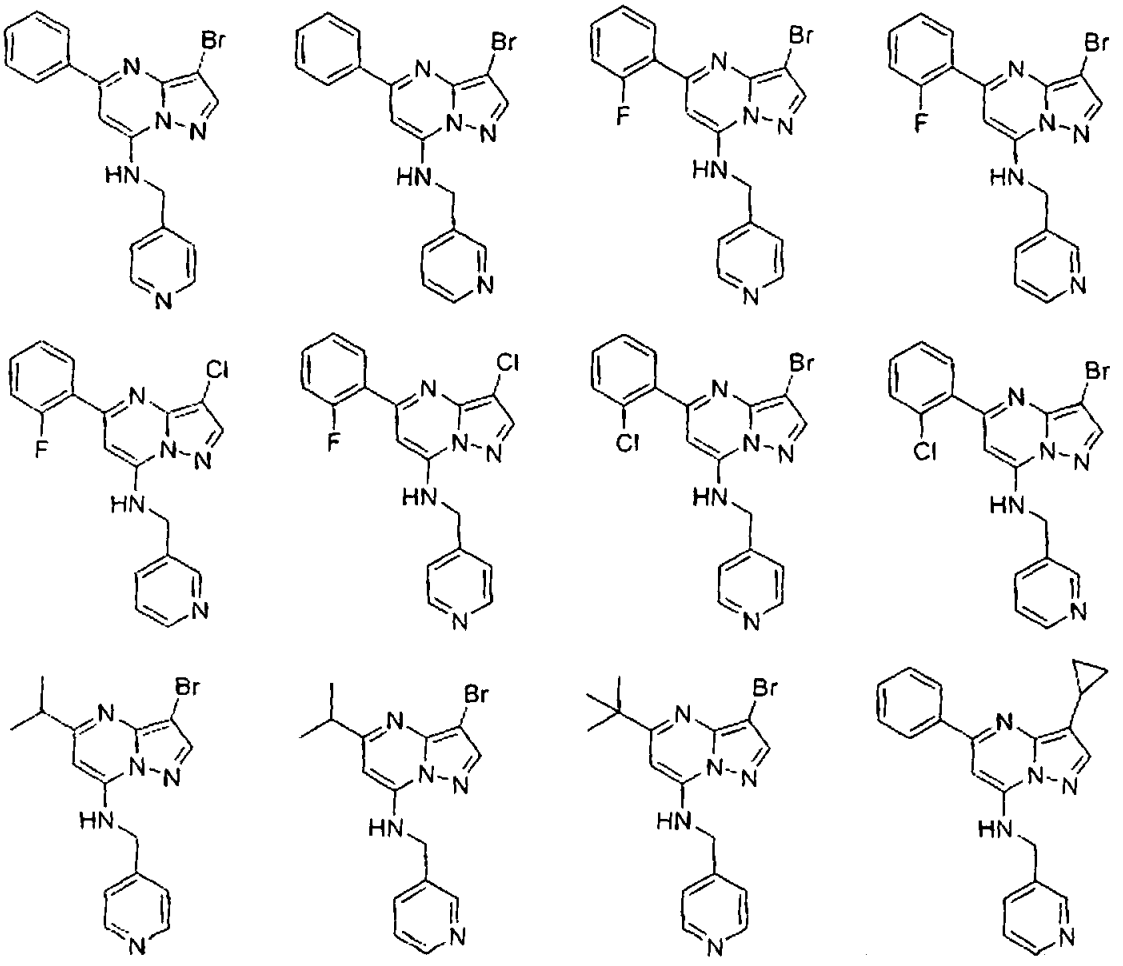
En otra realización, R es H, R^2 es halo y R^3 es heteroarilo.

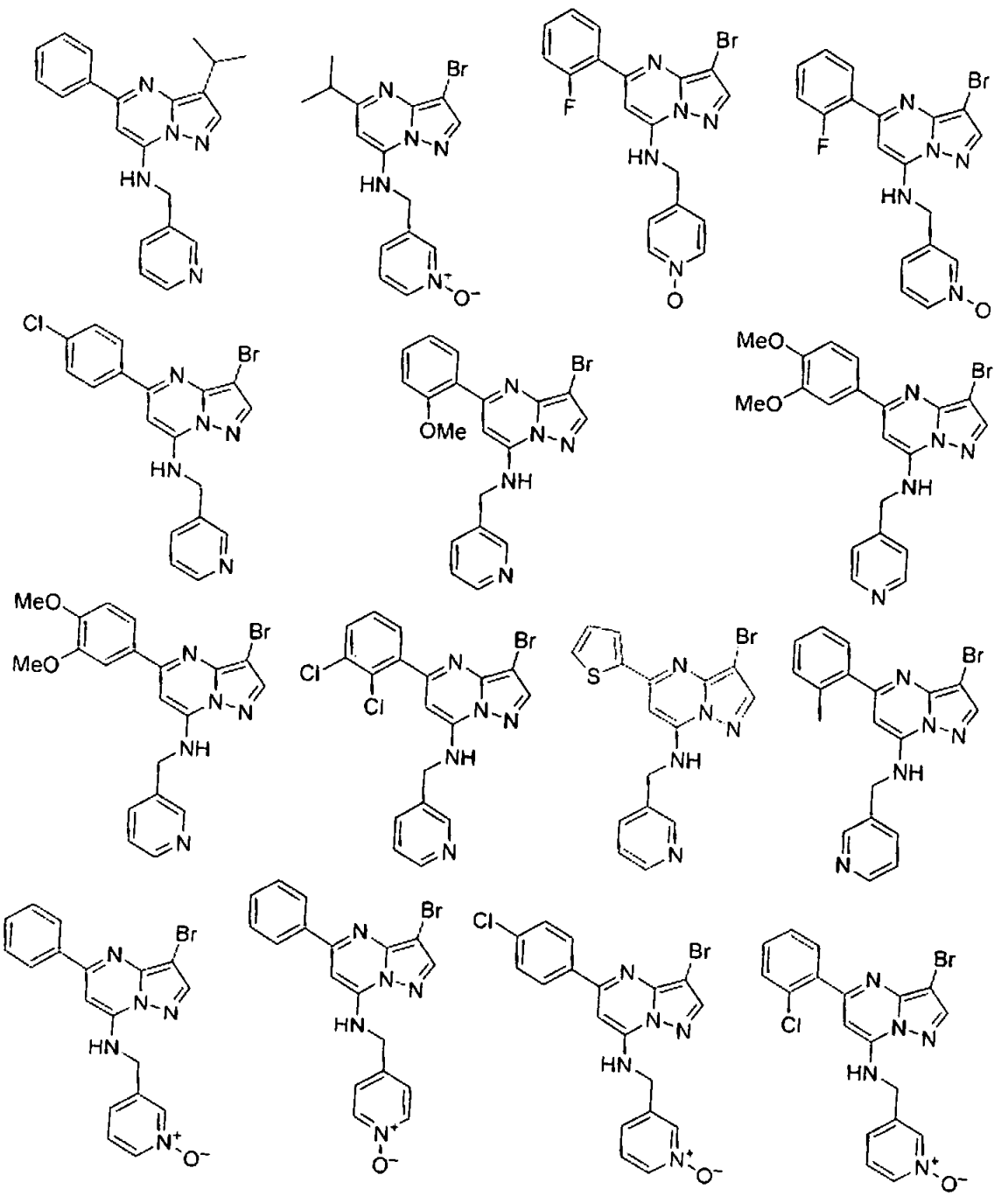
En otra realización, R es H, R^2 es halo y R^3 es arilo.

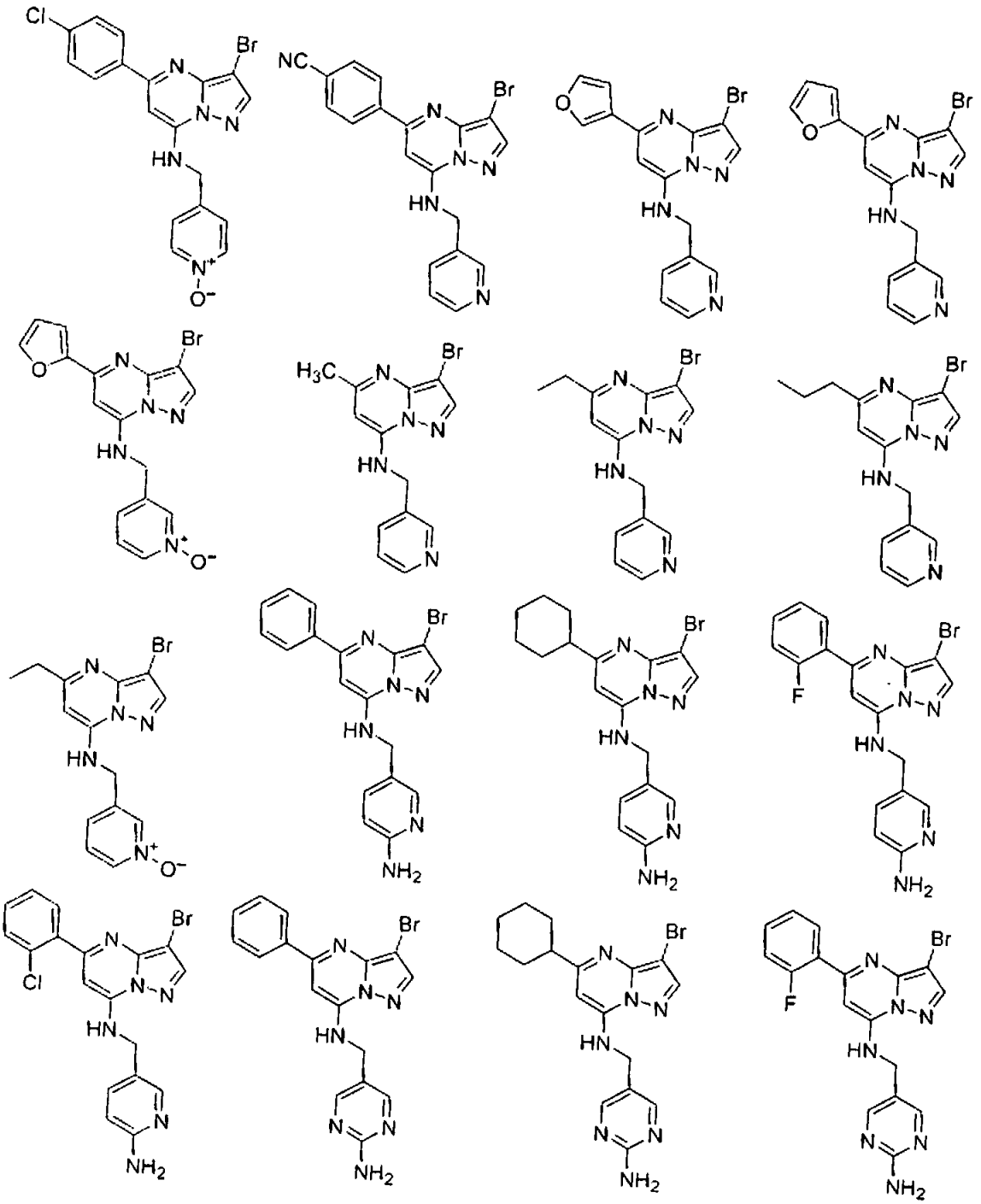
En otra realización, R es H, R^2 es halo y R^3 es heterociclilo.

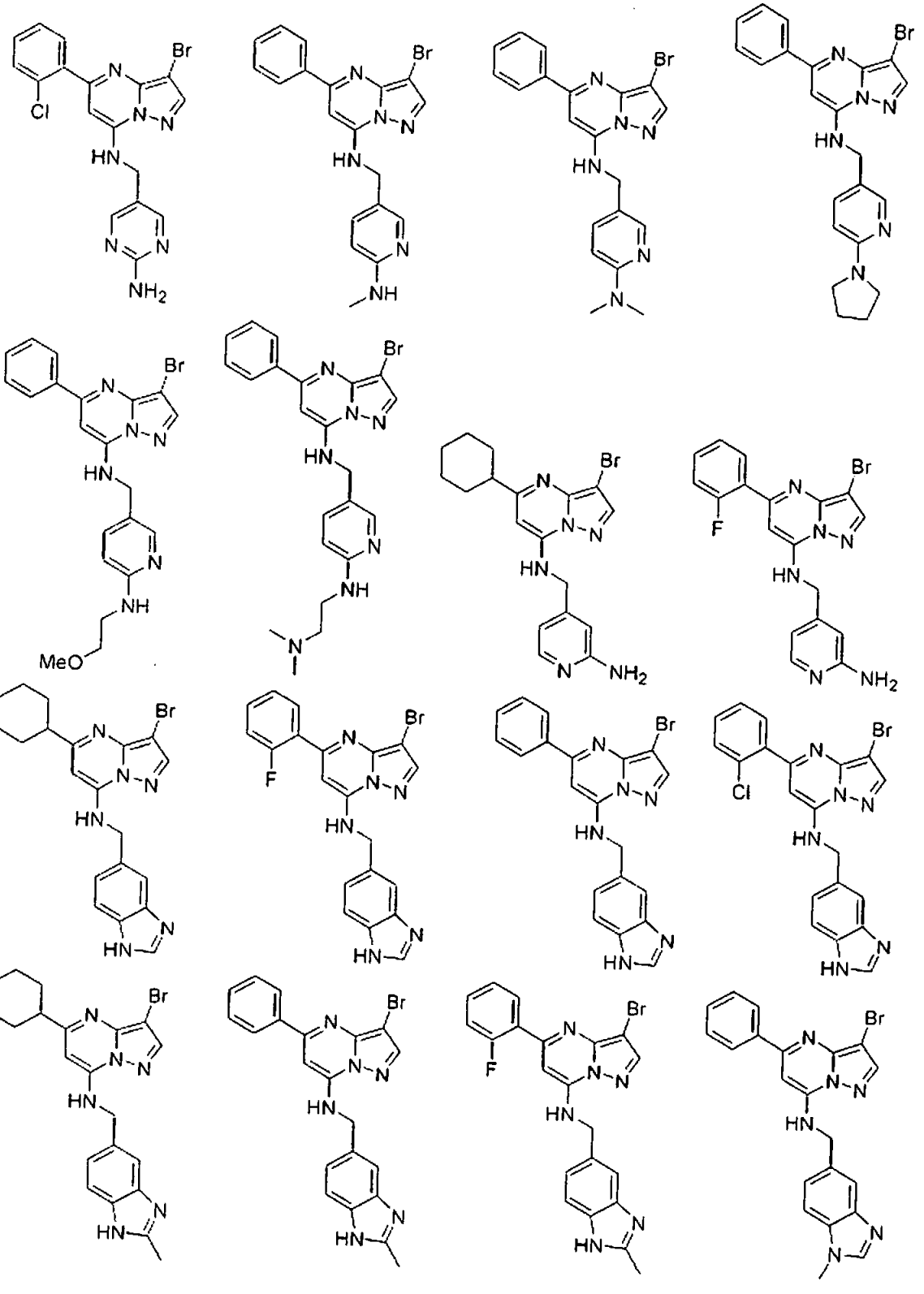
Otra realización describe los compuestos de la invención que se muestran en **Tabla 1**, los cuales exhiben una actividad inhibidora de CDK2 de aproximadamente 0,0001μM hasta > aproximadamente 5 μM. Los métodos de ensayo se describen posteriormente (desde la página 344 hacia adelante).

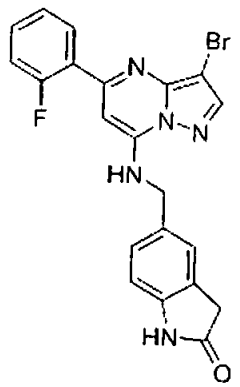
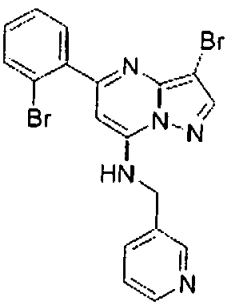
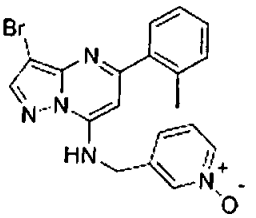
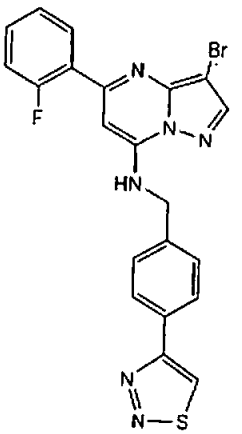
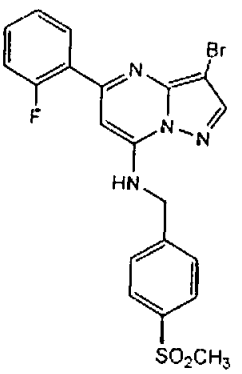
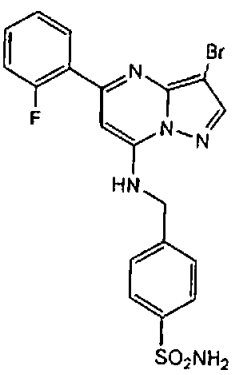
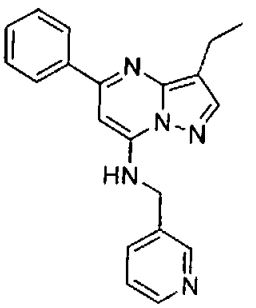
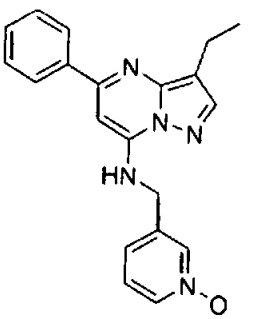
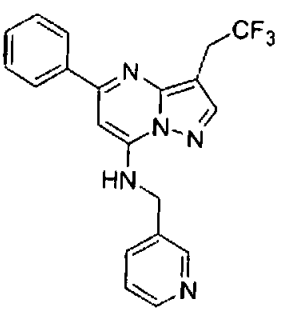
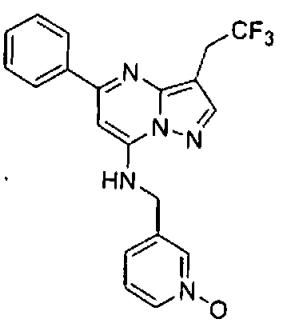
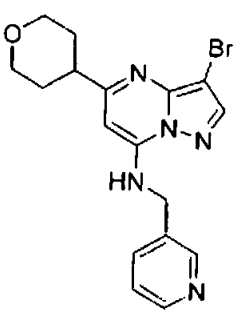
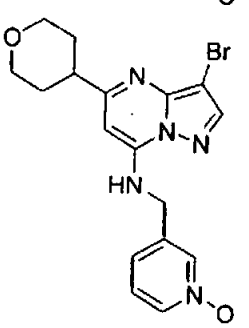
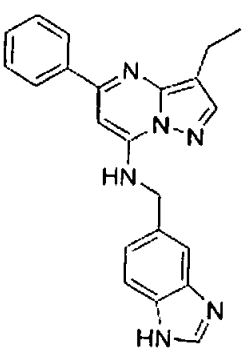
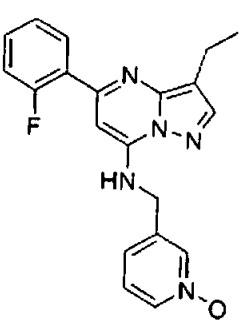
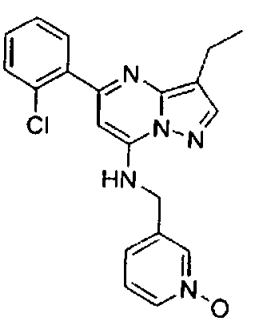
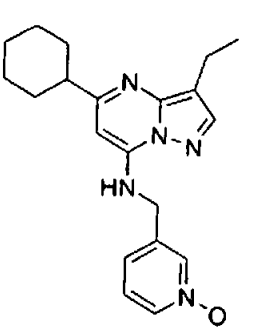
Tabla 1

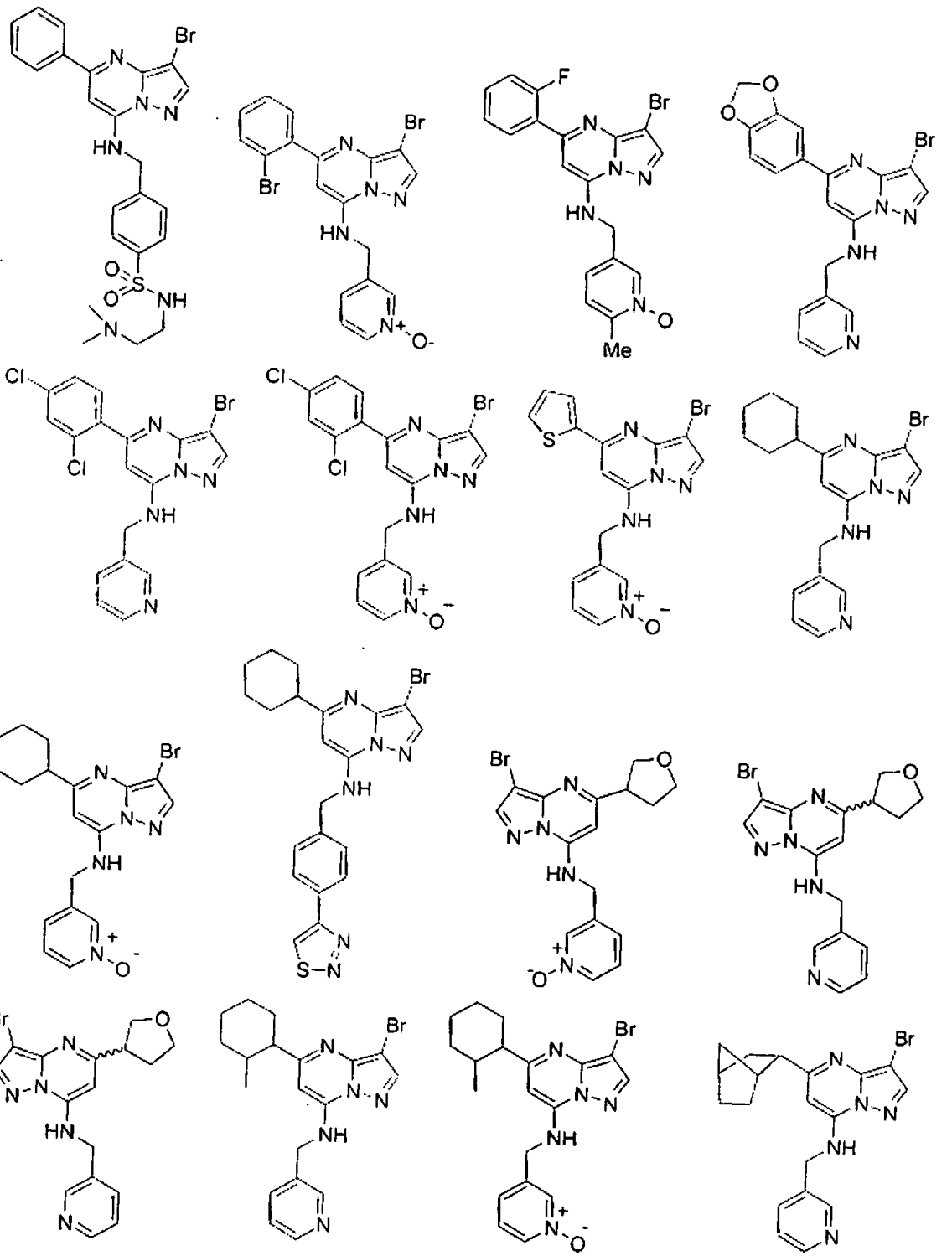


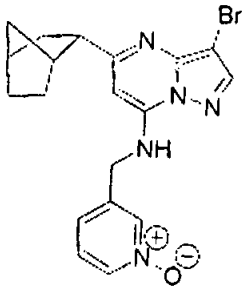


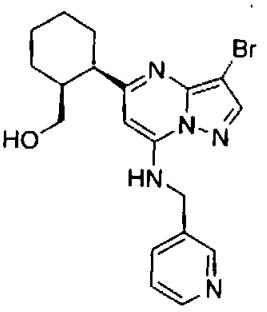


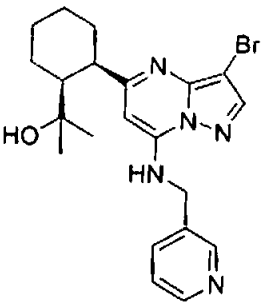


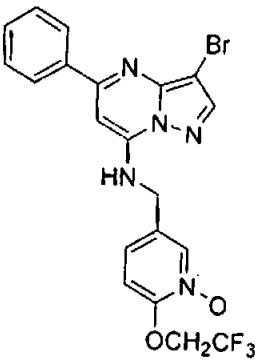

















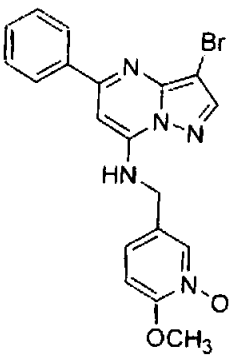


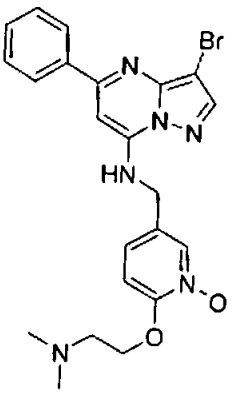


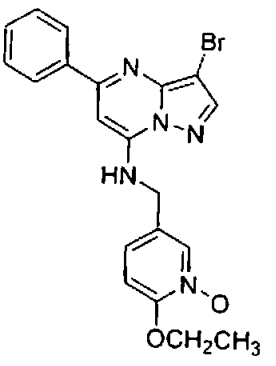


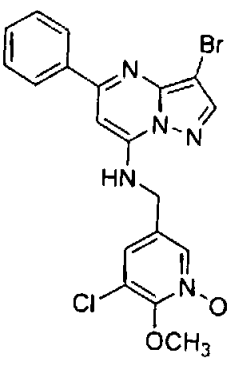


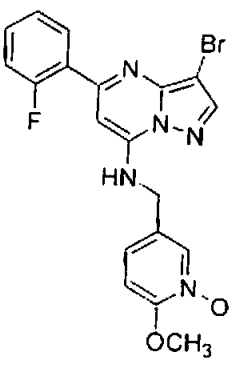


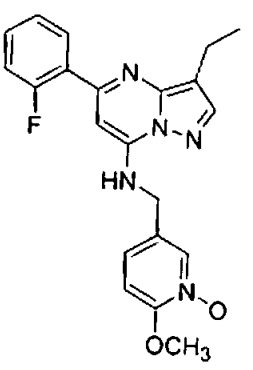


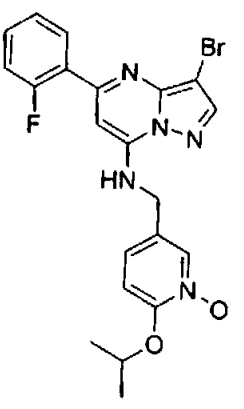


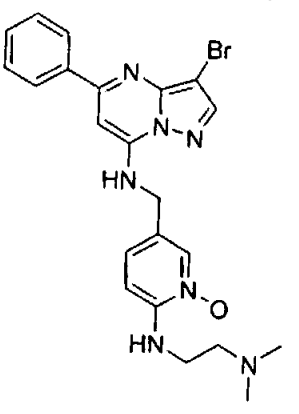


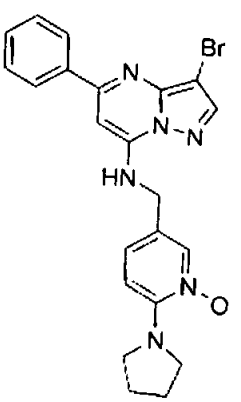


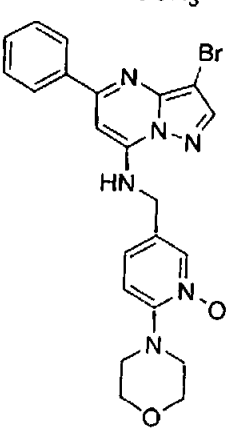


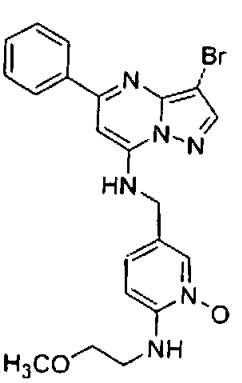


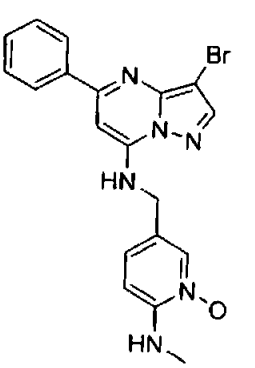


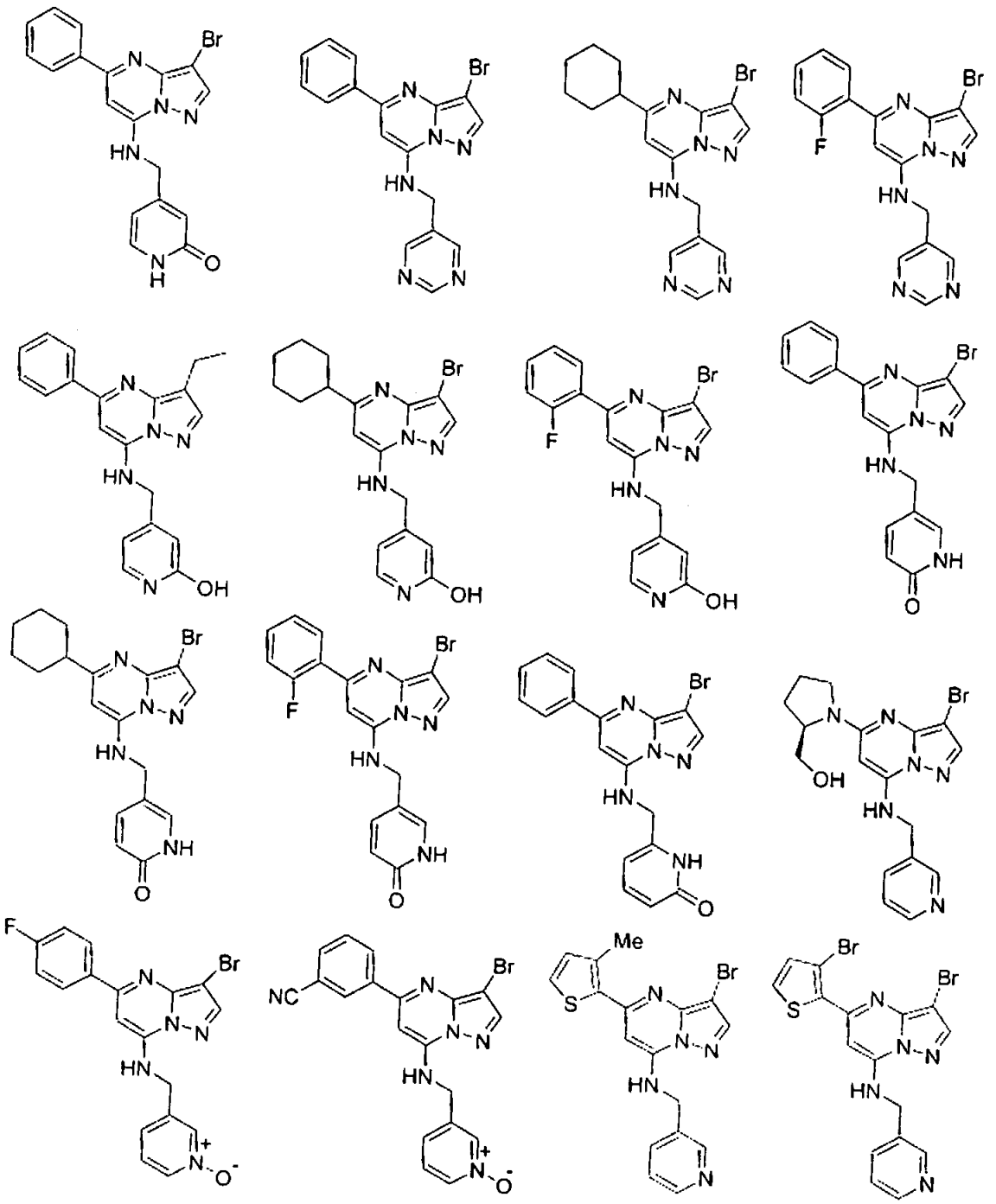


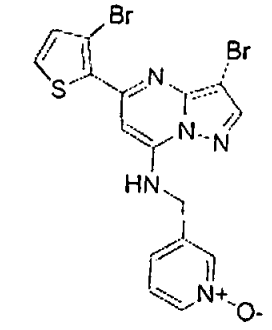
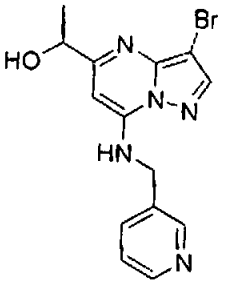
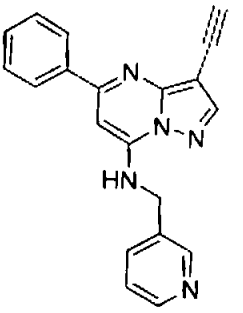
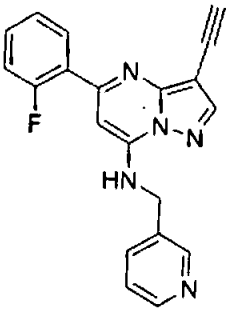
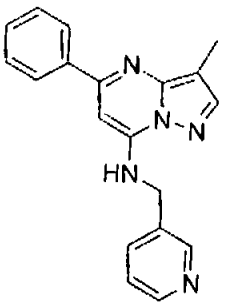
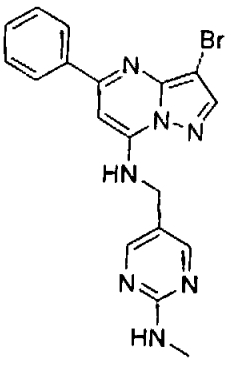
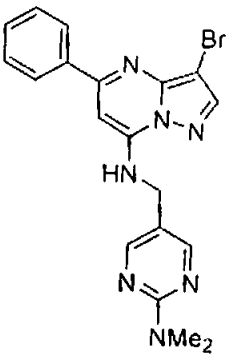
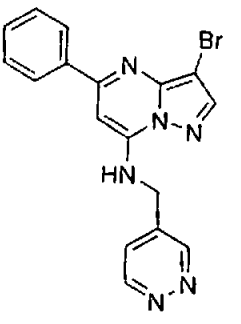
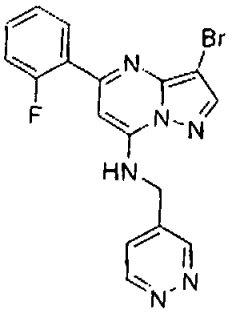
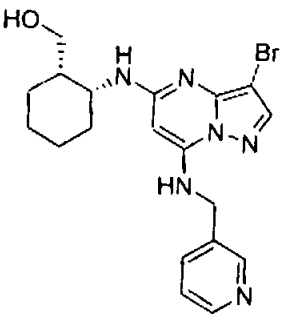
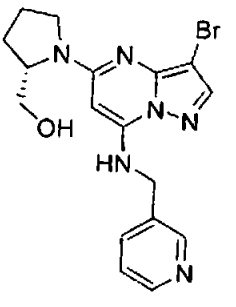
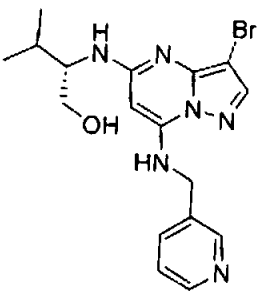
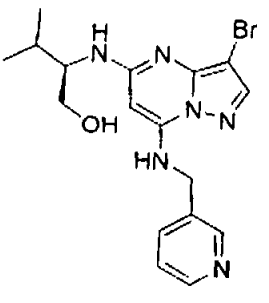
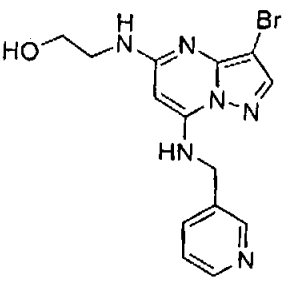
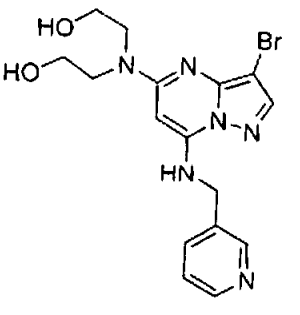
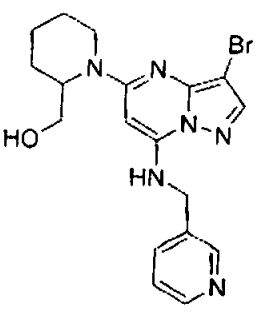
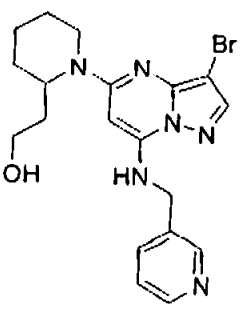
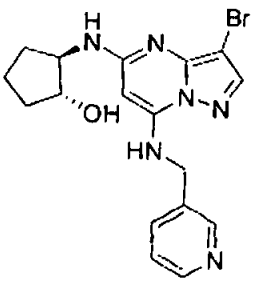
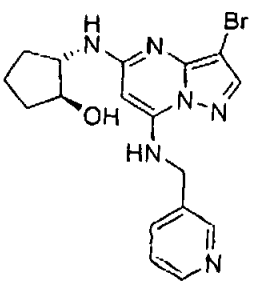




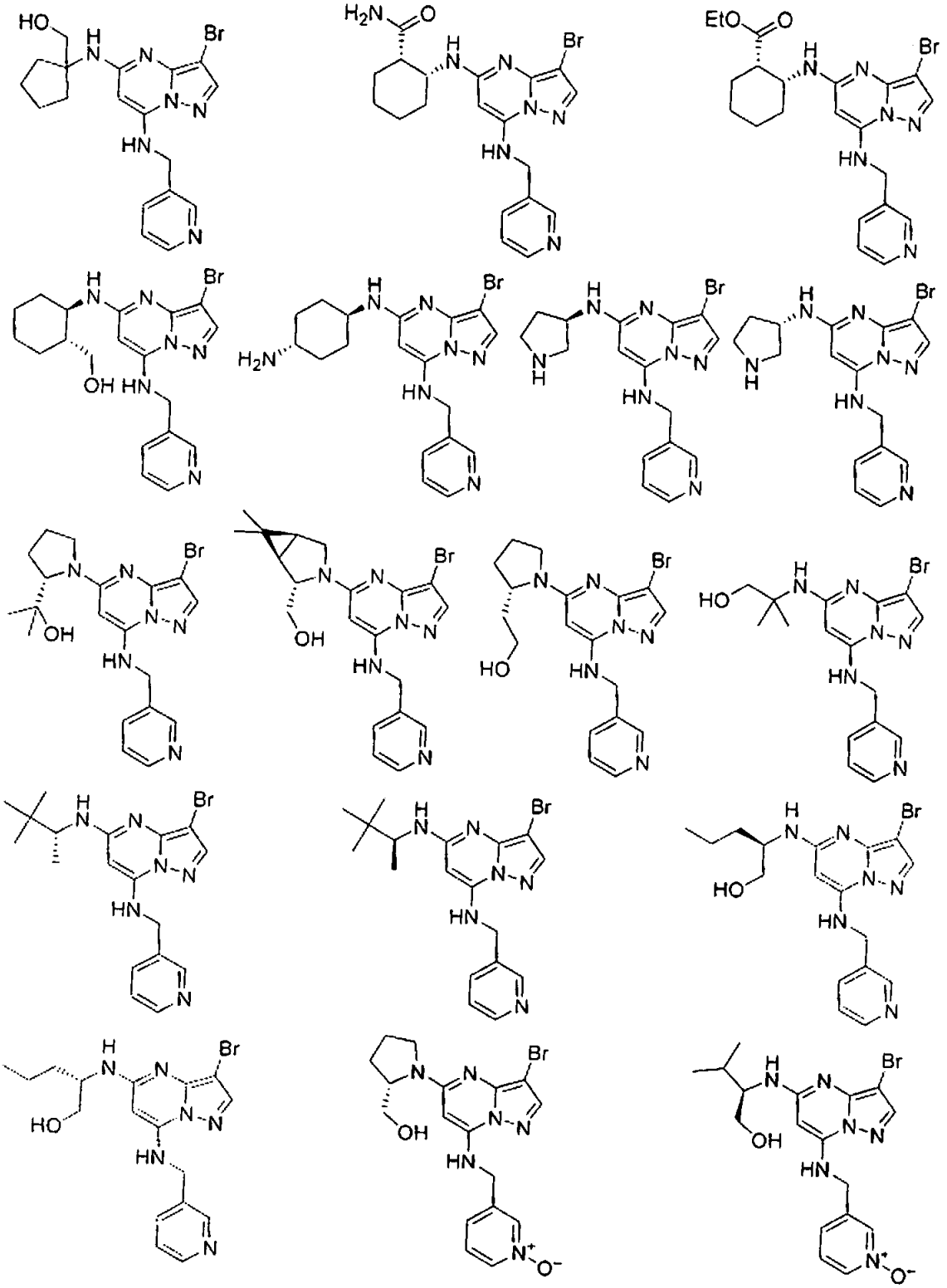


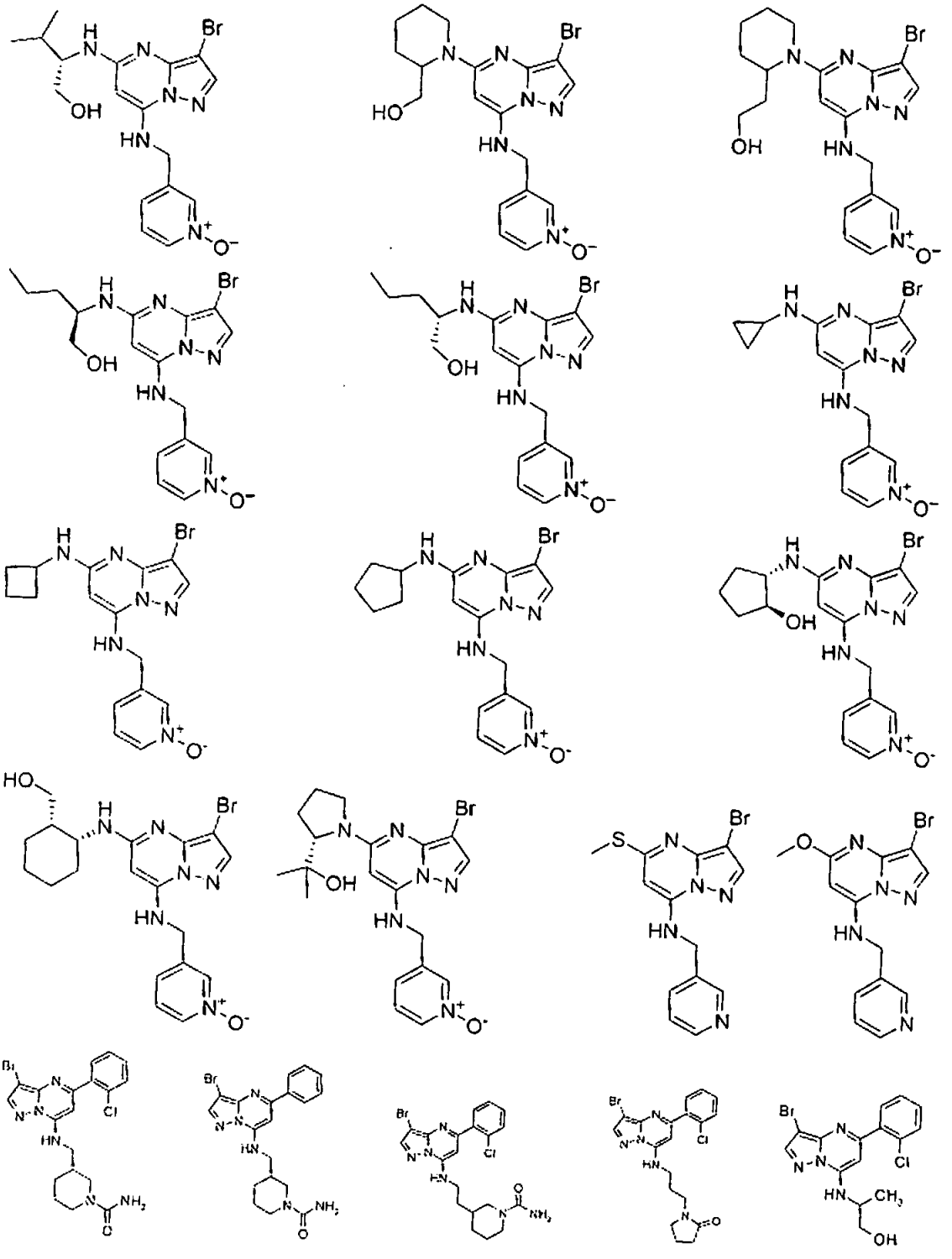


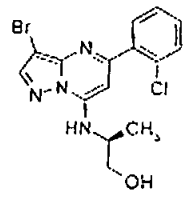
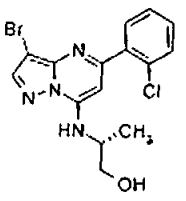
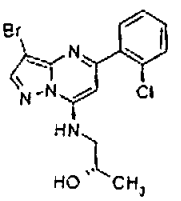
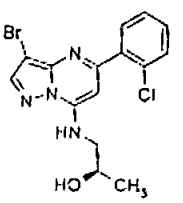
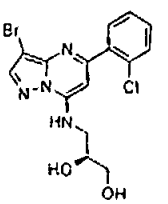
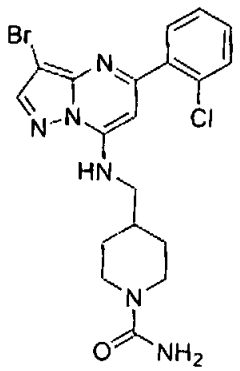
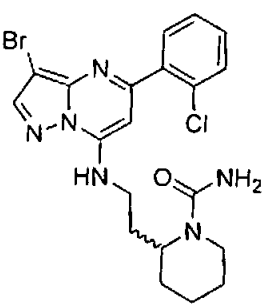
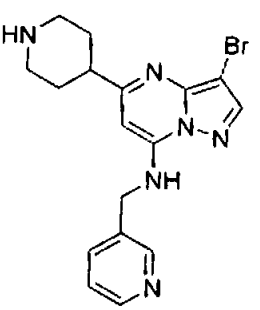
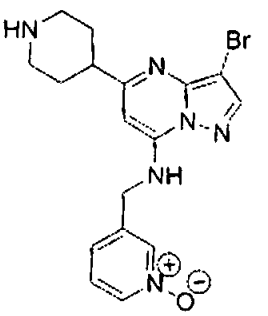
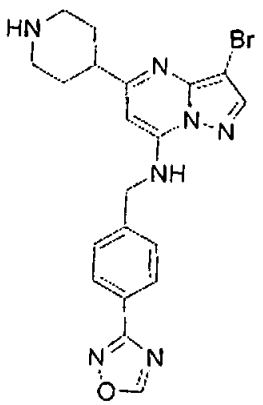
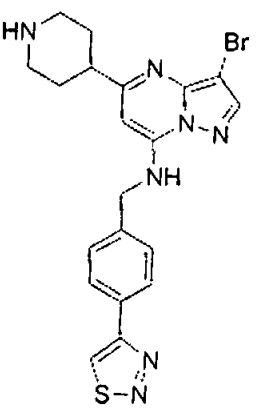
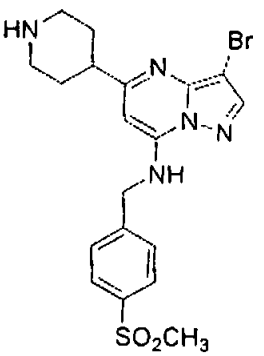
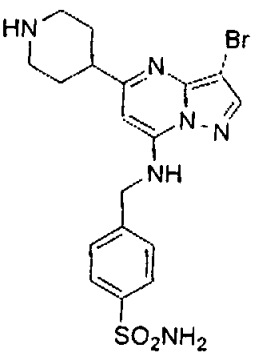
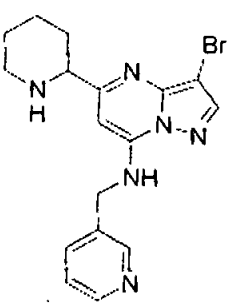
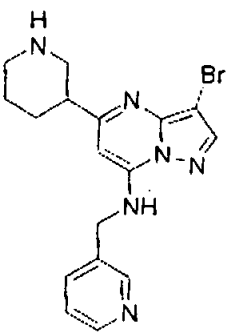
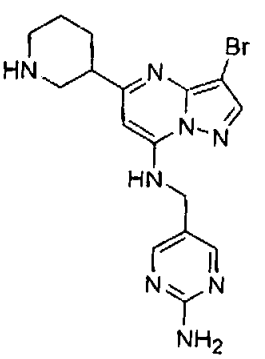
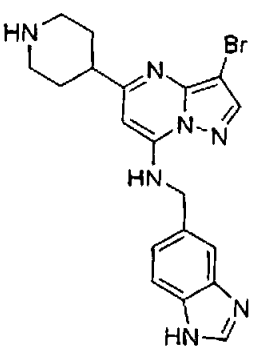


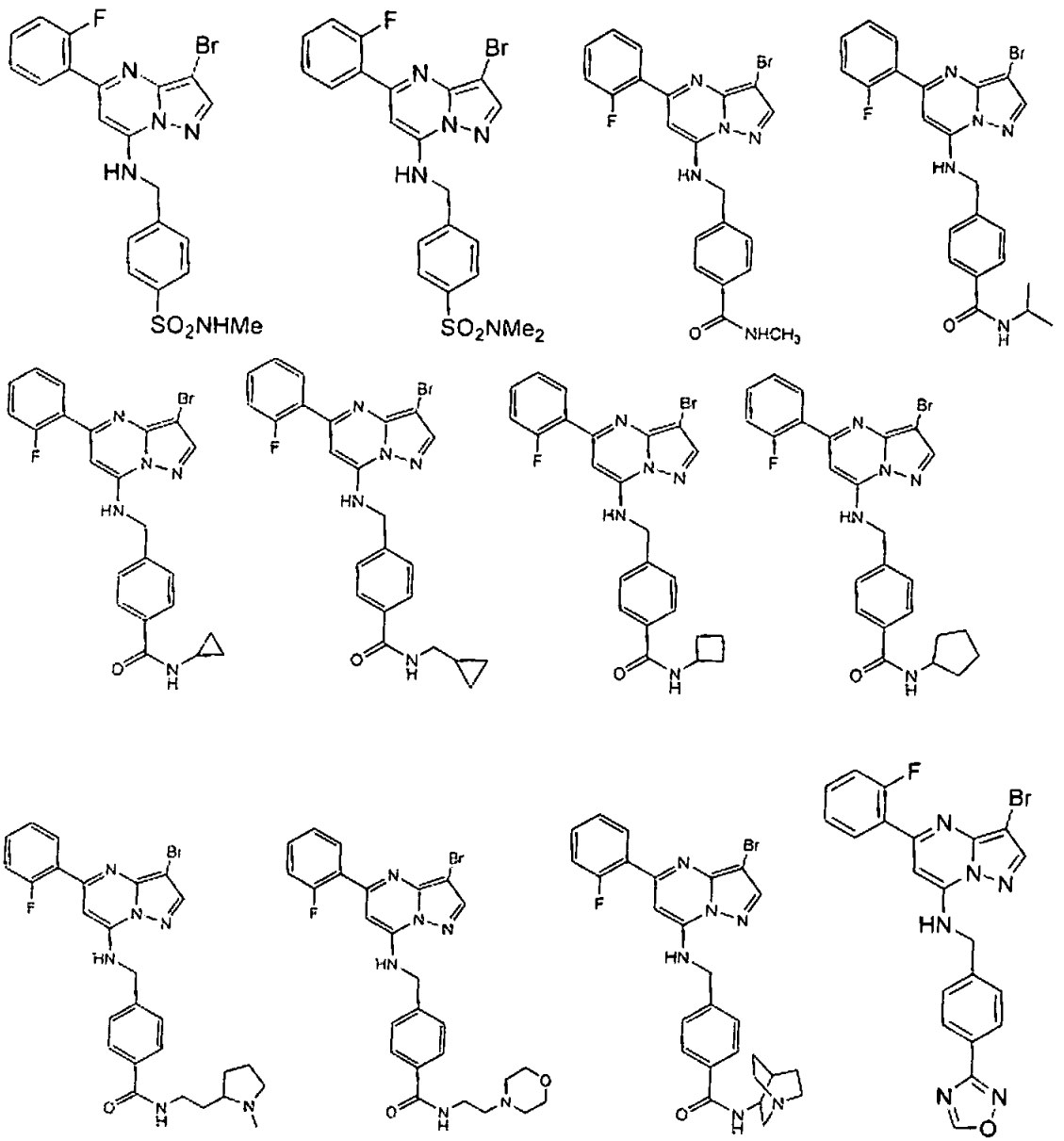




















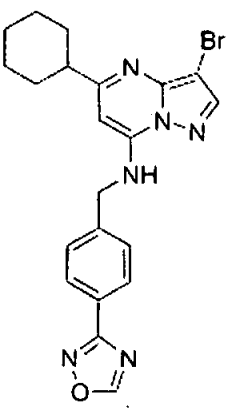
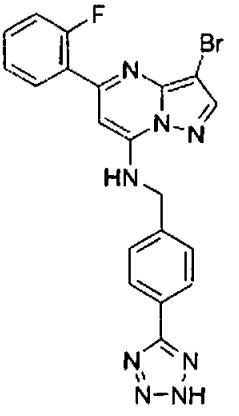
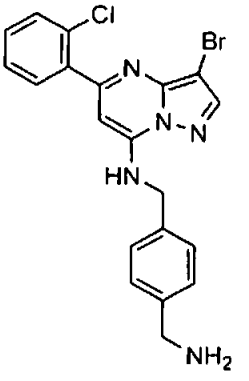
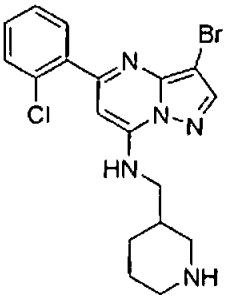
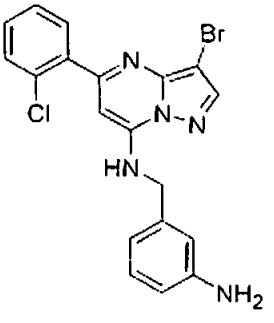
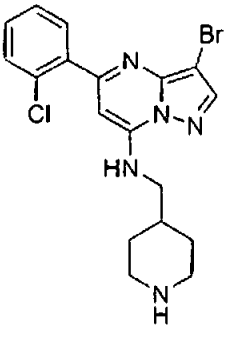
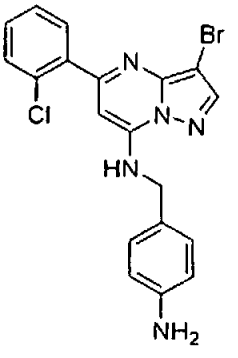
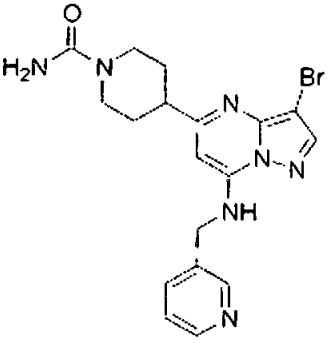
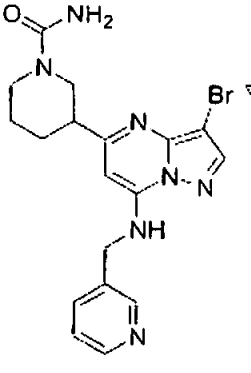
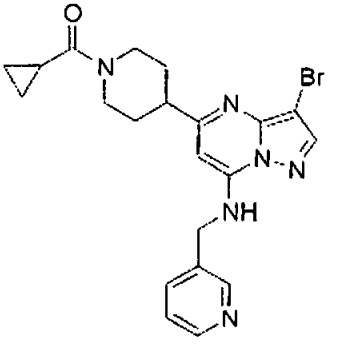
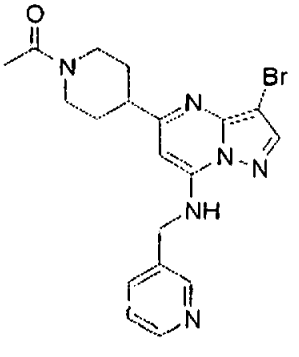
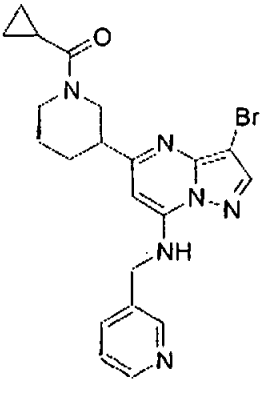
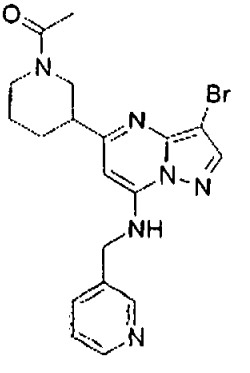
100

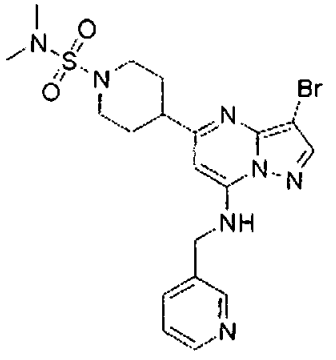


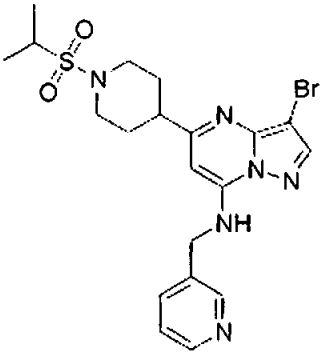


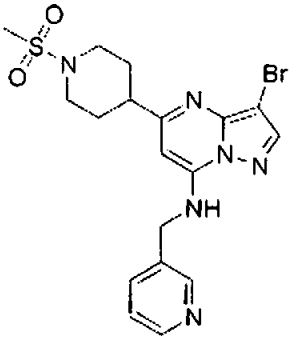


















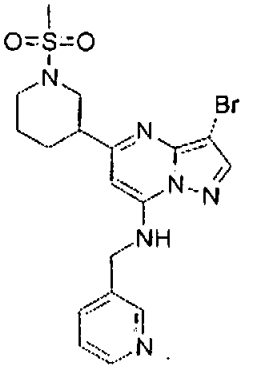

F
Br
N
N-N
HN
SO2NHMe
SO2NMe2
NHCH3
O
N
H

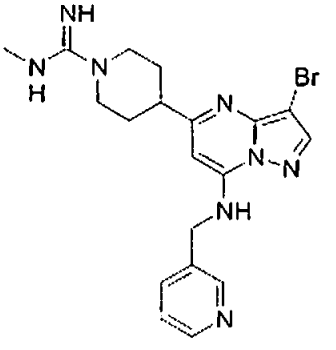














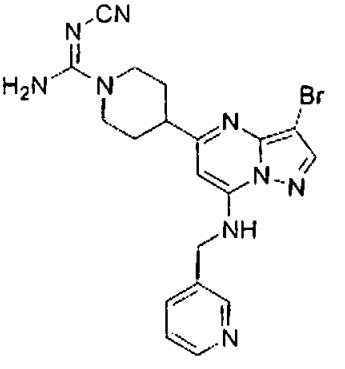


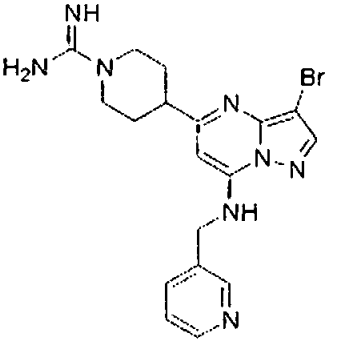


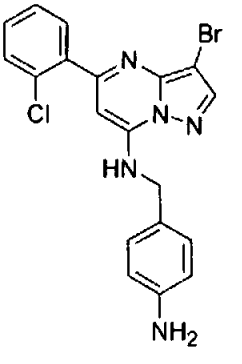


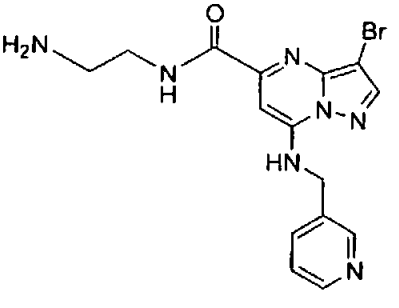


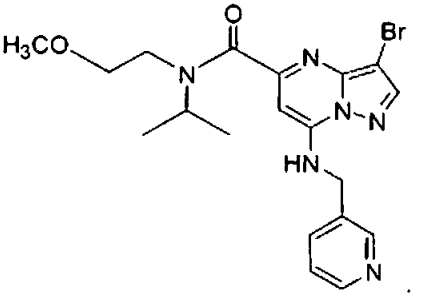




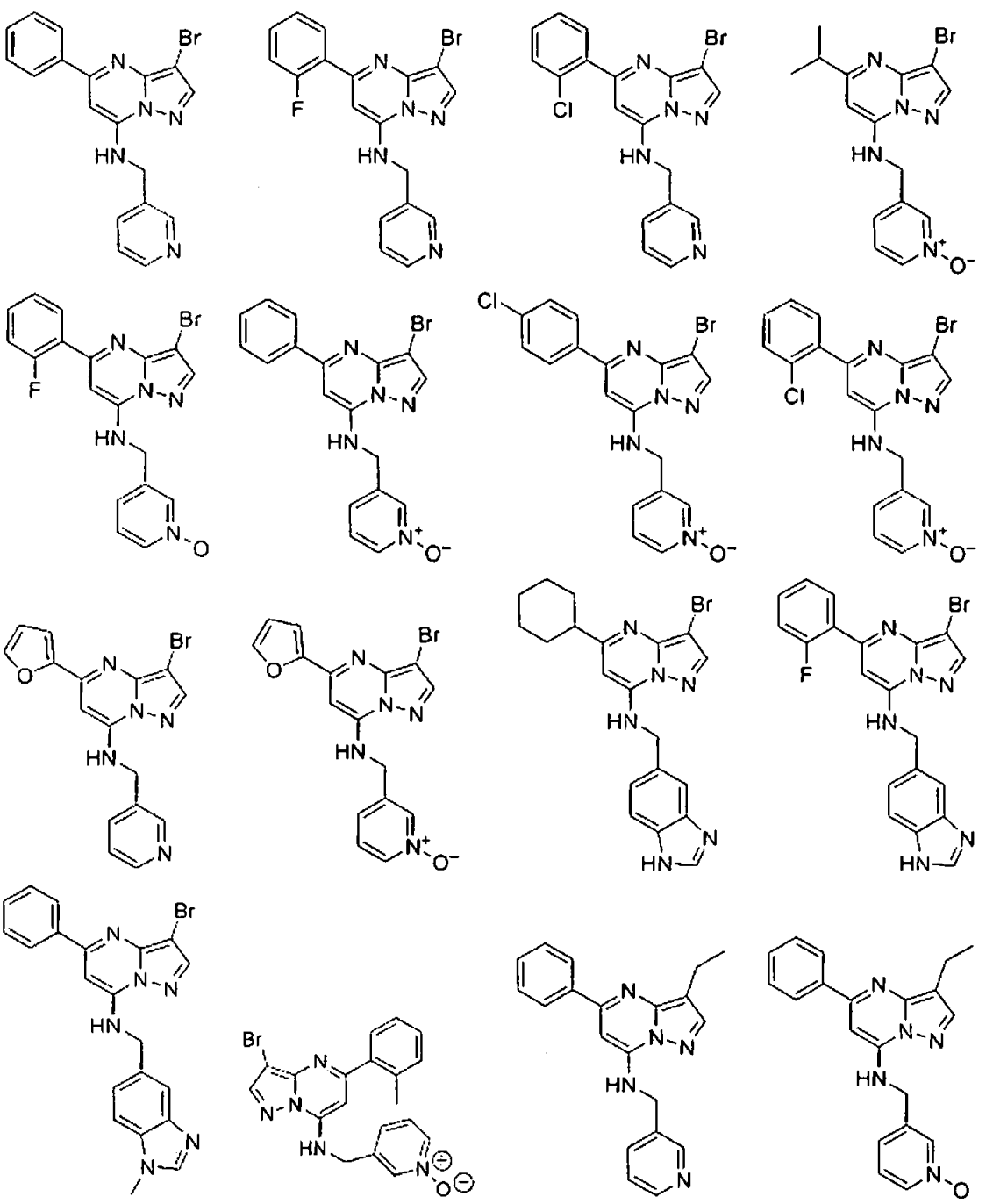


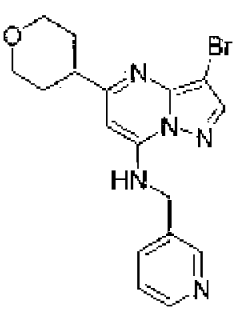
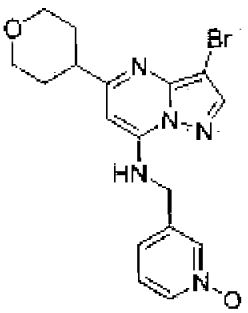
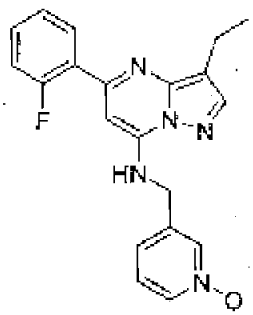
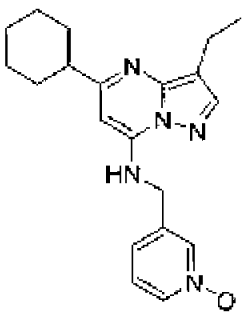
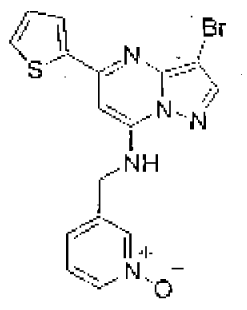
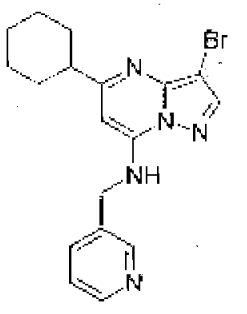
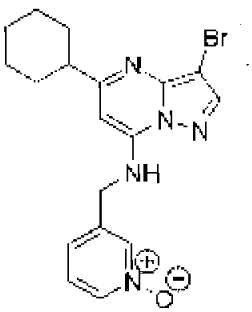
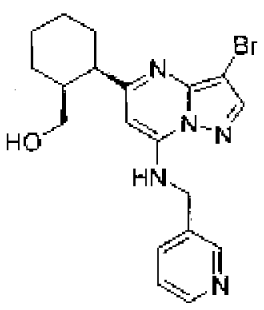
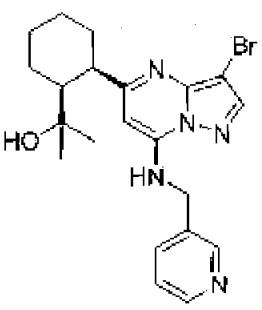
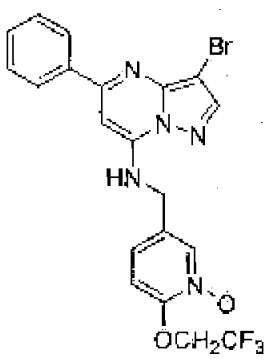
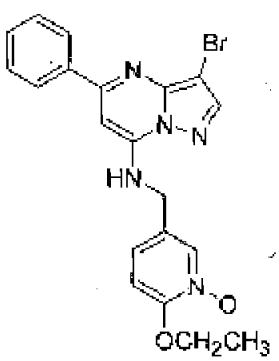
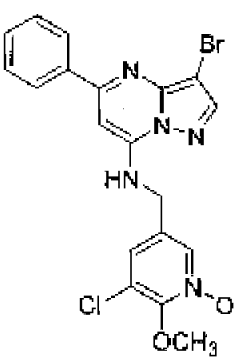
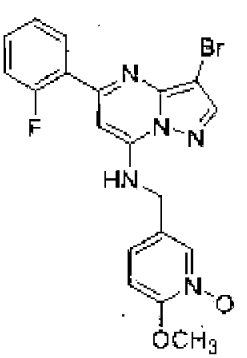
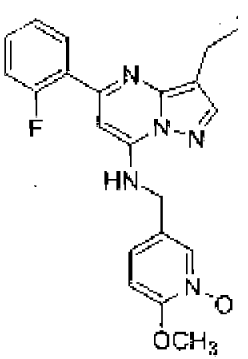
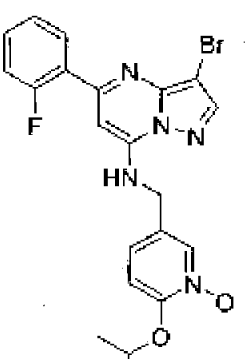
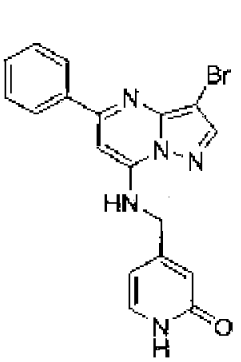


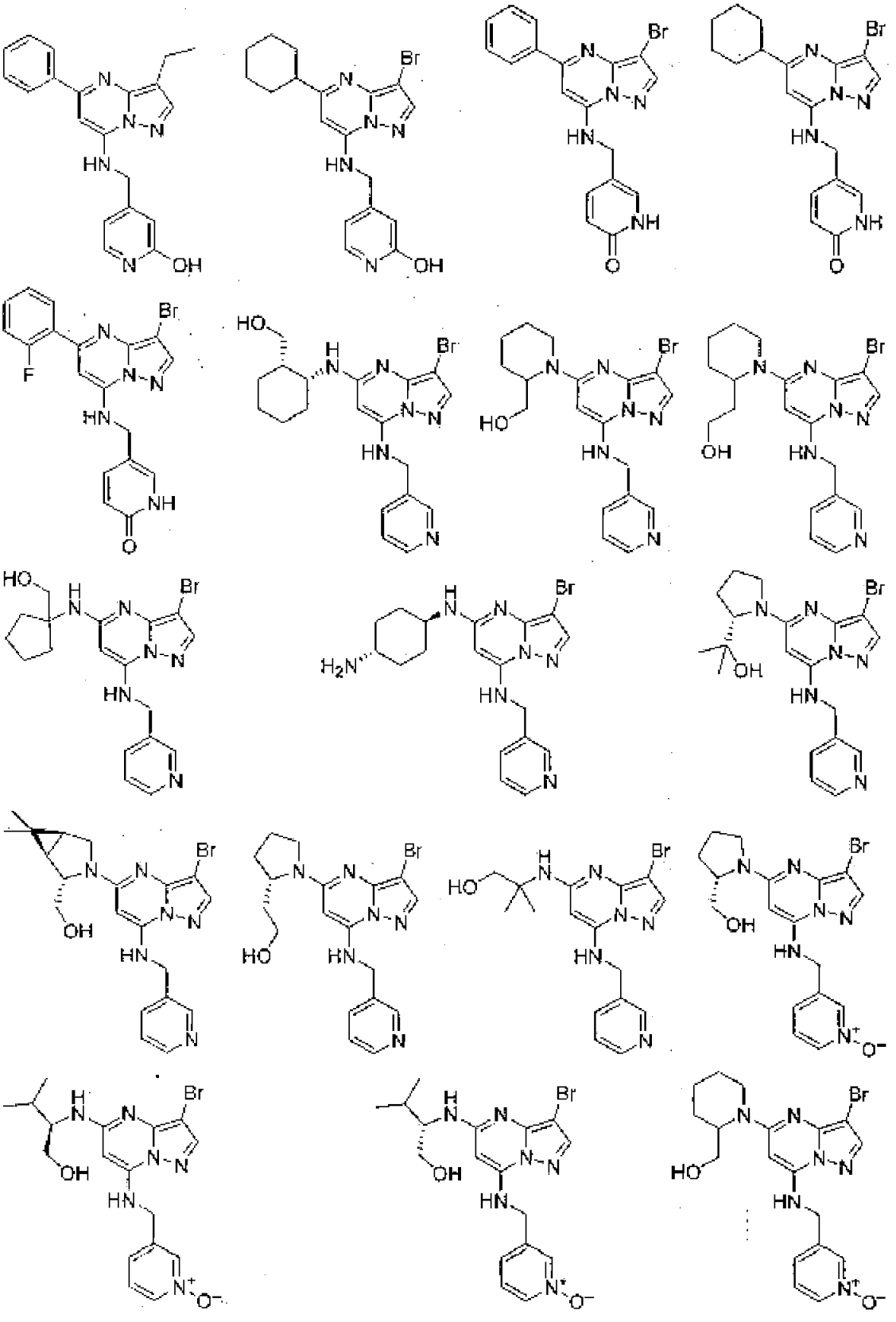


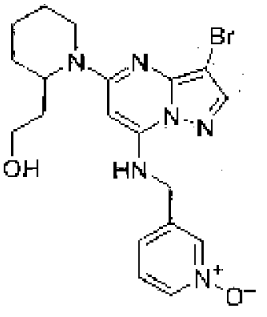


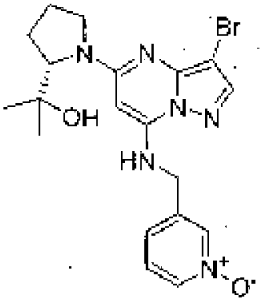
Otra realización de la invención describe los compuestos siguientes, los cuales exhiben una actividad inhibidora de CDK2 de aproximadamente 0,0001μM hasta aproximadamente 0,5μM:

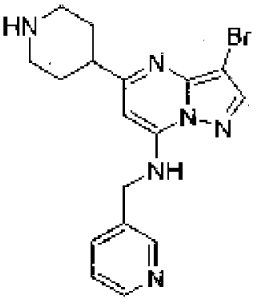


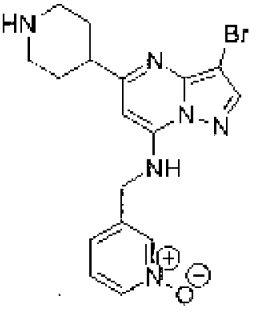

















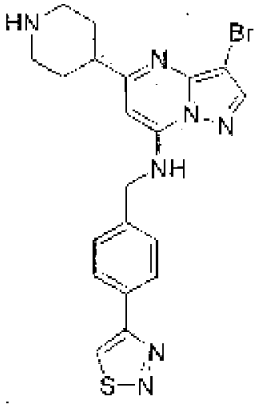


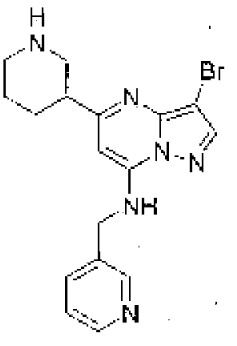


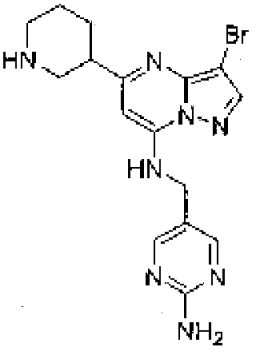


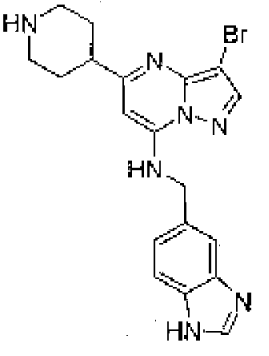


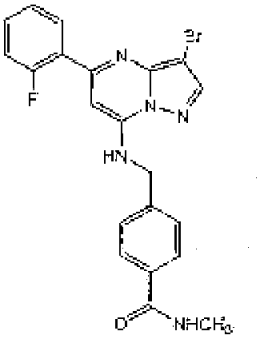


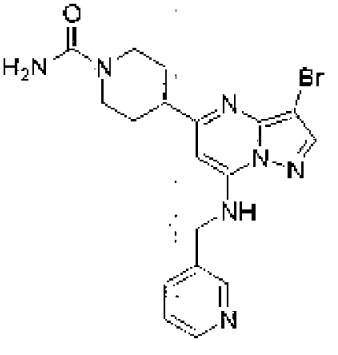


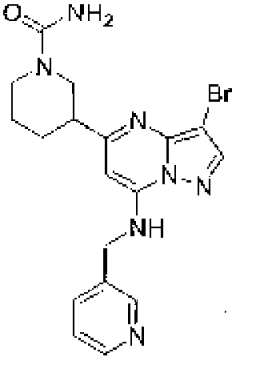


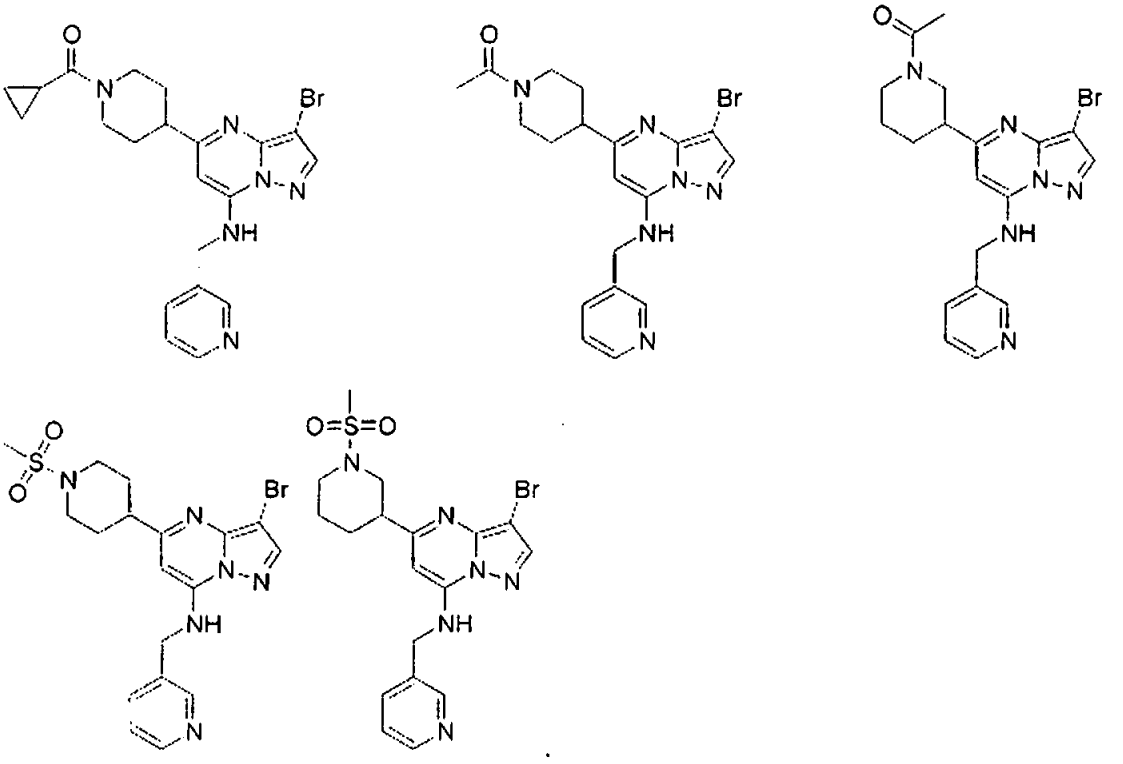




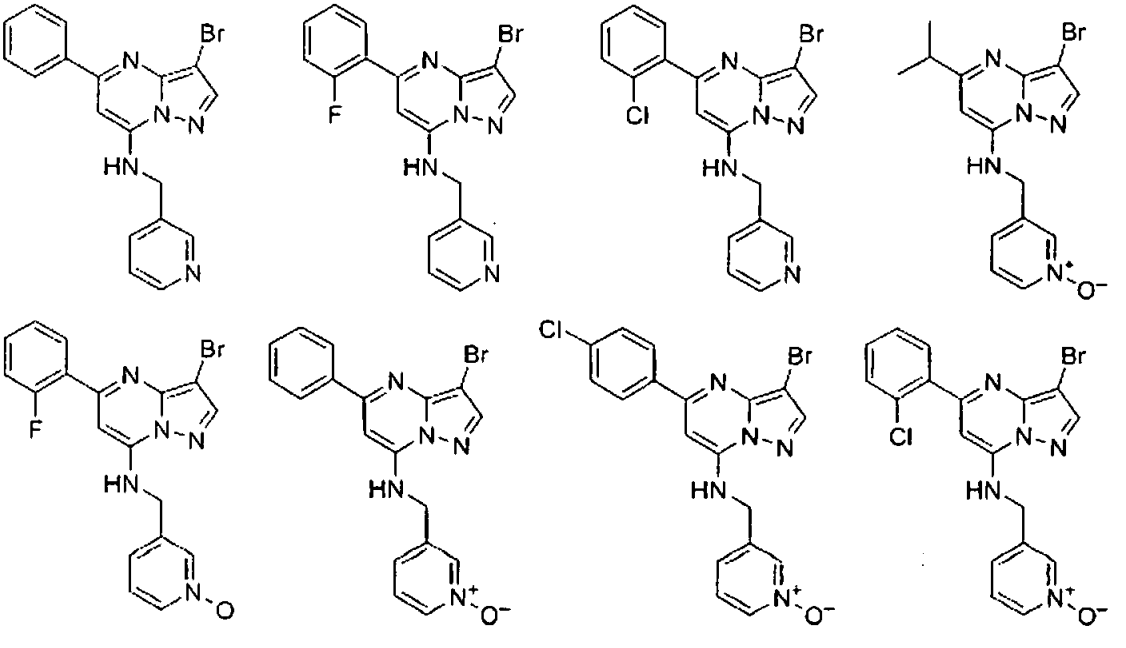


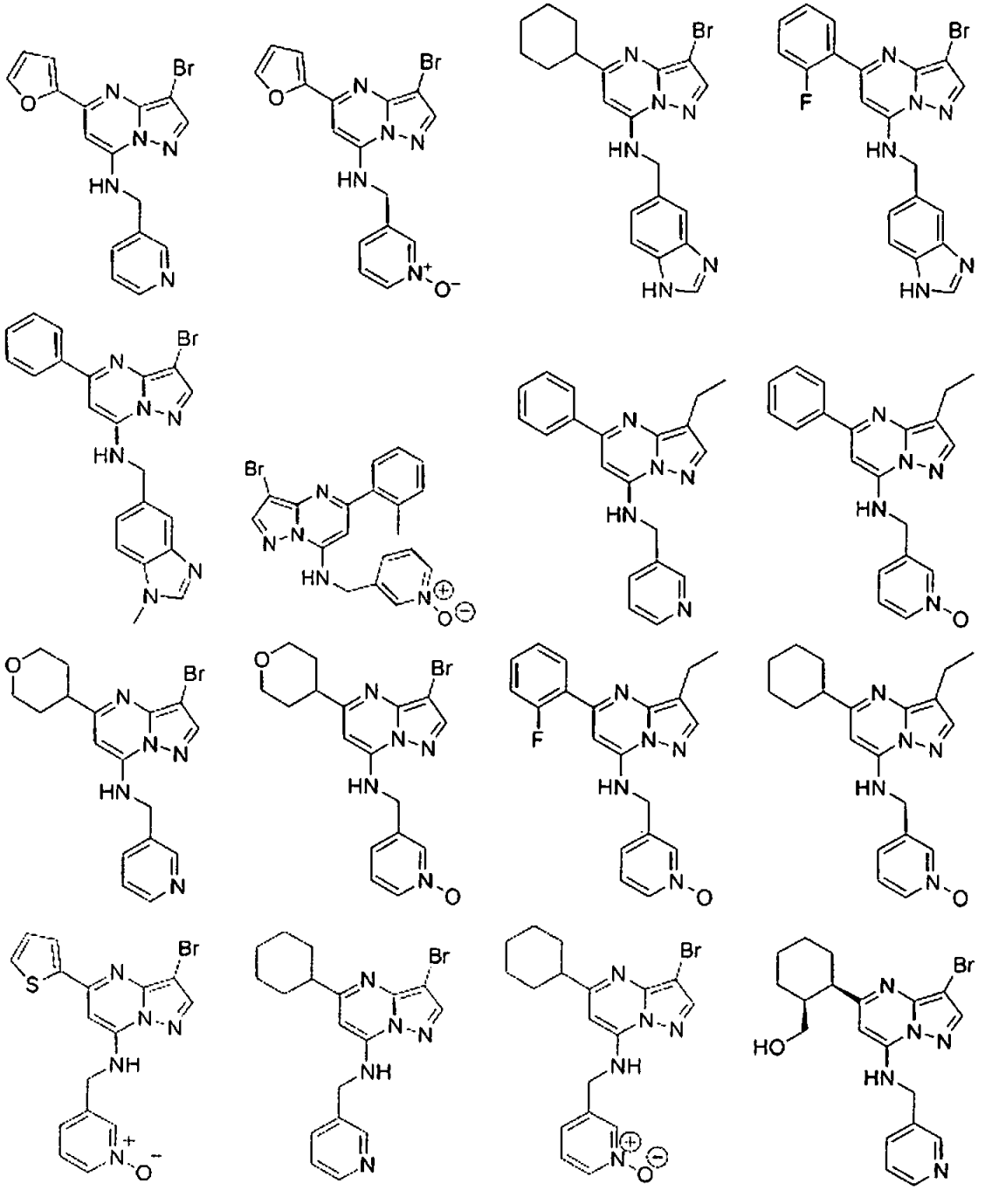


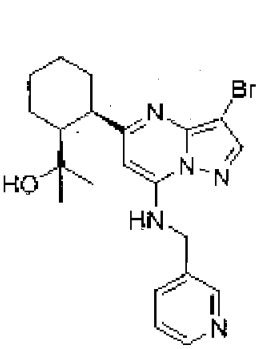
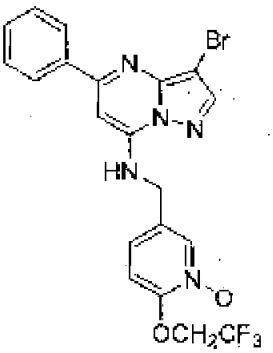
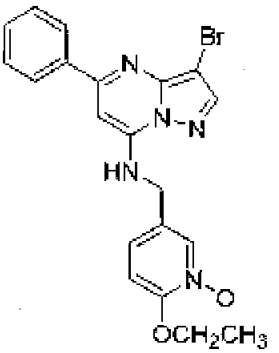
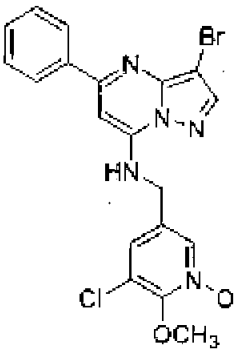
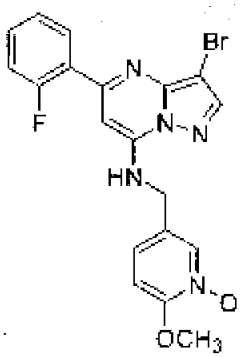
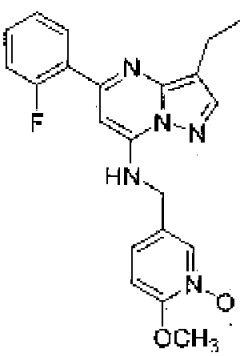
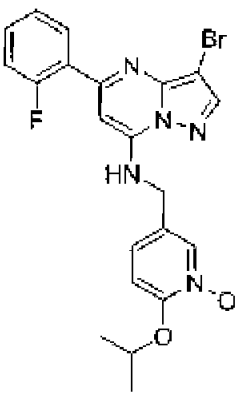
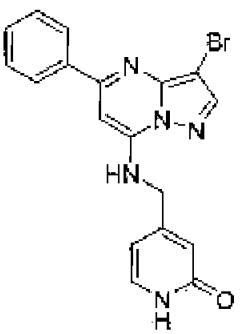
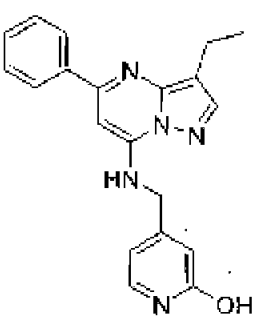
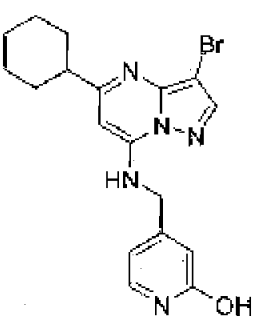
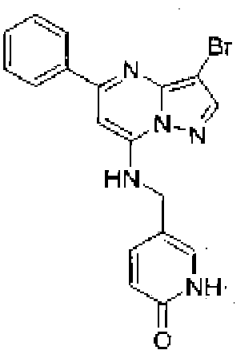
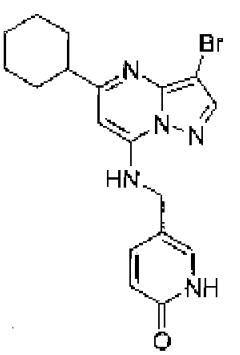
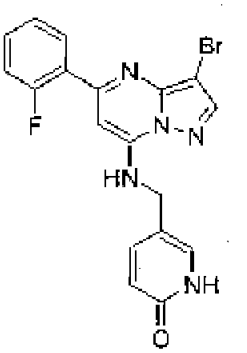
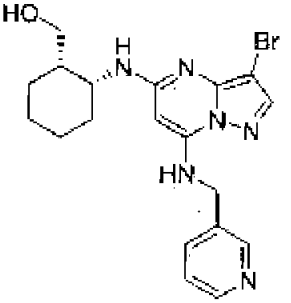
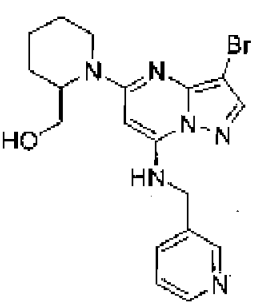
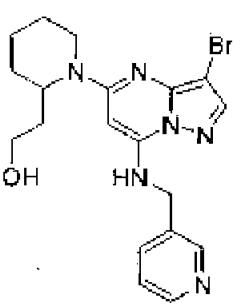


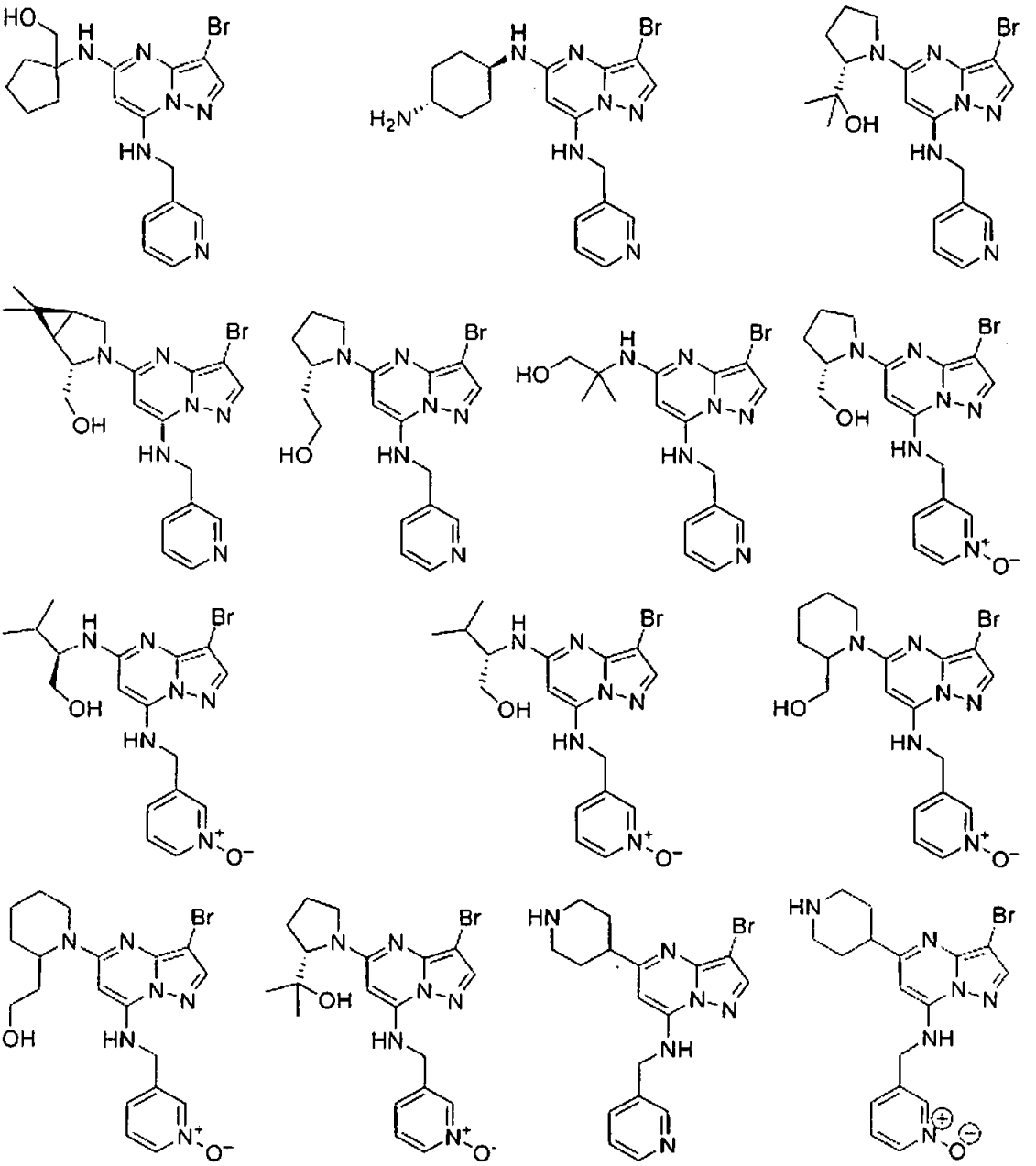


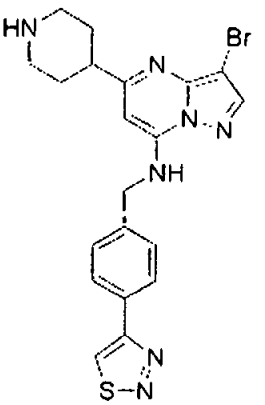
Otra realización de la invención describe los compuestos siguientes, los cuales exhiben una actividad inhibidora de CDK2 de aproximadamente 0,0001μM hasta aproximadamente 0,1μM:

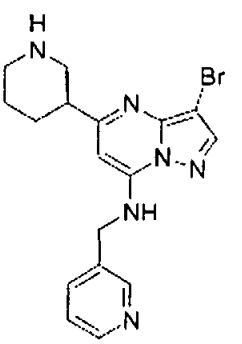


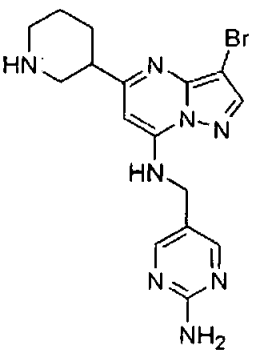


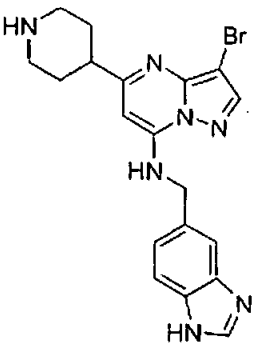

















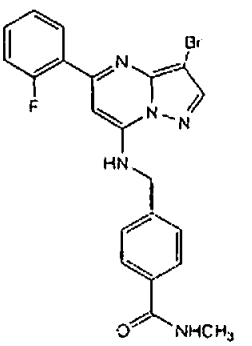


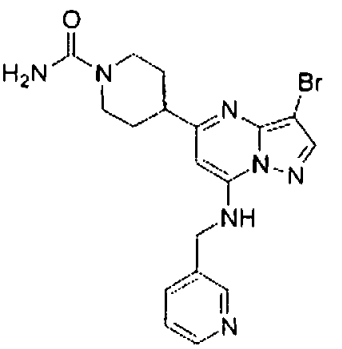


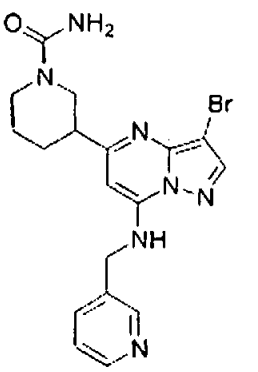


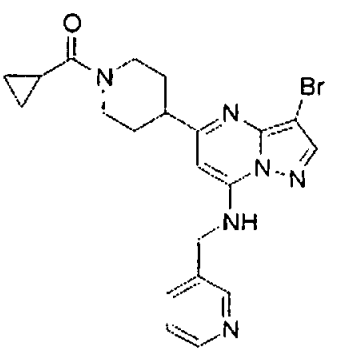


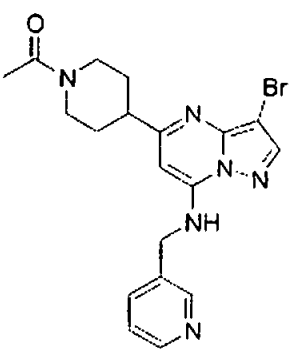


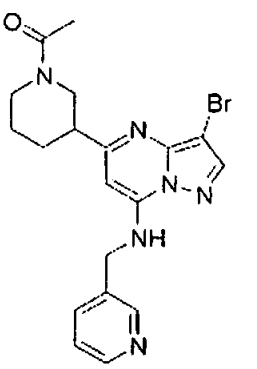


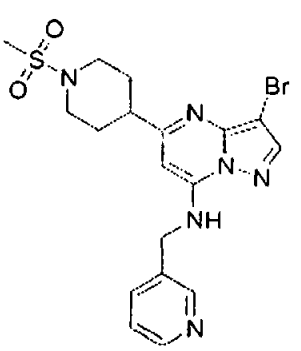


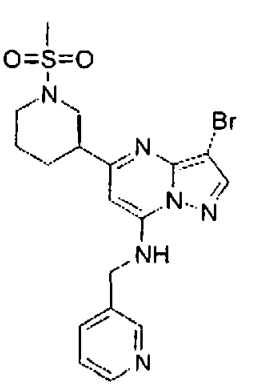




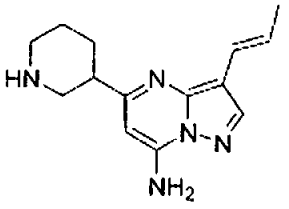
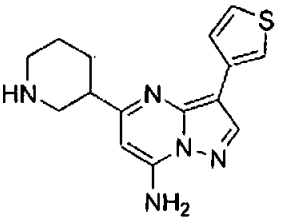
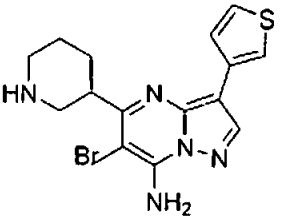
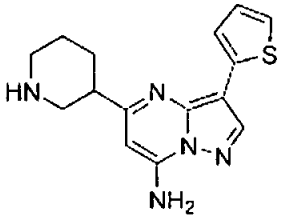
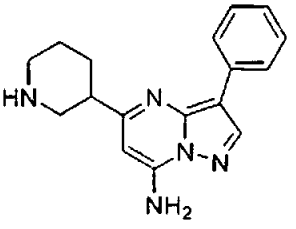
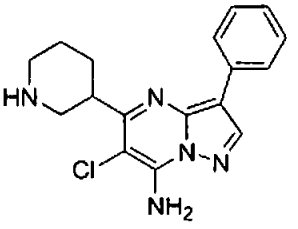
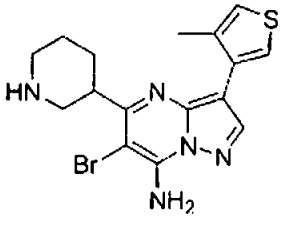
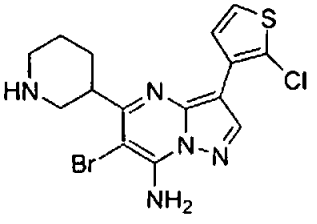
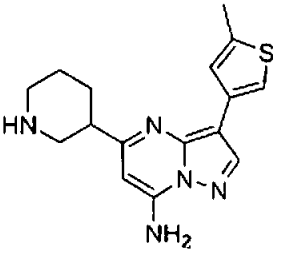
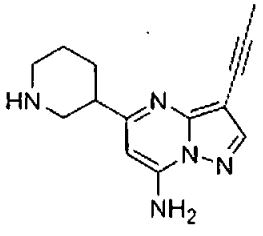
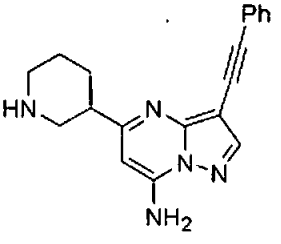
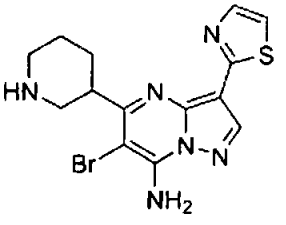
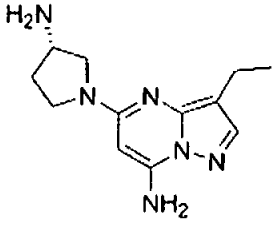
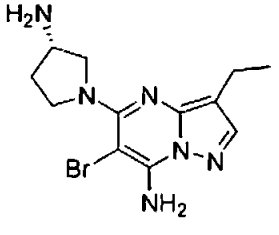
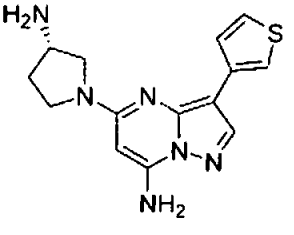
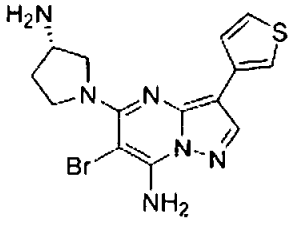
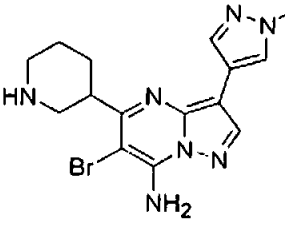
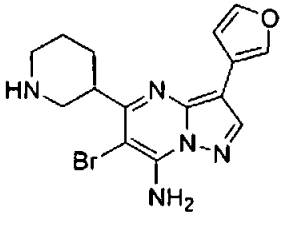


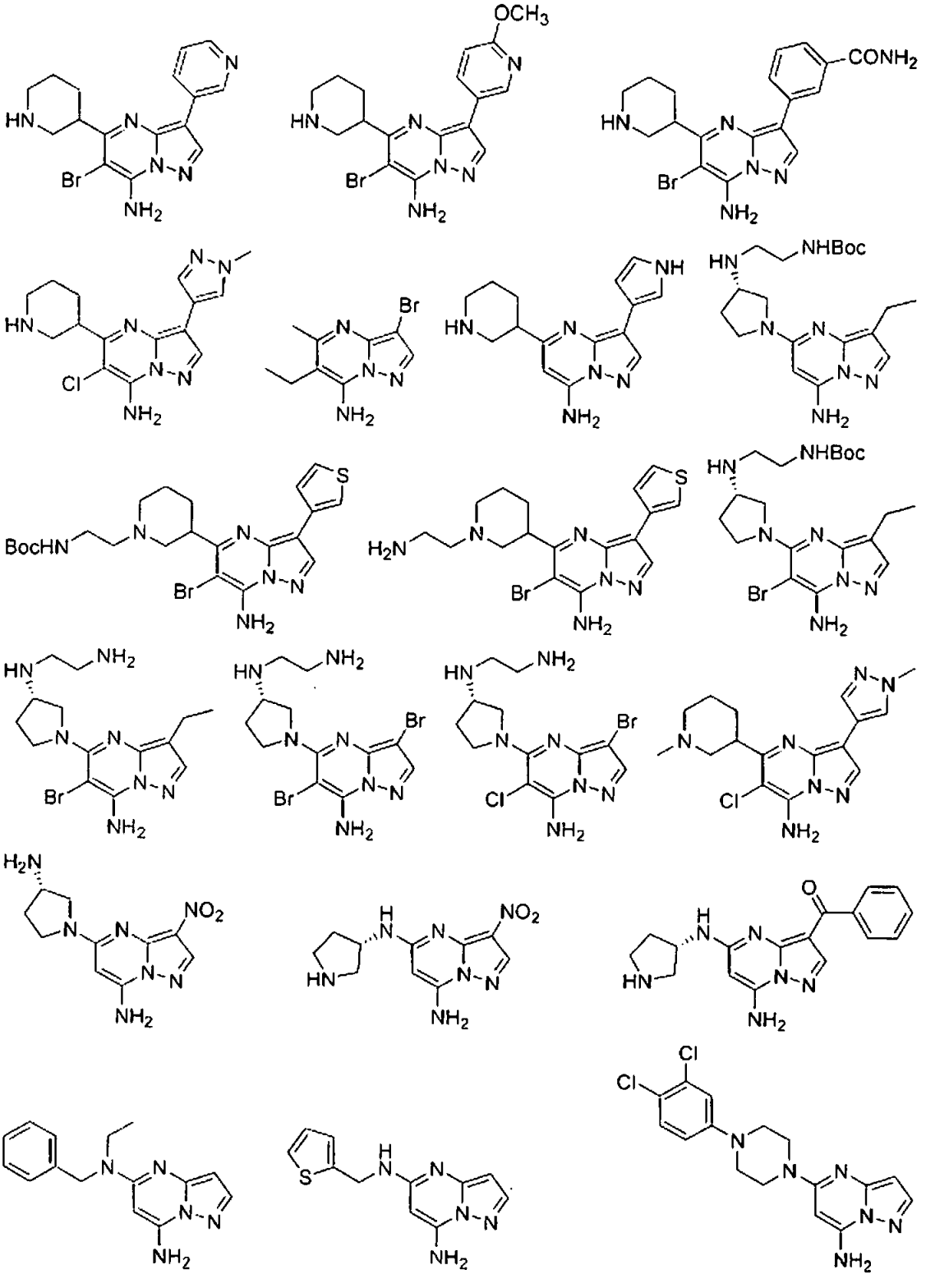


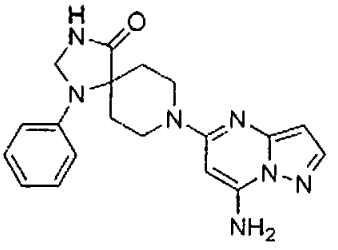


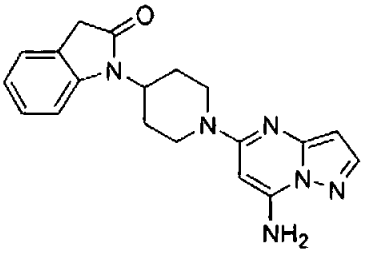


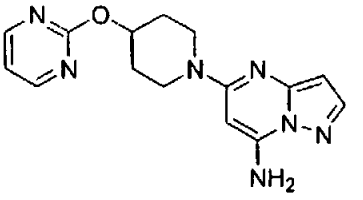
Adicionalmente se dan los compuestos siguientes:

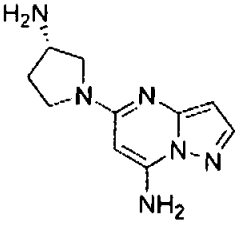



















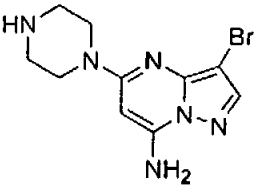


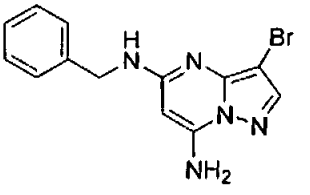


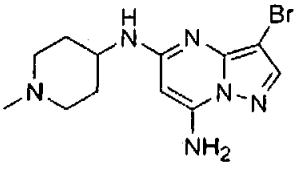


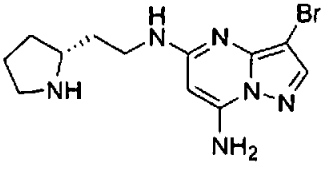


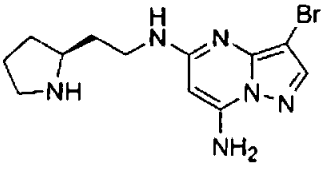


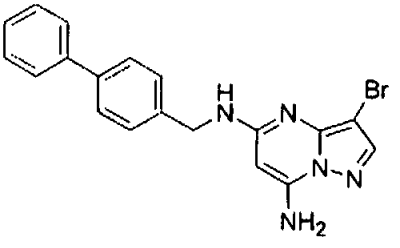


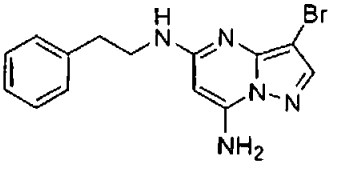


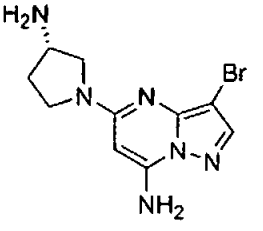


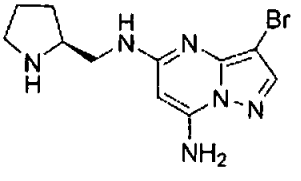


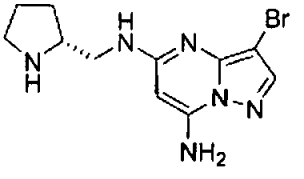


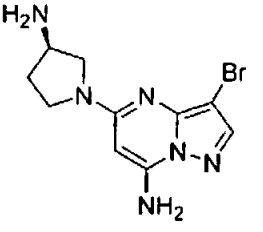


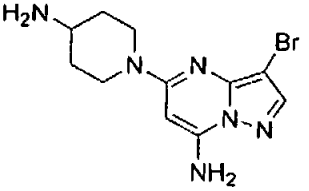


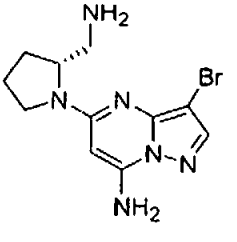


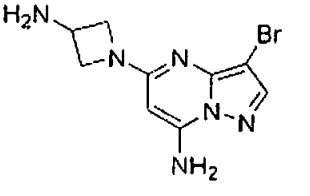


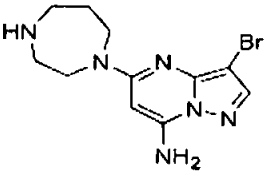


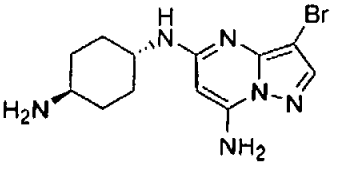


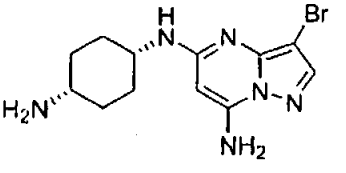


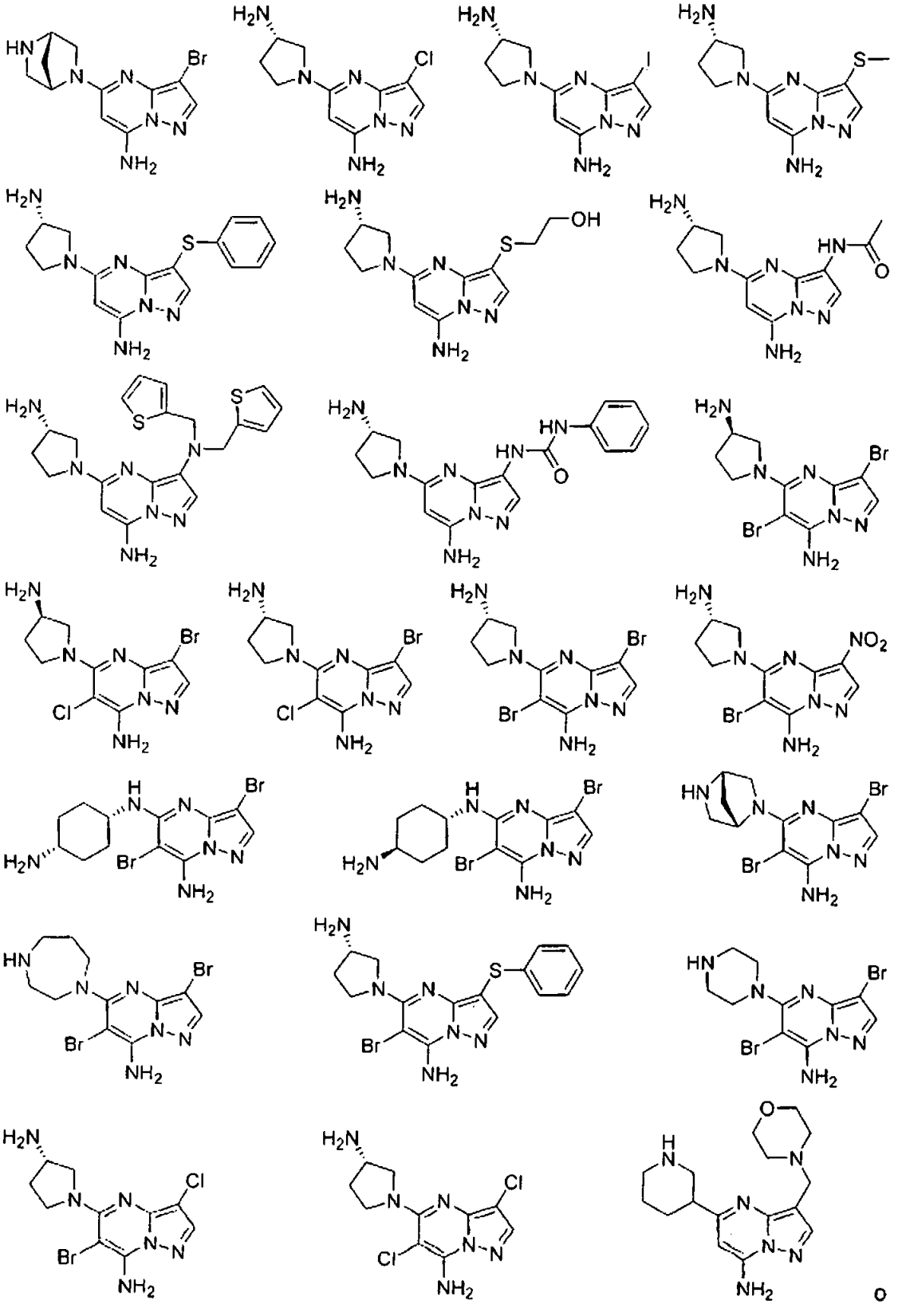


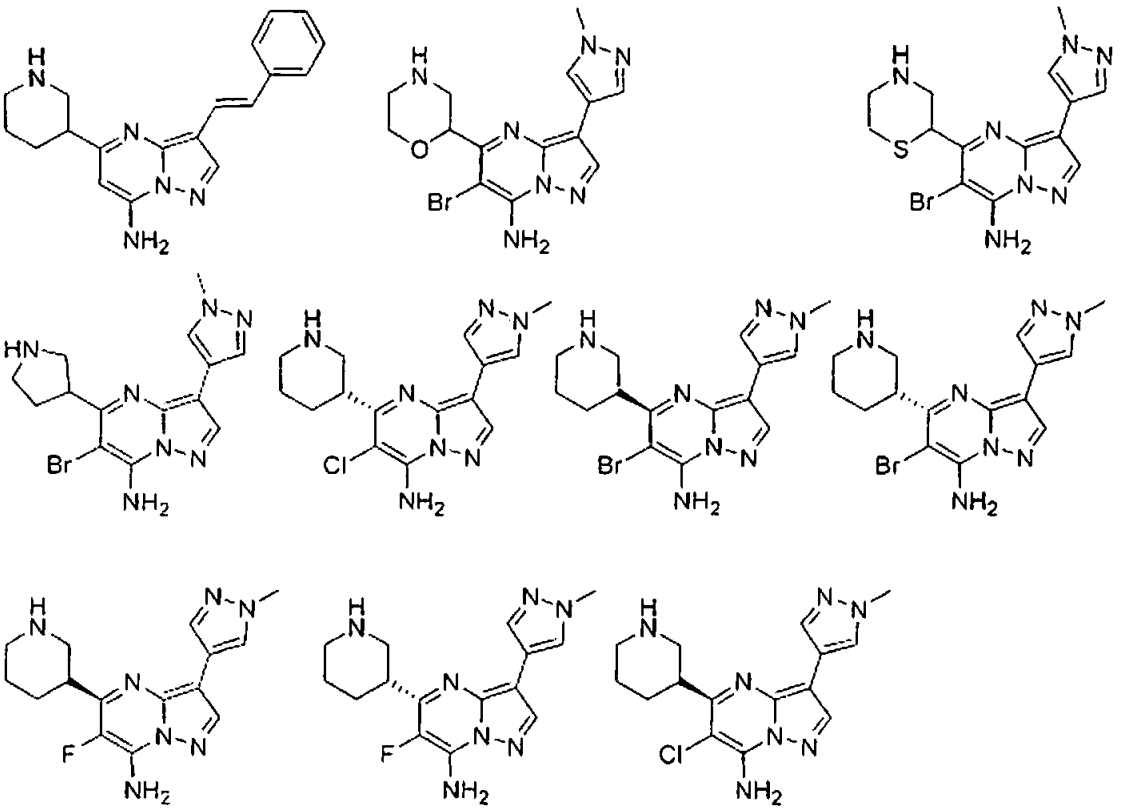












o una sal o solvato de éstos farmacéuticamente aceptable.

Tal como se usó anteriormente, y a través de toda esta descripción, los términos siguientes, a menos que se indique lo contrario, se interpretarán con los significados siguientes:

"Paciente" incluye tanto a seres humanos como a animales.

"Mamífero" significa seres humanos y otros animales mamíferos.

"Alquilo" significa un grupo hidrocarbonado alifático que puede ser recto o ramificado y que comprende aproximadamente 1 hasta aproximadamente 20 átomos de carbono en la cadena. Los grupos alquilo preferidos contienen aproximadamente 1 hasta aproximadamente 12 átomos de carbono en la cadena. Los grupos alquilo más preferidos contienen aproximadamente 1 hasta aproximadamente 6 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferior tales como metilo, etilo o propilo, están unidos a una cadena alquilo lineal. "Alquilo inferior" significa un grupo que tiene aproximadamente 1 hasta aproximadamente 6 átomos de carbono en la cadena que puede ser recto o ramificado. "Alquilo" puede estar no sustituido u

opcionalmente sustituido con uno más sustituyentes que pueden ser iguales o diferentes, donde cada sustituyente está independientemente seleccionado del grupo que consiste en halo, alquilo, arilo, cicloalquilo, ciano, hidroxi, alcoxi, alquiltio, amino, -NH(alquilo), -NH(cicloalquilo), -N(alquilo)$_2$, carboxi y –C(O)O-alquilo. Ejemplos no limitativos de grupos alquilo apropiados incluyen metilo, etilo, n-propilo, isopropilo y t-butilo.

"Alquenilo" significa un grupo hidrocarbonado alifático que contiene por lo menos un enlace doble de carbono a carbono y que puede ser recto o ramificado y que comprende aproximadamente 2 hasta aproximadamente 15 átomos de carbono en la cadena. Los grupos alquenilo preferidos tienen aproximadamente 2 hasta aproximadamente 12 átomos de carbono en la cadena; y más preferiblemente aproximadamente 2 hasta aproximadamente 6 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferior tales como metilo, etilo o propilo, están unidos a una cadena alquenilo lineal. "Alquenilo inferior" significa aproximadamente 2 hasta aproximadamente 6 átomos de carbono en la cadena que puede ser recta o ramificada. "Alquenilo" puede estar no sustituido u opcionalmente sustituido con uno o más sustituyentes que pueden ser iguales o diferentes, donde cada sustituyente está independientemente seleccionado del grupo que consiste en halo, alquilo, arilo, cicloalquilo, ciano, alcoxi y –S(alquilo). Ejemplos no limitativos de grupos alquenilo apropiados incluyen etenilo, propenilo, n-butenilo, 3-metilobut-2-enilo, n-pentenilo, octenilo y decenilo.

"Alquileno" significa un grupo difuncional obtenido por remoción de un átomo de hidrógeno de un grupo alquilo que se definió anteriormente. Ejemplos no limitativos de alquileno incluyen metileno, etileno y propileno.

"Alquinilo" significa un grupo hidrocarbonado alifático que contiene por lo menos un enlace triple de carbono a carbono y que puede ser recto o ramificado y que comprende aproximadamente 2 hasta aproximadamente 15 átomos de carbono en la cadena. Los grupos alquinilo preferidos tiene aproximadamente 2 hasta aproximadamente 12 átomos de carbono en la cadena; y más preferiblemente aproximadamente 2 hasta aproximadamente 4 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferior

722

tales como metilo, etilo o propilo, están unidos a una cadena alquinilo lineal. "Alquinilo inferior" significa aproximadamente 2 hasta aproximadamente 6 átomos de carbono en la cadena la cual puede ser recta o ramificada. Ejemplos no limitativos de grupos alquinilo apropiados incluyen etinilo, propinilo, 2-butinilo y 3-metilbutinilo. "Alquinilo" puede estar no sustituido u opcionalmente sustituido con uno o más sustituyentes que pueden ser iguales o diferentes, donde cada sustituyente está independientemente seleccionado del grupo que consiste en alquilo, arilo y cicloalquilo.

"Arilo" significa un sistema de anillo aromático monocíclico o multicíclico que comprende aproximadamente 6 hasta aproximadamente 14 átomos de carbono, preferiblemente aproximadamente 6 hasta aproximadamente 10 átomos de carbono. El grupo arilo puede estar opcionalmente sustituido con uno o más "sustituyentes del sistema de anillo" que pueden ser iguales o diferentes, y son tal como se definen aquí. Ejemplos no limitativos de grupos arilo apropiados incluyen fenilo y naftilo.

"Heteroarilo" significa un sistema de anillo aromático monocíclico o multicíclico que comprende aproximadamente 5 hasta aproximadamente 14 átomos en el anillo, preferiblemente aproximadamente 5 hasta aproximadamente 10 átomos en el anillo, donde uno o más de los átomos del anillo consisten en un elemento distinto de carbono, por ejemplo, nitrógeno, oxígeno o azufre, solo o en combinación. Los heteroarilos preferidos contienen aproximadamente 5 hasta aproximadamente 6 átomos del anillo. El "heteroarilo" puede estar opcionalmente sustituido con uno o más "sustituyentes del sistema de anillos" que pueden ser iguales o diferentes, y son tal como se definen aquí. El prefijo aza, oxa o tia antes del nombre de raíz heteroarilo, significa que por lo menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, está presente como átomo del anillo. Un átomo de nitrógeno de un heteroarilo puede estar opcionalmente oxidado al N-óxido correspondiente. Ejemplos no limitativos 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, benzimidazolilo, benzotienilo, quinolinilo, imidazolilo, tienopiridilo, quinazolinilo, tienopirimidilo, pirrolopiridilo, imidazopiridilo, isoquinolinilo, benzoazaindolilo, 1,2,4-triazinilo, benzotiazolilo y similares. El término "heteroarilo" se refiere también a porciones heteroarilo parcialmente saturadas tales como, por ejemplo, tetrahidroisoquinolilo, tetrahidroquinolilo y similares.

"Aralquilo" o "arilalquilo" significa un grupo aril-alquil- en el cual el arilo y el alquilo son tal como se han previamente descrito. Los aralquilos preferidos comprenden un grupo alquilo inferior. Ejemplos no limitativos de grupos aralquilo apropiados incluyen bencilo, 2-fenetilo y naftalenilmetilo. El enlace con la porción principal es a través del alquilo.

"Alquilarilo" significa un grupo alquil-aril- en el cual el alquilo y el arilo son tal como se han descrito previamente. Los alquilarilos preferidos comprenden un grupo alquilo inferior. Un ejemplo no limitativo de un grupo alquilarilo apropiado es tolilo. El enlace con la porción principal es a través del arilo.

"Cicloalquilo" significa un sistema de anillo no aromático mono- o multicíclico que comprende aproximadamente 3 hasta aproximadamente 10 átomos de carbono, preferiblemente aproximadamente 5 hasta aproximadamente 10 átomos de carbono. Los anillos cicloalquilo preferidos contienen aproximadamente 5 hasta aproximadamente 7 átomos en el anillo. El cicloalquilo puede estar opcionalmente sustituido con uno o más "sustituyentes del sistema de anillo" que pueden ser iguales o diferentes, y que son tal como se han definido anteriormente. Ejemplos no limitativos de cicloalquilos monocíclicos apropiados incluyen ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo y similares. Ejemplos no limitativos de cicloalquilos multicíclicos apropiados incluyen 1-decalinilo, norbornilo, adamantilo y similares.

"Cicloalquilalquilo" significa una porción cicloalquilo tal como la definida anteriormente ligada a través de una porción alquilo (definida anteriormente) a un núcleo principal. Ejemplos no limitativos de cicloalquilos apropiados incluyen ciclohexilmetilo, adamantilmetilo y similares.

"Cicloalquenilo" significa un sistema de anillo no aromático mono- o multicíclico que comprende aproximadamente 3 hasta aproximadamente 10

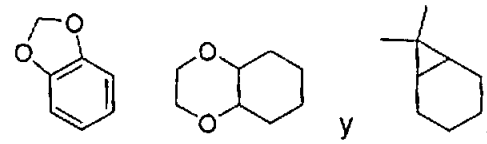
átomos de carbono, preferiblemente aproximadamente 5 hasta aproximadamente 10 átomos de carbono que contiene por lo menos un enlace doble de carbono a carbono. Los anillos cicloalquenilo preferidos contienen aproximadamente 5 hasta aproximadamente 7 átomos de anillo. El cicloalquenilo puede estar opcionalmente sustituido con uno o más "sustituyentes del sistema de anillos" que pueden ser iguales o diferentes, y que son tal como se han definido anteriormente. Ejemplos no limitativos de cicloalquenilos monocíclicos apropiados incluyen ciclopentenilo, ciclohexenilo, ciclohepta-1,3-dienilo, y similares. Un ejemplo no limitativo de un cicloalquenilo apropiado es norbornilenilo.

"Cicloalquenilalquilo" significa una porción cicloalquenilo tal como la definida anteriormente ligada a través de una porción alquilo (definida anteriormente) a un núcleo principal. Ejemplos no limitativos de cicloalquenilalquilos apropiados incluyen ciclopentenilmetilo, ciclohexenilmetilo y similares.

"Halógeno" significa flúor, cloro, bromo, o yodo. Se prefieren flúor, cloro y bromo.

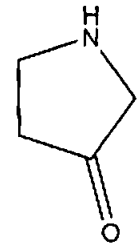
"Sustituyente del sistema de anillos" significa un sustituyente unido a un sistema de anillo aromático o no aromático el cual, reemplaza por ejemplo, un hidrógeno disponible en el sistema de anillo. Los sustituyentes del sistema de anillo pueden ser iguales o diferentes, y cada uno está independientemente seleccionado del grupo que consiste en 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, -C(=N-CN)-NH_2, -C(=NH)-NH_2, -C(=NH)-NH(alquilo), Y_1Y_2N-, Y_1Y_2N-alquilo-, $Y_1Y_2NC(O)$-, $Y_1Y_2NSO_2$- y -$SO_2NY_1Y_2$, donde Y_1 e Y_2 pueden ser iguales o diferentes y están independientemente seleccionados del grupo que consiste en hidrógeno, alquilo, arilo, cicloalquilo, y aralquilo. "Sustituyente del sistema de anillos" puede significar también una porción única la cual reemplaza simultáneamente dos hidrógenos disponibles sobre dos átomos de carbono adyacentes (un H en cada carbono) en

un sistema de anillo. Ejemplos de dicha porción son metilen dioxi, etilendioxi, -$C(CH_3)_2$- y similares que forman porciones tales como, por ejemplo:



"Heteroarilalquilo" significa una porción heteroarilo tal como la definida anteriormente ligada a través de una porción alquilo (definida anteriormente) a un núcleo principal. Ejemplos no limitativos de heteroarilos apropiados incluyen 2-piridinilmetilo, quinolinilmetilo y similares.

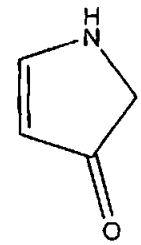
"Heterociclilo" significa un sistema de anillo no aromático saturado monocíclico o multicíclico que comprende aproximadamente 3 hasta aproximadamente 10 átomos en el anillo como preferiblemente aproximadamente 5 hasta aproximadamente 10 átomos en el anillo, donde 1 o más de los átomos en el sistema de anillo es un elemento distinto de carbono, por ejemplo, nitrógeno, oxígeno o azufre, solo o en combinación. No hay ningún átomo de oxígeno y/o azufre adyacente presente en el sistema de anillo. Los heterociclilos preferidos contienen aproximadamente 5 hasta aproximadamente 6 átomos en el anillo. El prefijo aza, oxa o tia antes del nombre de raíz heterociclilo significa que por lo menos un átomo de nitrógeno, oxígeno o azufre respectivamente está presente como un átomo del anillo. Cualquier –NH en un anillo heterociclilo puede existir protegido tal como, por ejemplo, como un grupo -N(Boc), -N(CBz), -N(Tos) y similares; dichas protecciones se consideran también parte de esta invención. El heterociclilo puede estar opcionalmente sustituido con uno o más "sustituyentes del sistema de anillos" que pueden ser iguales o diferentes, y son tal como se definen aquí. El átomo de nitrógeno o azufre del heterociclilo puede estar opcionalmente oxidado al N-óxido, S-óxido o S,S-dióxido. Ejemplos no limitativos de anillos monocíclicos heterociclilo incluyen piperidilo, pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, 1,4-dioxanilo, tetrahidrofuranilo, tetrahidrotiofenilo, lactama, lactona, y similares. "Heterociclilo" puede significar también una porción única (por ejemplo, carbonilo) que reemplaza simultáneamente dos hidrógenos disponibles en el mismo átomo de carbono en un sistema de anillo. Un ejemplo de dicha porción es pirrolidona:



"Heterociclilalquilo" significa una porción heterociclilo tal como la definida anteriormente ligada a través de una porción alquilo (definida anteriormente) a un núcleo principal. Ejemplos no limitativos de heterociclilalquilos apropiados incluyen piperidinilmetilo, piperazinilmetilo y similares.

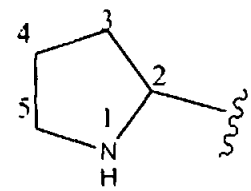
"Heterociclenilo" significa un sistema de anillo no aromático monocíclico o multicíclico que comprende aproximadamente 3 hasta aproximadamente 10 átomos en el anillo, preferiblemente aproximadamente 5 hasta aproximadamente 10 átomos en el anillo, en el cual uno o más de los átomos en el sistema de anillo son un elemento distinto de carbono, por ejemplo, un átomo de nitrógeno, oxígeno o azufre, solos o en combinación, y que contiene por lo menos un enlace doble de carbono a carbono o un enlace doble de carbono a nitrógeno. No hay ningún átomo de oxígeno y/o azufre adyacente presente en el sistema de anillo. Los anillos heterociclenilo preferidos contienen aproximadamente 5 hasta aproximadamente 6 átomos en el anillo. El prefijo aza, oxa o tia antes del nombre de raíz heterociclenilo significa que por lo menos un átomo de nitrógeno, oxígeno o azufre respectivamente está presente como un átomo del anillo. El heterociclenilo puede estar opcionalmente sustituido con uno o más sustituyentes del sistema de anillo donde "sustituyente del sistema de anillo" es tal como se ha definido anteriormente. El átomo de nitrógeno o azufre del heterociclenilo puede estar opcionalmente oxidado al N-óxido, S-óxido o S,S-dióxido correspondiente. Ejemplos no limitativos de grupos heterociclenilos 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, fluordihidrofuranilo, 7-oxabiciclo[2.2.1]heptenilo, dihidrotiofenilo, dihidrotiopiranilo, y similares. "Heterociclenilo" puede significar también una porción única (por ejemplo,

carbonilo) que simultáneamente reemplaza dos hidrógenos disponibles en el mismo átomo en un sistema de anillo, un ejemplo de dicha porción es pirrolidinona:



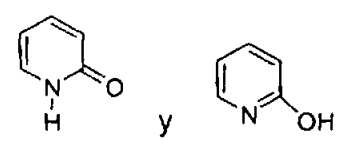
"Heterociclenilalquilo" significa una porción heterociclenilo tal como la definida anteriormente ligada a través de una porción alquilo (definida anteriormente) a un núcleo principal.

Cabe observar que en los sistemas de anillo de esta invención que contienen hetero-átomos, no hay ningún hidroxilo en los átomos de carbono adyacentes a un N, O o S, y tampoco hay ningún grupo N o S en el carbono adyacente a otro heteroátomo. Por lo tanto, por ejemplo, in el anillo:



no hay ningún -OH unido directamente a los carbonos 2 y 5.

Cabe observar también que las formas tautoméricas tales como, por ejemplo:



se consideran equivalentes en cierta realizaciones de esta invención.

"Alquinilalquilo" significa un grupo alquinil-alquil- en el cual el alquinilo y alquilo son tal como se han descrito previamente. Los alquinilalquilos preferidos contienen un grupo alquinilo inferior y un alquilo inferior. El enlace con la porción principal es a través del alquilo. Ejemplos no limitativos de grupos alquinilalquilo apropiados incluyen propargilmetilo.

"Heteroaralquilo" significa un grupo heteroaril-alquil- en el cual el heteroarilo y el alquilo son tal como se han descrito previamente. Los

heteroaralquilos preferidos contienen un grupo alquilo inferior. Ejemplos no limitativos de grupos aralquilo apropiados incluyen piridilmetilo, y quinolin-3-ilmetilo. El enlace con la porción principal es a través del alquilo.

"Hidroxialquilo" significa un grupo HO-alquil- en el cual el alquilo es tal como se ha definido previamente. Los hidroxialquilos preferidos contienen alquilo inferior. Ejemplos no limitativos de grupos de hidroxialquilo apropiados incluyen hidroximetilo y 2-hidroxietilo.

"Acilo" significa un grupo H-C(O)-, alquilo-C(O)- o cicloalquilo-C(O)-, en el cual los varios grupos son tal como se han descrito previamente. El enlace con la porción principal es a través del carbonilo. Los acilos preferidos contienen un alquilo inferior. Ejemplos no limitativos de grupos acilo apropiados incluyen formilo, acetilo y propanoilo.

"Aroilo" significa un grupo aril-C(O)- en el cual el grupo arilo es tal como se ha descrito previamente. El enlace con la porción principal es a través del carbonilo. Ejemplos no limitativos de grupos apropiados incluyen benzoilo y 1-naftoilo.

"Alcoxi" significa un grupo alquil-O- en el cual el grupo alquilo es tal como se ha descrito previamente. Ejemplos no limitativos de grupos alcoxi apropiados incluyen metoxi, etoxi, n-propoxi, isopropoxi y n-butoxi. El enlace con la porción principal es a través del oxigeno del éter.

"Ariloxi" significa un grupo aril-O- en el cual el grupo arilo es tal como se ha descrito previamente. Ejemplos no limitativos de grupos ariloxi apropiados incluyen fenoxi y naftoxi. El enlace con la porción principal es a través del oxígeno del éter.

"Aralquiloxi" significa un grupo aralquil-O- en el cual el grupo aralquilo es tal como se ha descrito previamente. Ejemplos no limitativos de grupos aralquiloxi apropiados incluyen benciloxi y 1- o 2-naftalenmetoxi. El enlace con la porción principal es a través del oxígeno del éter.

"Alquiltio" significa un grupo alquil-S- en el cual el grupo alquilo es tal como se ha descrito previamente. Ejemplos no limitativos de grupos alquiltio apropiados incluyen metiltio y etiltio. El enlace con la porción principal es a través del azufre.

"Ariltio" significa un grupo aril-S- en el cual el grupo arilo es tal como se ha descrito previamente. Ejemplos no limitativos de grupos ariltio apropiados incluyen feniltio y naftiltio. El enlace con la porción principal es a través del azufre.

"Aralquiltio" significa un grupo aralquil-S- en el cual el grupo aralquilo es tal como se ha descrito previamente. Un ejemplo no limitativo de un grupo aralquiltio apropiado es benciltio. El enlace con la porción principal es a través del azufre.

"Alcoxicarbonilo" significa un grupo alquil-O-CO-. Ejemplos no limitativos de grupos alcoxicarbonilo apropiados incluyen metoxicarbonilo y etoxicarbonilo. El enlace con la porción principal es a través del carbonilo.

"Ariloxicarbonilo" significa un grupo aril-O-C(O)-. Ejemplos no limitativos de grupos ariloxicarbonilo apropiados incluyen fenoxicarbonilo y naftoxicarbonilo. El enlace con la porción principal es a través del carbonilo.

"Aralcoxicarbonilo" significa un grupo aralquil-O-C(O)-. Un ejemplo no limitativo de un grupo aralcoxicarbonilo apropiado es benciloxicarbonilo. El enlace con la porción principal es a través del carbonilo.

"Alquilsulfonilo" significa un grupo alquil-$S(O_2)$-. Los grupos preferidos son aquellos en los cuales el grupo alquilo es alquilo inferior. El enlace con la porción principal es a través del sulfonilo.

"Arilsulfonilo" significa un grupo aril-$S(O_2)$-. El enlace con la porción principal es a través del sulfonilo.

El término "sustituido" significa que uno o más hidrógenos en el átomo designado se reemplazan con una selección de grupo indicado, con la condición de no exceder la valencia normal del átomo designado bajo las circunstancias existentes, y que la sustitución provea como resultado un compuesto estable. Las combinaciones de sustituyentes y/o variables son únicamente permisibles si dichas combinaciones dan como resultado un compuesto estable. Mediante "un compuesto estable" o "una estructura estable" se indica un compuesto que es suficientemente robusto para sobrevivir a la aislación hasta un grado útil de pureza a partir de una mezcla de reacción, y su formulación en un agente terapéutico eficaz.

El término "opcionalmente sustituido" significa una sustitución opcional con los grupos radicales o porciones especificadas.

El término "purificado", "en forma purificada" o "en forma aislada y purificada" para un compuesto se refiere al estado físico de dicho compuesto después de haber sido aislado de un procedimiento de síntesis o de una fuente natural o de combinaciones de éstos. Por lo tanto, el término "purificado", "en forma purificada" o "en forma aislada y purificada" para un compuesto se refiere al estado físico de dicho compuesto de haber sido obtenido a partir de un proceso o procesos de purificación descritos aquí o que son bien conocidos por un experto en la materia, con una pureza suficiente para ser caracterizable por técnicas analíticas convencionales tal como las que se describen aquí o que son bien conocidas por los expertos en la materia.

Cabe observar que cualquier carbono así como también heteroátomo con valencias no satisfechas en el texto, esquemas, ejemplos y tablas que se dan aquí se considera que tiene la cantidad suficiente de átomos de hidrógeno para satisfacer las valencias. Cuando un grupo funcional en un compuesto se denomina "protegido", esto significa que el grupo está en forma modificada para evitar cualquier reacción indeseable en el sitio protegido cuando el compuesto es sometido a una reacción. Los grupos protectores apropiados, serán reconocidos por los expertos en la materia así como también en las referencias a los libros de texto convencionales tales como, por ejemplo, T. W. Greene *et al*, *Protective Groups in organic Syntesis* (1991), Wiley, New York.

Cuando cualquier variable (por ejemplo, arilo, heterociclo, R^2, etc.) ocurre más de una vez en cualquier constituyente o en la Fórmula III, su definición cada vez que ocurre es independiente de su definición cada vez que vuelve a ocurrir.

Tal como se usa aquí, el término "composición" abarca un producto que comprende los ingredientes especificados en las cantidades especificadas, así como también cualquier producto, directo o indirecto, de la combinación de los ingredientes especificados en las cantidades especificadas.

Los profármacos y solvatos de los compuestos de la invención están también contemplados aquí. Una discusión de los profármacos es provista por T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 del A.C.S. Symposium Series, y en *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Farmaceutical Association and Pergamon Press. El término

"profármaco" significa un compuesto (por ejemplo, un precursor de un fármaco) que es transformado *in vivo* para proporcionar un compuesto de Fórmula (III) o una sal, hidrato o solvato del compuesto farmacéuticamente aceptable. La transformación puede ocurrir mediante varios mecanismos (por ejemplo, procesos metabólicos o químicos), tales como, por ejemplo, a través de hidrólisis en sangre. Una discusión del uso de profármacos ha sido provista por T. Higuchi and W. Stella, "Pro-drugs as Novel Delivery Systems," Vol. 14 del A.C.S. Symposium Series, y en Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Farmaceutical Association and Pergamon Press, 1987.

Por ejemplo, si un compuesto de Fórmula (III) o una sal, hidrato o solvato farmacéuticamente aceptable del compuesto contiene un grupo funcional de ácido carboxílico, un profármaco puede comprende 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), alcanoiloximetilo(C_2-C_{12}), 1-(alcanoiloxi)etilo que tiene de 4 a 9 átomos de carbono, 1-metil-1-(alcanoiloxi)-etilo que tiene de 5 a 10 átomos de carbono, alcoxicarboniloximetilo que tiene de 3 a 6 átomos de carbono, 1-(alcoxicarboniloxi)etilo que tiene de 4 a 7 átomos de carbono, 1-metil-1-(alcoxicarboniloxi)etilo que tiene de 5 a 8 átomos de carbono, N-(alcoxicarbonil)aminometilo que tiene de 3 a 9 átomos de carbono, 1-(N-(alcoxicarbonil)amino)etilo que tiene de 4 a 10 átomos de carbono, 3-ftalidilo, 4-crotonolactonilo, gamma-butirolacton-4-ilo, di-N,N- alquilamino(C_1-C_2) alquilo(C_2-C_3) (tal como β-dimetilaminoetilo), carbamoil- alquilo(C_1-C_2), N,N-di alquilcarbamoilo(C_1-C_2)- alquilo(C_1-C_2) y piperidino-, pirrolidino- o morfolino alquilo (C_2-C_3), y similares.

De manera similar, si un compuesto de Fórmula (III) contiene un grupo alcohol funcional, puede formarse un profármaco 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 alcanilo(C_1-C_4), arilacilo y α-aminoacilo, o α-aminoacilo-α-aminoacilo, donde cada grupo α-aminoacilo está independientemente seleccionado de los L-aminoácidos, $P(O)(OH)_2$, -P(O)(O

alquilo(C_1-C_6))$_2$ o glicosilo (el radical resultante de la remoción de un grupo hidroxilo de la forma hemiacetal de un carbohidrato), y similares.

Si un compuesto de Fórmula (III) incorpora un grupo funcional amina, puede formarse un profármaco 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 independientemente alquilo(C_1-C_{10}), cicloalquilo(C_3-C_7), bencilo, o R-carbonilo es un α-aminoacilo natural o α-aminoacilo natural, —C(OH)C(O)OY^1 donde Y^1 es H, alquilo(C_1-C_6) o bencilo, —C(OY^2)Y^3 donde Y^2 es alquilo(C_1-C_4) e Y^3 es alquilo(C_1-C_6), carboxi alquilo(C_1-C_6), amino alquilo(C_1-C_4) o mono-N—o di-N,N- alquilaminoalquilo(C_1-C_6), —C(Y^4)Y^5 donde 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 forma no solvatada así como también en forma solvatada con solventes farmacéuticamente aceptables tales como agua, etanol y similares, y se desea que la presente invención abarque tanto las formas solvatadas como las no solvatadas. "Solvato" significa una asociación física de un compuesto de esta invención con uno o más moléculas solventes. Esta asociación física involucra varios grados de unión iónica y covalente, incluyendo unión de hidrógeno. En algunos casos el solvato será capaz de aislación, por ejemplo, cuando se incorpora en una o más moléculas de solvente en el retículo cristalino del sólido cristalino. "Solvato" abarca tanto los solvatos en fase de solución como los aislables. Ejemplos no limitativos de solvatos apropiados incluyen etanolatos, metanolatos, y similares. "Hidrato" es un solvato en el cual la molécula solvente es H_2O.

Uno o más de los compuestos de la invención pueden convertirse opcionalmente a un solvato. La preparación de solvatos es generalmente conocida. Por lo tanto, por ejemplo, M. Caira *et al*, *J. Farmaceutical Sci.*, 93(3), 601-611 (2004) describen la preparación de los solvatos del fluconazol antifungal en acetato de etilo así como también en agua. Preparaciones similares de solvatos, himisolvatos, hidratos y otros han sido descritos por E. C. van Tonder *et al*, *AAPS FarmSciTech.*, 5(1), article 12 (2004); y A. L. Bingham *et al*, *Chem. Commun.*, 603-604 (2001). Un procedimiento típico, no limitativo, involucra

disolver el compuesto de la invención en las cantidades deseadas del solvente deseado (orgánico o agua o mezclas de éstos) a una temperatura superior a la temperatura ambiente, y enfriar la solución a un régimen suficiente para formar cristales que luego son aislados por métodos convencionales. Las técnicas analíticas tales como, por ejemplo, espectroscopia I. R., muestran la presencia del solvente (o agua) en los cristales como un solvato. (o hidrato).

"Cantidad eficaz" o "cantidad terapéuticamente eficaz" describe una cantidad de compuestos o una composición de la presente invención que es eficaz para inhibir las enfermedades antes mencionadas y que por lo tanto produce el efecto terapéutico, mejorador, inhibitorio o preventivo deseado.

Los compuestos de la Fórmula III pueden formar sales que están también dentro del alcance de esta invención. La referencia a un compuesto de Fórmula III como se da aquí, se interpreta que incluye referencia a sus sales, a menos que se indique lo contrario. El término "sal(es)", tal como se emplea aquí, denota las sales ácidas formadas con ácidos inorgánicos y/o orgánicos, así como también las sales básicas formadas con bases inorgánicas y/o orgánicas. Además, cuando un compuesto de Fórmula III contiene una porción básica, tal como, pero sin limitarlo a una piridina o imidazol, y una porción ácida, tal como, pero sin limitarlo a un ácido carboxílico, pueden formarse zwitteriones ("sales internas") y se incluirán dentro del término "sale(s)" tal como se usa aquí.

Se prefieren las sales farmacéuticamente aceptables (es decir, no tóxicas, fisiológicamente aceptables) aunque son también útiles otras sales. Las sales de los compuestos de la Fórmula III pueden formarse, por ejemplo, por reacción de un compuesto de Fórmula III con una cantidad de ácido o base, tal como una cantidad equivalente, en un medio tal como aquel en el cual precipitan la sal o en un medio acuoso seguido de liofilización.

Ejemplos de sales de adición de ácido incluyen acetatos, ascorbatos, benzoatos, bencensulfonatos, bisulfatos, boratos, butiratos, citratos, alcanforatos, alcanforsulfonatos, fumaratos, clorhidratos, bromhidratos, yodhidratos, lactatos, maleatos, metansulfonatos, naftalensulfonatos, nitratos, oxalatos, fosfatos, propionatos, salicilatos, succinatos, sulfatos, tartaratos, tiocianatos, toluensulfonatos (conocidos también como tosilatos), y similares. Adicionalmente,

los ácidos que generalmente son considerados apropiados para la formación de sales farmacéuticamente útiles a partir de compuestos farmacéuticos básicos, han sido discutidos, por ejemplo, por P. Stahl *et al*, Camille G. (eds.) *Handbook of Farmaceutical Salts. Properties, Selection and Use.* (2002) Zurich: Wiley-VCH; S. Berge *et al*, *Journal of Farmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Farmaceutics* (1986) 33 201-217; Anderson *et al*, *Te Practice of Medicinal Chemistry* (1996), Academic Press, New York; y en *The Orange Book* (Food & Drug Administration, Washington, D.C. en su sitio de la red). Estas descripciones se incorporan aquí como referencia.

Ejemplos de sales básicas incluyen sales de amonio, sales de metales alcalinos tales como sales de sodio, litio y potasio, sales de metales alcalino térreos tales como sales de calcio y magnesio, sales con bases orgánicas (por ejemplo, aminas orgánicas) tales diciclohexilaminas, t-butil aminas, y sales con amino ácidos tales como arginina, lisina y similares. Los grupos básicos que contienen nitrógeno, pueden cuaternizarse con agentes tales como aluros de alquil inferior (por ejemplo, cloruros, bromuros y yoduros de metilo, etilenbutilo), 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.

Todas dichas sales ácidas y sales básicas se consideran sales farmacéuticamente aceptables dentro del alcance de la invención y todas dichas sales ácidas y básicas se consideran equivalentes a las formas libres de los compuestos correspondientes para los propósitos de la invención.

Los ésteres farmacéuticamente aceptables de los presentes compuestos incluyen los grupos siguientes: (1) ésteres de ácido carboxílico obtenidos por esterificación de los grupos hidroxi, en los cuales la porción no carbonilo de la porción ácido carboxilo de la agrupación éster está seleccionada entre 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 opcionalmente sustituido 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 aminoácidos (por ejemplo, L-valilo o L-isoleucilo); (4) ésteres de fosfonato y (5) ésteres de mono-, di- o trifosfato. Los ésteres de fosfato pueden esterificarse adicionalmente mediante, por ejemplo, un alcohol C_{1-20} o un derivado reactivo de éste, o mediante un 2,3-di acilo(C_{6-24}) glicerol.

Los compuestos de Fórmula III, y las sales, solvatos, ésteres y profármacos de éstos pueden existir en su forma tautomérica (por ejemplo, en forma de una amida o imino éter).Todas dichas formas tautoméricas están contempladas aquí como parte de la presente invención.

Los compuestos de Fórmula (III) pueden contener centros quirales o asimétricos y por lo tanto existen en formas estereoisoméricas diferentes. Se considera que todas las formas estereoisoméricas de los compuestos de la Fórmula (III) así como también sus mezclas, incluyendo las mezclas racémicas, forman parte de la presente invención. Además, la presente invención abarca todos los isómeros geométricos y posicionales. Por ejemplo, si un compuesto de Fórmula (III) incorpora un enlace doble o un anillo fusionado, ambas formas cis- y trans-, así como también mezclas, están abarcadas dentro del alcance de la invención.

Las mezclas diastereoméricas pueden separarse en sus diastereómeros individuales en base a sus diferencias químico físicas por métodos que son bien conocidos por los expertos en la materia, tales como, por ejemplo, por cromatografía y/o por cristalización fraccionada. Los enantiómeros pueden separarse mediante conversión de la mezcla enantiomérica a una mezcla diaestereomérica por reacción con un compuesto óptimamente activo apropiado (por ejemplo, un auxiliar quiral tal como un alcohol quiral o un cloruro de ácido de Mosher), por separación de los diastereómeros y conversión (por ejemplo, hidrolización) de los diaestereómeros individuales a los enantiómeros puros correspondientes. Asimismo, algunos de los compuestos de Fórmula (III) pueden ser atropisómeros (por ejemplo, biarilos sustituidos) y se consideran parte de la invención. Los enantiómeros pueden separarse también mediante el uso de una columna quiral HPLC.

También es posible que los compuestos de Fórmula (III) puedan existir en formas tautoméricas diferentes, y todas dichas formas están abarcadas dentro del alcance de la invención. Asimismo, por ejemplo, todas las formas ceto-enol e imina-enamina de los compuestos están incluidos en la invención.

Todos los estereoisómeros (por ejemplo, los isómeros geométricos, los isómeros ópticos y similares) de los presentes compuestos (incluyendo aquellos de las sales, solvatos, ésteres y profármacos de los compuestos así como también las sales, solvatos y ésteres de los profármacos) tales como aquellos que pueden existir debido a los carbonos asimétricos en varios sustituyentes, incluyendo las formas enantioméricas (que pueden existir incluso en ausencia de carbonos asimétricos) las formas rotaméricas, los atropisómeros, y las formas diaestereoméricas, están contempladas dentro del alcance de la invención, así como también los isómeros posicionales (tales como, por ejemplo, 4-piridilo y 3-piridilo). (Por ejemplo, si un compuesto de Fórmula (III) incorpora un enlace doble o un anillo fusionado, tanto la forma cis- como la forma trans-, así como también las mezclas, están abarcadas dentro del alcance de la invención. Asimismo, por ejemplo, todas las formas de ceto-enol e imina-enamina de los compuestos están incluidas en la invención). Los estereoisómeros individuales de los compuestos de la invención pueden estar, por ejemplo, sustancialmente libres de otros isómeros, o pueden mezclarse, por ejemplo, como racematos o con todos los otros, o con otros estereoisómeros seleccionados. Los centros quirales de la presente invención pueden tener la configuración S o R que ha sido definida por las Recomendaciones *IUPAC* 1974. El uso de los términos "sal", "solvato", "éster", "profármaco" y similares, se aplica igualmente a la sal, solvato, éster y profármaco de los enantiómeros, estereoisómeros, rotámeros, tautómeros, isómeros posicionales, racematos o profármacos de los compuestos de la invención.

La presente invención abarca también los compuestos rotulados isotópicamente de la presente invención que son idénticos a los que se indican aquí, excepto por el hecho de que uno o más átomos son reemplazados con un átomo que tiene una maza atómica o un número de maza diferente de la maza atómica o número de maza que se encuentra usualmente en la naturaleza. Ejemplos de isótopos que pueden incorporarse a los compuestos de la invención

incluyen los isótopos de hidrógeno, carbono, nitrógeno, oxígeno, fósforo, flúor y cloro, tales como ^{2}H, ^{3}H, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{31}P, ^{32}P, ^{35}S, ^{18}F, y ^{36}Cl, respectivamente.

Algunos compuestos rotulados isotópicamente de la Fórmula (III) (por ejemplo, aquellos que están rotulados con ^{3}H y ^{14}C) son útiles en los ensayos de distribución de compuesto y/o tejido de sustrato. Los isótopos tritiados (es decir, ^{3}H) y de carbono-14 (es decir, ^{14}C) son particularmente preferidos por su facilidad de preparación y detectabilidad. Además, la sustitución con isótopos más pesados tales como deuterio (es decir, ^{2}H) pueden proporcionar ciertas ventajas terapéuticas que dan como resultado una estabilidad metabólica superior (por ejemplo, un aumento de la vida media *in vivo* o requisitos de dosificación reducidos), y por lo tanto pueden preferirse en algunas circunstancias. Los compuestos rotulados isotópicamente de Fórmula (III) pueden prepararse en general siguiendo procedimientos análogos a los descritos en los Esquemas y/o en los Ejemplos, sustituyendo un reactivo rotulado isotópicamente apropiado con un reactivo no rotulado isotópicamente.

Las formas polimórficas de los compuestos de la Fórmula III, y de las sales, solvatos ésteres y profármacos de los compuestos de la Fórmula III, se incluyen en la presente invención.

El término "composición farmacéutica" abarca tanto la composición en masa como las unidades de dosificación individuales que comprenden más de un (por ejemplo dos) agente farmacéuticamente activo tal como por ejemplo un compuesto de la presente invención y un agente adicional seleccionado de la lista de agentes adicionales que se describen aquí, junto con cualquier excipiente farmacéuticamente inactivo. La composición en masa y cada unidad de dosificación individual puede contener "más de un agente farmacéuticamente activo" antes mencionado. La composición en masa es un material que no ha sido formado todavía en unidades de dosificación individuales. Una unidad de dosificación ilustrativa es una dosis oral tal como tabletas, píldoras y similares. De manera similar, el método descrito aquí para el tratamiento de un paciente mediante la administración de una composición farmacéutica de la presente

invención abarca también la administración de la composición en masa antes mencionada y de las unidades de dosificación individuales.

Los compuestos de acuerdo con la invención tienen propiedades farmacológicas: en particular, los compuestos de Fórmula III pueden ser inhibidores de las proteinquinasas tales como por ejemplo los inhibidores de las quinasas dependientes de glicina, la proteinquinasa activada mitógeno (MAPK/ERK), la glicógeno sintasa quinasa 3(GSK3beta) y similares. Las quinasas dependen desde ciclina (CDKs) incluyen por ejemplo, CDC2 (CDK1), CDK2, CDK4, CDK5, CDK6, CDK7 CDK8 y CDK9. Se espera que los nuevos compuestos de Fórmula III serán útiles en la terapia de las enfermedades proliferativas tales como cáncer, enfermedades autoinmunitarias, enfermedades virales, enfermedades fúngicas, desórdenes neurológicos/neurodegenerativos, artritis, inflamación, enfermedad antiproliferativa (por ejemplo, retinopatía ocular), neuronal, alopecia y enfermedades cardiovasculares. Muchas de estas enfermedades y desórdenes están enumerados en la Patente Norteamericana 6.413.974 citada anteriormente cuya descripción se incorpora aquí.

Más específicamente, los compuestos de Fórmula III pueden ser útiles en el tratamiento de una variedad de cánceres, que incluyen (pero que no están limitados a) los siguientes:

carcinoma, incluyendo el de vesícula, mama, colon, riñón, hígado, pulmón, incluyendo cáncer pulmonar de células pequeñas, cáncer pulmonar de células no pequeñas, cáncer de cabeza y cuello, de esófago, de vesícula biliar, ovario, páncreas, estómago, cuello uterino, tiroides, próstata y piel, incluyendo carcinoma de células escamosas;

tumores hematopoyéticos de linaje linfoide, que incluyen leucemia, leucemia linfocítica aguda, leucemia linfoblástica, 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;

tumores hematopoyéticos de linaje mieloide que incluyen leucemias mielógenas agudas y crónicas, síndrome mielodisplásico y leucemia promielocítica;

tumores de origen mesenquimal, que incluyen fibrosarcoma y rabdomiosarcoma;

tumores del sistema nervioso central y periférico, que incluyen astrocitoma, neuroblastoma, glioma y schwannomas; y

otros tumores, que incluyen melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, queratoctantoma, cáncer folicular de tiroides y sarcoma de Kaposi.

Debido al rol principal de CDKs en la regulación de la proliferación celular en general, los inhibidores podrían actuar como agentes citostáticos reversibles que pueden ser útiles en el tratamiento de cualquier proceso de enfermedad caracterizado por proliferación celular anormal, por ejemplo, hiperplasia benigna de próstata, adenomatosis poliposis familiar, neuro-fibromatosis, ateroesclerosis, fibrosis pulmonar, artritis, soriasis, glomérulonefritis, restinosis después de angioplastia o cirugía vascular, formación hipertrófica de cicatrices, enfermedad inflamatoria del intestino, rechazo a los transplantes, shock endotóxico, e infecciones fúngicas.

Los compuestos de Fórmula III pueden también se útiles en el tratamiento de la enfermedad de Alzheimer, tal como ha sido sugerido por recientes descubrimientos de CDK5 está involucrado en la fosforilación de la proteína tau (*J. Biochem*, (1995) 117, 741-749).

Los compuestos de Fórmula III pueden inducir o inhibir apoptosis. La respuesta apoptótica es aberrante en una variedad de enfermedades humanas. Los compuestos de Fórmula III, como moduladores de apoptosis, serán útiles en el tratamiento del cáncer (incluyendo pero sin limitarlo a aquellos tipos mencionados anteriormente), infecciones virales (incluyendo pero sin limitarlo a herpevirus, enfermedades eruptivas víricas, virus de Epstein- Barr, virus de Sindbis y adenovirus), prevención del desarrollo del SIDA en individuos infectados con HIV, enfermedades autoinmunitarias (que incluyen pero que no están limitadas a lupus sistémico, eritematoso, glomérulonefritis intermediada por autoinmunidad, artritis reumatoidea, soriasis, enfermedad inflamatoria del intestino, y diabetes melitus autoinmunitaria), desórdenes neurodegenerativos

(que incluyen pero que no están limitados a la enfermedad de Alzheimer, demencia relacionada con SIDA, enfermedad de Parkinson, esclerosis lateral amiotrófica, retinitis pigmentosa, atrofia muscular espinal, y degeneración del cerebelo), síndromes mielodisplásicos, anemia aplásica, lesiones isquémicas asociadas con infartos del miocardio, apoplejía y lesiones por reperfusión, arritmia, ateroesclerosis, enfermedades hepáticas relacionadas con alcohol o inducidos por toxinas, enfermedades hematológicas (que incluyen pero que no están limitadas a anemia crónica y a anemia aplásica), enfermedades degenerativas del sistema musculoesqueletal (que incluyen pero que no están limitadas a osteoporosis y artritis), rinosinusitis sensible a la aspirina, fibrosis quística, esclerosis múltiple, enfermedades del riñón y dolor causado por cáncer.

Los compuestos de Fórmula III, como inhibidores de las CDKs, pueden modular el nivel de síntesis de RNA y ADN celular. Estos agentes serían por lo tanto útiles en el tratamiento de infecciones virales (que incluyen pero que no están limitadas a HIV, virus de papiloma humano, herpesvirus, enfermedades eruptivas víricas, virus de Epstein-Barr, virus de Sindbis y adenovirus).

Los compuestos de Fórmula III pueden ser también útiles en la quimioprevención del cáncer. La quimioprevención se define como la inhibición del desarrollo de cáncer invasivo ya sea por bloqueo del evento mutagénico iniciador o bien por bloqueo del progreso de células pre-malignas que han sufrido ya una agresión o por inhibición del relapso del tumor.

Los compuestos de Fórmula III pueden ser también útiles para inhibir la angiogénesis tumoral y la metástasis.

Los compuestos de Formula III pueden actuar también como inhibidores de otras quinasas como por ejemplo proteinquinasa C, her2, raf 1, MEK1, MAP quinase, receptor EGF, receptor PDGF, receptor IGF, PI3 quinasa, wee1 quinasa, Src, Abl y por lo tanto pueden ser eficaces en el tratamiento de enfermedades que están asociadas con otras proteinquinasas.

Otro aspecto de esta invención es un método para el tratamiento de un mamífero (por ejemplo un ser humano) que tiene una enfermedad o trastorno asociado con las CDKs y desde la administración de una cantidad terapéuticamente eficaz de por lo menos un compuesto de Formula III, o una sal o

solvato farmacéuticamente aceptable de dicho compuesto al mamífero.

Una dosis preferida es de aproximadamente 0,001 hasta 500 mg/kg de peso corporal/día del compuesto de Formula III. Una dosis especialmente preferida es de aproximadamente 0,01 hasta 25 mg/kg de peso corporal/día de un compuesto de Formula III, o una sal o solvato farmacéuticamente aceptable de dicho compuesto.

Los compuestos de esta invención pueden ser también útiles en combinación (administrados conjuntamente o consecutivamente) con uno o más de tratamientos anti-cáncer tales como terapia de radiación y/o uno o más agentes anti-cáncer seleccionados del grupo que consisten agentes citoestáticos, agentes citotóxicos (tales como por ejemplo, pero sin limitarlo a, agentes interactivos de ADN (tales como cisplatina o doxorubicina)); taxanos (por ejemplo, taxotero, taxol); inhibidores de topoisomerasa II (tales como etopida); inhibidores de topoisomerasa I (tales como irinotecan (o CPT-11), camptostar, o topotecan); agentes que interactúan con tubulina (tales como paclitaxel, docetaxel o las epotilonas); agentes hormonales (tales como tamoxifeno); inhibidores de timidilatos sintasa (tales como 5-fluoruracilo); anti-metabolitos (tales como metotrexatos); agentes alquilantes (tales como temozolomida (TEMODAR™ de Schering-Plough Corporation, Kenilworth, New Jersey), ciclofosfamida); inhibidores protein transferasa de Farnesilo (tales como, SARASAR™(4-[2-[4-[(11R)-3,10-dibromo-8-cloro-6,11-dihidro-5H-benzo[5,6]ciclohepta[1,2-b]piridin-11-il-]-1-piperidinil]-2-oxoetil]-1-piperidincarboxamida, o SCH 66336 de Schering-Plough Corporation, Kenilworth, New Jersey), tipifarnib (Zarnestra® o R115777 de Janssen Pharmaceuticals), L778,123 (un inhibidor de la proteína transferasa farnesilo, de Merck & Company, Whitehouse Station, New Jersey), BMS 214662 (un inhibidor de proteína transferasa farnesilo de Bristol-Myers Squibb Pharmaceuticals, Princeton, New Jersey); inhibidores de transducción de señales (tales como Iressa (de Astra Zeneca Pharmaceuticals, England), Tarceva (inhibidores de EGFR quinasas), anticuerpos para EGFR (por ejemplo, C225), GLEEVEC™ (un inhibidor de C-abl quinasa de Novartis Pharmaceuticals, East Hanover, New Jersey); interferones tales como por ejemplo, intron (de Schering-Plough Corporation), Peg-Intron (de Schering-Plough Corporation);

942

combinaciones de terapias hormonales; combinaciones de aromatasa; ara-C, adriamicina, citoxan, y gemcitabina.

Otros agentes anti-cáncer (conocidos también como anti-neoplásicos) incluyen pero no están limitados a Uracil mostaza, Clorometina, Ifosfamida, Melfalan, Clorambucilo, Pipobroman, Trietilenmelamina, Trietilenetiofosforamina, Busulfano, Carmustina, Lomustina, Streptozocina, Dacarbazina, Floxuridina, Citarabina, 6-Mercaptopurina, 6-Tioguanina, Fludarabina fosfato, oxaliplatina, leucovirina, oxaliplatina (ELOXATIN™ de Sanofi-Synthelabo Pharmaeuticals, France), Pentostatina, Vinblastina, Vincristina Vindesina, Bleomicina, Dactinomicina, Daunorubicina, Doxorubicina, Epirubicina, Idarubicina, Mitramicina, Deoxicoformicina, Mitomicina-C, L-Asparaginasa, Teniposida 17 α Etinilestradiol, Dietilstilbestrol, Testosterona, Prednisona, Fluoximesterona, propionato de Dromostanolona, Testolactona, Megestrolacetato, Metilprednisolona, Metiltestosterona, Prednisolona, Triamcinolona, Clorotrianiseno, Hidroxiprogesterona, Aminoglutetimida, Estramustina, Medroxiprogesteronacetato, Leuprolida, Flutamida, Toremifena, goserelina, Cisplatina Carboplatina, Hidroxiurea, Amsacrina, Procarbazina, Mitotano, Mitoxantrona, Levamisol, Navelbena, Anastrazol, Letrazol, Capecitabina, Reloxafina, Droloxafina, Hexametilmelamina, Avastina, herceptina, Bexxar, Velcade, Zevalin, Trisenox, Xeloda, Vinorelbine, Porfimer, Erbitux, Liposomal, Tiotepa, Altretamina, Melfalan, Trastuzumab, Lerozol, Fulvestrant, Exemestan, Fulvestrant, Ifosfomida, Rituximab, C225 (o Cetuximab de Merck KGaA, Darmstadt, Germany), y Campat.

Los compuestos de esta invención pueden ser útiles específicamente en combinación (administrados conjuntamente, concurrentemente o consecutivamente) con termozolomida y/o terapia de radiación.

Si se formulan en forma de una dosis fija, dichos productos de combinación empelan los compuestos de esta invención dentro de un rango de dosificación, como el que se describe aqui y los otros agentes farmacéuticamene activos o tratamientos dentro de su rango de dosificación. Por ejemplo, el inhibidor del CDC2 olomucina ha demostrado que actúa sinérgicamente con agentes citotóxicos conocidos para reducir la apoptosis (*J. Cell Sci.*, (1995) 108, 2897. Los

compuestos de Formula III pueden administrarse también consecutivamente con agentes anti-cánceres o citotóxicos conocidos cuando es inapropiada una formulación de combinación. La invención no está limitada a la secuencia de administración; los compuestos de Formula III pueden administrarse antes o después de la administración del agente citotóxico o anti-cáncer conocido. Por ejemplo, la actividad citotóxica del inhibidor de quinasa dependiendo de ciclina, flavopiridol, está afectado por la secuencia de administración con agentes anti-cáncer. *Cancer Research*, (1997) 57, 3375. Dichas técnicas están dentro de la experiencia de expertos en la materia así como también de médicos de cabecera.

Por consiguiente, en un aspecto, esta invención incluye combinaciones que comprenden una cantidad de por lo menos un compuesto de Formula III, o una sal o solvato de este farmacéuticamente aceptable, y una cantidad de uno o más tratamientos anti-cáncer y agentes anti-cáncer enumerados anteriormente donde las cantidades de los compuestos/tratamientos dan como resultado un efecto terapéutico deseado

Las propiedades farmacológicas de los compuestos de esta invención pueden confirmarse mediante una variedad de ensayos farmacológicos. Los ensayos farmacológicos ejemplificados que se describen a continuación fueron llevados a cabo con los compuestos de acuerdo con la invención y sus sales.

Esta invención está también dirigida a las composiciones farmacéuticas que comprenden por lo menos un compuesto de Formula III, o una sal o solvato de dicho compuesto farmacéuticamente aceptable, y por lo menos un portador farmacéuticamente aceptable.

Para preparar las composiciones farmacéuticas de los compuestos descriptos en esta invención, los portadores inertes, farmacéuticamente aceptables pueden ser sólidos o líquidos. Las preparaciones de forma sólida incluyen polvos, tabletas, gránulos dispersables, cápsulas, sellos y supositorios. Los polvos y tabletas pueden estar constituidos por desde aproximadamente 5 hasta aproximadamente 95% de ingrediente activo. Los portadores sólidos apropiados son conocidos en la materia, por ejemplo, carbonato de magnesio, estearato de magnesio, talco, azúcar o lactosa. Pueden usarse tabletas, polvos, sellos y cápsulas como formas de dosificación sólida apropiadas para

administración oral. Ejemplos de portadores farmacéuticamente aceptables y métodos de manufactura para varias composiciones pueden hallarse en A. Gennaro (ed.), *Remington's Pharmaceutical Sciences,* 18th Edición, (1990), Mack Publishing Co., Easton, Pennsylvania.

Las preparaciones de forma líquida incluyen soluciones, suspensiones y emulsiones. Como ejemplo pueden mencionarse agua o soluciones de agua - propilen glicol para inyección parenteral o adición de edulcorantes y opacantes para soluciones, suspensiones y emulsiones orales. Las preparaciones de forma líquida pueden incluir también soluciones para administración intranasal.

Las preparaciones en aerosol apropiadas para inhalación pueden incluir soluciones y sólidos en forma de polvos, que pueden estar en combinación con un portador farmacéuticamente aceptable tal como gas comprimido inerte por ejemplo nitrógeno.

Así mismo se incluyen las preparaciones de forma sólida que están destinadas a ser convertidas poco tiempo antes de su uso a preparaciones de forma líquida para administración oral o parenteral. Dichas formas líquidas incluyen soluciones, suspensiones y emulsiones. Los compuestos de la invención pueden ser también liverables o transdérmicamente. Las composiciones transdérmicas pueden tener la forma de cremas, lociones o aerosoles y/o emulsiones y pueden estar incluidas en un parche transdérmico del tipo de matriz o reservorio tal como los que son convencionales en la materia para este propósito.

Los compuestos de esta invención pueden ser también liverables por vía subcutánea.

Preferiblemente el compuesto se administra por vía oral o intravenosa.

Preferiblemente la preparación farmacéutica está en una forma de dosificación unitaria. En tal forma, la preparación se subdivide en dosis unitarias del tamaño apropiado que contienen cantidades apropiadas del componente activo por ejemplo una cantidad eficaz para lograr el propósito deseado.

La cantidad de compuesto activo en una dosis unitaria de preparación puede variar o puede ajustarse a desde aproximadamente 1mg hasta aproximadamente 100 mg, preferiblemente desde aproximadamente 1 mg hasta aproximadamente

50 mg, más preferiblemente desde aproximadamente 1 mg hasta aproximadamente 25 mg, de acuerdo con la aplicación particular.

La dosis real empleada puede variar dependiendo de los requisitos del paciente y de la gravedad del trastorno que se está tratando. La determinación del régimen de dosificación apropiado para una situación particular está dentro de la experiencia en la materia. Por razones de conveniencia, la dosis diaria total puede dividirse y administrarse en porciones durante el día cuando es necesario.

La cantidad y frecuencia de administración de los compuestos de la invención y/o de sus sales farmacéuticamente aceptables, se regulará de acuerdo con la opinión del médico de cabecera considerando factores tales como la edad, el estado y el peso del paciente así como también la gravedad de los síntomas que se están tratando. Un régimen de dosificación diaria típico recomendado para administración oral puede estar en un rango desde aproximadamente 1 mg/día hasta aproximadamente 500 mg/día, preferiblemente 1 mg/día a 200 mg/día, en dos o cuatro dosis dividida.

Otro aspecto de esta invención es un equipo que comprende una cantidad terapéuticamente eficaz de por lo menos un compuesto de Fórmula III o una sal o solvato de dicho compuesto farmacéuticamente aceptable y un portador vehículo o diluyente farmacéuticamente aceptable.

Un aspecto más de esta invención es un equipo que comprende una cantidad de por lo menos un compuesto de Fórmula III o una sal o solvato de dicho compuesto farmacéuticamente aceptable y una cantidad de por lo menos un agente anti-cáncer y/o terapia anti-cáncer enumerados anteriormente, donde las cantidades de los dos o más ingredientes dan como resultado un efecto terapéutico deseado.

La invención descripta aquí se ejemplifica mediante las preparaciones y ejemplos siguientes que deben considerarse limitativos del alcance de la descripción. Vías mecánicas alternativas y estructuras análogas resultarán aparentes para los expertos en la materia.

Cuando se presentan datos de los RMN, las espectrografía ^1H se obtuvieron con cualquiera de Varian VXR-200 (200 MHz, ^1H), Varian Gemini-300 (300 MHz) o XL-400 (400 MHz) y se informan acá como ppm campo abajo de Me_4Si, con la

cantidad de protones, las multiplicidades, y las constantes de acoplamiento en Hertz indicados entre paréntesis. Cuando se presentan los datos de LC/MS, el análisis se llevaron a cabo usando un espectrómetro de masa Applied Biosystems API-100 y columna LC Shimadzu SCL-10A Altech platino C18, 3 micron, 33mm x 7mm ID; gradiente de fluidez: 0 min – 10% CH_3CN, 5 min – 95% CH_3CN, 7 min – 95% CH_3CN, 7.5 min – 10% CH_3CN, 9 min – stop. En el tiempo de retención y el ión principal observado.

Los siguientes solventes y reactivos pueden mencionarse por sus abreviaturas entre paréntesis:

Cromatografía de capa delgada: TLC

diclorometano: CH_2Cl_2

acetato de etilo: AcOEt o EtOAc

metanol: MeOH

trifluoracetato: TFA

trietilamina: Et_3N o TEA

butoxicarbonilo: n-Boc o Boc

espectroscopia de resonancia magnética nuclear: RMN

espectrometría de masa por cromatografía líquida: LCMS

espectrometría de masa de alta resolución: HRMS

mililitros: mL

milimoles: mmoles

microlitros: µl

gramos: g

miligramos: mg

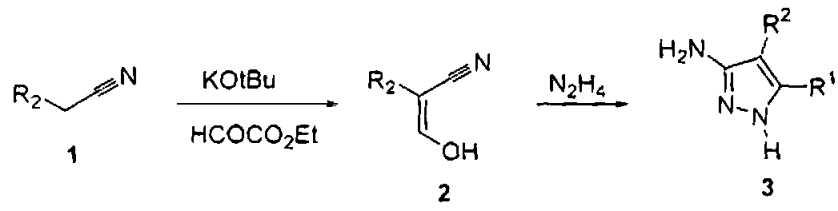
temperatura ambiente o rt (ambiente): aproximadamente 25°C.

dimetoxietano: DME

EJEMPLOS

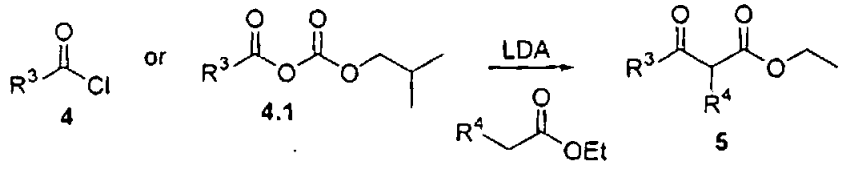
En general, los compuestos que se describen en esta invención pueden prepararse a través de las vías generales que se describen a continuación en el Esquema 1. El tratamiento del

Esquema 1



nitrilo de partida con t-butóxido de potasio y formiato de etilo da lugar al intermediario enol 2 el cual por tratamiento con hidrazina proporciona 3-aminopirazol sustituido deseado. La condensación de los compuestos de tipo 3 con el ceto éster de tipo 5 apropiadamente funcionalizado da lugar a las piridonas 6 tal como se muestra en el Esquema 3. Los ceto ésteres que se usan en esta vía general son comercialmente obtenibles o bien pueden prepararse tal como se ilustra en el Esquema 2.

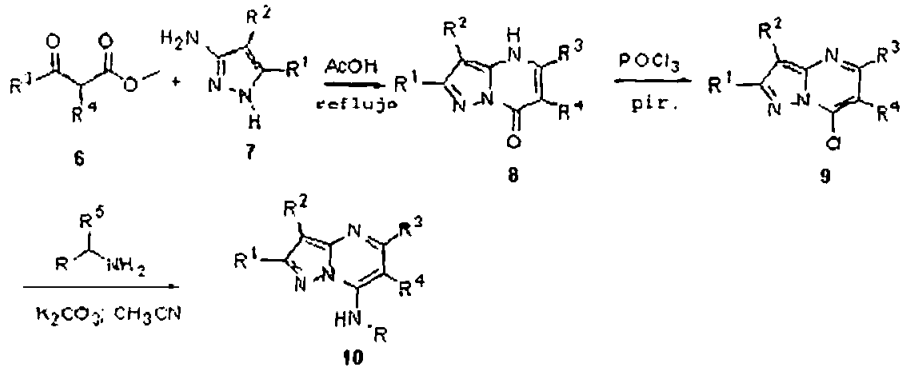
Esquema 2



Los cloruros de tipo 9 pueden prepararse por tratamiento de las piridonas 8 con $POCl_3$. Cuando R^2 es igual a H, la sustitución en esta posición es posible en los compuestos de tipo 9 por halogenación electrofílica, acilación, y varios otras sustituciones aromáticas electrofílicas.

La introducción de la funcionalidad de N7-amino puede lograrse a través del desplazamiento del cloruro de los compuestos de tipo 9 por reacción con la amina apropiada tal como se muestra en el Esquema 3.

Esquema 3



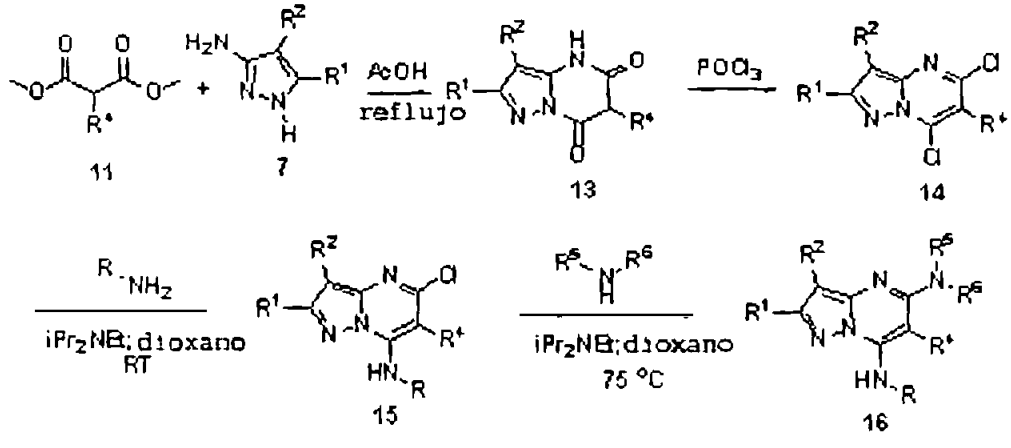
6 7 8 9 10

La condensación de los compuestos de tipo 7 con el éster de malonato apropiadamente funcionalizado de tipo 11 da lugar a las piridonas 13 tal como se muestra en el Esquema 4.

Los cloruros de tipo 14 pueden prepararse por tratamiento de las piridonas 13 con $POCl_3$. Cuando R^2 es H, la sustitución en esta posición es posible en los compuestos de tipo 9 por halogenación electrofílica, acilación, y varias otras sustituciones aromáticas electrofílicas.

La incorporación de la funcionalidad N7-amino puede lograrse a través del desplazamiento regioselectivo del cloruro del compuesto de tipo 14. La incorporación de la funcionalidad N5-amino por adición de una amina apropiada a temperatura elevada.

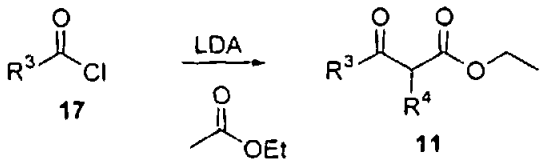
Esquema 4



11 7 13 14 15 16

Alternativamente, las condensaciones de los aminopirazoles de tipo 7 con un ceto éster apropiadamente funcionalizado tal como se preparó en el Esquema 5, conduce a los compuestos de tipo 13 que se muestran en el Esquema 4.

Esquema 5

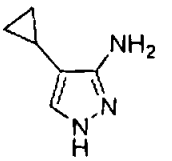


Los cloruros de tipo 14 pueden prepararse por tratamiento de las piridonas 13 con $POCl_3$. Cuando R^2 es igual a H, la sustitución en esta posición es posible en los compuestos de tipo 14 para la halogenación electrofílica, acilación, y varias otras sustituciones aromáticas electrofílicas.

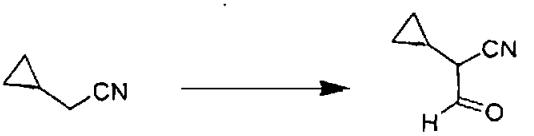
La incorporación de la funcionalidad N7-amino pude lograrse a través del desplazamiento del cloruro de los compuestos de tipo 15.

Ejemplos Preparativos:

EJEMPLO PREPARATIVO 1:



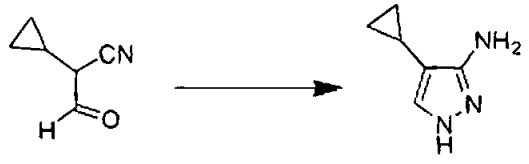
Etapa A:



Se siguió un procedimiento de la patente Alemana DE 19834047 A1, página 19. A una solución de KOtBu (6,17 g, 0,055 mol) en THF anhidro THF (40 mL) se agregó, por goteo, una solución de ciclopropilacetonitrilo (2,0 g, 0,025 mol) y formiato de etilo (4,07 g, 0,055 mol) en THF anhidro (4 mL). Inmediatamente se formó un precipitado. Esta mezcla se agitó durante 12 horas. Se concentró al vacío y el residuo se agitó con Et_2O (50 mL). El residuo resultante se decantó y lavó con Et_2O (2 x 50 mL) y el Et_2O se removió del residuo bajo vacío. El residuo

se disolvió en H_2O frío (20 mL) y el pH se ajustó a 4 – 5 con HCl 12 N. La mezcla se extrajo con CH_2Cl_2 (2 x 50 mL). Las capas orgánicas se combinaron, se secaron sobre $MgSO_4$ y se concentraron bajo vacío para proporcionar el aldehído en forma de un líquido de color tostado.

Etapa B:

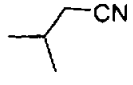
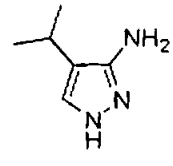
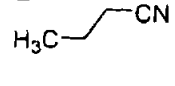
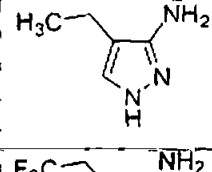
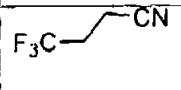
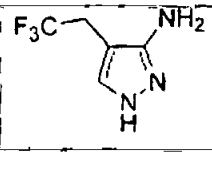


El producto del Ejemplo Preparativo 1, Etapa A (2,12 g, 0,0195 mol), $NH_2NH_2 \cdot H_2O$ (1,95 g, 0,039 mol) y 1,8 g (0,029 mol) de CH_3CO_2H glacial (1,8 g, 0,029 mol) se disolvieron en EtOH (10 mL). Se reflujó durante 6 horas y se concentró al vacío. El residuo se suspendió en CH_2Cl_2 (150 mL) y el pH se ajustó a 9 con NaOH 1N. La capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío para proporcionar el producto en forma de un sólido anaranjado ceroso.

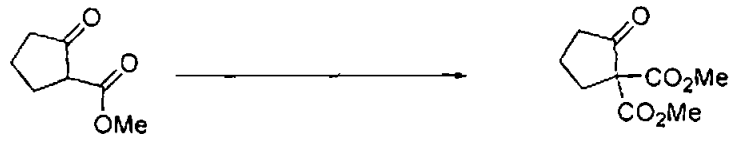
EJEMPLOS PREPARATIVOS 2-4:

Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo preparativo 1, sustituyendo únicamente el nitrilo que se muestra en la Columna 2 de la Tabla 2, se prepararon los compuestos de la Columna 3 de la Tabla 2:

TABLA 2

Ej. Prep.	Columna 2	Columna 3
2		
3		
3.10		

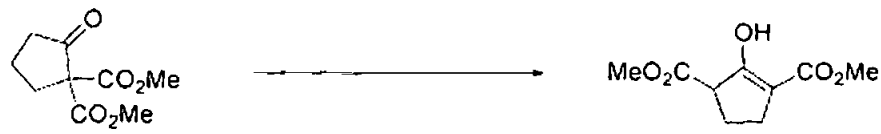
EJEMPLO PREPARATIVO 4



Se agregó por goteo 2-carbometoxiciclopentanona (6,6 ml, 0,05 mol) en THF (15 ml) a una suspensión de NaH agitada vigorosamente (60% en aceite mineral, 4 g, 0,1 mol) en THF (100 ml) a 0 – 10°C. Cuando cesó el burbujeo, la mezcla de reacción se trató a la misma temperatura con ClCOOMe (7,8 ml, 0,1 mol) en THF (15 ml). La suspensión blancuzca resultante se agitó durante 30 minutos a temperatura ambiente y 30 minutos bajo reflujo. La reacción se monitoreo por TLC para determinar la desaparición del material de partida. La mezcla de reacción se apagó con agua cuidadosamente y se dividió entre acetato de etilo y solución de cloruro de amonio saturada en un embudo. Se agitó y separó, y la capa orgánica se lavó con salmuera y se secó sobre sulfato de sodio anhidro. Los solventes se removieron, y el residuo se purificó por cromatografía evaporativa, y se eluyó con 5% y luego con 10% de acetato de etilo en hexano. Se obtuvieron 9,4 g de aceite incoloro con un rendimiento del 94%. ^{1}H RMN ($CDCl_3$) δ 3,90(s, 3H), 3,73(s, 3H), 2,65(m, 4H), 1,98(m, 2H).

EJEMPLO PREPARATIVO 5

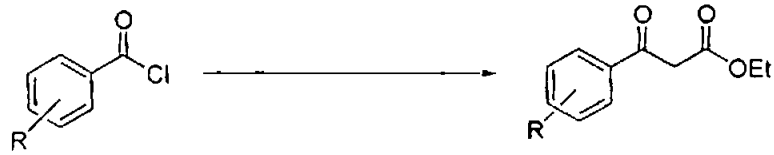
A una solución de diisopropilamida de litio en THF (2,0 N, 0,04 mol) a



-65°C, se agregó por goteo 2,2-dicarbometoxiciclopentanona (4 g, 0,02 mol) en THF (60 ml). La mezcla de reacción resultante se agitó a la misma temperatura antes de agregar cloroformiato de metilo (1,54 ml, 0,02 mol). La mezcla de reacción se agitó durante 1 hora y se vertió en una solución saturada de cloruro de amonio con un poco de hielo. Esta solución se extrajo tres veces con éter, y

las capas etéreas combinadas se secaron sobre sulfato de sodio. Los solventes se removieron al vacío, y el residuo se purificó por cromatografía evaporativa, se eluyó con 30% incrementado hasta 50% de acetato de etilo en hexano. Se obtuvieron 2,3 g de un aceite amarillento con un rendimiento del 58%. ^{1}H RMN ($CDCl_3$) δ 3,77(s, 6H), 3,32(t, 1H), 3,60-3,10(m, 4H).

EJEMPLO PREPARATIVO 6:

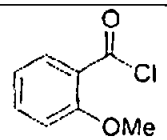
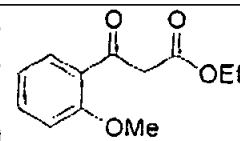


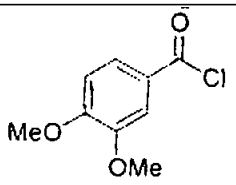
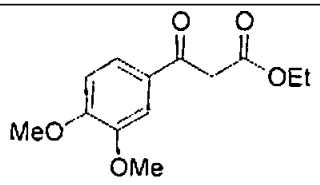
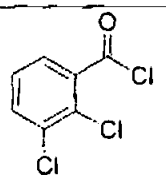
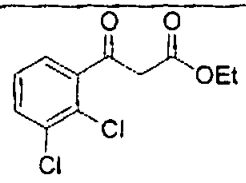
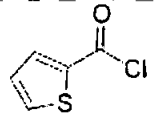
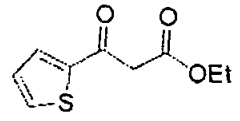
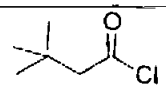
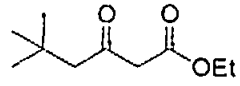
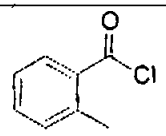
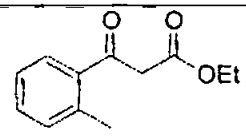
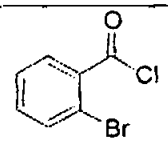
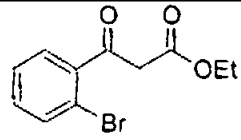
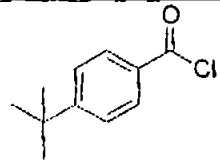
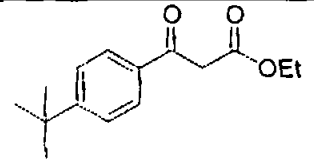
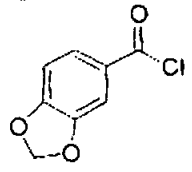
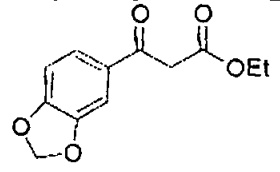
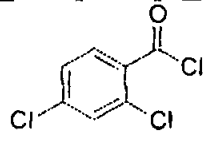
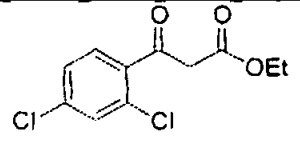
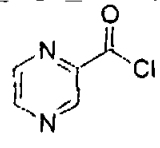
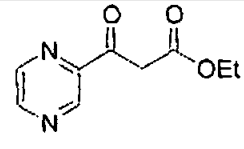
Las reacciones se efectuaron tal como se señaló en (K. O. Olsen, *J. Org. Chem.*, (1987) 52, 4531 – 4536). De este modo, a una solución agitada de diisopropilamida de litio en THF a -65 hasta -70°C, se agregó por goteo acetato de etilo recientemente destilado. La solución resultante se agitó durante 30 minutos y se agregó cloruro ácido en forma de una solución en THF. La mezcla de reacción se agitó a -65 hasta -70°C durante 30 minutos y luego se terminó con la adición de una solución de HCl 1N. La mezcla de dos fases resultante se dejó calentar a temperatura ambiente. La mezcla resultante se diluyó con EtOAc (100 mL) y se recogió la capa orgánica. La capa acuosa se extrajo con EtOAc (100 mL). Las capas orgánicas se combinaron, se lavaron con salmuera, se secaron (Na_2SO_4), y se concentraron *al vacío* para proporcionar los β-ceto ésteres crudos, que se usaron en las condensaciones subsiguientes.

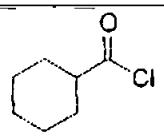
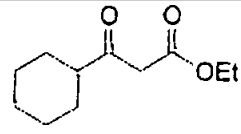
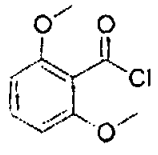
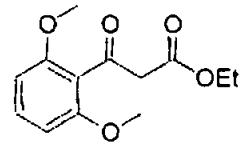
EJEMPLOS PREPARATIVOS 7-19:

Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo preparativo 6 sustituyendo únicamente los cloruros ácidos que se muestran en la Columna 2 de la Tabla 3, se prepararon los β-ceto ésteres que se muestran en la Columna 3 de la Tabla 3:

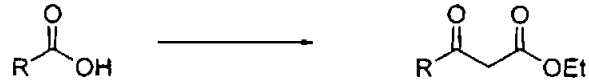
TABLA 3

Ej. Prep.	Columna 2	Columna 3	DATOS
7			LCMS: MH^+ = 223

8			LCMS: MH^+ = 253
9			LCMS: MH^+ = 261
10			MH^+ = 199
11			
12			
13			LCMS: MH^+ = 271
14			Rendimiento = cuant. MH^+ =249
15			Rendimiento = cuant. MH^+ =237
16			Rendimiento = cuant. MH^+ = 262
17			Rendimiento = 48 MH^+ = 195

18			Rendimiento = 99 MH^+ =199
19			Rendimiento = 77% ^1H RMN ($CDCl_3$) δ 7.42(t, 1H), 6,68(d, 2H), 4,29(q, 2H), 3,97(d, 2H), 3,95(s, 3H), 1,38(t, 3H).

EJEMPLO PREPARATIVO 20:

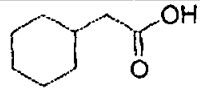
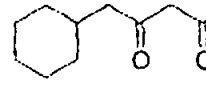


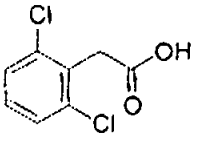
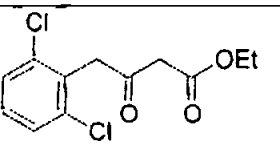
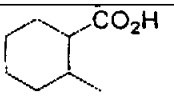
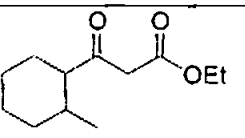
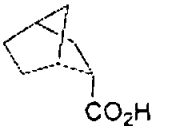
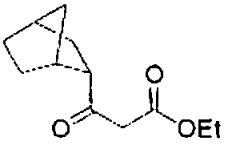
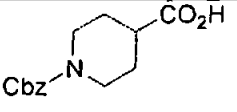
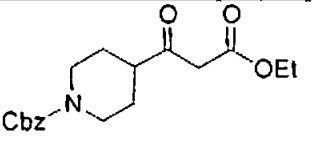
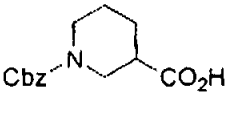
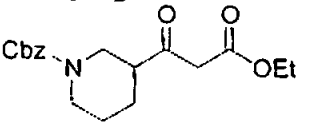
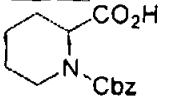
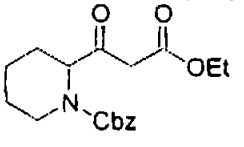
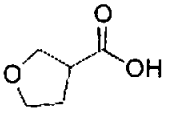
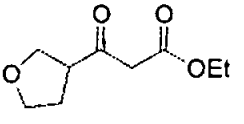
A una solución del ácido en THF se agregó Et_3N, seguido de cloroformiato de isobutilo a -20 hasta -30°C. Después de agitar la mezcla durante 30 minutos a -20 hasta -30°C, se separó por filtración el clorhidrato de trietilamina bajo argón, y el filtrado se agregó a la mezcla de reacción LDA-EtOAc (preparado tal como se señaló en el Método A) a -65 hasta -70°C. Después de adición de HCl 1N, seguido de elaboración rutinaria de la mezcla de reacción y evaporación de los solventes, se aislaron los β-ceto ésteres crudos. El material crudo se usó en las condensaciones subsiguientes.

EJEMPLOS PREPARATIVOS 21 - 28:

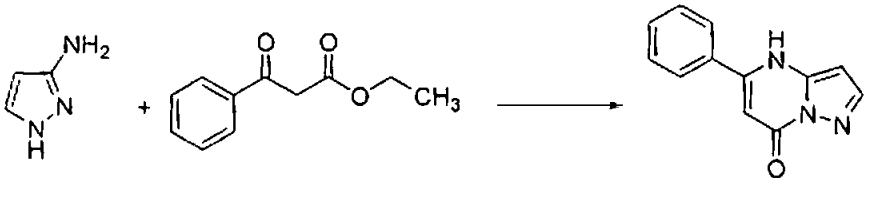
Siguiendo esencialmente las mismas condiciones que se indican en el Ejemplo preparativo 20 sustituyendo únicamente el ácido carboxílico que se muestra en la Columna 2 de la Tabla 4, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 4:

TABLA 4

Ej. Prep.	Columna 2	Columna 3	CMPD
21			Rendimiento = 99% MH^+ = 213

22			Rendimiento = 70% MH^+ = 275
23			Rendimiento = cuant. MH^+ =213
24			Rendimiento = cuant. MH^+ =211
25			Rendimiento = 99 MH^+ = 334
26			Rendimiento = 99 MH^+ = 334
27			Rendimiento = 99 MH^+ = 334
28			Rendimiento = 77% ^1H RMN ($CDCl_3$) δ 4,21(q, 2H), 3,95(d, 2H), 3,93-3,79(m, 4H), 3,52(s, 2H), 2,65(m, 1H), 1,25(t, 3H), 1,23-1,2(m, 2H).

EJEMPLO PREPARATIVO 29:

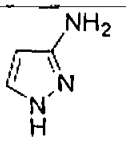
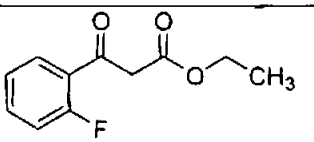
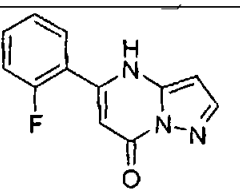
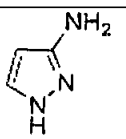
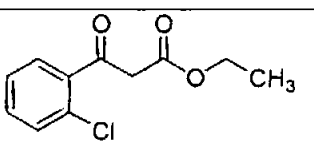
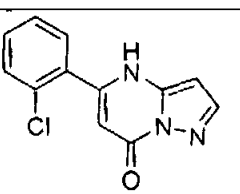
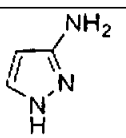
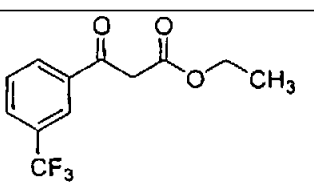
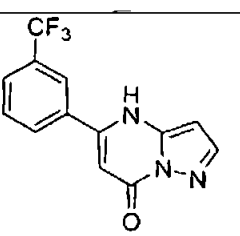
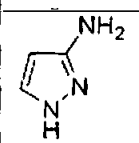
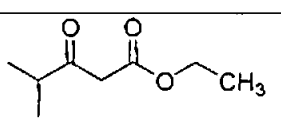
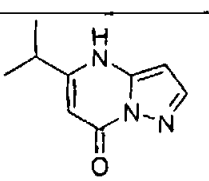


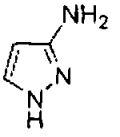
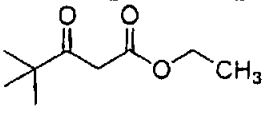
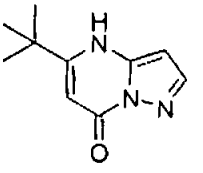
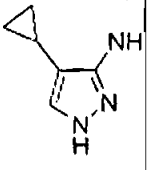
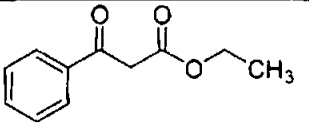
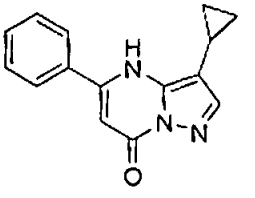
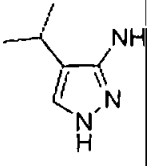
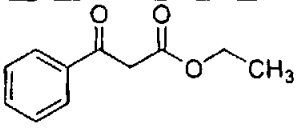
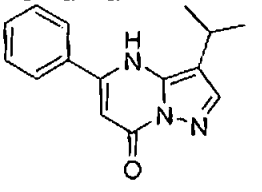
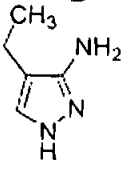
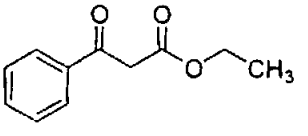
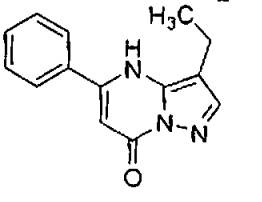
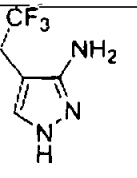
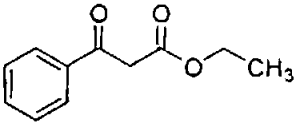
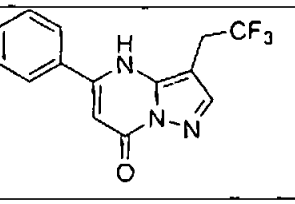
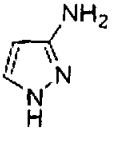
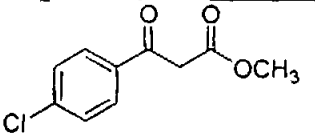
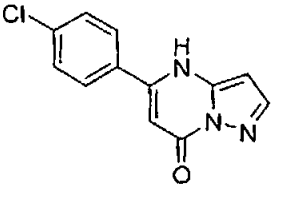
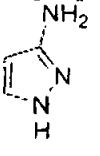
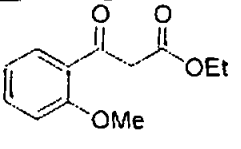
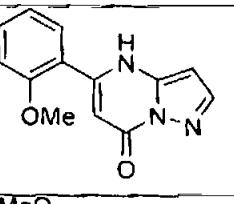
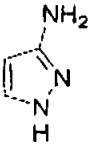
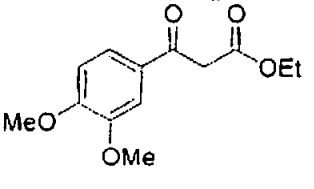
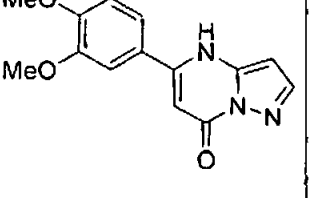
Una solución de 3-aminopirazol (2,0g, 24,07 mmoles) y benzoilacetato de etilo (4,58 mL, 1,1 eq.) en AcOH (15 mL) se calentaron a reflujo durante 3 horas. La mezcla de reacción se enfrió a temperatura ambiente y se concentró *al vacío*. El sólido resultante se diluyó con EtOAc y se filtró para proporcionar un sólido blanco (2,04 g, rendimiento 40%).

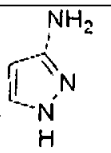
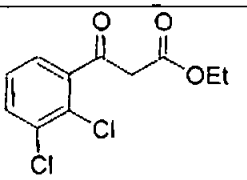
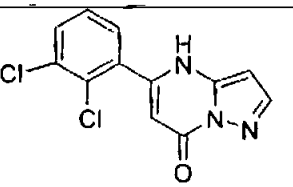
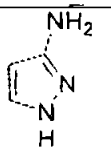
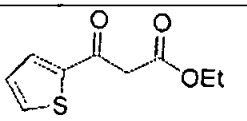
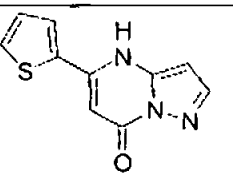
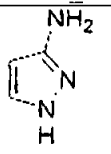
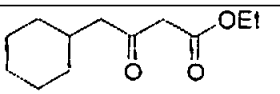
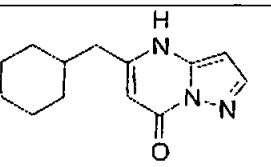
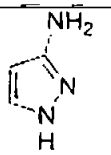
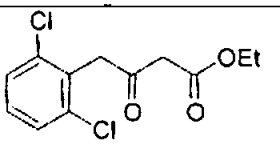
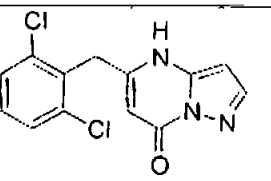
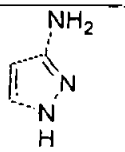
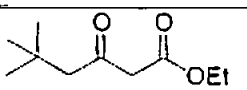
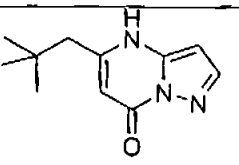
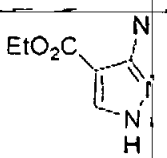
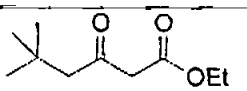
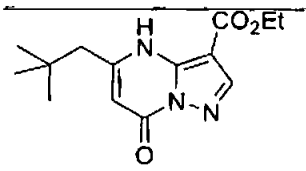
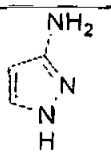
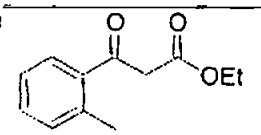
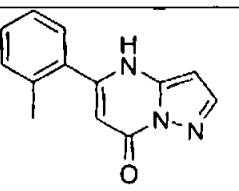
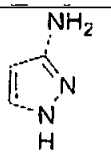
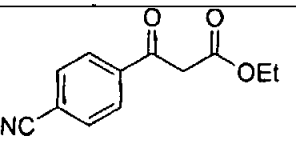
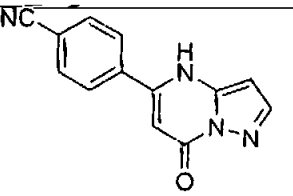
EJEMPLOS PREPARATIVOS 30-73:

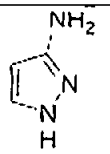
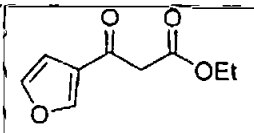
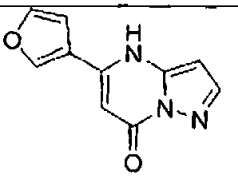
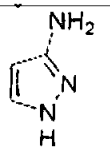
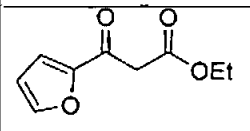
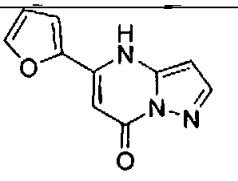
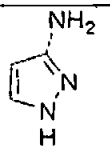
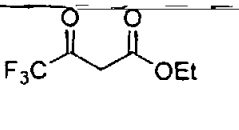
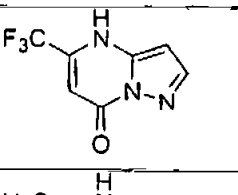
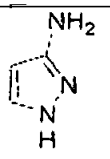
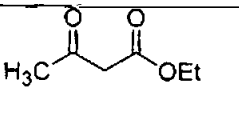
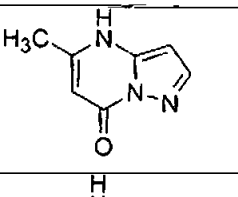
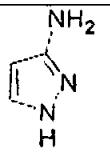
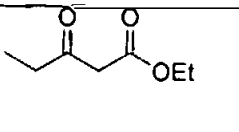
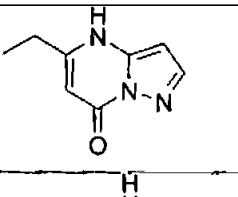
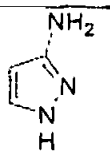
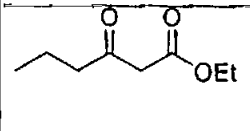
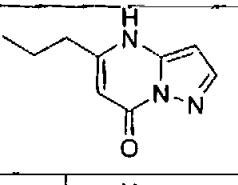
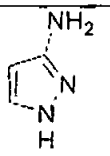
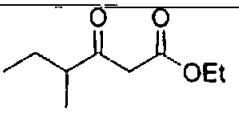
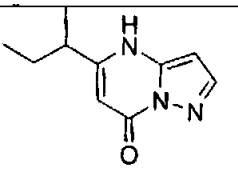
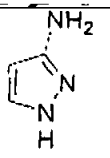
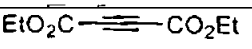
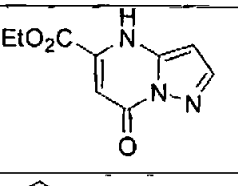
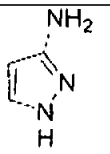
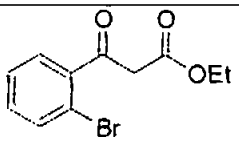
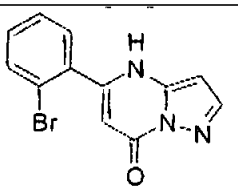
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo preparativo 29 sustituyendo únicamente el aminopirazol que se muestra en la Columna 2 de la Tabla 5, y el éster que se muestra en la Columna 3 de la Tabla 5, se prepararon los compuestos que se muestran en la Columna 4 de la Tabla 5:

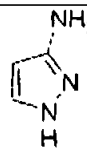
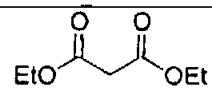
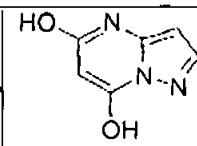
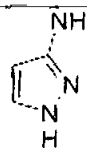
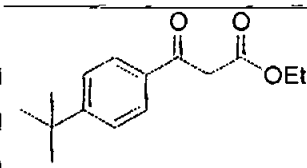
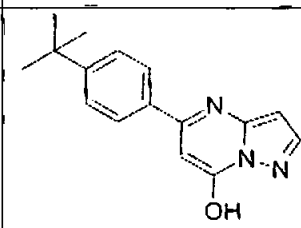
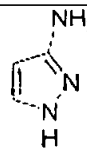
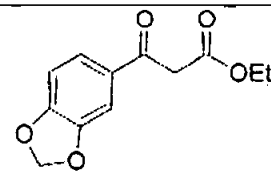
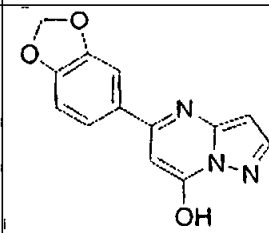
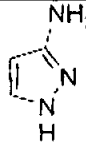
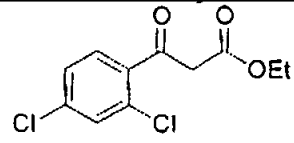
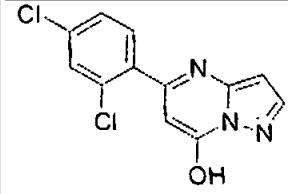
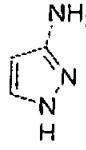
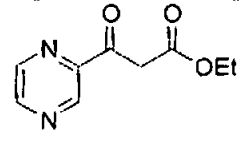
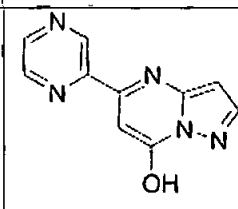
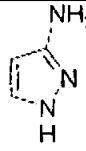
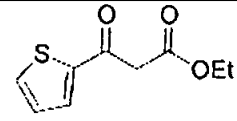
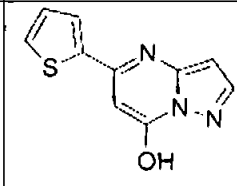
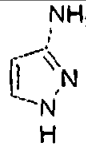
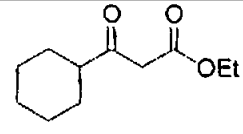
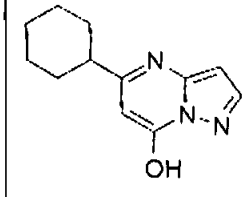
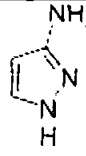
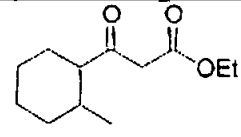
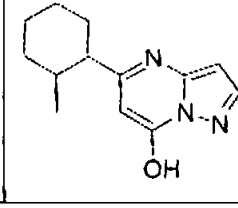
TABLA 5

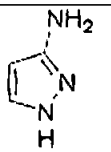
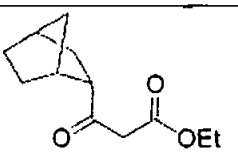
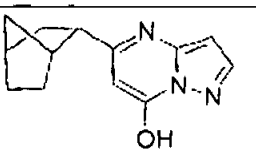
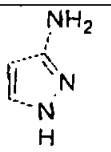
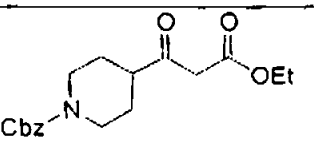
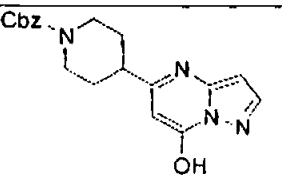
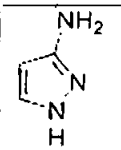
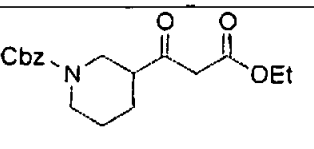
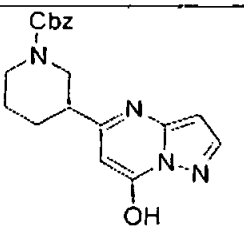
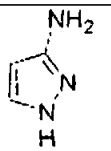
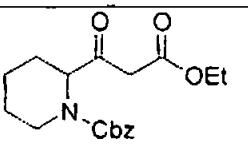
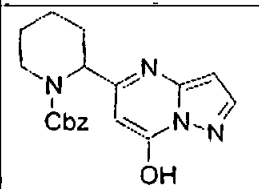
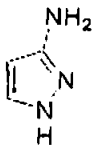
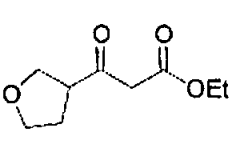
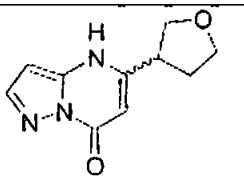
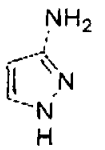
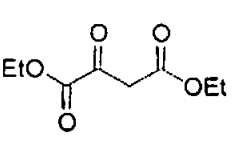
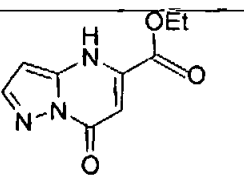
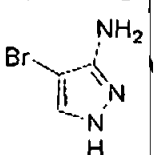
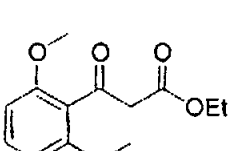
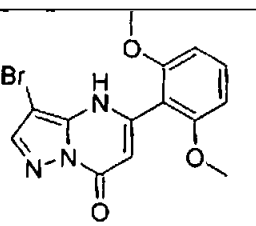
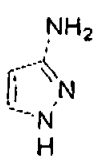
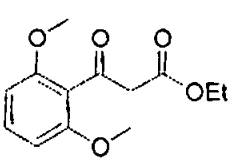
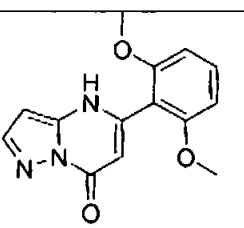
Ej. Prep.	Columna 2	Columna 3	Columna 4	Columna 5
30				
31				
32				
33				

34				
35				
36				
37				
37.10				
38				
39				
40				

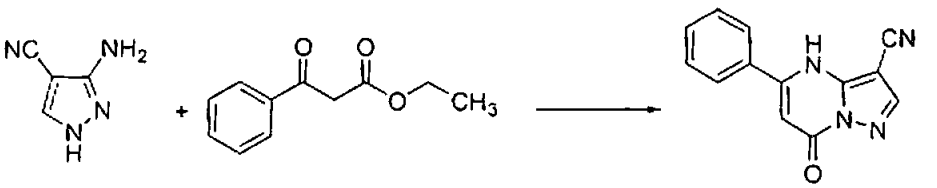
41				
42				
43				
44				
45				
46				
47				
48				

49				
50				
51				
52				
53				
54				
55				
56				
57				

58				Rendimiento = 68 MH^+ = 152
59				Rendimiento = 46 MH^+ = 268
60				Rendimiento = 63 MH^+ = 255
61				Rendimiento = 80 MH^+ = 280
62				Rendimiento = 72 MH^+ = 214
63				Rendimiento = 51 MH^- = 218
64				Rendimiento = 82 MH^+ =218
65				Rendimiento = 39 MH^+ =232

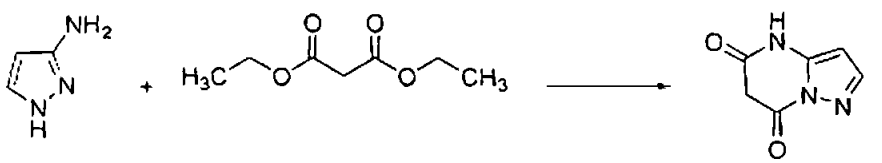
66				Rendimiento = 30 MH^+ =230
67				Rendimiento = 80 MH^+ =353
68				Rendimiento = 49 MH^+ =353
69				Rendimiento = 42 MH^+ =353
70				
71				
72				
73				

EJEMPLO PREPARATIVO 74:



Se calentaron a reflujo durante 72 horas benzoilacetato de etilo (1,76 mL, 1,1 eq.) y 3-amino-4-cianopirazol (1,0 g, 9,25 mmoles) en AcOH (5,0 mL) y H_2O (10 mL). La solución resultante se enfrió a temperatura ambiente, se concentró *al vacío*, y se diluyó con EtOAc. El precipitado resultante se filtró, se lavó con EtOAc, y se secó *al vacío* (0,47 g, 21% de rendimiento).

EJEMPLO PREPARATIVO 75

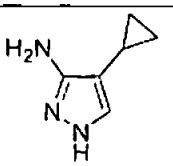
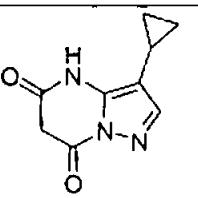
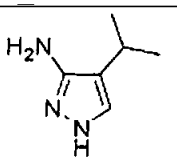
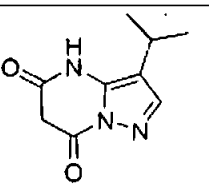
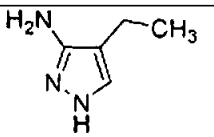
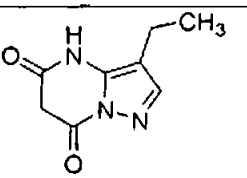


Se siguió un procedimiento de la Patente Norteamericana 3.907.799. Se agregó en porciones sodio (2,3 g, 2 eq.) a EtOH (150 mL). Cuando el sodio estuvo completamente disuelto, se agregaron 3-aminopirazol (4,2 g, 0,05 mol) y malonato de dietilo (8,7 g, 1,1 eq.) y la solución resultante se calentó a reflujo durante 3 horas. La suspensión resultante se enfrió a temperatura ambiente y se filtró. La torta de filtro se lavó con EtOH (100 mL) y se disolvió en agua (250 mL). La solución resultante se enfrió en un baño de hielo y el pH se ajustó a 1-2 con HCl concentrado. La suspensión resultante se filtró, se lavó con agua (100 mL) y se secó al vacío para proporcionar un sólido blanco (4,75 g, 63% de rendimiento).

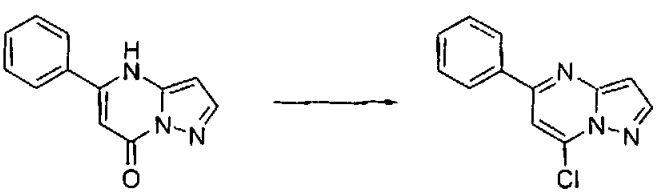
EJEMPLOS PREPARATIVOS 76-78:

Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo preparativo 75 sustituyendo únicamente el compuesto que se muestra en la Columna 2 de la Tabla 6, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 6:

TABLA 6

Ej. Prep.	Columna 2	Columna 3
76		
77		
78		

EJEMPLO PREPARATIVO 79:

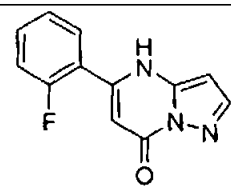
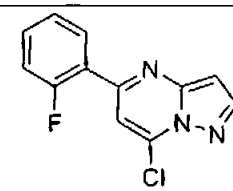
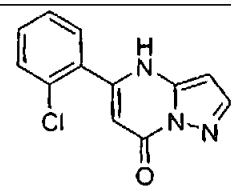
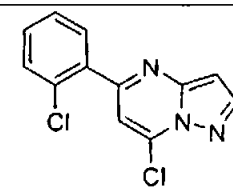
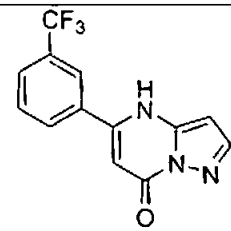
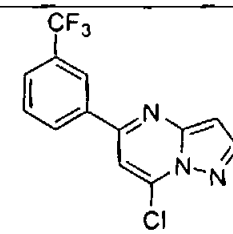
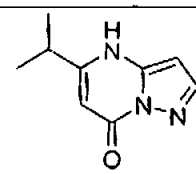
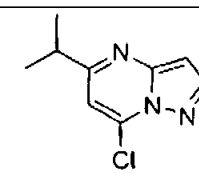
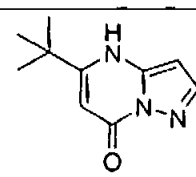
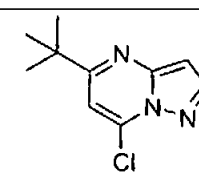


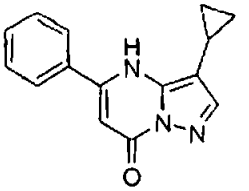
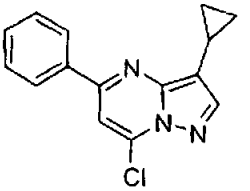
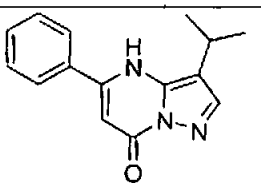
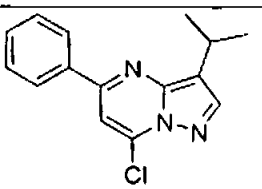
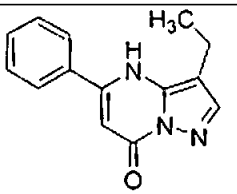
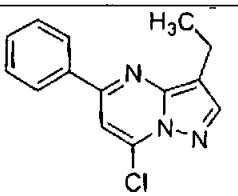
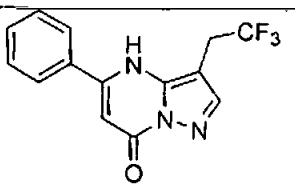
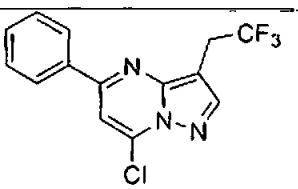
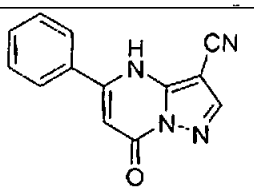
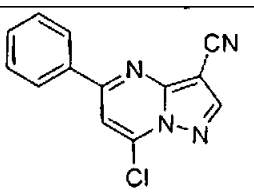
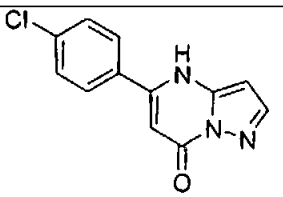
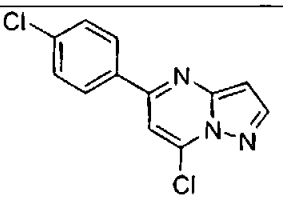
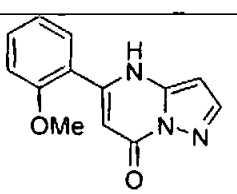
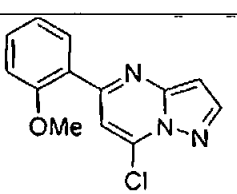
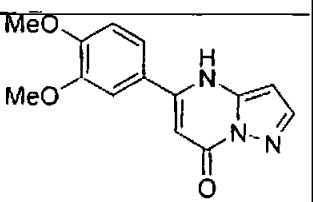
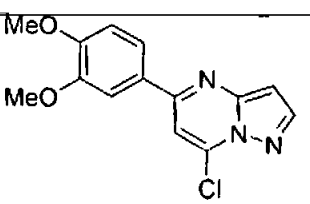
Una solución del compuesto preparado en el Ejemplo preparativo 29 (1,0 g, 4,73 mmoles) en $POCl_3$ (5 mL) y piridina (0,25 mL) se agitó a temperatura ambiente 3 días. La suspensión resultante se diluyó con Et_2O, se filtró, y el residuo sólido se lavó con Et_2O. Las lavazas de Et_2O combinadas se enfriaron a 0°C y se trataron con hielo. Cuando cesó la reacción vigorosa, la mezcla resultante se diluyó con H_2O, se separó, y la capa acuosa se extrajo con Et_2O. Los orgánicos combinados se lavaron con H_2O y con NaCl saturado, se secaron sobre Na_2SO_4, se filtraron, y se concentraron para proporcionar una sólido de color amarillo pálido (0,86 g, 79% de rendimiento). LCMS: MH^+=230.

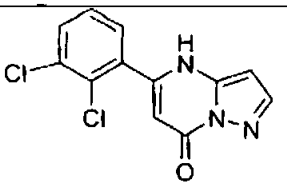
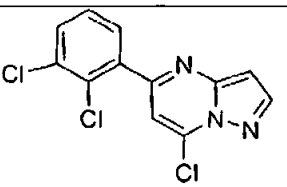
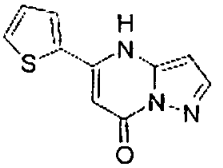
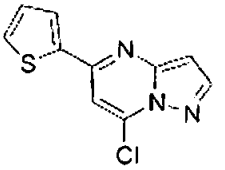
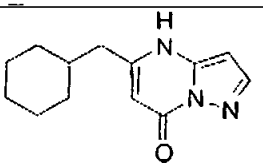
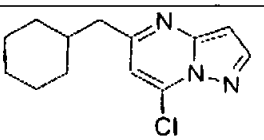
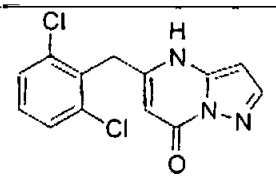
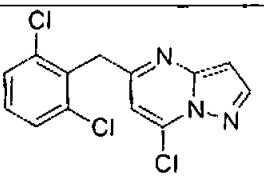
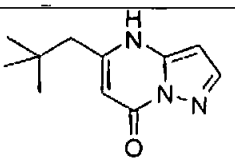
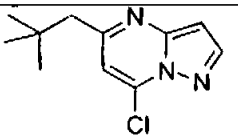
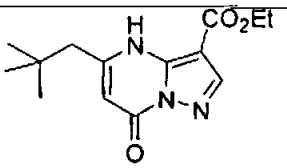
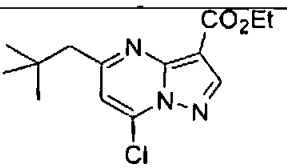
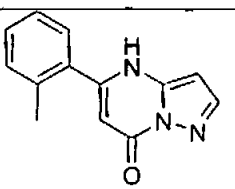
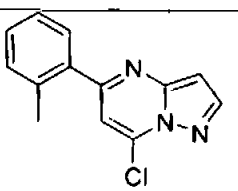
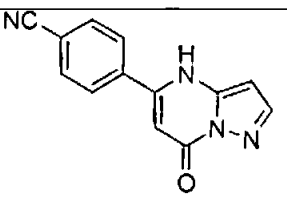
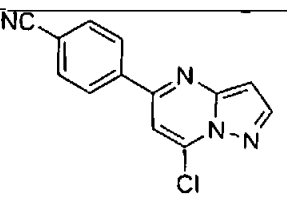
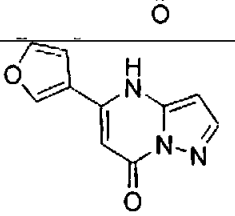
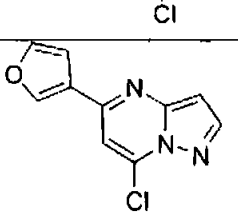
EJEMPLOS PREPARATIVOS 80-122:

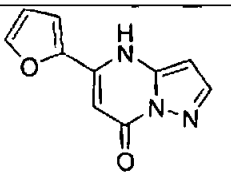
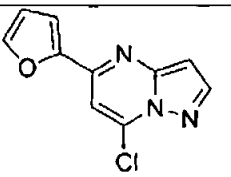
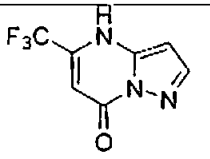
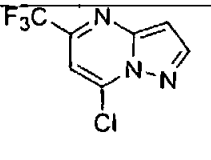
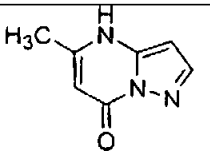
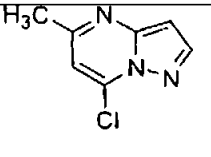
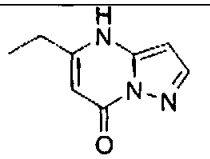
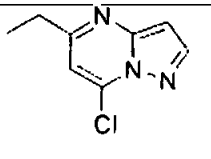
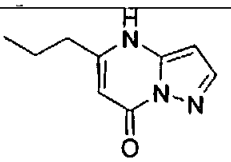
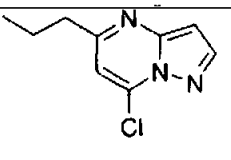
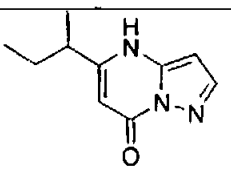
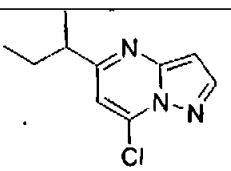
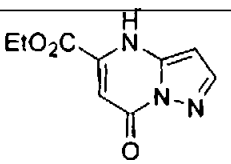
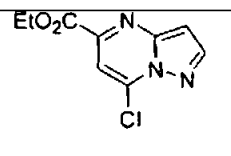
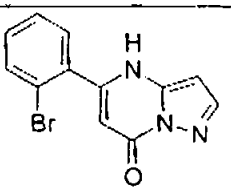
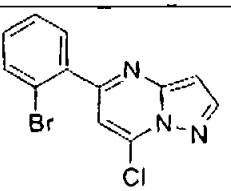
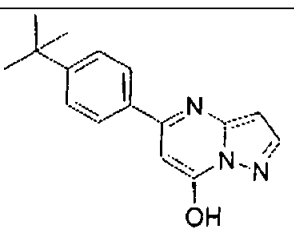
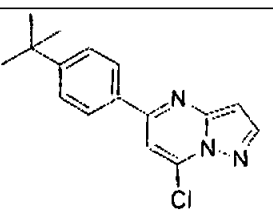
Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo preparativo 79 sustituyendo únicamente el compuesto que se muestra en la Columna 2 de la Tabla 7, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 7:

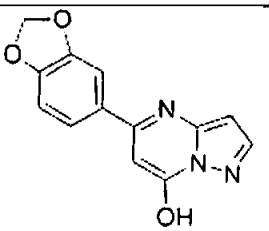
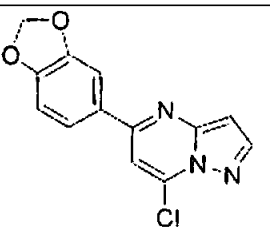
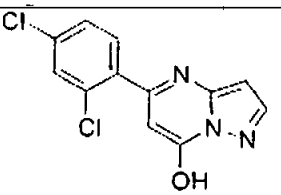
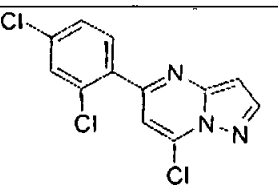
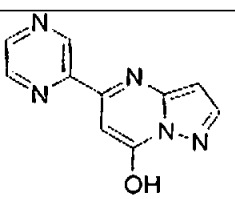
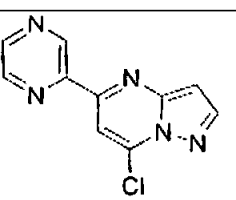
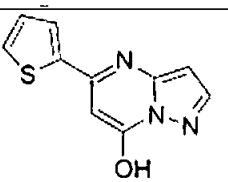
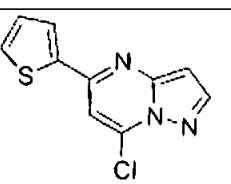
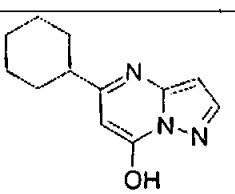
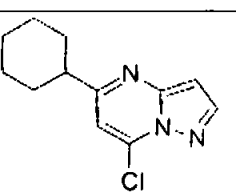
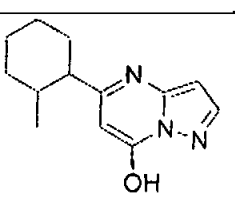
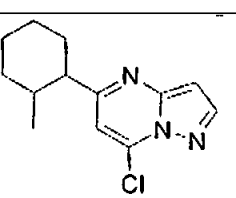
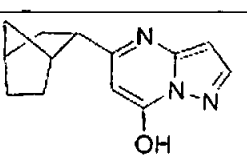
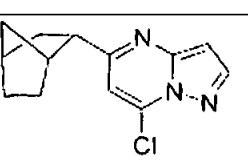
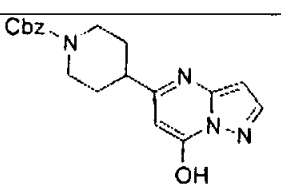
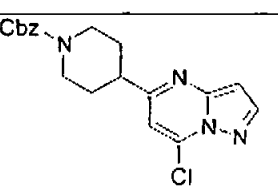
TABLA 7

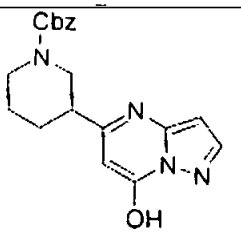
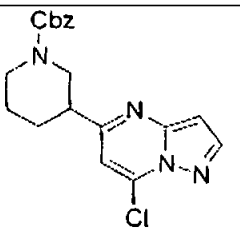
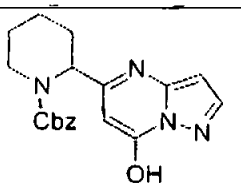
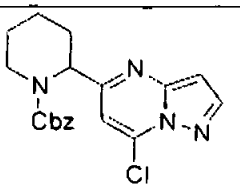
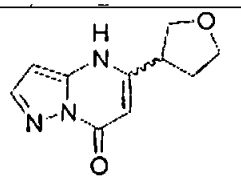
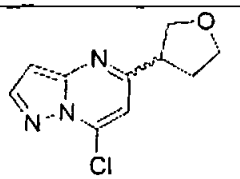
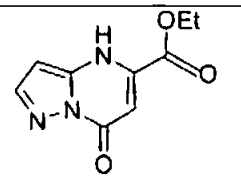
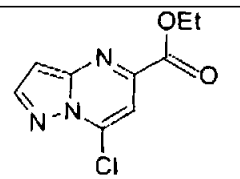
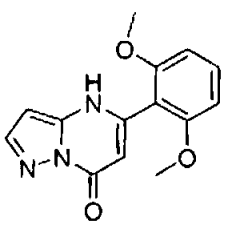
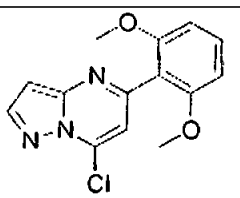
Prep. Ej.	Columna 2	Columna 3	COMP.
80			EM: MH^+=248
81			
82			EM: MH^+=298
83			EM: MH^+=196
84			EM: MH^+=210

85			
86			EM: MH^+=272
87			
87.10			
88			EM: MH^+=255
89			
90			Rendimiento = 65% EM: MH^+ = 260
91			Rendimiento = 35% EM: MH^+ = 290

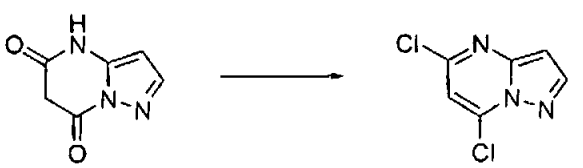
92			Rendimiento = 32% EM: MH^+ = 298
93			Rendimiento = 45% EM: MH^+ = 236
94			Rendimiento = 100% LCMS: MH^+ = 250
95			Rendimiento = 88% EM: MH^+ = 314
96			Rendimiento = 43% EM: MH^+=223
97			Rendimiento = 30% EM: MH^+=295
98			Rendimiento = 98% EM: MH^+=244
99			
100			

101			
102			
103			
104			
105			
106			
107			45% de rendimiento; EM: MH^+=226
108			EM: MH^+ = 308
109			Rendimiento = cuant. MH^+ = 286

110			Rendimiento = 50 MH^+ = 272
111			Rendimiento = 85 MH^+ = 299
112			Rendimiento = 97 MH^+ = 231
113			Rendimiento = 45 MH^+ = 236
114			Rendimiento = cuant. MH^+ =236
115			Rendimiento = 57 MH^+ =250
116			Rendimiento = 89 MH^+ =248
117			Rendimiento = 96 MH^+ =371

118			Rendimiento = 99 MH^+ =371
119			Rendimiento = 50 MH^+ =371
120			Rendimiento = 57% LCMS: MH^+=224
121			Rendimiento= 34% LCMS: MH^+=226
122			Rendimiento = 100% ^{1}H RMN ($CDCl_3$) δ 8,53(d, 1H), 7,66(t, 1H), 7,51(s, 1H), 7,45(d, 1H), 6,84(d, 2H).

EJEMPLO PREPARATIVO 123



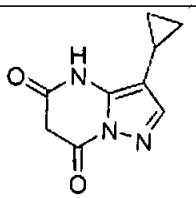
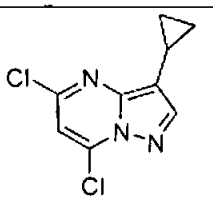
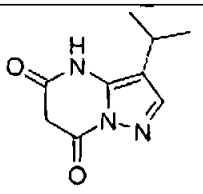
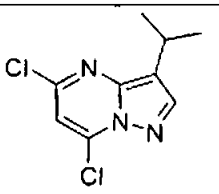
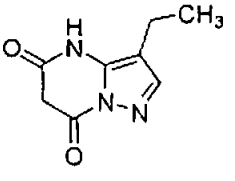
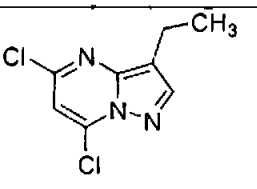
Se enfrió $POCl_3$ (62 mL) a 5ºC bajo nitrógeno y dimetilanilina (11,4 g, 2,8 eq.) y el compuesto se preparó en el Ejemplo preparativo 75 (4,75 g, 0,032 mol).

La mezcla de reacción se calentó a 60°C y se agitó durante la noche. La mezcla de reacción se enfrió a 30°C, y el $POCl_3$ se separó por destilación bajo presión reducida. El residuo se disolvió en CH_2Cl_2 (300 mL) y se vertió en hielo. Después de agitar durante 15 minutos, el pH de la mezcla se ajustó a 7-8 con $NaHCO_3$ sólido. Las capas se separaron, y la capa orgánica se lavó con H_2O (3 x 200 mL), se secó sobre $MgSO_4$, se filtró, y se concentró. El producto crudo se purificó por cromatografía evaporativa usando una solución de 50 : 50 CH_2Cl_2 : hexanos como eluyente para eluir la dimetil anilina. El eluyente se cambió luego a 75 : 25 CH_2Cl_2 : hexanos para eluir el producto deseado (4,58 g, 77% de rendimiento). EM: MH^+=188.

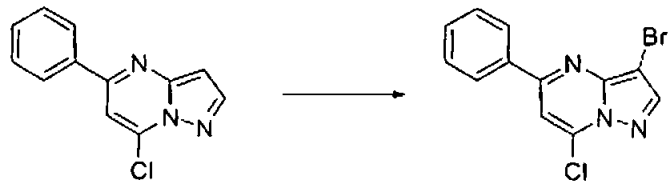
EJEMPLOS PREPARATIVOS 124-126

Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo preparativo 123 sustituyendo únicamente el compuesto de la Columna 2 de la Tabla 8, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 8:

TABLA 8

Ej. Prep.	Columna 2	Columna 3
124		
125		
126		

EJEMPLO PREPARATIVO 127:

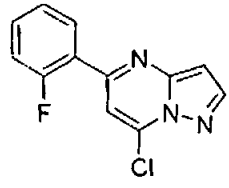
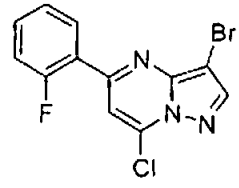
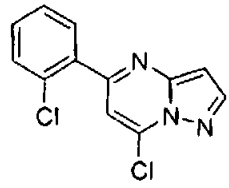
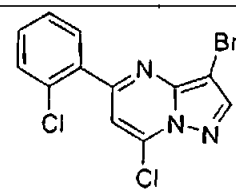


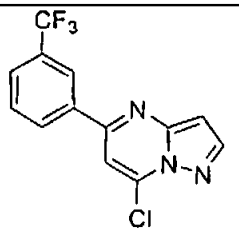
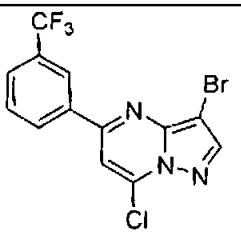
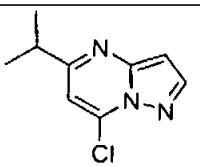
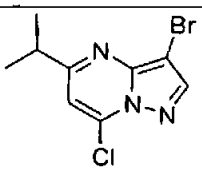
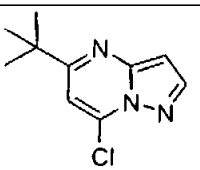
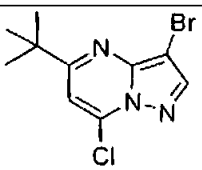
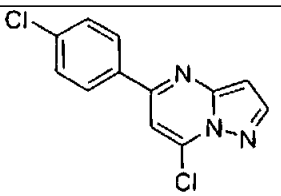
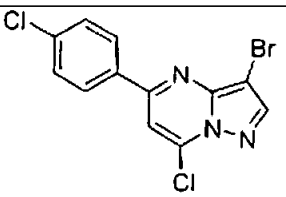
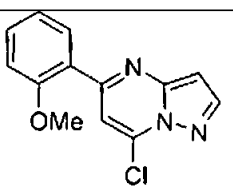
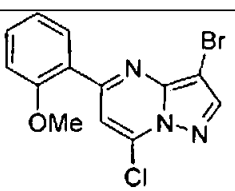
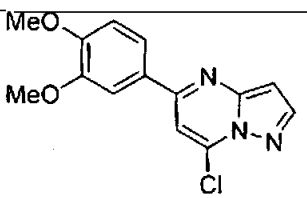
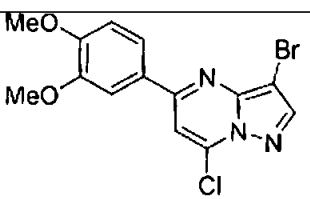
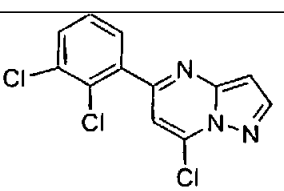
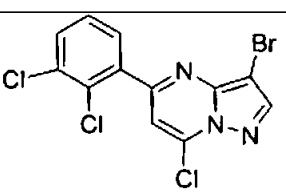
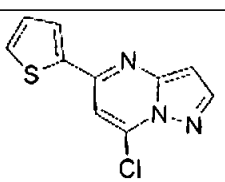
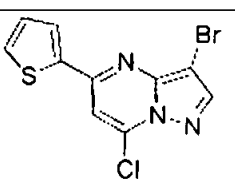
Una solución del compuesto preparado en el Ejemplo preparativo 79 (0,10g, 0,435 mmoles) en CH_3CN (3 mL) se trató con NBS (0,085 g, 1,1 eq.). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía evaporativa usando una solución al 20% de EtOAc-en-hexanos como eluyente (0,13 g, 100% de rendimiento). LCMS:MH^+=308.

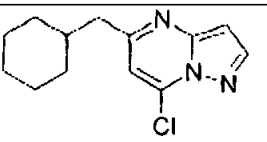
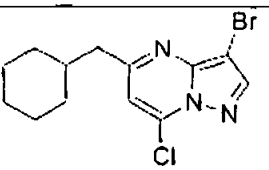
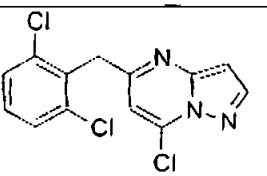
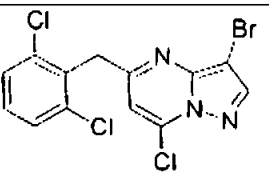
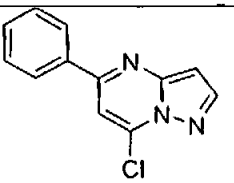
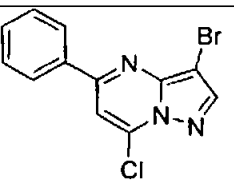
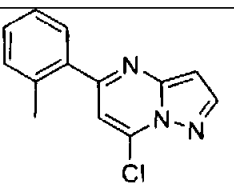
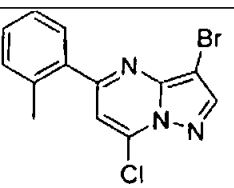
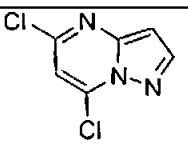
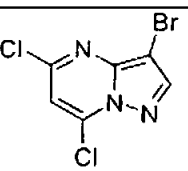
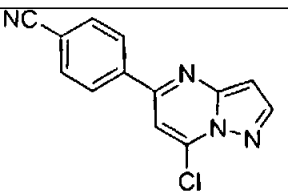
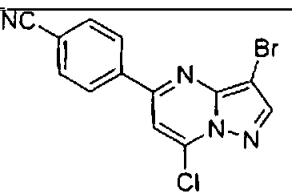
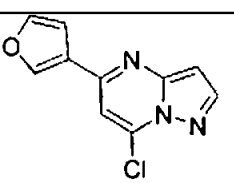
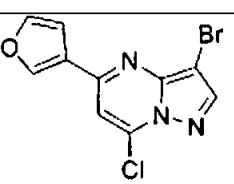
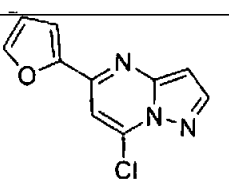
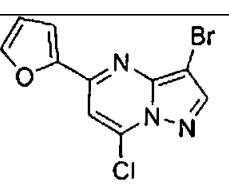
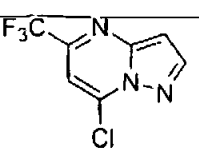
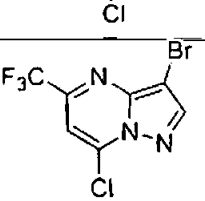
EJEMPLOS PREPARATIVOS 128-164:

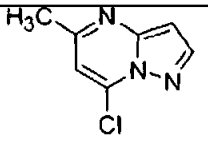
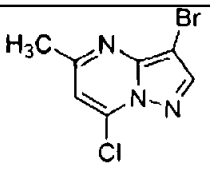
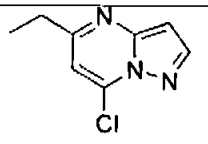
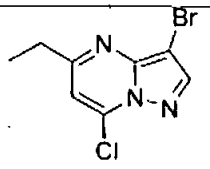
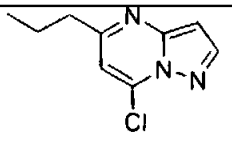
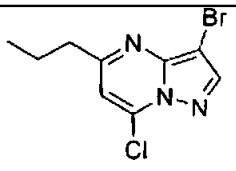
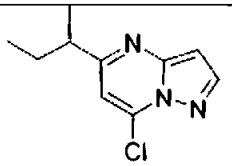
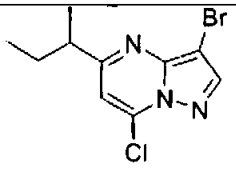
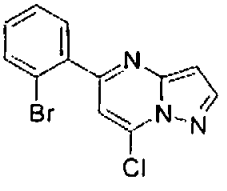
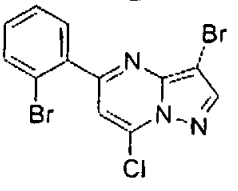
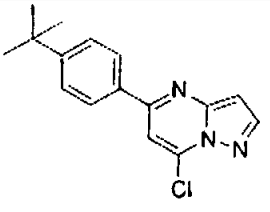
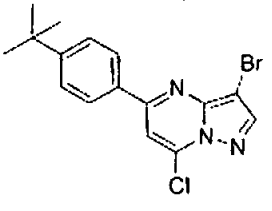
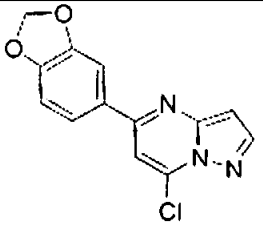
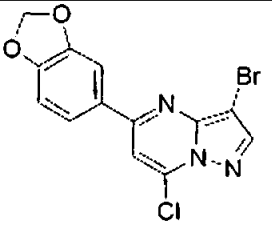
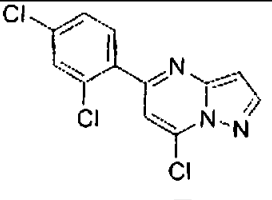
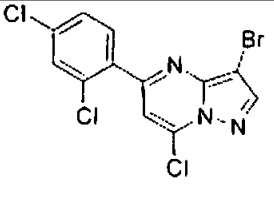
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo preparativo 127 sustituyendo únicamente los compuestos que se muestran en la Columna 2 de la Tabla 9, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 9:

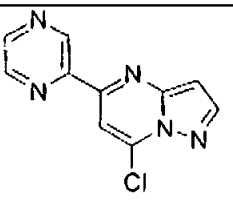
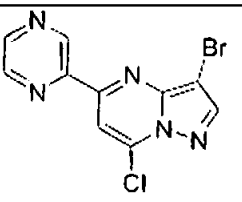
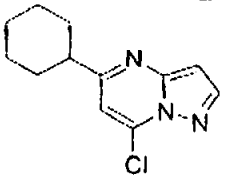
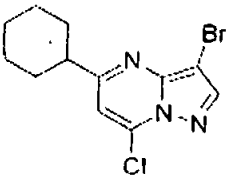
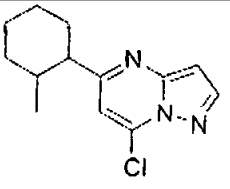
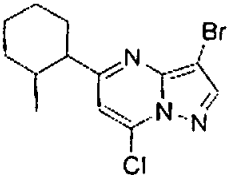
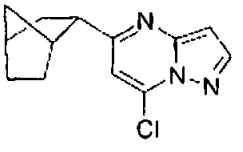
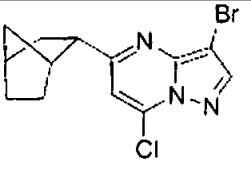
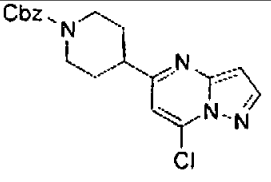
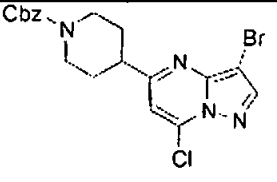
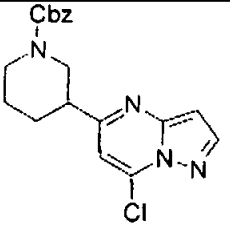
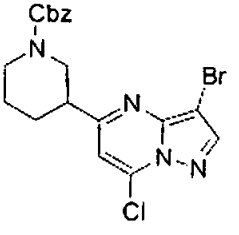
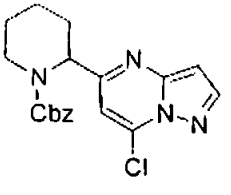
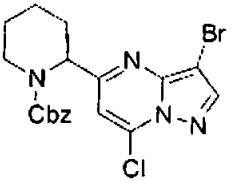
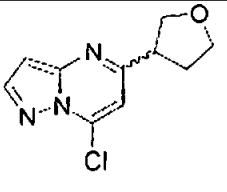
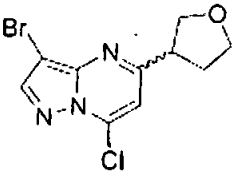
TABLA 9

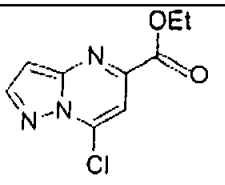
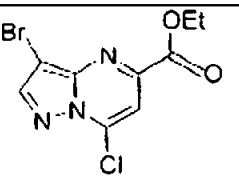
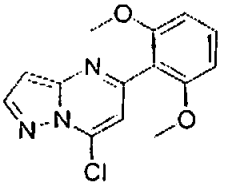
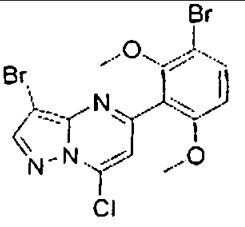
Prep. Ej.	Columna 2	Columna 3	COMP.
128			EM: MH^+= 326
129			EM: MH^+= 342

130			EM: MH^+ = 376
131			EM: MH^+=274
132			EM: MH^+=288
133			
134			Rendimiento = 75% EM: MH^+ = 338
135			Rendimiento = 52% EM: MH^+ = 368
136			Rendimiento = 87% EM: MH^+ = 376
137			Rendimiento = 100% EM: MH^+ = 316

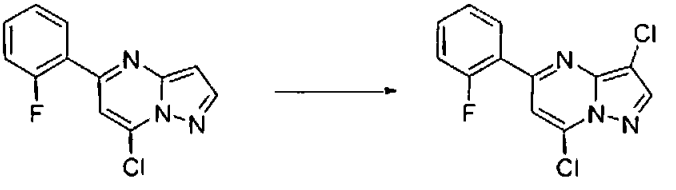
138			Rendimiento = 92% EM: MH^+ = 330
139			Rendimiento = 82% EM: MH^+ = 395
140			Rendimiento = 88% EM: MH^+=308
141			Rendimiento = 100% EM: MH^+=322
142			MH^+=266
143			
144			
145			
146			

147			
148			
149			
150			
151			LCMS: MH^+ = 386
152			Rendimiento = cuant. MH^+ = 364
153			Rendimiento = cuant. MH^+ = 353
154			Rendimiento = 95 MH^- = 378

155			Rendimiento = 77 MH$^+$ = 311
156			Rendimiento =cuant. MH$^+$ =314
157			Rendimiento = 99 MH$^+$ =328
158			Rendimiento = 98 MH$^+$ =326
159			Rendimiento = 99 MH$^+$ =449
160			Rendimiento = 95 MH$^+$ =449
161			Rendimiento = 72 MH$^+$ =449
162			Rendimiento =98% LCMS: MH$^+$=302

163			Rendimiento =95% LCMS: MH^+=305
164			Rendimiento =50% ^{1}H RMN ($CDCl_3$) δ 8,36(s, 1H), 7,72(d, 1H), 7,20(s, 1H), 6,82(d, 1H), 3,99(s, 3H), 3,90(s, 3H);

EJEMPLO PREPARATIVO 165:

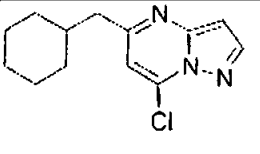
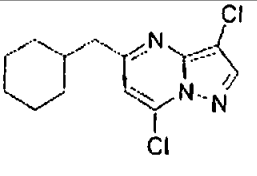


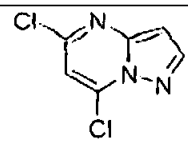
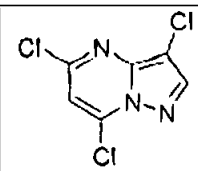
Una solución del compuesto preparado en el Ejemplo preparativo 80 (0,3 g, 1,2 mmoles) en CH_3CN (15 mL) se trató con NCS (0,18 g, 1,1 eq.) y la solución resultante se calentó a reflujo durante 4 horas. Se agregó NCS (0,032 g, 0,2 eq.) adicional y la solución resultante se agitó durante la noche a reflujo. La mezcla de reacción se enfrió a temperatura ambiente, se concentró *al vacío* y el residuo se purificó por cromatografía evaporativa usando EtOAc al 20% en solución de hexanos como eluyente (0,28 g, 83% de rendimiento). LCMS: MH^+= 282.

EJEMPLOS PREPARATIVOS 166-167:

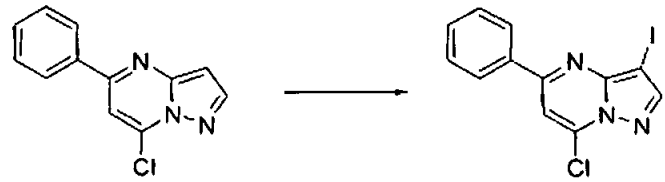
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo preparativo 165 sustituyendo únicamente el compuesto que se muestra en la Columna 2 de la Tabla 10, se preparó el compuesto que se muestra en la Columna 3 de la Tabla 10:

TABLA 10

Ej. Prep.	Columna 2	Columna 3	COMP.
166			Rendimiento = 82% LCMS: MH^+ = 286

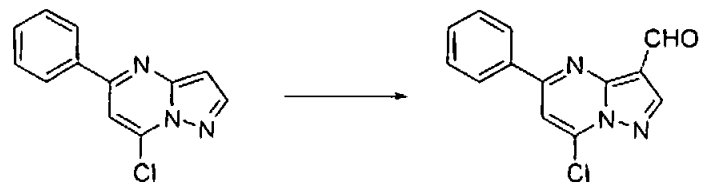
167			

EJEMPLO PREPARATIVO 167.10:



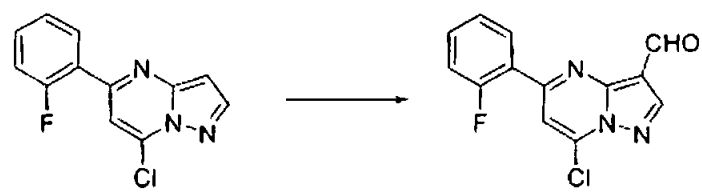
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo preparativo 165 pero sustituyendo N-iodosuccinimida, se preparó el compuesto anterior.

EJEMPLO PREPARATIVO 168:



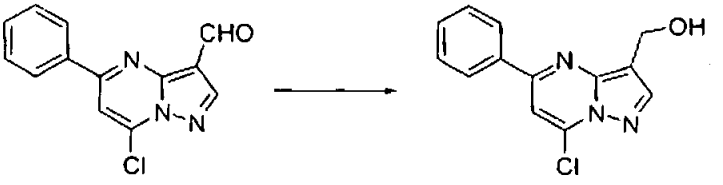
A una solución del compuesto del Ejemplo preparativo 79 (1,0 g, 4,35 mmoles) en DMF (6 mL) se agregó $POCl_3$ (1,24 mL, 3,05 eq.) y la mezcla resultante se agitó a temperatura ambiente durante la noche. La mezcla de reacción se enfrió a 0°C y el exceso de $POCl_3$ se apagó por adición de hielo. La solución resultante se neutralizó con NaOH 1N, se diluyó con H_2O, y se extrajo con CH_2Cl_2. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, y se concentraron *al vacío*. El producto crudo se purificó por cromatografía evaporativa usando una solución al 5% de MeOH en CH_2Cl_2 como eluyente (0,95 g, 85% de rendimiento). LCMS: MH^+=258.

EJEMPLO PREPARATIVO 169:



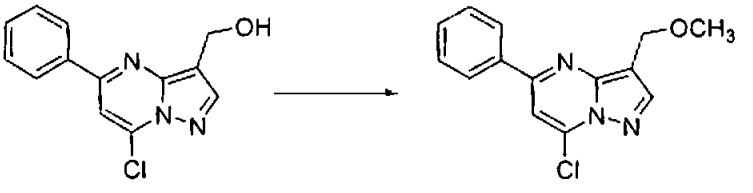
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo preparativo 168 sustituyendo únicamente el compuesto preparado en el Ejemplo preparativo 80, se preparó el compuestos anterior (0,45 g, 40% de rendimiento).

EJEMPLO PREPARATIVO 170:



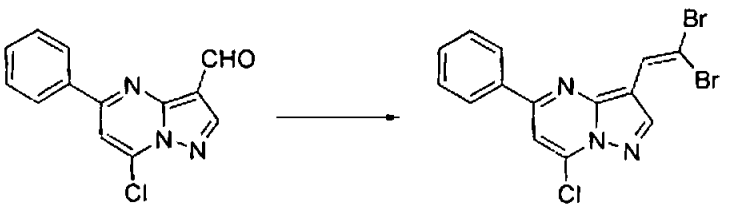
A una solución del producto del Ejemplo preparativo 169 (0,25 g, 0,97 mmoles) en THF se agregó $NaBH_4$ (0,041 g, 1,1 eq.) y la solución resultante se agitó a temperatura ambiente durante la noche. La mezcla de reacción se apagó por adición por H_2O y se extrajo con CH_2Cl_2. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por cromatografía evaporativa usando una mezcla de 60:40 de hexanos : EtOAc como eluyente (0,17 g, 69% de rendimiento). EM: MH^+=260.

EJEMPLO PREPARATIVO 171:



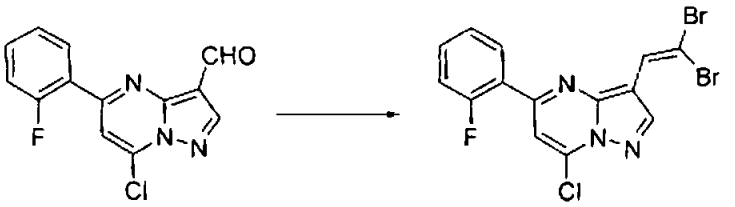
Una solución del compuesto preparado en el Ejemplo preparativo 170 (0,12 g, 0,462 mmoles), sulfato de dimetilo (0,088 mL, 2,0 eq), 50% NaOH (0,26 mL) y Bu_4NBr catalítico en CH_2Cl_2 (4 mL) se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con H_2O y se extrajo con CH_2Cl_2. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por cromatografía evaporativa usando una solución al 30% de EtOAc-en-hexanos como eluyente (0,062 g, 48% de rendimiento).

EJEMPLO PREPARATIVO 172



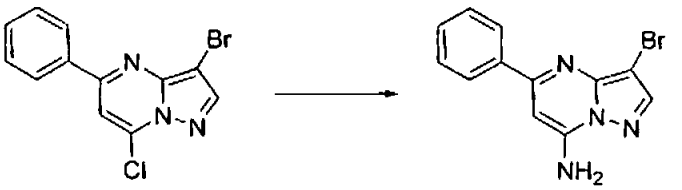
A una solución de PPh_3 (4,07 g, 4,0 eq.) y CBr_4 (2,57 g, 2,0 eq.) en CH_2Cl_2 (75 mL) a 0°C se agregó el compuesto preparado en el Ejemplo preparativo 168 (1,0 g, 3,88 mmoles). La solución resultante se agitó a 0°C durante 1 hora y se concentró bajo presión reducida. El residuo se purificó por cromatografía evaporativa usando una solución de EtOAc al 20% en hexanos como eluyente (1,07 g, 67% de rendimiento).

EJEMPLO PREPARATIVO 173:



Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo preparativo 172 sustituyendo únicamente el compuesto preparado en el Ejemplo preparativo 169, se preparó el compuesto anterior (0,5 g, 70% de rendimiento).

EJEMPLO PREPARATIVO 174:

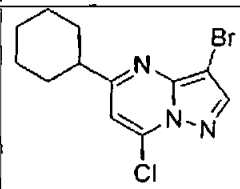
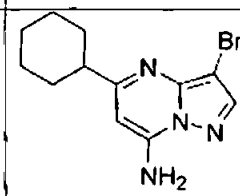
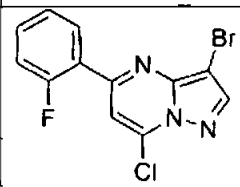
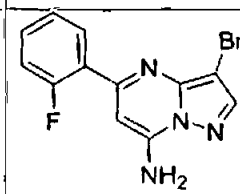
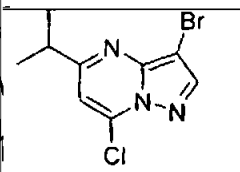
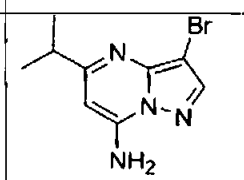
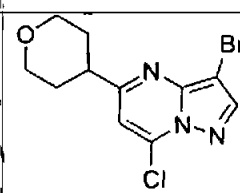
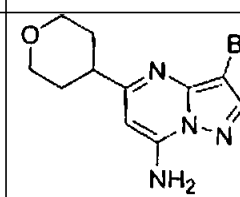
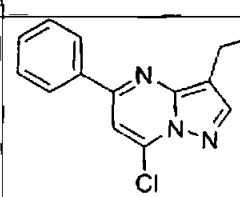
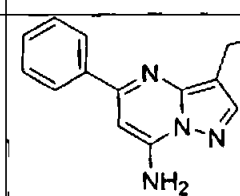


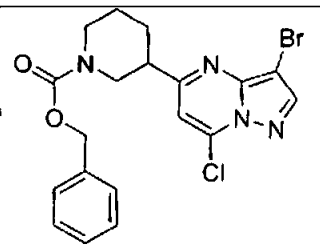
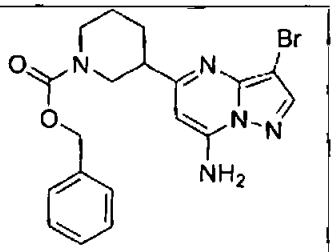
El compuesto preparado en el Ejemplo preparativo 127 (3,08 g, 10,0 mmoles), 2,0 M NH_3 en 2-propanol (50 mL, 100,0 mmoles), y NH_3 acuoso al 37% (10,0 mL) se agitaron en un recipiente cerrado, bajo presión, a 50°C durante 1 día. El solvente se evaporó y el producto crudo se purificó por cromatografía evaporativa usando 3:1 CH_2Cl_2:EtOAc como eluyente. Se obtuvo un sólido de color amarillo pálido (2,30 g, 80%). LCMS: M^+=289.

EJEMPLOS PREPARATIVOS 175-180:

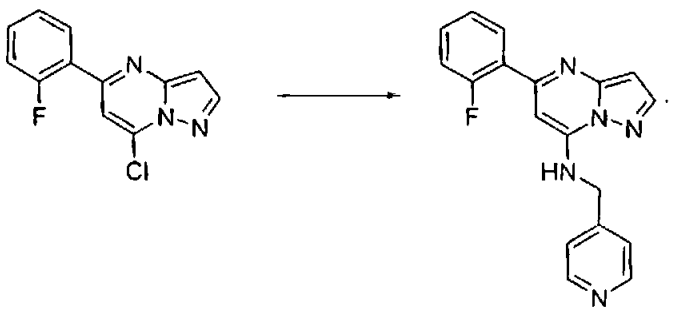
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo preparativo 174 sustituyendo únicamente el compuesto que se muestra en la Columna 2 de la Tabla 11, se prepararon los compuestos que se muestran Columna 3 de la Tabla 11.

TABLA 11

Ej. Prep.	Columna 2	Columna 3
175		
176		
177		
178		
179		

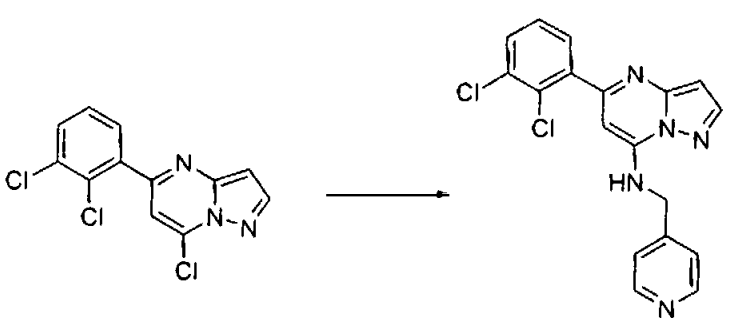
180		

EJEMPLO PREPARATIVO 181:



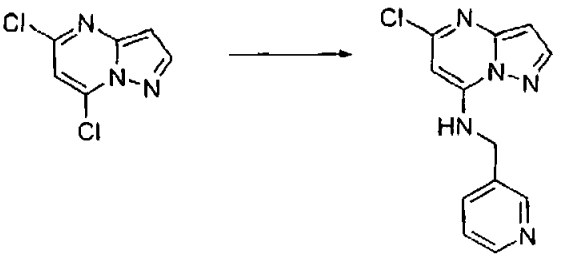
El compuesto preparado en el Ejemplo preparativo 80 (0,3 g, 1,2 mmoles), K_2CO_3 (0,33 g, 2 eq.), y 4-aminometilpiridina (0,13 mL, 1,1 eq.) se calentó a reflujo durante la noche. La mezcla de reacción se enfrió a temperatura ambiente y se concentró bajo presión reducida. El residuo se diluyó con H_2O y se extrajo con CH_2Cl_2. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, y se concentraron. El producto crudo se purificó por cromatografía evaporativa usando una solución al 5% (10% NH_4OH en MeOH) en CH_2Cl_2 como eluyente (0,051 g, 40% de rendimiento). LCMS: MH^+=320.

EJEMPLO PREPARATIVO 182:



Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo preparativo 181 sustituyendo únicamente el compuesto descrito en el Ejemplo preparativo 92, se preparó el compuesto anterior. LCMS: MH^+=370.

EJEMPLO PREPARATIVO 183:

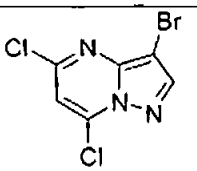
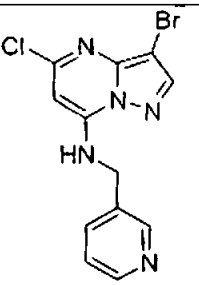


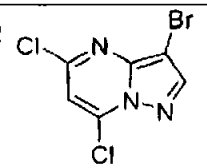
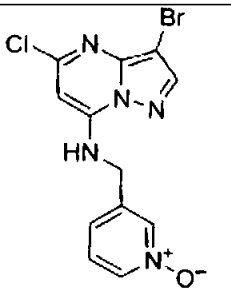
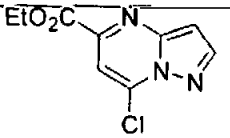
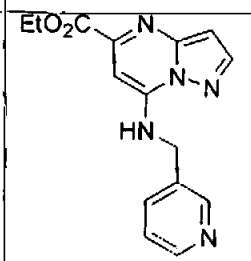
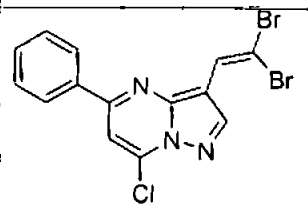
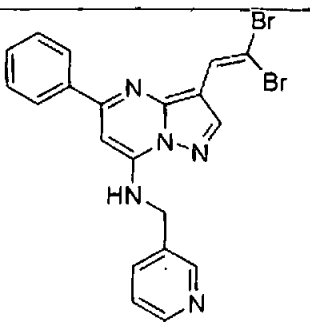
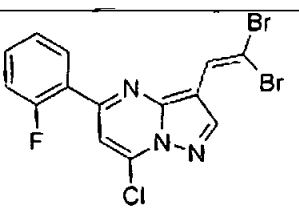
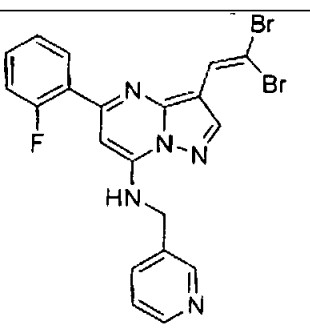
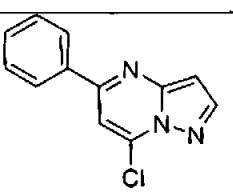
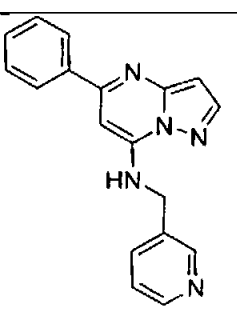
A una solución del compuesto preparado en el Ejemplo preparativo 123 (0,25 g, 1,3 mmoles) en dioxano (5 mL) se agregó iPr_2NEt (0,47 mL, 2,0 eq.) y 3-aminometilpiridina (0,15 ml, 1.1 eq.). La solución resultante se agitó a temperatura ambiente durante 72 horas. La mezcla de reacción se diluyó con H_2O y se extrajo con EtOAc. Los orgánicos combinados se lavaron con H_2O y con NaCl saturado, se secaron sobre Na_2SO_4, se filtraron, y se concentraron al vacío. El producto crudo se purificó por cromatografía evaporativa usando una solución al 5% de MeOH en CH_2Cl_2 como eluyente (0,29 g, 83% de rendimiento). EM: MH^+=260.

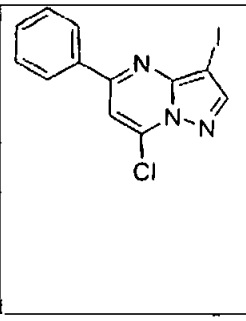
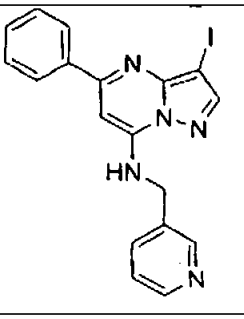
EJEMPLOS PREPARATIVOS 184-187:

Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo preparativo 183 sustituyendo únicamente el compuesto que se muestra en la Columna 2 de la Tabla 12, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 12.

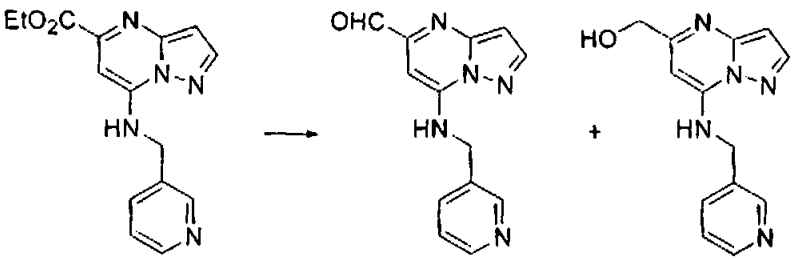
TABLA 12

Ej. Prep.	Columna 2	Columna 3
184		

184.1		
185		
186		
187		
187.1		

187.11		

EJEMPLO PREPARATIVO 188 y EJEMPLO PREPARATIVO 189:

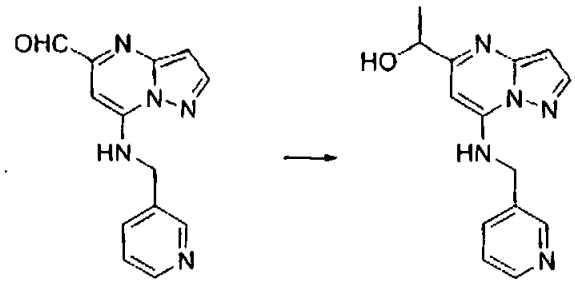


A una solución del compuesto preparado en el Ejemplo preparativo 185 (1,18 g, 3,98 mmoles) en THF (35 mL) a -78°C se agregó LAH (4,78 mL, 1M en Et_2O, 1,0 eq.) por goteo. La mezcla de reacción se agitó a -78°C durante 3 horas momento en el cual se agregó por goteo LAH adicional (2,0 mL, 1M en Et_2O, 0,42 eq.). La mezcla de reacción se agitó durante 1,25 horas adicionales y se apagó por adición de Na_2SO_4 saturado (8,5 mL). La mezcla de reacción se diluyó con EtOAC (23 mL), H_2O (2 mL), y CH_3OH (50 mL). La solución resultante se filtró a través de un tapón de Celite. El Celite se lavó con CH_3OH y el filtrado se secó con Na_2SO_4, se filtró, y se concentró. el producto se purificó por cromatografía evaporativa usando una solución de CH_2Cl_2 : CH_3OH (93 : 7) como eluyente para proporcionar el aldehído como primer producto de elución y alcohol como el segundo producto de elución.

Ejemplo preparativo 188: (aldehído): 0.4 g, 39% de rendimiento. EM: MH^+ = 254.

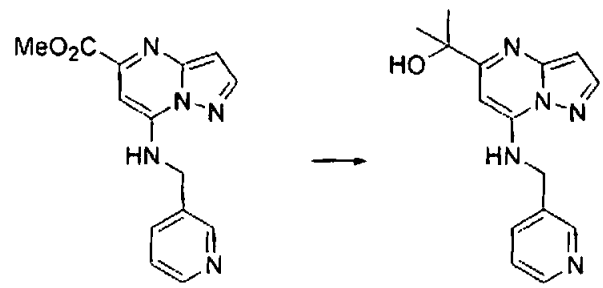
Ejemplo preparativo 189: (alcohol): 0.25 g, 24% de rendimiento. EM: MH^+ = 256.

EJEMPLO PREPARATIVO 190:



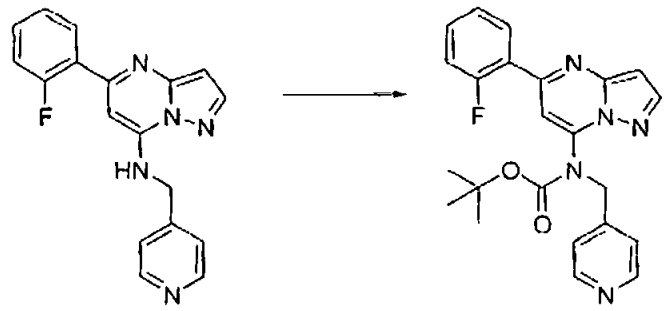
A una solución el compuesto preparado en el Ejemplo preparativo 188 (0,075 g, 0,30 mmoles) en THF (2,0 mL) a 0°C se agregó CH_3MgBr (0,3 mL, solución 3,0M en Et_2O, 3,0 eq.) por goteo. La solución resultante se agitó a 0°C durante 1,5 horas adicionales, se calentó a temperatura ambiente, y se agitó durante la noche. Se agregó CH_3MgBr (0,15 mL, 3,0M en Et_2O, 1. eq.) adicional y la solución resultante se agitó durante 1,5 horas más. La mezcla de reacción se enfrió a 0°C y se apagó por adición de NH_4Cl saturado. La solución resultante se diluyó con CH_2Cl_2 y H_2O y se extrajo con CH_2Cl_2. Los orgánicos combinados se lavaron con NaCl saturado y se secaron sobre Na_2SO_4, se filtraron, y se concentraron. El producto crudo se purificó por cromatografía evaporativa usando una solución de CH_2Cl_2 : CH_3OH (90 : 10) como eluyente (0,048 g, 60% de rendimiento). EM: MH^+ = 270.

EJEMPLO PREPARATIVO 191:



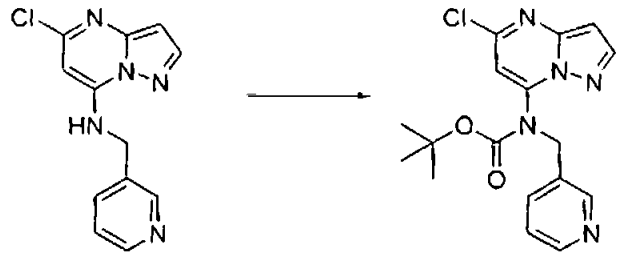
Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo preparativo 190 sustituyendo únicamente el compuesto preparado en el Ejemplo preparativo 185 y usando un exceso de MeMgBr (5 eq.), se preparó el compuesto anterior.

EJEMPLO PREPARATIVO 192:



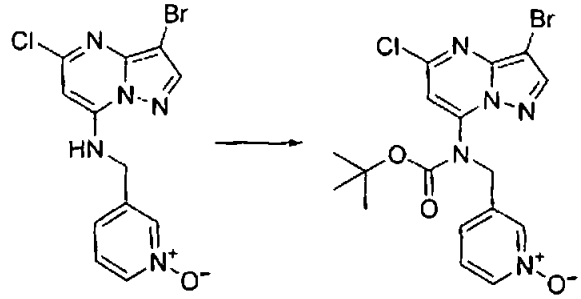
El compuesto preparado en el Ejemplo preparativo 181 (0,29 g, 0,91 mmoles), BOC_2O (0,22 g, 1,1 eq), y DMAP (0,13 g, 1,1 eq.) en dioxano (10 mL) se agitó a temperatura ambiente durante 3 días. Se agregó BOC_2O (0,10g, 0,5 eq.) adicional y la mezcla de reacción se agitó durante 4 horas. La mezcla de reacción se concentró *al vacío*, se diluyó con $NaHCO_3$ saturado (15 mL), y se extrajo con CH_2Cl_2 (2 x 100 mL). Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por cromatografía evaporativa usando una solución al 5% (10% NH_4OH en MeOH) en CH_2Cl_2 como eluyente (0,35 g, 91% de rendimiento). LCMS: MH^+= 420.

EJEMPLO PREPARATIVO 193:



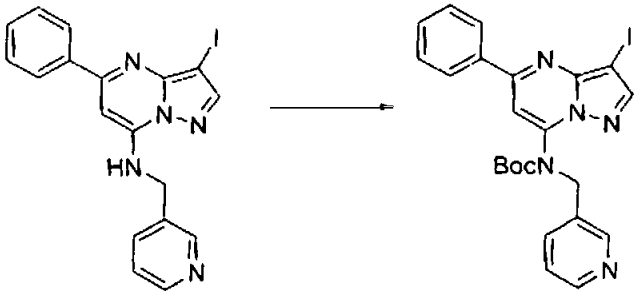
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo preparativo 192 sustituyendo únicamente el compuesto preparado en el Ejemplo preparativo 183, se preparó el compuesto siguiente. EM: MH^+ = 360.

EJEMPLO PREPARATIVO 193.10:



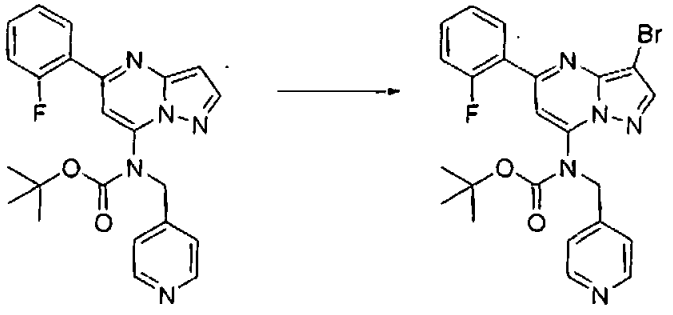
Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo preparativo 192 sustituyendo únicamente el compuesto preparado en el Ejemplo preparativo 184,1, se preparó el compuesto anterior. EM: MH^+ = 454.

EJEMPLO PREPARATIVO 194:



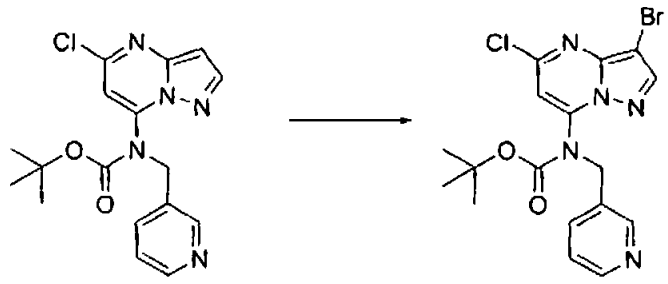
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo preparativo 192 sustituyendo únicamente el compuesto anterior preparado en el Ejemplo preparativo 187.11, se preparó el compuesto anterior (0,223 g, 88% de rendimiento). EM: MH^+ = 528.

EJEMPLO PREPARATIVO 195:



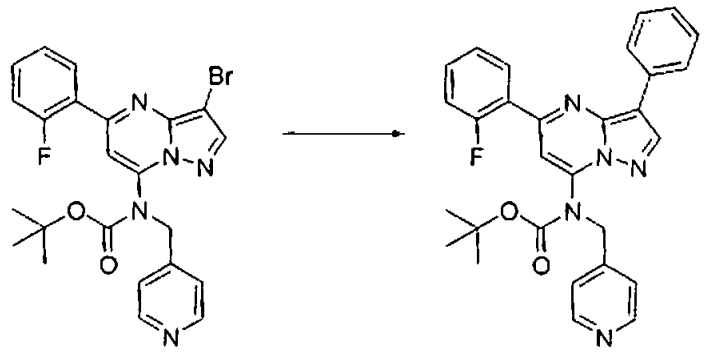
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo preparativo 127 sustituyendo únicamente el compuesto preparado en el Ejemplo preparativo 192, se preparó el compuesto anterior (0,38 g, 95% de rendimiento). LCMS: MH^+= 498.

EJEMPLO PREPARATIVO 196:



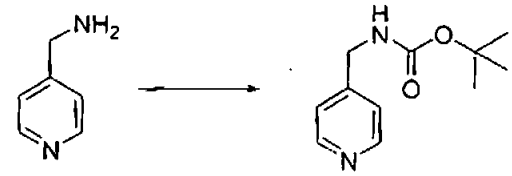
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo preparativo 195, sustituyendo únicamente el compuesto preparado en el Ejemplo preparativo 193, se preparó el compuesto anterior (0,3 g, 83% de rendimiento). EM: MH^+ = 438.

EJEMPLO PREPARATIVO 197:



Una solución del compuesto preparado en el Ejemplo preparativo 195 (0,15 g, 0,3 mmoles), ácido fenilborónico (0,073 g, 2,0 eq.), K_3PO_4 (0,19 g, 3,0 eq.), y $Pd(PPh_3)_4$ (0,017 g, 5 mol %) se calentó a reflujo en DME (16 mL) y H_2O (4 mL) durante 7 horas. La solución resultante se enfrió a temperatura ambiente, se diluyó con H_2O (10 mL), y se extrajo con CH_2Cl_2 (3 x 50 mL). Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, y se concentraron. El producto crudo se purificó por cromatografía evaporativa usando una solución al 2,5% (10% NH_4OH en MeOH) en CH_2Cl_2 como eluyente (0,16 g, 100% de rendimiento).

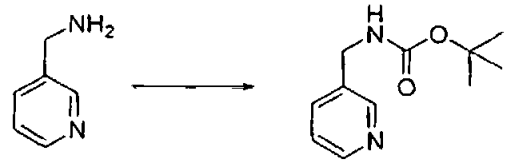
EJEMPLO PREPARATIVO 198:



A una solución de 4-aminometilpiridina (1,41 mL, 13,87 mmoles) en CH_2Cl_2 (50 mL) se agregó BOC_2O (3,3 g, 1,1 eq.) y TEA y la solución resultante se agitó a

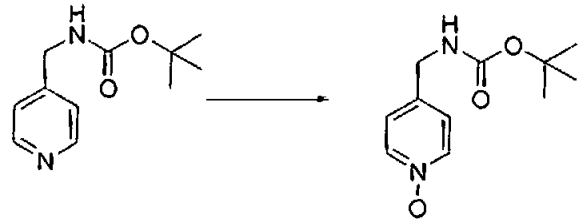
temperatura ambiente durante 2 horas. La mezcla de reacción se diluyó con H_2O (50 mL) y se extrajo con CH_2Cl_2. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron y se concentraron bajo presión reducida. El producto crudo se purificó por cromatografía evaporativa usando una solución al 5% (10% NH_4OH en MeOH) en CH_2Cl_2 como eluyente para proporcionar un sólido amarillo (2,62 g, 91% de rendimiento). LCMS: MH^+= 209.

EJEMPLO PREPARATIVO 199:



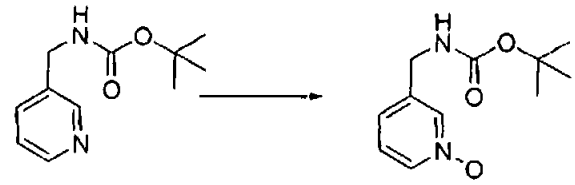
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo preparativo 198 sustituyendo únicamente 3-aminometilpiridina, se preparó el compuesto anterior en forma de un aceite amarillo (2,66 g, 92% de rendimiento). LCMS: MH^+= 209.

EJEMPLO PREPARATIVO 200:



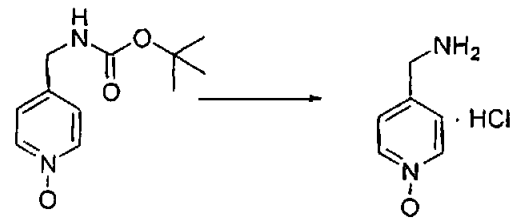
A una solución del compuesto preparado en el Ejemplo preparativo 198 (0,20 g, 0,96 mmoles) en CH_2Cl_2 (5 mL) a 0°C se agregó *m*-CPBA (0,17 g, 1,0 eq) y la solución resultante se agitó a 0°C durante 2 horas y se almacenó a 4°C durante la noche momento en el cual la mezcla de reacción se calentó a temperatura ambiente y se agitó durante 3 horas. La mezcla de reacción se diluyó con H_2O y se extrajo con CH_2Cl_2. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, y se concentraron. El producto crudo se purificó por cromatografía evaporativa usando una solución al 10% (10% NH_4OH en MeOH) como eluyente: LCMS: MH^+= 255.

EJEMPLO PREPARATIVO 201:



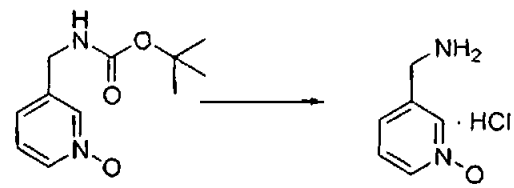
Una solución de oxona (58,6 g) en H_2O (250 mL) se agregó por goteo al compuesto preparado en el Ejemplo preparativo 199 (27 g, 0,13 mol) y $NaHCO_3$ (21,8 g, 2,0 eq.) en MeOH (200 mL) y H_2O (250 mL). La solución resultante se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con CH2Cl2 (500 mL) y se filtró. Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida para proporcionar un sólido blanco (21,0 g, 72% de rendimiento). EM: MH^+= 255.

EJEMPLO PREPARATIVO 202:



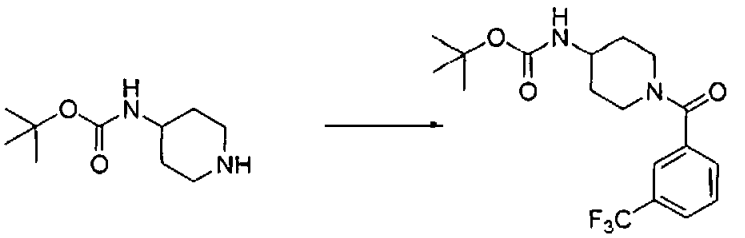
El compuesto preparado en el Ejemplo preparativo 200 (0,29 g, 1,29 mmoles) se agitó a temperatura ambiente en HCl 4M en dioxano (0,97 mL) durante 2 horas. La mezcla de reacción se concentró al vacío y se usó sin purificación adicional. LCMS: MH^+= 125.

EJEMPLO PREPARATIVO 203:



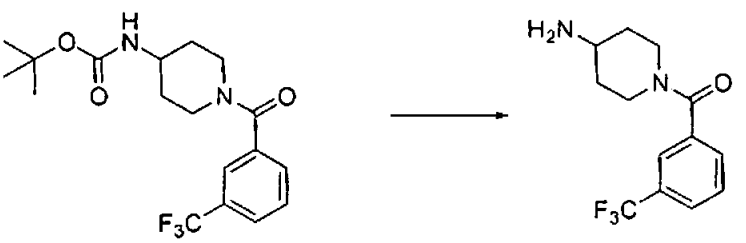
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo preparativo 202 sustituyendo únicamente el compuesto preparado en el Ejemplo preparativo 201, se preparó el compuesto que se mostró anteriormente. LCMS: MH^+= 125.

EJEMPLO PREPARATIVO 204:



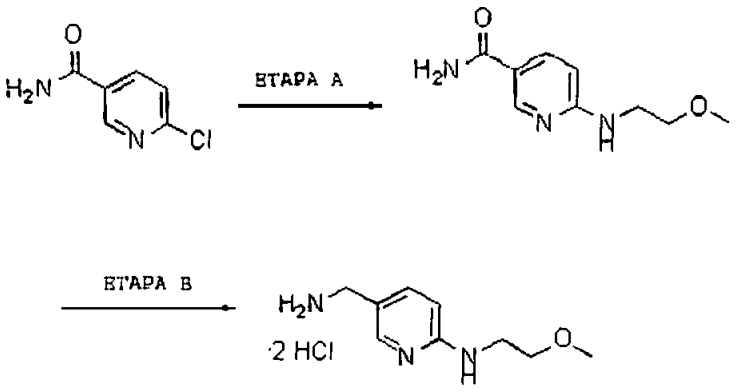
A 4-N-t-butoxicarbonilaminopiperidina (0,8 g, 4,0 mmoles) en CH_2Cl_2 (10 mL) a 0°C se agregó TEA (1,40 mL, 2,5 eq.) y cloruro de 3-trifluormetilbenzoilo (1,05 g, 1,25 eq.). La solución resultante se agitó durante 5 minutos y se calentó a temperatura ambiente y se agitó durante 3 horas. La mezcla de reacción se diluyó con CH_2Cl_2 y se lavó con Na_2CO_3 al 5% (2 x 100 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró para proporcionar un sólido de color amarillo pálido (rendimiento cuantitativo del crudo).

EJEMPLO PREPARATIVO 205:



A una solución del compuesto preparado en el Ejemplo preparativo 204 (1,0 g, 2,76 mmoles) en CH_2Cl_2 (15 mL) a 0°C se agregó TFA (8 mL) y la solución resultante se agitó a 0°C durante 30 minutos y a temperatura ambiente durante 1 hora. La mezcla de reacción se vertió sobre Na_2CO_3 (40 g) y se agregó H_2O (400 mL) y la mezcla resultante se extrajo con CH_2Cl_2. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por cromatografía evaporativa usando una solución al 20% (7N NH_3 en MeOH) en CH_2Cl_2 como eluyente (0,6 g, 82% de rendimiento),

EJEMPLO PREPARATIVO 206:



ETAPA A:

A una solución de 6-cloronicotinamida (1g, 6,39 mmoles) en alcohol isoamílico (15 mL) a temperatura ambiente se agregó Na_2CO_3 (0,81g, 7,67 mmoles) seguido de metoxietilamina (0,67 mL, 7,67 mmoles). La mezcla se calentó a 130°C durante 16 horas, se enfrió a temperatura ambiente, y se filtró a través de un filtro medio de vidrio fritado. El filtrado resultante se concentró bajo presión reducida y el sólido resultante se trituró con Et_2O (2 x 10 mL). El sólido crudo se colocó bajo alto vacío para proporcionar 1,2 g (96%) de un sólido de color amarillo claro. M+H = 196.

ETAPA B:

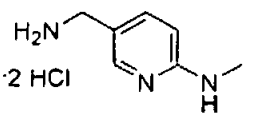
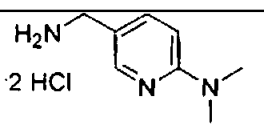
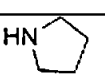
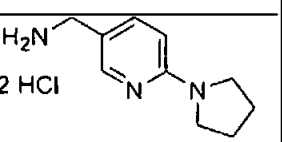
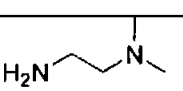
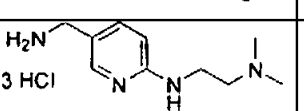
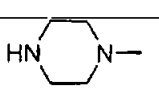
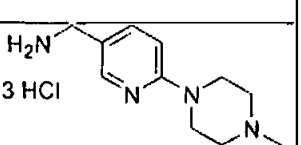
A una solución de amida (1,2 g, 6,12 mmoles) del Ejemplo preparativo 206, Etapa A en THF (5 mL) a 0°C se agregó una solución de BH_3-THF (43 mL; 43 mmoles) por goteo en 10 minutos. La solución resultante se calentó a temperatura ambiente y se agitó durante 14 horas. La mezcla se enfrió a 0°C y se trató consecutivamente con HCl 6M (35 mL), agua (30 mL), y MeOH (150 mL). La mezcla se agitó durante 8 horas y luego se concentró bajo presión reducida. El residuo crudo se trituró con MeOH, se concentró bajo presión reducida, y se colocó bajo alto vacío para obtener 1,6 g (82%) de un sólido blanco en forma de la sal de diclorhidrato. M+H (base libre) = 182.0. Este material se usó crudo en el acoplamiento con los aductos 7-Cl.

EJEMPLOS PREPARATIVOS 207-211:

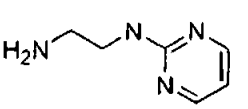
Siguiendo esencialmente el mismo procedimiento conocido que se indica en el Ejemplo preparativo 206 utilizando únicamente las aminas que se muestran

en la Columna 2 de la Tabla 13 y las aminas que se muestran en la Columna 3 de la Tabla 13 se prepararon:

TABLA 13

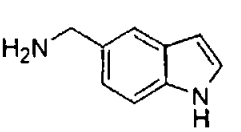
Ej. Prep.	Columna 2 (Amina)	Columna 3 (Amina)	COMP M+H (base libre)
207			M+H = 138
208			M+H = 152
209			M+H = 178
210			M+H = 195
211			M+H = 207

EJEMPLO PREPARATIVO 212:



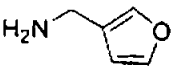
Se preparó el compuesto anterior de acuerdo con los métodos descritos en la WO 91/18904.

EJEMPLO PREPARATIVO 213:



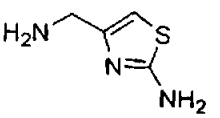
Se preparó el compuesto anterior de acuerdo con los métodos descritos en la US 6.180.627 B1.

EJEMPLO PREPARATIVO 214:



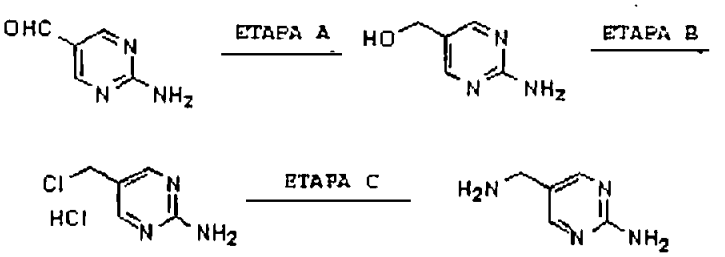
Se preparó la amina conocida tal como se describió en *J. Med. Chem.* (2001), *44*, 4505-4508.

EJEMPLO PREPARATIVO 215:



Se preparó la amina conocida tal como se describió en *J. Med. Chem.* (1997), *40*, 3726-3733.

EJEMPLO PREPARATIVO 216:



ETAPA A:

Una solución de aldehído (50 g, 0,41 mol) [WO 0232893] en MeOH (300 mL) se enfrió a 0°C y se trató cuidadosamente con $NaBH_4$ (20g, 0,53 mol en 6 tandas) durante 20 minutos. Luego se dejó calentar la reacción a 20°C y se agitó durante 4 horas. La mezcla se agitó nuevamente a 0°C, apagándola cuidadosamente con NH_4Cl acuosa saturado, y se concentró. La cromatografía evaporativa (5–10% 7N NH_3-MeOH/CH_2Cl_2) proporcionó el alcohol primario (31g, 62%) en forma de un sólido de color amarillo claro.

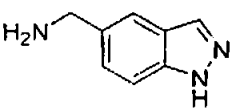
ETAPA B:

Una suspensión de alcohol (31 g, 0,25 mol) del Ejemplo preparativo 216, Etapa A en CH_2Cl_2 (500 mL) se enfrió a 0°C y se trató lentamente con $SOCl_2$ (55mL, 0,74 moles en 30 minutos). La reacción se agitó luego durante la noche a 20°C. El material se concentró, se suspendió en acetona, y luego se filtró. El sólido beige resultante se secó durante la noche al vacío (38,4g, 52%, sal de HCl).

ETAPA C:

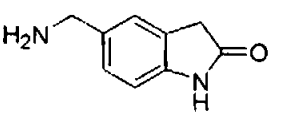
A un tubo de presión de 15 mL cargado con una barra agitadora se agregó cloruro (150 mg, 0,83 mmoles) del Ejemplo preparativo 216, Etapa B seguido de NH_3 7M/MeOH (10 mL). La solución resultante se agitó durante 48 horas a temperatura ambiente después de lo cual la mezcla se concentró bajo presión reducida para proporcionar un sólido de color amarillo claro (0,146 g, 83%). M+H (base libre) = 140.

EJEMPLO PREPARATIVO 217:



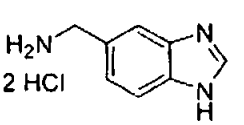
Se preparó el compuesto anterior de acuerdo con los métodos descritos en WO 00/26210.

EJEMPLO PREPARATIVO 218:



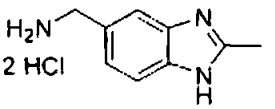
Se preparó el compuesto anterior de acuerdo con los métodos descritos en WO 99/10325.

EJEMPLO PREPARATIVO 219:



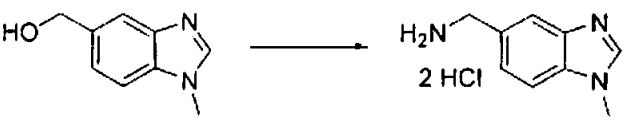
Se preparó el diclorhidrato de amina conocido de acuerdo con los métodos descritos en WO 02/64211.

EJEMPLO PREPARATIVO 220:



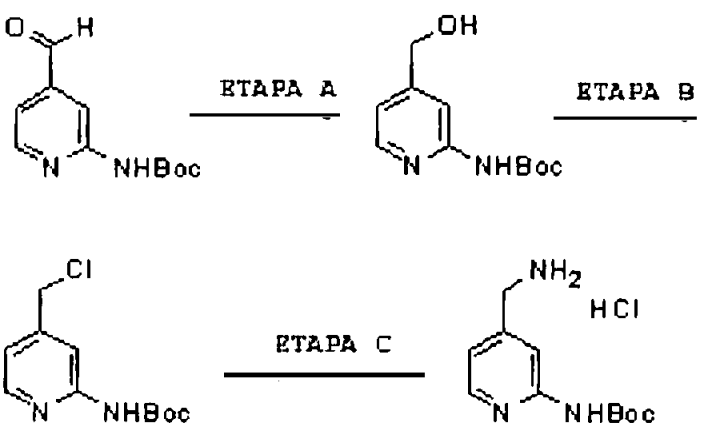
Se preparó el compuesto anterior de acuerdo con los métodos descritos en la WO 02/64211.

EJEMPLO PREPARATIVO 221:



Se preparó el alcohol primario conocido de acuerdo con la WO 00/37473 y se convirtió al diclorhidrato de amina deseado de manera análoga a la del Ejemplo preparativo 220 de acuerdo con la WO 02/064211.

EJEMPLO PREPARATIVO 222:



ETAPA A:

A una solución de aldehído (WO 02/32893) (0,46 g, 2,07 mmoles) en MeOH/THF (2 mL/2 mL) a 0°C se agregó $NaBH_4$ (94 mg, 2,48 mmoles) en una porción. La mezcla resultante se agitó durante 12 horas a temperatura ambiente y

se diluyó con NH_4Cl acuoso saturado (3 mL). La mezcla se concentró bajo presión reducida y la capa acuosa resultante se extrajo con CH_2Cl_2 (3 x 5 mL). Las capas orgánicas se combinaron, se lavaron con salmuera (1 x 5 mL), se secaron (Na_2SO_4), y se filtraron. La capa orgánica se concentró bajo presión reducida para proporcionar 417 mg (90% de rendimiento) de un sólido blanco. M+H = 225.

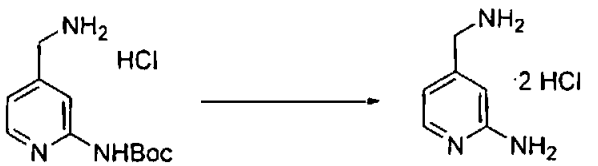
ETAPA B:

Al alcohol crudo del Ejemplo preparativo 222, etapa A (0,4 g, 1,78 mmoles) en CH_2Cl_2 (4 mL) se agregó $SOCl_2$ (0,65 mL, 8,91 mmoles) y la mezcla se agitó durante 2 horas a temperatura ambiente. La mezcla se concentró bajo presión reducida para proporcionar 407 mg (94%) de un sólido de color amarillo claro. M+H = 243. El producto crudo se recogió sin purificación adicional.

ETAPA C:

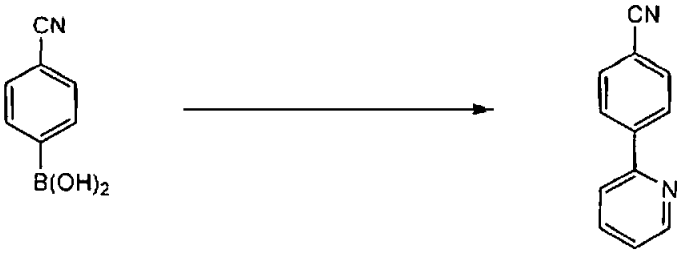
A una solución de cloruro crudo del Ejemplo preparativo 222, Etapa B (0,33 g, 1,36 mmoles) en un tubo de presión se cargó NH_3 7M/MeOH (35 mL) y la mezcla se agitó durante 72 horas. La mezcla se concentró bajo presión reducida para proporcionar 257 mg (85%) de un semisólido amarillo. M+H (base libre) = 224.

EJEMPLO PREPARATIVO 223:



A un frasco de fondo redondo cargado con clorhidrato de amina (0,24 g, 1,1 mmoles) del Ejemplo preparativo 222 y barra agitadora, se agregó HCl 4N/dioxano (10 mL). La solución resultante se agitó durante 12 horas a temperatura ambiente, se concentró bajo presión reducida, y se trituró con CH_2Cl_2 (3 x 5 mL). El producto crudo se filtró, se lavó con Et2O (2 x 5mL), y se secó bajo alto vacío para proporcionar 0,19g (91%) como sal de diclorhidrato. M+H (base libre) = 124.

EJEMPLO PREPARATIVO 224:

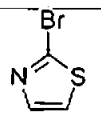
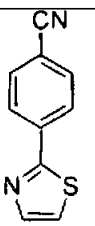
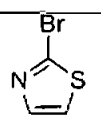
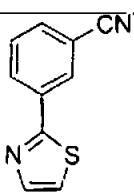


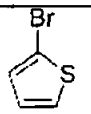
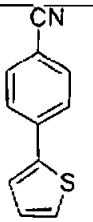
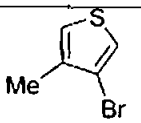
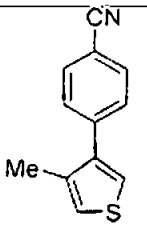
Se agregó $Pd(PPh_3)_4$ (0,404 gm, 0,35 mmoles) a una solución desgasificada de ácido 4-cianobencen borónico (1,029 g, 7 mmoles) y 2-bromopiridina (1,11 g, 7 mmoles) en 75 mL de acetonitrilo. Se agregó una solución de carbonato de sodio 0,4 M (35 mL) a la mezcla de reacción y la solución resultante se reflujó a 90°C bajo Ar durante 24 horas (el progreso de la reacción se monitoreó por TLC). La mezcla de reacción se enfrió y se separó la capa acuosa. La capa orgánica que contenía el producto y el catalizador agotado se mezclaron con gel de sílice (15 g) y se concentraron hasta sequedad. Se aisló el 4-(2-piridil)-benzonitrilo por cromatografía en columna (0,850 g, 68%). LCMS: MH^+ = 181; ^1H RMN ($CDCl_3$) δ 8,85 (d, 1H), 8,7 (dd, 1H), 7,9 (dd, 1H), 7,75 (d, 2H), 7,7 (d, 2H), 7,4 (dd, 1H).

EJEMPLOS PREPARATIVOS 225-228:

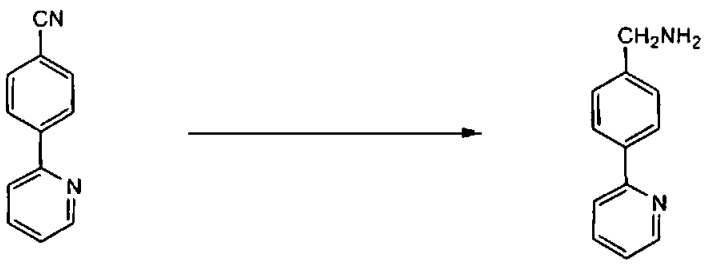
Siguiendo esencialmente el mismo procedimiento que se describió en el Ejemplo preparativo 224, sustituyendo únicamente los bromuros en la columna 2 de la Tabla 14, se prepararon los compuestos de la columna 3 de la Tabla 14.

Tabla 14

Ej. Prep.	Columna 2	Columna 3	Columna 4
225			Rendimiento = 70% LCMS: MH^+ = 187
226			Rendimiento = 60% LCMS: MH^+ = 187

227			Rendimiento = 70% LCMS: MH^+ = 186
228			Rendimiento = 70% LCMS: MH^+ = 200

EJEMPLO PREPARATIVO 229:

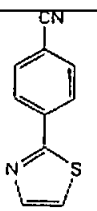
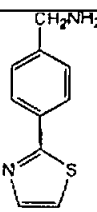
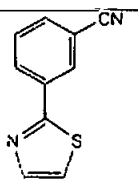
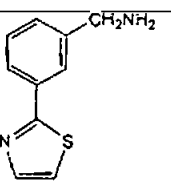
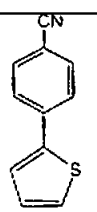
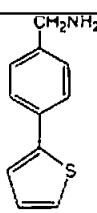
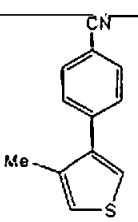
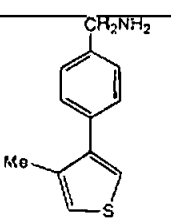


Se agregó lentamente una solución de BH_3-THF (1 M, 24 mL, 5 eq) a una solución bajo agitación de 4-(2-piridil)-benzonitrilo (0,85 g, 4,72 mmoles) en THF anhidro (25 mL) bajo Ar, y la solución resultante se reflujó durante aproximadamente 12 horas. La solución se enfrió a 0°C usando agua helada. Se agregó metanol por goteo (15 mL) a la mezcla de reacción fría y se agitó durante 1 hora para destruir el exceso de BH_3. Se agregó HCl – metanol (1M, 10 mL) lentamente a la mezcla de reacción y se reflujó durante 5 horas. La solución se concentró hasta sequedad y el residuo se disolvió en 25 mL de agua y se extrajo con éter para remover cualquier material no reaccionado. La solución acuosa se neutralizó con carbonato de potasio sólido a pH 10-11. La amina libre, así formada se extrajo con éter, se secó sobre carbonato de potasio (0,45 g, 50%). LCMS: MH+ = 185; ^{1}H RMN ($CDCl_3$) δ 8,85 (d, 1H), 8,7 (dd, 1H), 7,9 (dd, 1H), 7,75 (d, 2H), 7,7 (d, 2H), 7,4 (dd, 1H), 3,7 (t, 2H), 1,7 (t, 2H).

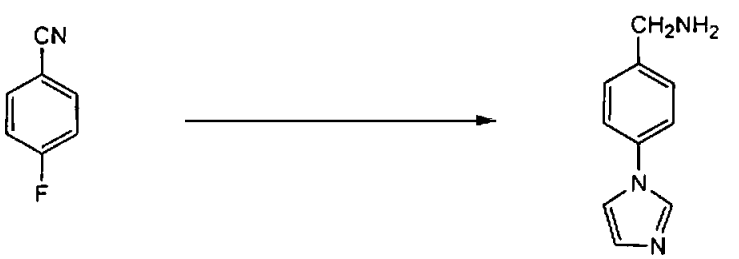
EJEMPLOS PREPARATIVOS 230-233:

Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo preparativo 229, se prepararon los compuestos de la columna 3 de la Tabla 15.

Tabla 15

Ej. Prep.	Columna 2	Columna 3	Columna 4
230			Rendimiento = 60% LCMS: MH^+ = 191
231			Rendimiento = 60% LCMS: MH^+ = 191
232			Rendimiento = 70% LCMS: MH^+ = 190
233			Rendimiento = 70% LCMS: MH^+ = 204

EJEMPLO PREPARATIVO 234:



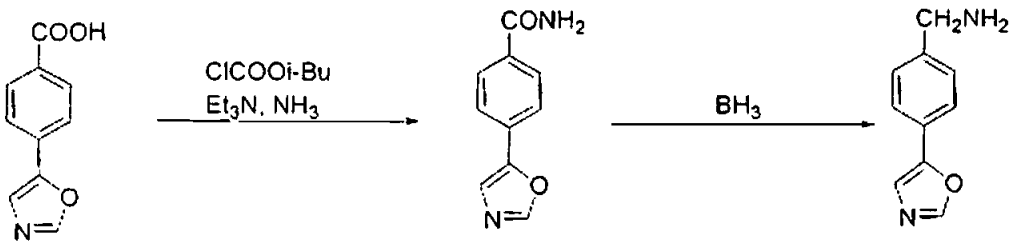
Etapa A:

Una mezcla de 4-fluorbenzonitrilo (3 g, 25 mmoles) e imidazolilo sodio (2,48 g, 27,5 mmoles) en DMF (50 mL) se agitó a 80°C bajo Ar durante 12 horas. El progreso de la reacción se monitoreo por TLC. La mezcla de reacción se concentró *al vacío* y el residuo se diluyó con 50 mL de agua y se agitó. La mezcla acuosa se extrajo con EtOAc (2 x 50 mL). Los extractos de EtOAc combinados se secaron sobre MgSO4 anhidro, se concentraron, y se aisló el 4-(1-imidazolil)-benzonitrilo por cromatografía en columna (3,6 g, 78%). LCMS: MH^+ = 170; ^1H RMN ($CDCl_3$) δ 8,0 (s, 1H), 7,5 (d, 2H), 7,4 (m, 3H), 7,3 (d, 1H)

Etapa B:

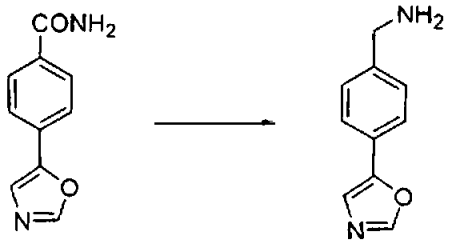
Se disolvió 4-(1-imidazolil)-benzonitrilo (1g, 5,92 mmoles) en THF anhidro (10 mL) y se agregó por goteo a una solución bajo agitación LAH –THF (1 M en THF, 18 mL) a temperatura ambiente. La mezcla de reacción se reflujó bajo Ar durante 2 horas y el progreso se monitoreo por TLC. La mezcla se enfrió a 0°C y se apagó por adición por goteo de una solución saturada de Na_2SO_4 – H_2O. La mezcla se agitó durante 1 hora y se filtró para remover las sales de litio. El filtrado se secó sobre $MgSO_4$ anhidro y se concentró para obtener 4-(1-imidazolil)-bencilamina (0,8 g, 80%). LCMS: MH^+ = 174.

EJEMPLO PREPARATIVO 235:



Una mezcla de ácido 4-(5-oxazolil)benzoico (1,0 g, 5,46 mmoles) y Et_3N (552 mg, 5,46 mmoles) en 25 mL en THF se enrió a 0°C y se agregó por goteo ClCOO*i*-Bu (745 mg, 5,46 mmoles). Una vez terminada la adición, la mezcla de reacción se agitó durante 5 minutos adicionales y luego se agregó NH_4OH acuoso (0,63 mL de una solución al 28%, 10,46 mmoles). Después de agitar durante la noche, el solvente se evaporó, y el residuo se recogió en agua y se basificó a pH 9. El sólido precipitado se filtró, se lavó con agua y se secó sobre P_2O_5 en un desecador al vacío para proporcionar 500 mg (48%) de la 4-(5-oxazolil)-benzamida: ^1H RMN (DMSO-d6) δ 8,50 (s, 1H), 8,20-7,80 (m, 5H).

EJEMPLO PREPARATIVO 236:

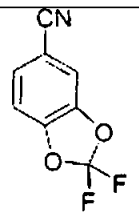
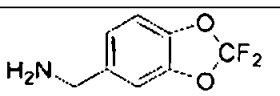
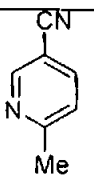
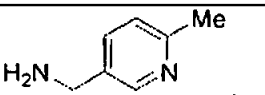


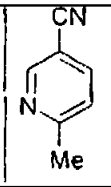
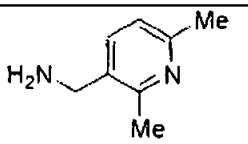
Una suspensión de 4-(5-oxazolil)benzamida (500 mg, 2,657 mmoles) en 10 mL de THF seco se enfrió a 0°C y se agregaron 10 mL de BH_3.THF 1M (10,00 mmoles). El contenido se reflujó durante la noche y se destruyó el exceso de borano por adición por goteo de metanol. El solvente se evaporó y el residuo se trató con HCl metanólico para descomponer el complejo amina-borano. Después de la evaporación del metanol, el residuo se recogió en agua, se basificó a pH 10 y el producto se extrajo en DCM. La capa de DCM se secó (K_2CO_3) y el solvente se removió para proporcionar 150 mg (32%) de 4-(5-oxazolil)bencilamina: ^{1}H RMN ($CDCl_3$) δ 7,90 (s, 1H), 7,60 (d, 2H), 7,40 (d, 2H), 7,30 (s, 1H), 3,90 (s, 2H).

EJEMPLOS PREPARATIVOS 237-239:

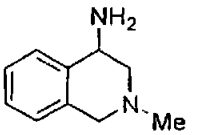
Siguiendo esencialmente los mismos procedimientos que se indicaron anteriormente, los compuestos en la Columna 2 de la Tabla 16 se redujeron usando el método indicado en la Columna 3 de la Tabla 16 para proporcionar la amina que se indica en la Columna 4 de la Tabla 16.

Tabla 16

Ej. Prep.	Columna 2	Columna 3	Columna 4	COMP
237		BH_3		^{1}H RMN ($CDCl_3$) δ 7.15-6,90 (m, 3H), 3,85 (s, 2H), 1,45 (s, 2H)
238		H_2		^{1}H RMN ($CDCl_3$) δ 8,40(s, 1H), 7,55 (dd, 1H), 7,10 (d, 1H), 3,85 (s, 2H), 2,50 (s, 3H), 1,70 (bs, 2 H)

239		BH_3		

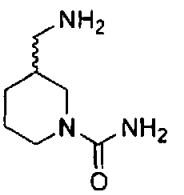
EJEMPLO PREPARATIVO 240



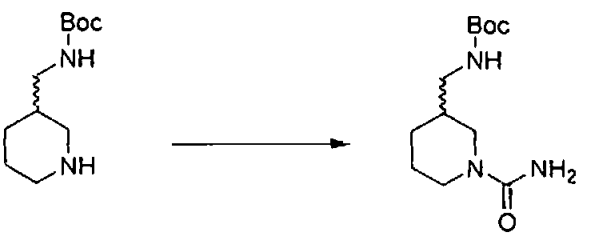
Se preparó por el procedimiento de la literatura (PCT Solicitud Int., WO 0105783): ^{1}H RMN ($CDCl_3$) δ 7,35 (d, 1H), 7,24-7,10 (m, 2 H), 7,02 (d, 1H), 3,95 (t, 1H), 3,70 (d, 1H), 3,37 (d, 1H), 2,65 (m, 2H), 2,45 (s, 3H), 1,90 (bs, 2H).

EJEMPLO PREPARATIVO 241:

3-(AMINOMETIL)PIPERIDIN-1-CARBOXAMIDA



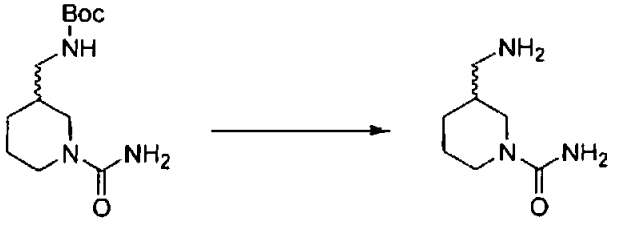
A. 3-(*ter*-BUTOXICARBONILAMINOMETIL)PIPERIDIN-1-CARBOXAMIDA



Se disolvió 3(R/S)-(*ter*-butoxicarbonilaminometil)piperidina (3g, 14,0 mmoles) en diclorometano anhidro (50mL) y se agregó isocianato de trimetilsililo (9,68g, 11,4mL, 84,0 mmoles). La mezcla se agitó bajo argón a 25°C durante 68 horas. Se agregó isocianato de trimetilsililo adicional (4,84g, 5,7mL, 42,0 mmoles) y la mezcla se agitó a 25°C por un total de 90 horas. La mezcla se evaporó hasta sequedad y se cromatografió sobre una columna de gel de sílice (30x5cm) usando 2% (hidróxido de amonio concentrado al 10% en metanol)-diclorometano como eluyente para proporcionar 3-(*ter*-butoxicarbonilaminometil)piperidin-1-carboxamida (3,05g, 85%): FABMS: m/z 258,1 (MH^+); HRFABMS: m/z 258,1816

(MH^+). Calc. para $C_{12}H_{24}O_3N_3$: m/z 258,1818; δ_H ($CDCl_3$) 1,22 91H, m, CH_2), 1,42 (9H, s, -COOC($C\underline{H}_3$)$_3$), 1,48 (1H, m, CH_2), 1,67 (2H, m, CH_2), 1,78 (1H, m, CH), 2,80 (1H, m, CH_2), 2,99, 3H, m, CH_2), 3,59 (1H, m, $CH_2$0 3,69 (1H, m, CH_2), 4,76 (2H, bm, $CONH_2$) y 4,98ppm (1H, bm, NH); δ_C ($CDCl_3$) CH_3: 28,5, 28,5, 28,5; CH_2: 24,0, 28,3, 43,2, 45,1, 47,8; CH: 36,5; C: 79,4, 156,3, 158,5.

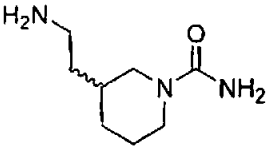
B. 3-(AMINOMETIL)PIPERIDIN-1-CARBOXAMIDA



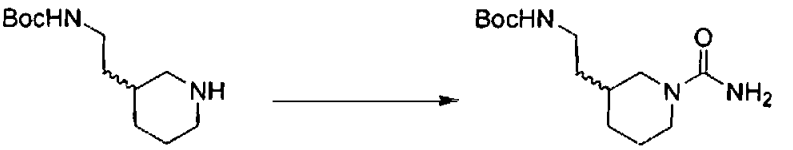
3-(*ter*-butoxicarbonilaminometil)piperidin-1-carboxamida (150mg, 0,583 mmoles) (preparada tal como se describió en el Ejemplo preparativo 241, Etapa A anterior) se disolvió en metanol (3mL). Se agregó ácido sulfúrico concentrado al 10% en 1,4-dioxano (7,9mL) y la mezcla se agitó a 25°C durante 1 hora. La mezcla se diluyó con metanol y se agregó resina BioRad AG1-X8 (forma OH^-) hasta que el pH fue básico. La resina se separó por filtración, se lavó con metanol, se evaporó hasta sequedad y se cromatografió sobre una columna de gel de sílice (15x2cm) usando diclorometano seguido de 15% (hidróxido de amonio concentrado al 10% en metanol)-diclorometano como eluyente para proporcionar la 3-(aminometil)piperidin-1-carboxamida (80mg, 87%): FABMS: m/z 158,1 (MH^+); HRFABMS: m/z 158,1294 (MH^+). Calc. para $C_7H_{16}N_3O$: m/z 158,1293; δ_H ($CDCl_3$ + gota CD_3OD) 1,20 (1H, m, CH_2), 1,48 (1H, m, CH_2), 1,60 (1H, m, CH), 1,68 (1H, m, CH_2), 1,83 (1H, m, CH_2), 2,64 (bm, 2H, -$CH_2N\underline{H}_2$), 2,82 (1H, m, CH_2), 3,02 (1H, m, CH_2), 2,98 (2H, m, CH_2), 3,70 (1H, m, -$C\underline{H}_2NH_2$), 3,78 (1H, m, -$C\underline{H}_2NH_2$) y 5,24 ppm (1H, bs, NH); δ_C ($CDCl_3$ + gota CD_3OD) CH_2: 24,1, 28,6, 44,0, 44,8, 47,9; CH: 38,3; C: 159,0.

EJEMPLO PREPARATIVO 242:

3-(2-AMINOETIL)PIPERIDIN-1-CARBOXAMIDA



A. 3-(2-ter-BUTOXICARBONILAMINOETIL)PIPERIDIN-1-CARBOXAMIDA



3-(2-*ter*-Butoxicarbonilaminoetil)piperidina (500mg, 2,19 mmoles) se disolvieron en diclorometano anhidro (10mL) y se agregó isocianato de trimetilsililo (2,96mL, 21,9mmoles). La mezcla se agitó bajo argón a 25°C durante 3,35horas. La mezcla se diluyó con diclorometano y se lavó con bicarbonato de sodio acuoso saturado. La capa orgánica se secó ($MgSO_4$), se filtró, y se evaporó hasta sequedad y se cromatografió sobre una columna de gel de sílice (15x5cm) usando 5% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente para proporcionar 3-(2-*ter*-butoxicarbonil aminoetil)piperidin-1-carboxamida (417,7mg, 70%): FABMS: m/z 272,0 (MH^+); HRFABMS: m/z 272,1979 (MH^+). Calc. para $C_{13}H_{26}O_3$: m/z 272,1974; δ_H ($CDCl_3$) 1,16 (1H, m, CH_2), 1-30-1,60 (5H, m, CH/CH_2), 1,46 (9H, s, $-COOC(C\underline{H}_3)_3$), 1,68 (1H, m, CH_2), 1 84 (1H, m, CH_2), 2,54 (1H, dd, CH_2), 2,73 (1H, m, CH_2), 3,08 (1H, m, CH_2), 3,42 (1H, m, CH_2), 4,02 (1H, m, CH_2), 4,10 (1H, m, CH_2), 4,84 (1H, m, NH) y 4,96 ppm (2H, bm, $CONH_2$); δ_C ($CDCl_3$) CH_3: 28,5, 28,5, 28,5; CH_2: 25,2, 31,7, 34,9, 37,3, 44,6, 50,3; CH: 32,9; C: 79,5, 156,4, 158,2.

B. 3-(2-AMINOETIL)PIPERIDIN-1-CARBOXAMIDA

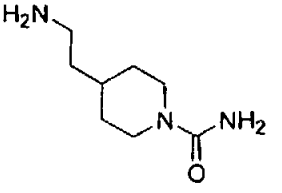


3-(2-*ter*-Butoxicarbonilaminoetil)piperidin-1-carboxamida (392,7mg, 1,45 mmoles) (preparada tal como se describió en el Ejemplo preparativo 242, Etapa A anterior) se disolvió en metanol (7,5mL) y se agregó ácido sulfúrico concentrado al 10% en 1,4-dioxano (19,5mL). La mezcla se agitó a 25°C durante 1,25horas. La mezcla se diluyó con metanol y se agregó resina BioRad AG1-X8 (forma OH^-) hasta que el pH fue básico. La resina se separó por filtración, se lavó con metanol, se evaporó hasta sequedad y se cromatografió sobre una columna de gel de sílice (30x2,5cm) usando 15% (hidróxido de amonio concentrado al 10% en metanol)-diclorometano como eluyente para proporcionar 3-(2-aminoetil)piperidin-

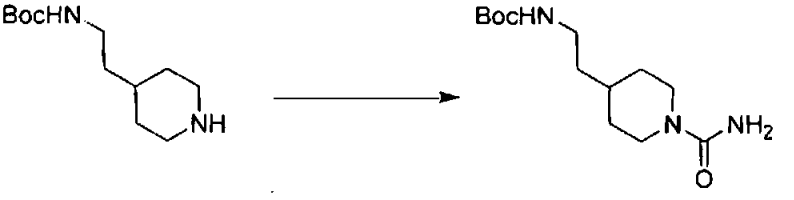
1-carboxamida (233mg, 94%): FABMS: m/z 172,1 (MH^+); HRFABMS: m/z 172,1444(MH^+). Calc. para $C_8H_{18}N_3O$ requiere: m/z 172,1450; δ_H ($CDCl_3$ + 3% CD_3OD) 1,14 (1H, m, CH_2), 1,40 (2H, m, CH_2), 1,49 (1H, m, CH), 1,58 (1H, m, CH_2), 1,69 (1H, m, CH_2), 1,85 (1H, m, CH_2), 2,55 (1H, m, CH_2), 2,67 (5H, m, CH_2/NH_2), 2,76 (1H, bm, CH_2), 2,84 (1H, m, CH_2) y 3,82 ppm (2H, m, $CONH_2$); δ_C ($CDCl_3$ + 3% CD_3OD) CH_2: 24,8, 30,9, 36,6, 38,9, 44,9, 50,0; CH: 33,4.

EJEMPLO PREPARATIVO 243:

4-(2-AMINOETIL)PIPERIDIN-1-CARBOXAMIDA

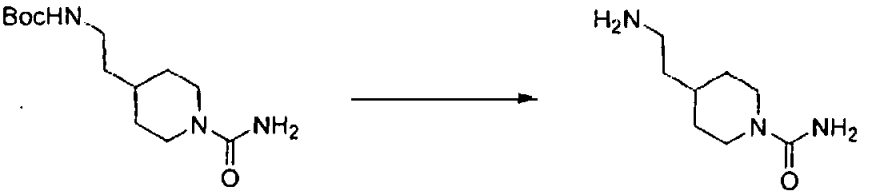


A. 4-(2-ter-BUTOXICARBONILAMINOETIL)PIPERIDIN-1-CARBOXAMIDA



4-(2-*ter*-Butoxicarbonilaminoetil)piperidina (500mg, 2,19 mmoles) se disolvió en diclorometano anhidro (10mL) y se agregó isocianato de trimetilsililo (2,96mL, 21,9 mmoles). La mezcla se agitó bajo argón 25°C durante 3,25 horas. La mezcla se diluyó con diclorometano y se lavó con bicarbonato de sodio acuoso saturado. La capa orgánica se secó ($MgSO_4$), se filtró, se evaporó hasta sequedad y se cromatografió sobre una columna de gel de sílice (15x5cm) usando 5% (hidróxido de amonio concentrado al 10% en metanol)-diclorometano como eluyente para 4-(2-*ter*-butoxicarbonilaminoetil)piperidin-1-carboxamida (308,2mg, 52%): FABMS: m/z 272,0 (MH^+); HRFABMS: m/z 272,1965 (MH^+). Calc. para $C_{13}H_{26}O_3N_3$: m/z 272,1974; δ_H ($CDCl_3$) 1,20 (2H, m, CH_2), 1,47 (9H, s, $-COOC(C\underline{H}_3)_3$), 1,45-1,55 (3H, m, CH/CH_2), 1,75 (2H, m, CH_2), 2,82 (2H, m, CH_2), 3,19 (2H, m, CH_2), 3,96 (2H, m, CH_2), 4,64 (2H, m, CH_2) y 4,70 ppm (1H, bm, NH); δ_C ($CDCl_3$) CH_3: 28,5, 28,5, 28,5; CH_2: 31,8, 31,8, 36,7, 38,0, 44,5, 44,5; CH: 33,4; C: 79,2, 156,7, 158,1.

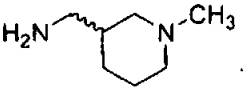
A. 3-(2-AMINOETIL)PIPERIDIN-1-CARBOXAMIDA



4-(2-*ter*-Butoxicarbonilaminoetil)piperidin-1-carboxamida (283,3mg, 1,04 mmoles) (preparada tal como se describió en el Ejemplo preparativo 243, Etapa A anterior) se disolvió en metanol (5,4mL) y se agregó ácido sulfúrico concentrado al 10% en 1,4-dioxano (14,2mL) y la mezcla se agitó a 25°C durante 1,25 horas. La mezcla se diluyó con metanol y se agregó resina BioRad AG1-X8 (forma OH^-) hasta que el pH fue básico. La resina se separó por filtración, se lavó con metanol, se evaporó hasta sequedad y se cromatografió sobre una columna de gel de sílice (30x2,5cm) usando 15% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente para proporcionar la 3-(2-aminoetil) piperidin-1-carboxamida (170mg, 95%): FABMS: m/z 172,1 (MH^+); HRFABMS: m/z 172,1442. Calc. para $C_8H_{18}N_3O$ requiere: m/z 172,1450; δ_H ($CDCl_3$ + 3% CD_3OD) 1,16 (2H, m, CH_2), 1,43 (2H, m, CH_2), 1,52 (1H, m, CH), 1,70 (2H, m, CH_2), 2,70-2,85 (8H, m, CH_2) y 3,92 ppm (2H, m, $CONH_2$); δ_C ($CDCl_3$ + 3% CD_3OD) CH_2: 31,9, 31,9, 39,0, 39,7, 44,4, 44,4; CH: 33,5; C: 158,7.

EJEMPLO PREPARATIVO 244:

3-(AMINOMETIL)-1-METILPIPERIDINA



A. 3-(BROMOMETIL)-1-METILPIPERIDINA



Se disolvió 3-(hidroximetil)-1-metilpiperidina (2g, 15,5 mmoles) en acetonitrilo anhidro (32mL) y se agregó piridina anhidra (2,02mL, 24,8 mmoles) y la solución se enfrió a 0°C. Se agregó dibromotrifenilfosforano (8,49g, 20,2 mmoles) a 0°C y la mezcla se dejó calentar a 25°C y se agitó durante 94 horas. La mezcla se evaporó hasta sequedad y el residuo se cromatografió sobre una columna de gel

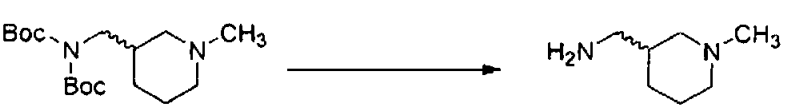
de sílice (30x5cm) usando un gradiente de elución con diclorometano, 35% de éter dietílico en diclorometano y 5-10% de metanol en diclorometano como eluyente para proporcionar 3-(bromometil)-1-metilpiperidina (3,13g, 100%): FABMS: m/z 192,1 (MH^+); δ_H ($CDCl_3$) 1,52 (1H, m, CH_2), 1,99 (2H, m, CH_2), 2,43 (1H, m, CH_2), 2,75 (2H, m, CH_2), 2,82 (1H, m, CH), 2,86/2,88 (3H, s, NCH_3), 3,42/3,49 (2H, dd, -$C\underline{H}_2$Br) y 3,56 ppm (2H, m, CH_2); δ_C ($CDCl_3$) CH_3: 44,3; CH_2: 22,1, 26,6, 35,4, 54,8, 58,2; CH: 34,6.

A. 3-(Di-ter-BUTOXICARBONILAMINOMETIL)-1-METILPIPERIDINA



3-(Bromometil)-1-metilpiperidina (1,5g, 7,81 mmoles) (del Ejemplo preparativo 244, Etapa A anterior) y di-*ter*-butiliminodicarboxilato (1,697g, 7,81 mmoles) se disolvieron en acetonitrilo anhidro (25mL). Se agregaron carbonato de cesio (5,1g, 15,6 mmoles) e ioduro de litio (52mg, 0,391 mmoles) y la mezcla se agitó a 70°C durante 20 horas. La mezcla se evaporó hasta sequedad y el residuo se dividió entre diclorometano y bicarbonato de sodio acuoso saturado. La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó hasta sequedad. El residuo se cromatografió sobre una columna de gel de sílice (30x5 cm) usando 3% de metanol en diclorometano como eluyente para proporcionar 3-(di-*ter*-butoxicarbonilamino)-1-metilpiperidina (1,331 g, 52%): FABMS: m/z 329,2 (MH^+); HRFABMS: m/z 329,2438 (MH^+), Calc. para $C_{17}H_{33}N_2O_4$: m/z 329,2440; δ_H ($CDCl_3$) 1,10 (1H, m, CH_2), 1,54 (18H, s, -$COOC(CH_3)_3$), 1,86 (2H, m, CH_2), 2,01 (1H, m, CH_2), 2,19 (1H m, CH), 2,34 (2H, bm, CH_2), 2,59 (3H, -NCH_3), 3,19 (2H, m, CH_2) y 3,52/3,52 ppm (2H, -CH_2N-); δ_C ($CDCl_3$) CH_3: 28,5, 28,5, 28,5, 28,5, 28,5, 28,5, 47,2; CH_2: 25,4, 28,3, 50,4, 56,8, 60,8; CH: 37,2; C: 83,0, 83,0,153,5, 153,5.

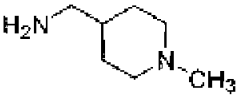
A. 3-(AMINOMETIL)-1-METILPIPERIDINA



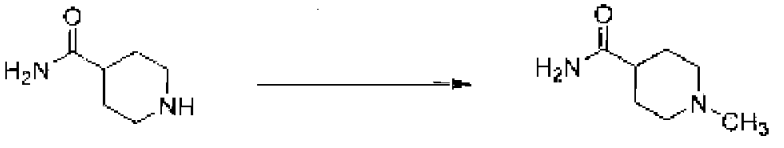
3-(Di-*ter*-butoxicarbonilamino)-1-metilpiperidina (500 MG, 1,52 mmoles) (del Ejemplo Preparativo 244, Etapa B anterior) se disolvió en metanol (7,5 mL) y se agregó ácido sulfúrico concentrado al 10% (v/v) en 1,4-dioxano (19,75 mL). La solución se agitó a 25°C durante 0,5 horas. Se agregó metanol (300 mL), seguido de resina BioRad AG1-X8 (forma OH^-) hasta que el pH fue de ~10. La resina se separó por filtración y se lavó con metanol (2x200 mL). Los eluatos combinados se evaporaron hasta sequedad y el residuo se cromatografió sobre una columna de gel de sílice (30x2,5 cm) usando 10% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente para proporcionar 3-(aminometil)-1-metilpiperidina (69,2 mg, 35%): FABMS: m/z 129,1 (MH^+); HRFABMS: m/z 129,1392 (MH^+), Calc. para $C_7H_{17}N_2$: m/z 129,1392; δ_H ($CDCl_3$) 0,90 (2H, m, CH_2), 1,65 (2H, m, CH_2), 1,72 (1H, m, CH), 1,79 (1H, m, CH_2), 1,91 (1H, m, CH_2), 2,30 (3H, s, $-NCH_3$), 2,64 (2H, m, CH_2), 2,82 (1H, m, $-C\underline{H}_2NH_2$) y 2,92 ppm (1H, m, $-C\underline{H}_2NH_2$); δ_C ($CDCl_3$) CH_3: 46,7; CH_2: 25,2; 28,0, 46,3, 56,4, 60,3; CH: 39,9.

EJEMPLO PREPARATIVO 245:

4-(AMINOMETIL)-1-METILPIPERIDINA



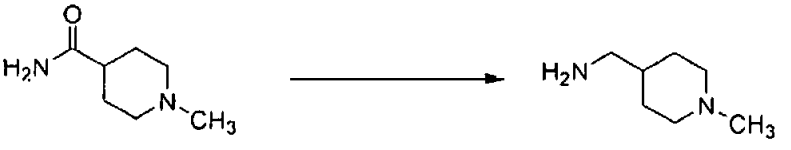
A. 1-METILISONIPECOTAMIDA



Se disolvió isonipecotamida (10 g, 78,0 mmoles) en agua destilada (100 mL) y se agregó formaldehido acuoso al 37% (7,6 mL, equivalente a 2,81g HCHO, 93,6 mmoles). Se agregó Pd-C al 10% húmedo (espátulas de 8 cucharadas) bajo argón y la mezcla se hidrogenó a 25°C y 344,5 kPa (50psi) durante 43 horas. El catalizador se separó por filtración a través de Celite y éste último se lavó con agua y metanol. Los filtrados combinados se evaporaron hasta sequedad y el residuo se cromatografió sobre una columna de gel de sílice (60x5 cm) usando

8%-10%-20% (hidróxido de amonio concentrado al 10% en metanol)-diclorometano como eluyente para proporcionar 1-metilisonipecotamida (7,15 g, 64%): FABMS: m/z 143,1 (MH^+); HRFABMS: m/z 143,1184 (MH^+). Calc. para $C_7H_{15}N_2O$: m/z 143,1184; δ_H (d_6-DMSO) 1,50/1,57 (4H, m, CH_2), 1,76/1,94 (4H, m, CH_2), 2,10 (3H, s, $-NCH_3$), 2,72 (1H, m, CH) y 6,68/7,18 ppm (2H, m, $CONH_2$); δ_C (d_6-DMSO) CH_3: 41,2; CH_2: 28,5, 28,5, 54,9, 54,9; CH: 46,2; C: 176,7.

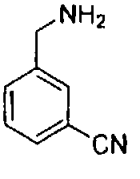
B. 4-(AMINOMETIL)-1-METILPIPERIDINA



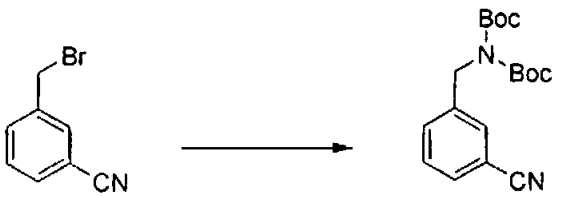
1-Metilisonipecotamida (6,75 g, 47,5 mmoles) (preparada tal como se describió en el Ejemplo Preparativo 245, Etapa A anterior) se disolvió en THF anhidro (350 mL) y la mezcla resultante se agregó en porciones a una suspensión agitada de hidruro de litio aluminio (1,8 g, 47,5 mmoles) en THF anhidro (100 mL) a 0°C bajo nitrógeno. La mezcla se agitó a 0°C durante 30 minutos y luego se calentó a 66°C durante 25 horas bajo nitrógeno. Se agregó agua destilada (1,88 mL) por goteo a la mezcla agitada a 0°C, seguido de hidróxido de sodio acuoso al 20% (1,42 mL) y luego agua destilada (6,75 mL) y la mezcla se agitó durante 15 minutos. La mezcla se filtró y los sólidos se lavaron con THF en diclorometano. Los filtrados combinados se evaporaron hasta sequedad y se cromatografiaron sobre una columna de gel de sílice (30x5 cm) usando 15%-20% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente para proporcionar 4-(aminometil)-1-metilpiperidina (0,678 g, 11%): FABMS: m/z 129,1 (MH^+); HRFABMS: m/z 129,1389 (MH^+), Calc. para $C_7H_{17}N_2$: m/z 129,1392; δ_H (d_6-DMSO): 2,08ppm (3H, s, $-NCH_3$); δ_C (d_6-DMSO): CH_3: bajo picos DMSO; CH_2: 29,6, 29,6, 46,7, 55,2, 55,2; CH: 46,2.

EJEMPLO PREPARATIVO 246:

3-(AMINOMETIL)BENZONITRILO

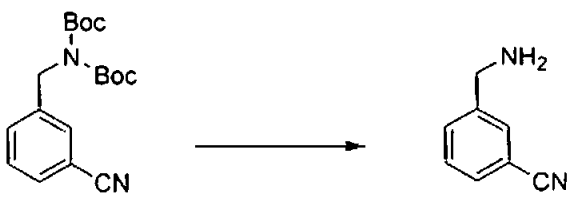


A. 3-(Di-*TER*-BUTOXICARBONILAMINO)BENZONITRILO



3-(Bromometil)benzonitrilo (5 g, 25,5 mmoles) y di-ter-butiliminodicarboxilato (5,54 g, 25,5 mmoles) se disolvieron en THF anhidro (50 mL) y se agregaron carbonato de cesio (16,62 g, 25,5 mmoles) y ioduro de litio (170,5 mg, 1,275 mmoles). La mezcla se agregó a 70°C durante 22 horas y la reacción se elaboró tal como se describió en el Ejemplo Preparativo 89, Etapa B anterior. El residuo se cromatografió sobre una columna de gel de sílice (60x5 cm) usando 5% acetato de etilo en hexano como eluyente para proporcionar 3-(di-*ter*-butoxicarbonilamino)benzonitrilo (7,39 g, 87%): FABMS: m/z 333,2 (MH^+); HRFABMS: m/z 333,1815 (MH^+); Calc. para $C_{18}H_{25}N_2O_4$: m/z 333,1814; δ_H ($CDCl_3$) 1,52 (18H, s, $-COOC(CH_3)_3$), 4,84 (2H, s, CH_2), 7,48 (1H, m, Ar-H), 7,60 (2H, m, Ar-H) y 7,65 ppm (1H, m, Ar-H); δ_C ($CDCl_3$) CH_3: 28,1, 28,1, 28,1, 28,1, 28,1, 28,1; CH_2: 48,4; CH: 129,2, 131,0, 131,0, 131,9; C: 83,2, 83,2, 112,5, 118,8, 140,1, 152,5, 152,5.

B. 3-(AMINOMETIL)BENZONITRILO

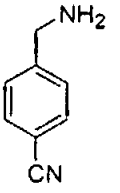


3-(Di-*ter*-butoxicarbonilamino)benzonitrilo (2 g, 6,0 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 246, Etapa A anterior) se disolvió en metanol (30 mL) y se agregó 10%(v/v) (10% de ácido sulfúrico concentrado en 1,4-dioxano) (79 mL). La solución se agitó a 25°C durante 0,25 horas y se elaboró tal como se describió en el Ejemplo Preparativo 89, Etapa C anterior). El residuo se cromatografió sobre una columna de gel de sílice (15x5 cm) usando 3% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente

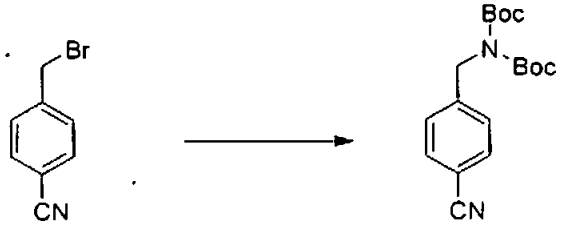
para proporcionar el compuesto del título (651,4 mg, 82%): FABMS: m/z 133,1 (MH^+); HRFABMS: m/z 133,0762 (MH^+), Calc. para $C_8H_9N_2$: m/z 133,0766; δ_H ($CDCl_3$) 2,57 (2H, s, $-CH_2\underline{N}H_2$), 3,92 (2H, s, $-C\underline{H}_2NH_2$), 7,46 (1H, m, Ar-H), 7,57 (2H, m, Ar-H) y 7,64 ppm (1H, m, Ar-H); δ_C ($CDCl_3$) CH_2: 45,2; CH: 129,4, 130,7, 130,7, 131,8; C: 112,4, 118,8, 143,8.

EJEMPLO PREPARATIVO 247:

4-(AMINOMETIL)BENZONITRILO

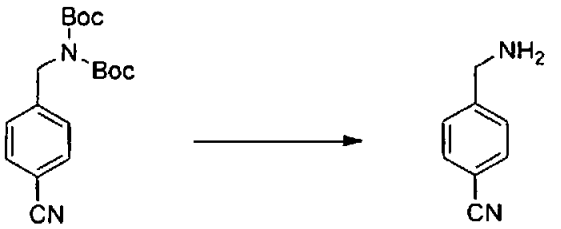


A. 3-(Di-*ter*-BUTOXICARBONILAMINOMETIL)BENZONITRILO



4-(Bromometil)benzonitrilo (5 g, 25,5 mmoles) y di-ter-butiliminodicarboxilato (5,54 g, 25,5 mmoles) se disolvieron en THF anhidro (50 mL) y se agregaron carbonato de cesio (16,62 g, 25,5 mmoles) y ioduro de litio (170,5 mg, 1,275 mmoles). La mezcla se agitó a 70°C durante 23 horas y la reacción se elaboró tal como se describió en el Ejemplo Preparativo 244, Etapa B anterior. El residuo se cromatografió sobre una columna de gel de sílice (50x5 cm) usando 5% de acetato de etilo en hexano como eluyente para proporcionar 4-(di-*ter*-butoxicarbonilaminometil)benzonitrilo (7,07 g, 83%): FABMS: m/z 333,2 (MH^+); HRFABMS: m/z 333,1816 (MH^+), Calc. para $C_{18}H_{25}N_2O_4$: m/z 333,1814; δ_H ($CDCl_3$) 1,45 (18H, s, $-COOC(CH_3)_3$), 4,81 (2H, s, CH_2), 7,37 (2H, d, Ar-H) y 7,62 ppm (2H, d, Ar-H); δ_C ($CDCl_3$) CH_3: 28,1, 28,1, 28,1, 28,1, 28,1, 28,1, 28,1; CH_2: 49,2; CH: 127,8, 127,8, 132,3, 132,3; C: 83,2, 83,2, 111,1, 118,9, 144,1, 152,4, 152,4.

B. 4-(AMINOMETIL)BENZONITRILO



4-(Di-*ter*-butoxicarbonilaminometil)benzonitrilo (2 g, 6,0 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 247, Etapa A anterior) se disolvió en TFA (4 mL) y la solución se agitó a 25°C durante 0,25 horas. La mezcla de reacción se diluyó con diclorometano y se extrajo con hidróxido de sodio 1N. La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó hasta sequedad. El residuo se cromatografió sobre una columna de gel de sílice (15x5 cm) usando 3% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente para proporcionar 4-(aminometil)benzonitrilo (108 mg, 68%): FABMS: m/z 133,1 (MH^+); HRFABMS: m/z 133,0764 (MH^+), Calc. para $C_8H_9N_2$: m/z 133,0766; δ_H ($CDCl_3$) 2,04 (2H, s, -$CH_2N\underline{H}_2$), 3,89 (2H, s, -$C\underline{H}_2NH_2$), 7,40 (2H, d, Ar-H) y 7,59 ppm (2H, d, Ar-H); δ_C ($CDCl_3$) CH_2: 45,7; CH: 127,8, 127,8, 132,4, 132,4; C: 110,6, 118,9, 148,0.

EJEMPLO PREPARATIVO 248

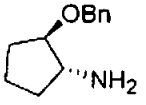
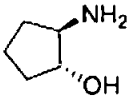
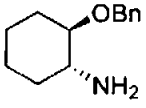
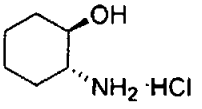
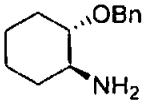
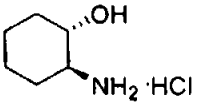


A una solución de (1*S*,2*S*)-2-benciloxiciclopentil amina (1,5 g, 7,84 mmoles) en MeOH (50 mL) a temperatura ambiente se agregó 10 % de Pd/C (50% húmedo, 1,0 g) seguido de adición por goteo de HCl concentrado (0,7 mL). La mezcla se agitó bajo un balón de H_2 durante 14 horas y luego el catalizador se separó por filtración a través de una almohadilla de Celite. La almohadilla de Celite se lavó con MeOH (2 x 10 mL) y el filtrado resultante se concentró bajo presión reducida para proporcionar 0,97 g (90%) de un semisólido amarillo; M+H (base libre) = 102

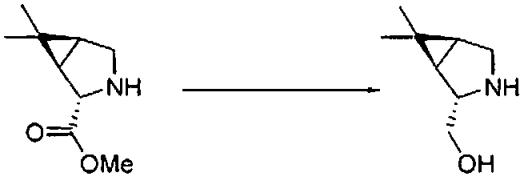
EJEMPLOS PREPARATIVOS 249-251

De manera análoga al Ejemplo Preparativo 248, las aminas cicloalquilo protegidas (Columna 2) se convirtieron a los derivados de clorhidrato de aminocicloalcanol deseados (Columna 3) tal como se indica en la Tabla 17.

TABLA 17

Ej.	Columna 2 (Amina)	Columna 3 (Método de disociación)	COMP. M+H
249			M+H = 102 (base libre)
250			M+H = 116 (base libre)
251			M+H = 116 (base libre)

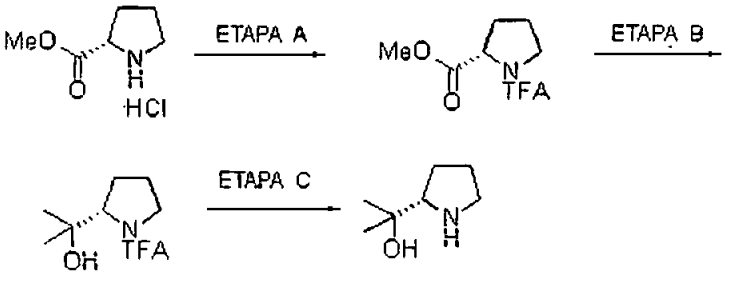
EJEMPLO PREPARATIVO 252



A una solución de éster (preparada de acuerdo con *J. Org. Chem.* (1999), *64*, 330) (0,5 g, 2,43 mmoles) en THF (8 mL) a 0°C se agregó $LiAlH_4$ (0,37 g, 9,74 mmoles) en una sola porción. La mezcla resultante se calentó a reflujo durante 12 horas y se enfrió a 0°C. La mezcla se trató consecutivamente con H_2O (1 mL), NaOH 1M (1 mL), y H_2O (3 mL). Se agregó CH_2Cl_2 (10 mL) a la mezcla la cual se

agitó vigorosamente durante 30 minutos. La mezcla se filtró a través de una almohadilla de Celite la cual se lavó generosamente con CH_2Cl_2 (3 x 5 mL). El filtrado resultante se concentró bajo presión reducida para proporcionar 0,41 g (85%) de un sólido de color amarillo/anaranjado. M+H = 142.

EJEMPLO PREPARATIVO 253



ETAPA A:

A una solución de Clorhidrato de éster metílico de L-prolina (0,50 g, 3,0 mmoles) en CH_2Cl_2 (15 mL) a 0°C se agregó Et_n. (1,1 mL, 7,55 mmoles) seguido de TFAA (0,56 mL, 3,92 mmoles). La mezcla se agitó durante 12 horas a temperatura ambiente y se agregó HCl 1N (25 mL). Las capas se separaron y la capa orgánica se lavó consecutivamente con $NaHCO_3$ acuoso saturado (1 x 25 mL), y salmuera (1 x 25 mL). La capa orgánica se secó (Na_2SO_4), se filtraron, y se concentraron bajo presión reducida para proporcionar 0,72 g (100%) de un aceite de color amarillo. M+H = 226. El material crudo se recogió en la Etapa B sin purificación adicional.

ETAPA B:

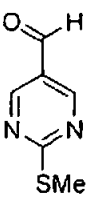
A una solución del compuesto preparado en el Ejemplo Preparativo 253, Etapa A (0,68 g, 3,0 mmoles) en THF (20 mL) a 0°C se agregó MeMgI (5,1 mL, 3,0M en Et_2O) por goteo durante 10 minutos. La solución resultante se agitó durante 16 horas a temperatura ambiente después de lo cual la mezcla se apagó por adición de NH_4Cl acuoso saturado. La mezcla se concentró hasta sequedad y el residuo resultante se agitó con EtOAc (100 mL) durante 45 minutos y se filtró. El filtrado se concentró bajo presión reducida para proporcionar 0,68 g (100%) de

un aceite de color amarillo/anaranjado. M+H = 226. El material crudo se recogió en la Etapa C sin purificación adicional.

ETAPA C:

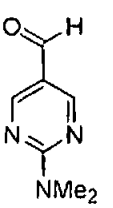
A una solución del compuesto preparado en el Ejemplo Preparativo 253, Etapa B (0,68 g, 3,0 mmoles) en MeOH (5 mL) se agregó una solución de KOH (0,68 g, 12,1 mmoles) en MeOH (5 mL). La mezcla se agitó a reflujo durante 12 horas y a temperatura ambiente durante 72 horas después de lo cual la mezcla se concentró hasta sequedad. El residuo crudo se suspendió en EtOAc (50 mL) y se agitó vigorosamente durante 30 minutos y se filtró. Este procedimiento se repitió dos veces más y el filtrado resultante se concentró bajo presión reducida para proporcionar 128 mg (33%) de un aceite de color rojo oscuro/anaranjado. M+H = 130. Este material se usó sin purificación en la etapa de acoplamiento subsiguiente.

EJEMPLO PREPARATIVO 254:



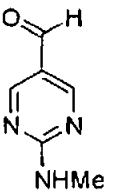
El aldehído se preparó de acuerdo con el procedimiento de Gupton (*J. Heterocyclic Chem.* (1991), *28*, 1281).

EJEMPLO PREPARATIVO 255



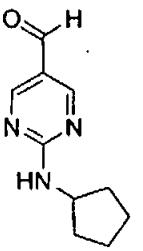
Usando el aldehído del Ejemplo Preparativo 254, se empleo el procedimiento de Gupton (*J. Heterocyclic Chem.* (1991), *28*, 1281) para preparar el aldehído del título.

EJEMPLO PREPARATIVO 256



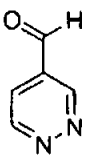
Se preparó el aldehído del título de acuerdo con el procedimiento de Ragan et. al *Synlett* (2000), *8*, 1172-1174.

EJEMPLO PREPARATIVO 257



La reacción del clorhidrato de ciclopentil guanidina conocido (*Org. Lett.* (2003), *5*, 1369-1372) bajo las condiciones de Ragan (*Synlett* (2000), *8*, 1172-1174) proporcionó el aldehído del título.

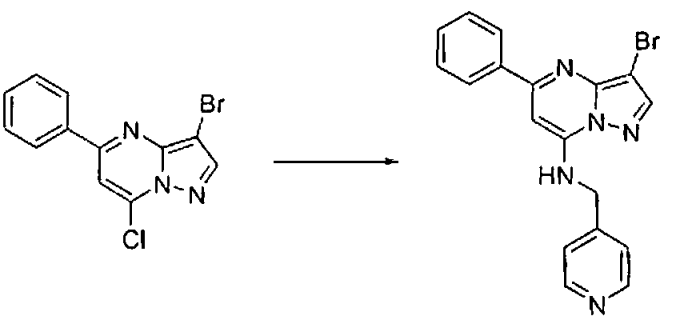
EJEMPLO PREPARATIVO 258



Se preparó el compuesto del título de acuerdo con la literatura conocida *Monatshefte fur Chemie* (1973), *104*, 1372-1382.

EJEMPLOS

EJEMPLO 1:

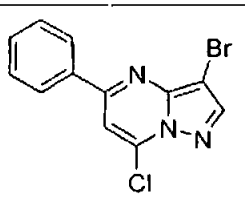
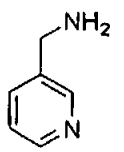
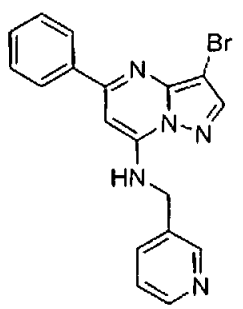
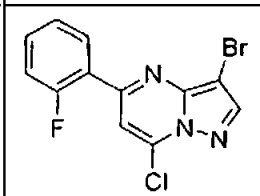
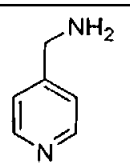
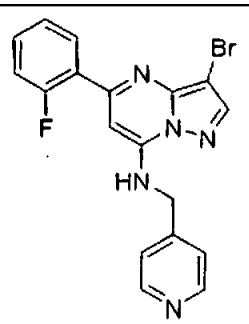


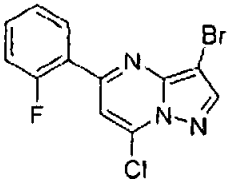
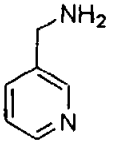
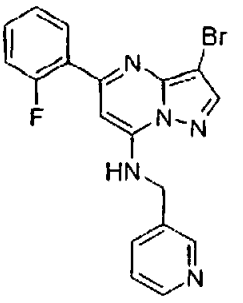
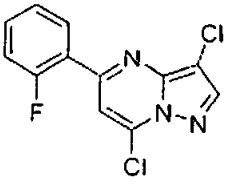
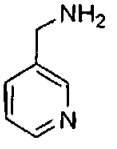
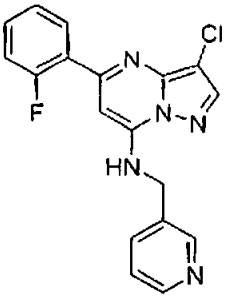
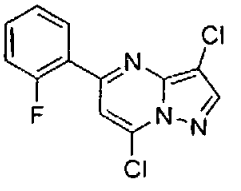
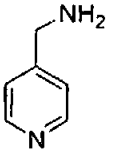
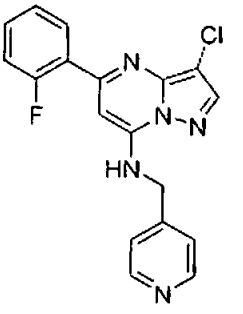
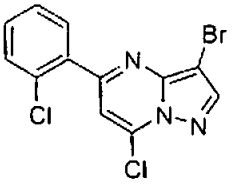
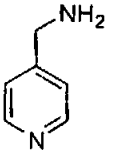
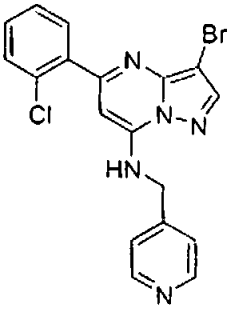
Una solución del producto del Ejemplo Preparativo 127 (0,27 g, 0,875 mmoles), 4-aminometilpiridina (0,12 g, 1,3 eq.), y K_2CO_3 (0,24 g, 2 eq.) en CH_3CN (5 mL) se agitó a temperatura ambiente durante 48 horas. La mezcla de reacción se diluyó con H_2O y se extrajo con CH_2Cl_2. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron y se concentraron. El producto crudo se purificó por cromatografía evaporativa usando una solución al 4% en peso de MeOH en CH_2Cl_2 como eluyente (0,28 g, rendimiento 93%). LCMS: MH^+=380; p.f.= >205°C (desc.).

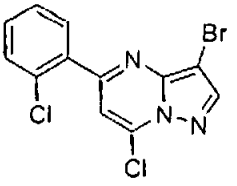
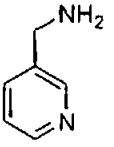
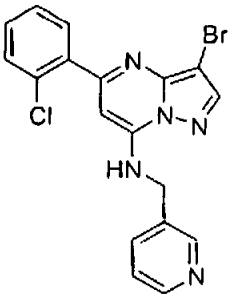
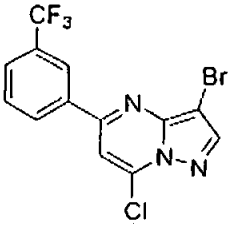
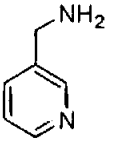
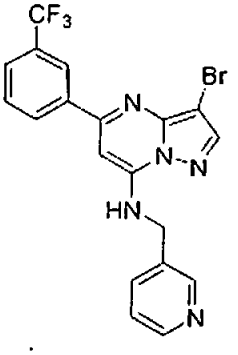
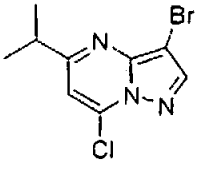
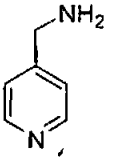
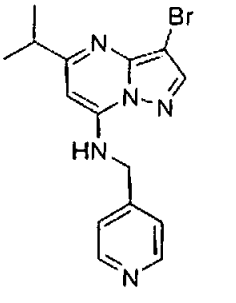
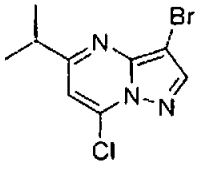
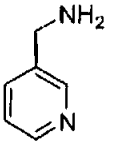
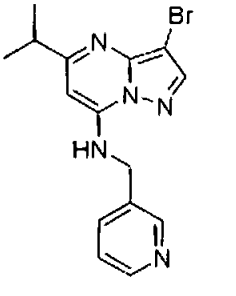
EJEMPLOS 2-210:

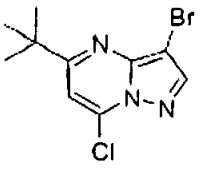
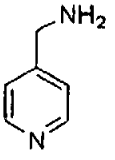
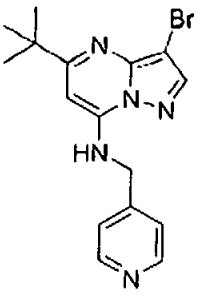
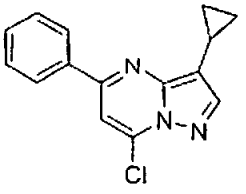
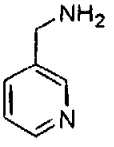
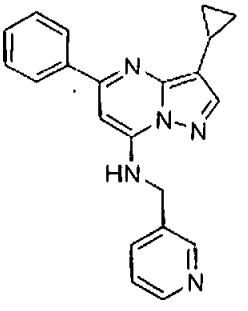
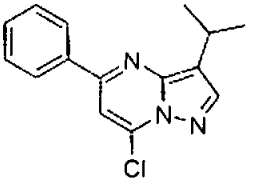
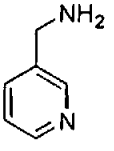
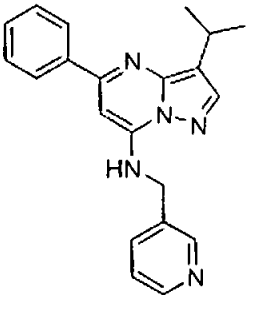
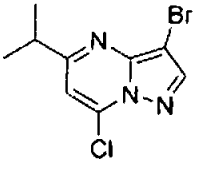
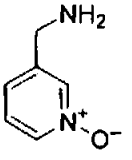
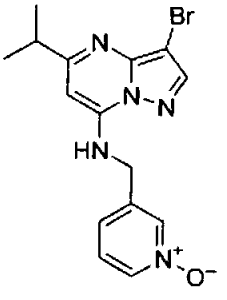
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo 1, únicamente que se sustituyen los cloruros que se muestran en la Columna 2 de la Tabla 18 y las aminas que se muestran en la Columna 3 de la Tabla 18, se prepararon los compuestos de la Columna 4 de la Tabla 18:

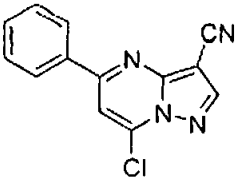
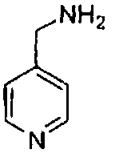
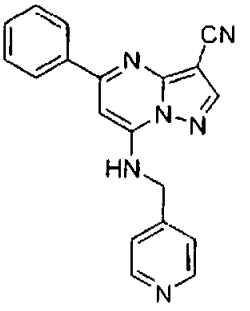
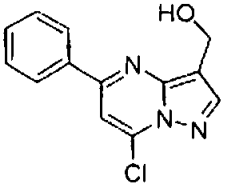
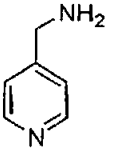
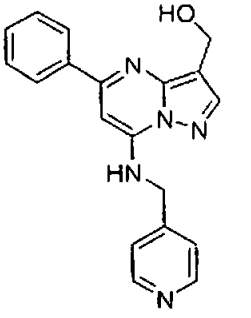
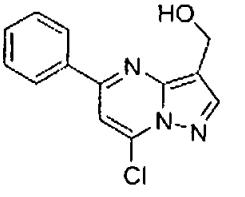
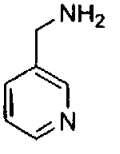
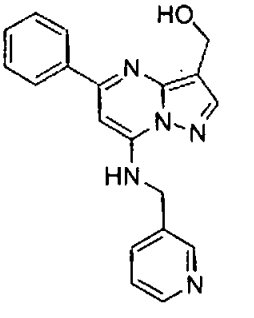
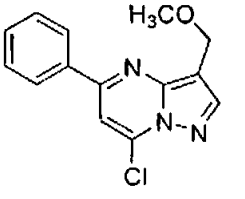
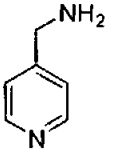
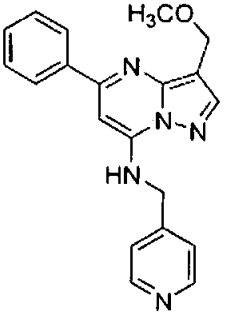
TABLA 18

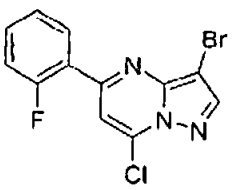
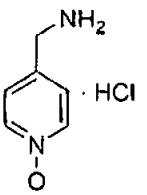
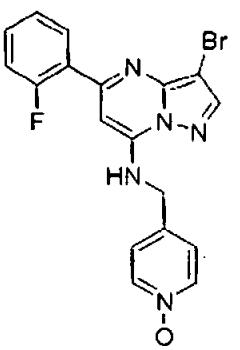
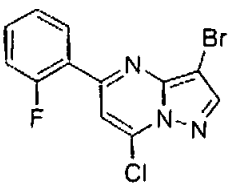
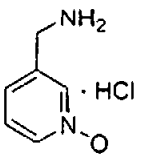
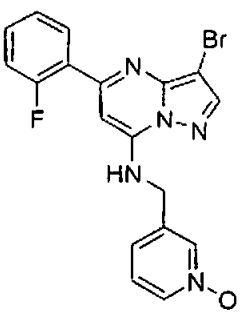
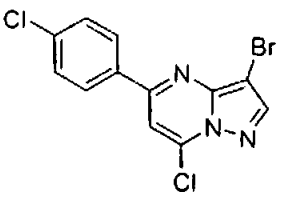
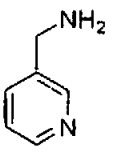
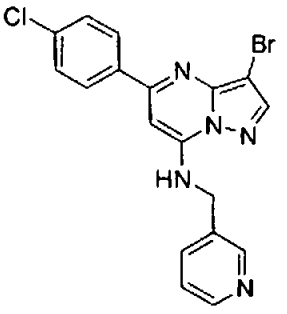
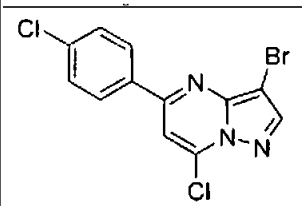
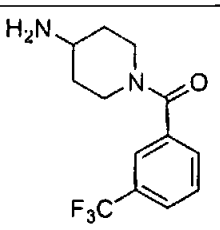
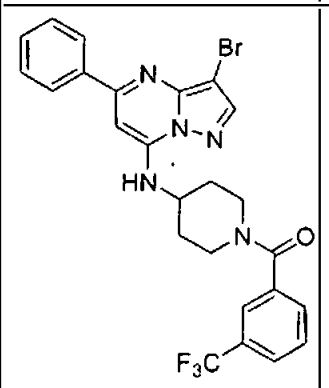
Ej.	Columna 2	Columna 3	Columna 4	Datos
2				LCMS: MH^+= 380; p.f.=175-176°C
3				LCMS: MH^+= 398; p.f.= 156-157°C

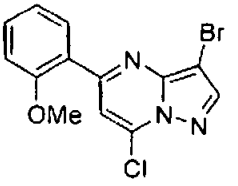
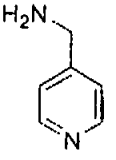
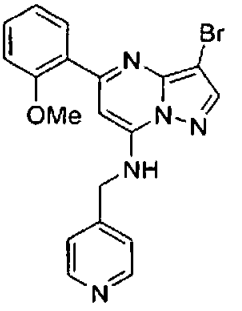
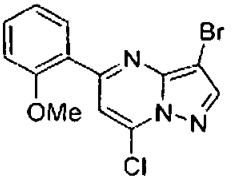
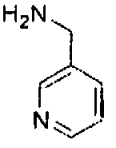
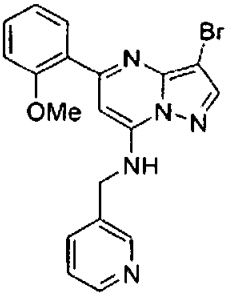
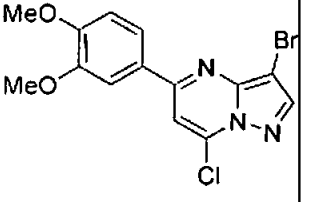
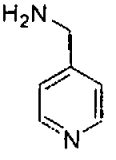
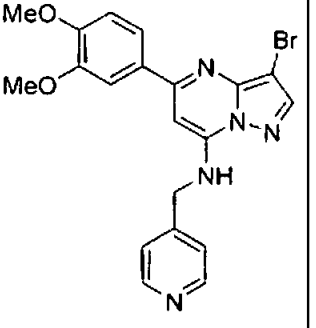
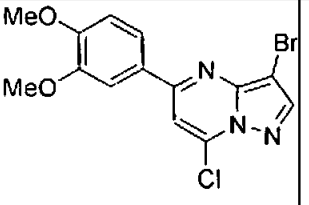
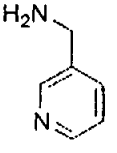
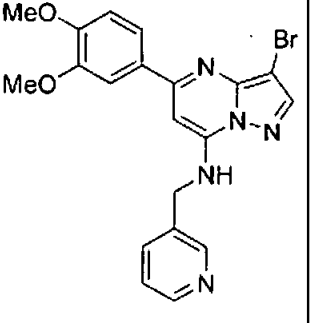
4				LCMS: MH^+ = 398; p.f.= 45-49°C
5				LCMS: MH^+ = 354; p.f.= 43-46°C
6				LCMS: MH^+ = 354; p.f.= 149-150°C
7				LCMS: MH^+ = 414; p.f.= 86-92°C

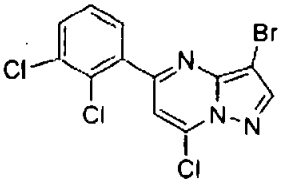
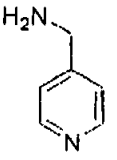
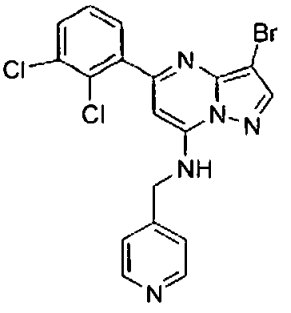
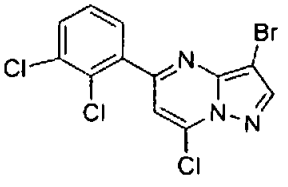
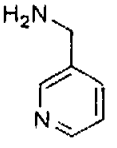
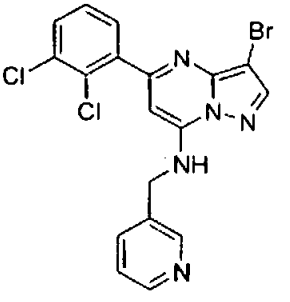
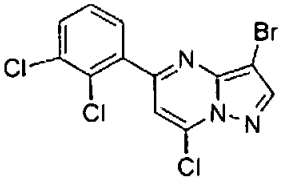
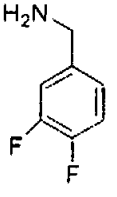
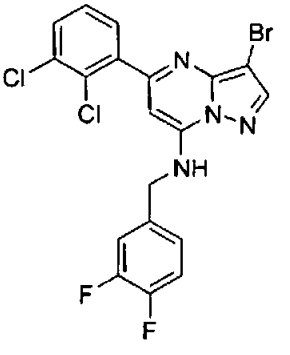
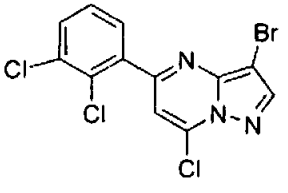
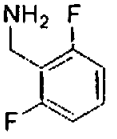
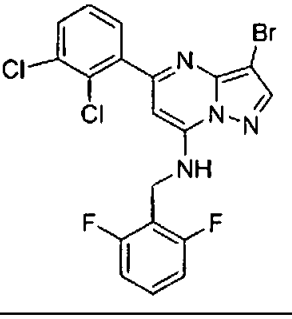
8				LCMS: MH^+= 414; p.f.= 185-186°C
9				LCMS: MH^+= 448; p.f.= 167-168°C
10				LCMS: MH^+= 346; p.f.= 57-58°C
11				LCMS: MH^+= 347; p.f.=122,9-125,3°C

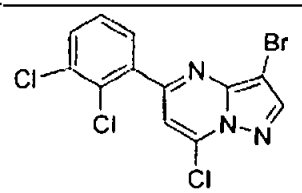
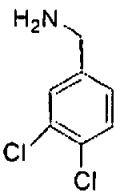
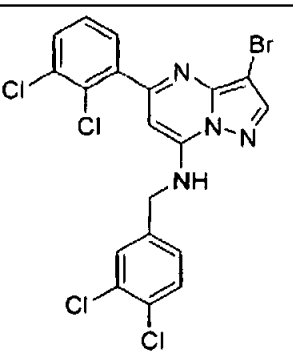
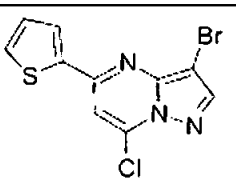
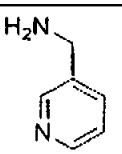
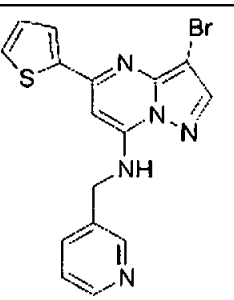
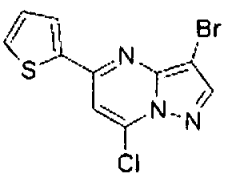
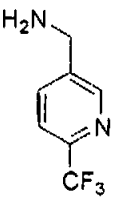
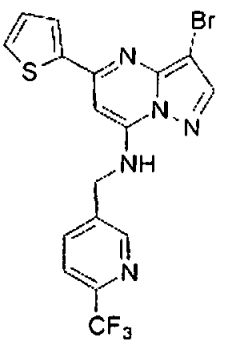
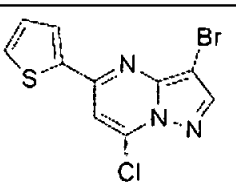
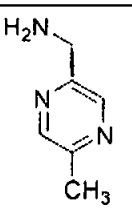
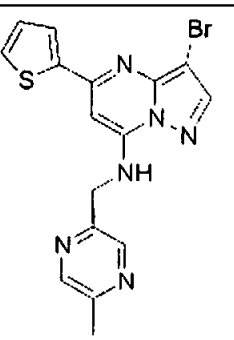
12				LCMS: MH$^+$= 360; p.f.= 127-128°C
13				LCMS: MH$^+$= 342; p.f.= 133-135°C
14				LCMS: MH$^+$= 344; p.f.= 152-155°C
15				LCMS: MH$^+$= 362; p.f.= 164-167°C

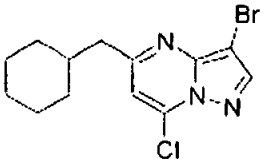
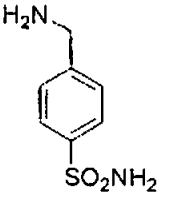
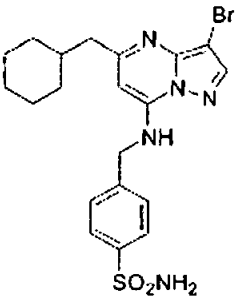
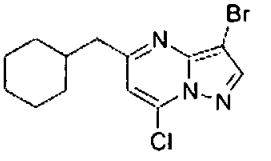
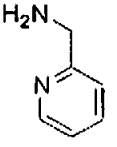
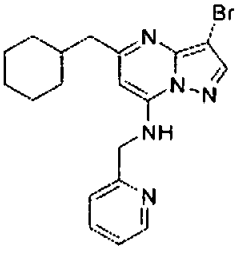
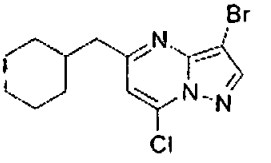
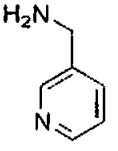
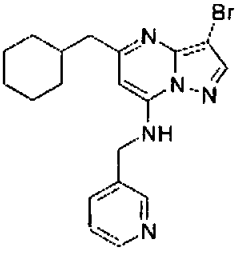
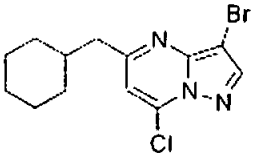
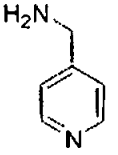
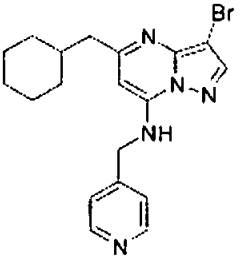
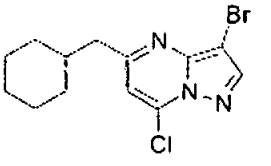
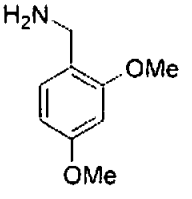
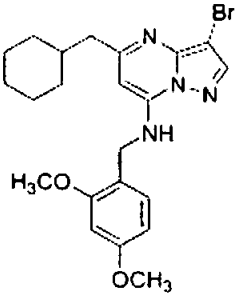
16				LCMS: MH⁺= 327; p.f.= 146-155°C
17				LCMS: MH⁺= 332; p.f.= 71-82°C
17.1				MS: MH⁺ = 332,
18				LCMS: MH⁺= 346; p.f.= 58-65°C

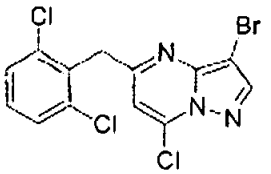
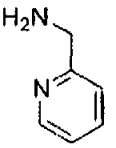
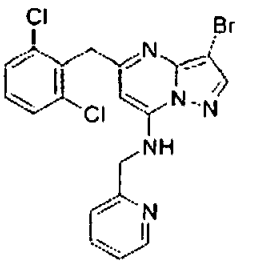
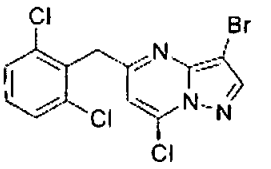
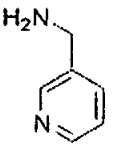
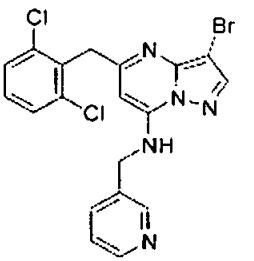
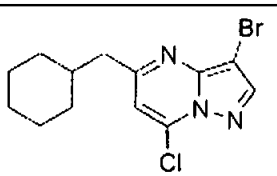
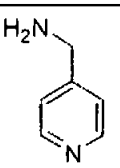
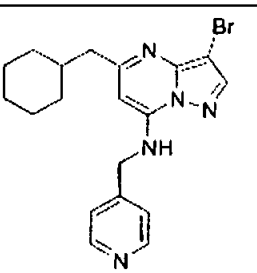
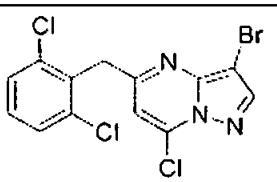
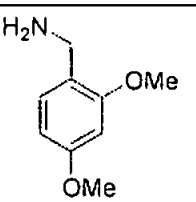
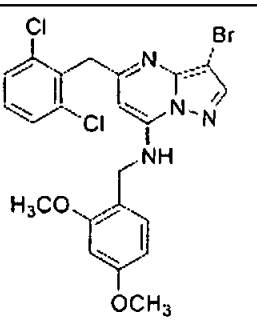
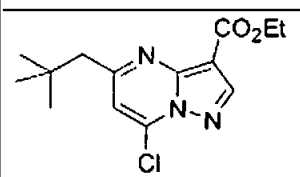
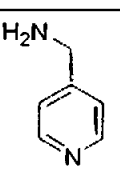
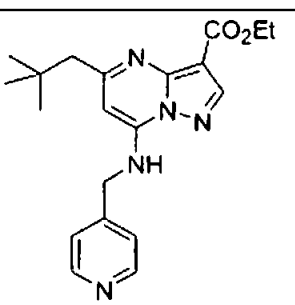
19				LCMS: MH^+= 414; p.f.= 211-213°C
20				LCMS: MH^+= 414; p.f.= 194-197°C
21				EM: MH^+ = 414 p.f.: 211 – 216°C
22				LCMS: MH^+= 544; p.f.= 104-107°C

23				Rend. = 83% LCMS: MH^+ = 410,
24				Rend. = 84% LCMS: MH^+ = 410,
25				Rend. = 96% LCMS: MH^+ = 440,
26				Rend. = 99% LCMS: MH^+ = 440,

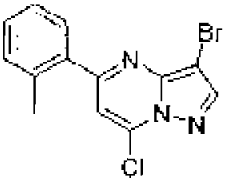
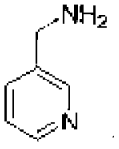
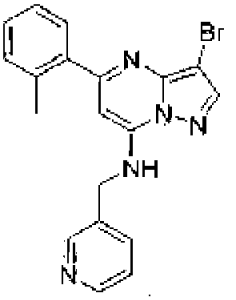
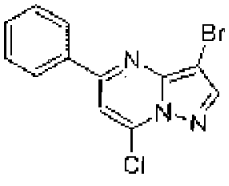
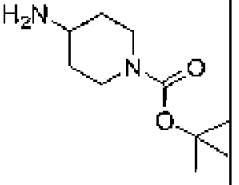
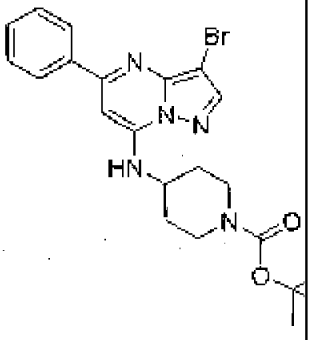
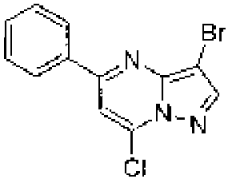
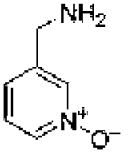
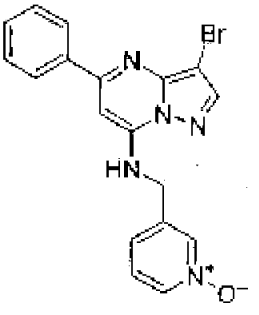
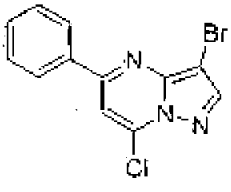
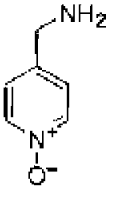
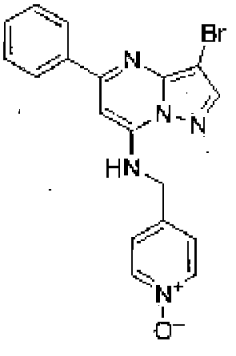
27				Rend. = 89% LCMS: MH^+ = 448,
28				Rend. = 78% LCMS: MH^+ = 448,
30				Rend. = 96% LCMS: MH^+ = 483,
31				Rend. = 35% LCMS: MH^+ = 483,

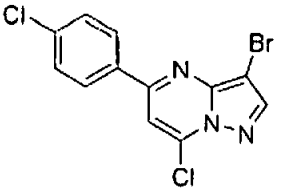
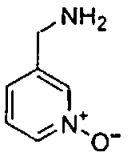
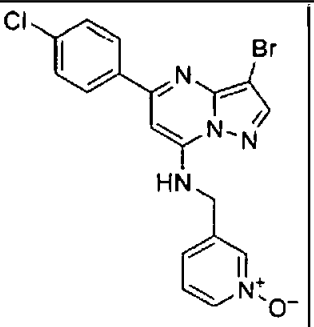
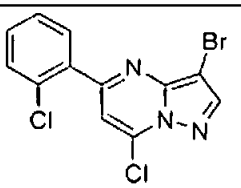
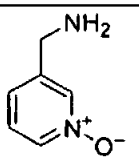
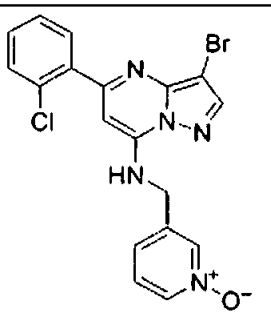
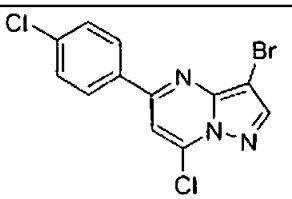
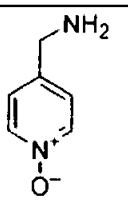
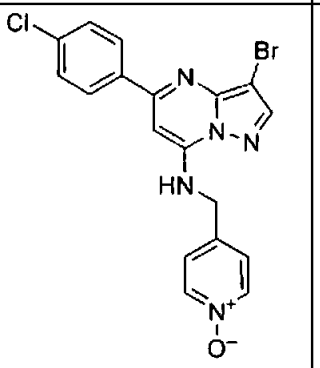
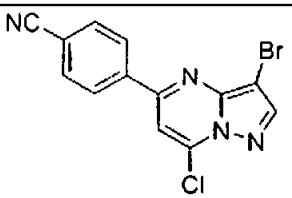
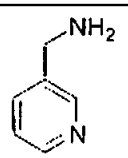
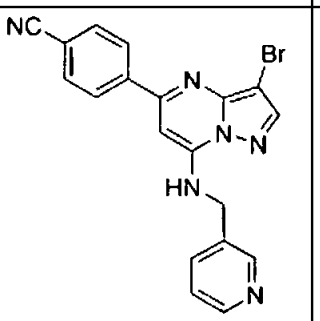
32				Rend. = 77% LCMS: MH^+ = 515,
33				Rend. = 100% p.f.: 179°C LCMS: MH^+ = 388
34				Rend. = 99% p.f.: 186°C LCMS: MH^+ = 456
35				Rend. = 98% p.f.: 181°C LCMS: MH^+ = 401

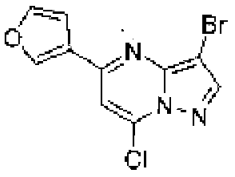
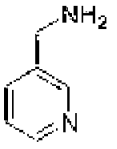
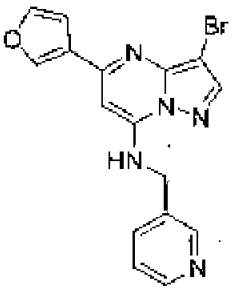
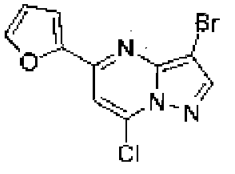
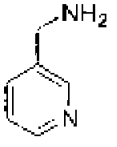
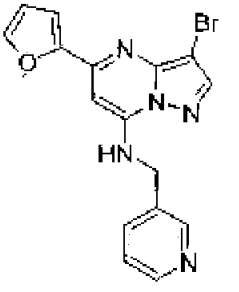
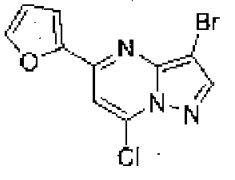
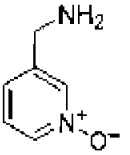
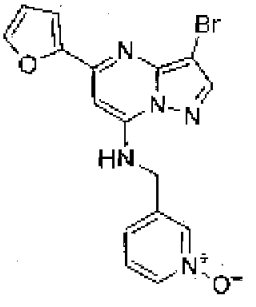
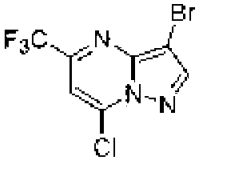
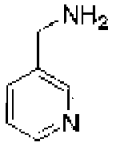
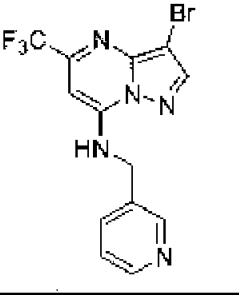
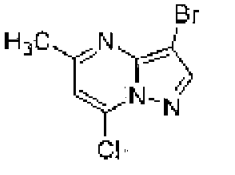
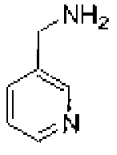
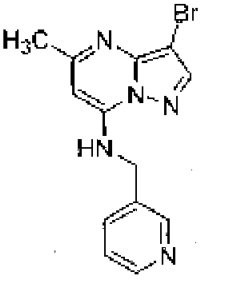
36				Rend. = 63% p.f.: 192°C LCMS: MH^+ = 480
37				Rend. = 75% p.f.: 126 – 127°C LCMS: MH^+ = 400
38				Rend. = 94% p.f.: 132 - 133°C LCMS: MH^+ = 400
39				Rend. = 95% p.f.: 121 – 122°C LCMS: MH^+ = 400
40				Rend. = 98% LCMS: MH^+ = 460

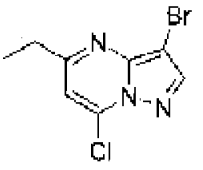
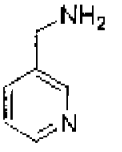
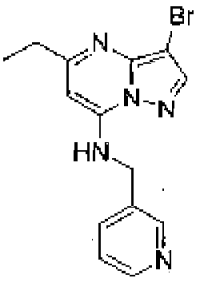
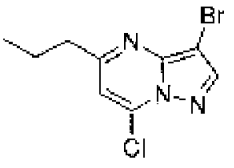
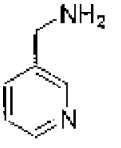
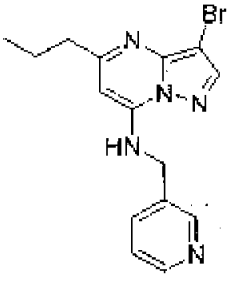
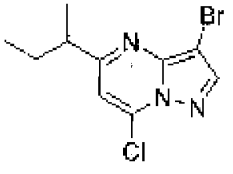
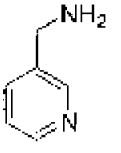
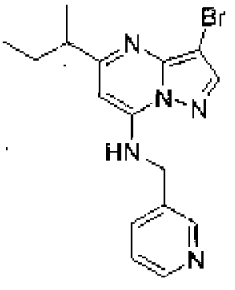
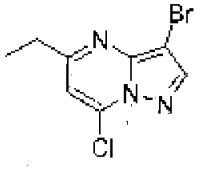
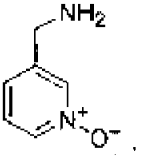
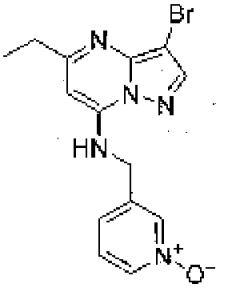
41				Rend. = 87% p.f.: 170 - 171°C LCMS: MH^+ = 464
42				Rend. = 84% p.f.: 216 - 217°C LCMS: MH^+ = 464
43				Rend. = 96% p.f.: 214°C LCMS: MH^+ = 464
44				Rend. = 95% p.f.: 158°C LCMS: MH^+ = 522
45				Rend.=90% LCMS: MH^+= 278

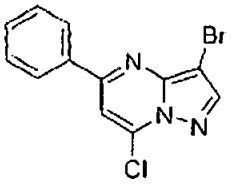
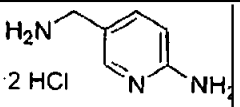
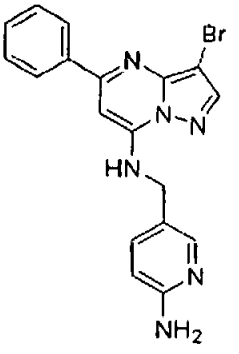
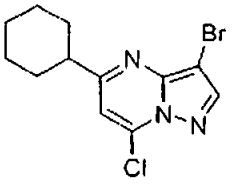
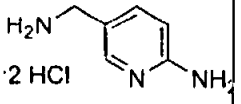
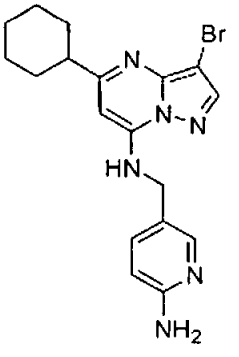
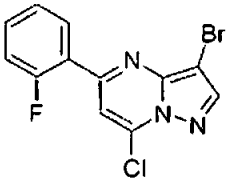
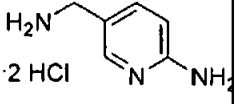
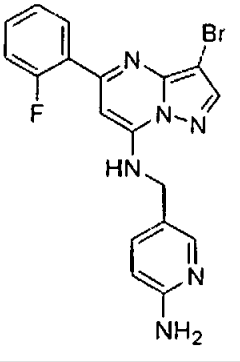
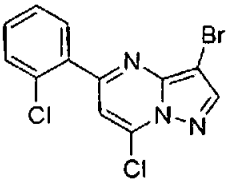
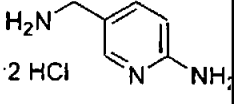
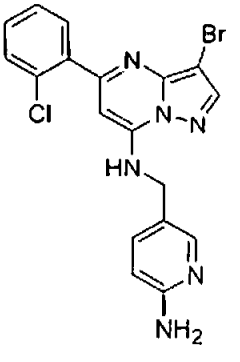
628

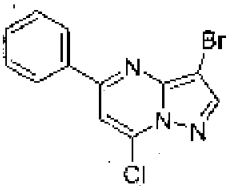
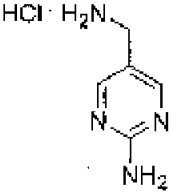
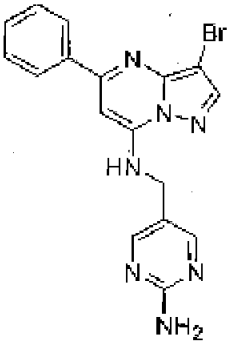
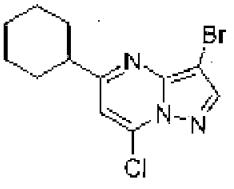
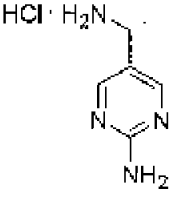
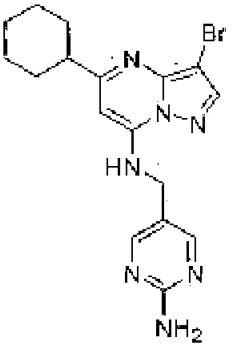
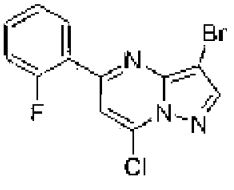
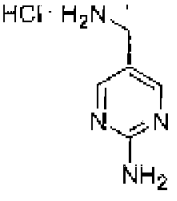
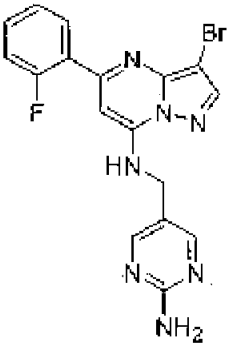
46				Rend.=100 %; LCMS: MH^+=394
47				LCMS: MH+ = 473 p.f.: 84 - 87°C
48				EM: MH^+ = 396 p.f.: 91,5 – 93,3°C
49				EM: MH^+ = 396 p.f.: 196 – 199°C

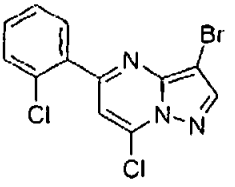
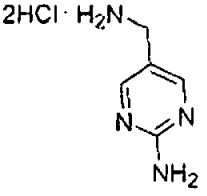
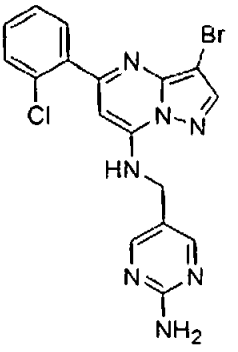
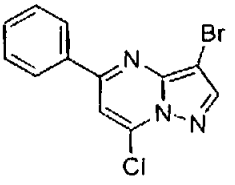
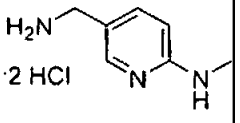
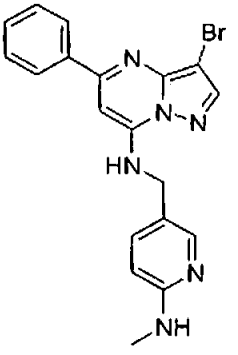
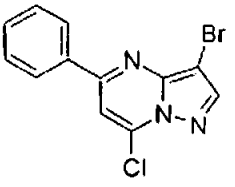
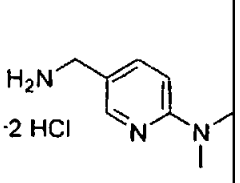
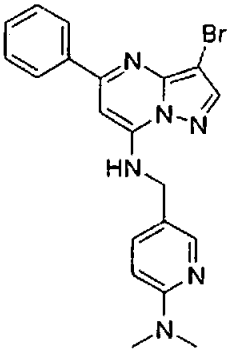
50				EM: MH^+ = 430 p.f.: 242 – 244°C
51				EM: MH^+ = 430 p.f.: 218°C
52				EM: MH^- = 430 p.f.: 230 – 233°C
54				EM: MH^+ = 405 p.f.: 185 – 188°C

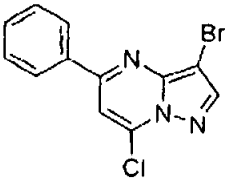
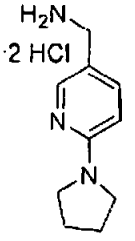
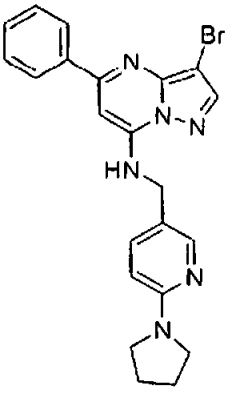
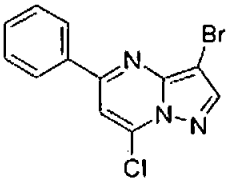
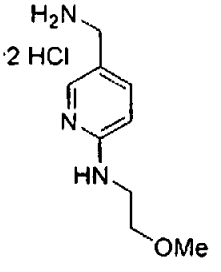
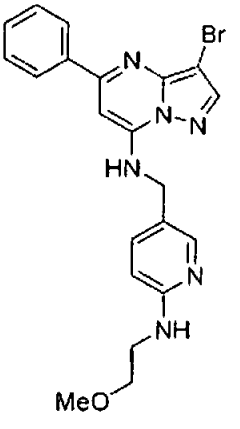
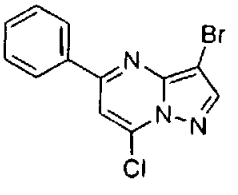
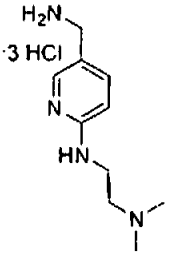
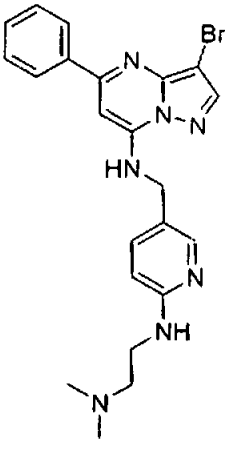
55				EM: MH^+ = 370 p.f.: 229 – 232°C
56				EM: MH^+ = 370 p.f.: 85 – 90°C
57				EM: MH^+ = 386 p.f.: 227 – 230°C
58				EM: MH^+ = 372 p.f.: 212 – 215°C
59				EM: MH^+ = 318 p.f.: 169 – 171°C

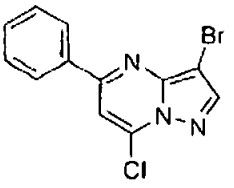
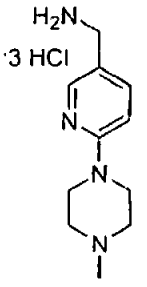
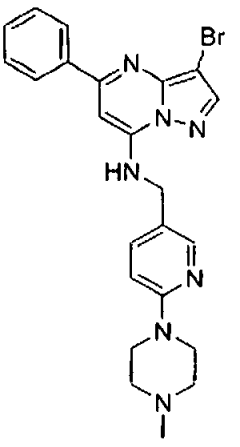
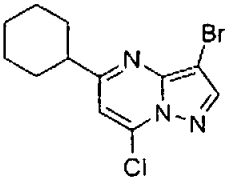
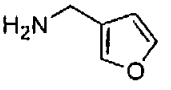
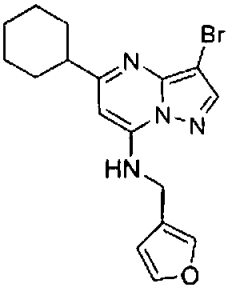
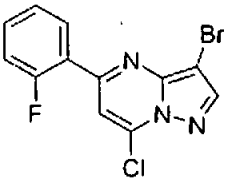
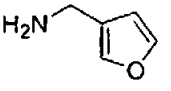
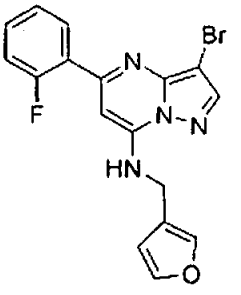
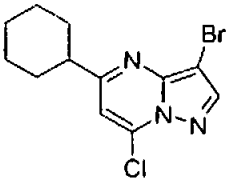
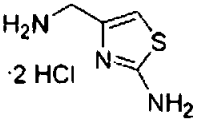
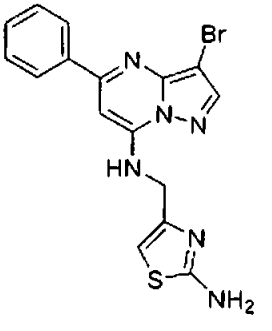
60				EM: MH^+ = 332 p.f.: 170 – 173°C
61				EM: MH^+ = 346 p.f.: 156 – 159°C
62				EM: MH^+ = 360 p.f.: 114 – 116°C
63				EM: MH^- = 348 p.f.: 197 – 200°C

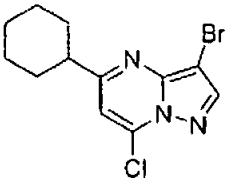
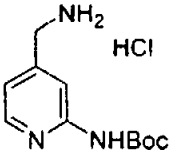
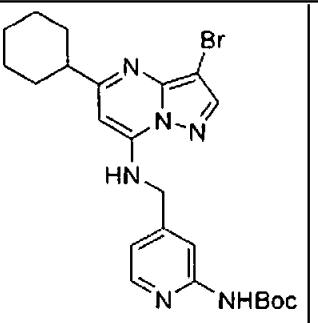
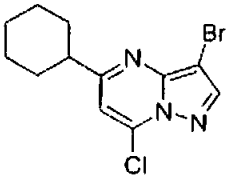
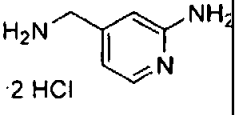
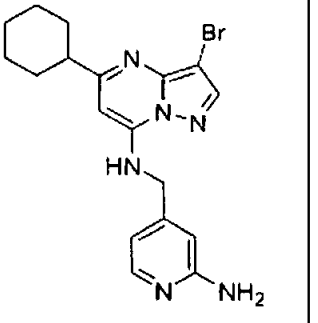
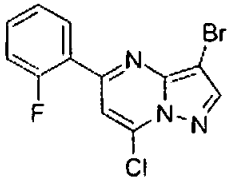
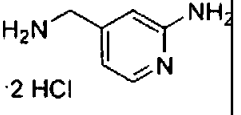
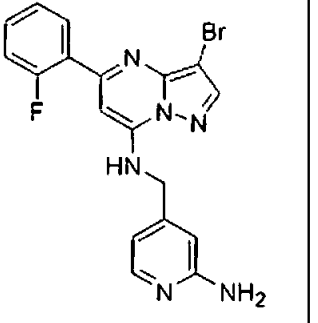
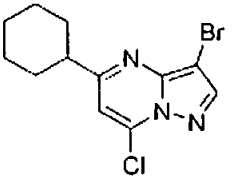
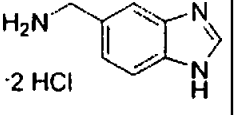
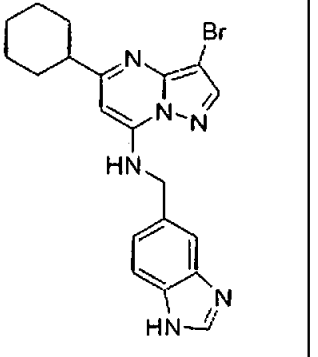
64				1. P.f.: 230-232 2. M+H = 396
65				1. P.f.: 205-207 2. M+H = 402
66				1. P.f.: 220-223 2. M+H = 414
67				1. P.f.: 191-193 2. M+H = 431

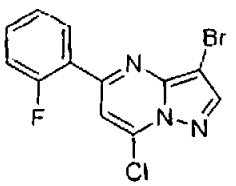
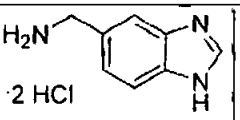
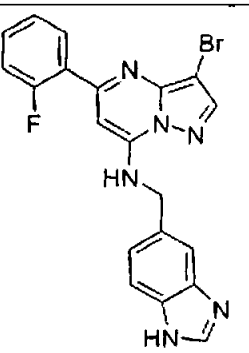
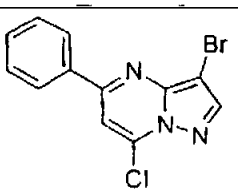
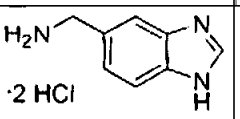
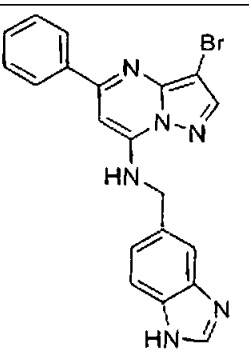
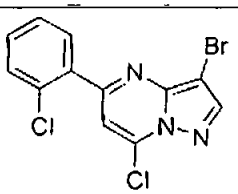
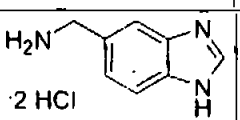
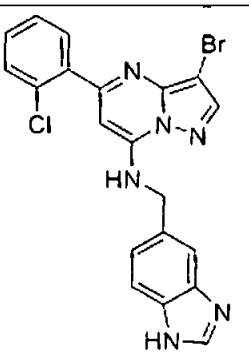
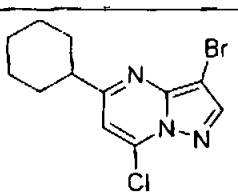
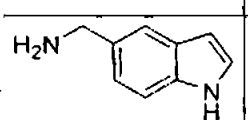
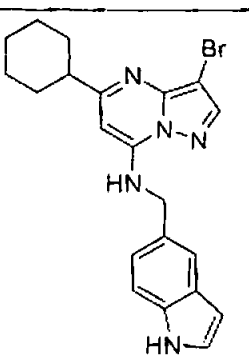
68				1. P.f.: 235-237 2. M+H = 397
69				1. P.f.: >250 2. M+H = 403
70				1. P.f.: 230-232 2. M+H = 415

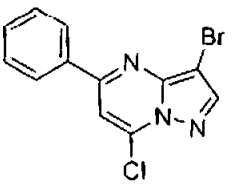
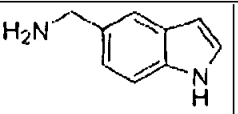
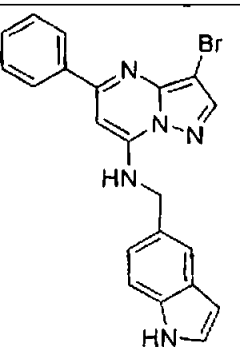
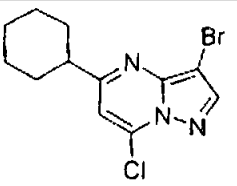
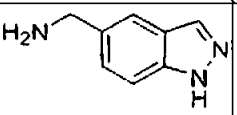
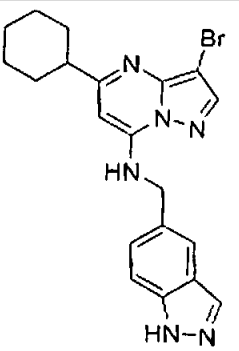
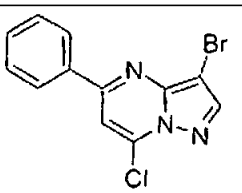
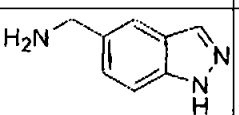
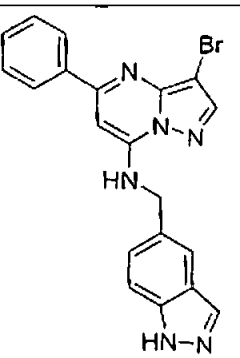
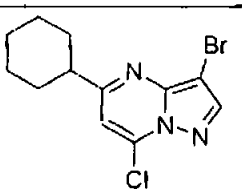
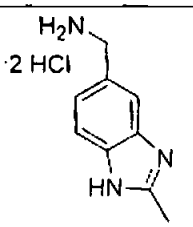
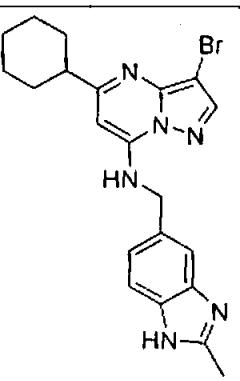
71				1. P.f.: 235-238 2. M+H = 431
72				1. P.f.: 186-188 2. M+H = 410
73				1. P.f.: 136-138 2. M+H = 424

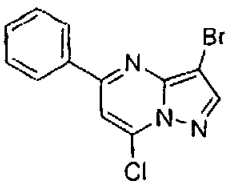
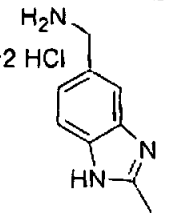
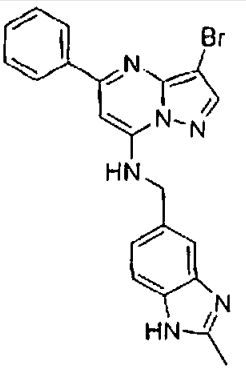
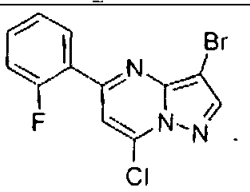
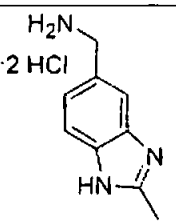
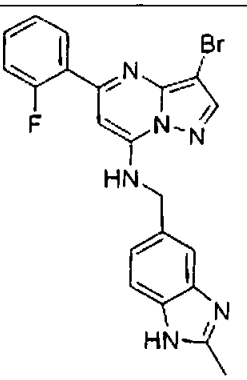
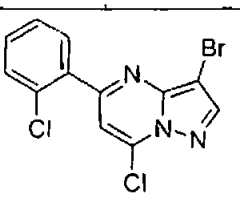
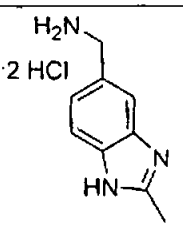
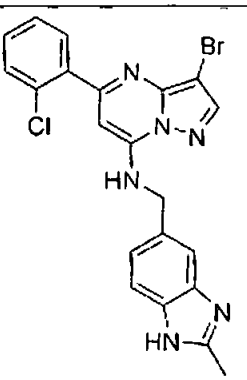
74				1. P.f.: 192-195 2. M+H = 450
75				1. P.f.: 88-90 2. M+H = 454
76				1. P.f.: 230-232 2. M+H = 467

77				1. P.f.: 131-133 2. M+H = 479
78				1. P.f.: 85-88 2. M+H = 376
79				1. P.f.: 131-133 2. M+H = 388
80				1. P.f.: 206-208 2. M+H = 408

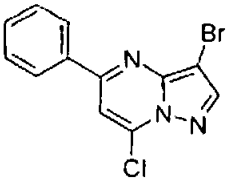
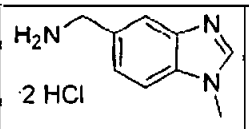
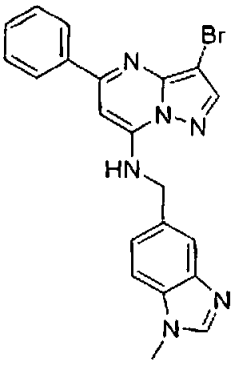
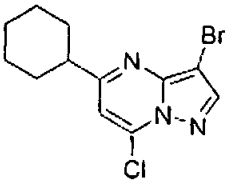
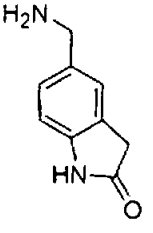
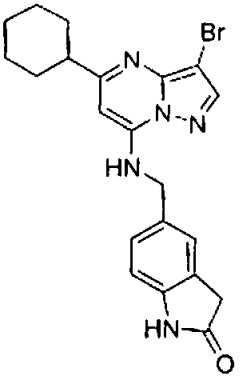
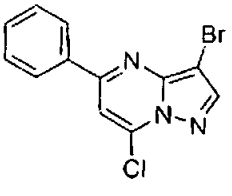
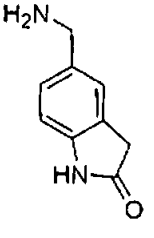
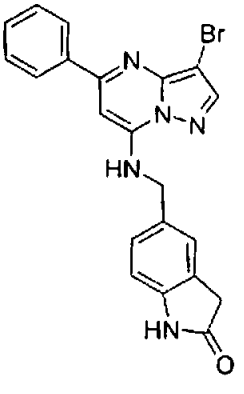
81				1. P.f.: 108-110 2. M+H = 502
82				1. P.f.: 83-85 2. M+H = 402
83				1. P.f.: 220 2. M+H = 414
84				1. P.f.: 154-156 2. M+H = 426

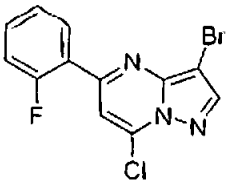
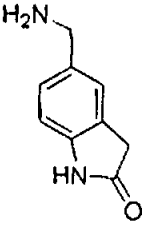
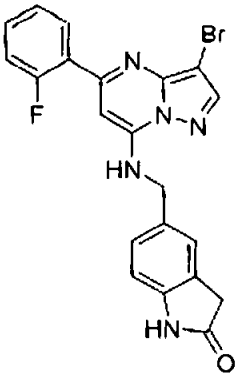
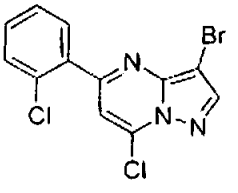
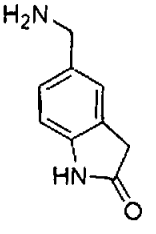
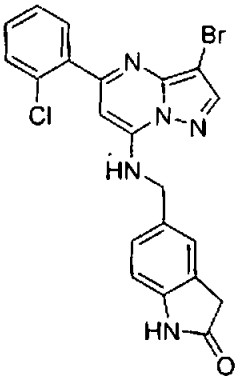
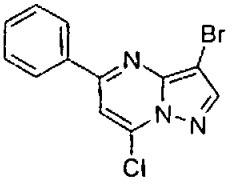
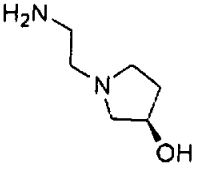
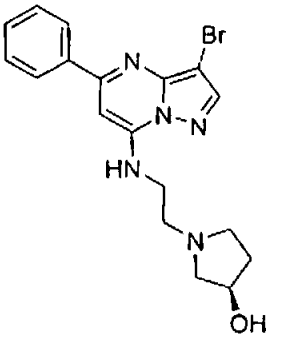
85		 ·2 HCl		1. P.f.: 152-153 2. M+H = 438
86		 ·2 HCl		1. P.f.: 159-161 2. M+H = 420
87		 ·2 HCl		1. P.f.: >220 2. M+H = 455
88				1. P.f.: 223-225 2. M+H = 425

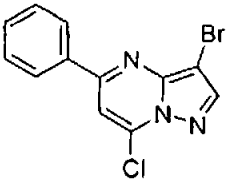
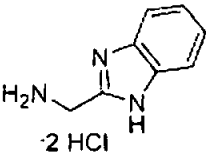
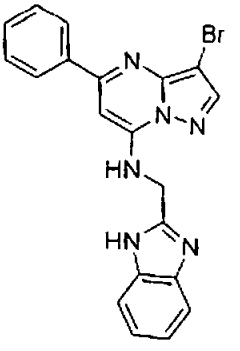
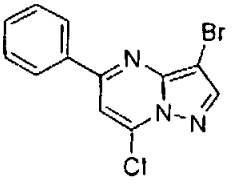
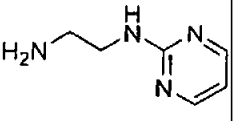
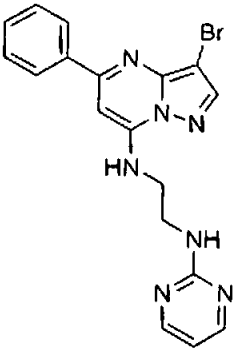
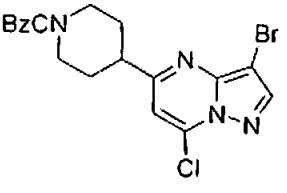
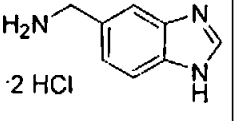
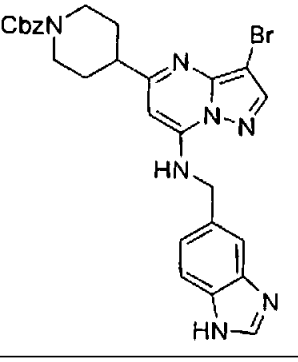
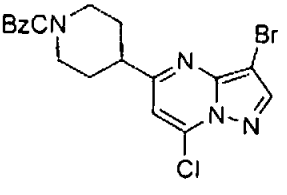
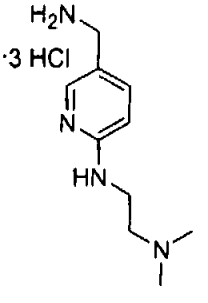
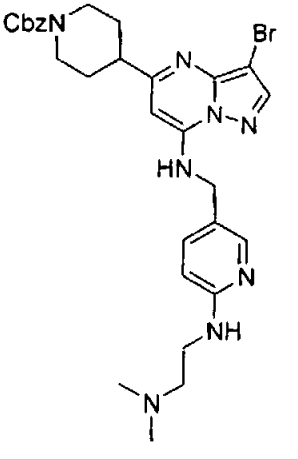
89				1. P.f.: 199-201 2. M+H = 419
90				1. P.f.: 184-186 2. M+H = 426
91				1. P.f.: 196-198 2. M+H = 420
92				1. P.f.: 156-159 2. M+H = 440

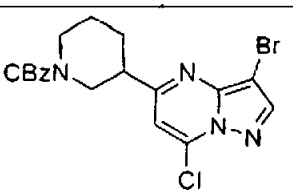
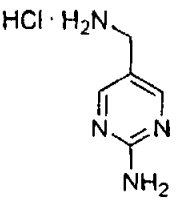
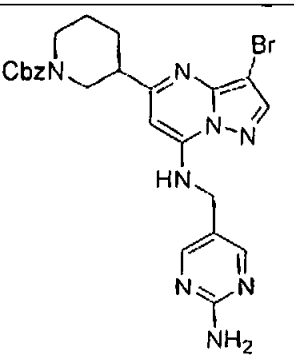
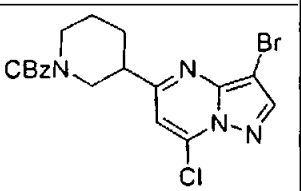
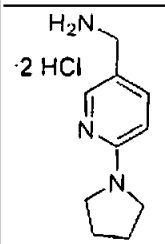
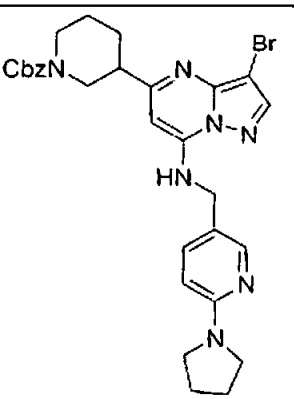
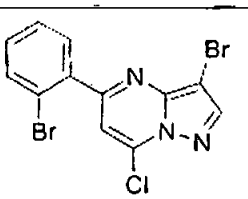
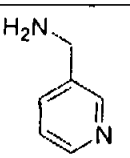
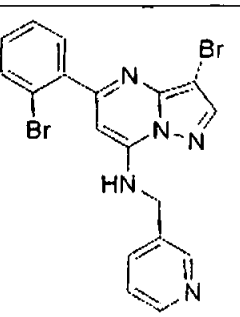
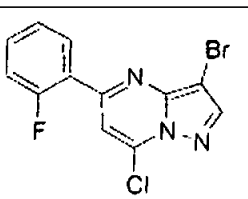
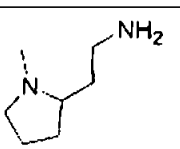
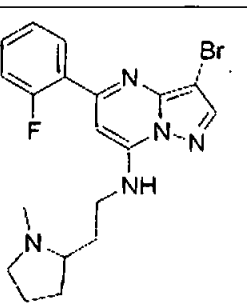
93				1. P.f.: 173-176 2. M+H = 434
94				1. P.f.: 173-175 2. M+H = 452
95				1. P.f.: 174-176 2. M+H = 469

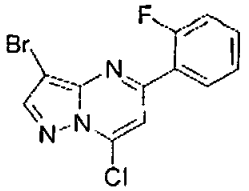
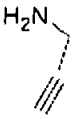
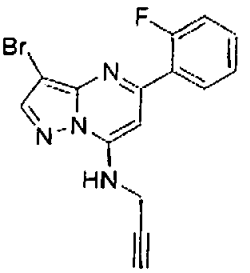
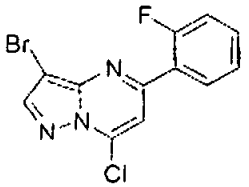
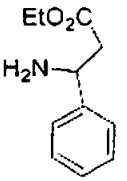
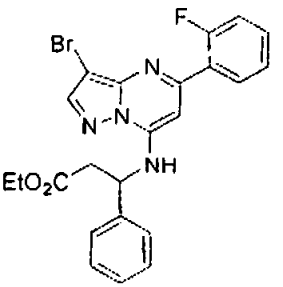
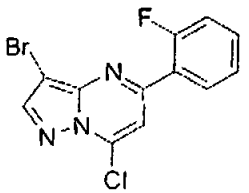
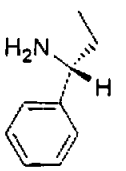
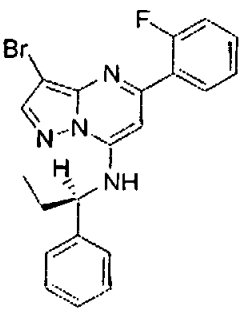
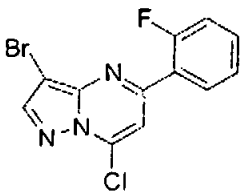
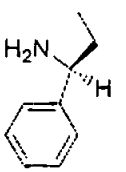
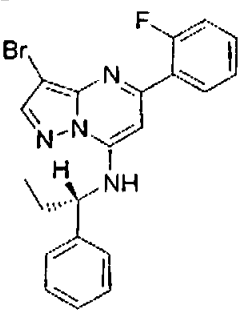
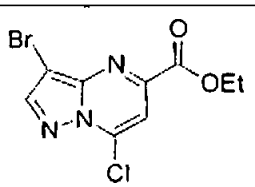
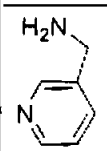
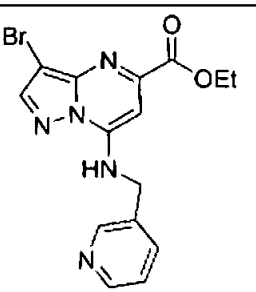
298

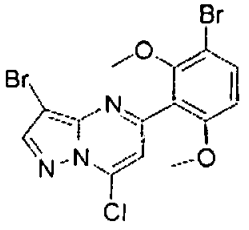
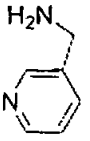
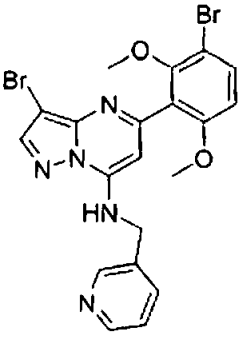
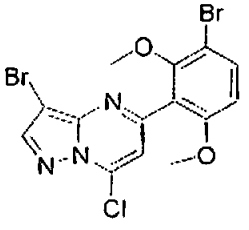
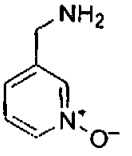
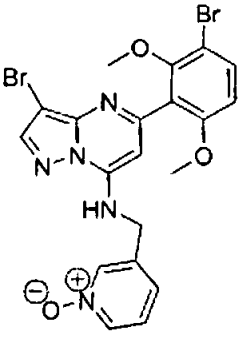
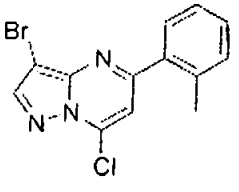
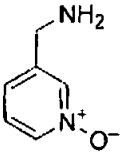
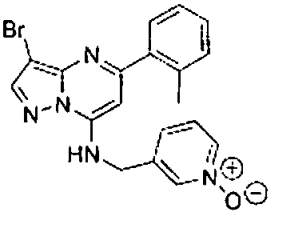
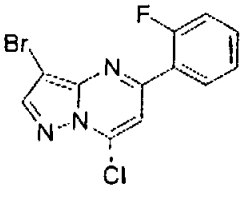
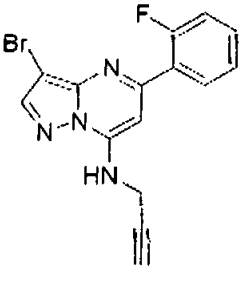
96		 ·2 HCl		1. P.f.: 230-234 2. M+H = 434
97				1. P.f.: 191-193 2. M+H = 441
98				1. P.f.: 202-205 2. M+H = 434

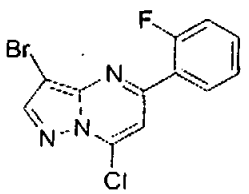
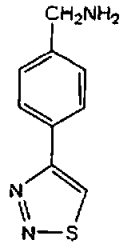
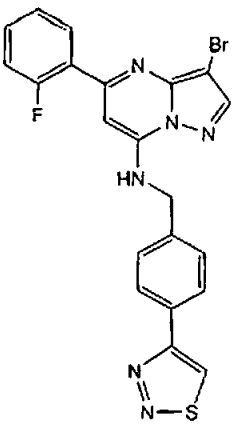
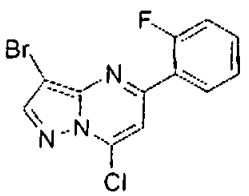
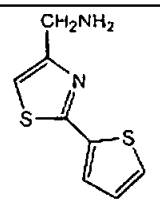
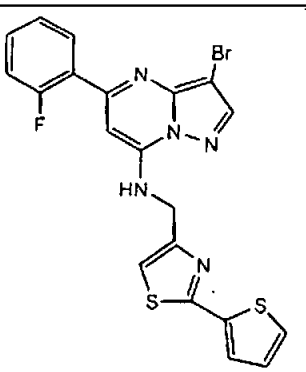
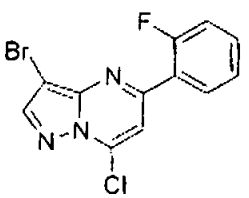
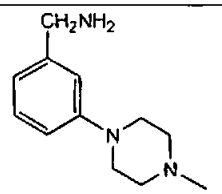
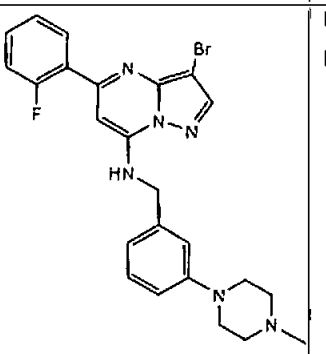
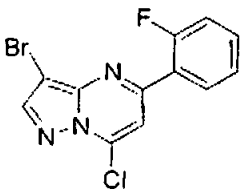
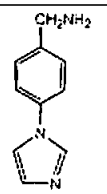
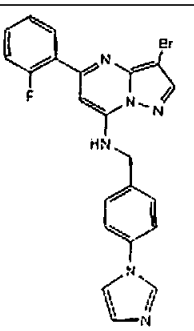
99				1. P.f.: 209-212 2. M+H = 453
100				1. P.f.: 219-221 2. M+H = 469
101				1. P.f.: 64-66 2. M+H = 403

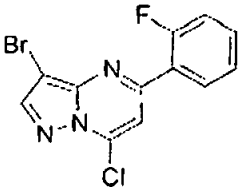
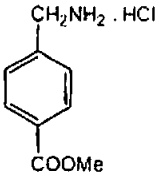
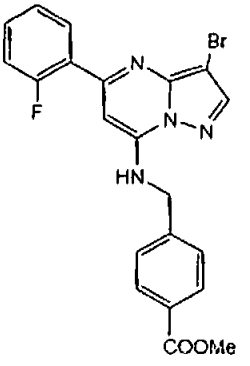
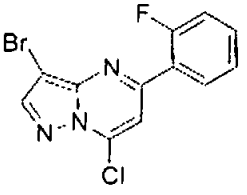
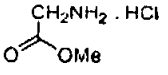
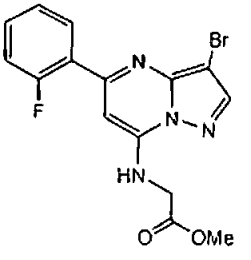
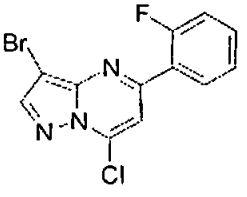
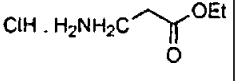
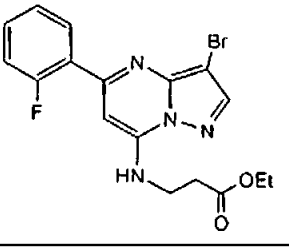
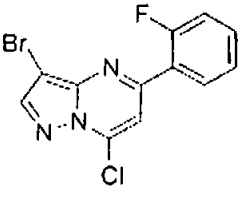
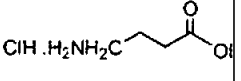
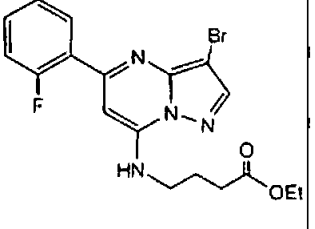
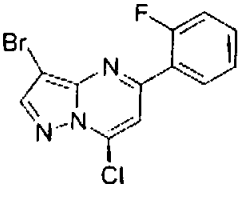
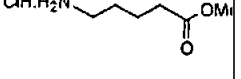
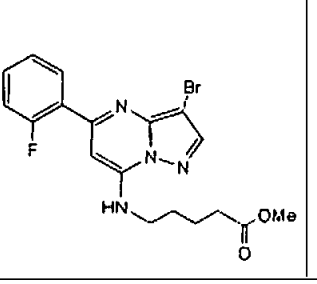
102				1. P.f.: 168-170 2. M+H = 420
103				1. P.f.: 213-216 2. M+H = 411
104				1. P.f.: 98-100 2. M+H = 561
105				1. p.f. 70-72 2. M+H = 608

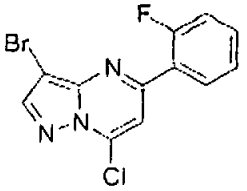
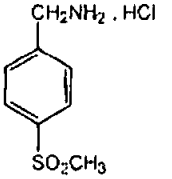
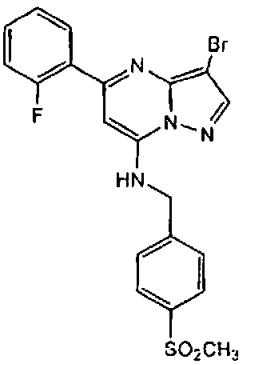
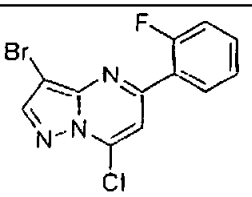
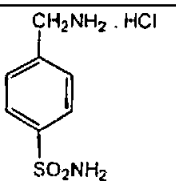
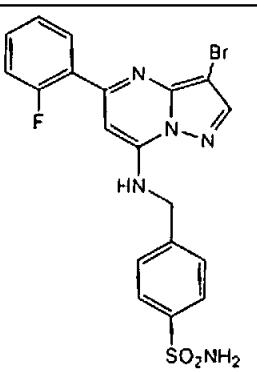
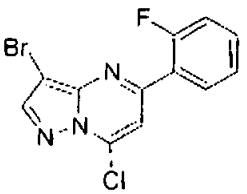
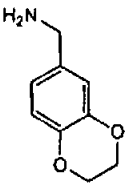
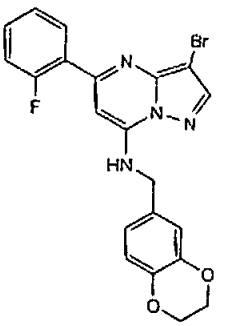
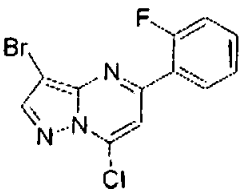
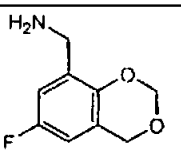
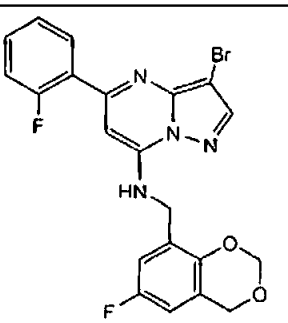
106				1. p.f. 168-170 2. M+H = 538
107				1. p.f. 189-191 2. M+H = 592
108				LCMS: MH^+ = 458;
109				Rend. = 89 LCMS: MH^+ = 418 p.f.: 131-132°C

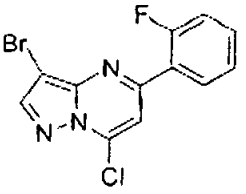
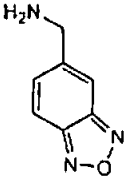
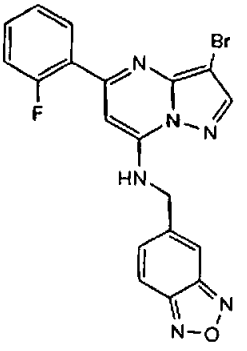
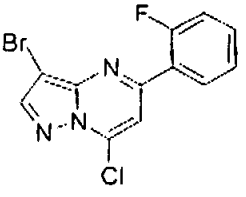
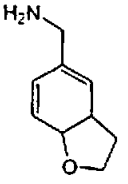
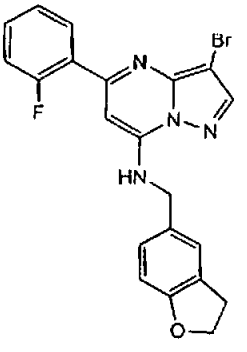
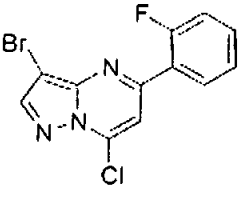
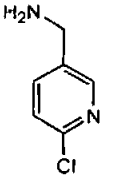
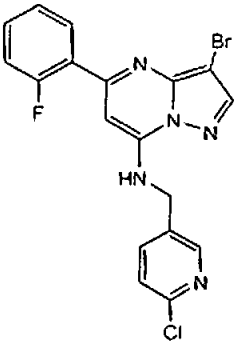
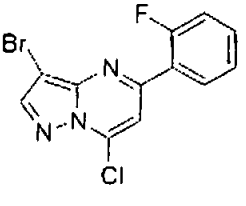
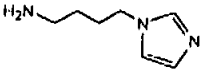
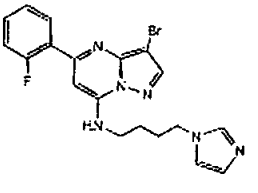
110				Rend.=95% LCMS: MH$^+$= 347
111				Rend.=91% 3H); LCMS: MH$^+$= 484
112				Rend.=87% LCMS: MH$^+$= 427
113				Rend.=80% LCMS: MH$^+$= 427
114				Rend.=91% LCMS: MH$^+$= 378

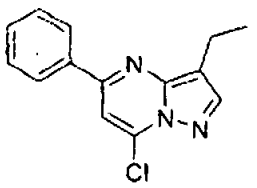
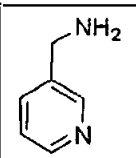
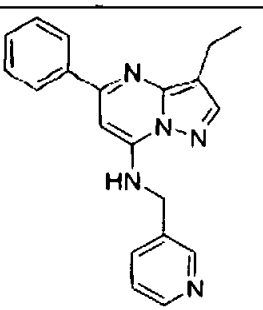
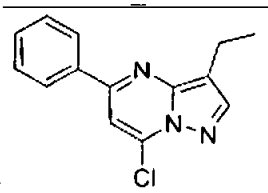
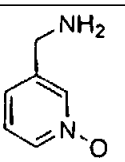
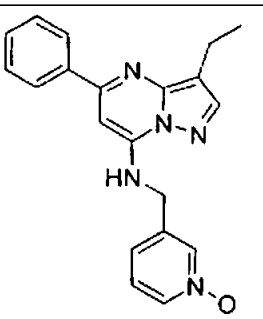
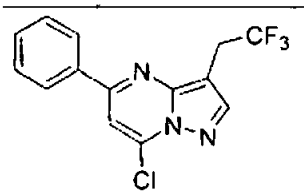
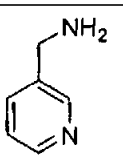
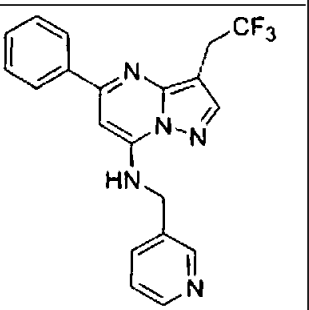
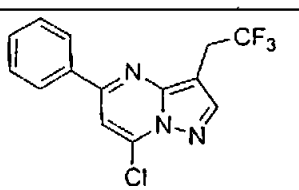
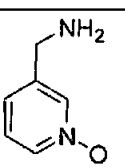
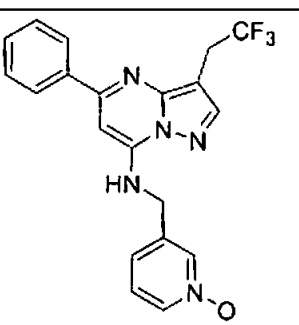
115				Rend.=92% , 3H); LCMS: MH⁺=520
116				Rend.=98% LCMS: MH⁺=536
117				Rend.=82% LCMS: MH⁺=410
118				Rend.=95% LCMS: MH⁺= 347

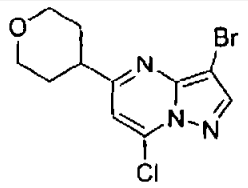
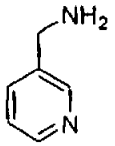
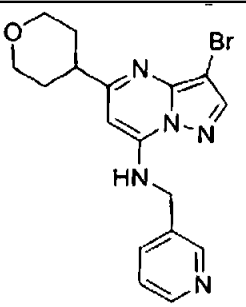
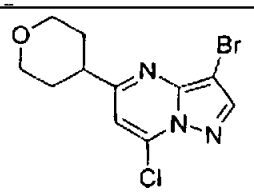
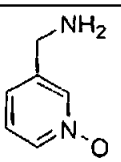
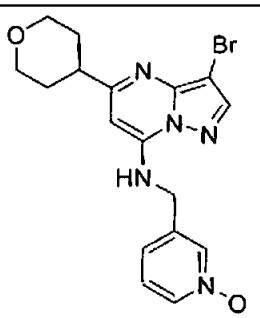
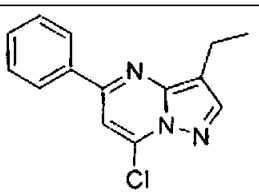
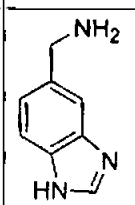
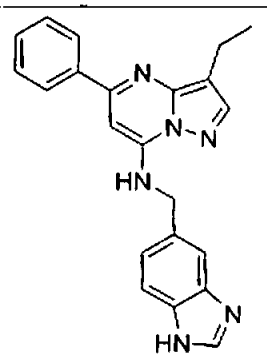
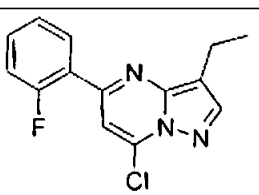
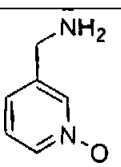
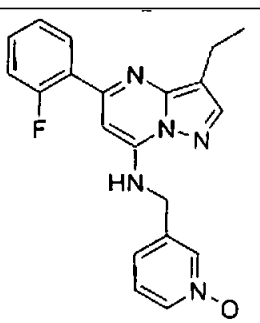
121				Rend. = 65% LCMS: MH^+ = 481,02
126				Rend.=71% MH^+ = 486
127				Rend.=71% MH^+ = 495,1
128				Rend.=55% MH^+ = 463

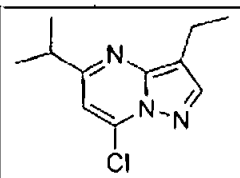
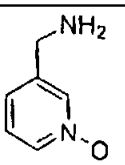
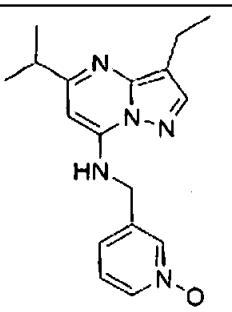
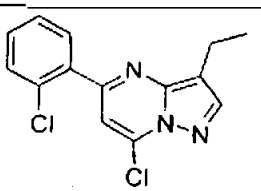
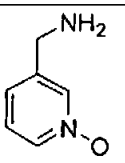
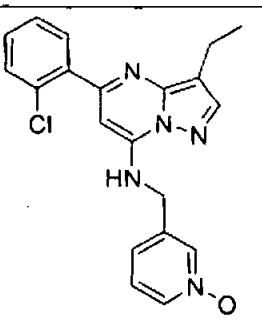
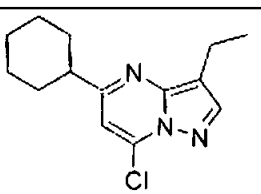
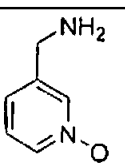
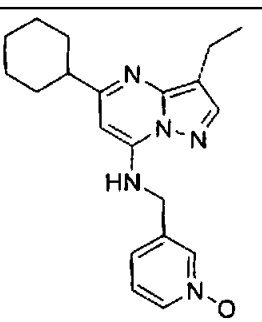
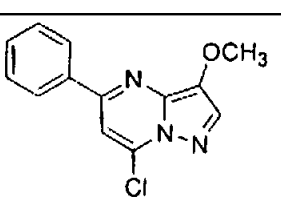
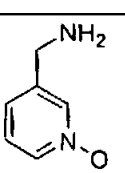
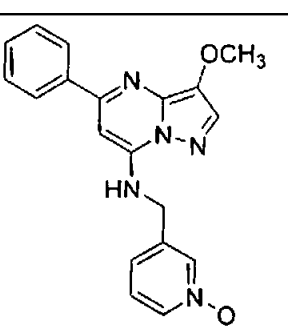
129				Rend. = 77% LCMS: MH^+ = 455
130				^1H RMN (Rend. = 75% LCMS: MH^+ = 379
131				Rend. = 75% LCMS: MH^+ = 407
132				Rend. = 75% LCMS: MH^+ = 421
133				Rend. = 70% LCMS: MH^+ = 421

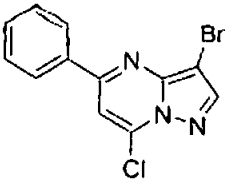
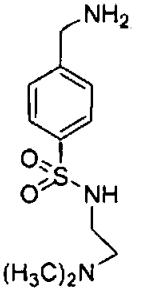
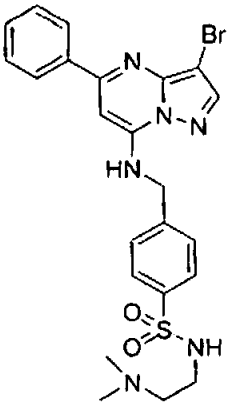
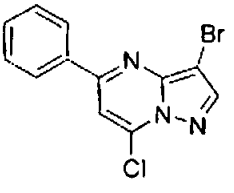
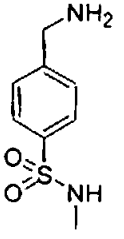
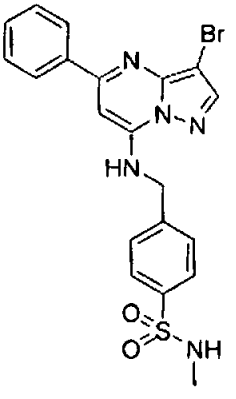
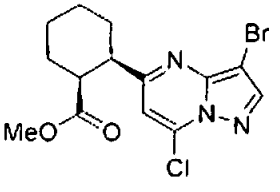
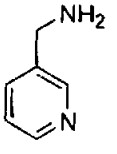
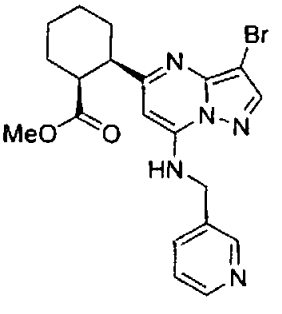
134				Rend. = 78% LCMS: MH^+ = 475
135				Rend. = 75% LCMS: MH^+ = 476
136				Rend. = 65% LCMS: MH^+ = 455
137				Rend. = 55% LCMS: MH^+ = 473

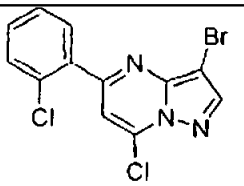
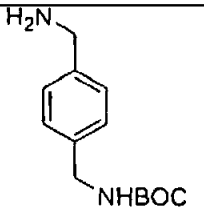
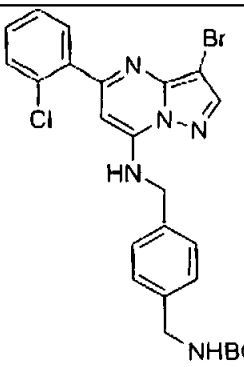
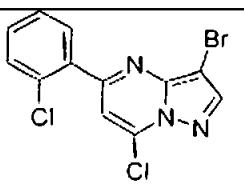
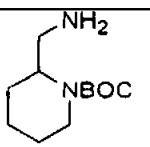
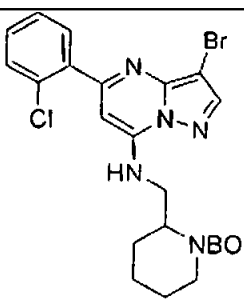
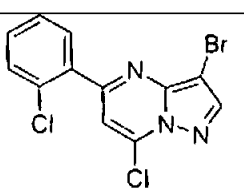
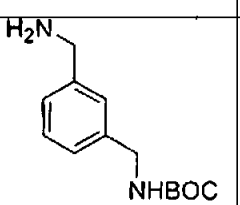
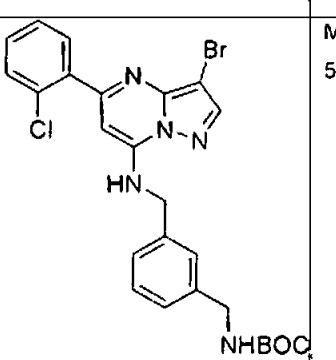
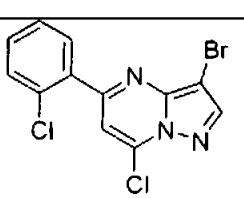
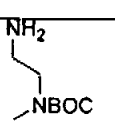
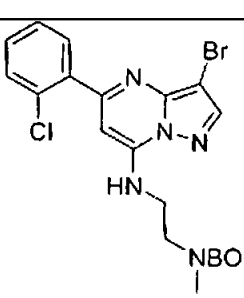
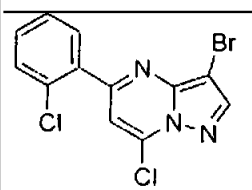
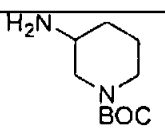
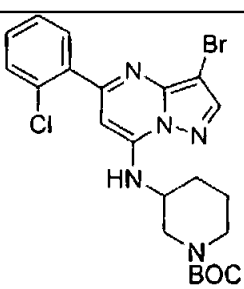
138				Rend. = 60% LCMS: MH^+ = 439
139				Rend. = 65% LCMS: MH^+ = 441
140				Rend. = 80% LCMS: MH^+ = 432
141				Rend. = 60% LCMS: MH^+ = 429

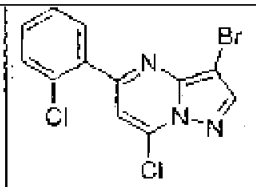
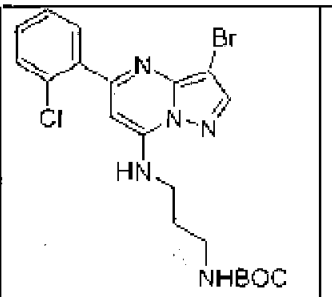
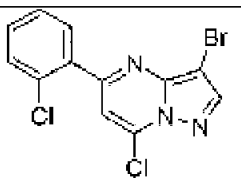
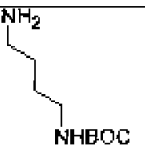
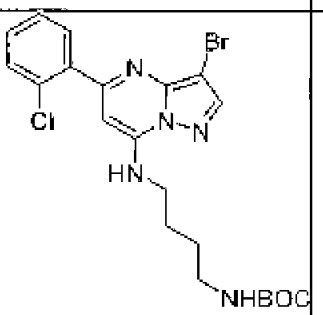
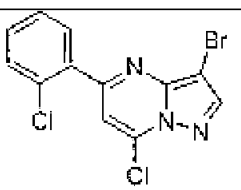
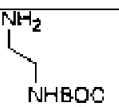
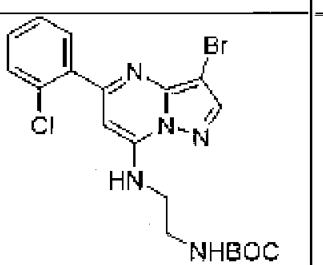
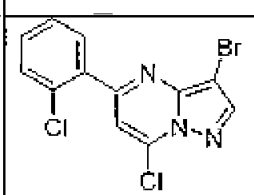
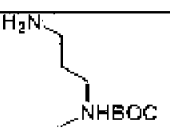
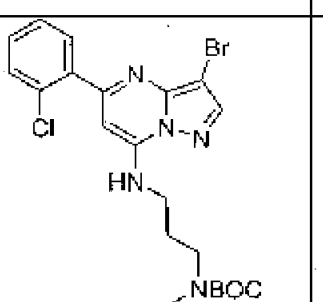
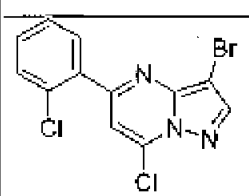
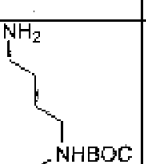
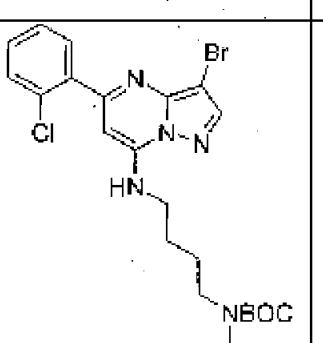
142				LCMS: MH$^+$=330; p.f.=109-111°C
143				LCMS: MH$^+$=346; p.f.=186-188°C
144				LCMS: MH$^+$=384; p.f.=148-150°C
145				LCMS: MH$^+$=400; p.f.=186-188°C

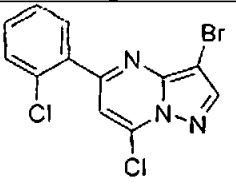
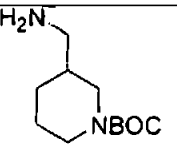
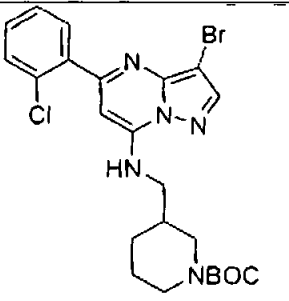
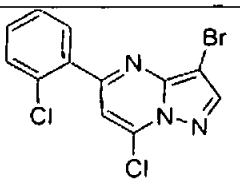
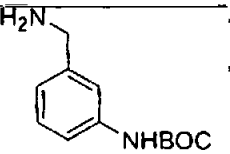
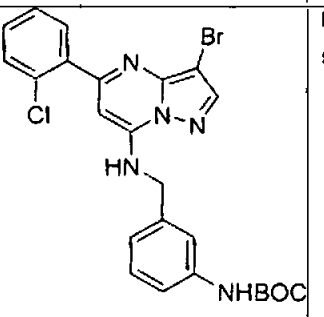
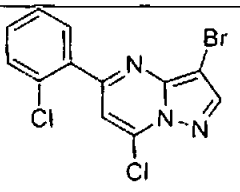
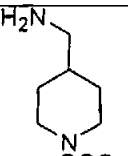
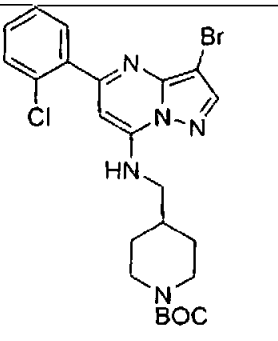
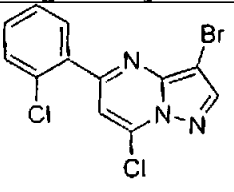
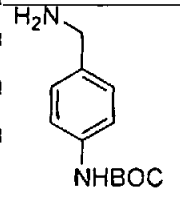
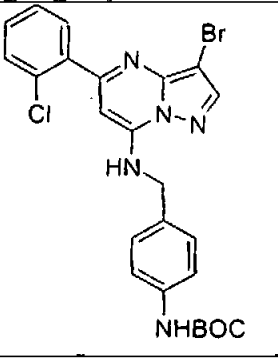
146				LCMS: M2H$^+$=390; p.f.=192-194°C
147				LCMS: M$^+$=404; p.f.=220-222°C
148				LCMS: MH$^+$=369; P.f.: >230°C
149				LCMS: MH$^+$=364; p.f.=186-188°C

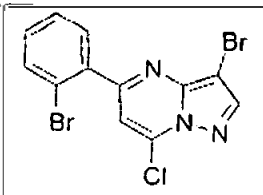
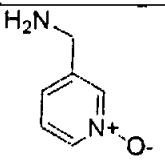
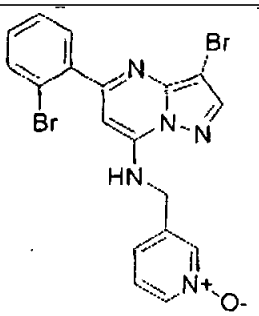
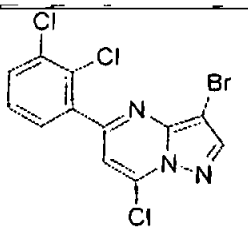
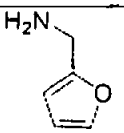
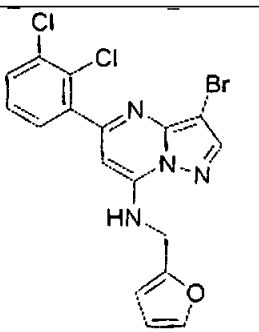
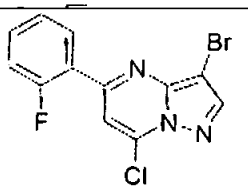
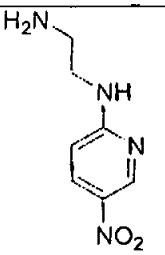
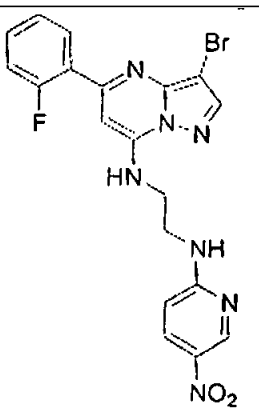
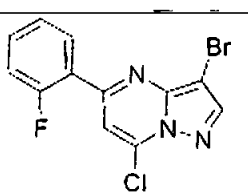
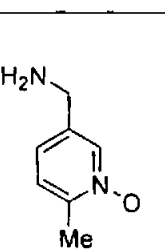
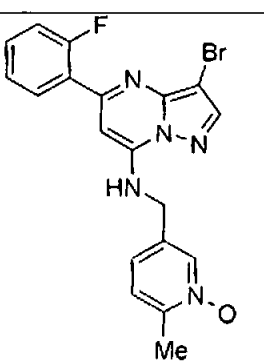
150				LCMS: MH^+=312; p.f.=138-140°C
151				LCMS: M^+=380; p.f.=172-174°C
152				LCMS: MH^+=352; p.f.=201-203°C
153				LCMS: MH^+=348; p.f.=166-168°C

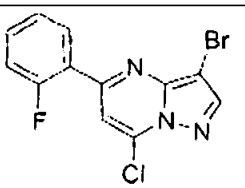
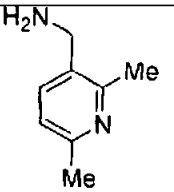
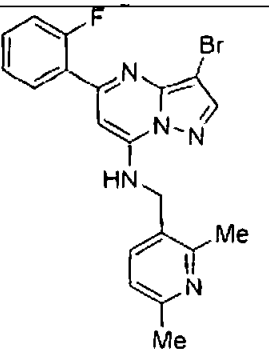
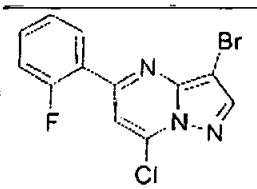
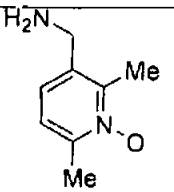
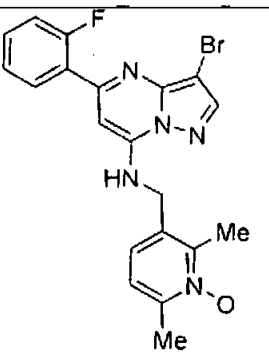
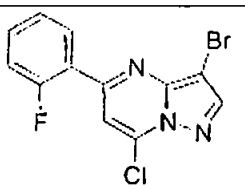
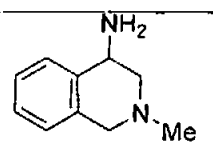
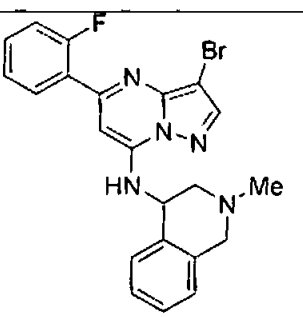
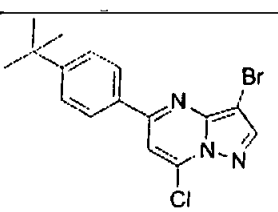
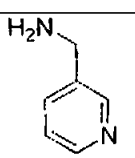
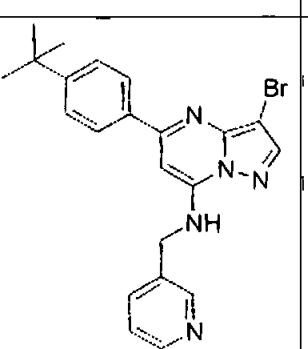
154				LCMS: M2H$^+$=531; p.f.=78-80°C
155				LCMS: M2H$^+$=474; p.f.=161-163°C
156				LCMS: M$^+$=444; p.f.=48-51°C

157				MH^+ = 542,1
158				MH^+ = 520,1
159				MH^+ = 542,1
160				MH^+ = 480,1
161				MH^+ = 506,1

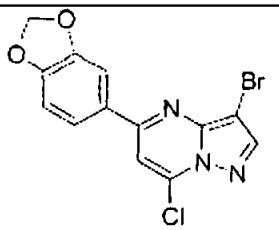
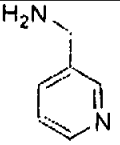
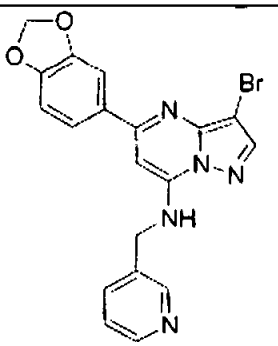
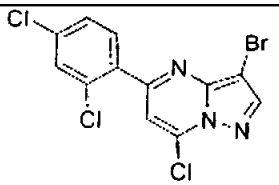
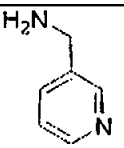
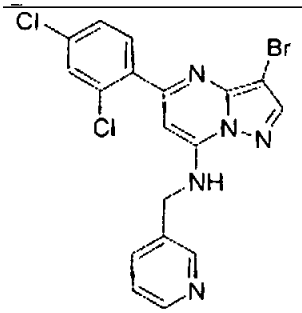
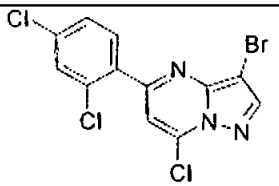
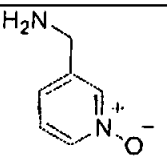
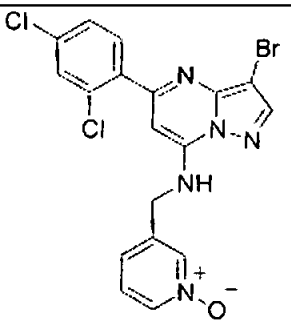
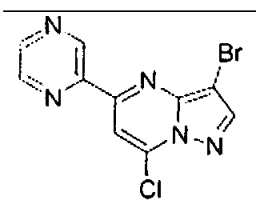
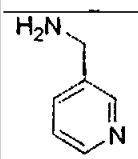
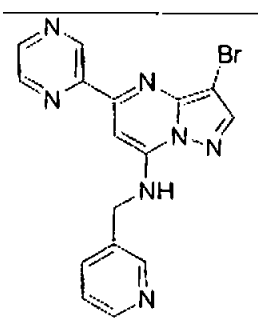
162				MH^+ = 480,1
163				MH^+ = 494,1
164				MH^+ = 466,1
165				MH^+ = 494,1
166				MH^+ = 508,1

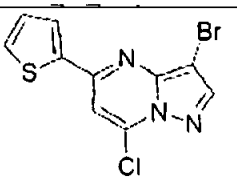
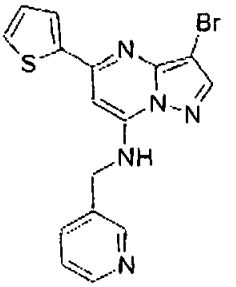
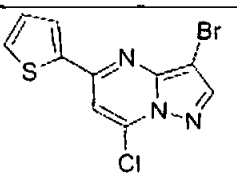
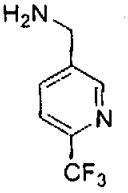
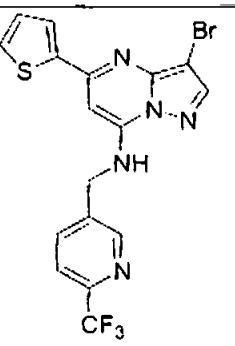
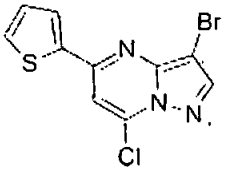
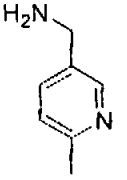
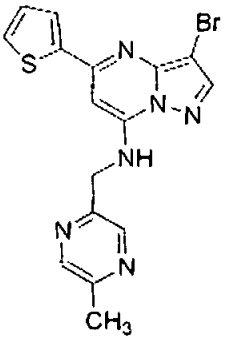
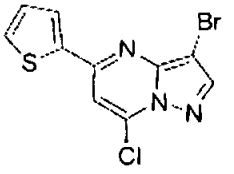
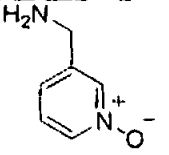
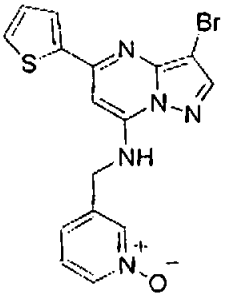
167				MH^+ = 520,1
168				MH^+ = 528,1
169				MH^+ = 520,1
170				MH^+ = 528,1

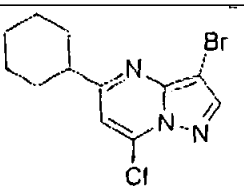
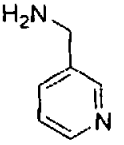
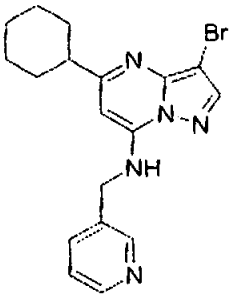
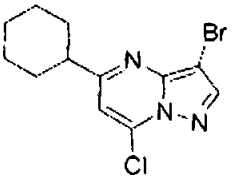
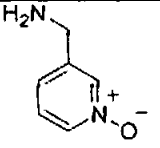
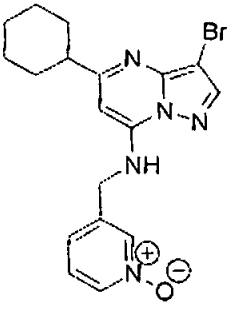
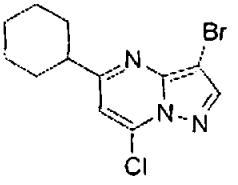
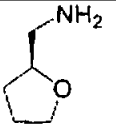
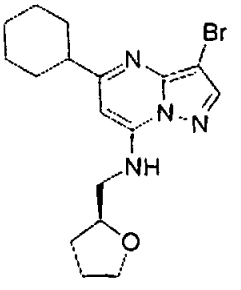
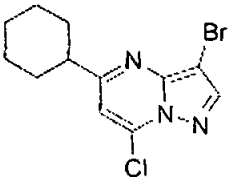
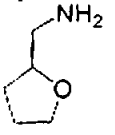
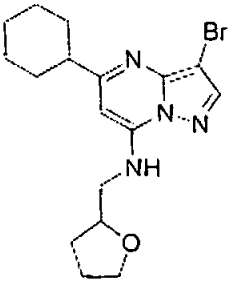
171				LCMS: MH$^+$ = 474;
172				LCMS: MH$^+$ = 437;
173				LCMS: MH$^+$ = 472;
174				LCMS: MH$^+$ = 428,1

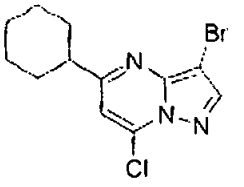
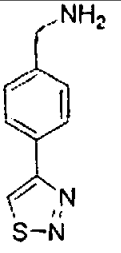
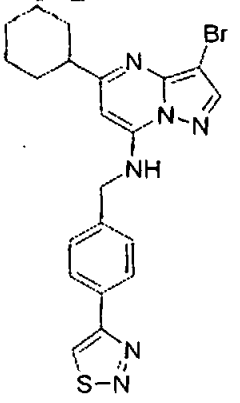
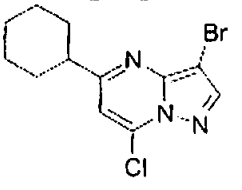
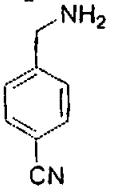
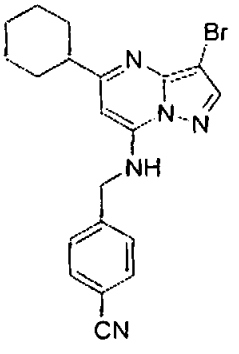
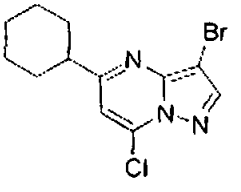
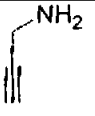
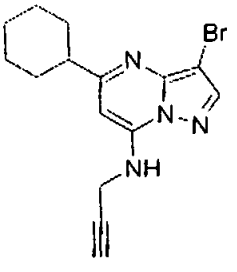
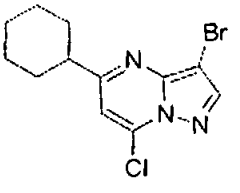
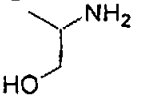
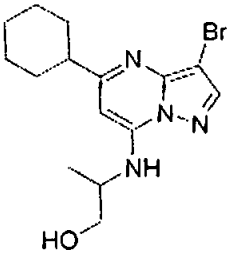
175				LCMS: MH$^+$ = 426,2
176				LCMS: MH$^+$ = 442,0
177				LCMS: MH$^+$ = 452,0
178				Rend. = 90 MH$^+$ =436 p.f. = 89,1°C

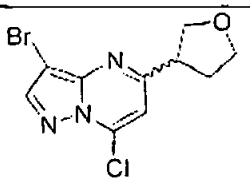
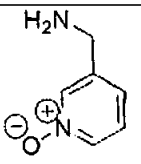
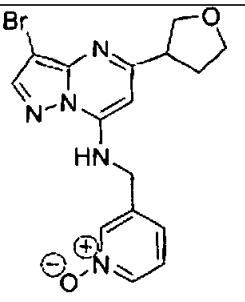
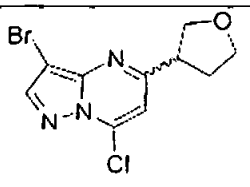
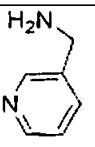
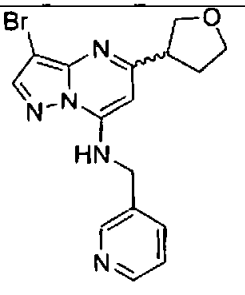
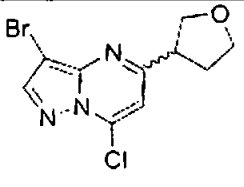
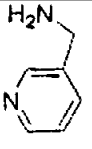
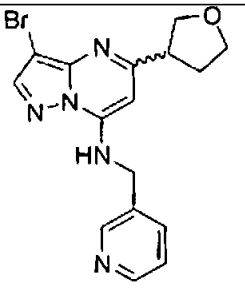
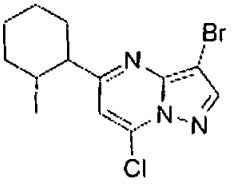
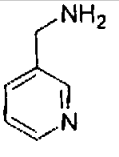
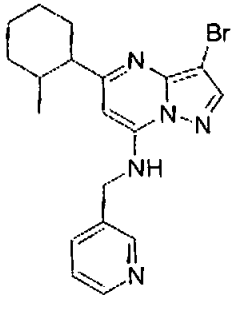
198

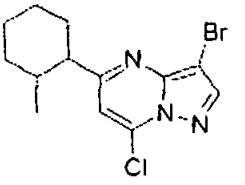
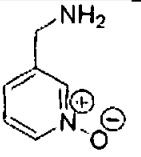
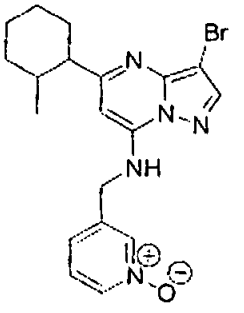
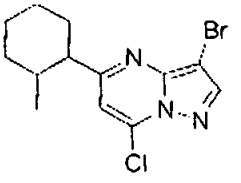
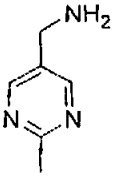
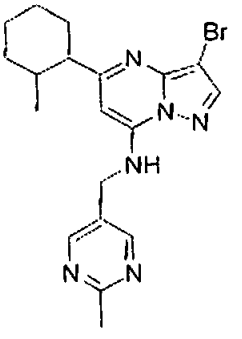
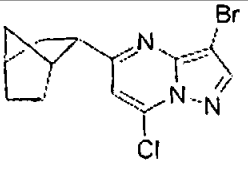
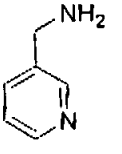
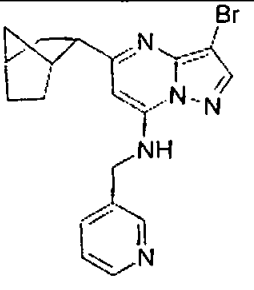
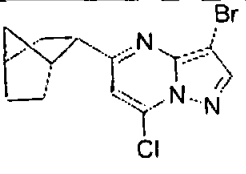
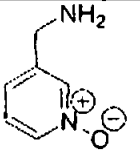
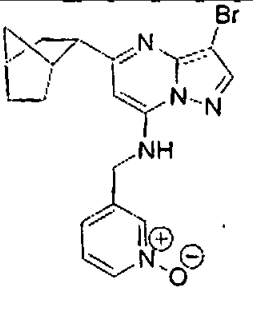
179				MH$^+$ =424 p.f. = 188,2°C
180				MH$^+$ =448 p.f. = 211,3°C
181				Rend. = cuant. MH$^+$ = 464
182				MH$^+$ = 382 p.f. = 185,8°C

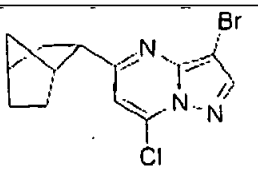
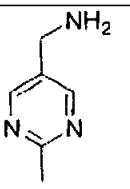
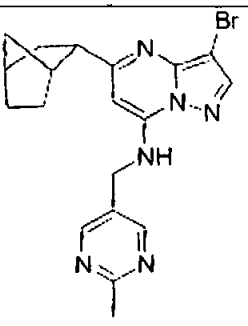
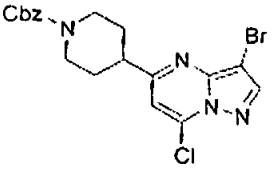
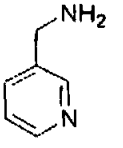
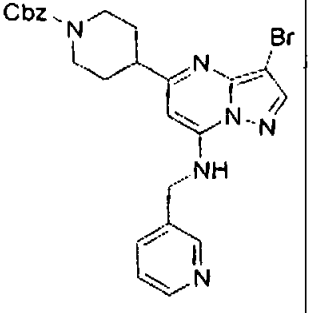
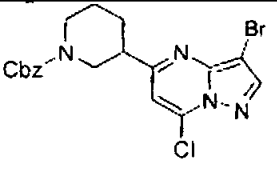
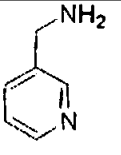
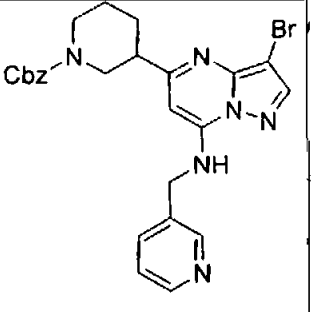
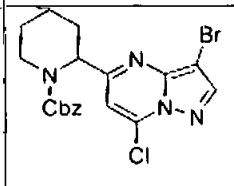
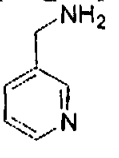
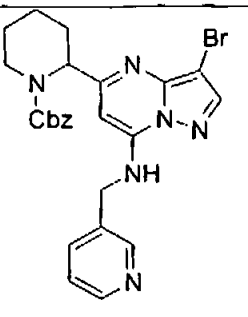
183				MH^+ = 387 p.f. = 181 – 182°C
184				MH^+ = 453
185				MH^+ = 401 p.f. = 178,3°C
186				MH^+ = 402

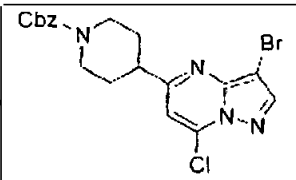
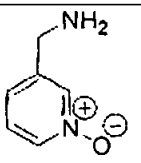
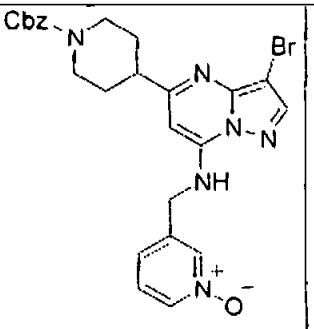
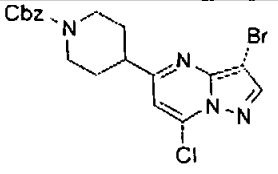
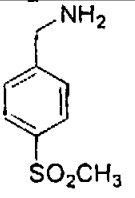
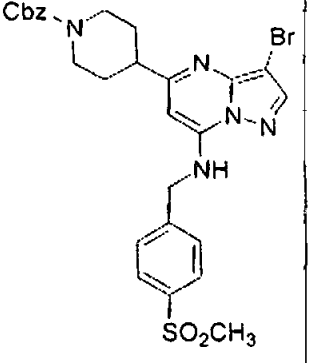
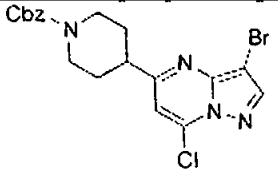
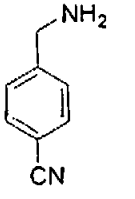
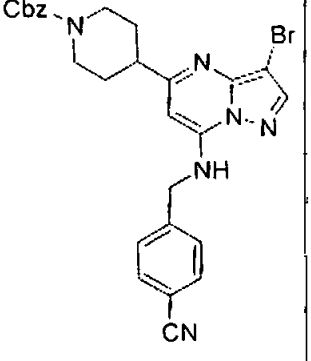
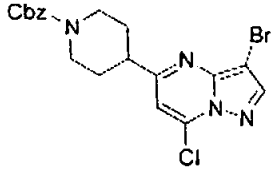
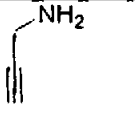
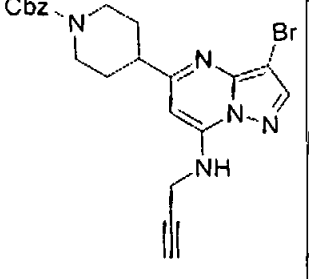
187				Rend. = 91 MH$^+$ = 386 p.f. = 148,3°C
188				Rend. = 65 MH$^+$ = 402 p.f.: 174,5°C
189				MH$^+$ = 379 p.f. = 82 – 83°C
190				MH$^+$ = 379 p.f. = 50,7°C

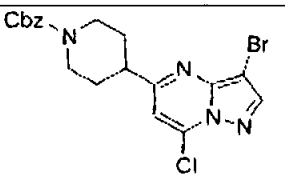
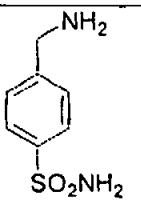
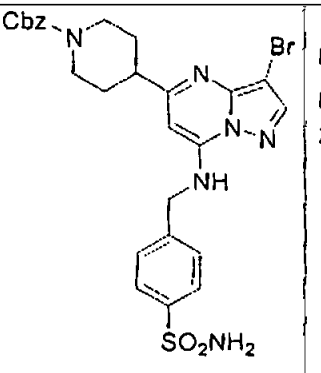
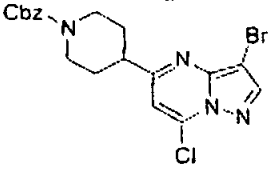
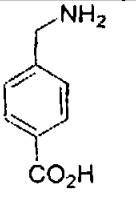
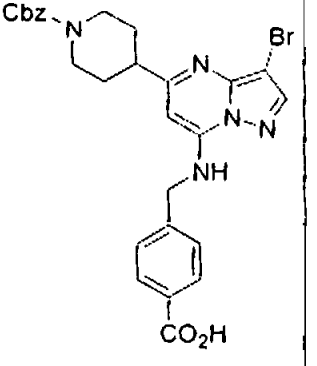
191				Rend. = 89 MH^+ = 469 p.f. = 186,7°C
192				Rend. = 93 MH^+ = 410 p.f. = 66,7°C
193				Rend. = 76 MH^+ = 333 p.f. = 120,3°C
194				Rend. = 86 MH^+ = 353 p.f. = 188,9°C

195				Rend.=11% LCMS:374 MH^+= 390
196				Rend.=88% LCMS:374 MH^+= 346
197				Rend.=88% LCMS:374 MH^+= 346
198				Rend. = MH^+ = 400 p.f. = 111,5 – 112,2°C

199				MH$^+$ = 416
200				MH$^+$ = 415
201				MH$^+$ =398 p.f.: 156,5°C
202				MH$^+$ = 414 p.f.: 89,5°C

203				MH⁺ = 413
204				Rend. = 86 MH⁺ = 521 p.f.: 79,9°C
204.10				
204.11				Rend. = 87 MH⁺ = 521 p.f.: 128,6°C

205				Rend. = 99 MH$^+$ = 537 p.f.: 83,5°C
206				Rend. = 94 MH$^+$ = 598 p.f.: 110,8°C
207				Rend. = cuant. MH$^+$ = 545
208				Rend. = 96 MH$^+$ = 468 p.f.: 69,2°C

209				MH⁺ = 498 p.f.: 226,5°C
210				MH⁺ = 564 p.f.: 174,2°C

Datos adicionales para ejemplos seleccionados que se dan a continuación.

Ejemplo 23: ^{1}H RMN (CD_3OD) δ 8,63 (d, J = 5,7 Hz, 2H), 8,18 (s, 1H), 7,81 (dd, J = 8,1 Hz, 2,1 Hz, 1H), 7,58 (d, J = 6,0 Hz, 2H), 7,48 (m, 1H), 7,15-7,10 (m, 2H), 6,50 (s, 1H), 4,86 (s, 2H), 3,70 (s, 3H).

Ejemplo 24: ^{1}H RMN ($CDCl_3$) δ 8,82 (s, 1H), 8,73 (d, J = 4,2 Hz, 1H), 8,11 (s, 1H), 8,06 (dd, J = 7,8 Hz, 1,8 Hz, 1H), 7,91 (d, J = 8,1 Hz, 1H), 7,53-7,47 (m, 2H), 7,20 (m, 1H), 7,08 (d, J = 8,1 Hz, 1H), 6,75 (s, 1H), 4,81 (d, J = 4,5 Hz, 2H), 3,86 (s, 3H).

Ejemplo 25: ^{1}H RMN ($CDCl_3$) δ 8,75 (d, J = 5,7 Hz, 2H), 8,12 (s, 1H), 7,81 (d, J = 2,1 Hz, 1H), 7,53 (dd, J = 8,4, 2,1 Hz, 1H), 7,45 (d, J = 6,0 Hz, 2H), 6,96 (t, J = 6,0 Hz, 2H), 6,33 (s, 1H), 4,85 (d, J = 6,0 Hz, 2H), 4,09 (s, 3H), 4,03 (s, 3H).

Ejemplo 26: ^{1}H RMN ($CDCl_3$) δ 8,82 (s, 1H), 8,72 (s, 1H), 8,09 (m, 1H), 7,87-7,83 (m, 2H), 7,60 (m, 1H), 7,45 (m, 1H), 7,03 (d, J = 8,4 Hz, 1H), 6,87 (s, 1H), 6,43 (s, 1H), 4,83 (d, J = 4,5 Hz, 2H), 4,11 (s, 3H), 4,04 (s, 3H).

Ejemplo 27: ^{1}H RMN ($CDCl_3$) δ 8,75 (d, J = 4,5 Hz, 2H), 8,19 (s, 1H), 7,63 (d, J = 7,8 Hz, 2H), 7,44-7,40 (m, 3H), 7,07 (m, 1H), 6,26 (s, 1H), 4,83 (d, J = 5,1 Hz, 2H).

Ejemplo 28: ^{1}H RMN ($CDCl_3$) δ 8,86 (s, 1H), 8,74 (m, 1H), 8,17 (s, 1H), 7,97 (m, 1H), 7,66-7,63 (m, 2H), 7,62 (m, 1H), 7,41 (m, 1H), 7,07 (m, 1H), 6,35 (s, 1H), 4,87 (d, J = 6,0 Hz, 2H).

Ejemplo 30: ^{1}H RMN ($CDCl_3$) δ 8,16 (s, 1H), 7,66-7,62 (m, 2H), 7,41 (m, 1H), 7,33-7,22 (m, 3H), 6,96 (t, J = 6,0 Hz, 1H), 6,33 (s, 1H), 4,73 (d, J = 6,0 Hz, 2H).

Ejemplo 31: ^{1}H RMN ($CDCl_3$) δ 8,13 (s, 1H), 7,66 (d, J = 7,8 Hz, 2H), 7,45-7,40 (m, 2H), 7,10-7,04 (m, 2H), 6,93 (t, J = 6,6 Hz, 1H), 6,60 (s, 1H), 4,84 (d, J = 6,6 Hz, 2H).

Ejemplo 32: ^{1}H RMN ($CDCl_3$) δ 8,16 (s, 1H), 7,66-7,62 (m, 2H), 7,57-7,55 (m, 2H), 7,41 (t, J = 7,8 Hz, 1H), 7,31 (dd, J = 7,8, 1,8 Hz, 1H), 6,99 (t, J = 6,0 Hz, 1H), 6,32 (s, 1H), 4,73 (d, J = 6,0 Hz, 2H).

Ejemplo 40: ^{1}H RMN ($CDCl_3$) δ 8,01 (s, 1H), 7,31 – 7,24 (d, J = 8,2 Hz, 1H), 6,72 – 6,64 (br t, J = 5,4 Hz, 1H), 6,62 – 6,52 (m, 2H), 6,05 – 6,01 (s, 1H), 5,56 – 4,64 (d, J = 6,0 Hz, 2H), 4,03 – 3,93 (s, 3H), 3,94 – 3,86 (s, 3H), 2,79 – 2,70 (d, J = 8,1 Hz, 2H), 2,02 – 1,66 (m, 6H), 1,43 –1,22 (m, 3H), 1,20 – 1,02 (m, 2H).

Ejemplo 45: ^{1}H RMN ($CDCl_3$) δ 8,73(d, 2H), 8,54(s, 1H), 7,41(d, 2H), 7,02(br, 1H), 5,90(s, 1H), 4,80(s, 2H), 4,48(q, 2H), 2,75(s, 2H), 1,50(t, 2H), 1,06(s, 9H).

Ejemplo 46: ^{1}H RMN ($CDCl_3$) δ 8,79(s, 1H), 8,72(d, 1H), 8,14(s, 1H), 7,84(d, 1H), 7,54-7,33(m, 4H), 6,97(t, 1H), 6,18(s, 1H), 4,79(d, 2H), 2,47(s, 3H).

Ejemplo 108: ^{1}H RMN ($CDCl_3$) δ 8,79 (s, 1H), 8,72 (d, J = 3,0 Hz, 1H), 8,16 (s, 1H), 7,84 (d, J = 7,8 Hz, 1H), 7,74 (d, J = 7,5 Hz, 2H), 7,55-7,35 (m, 3H), 6,92 (t, J = 6,3 Hz, 1H), 6,42 (s, 1H), 4,81 (d, J = 6,3 Hz, 2H).

Ejemplo 110: ^{1}H RMN ($CDCl_3$) δ 8,18(t, 1H), 8,03(s, 1H), 7,44(m, 1H), 7,30(t, 1H), 7,17(q, 1H), 6,66(s, 1H), 6,56(br, 1H), 4,28(d, 2H), 2,38(s, 1H).

Ejemplo 111: ^{1}H RMN ($CDCl_3$) δ 8,72(br, 1H), 8,59(d, 1H), 8,11(t, 1H), 8,06(s, 1H), 7,73(d, 1H), 7,44(d, 1H), 7,42-7,21(m, 3H), 7,07(q, 1H), 6,39(d, 1H), 5,21(q, 1H), 4,16(q, 2H), 3,08(d, 2H), 1,22(t, 3H).

Ejemplo 112: ^{1}H RMN ($CDCl_3$) δ 8,22(t, 1H), 8,15(s, 1H), 7,51-7,33(m, 7H), 7,21(q, 1H), 6,82(d, 1H), 6,51(s, 1H), 4,68(q, 1H), 2,18(m, 2H), 1,17(t, 3H).

Ejemplo 113: ^{1}H RMN ($CDCl_3$) δ 8,22(t, 1H), 8,14(s, 1H), 7,51-7,33(m, 7H), 7,21(q, 1H), 6,82(d, 1H), 6,51(s, 1H), 4,68(q, 1H), 2,18(m, 2H), 1,17(t, 3H).

Ejemplo 114: ^{1}H RMN ($CDCl_3$) δ 8,81(s, 1H), 8,75(d, 1H), 8,21(s, 1H), 7,84(d, 1H), 7,47(q, 1H), 6,96(s, 1H), 6,94(t, 1H), 4,85(d, 2H), 4,60(q, 2H), 1,58(t, 3H).

Ejemplo 115: ^{1}H RMN ($CDCl_3$) δ 8,77(s, 1H), 8,72(d, 1H), 8,14(s, 1H), 7,83(d, 1H), 7,65(d, 1H), 7,44(q, 1H), 7,80(t, 1H), 7,6(d, 1H), 6,18(s, 1H), 4,75(d, 2H), 3,91(s, 3H), 3,81(s, 3H).

Ejemplo 116: ^{1}H RMN ($CDCl_3$) δ 8,67(s, 1H), 8,55(d, 1H), 8,50(s, 1H), 7,92(d, 1H), 7,90(d, 1H), 7,78(t, 1H), 7,10(d, 1H), 6,97(s, 1H), 5,11(s, 2H), 3,77(s, 6H).

Ejemplo 117: ^{1}H RMN ($CDCl_3$) δ 8,38(s, 1H), 8,30(d, 1H), 8,17(s, 1H), 7,52-7,37(m, 6H), 6,97(t, 1H), 6,13(s, 1H), 4,77(d, 2H), 2,50(s, 3H).

Ejemplo 118: ^{1}H RMN ($CDCl_3$) δ 8,18(t, 1H), 8,03(s, 1H), 7,44(m, 1H), 7,30(t, 1H), 7,17(q, 1H), 6,66(s, 1H), 6,56(br, 1H), 4,28(d, 2H), 2,38(s, 1H).

Ejemplo 121: ^{1}H RMN ($CDCl_3$) δ 8,6 (S, 1H), 8,15 (dt,1H), 8,1 (s, 1H), 8,0 (d, 2H), 7,5 (d, 2H), 7,4 (dd, 1H), 7,2 (d, 1H), 7,15 (dd, 1H), 6,8 (t, 1H), 6,6 (s, 1H), 4,75 (d, 2H).

Ejemplo 126: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,5 (d, 1H), 7,42 – 7,35 (m, 2H), 7,3 –7,2 (m, 2H), 7,15 (dd, 1H), 7,1 (dd, 1H), 7,0 (t, 1H), 6,6 (s, 1H), 4,8 (d, 2H).

Ejemplo 127: ^{1}H RMN ($CDCl_3$) δ 8,2 (dt, 1H), 8,0 (s,1H), 7,4 (dd, 1H), 7,3- 7,25 (m, 3H), 7,1 (dd, 1H), 6,9 - 6,85 (m, 2H), 6,7 (t, 1H), 6,6 (s, 1H), 4,6 (d, 2H), 3,2 (m, 4H), 2,6 (m, 4H), 2,3 (s, 3H).

Ejemplo 128: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt,1H), 8,1 (s, 1H), 8,0 (d, 2H), 7,5 (d, 2H), 7,4 (m, 2H), 7,25 (d, 1H), 7,2 (s,1H), 7,15 (dd, 1H), 7,0 (s, 1H), 6,8 (t, 1H), 6,6 (s, 1H), 4,75 (d, 2H).

Ejemplo 129: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,05 (s, 1H), 8,0 (d, 2H), 7,5 (d, 2H), 7,4 (m, 1H), 7,3 (dd, 1H), 7,15 (dd, 1H), 6,9 (t, 1H), 6,5 (s, 1H), 4,75 (d, 2H), 3,85 (s, 3H).

Ejemplo 130: ^{1}H RMN ($CDCl_3$) δ 8,2 (dt,1H), 8,0 (s, 1H), 7,4 (dd, 1H), 7,3(dd, 1H), 7,15 (dd, 1H), 6,8 (t, 1H), 6,4 (s,1H), 4,2 (d, 2H), 3,8 (s, 3H).

Ejemplo 131: ^{1}H RMN ($CDCl_3$) δ 8,2 (dt, 1H), 8,0 (s,1H), 7,4 – 7,15 (m, 3H), 6,7 (t, 1H), 4,2 (q, 2H), 3,8 (dt, 2H), 2,8 (t, 2H), 1,2 (t, 3H).

Ejemplo 132: ^{1}H RMN ($CDCl_3$) δ 8,2 (dt, 1H), 8,0 (s,1H), 7,4 – 7,15 (m, 3H), 6,7 (t, 1H), 4,2 (q, 2H), 3,8 (dt, 2H), 2,8 (t, 2H), 2,05 (m, 2H) 1,2 (t, 3H).

Ejemplo 133: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s,1H), 7,4 (m, 1H), 7,3 (dd 1H), 7,2 (dd, 1H), 6,5 (s, 1H), 6,4 (t,1H), 3,7 (s, 3H), 3,5 (dd,2H),2,4 (t, 2H), 1,8 (m, 4H).

Ejemplo 134: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,95 (d, 2H), 7,6 (d, 2H), 7,4 (m, 1H), 7,25 (dd, 1H), 7,1 (dd, 1H), 6,9 (t, 1H), 6,5 (s, 1H), 4,8 (d, 2H), 3,0 (s, 3H).

Ejemplo 135: ^{1}H RMN (DMSO d6) δ 9,1 (bs, 2H), 8,4 (s,1H), 8,0 (t, 1H), 7,85 (d, 2H), 7,7 (d, 2H), 7,6 (m, 1H), 7,4 (m, 2H), 6,6 (s, 1H), 4,8 (bs, 2H).

Ejemplo 136: ^{1}H RMN ($CDCl_3$) δ 8,2 (dt, 1H), 8,0 (s,1H), 7,4 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 6,9 (m, 3H), 6,7 (t, 1H), 6,5 (s, 1H), 4,5 (d, 2H), 4,2 (s, 4H).

Ejemplo 137: ^{1}H RMN ($CDCl_3$) δ 8,2 (dt, 1H), 8,0 (s, 1H), 7,4 (m, 1H), 7,3 (dd, 1H), 7,2 (dd, 1H), 6,9 (dd, 1H), 6,8 (t, 1H), 6,7 (m, 1H), 6,6 (s, 1H), 5,3 (s, 2H), 4,85 (s, 2H), 4,6 (d, 2H).

Ejemplo 138: ^{1}H RMN ($CDCl_3$) δ 8,2 (dt, 1H), 8,0 (s, 1H), 7,9 (d,1H), 7,8 (d, 1H), 7,4 (m, 2H), 7,3 (dd, 1H), 7,1 (dd, 1H), 6,9 (t, 1H), 6,6 (s, 1H), 4,8 (d, 2H).

Ejemplo 139: ^{1}H RMN ($CDCl_3$) δ 8,2 (dt, 1H), 8,0 (s, 1H), 7,4 (m, 1H), 7,3 (m, 2H), 7,2 (dd, 1H), 7,1 (dd, 1H), 6,8 (d, 1H), 6,7 (t, 1H), 6,6(s, 1H), 4,6 (m, 4H), 3,2 (t, 2H).

Ejemplo 140: ^{1}H RMN ($CDCl_3$) δ 8,45 (s, 1H), 8,2 (dt, 1H), 8,0 (s, 1H), 7,7 (dd, 1H), 7,4 – 7,3 (m, 3H), 7,15 (dd, 1H), 6,8 (t, 1H), 6,6 (s,1H), 4,7 (d, 2H).

Ejemplo 141: ^{1}H RMN ($CDCl_3$) δ 8,2 (dt, 1H), 8,0 (s, 1H), 7,45 - 7,1 (m, 7H), 6,6 (s, 1H), 4,4 (dt, 2H), 2,6 (t, 2H), 1,8 (m, 2H), 1,4 (m, 2H).

Ejemplo 171: ^{1}H RMN (CD_3OD) δ 8,41 (s, 1H), 8,25 (d, J = 6,3 Hz, 1H), 8,15 (s, 1H), 7,67 (d, J = 7,8 Hz, 2H), 7,55-7,48 (m, 2H), 7,45 (dd, J = 7,5, 1,2 Hz, 1H), 7,34 (dd, J = 7,5, 1,8 Hz, 1H), 6,28 (s, 1H), 4,79 (s, 2H).

Ejemplo 172: ^{1}H RMN ($CDCl_3$) δ 8,64 (s, 1H), 7,68-7,64 (m, 2H), 7,52 (m, 1H), 7,43 (t, J = 7,8 Hz, 1H), 6,89 (t, J = 6,0 Hz, 1H), 6,51 (s, 1H), 6,48 (m, 2H), 4,74 (d, J = 6,0 Hz, 2H).

674

Ejemplo 173: ^{1}H RMN (DMSO-d_6) δ 8,86 (s, 1H), 8,46 (s, 1H), 8,32-8,28 (m, 2H), 7,97 (m, 1H), 7,87 (m, 1H), 7,52 (m, 1H), 7,35-7,24 (m, 2H), 6,57 (s, 1H), 6,46 (m, 1H), 3,65 (m, 4H).

Ejemplo 174: ^{1}H RMN ($CDCl_3$) d 8,37 (s, 1H), 8,16 (t, J = 7,5 Hz, 1H), 7,45-7,35 (m, 1H), 7,32-7,20 (m, 3H), 7,17-7,07 (m, 1H), 6,92 (t, J = 6 Hz, 1H), 6,48 (s, 1H), 4,65 (d, 2H), 2,50 (s, 3H).

Ejemplo 175: ^{1}H RMN ($CDCl_3$) d 8,16 (t, J = 9 Hz, 1H), 8,00 (s, 1H), 7,49 (d, J= 9 Hz, 1H), 7,46-7,36 (m, 1H), 7,18-7,08 (m, 1H), 7,00 (d, J = 9 Hz, 1H), 6,62-6,50 (m, 2H), 2,60 (s, 3H), 2,55 (s, 3H).

Ejemplo 176: ^{1}H RMN ($CDCl_3$) d 8,15 (t, J = 9 Hz, 1H), 8,00 (s, 1H), 7,45-7,35 (m, 1H), 7,32-7,20 (m, 1H), 7,20-7,05 (m, 3H), 6,80 (t, 1H), 6,50 (s, 1H), 4,65 (d, 2H), 2,65 (s, 3H), 2,50 (s, 3H).

Ejemplo 177: ^{1}H RMN ($CDCl_3$) d 8,20 (t, 1H), 7,90 (s, 1H), 7,50-7,05 (m, 8H), 6,80 (s, 1H), 5,05-4,90 (m, 2H), 3,80 (d, 1H), 3,45 (d, 1H), 3,00 (dd, 1H), 2,90 (dd, 1H), 2,50 (s, 3H).

Ejemplo 181: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,41 (s, 1H), 8,28 – 8,23 (d, 1H), 8,15 (s, 1H), 7,69 –7,60 (d, 1H), 7,62 – 7,50 (m, 3H), 7,50 – 7,47 (dd, 1H), 6,35 (s, 1H), 5,36 (s, 1H), 4,80 (s, 2H).

Ejemplo 184: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,96 - 8,90 (s, 1H), 8,08 (s, 1H), 8,04 (d, 1H), 7,72 (d, 1H), 7,70 – 7,61 (dd, 1H), 7,24 – 7,20 (dd, 1H), 6,92 – 6,84 (t, 1H), 6,36 (s, 1H), 4,96 – 4,89 (d, 2H).

Ejemplo 186: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,96 - 8,90 (s, 1H), 8,08 (s, 1H), 8,44 (s, 1H), 8,27 – 8,24 (d, 1H), 8,02 (s, 1H), 7,78 – 7,76 (d, 1H), 7,73 – 7,70 (d, 1H), 7,58 – 7,51 (m, 2H), 7,13 –7,08 (dd, 1H), 5,51 (s, 2H).

Ejemplo 195: ^{1}H RMN (CD_3OD) δ 8,40(s, 1H), 8,27(d, 1H), 8,03(s, 1H), 7,75-7,50(m, 2H), 6,10(s, 1H), 4,76(s, 2H), 4,05(m, 2H), 3,88(m, 2H), 3,52(m, 1H), 2,33(m, 1H), 2,20(m, 1H).

Ejemplo 196: ^{1}H RMN (CD_3OD) δ 8,73(d, 1H), 8,58(q, 1H), 8,12(s, 1H), 8,00(d, 1H), 7,54(q, 1H), 6,19(s, 1H), 4,86(s, 2H), 4,22-4,08(m, 2H), 4,03-3,93(m, 2H), 3,63(m, 1H), 2,50-2,39(m, 1H), 2,32-2,21(m, 1H).

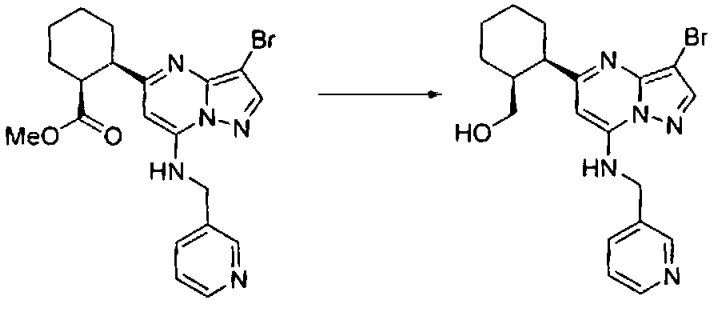
Ejemplo 197: ^{1}H RMN (CD_3OD) δ 8,73(d, 1H), 8,58(q, 1H), 8,12(s, 1H), 8,00(d, 1H), 7,54(q, 1H), 6,19(s, 1H), 4,86(s, 2H), 4,22-4,08(m, 2H), 4,03-3,93(m, 2H), 3,63(m, 1H), 2,50-2,39(m, 1H), 2,32-2,21(m, 1H).

Ejemplo 199: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,29 (s, 1H), 8,15 (br s, 1H), 7,95 (s, 1H), 7,28 (d, 1H), 7,05 - 6,95 (appt t, 1H), 5,70 (s, 1H), 4,62 (d, 2H), 2,90 (m, 1H), 2,30 (m, 1H), 1,9 – 1,2 (m, 8H), 0,65 (d, 3H).

Ejemplo 200: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,71 (s, 2H), 8,00 (s, 1H), 6,13 (s, 1H), 3,59 (s, 2H), 3,01 – 2,58 (m, 1H), 2,51 – 2,45 (m, 1H), 2,44 –2,30 (m,1H), 2,20 (s, 3H), 2,09 – 1,95 (m, 2H), 1,85 –1,70 (m, 2H), 0,80 – 0,76 (d, 3H).

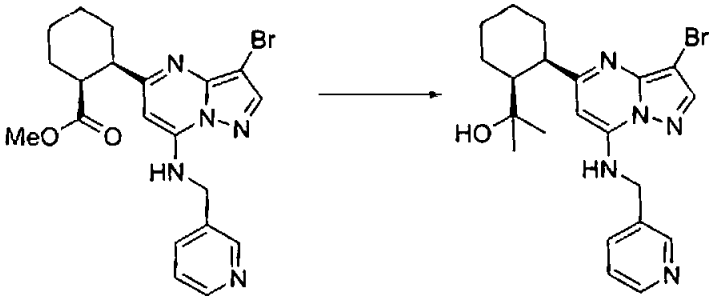
Ejemplo 203: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,10 (s, 1H), 8,08 (s, 1H), 6,27 (s, 2H), 4,95 (s, 2H), 3,00 – 2,90 (dd, 2H), 2,60 (m, 2H), 2,48 (br s, 1H), 2,39 (s, 3h), 2,25 m, 1H), 1,95 – 1,70 (m, 3H).

EJEMPLO 211:



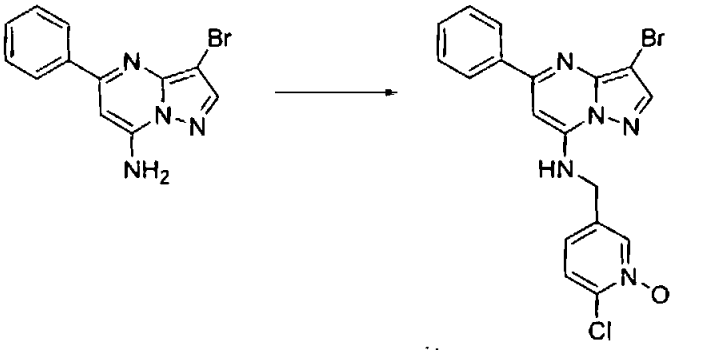
A una solución del compuesto preparado en el Ejemplo 156 (100 mg, 0,23 mmoles) en THF seco (4 mL) se agregó $LiAlH_4$ (1,0 M en THF, 0,110 mL, 0,110 mmoles) a 0°C bajo N_2. La mezcla se agitó a 0°C durante 1 hora, se calentó a 25°C, luego se agregó $LiAlH_4$ adicional (1,0 M en THF, 0,400 mL), la mezcla se agitó durante 20 minutos y luego se apagó con MeOH (2,0 mL). El solvente se evaporó y el producto crudo se purificó por cromatografía evaporativa usando 10:1 CH_2Cl_2:MeOH como eluyente. Se obtuvo un sólido blanco (46 mg, 49%). LCMS: M^+= 416. P.f.=71-72°C.

EJEMPLO 212:



A una solución del compuesto preparado en el Ejemplo 156 (70 mg, 0,16 mmoles) en THF seco (3 mL) se agregó MeMgBr (3,0 M en Et_2O, 1,10 mL, 3,20 mmoles) bajo N_2. La mezcla se agitó a 25°C durante 45 minutos y luego se apagó con NH_4Cl acuoso saturado (5,0 mL). La mezcla se vertió en NH_4Cl acuoso saturado (30 mL) y se extrajo con CH_2Cl_2 (3x20 mL). Los extractos se secaron sobre Na_2SO_4 y se filtraron. El solvente se evaporó y el producto crudo se purificó por cromatografía evaporativa usando 20:1 de CH_2Cl_2:MeOH como eluyente. Se obtuvo un sólido blanco (25 mg, 36%). LCMS: M^+= 444. P.f.=76-80°C.

EJEMPLO 213:



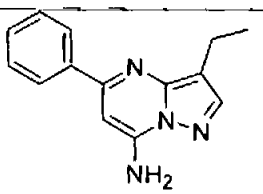
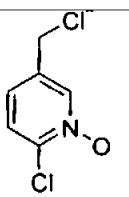
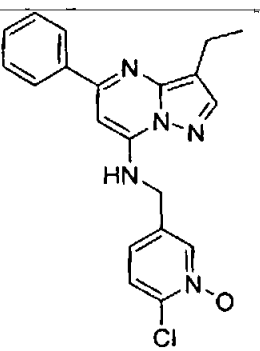
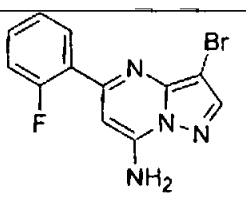
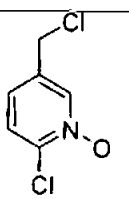
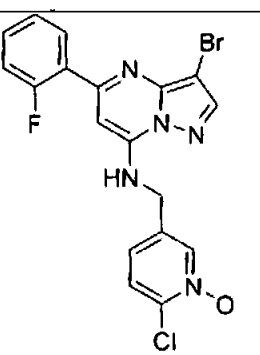
DMF anhidro (40 mL) se agregó bajo N_2 al compuesto preparado en el Ejemplo Preparativo 174 (2,50 g, 8,65 mmoles) y 60% de NaH en aceite mineral (346 mg, 8,65 mmoles). La mezcla se agitó a 25°C durante 1 hora, y luego se agregó lentamente N-óxido de 2-cloro-5-clorometilpiridina (1,54 g, 8,65 mmoles) en DMF anhidro (20 mL). La mezcla se agitó a 25°C durante 18 horas, el solvente se evaporó y el producto crudo se purificó por cromatografía evaporativa usando 30:1 CH_2Cl_2:MeOH como eluyente. El sólido así obtenido se trituró con 50 mL de

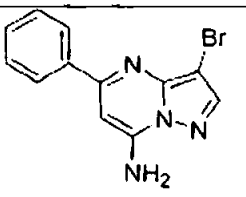
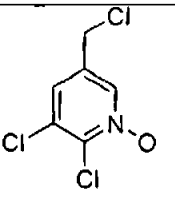
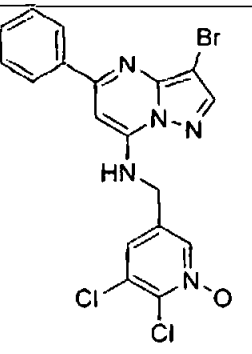
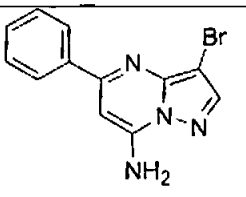
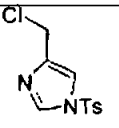
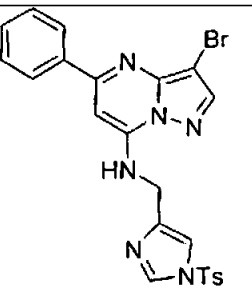
1:1 de EtOAc: hexano. Se obtuvo un sólido de color amarillo pálido (1,25 g, 34%). LCMS: MH^+=432. P.f.=224-226°C.

EJEMPLOS 214-217:

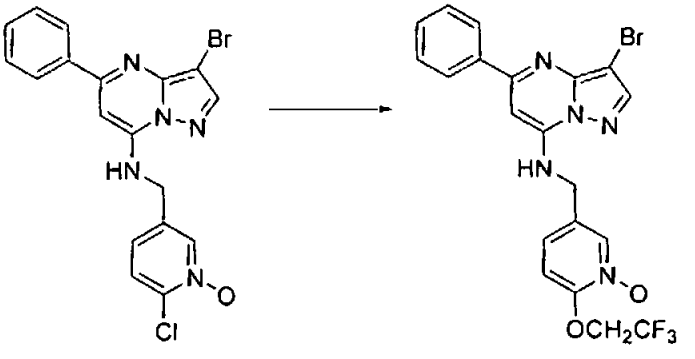
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo 213 combinando los compuestos que se muestran en la Columna 2 de la Tabla 19 con los compuestos de la Columna 3 de la Tabla 19, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 19.

TABLA 19

Ej.	Columna 2	Columna 3	Columna 4	COMP.
214				LCMS: MH^+=380; p.f.=°C
215				LCMS: MH^+=450; p.f.=218-222°C

216				LCMS: MH^+=466; p.f.=126-128°C
217				LCMS: M^+=523

EJEMPLO 218:

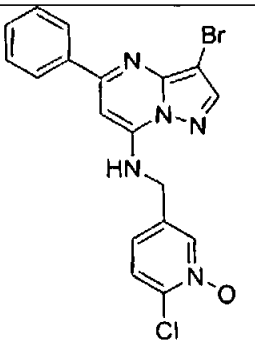
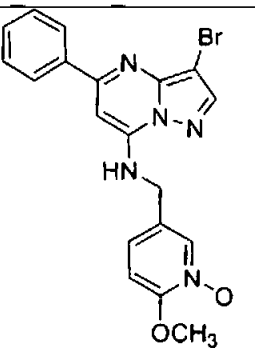
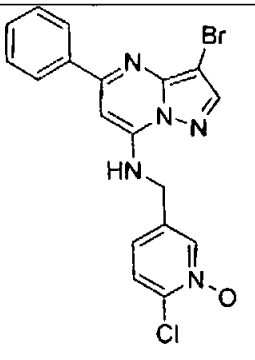
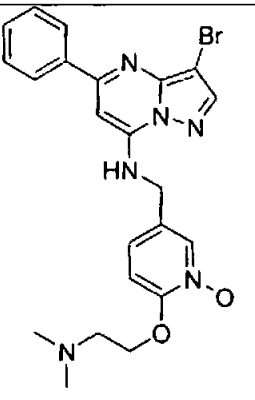
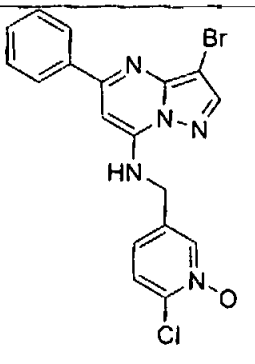
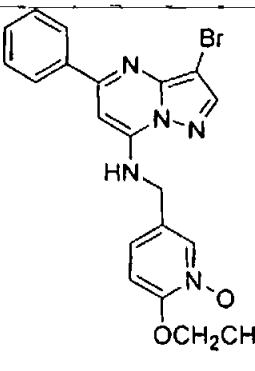


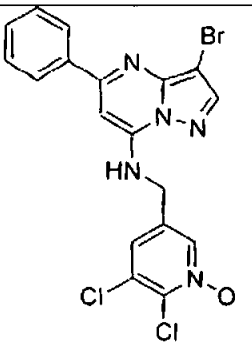
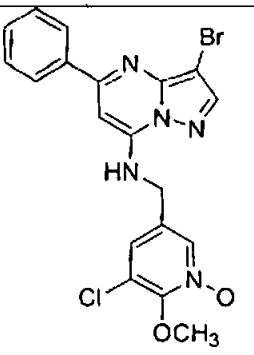
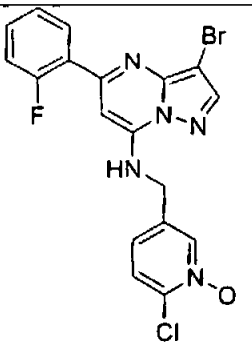
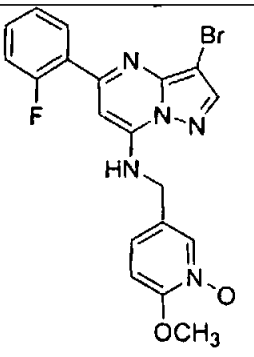
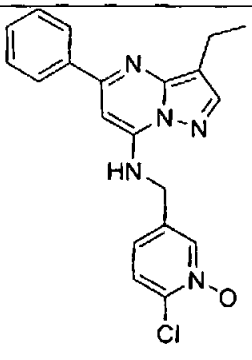
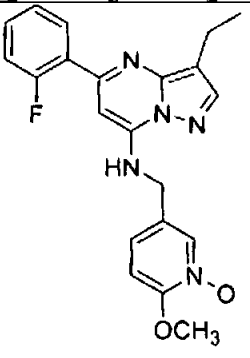
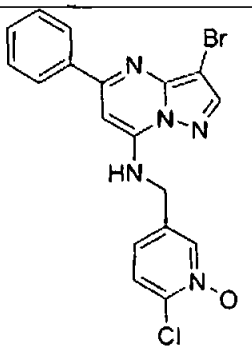
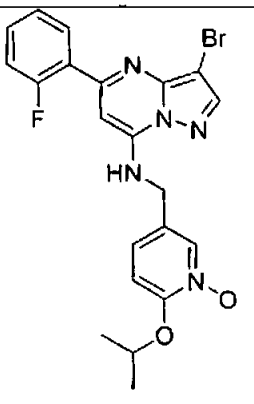
Se agregó CF_3CH_2OH (3,0 mL) bajo N_2 a NaH al 60% en aceite mineral (40 mg, 1,0 mmoles), la mezcla se agitó durante 20 minutos y luego se agregó el producto preparado en el Ejemplo 213 (50 mg, 0,12 mmoles). La mezcla se reflujo durante 20 horas, el solvente se evaporó, y el residuo se purificó por cromatografía evaporativa usando 20:1 CH_2Cl_2:MeOH como eluyente para proporcionar un sólido de color amarillo pálido (35 mg, 61%). LCMS: $M2H^+$=496. P.f.=208-210°C.

EJEMPLOS 219-225:

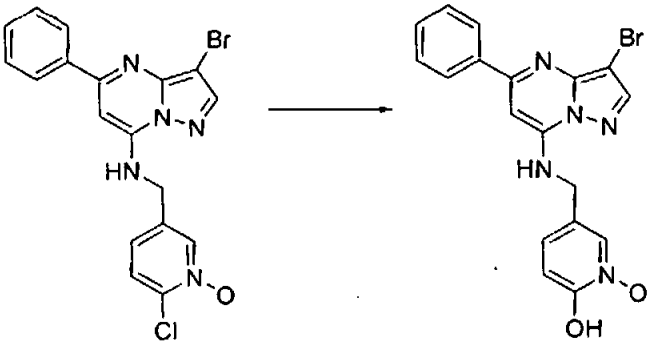
Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo 218 combinando los compuestos que se muestran en la Columna 1 de la Tabla 20 con el alcohol apropiado, se prepararon los compuestos que se muestran en la Columna 2 de la Tabla 20.

TABLA 20

Ej.	Columna 1	Columna 2	Datos
219			LCMS: M^+=426; p.f.=126-128°C
220			LCMS: M^+=483; p.f.=89-91°C
221			LCMS: $M2H^+$=442; p.f.=112-114°C

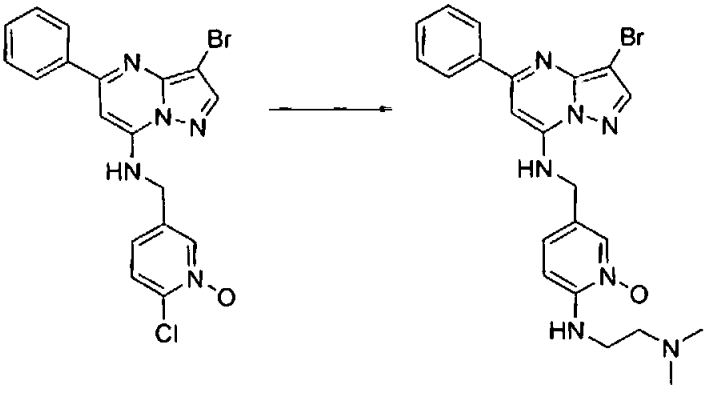
222			LCMS: MH^+=462; p.f.=121-123°C
223			LCMS: MH^+=444; p.f.=112-114°C
224			LCMS: M^+=376; p.f.=°C
225			LCMS: MH^+=; p.f.=°C

EJEMPLO 226:



Una mezcla del producto preparado en el Ejemplo 213 (100 mg, 0,23 mmoles) y KOH (95 mg, 1,70 mmoles) en 1,2-dimetoxietano (3 mL) y H_2O (1,5 mL) se reflujo bajo N_2 durante 20 horas, se apagó con ácido acético (0,30 mL), y el solvente se evaporó. El residuo se suspendió en H_2O (15 mL), se filtró y el sólido se lavó con H_2O (15 mL) y Et_2O (10 mL). Luego se mezcló con CH_2Cl_2 (2 mL) y Et_2O (2 mL) y se filtró. Se agregó el Et_2O (5 mL) al filtrado y la mezcla se dejó reposar durante la noche. El sólido se removió por filtración, se lavó con Et_2O y luego se disolvió en MeOH (5 mL). La solución se filtró y el solvente del filtrado se evaporó. Se obtuvo un sólido blancuzco (5 mg, 5%). LCMS: M^+=412. P.f.= 206-208°C.

EJEMPLO 227:



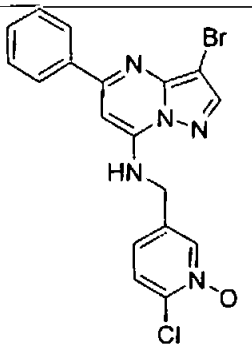
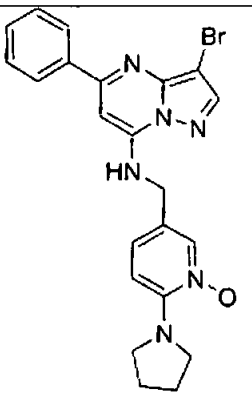
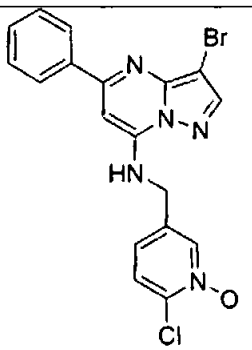
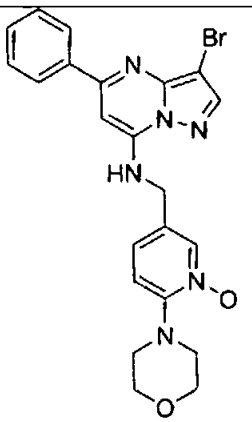
Una mezcla del producto preparado en el Ejemplo 213 (129 mg, 0,30 mmoles), N,N-dimetiletilendiamina (0,165 mL, 1,50 mmoles), y diisopropiletilamina (0,10 mL) en N-metilpirrolidinona anhidra (1,0 mL) se agitó a 100°C durante 24 horas. El solvente se evaporó, y el residuo se purificó por cromatografía

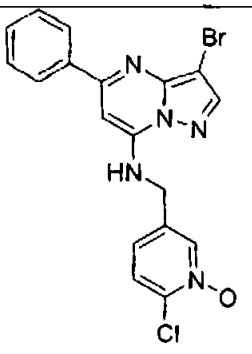
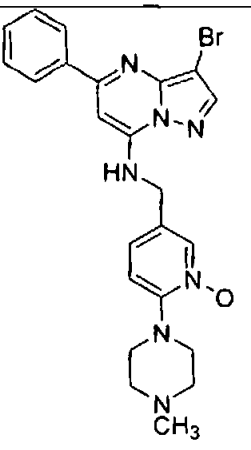
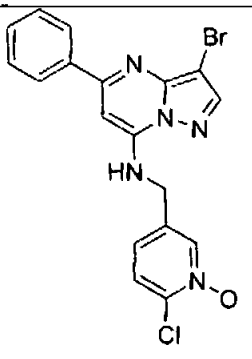
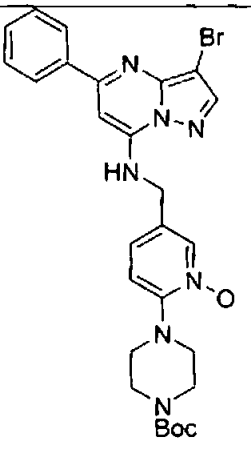
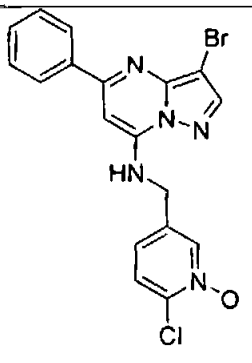
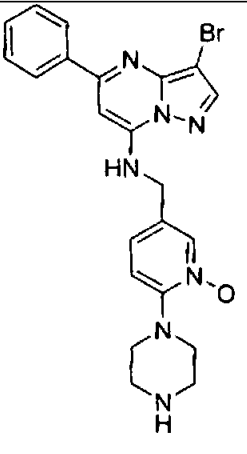
evaporativa usando 20:1 CH_2Cl_2: 7N NH_3 en MeOH como eluyente para proporcionar un sólido de color amarillo pálido (110 mg, 76%). LCMS: M^+=482. P.f.=76-78°C.

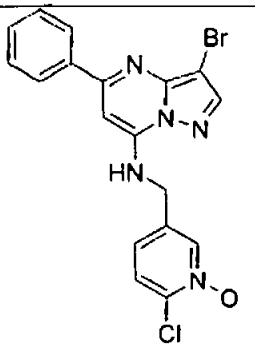
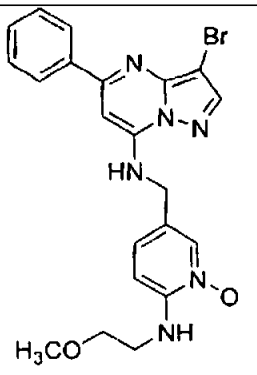
EJEMPLOS 228-233:

Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo 227, combinando los compuestos que se muestran en la Columna 1 de la Tabla 21 con la amina apropiada, se prepararon los compuestos que se muestran en la 2 de la Tabla 21.

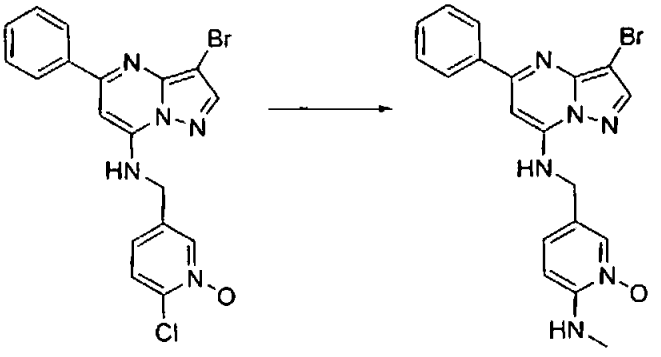
TABLA 21

Ej.	Columna 1	Columna 2	Datos
228			LCMS: M2H$^+$=467; p.f.: 126-128=°C
229			LCMS: M$^+$=481; p.f.: 128-130°C

230			LCMS: M^+=494; p.f.: 108-110°C
231			LCMS: $M2H^+$=482; p.f.: 129-133°C
232			LCMS: $M2H^+$=482; p.f.: 124-126°C

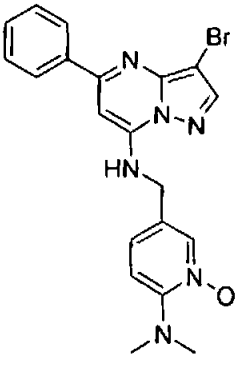
233			LCMS: $M2H^+$=471; p.f.: 88-90°C

EJEMPLO 234:



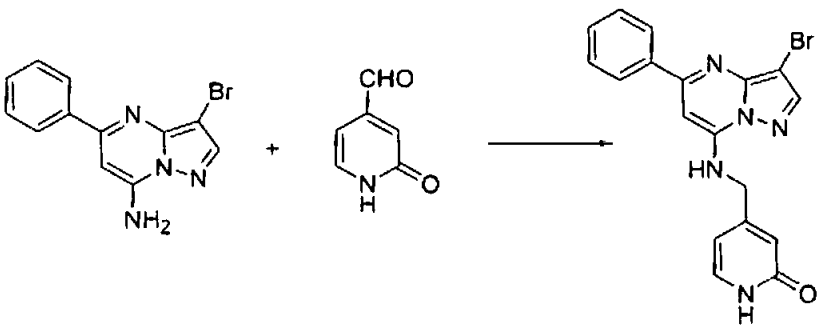
Una mezcla del producto preparado en el Ejemplo 213 (80 mg, 0,19 mmoles) y metilamina 2,0 M en THF se agitó en un recipiente cerrado bajo presión a 50°C durante 72 horas. El solvente se evaporó, y el residuo se purificó por cromatografía evaporativa usando 10:1 de CH_2Cl_2:MeOH como eluyente para proporcionar un sólido amarillo pálido (40 mg, 51%). LCMS: $M2H^+$=427. P.f.=217-219 °C.

EJEMPLO 235:



Esencialmente mediante el mismo procedimiento que se indica en el Ejemplo 234, se preparó el compuesto que se muestra anteriormente. LCMS: $M2H^+$=441. P.f.=98-101°C.

EJEMPLO 236:

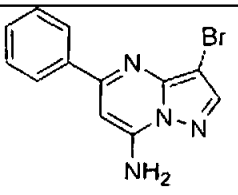
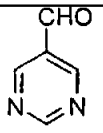
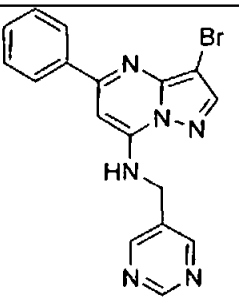
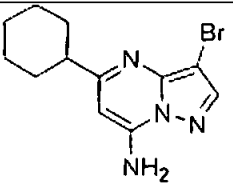
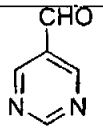
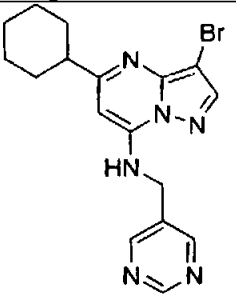
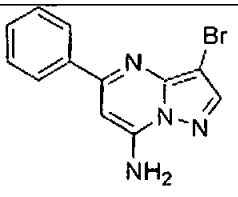
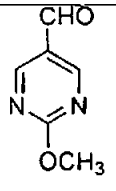
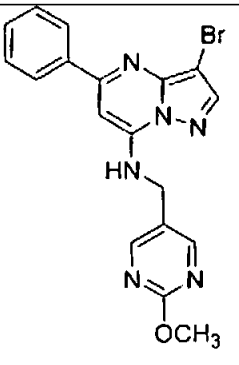
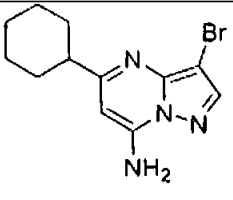
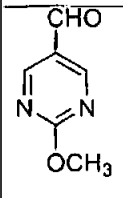
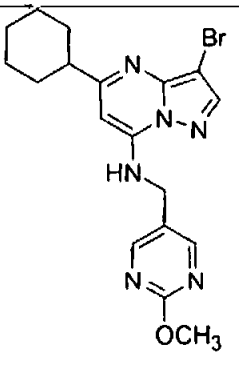


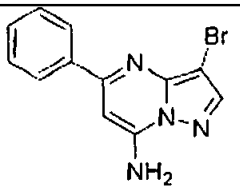
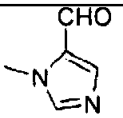
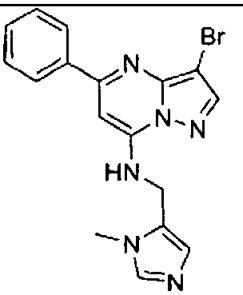
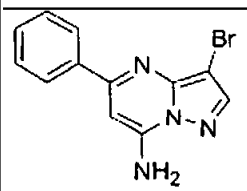
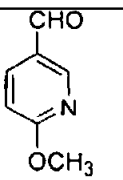
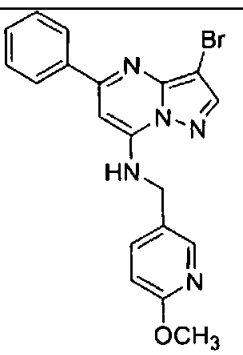
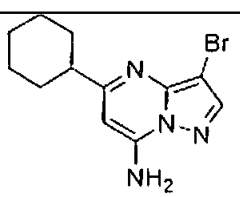
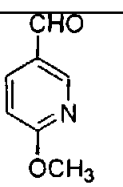
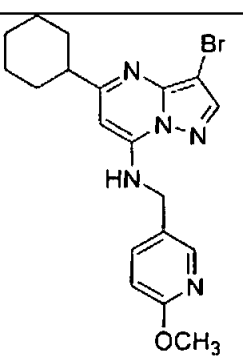
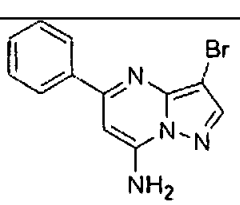
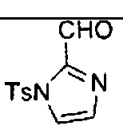
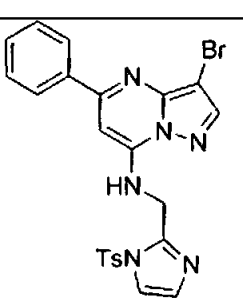
El compuesto preparado en Ejemplo Preparativo 174 (140 mg, 0,48 mmoles) y el aldehído (71 mg, 0,58 mmoles) se agitaron en THF anhidro (4 mL) a 50°C bajo N_2. Se agregó $Ti(OiPr)_4$ (0,574 mL, 1,92 mmoles), la mezcla se agitó a 50°C durante 3 horas, y se enfrío a 25°C. Se agregó $NaBH_3CN$ (181 mg, 2,88 mmoles), la mezcla se agitó durante 2 horas más, y luego se vertió en Na_2CO_3 acuoso al 10% (100 mL), y se extrajo con CH_2Cl_2 (3 x 50 mL). Los extractos combinados se secaron sobre Na_2SO_4, se filtraron, y el solvente se evaporó. El residuo se purificó por cromatografía evaporativa usando 15:1 CH_2Cl_2:MeOH como eluyente para proporcionar un sólido de color amarillo pálido (40 mg, 21%). LCMS: MH^+=398. P.f.: >230 °C.

EJEMPLOS 237-256:

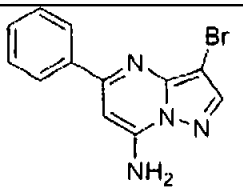
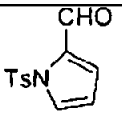
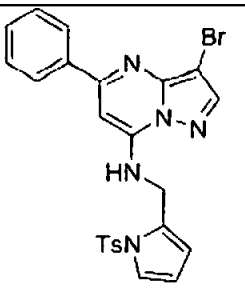
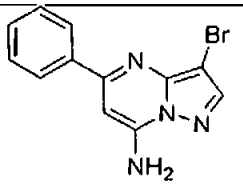
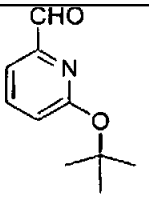
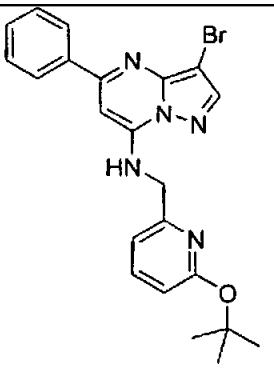
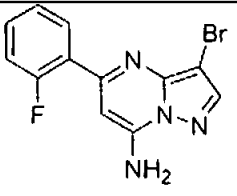
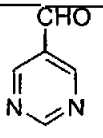
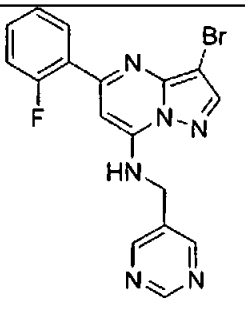
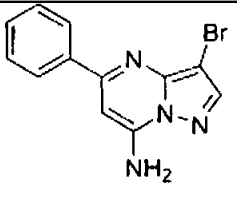
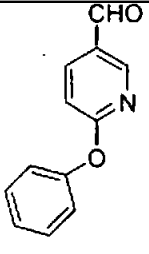
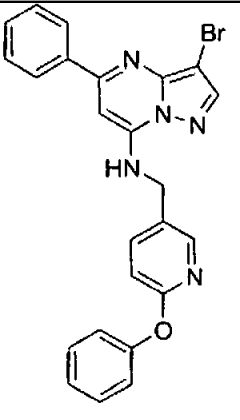
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo 236 combinando los compuestos que se muestran en la Columna 2 y 3 de la Tabla 22, se prepararon los compuestos que se muestran en la Columna 4 de la Tabla 22.

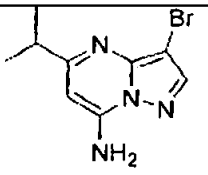
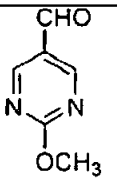
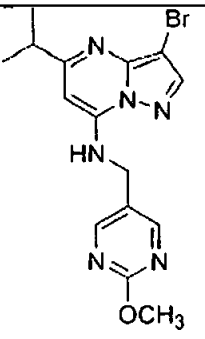
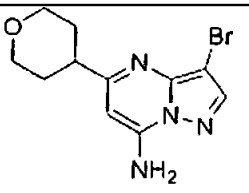
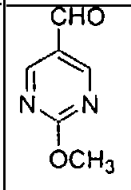
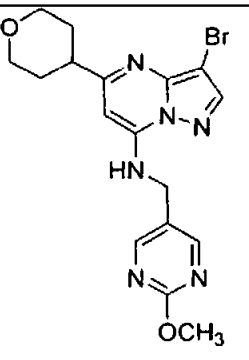
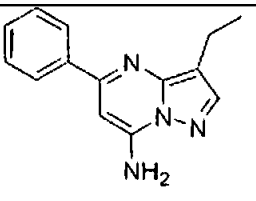
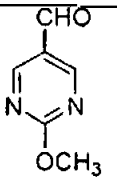
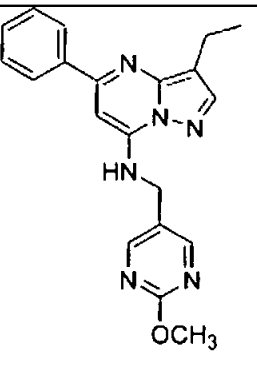
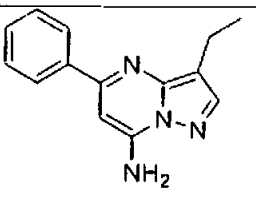
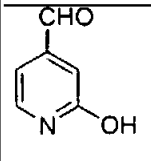
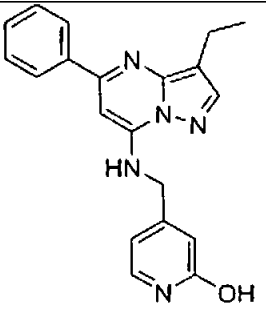
TABLA 22

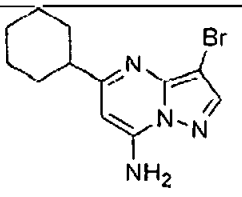
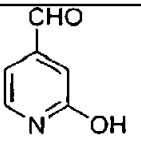
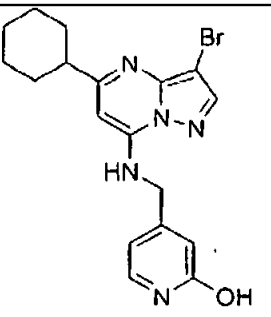
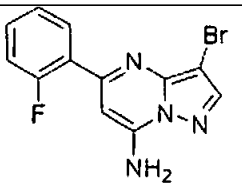
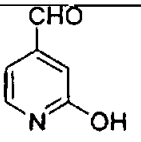
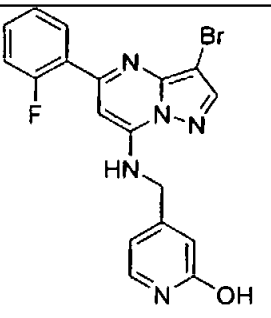
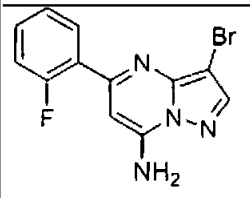
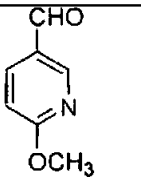
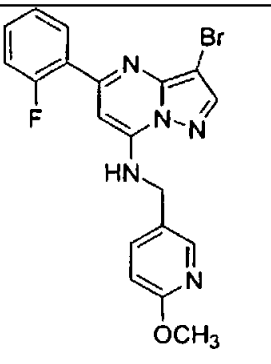
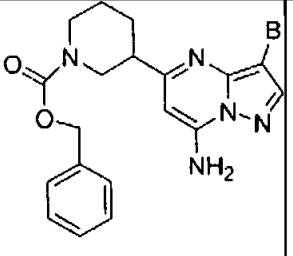
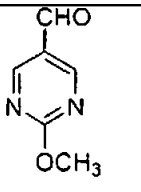
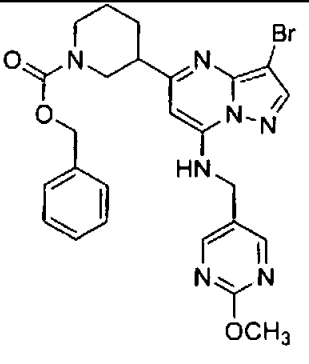
Ej.	Columna 2	Columna 3	Columna 4	Datos
237				LCMS: M^+=381; p.f.: >200°C
238				LCMS: M^+=387; p.f.: °C
239				LCMS: MH^+=413; p.f.: 157-159°C
240				LCMS: $M2H^+$=419; p.f.: 77-79°C

241				LCMS: M2H⁺=385; p.f.: 214-216°C
242				LCMS: MH⁺=; p.f.: °C
243				LCMS: M⁺=416; p.f.: 80-82°C
244				

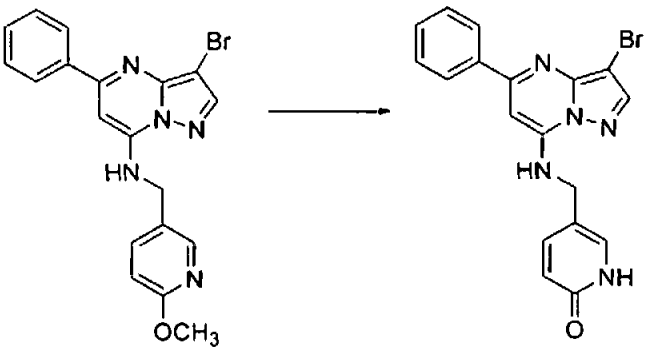
288

245				
246				LCMS: M^+=452; p.f.: 54-56°C
247				LCMS: MH^+= 401; p.f.: >200°C
248				LCMS: $M2H^+$= 474; p.f.: >200.0.°C dec.

249				LCMS: MH^+= 377; p.f.: 65-67°C
250				LCMS: $M2H^+$=421; p.f.: 87-93°C
251				LCMS: MH^+=361; p.f.: >225°C
252				LCMS: MH^+=346; p.f.: 270-271°C

253				LCMS: MH^+=402; p.f.: 250-255°C
254				LCMS: MH^+=416; p.f.: 210-215°C
255				LCMS: MH^+=428; p.f.: 145°C
256				LCMS: MH^+=; p.f.: °C

EJEMPLO 257:

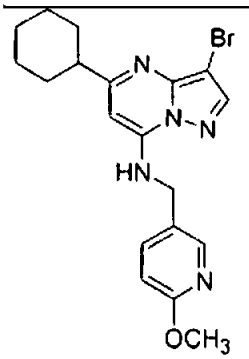
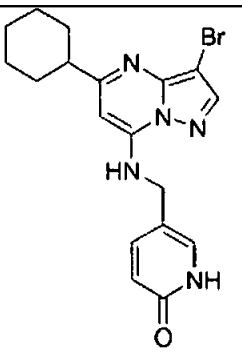


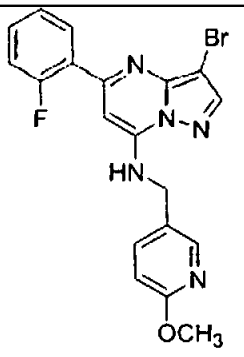
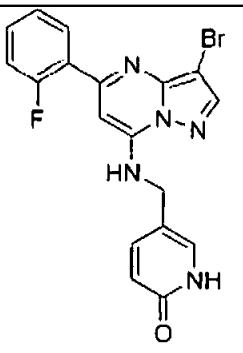
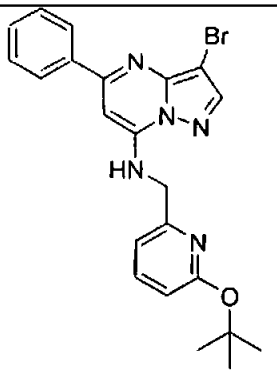
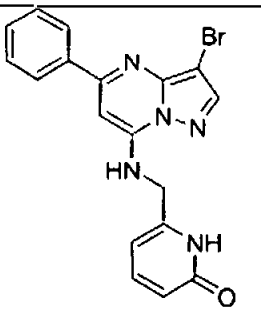
Una mezcla del compuesto preparado en el Ejemplo 242 (100 mg, 0,24 mmoles), HCl acuoso concentrado (1,0 mL) y ácido acético (2,0 mL) se agitaron a 100°C bajo N_2 durante 2 horas, y luego se vertieron sobre Na_2CO_3 (15 g), y se extrajeron con 1:1 de acetona:CH_2Cl_2 (3 x 30 mL). Los extractos combinados se filtraron, y el solvente se evaporó. El residuo se purificó por cromatografía evaporativa usando 10:1 de CH_2Cl_2:MeOH como eluyente para proporcionar un sólido de color amarillo pálido (36 mg, 37%). LCMS: $M2H^+$=398.

EJEMPLOS 258-260:

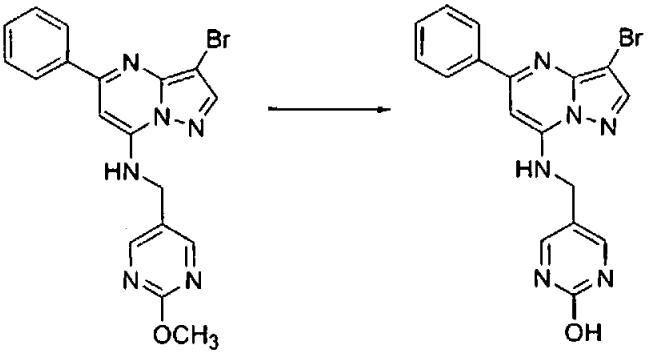
Siguiendo esencialmente el mismo procedimiento indicado en el Ejemplo 257 a partir de los compuestos que se muestran en la Columna 1 de la Tabla 23, se prepararon los compuestos que se muestran en la Columna 2 de la Tabla 23.

TABLA 23

Ej.	Columna 1	Columna 2	Datos
258			LCMS: M^+=402; p.f.=229-231°C

259			LCMS: MH^+=416; p.f.=215-218°C
260			LCMS: $M2H^+$=398; P.f.: >230°C

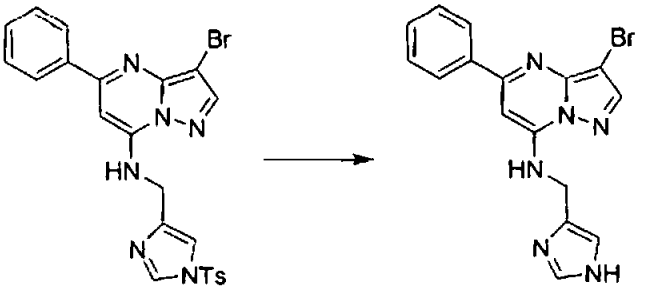
EJEMPLO 261:



A una solución agitada del compuesto preparado en el Ejemplo 239 (41 mg, 0,10 mmoles) en CH_2Cl_2 se agregó M BBr_3 1,0M (0,30 mL, 0,30 mmoles) en CH_2Cl_2 a -78°C. La mezcla se agitó a -78°C durante 5 minutos y luego a 24°C durante 3 horas, y luego se agregó MeOH (2,0 mL) y la mezcla se agitó durante 10 minutos. El solvente se evaporó y el residuo se purificó por cromatografía evaporativa usando 5:1:0.1 CH_2Cl_2:MeOH:NH_4OH conc. como eluyente para proporcionar un sólido blanco (39 mg, 99%). LCMS: M^+=397. P.f.: >230 °C.

249

EJEMPLO 262:

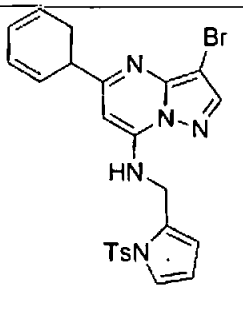
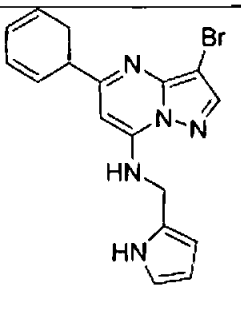


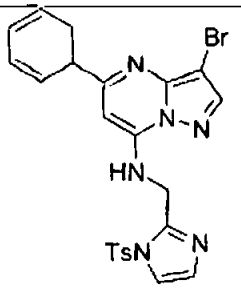
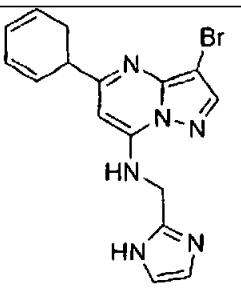
Una mezcla del producto preparado en el Ejemplo 217 (40 mg, 0,077 mmoles) y NaOH acuoso 5,0M (0,8 mL) en MeOH (3,0 mL) se reflujó bajo N_2 durante 1 hora. Se agregó $NaHCO_3$ (700 mg), el solvente se evaporó, y el residuo se purificó por cromatografía evaporativa usando 10:1:0.1 CH_2Cl_2: MeOH:NH_4OH concentrado como eluyente para proporcionar un sólido blanco (10 mg, 35%). LCMS: $M2H^+$=371. P.f.=237-239°C.

EJEMPLOS 263-264:

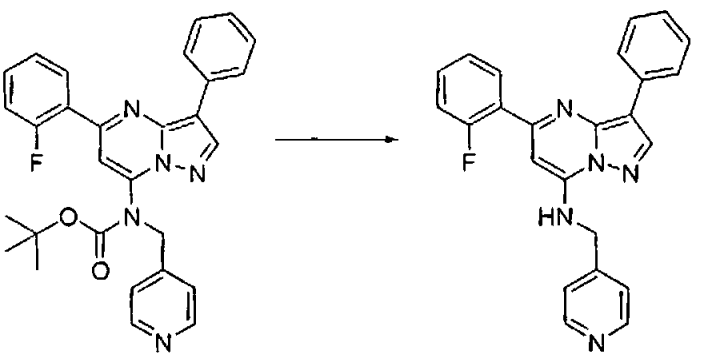
Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo 262 a partir de los compuestos que se muestran en la Columna 1 de la Tabla 24, se prepararon los compuestos que se muestran en la Columna 2 de la Tabla 24.

TABLA 24

Ej.	Columna 1	Columna 2	Datos
263			LCMS: $M2H^+$=370; p.f.=166-168°C

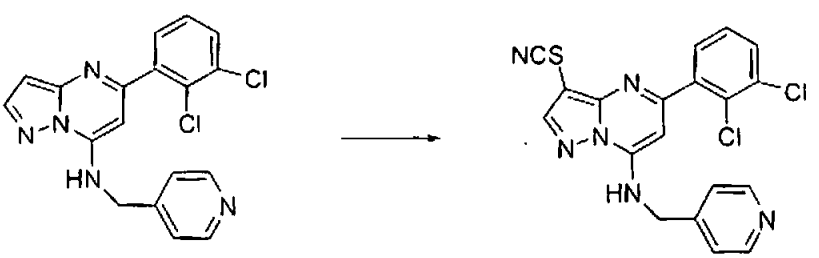
264			LCMS: $M2H^+$=371; p.f.=180-182°C

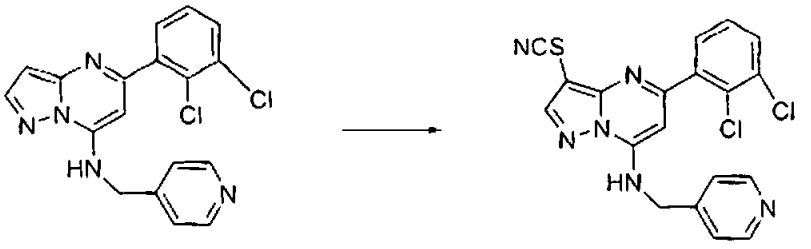
EJEMPLO 265:



Se agregó TFA (0,5 mL) a una solución del compuesto preparado en el Ejemplo Preparativo 197 (0,08 g, 0,16 mmoles) en CH_2Cl_2 (2,0 mL) a 0°C y la solución resultante se agitó durante 2,5 horas y se almacenó a 4°C durante la noche momento en el cual se agregó TFA adicional (0,5 mL). La solución resultante se agitó durante 4 horas y se concentró *al vacío*. El residuo se neutralizó con NaOH 1N y se extrajo con CH_2Cl_2. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por cromatografía evaporativa usando 2,5% (10% de NH_4OH en MeOH) en una solución de CH_2Cl_2 como eluyente (0,009 g, 15% de rendimiento). LCMS: MH^+=396; p.f.= 53-54°C.

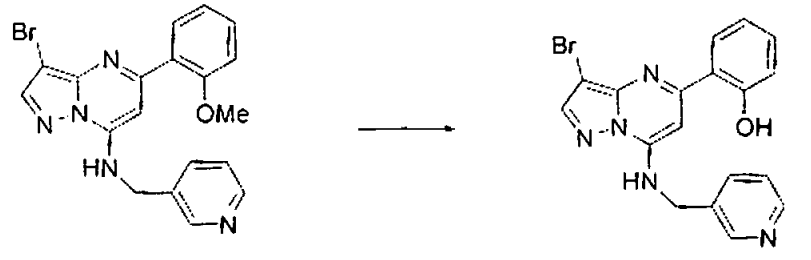
EJEMPLO 266:





Una solución del compuesto preparado en el Ejemplo Preparativo 182 (26 mg, 0,070 mmoles) y tiocianato de potasio (13 mg, 0,14 mmoles) en MeOH (1 mL) se enfrió en un baño de agua fría. A esto se agregó una solución de bromo (22 mg, 0,14 mmoles) en MeOH (0,7 mL) por goteo. La mezcla de reacción resultante se agitó durante 4 horas a temperatura ambiente y los volátiles se removieron bajo presión reducida. El residuo obtenido se suspendió en una pequeña cantidad de CH_2Cl_2. El bromuro de potasio se separó por filtración y se ajusto el pH del filtrado hasta aproximadamente 7 por adición de amoníaco acuoso. Se concentró bajo presión reducida y el aceite residual se purificó por cromatografía de capa delgada preparativa usando 15% de MeOH en CH_2Cl_2 como eluyente (26 mg, 87% de rendimiento). ^1H RMN ($CDCl_3$) δ 8,75 (d, J = 4,2 Hz, 2H), 8,38 (s, 1H), 7,68-7,64 (m, 2H), 7,46-7,39 (m, 3H), 7,22 (t, J = 6,3 Hz, 1H), 6,43 (s, 1H), 4,84 (d, J = 6,3 Hz, 2H); LCMS: MH^+ = 427.

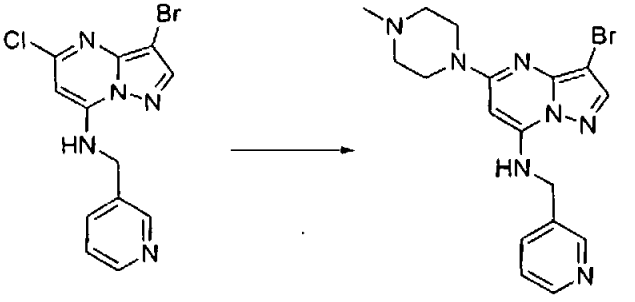
EJEMPLO 267:



Se agregó por goteo tribomuro de boro (1 M en CH_2Cl_2, 0,60 mL, 0,60 mmoles) a una solución agitada enfriada con hielo del compuesto preparado en el Ejemplo 24 (50 mg, 0,12 mmoles) en CH_2Cl_2 (1,5 mL) bajo atmósfera de argón. La mezcla de reacción resultante se agitó a 0°C durante 30 minutos, se dejó calentar a temperatura ambiente y se agitó durante la noche. La mezcla se apagó con

adición de una pequeña cantidad de agua y se extrajo con CH_2Cl_2. La capa orgánica se secó sobre sulfato de magnesio y se concentró *al vacío* (45 mg, 94% de rendimiento). ^{1}H RMN (CD_3OD) δ 9,16 (s, 1H), 8,95 (s, 1H), 8,88 (d, J = 8,1 Hz, 1H), 8,24 (t, J = 6,9 Hz, 1H), 8,18 (s, 1H), 7,95 (d, J = 7,8 Hz, 1H), 7,40 (t, J = 7,8 Hz, 1H), 7,00-6,96 (m, 2H), 6,86 (s, 1H), 5,28 (s, 2H); LCMS: MH^+ = 396.

EJEMPLO 268:

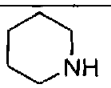
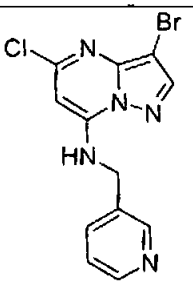
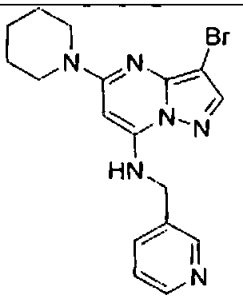
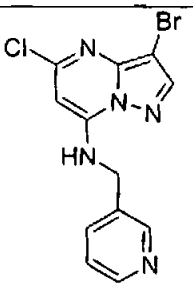
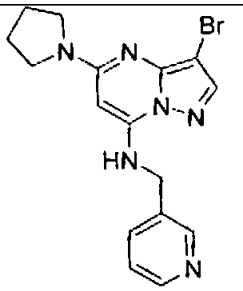
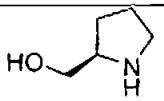
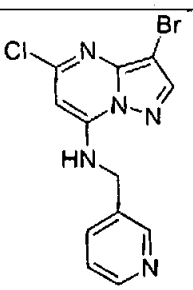
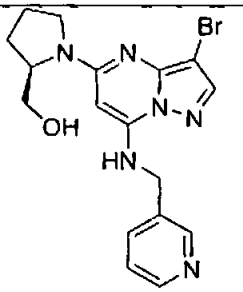
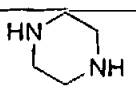
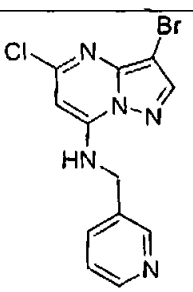
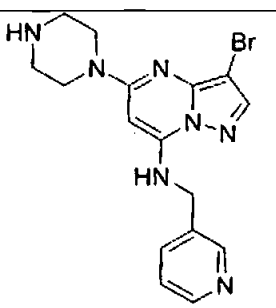


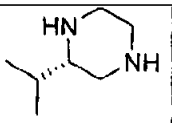
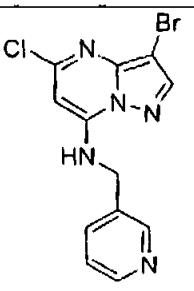
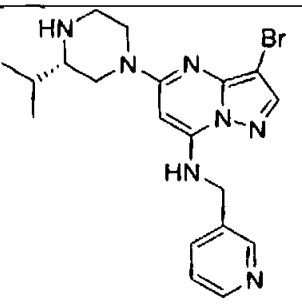
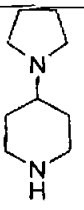
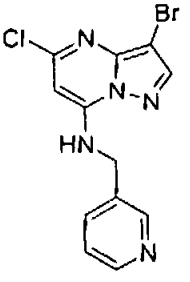
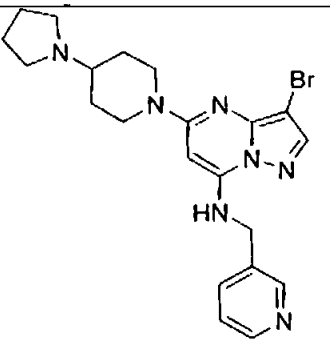
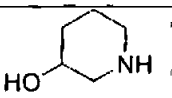
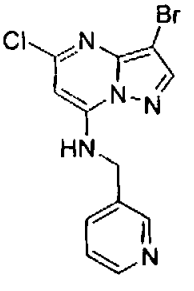
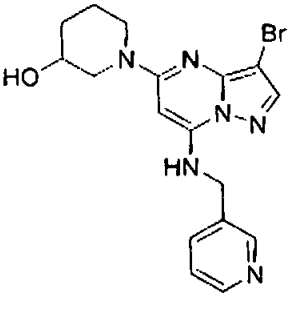
Una solución del compuesto del Ejemplo Preparativo 184 (0,05 g, 0,15 mmoles), N-metilpiperazina (20 µL, 1,2 eq.) y iPr_2Et (52 µL, 2,0 eq.) en dioxano (1 mL) se calentó a 70°C durante la noche. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con H_2O y $NaHCO_3$ saturado. La mezcla resultante se extrajo con CH_2Cl_2, los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por TLC Preparativo usando una solución al 5% (10% NH_4OH en MeOH) en CH_2Cl_2 como eluyente (0,028 g, 47% de rendimiento). EM: MH^+= 402. P.f.: 210°C (desc.)

EJEMPLOS 269-275:

Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo 268, únicamente que se sustituye la amina de la Columna 2 de la Tabla 25 y los cloruros de la Columna 3 de la Tabla 25, se prepararon los compuestos que se muestran en la Columna 4 de la Tabla 25:

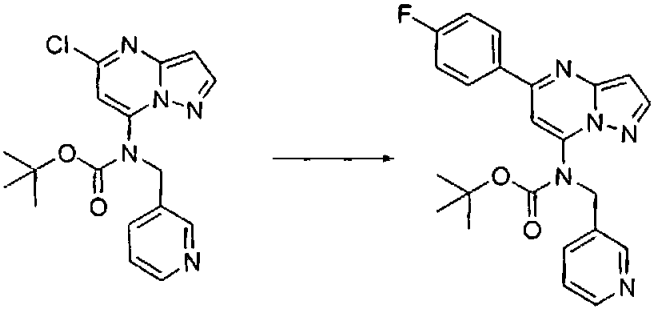
TABLA 25

Ej.	Columna 2	Columna 3	Columna 4	COMP.
269				EM: MH^+ = 387 p.f.: 182 – 183°C
270				EM: MH^+ = 373 p.f.: 190 – 191°C
271				EM: MH^+ = 403 p.f.: 227 – 230°C
272				EM: MH^+ = 388 p.f.: 198 – 201°C

273				EM: MH^+ = 430 p.f.: 100-103°C
274				EM: MH^+ = 456 p.f.: 175 – 178°C
275				EM: MH^+ = 403 p.f.: 218°C

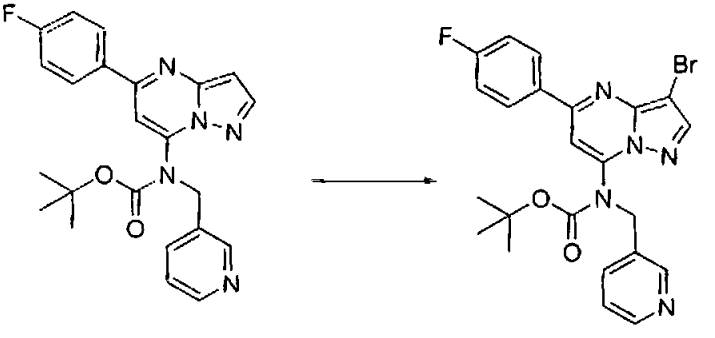
EJEMPLO 276:

Etapa A:



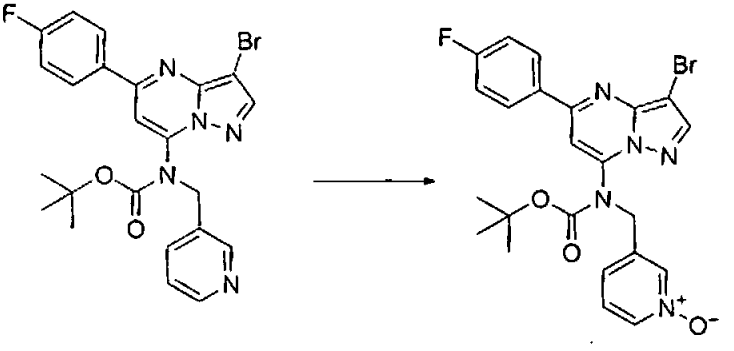
Se agregó bromuro de 4-fluorofenil magnesio (0,68 mL, 1,2 eq.) al compuesto preparado en el Ejemplo Preparativo 193 (0,20 g, 0,55 mmoles) y $PdCl_2(dppf)_2$ (0,037 g, 10 mol%) en THF y la solución resultante se agitó a temperatura ambiente durante 72 horas. La mezcla de reacción se diluyó con NH_4Cl saturado y se extrajo con EtOAc. Los orgánicos combinados se lavaron con NaCl saturado, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El producto crudo se purificó por cromatografía evaporativa usando EtOAc neto como eluyente (0,15 g, 65% de rendimiento). EM: MH^+ = 420.

Etapa B:



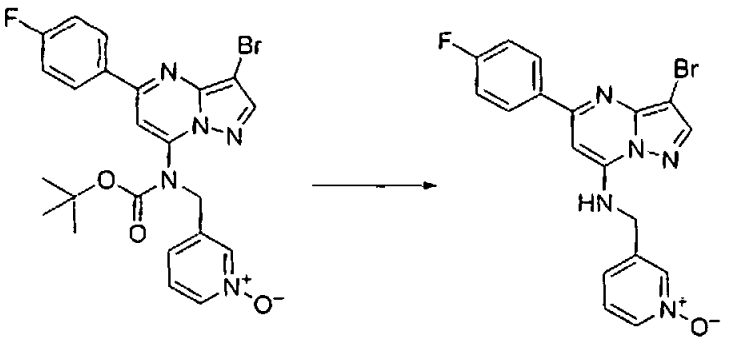
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo Preparativo 127, sustituyente únicamente el compuesto preparado en e Ejemplo 276, Etapa A, se preparó el compuesto anterior (0,17 g, 94% de rendimiento).

Etapa C:



Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo Preparativo 200 sustituyendo únicamente el compuesto preparado en el Ejemplo 276, Etapa B, se preparó el compuesto anterior (0,1 g, 100% de rendimiento).

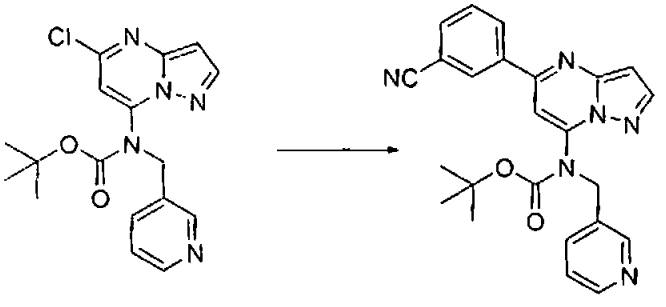
Etapa D:



Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo 265, sustituyendo únicamente el compuesto preparado en el Ejemplo 276, Etapa C, se preparó el compuesto anterior (0,049 g, 62% de rendimiento). EM: MH^+ = 414; p.f.: 110-115°C.

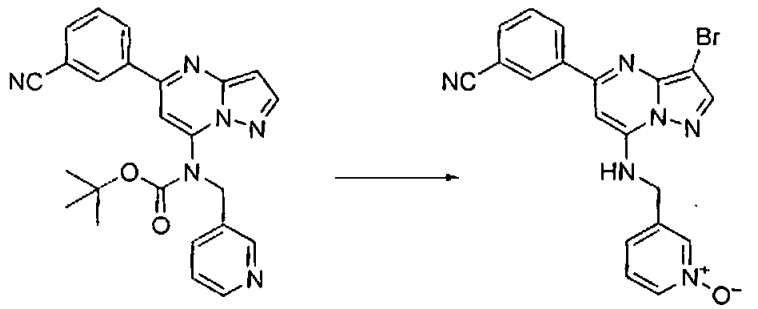
EJEMPLO 277:

Etapa A:



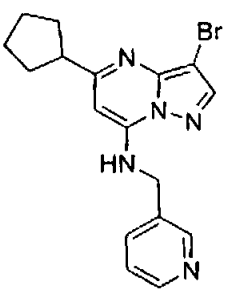
Se agregó $Pd(PPh_3)_4$ (0,065 g, 10 mol%) a yoduro de 3-cianofenil zinc (2,2 mL, solución 0,5 M en THF, 2 eq.) y el compuesto preparado en el Ejemplo Preparativo 193 (0,2 g, 0,56 mmoles) en DMF (2,0 mL) y la solución resultante se calentó a 80°C g durante 144 horas. La mezcla de reacción se enfrió a temperatura ambiente, se diluyó con NH_4Cl saturado y se extrajo con EtOAc. Los orgánicos combinados se lavaron con H_2O y salmuera, se secaron sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por cromatografía evaporativa usando una solución EtOAC neta como eluyente (0,07 g, 29% de rendimiento). EM: MH^+ = 427.

Etapa B hasta Etapa D:



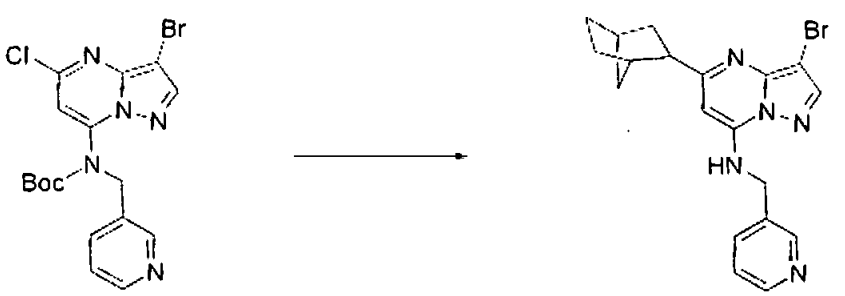
Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo 276, Etapa B hasta Etapa D, se preparó el compuesto anterior (0,023 g, 53% de rendimiento). EM: MH^+ = 421; p.f.: 230°C (desc.)

EJEMPLO 278:



Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo 276 únicamente que se sustituyó el bromuro de ciclopropilmagnesio apropiado en la Etapa A, se preparó el compuesto. EM: MH^+ = 372; p.f.: 96-98°C.

EJEMPLO 279:



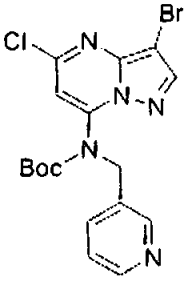
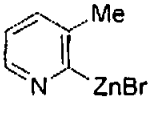
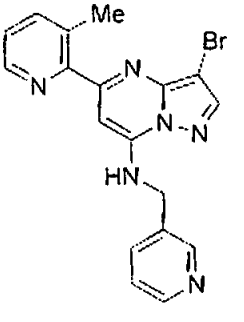
Se llevó a cabo la reacción de acoplamiento cruzado de zinc catalizado por paladio de manera similar al procedimiento descripto en *J. Org. Chem.* (1999), 453. Una solución de la cloropirazolopirimidina (200 mg, 0,458 mmoles),

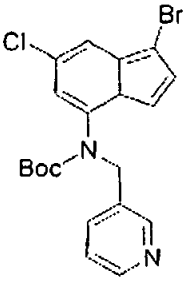
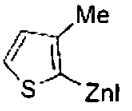
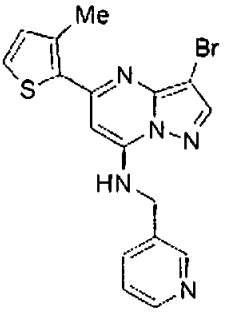
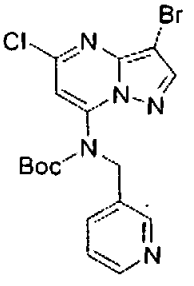
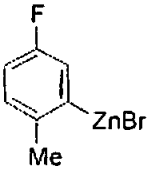
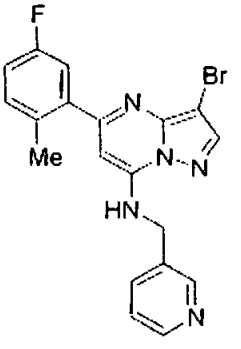
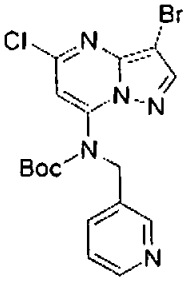
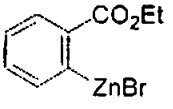
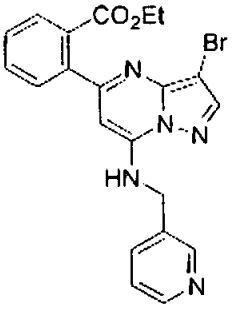
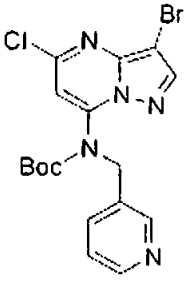
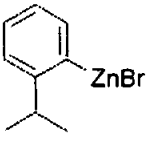
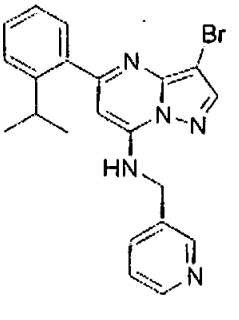
$Pd(PPh_3)_4$ (53 mg, 0,046 mmoles), y bromuro de *exo*-2-norbonilzinc (0,5 M en THF, 0,95 mL, 0,47 mmoles) en DMF (2 mL) se reflujó a 100°C (baño de aceite temp.) durante la noche. La mezcla de reacción se apagó con NH_4Cl medio-saturado y se extrajo con CH_2Cl_2. La fase orgánica se secó sobre $MgSO_4$ y se concentró bajo presión reducida. El residuo se purificó por cromatografía evaporativa usando una solución al 50% de EtOAc en hexanos como eluyente. Una solución del producto *N*-Boc-protegido (121 mg, 53% rendimiento, LCMS: MH^+ = 498) y TFA (1 mL) en CH_2Cl_2 (2 mL) se agitó a temperatura ambiente durante 2 horas. Los volátiles se removieron bajo presión reducida. El residuo se disolvió en CH_2Cl_2, se neutralizó con $NaHCO_3$ saturado, y se extrajo con CH_2Cl_2. La fase orgánica se secó sobre $MgSO_4$ y se concentro *al vacío* (96 mg, 99% de rendimiento). LCMS: MH^+ = 398; ^1H RMN ($CDCl_3$) δ 8,78 (s, 1H), 8,71 (d, J = 4,2 Hz, 1H), 8,04 (d, J = 3,9 Hz, 1H), 7,80 (d, J = 7,8 Hz, 1H), 7,44 (m, 1H), 6,73 (m, 1H), 5,98 (d, J = 7,5 Hz, 1H), 4,74 (d, J = 5,4 Hz, 2H), 3,40-1,00 (m, 11H).

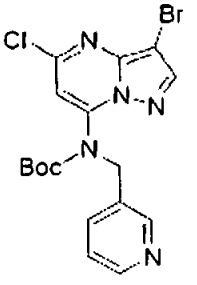
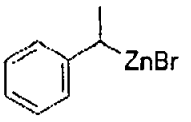
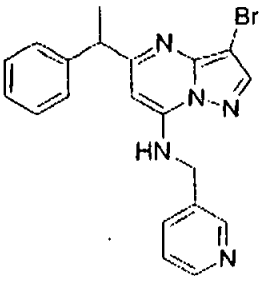
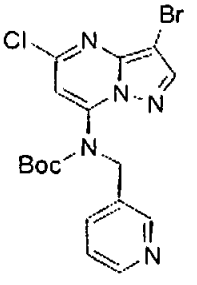
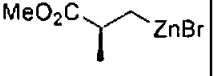
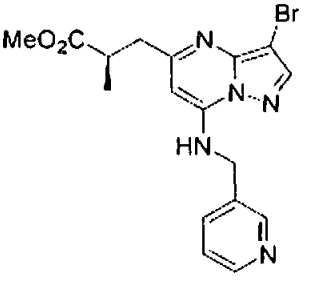
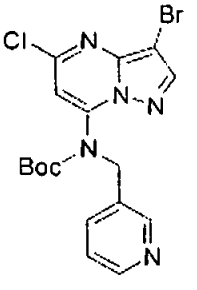
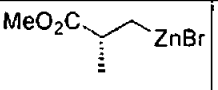
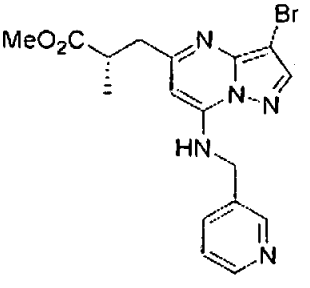
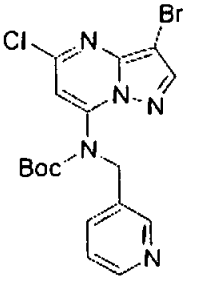
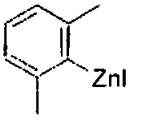
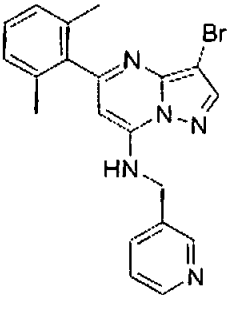
EJEMPLOS 280-294:

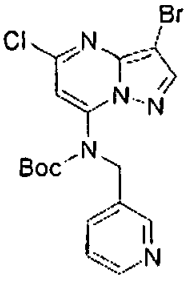
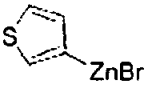
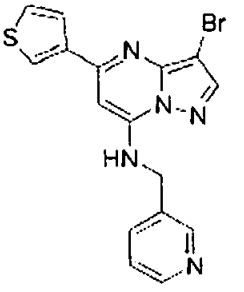
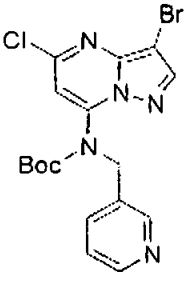
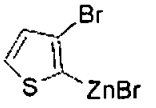
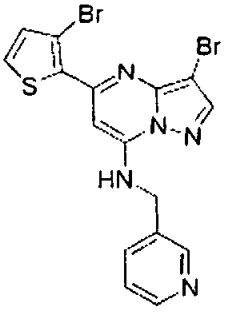
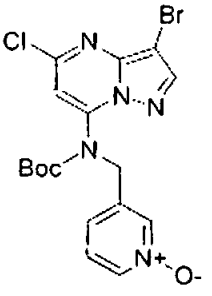
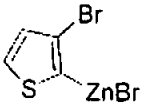
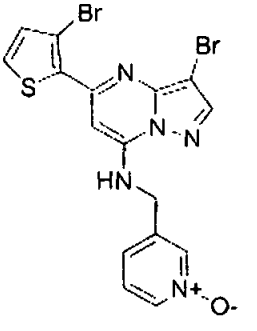
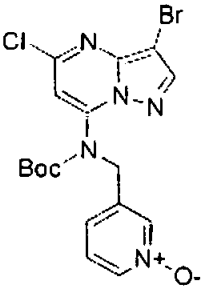
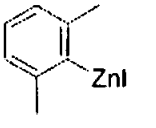
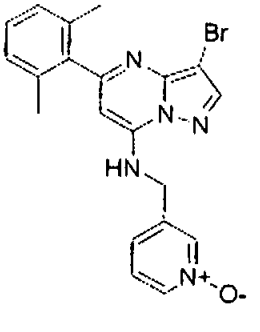
Siguiendo el mismo procedimiento que se indicó en el Ejemplo 279 sustituyendo únicamente los cloruros que se muestran en la Columna 2 de la Tabla 26 y los reactivos de organozinc que se muestran en la Columna 3 de la Tabla 26, se prepararon los compuestos de la Columna 4 de la Tabla 26:

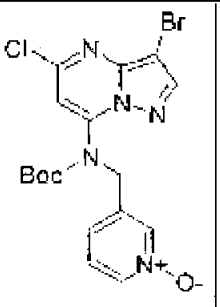
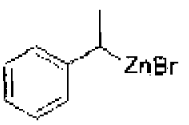
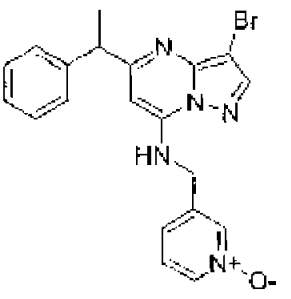
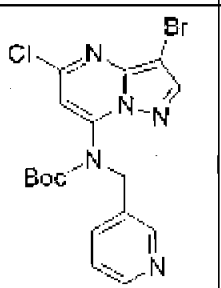
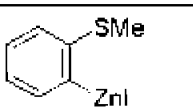
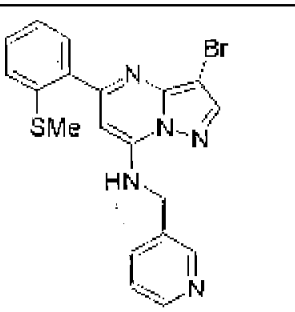
Tabla 26

Ej.	Columna 2	Columna 3	Columna 4	Datos
280				LCMS: MH^+ = 395

281				LCMS: MH^+ = 400
282				LCMS: MH^+ = 412
283				LCMS: MH^+ = 452
284				LCMS: MH^+ = 422

285				LCMS: MH^+ = 408
286				LCMS: MH^+ = 404
287				LCMS: MH^+ = 404
288				LCMS: MH^+ = 408

289				LCMS: MH^+ = 386
290				LCMS: MH^+ = 464
291				LCMS: MH^+ = 480
292				LCMS: MH^+ = 424

293				LCMS: MH^+ = 424
294				LCMS: MH^+ = 426

Los datos adicionales para los compuestos seleccionados se muestran a continuación.

EJEMPLO 280: ^{1}H RMN ($CDCl_3$) δ 8,65 (s, 1H), 8,57 (d, J = 4,2 Hz, 1H), 8,50 (d, J = 4,5 Hz, 1H), 8,01 (s, 1H), 7,69 (d, J = 7,5 Hz, 1H), 7,61 (d, J = 7,8 Hz, 1H), 7,31-7,22 (m, 2H), 6,77 (m, 2H), 4,71 (d, J = 5,4 Hz, 2H), 2,68 (s, 3H).

EJEMPLO 281: ^{1}H RMN ($CDCl_3$) δ 8,80 (s, 1H), 8,72 (d, J = 4,8 Hz, 1H), 8,08 (s, 1H), 7,85-7,40 (m, 3H), 7,02 (d, J = 5,1 Hz, 1H), 6,90 (t, J = 6,0 Hz, 1H), 6,29 (s, 1H), 4,79 (d, J = 6,0 Hz, 2H), 2,61 (s, 3H).

EJEMPLO 282: ^{1}H RMN ($CDCl_3$) δ 8,67 (s, 1H), 8,61 (d, J = 3,9 Hz, 1H), 8,03 (s, 1H), 7,72-7,31 (m, 3H), 7,22-7,00 (m, 2H), 6,81 (t, J = 6,0 Hz, 1H), 6,03 (s, 1H), 4,68 (d, J = 6,0 Hz, 2H), 2,28 (s, 3H).

EJEMPLO 283: ^{1}H RMN ($CDCl_3$) δ 8,68 (s, 1H), 8,63 (d, J = 4,0 Hz, 1H), 8,00 (s, 1H), 7,80-7,72 (m, 2H), 7,54-7,47 (m, 3H), 7,35 (m, 1H), 6,74 (t, J = 6,0 Hz, 1H), 6,19 (s, 1H), 4,67 (d, J = 6,0 Hz, 2H), 4,21 (q, J = 7,2 Hz, 2H), 1,13 (t, J = 7,2 Hz, 3H).

EJEMPLO 284: ^{1}H RMN ($CDCl_3$) δ 7,97 (s, 1H), 7,65 (d, J = 7,2 Hz, 1H), 7,33-7,15 (m, 5H), 6,73 (t, J = 5,4 Hz, 1H), 5,99 (s, 1H), 4,61 (d, J = 5,4 Hz, 2H), 3,09 (sept, J = 6,9 Hz, 1H), 1,11 (d, J = 6,9 Hz, 6H).

EJEMPLO 285: ^{1}H RMN ($CDCl_3$) δ 8,56-8,55 (m, 2H), 7,94 (s, 1H), 7,54 (m, 1H), 7,30-7,22 (m, 6H), 6,59 (t, J = 5,7 Hz, 1H), 5,66 (s, 1H), 4,47 (d, J = 5,7 Hz, 2H), 4,26 (q, J = 7,2 Hz, 1H), 1,68 (d, J = 7,2 Hz, 3H).

EJEMPLO 286: ^{1}H RMN ($CDCl_3$) δ 8,67 (m, 2H), 7,94 (s, 1H), 7,69 (d, J = 7,8 Hz, 1H), 7,34 (m, 1H), 6,63 (t, J = 5,7 Hz, 1H), 5,87 (s, 1H), 4,62 (d, J = 5,7 Hz, 2H), 3,64 (s, 3H), 3,13 (m, 2H), 2,82 (m, 1H), 1,22 (m, 3H).

EJEMPLO 287: ^{1}H RMN ($CDCl_3$) δ 8,66 (m, 2H), 7,94 (s, 1H), 7,68 (d, J = 7,8 Hz, 1H), 7,34 (m, 1H), 6,62 (t, J = 6,0 Hz, 1H), 5,87 (s, 1H), 4,62 (d, J = 6,0 Hz, 2H), 3,64 (s, 3H), 3,13 (m, 2H), 2,81 (m, 1H), 1,22 (m, 3H).

EJEMPLO 288: ^{1}H RMN ($CDCl_3$) δ 8,64 (s, 1H), 8,60 (d, J = 3,6 Hz, 1H), 8,04 (s, 1H), 7,68 (m, 1H), 7,31 (m, 1H), 7,16 (m, 1H), 7,07-7,05 (m, 2H), 6,80 (t, J = 6,3 Hz, 1H), 5,93 (s, 1H), 4,64 (d, J = 6,3 Hz, 2H), 2,08 (s, 6H).

EJEMPLO 289: ^{1}H RMN ($CDCl_3$) δ 8,72 (s, 1H), 8,62 (d, J = 4,8 Hz, 1H), 7,99-7,97 (m, 2H), 7,73-7,69 (m, 2H), 7,40-7,33 (m, 2H), 6,67 (t, J = 6,0 Hz, 1H), 6,29 (s, 1H), 4,71 (d, J = 6,0 Hz, 2H).

EJEMPLO 290: ^{1}H RMN ($CDCl_3$) δ 8,73 (s, 1H), 8,62 (d, J = 4,5 Hz, 1H), 8,01 (s, 1H), 7,76 (m, 1H), 7,41 (d, J = 5,1 Hz, 1H), 7,34 (dd, J = 8,1, 5,1 Hz, 1H), 7,05 (d, J = 5,1 Hz, 1H), 7,01 (s, 1H), 6,79 (t, J = 6,0 Hz, 1H), 4,74 (d, J = 6,0 Hz, 2H).

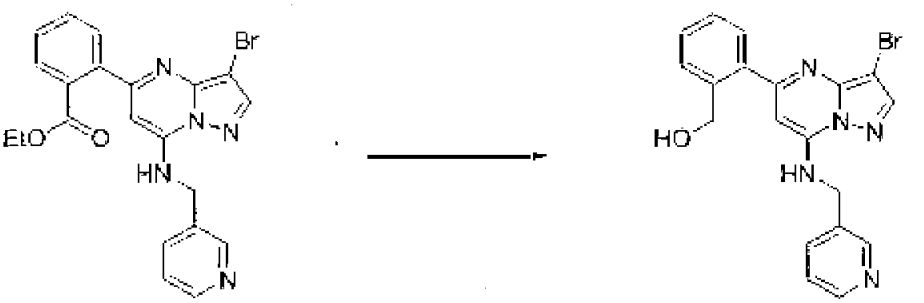
EJEMPLO 291: ^{1}H RMN (DMSO-d_6) δ 9,12 (s, 1H), 8,40 (s, 1H), 8,33 (s, 1H), 8,13 (m, 1H), 7,82 (d, J = 5,1 Hz, 1H), 7,40-7,39 (m, 2H), 7,22 (d, J = 5,1 Hz, 1H), 6,86 (s, 1H), 4,86 (s, 2H).

EJEMPLO 292: ^{1}H RMN ($CDCl_3$) δ 8,23 (s, 1H), 8,16 (d, J = 6,0 Hz, 1H), 8,06 (s, 1H), 7,31-7,05 (m, 5H), 6,86 (m, 1H), 5,87 (s, 1H), 4,62 (d, J = 6,3 Hz, 2H), 2,09 (s, 6H).

EJEMPLO 293: ^{1}H RMN ($CDCl_3$) δ 8,14 (s, 1H), 8,12 (d, J = 6,3 Hz, 1H), 7,94 (s, 1H), 7,29-7,16 (m, 6H), 7,07 (m, 1H), 6,78 (t, J = 6,0 Hz, 1H), 5,54 (s, 1H), 4,44 (d, J = 6,0 Hz, 2H), 4,24 (t, J = 7,2 Hz, 1H), 1,68 (d, J = 7,2 Hz, 3H).

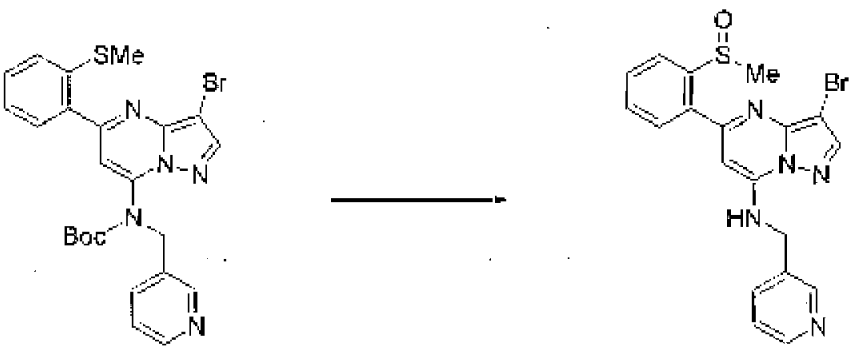
EJEMPLO 294: ^{1}H RMN ($CDCl_3$) δ 8,67 (s, 1H), 8,59 (d, J = 4,8 Hz, 1H), 8,01 (s, 1H), 7,71 (m, 1H), 7,52 (dd, J = 7,8, 1,8 Hz, 1H), 7,40-7,19 (m, 4H), 6,78 (t, J = 6,0 Hz, 1H), 6,32 (s, 1H), 4,67 (d, J = 6,0 Hz, 2H), 2,38 (s, 3H).

EJEMPLO 295:



A una suspensión de hidruro de litio aluminio (10 mg, 0,26 mmoles) en THF anhidro (2 mL) a 0°C se agregó por goteo una solución del compuesto preparado en el Ejemplo 283 (20 mg, 0,044 mmoles) en THF anhidro (2 mL). La mezcla resultante se reflujó durante 1 hora y se agitó a temperatura ambiente durante la noche, se neutralizó con ácido sulfúrico diluido y se extrajo con EtOAc. La fase orgánica se secó sobre $MgSO_4$ y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía de capa delgada preparativa usando MeOH al 5% en solución de EtOAc como eluyente (15 mg, 83% de rendimiento). LCMS: MH^+ = 410; ^{1}H RMN ($CDCl_3$) δ 8,69 (s, 1H), 8,61 (d, J = 3,9 Hz, 1H), 8,05 (d, J = 2,1 Hz, 1H), 7,74 (d, J = 7,8 Hz, 1H), 7,52-7,31 (m, 5H), 6,97 (t, J = 6,3 Hz, 1H), 6,55 (d, J = 2,7 Hz, 1H), 6,20 (s, 1H), 4,71 (d, J = 6,3 Hz, 2H), 4,52 (s, 2H).

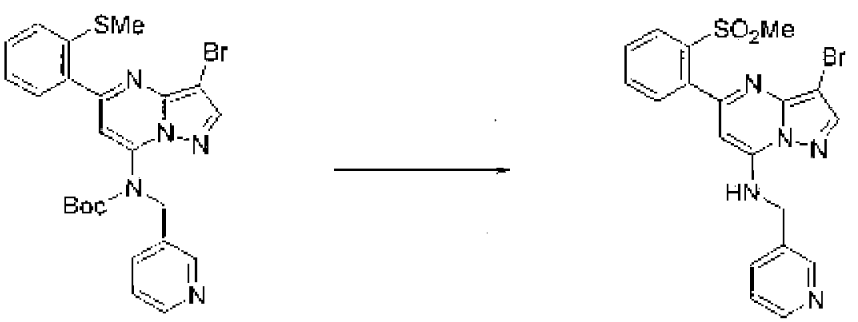
EJEMPLO 296:



808

A una solución del compuesto *N*-Boc-protegido preparado en el Ejemplo 294 (45 mg, 0,085 mmoles) en CH_2Cl_2 (4 mL) a –50°C se agregó *m*-CPBA (18 mg, 0,10 mmoles). Después de agitar durante 1 hora a –50°C se agregó más *m*-CPBA (4 mg, 0,02 mmoles). La mezcla se agitó durante 2 horas más, se diluyó con CH_2Cl_2 (20 mL), y se lavó con $NaHCO_3$ saturado (20 mL). La fase orgánica se secó sobre $MgSO_4$ y se concentró bajo presión reducida. El residuo se purificó por cromatografía de capa delgada preparativa usando 2,5% de MeOH en solución de CH_2Cl_2 como eluyente. Una solución del producto *N*-Boc-protegido (37 mg, 80% de rendimiento, LCMS: MH^+ = 542) y TFA (1 mL) en CH_2Cl_2 (2 mL) se agitó a temperatura ambiente durante 2 horas. Los volátiles se removieron bajo presión reducida. El residuo se disolvió en CH_2Cl_2, se neutralizó con $NaHCO_3$ saturado, y se extrajo con CH_2Cl_2. La fase orgánica se secó sobre $MgSO_4$ y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía de capa delgada preparativa usando una solución al 5% de MeOH en EtOAc como eluyente (26 mg, 89% de rendimiento). LCMS: MH^+ = 442; ^1H RMN ($CDCl_3$) δ 8,71 (s, 1H), 8,64 (d, J = 3,9 Hz, 1H), 8,41 (m, 1H), 8,03 (s, 1H), 7,75-7,54 (m, 4H), 7,36 (dd, J = 8,1, 5,1 Hz, 1H), 6,81 (t, J = 6,0 Hz, 1H), 6,34 (s, 1H), 4,74 (d, J = 6,0 Hz, 2H), 3,25 (s, 3H).

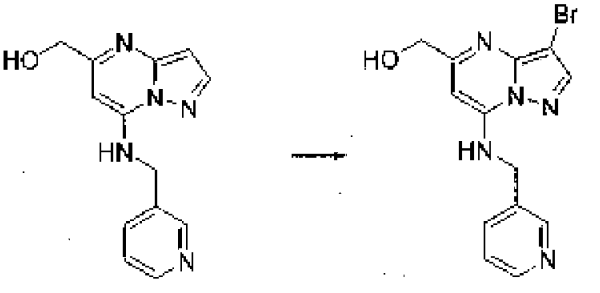
EJEMPLO 297:



A una solución del compuesto *N*-Boc-protegido preparado en el Ejemplo 294 (56 mg, 0,11 mmoles) en CH_2Cl_2 (4 mL) a 0°C se agregó *m*-CPBA (42 mg, 0,24 mmoles). Después de agitar durante 2 horas a temperatura ambiente se agregó más *m*-CPBA (13 mg, 0,075 mmoles). La mezcla se agitó a temperatura ambiente durante la noche, se diluyó con CH_2Cl_2 (20 mL), y se lavó con $NaHCO_3$ saturado (20 mL). La fase orgánica se secó sobre $MgSO_4$ y se concentró bajo presión reducida. El residuo se purificó por cromatografía de capa delgada

preparativa usando una solución al 2,5% de MeOH en EtOAc como eluyente. Una solución del producto *N*-Boc-protegido (29 mg, 49% de rendimiento, LCMS: MH^+ = 558) y TFA (1 mL) en CH_2Cl_2 (2 mL) se agitó a temperatura ambiente durante 2 horas. Los volátiles se removieron bajo presión reducida. El residuo se disolvió en CH_2Cl_2, se neutralizó con $NaHCO_3$ saturado, y se extrajo con CH_2Cl_2. La fase orgánica se secó sobre $MgSO_4$ y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía de capa delgada preparativa usando una solución al 2,5% de MeOH en EtOAc como eluyente (21 mg, 90% de rendimiento). LCMS: MH^+ = 458; ^1H RMN ($CDCl_3$) δ 8,64 (s, 2H), 8,20 (m, 1H), 8,01 (s, 1H), 7,73-7,60 (m, 3H), 7,46 (m, 1H), 7,35 (s, 1H), 6,82 (t, J = 5,9 Hz, 1H), 6,17 (s, 1H), 4,65 (d, J = 5,7 Hz, 2H), 3,60 (s, 3H).

EJEMPLO 298

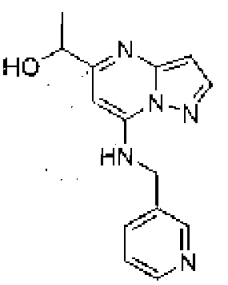
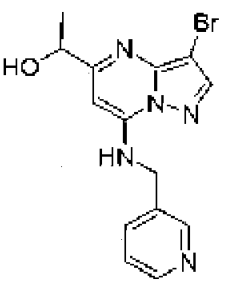
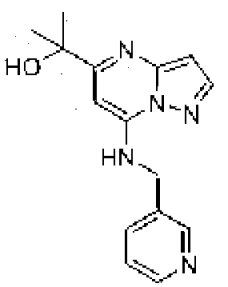
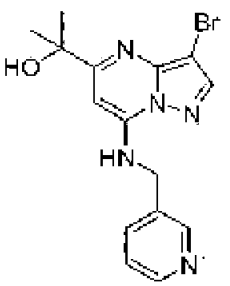


Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo Preparativo 127 sustituyendo únicamente el compuesto preparado en el Ejemplo Preparativo 189, se preparó el compuesto anterior. EM: MH^+ = 334; p.f.: 170-173°C.

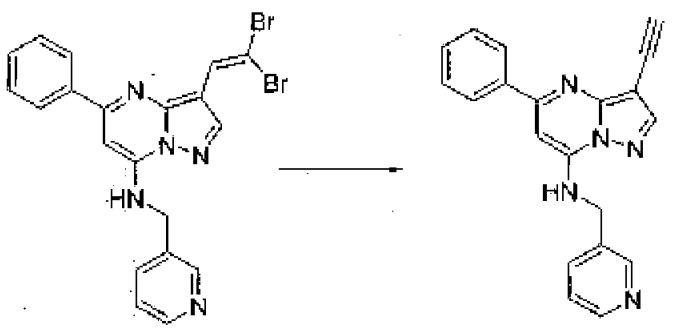
Ejemplos 299-300:

Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo 298, sustituyendo únicamente el compuesto que se muestra en la Tabla 27, Columna 2, se prepararon los compuestos que se muestran en la Tabla 27, Columna 3:

Tabla 27

Ej.	Columna 2	Columna 3	COMP.
299			EM: MH^+ = 348 p.f.: 73 – 83°C
300			EM: MH^+ = 362 p.f.: 165 – 175°C

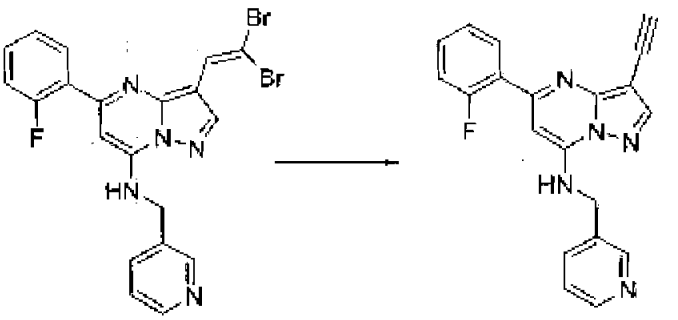
EJEMPLO 301:



A una solución del compuesto preparado en el Ejemplo Preparativo 186 (0,1 g, 0,21 mmoles) en THF (4,0 mL) a -78°C se agregó nBuLi (0,57 mL, 2,16M en hexanos, 5,0 eq.) a -78°C. La mezcla de reacción se agitó durante 2 horas a -78°C, se apagó con H_2O, se calentó a temperatura ambiente y se extrajo con EtOAc. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por TLC

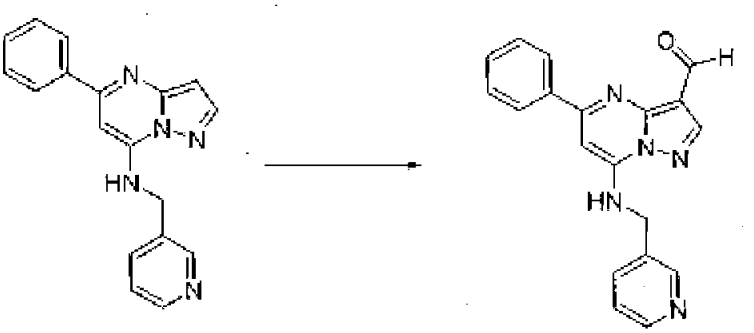
Preparativo usando una solución al 2,5% (10%NH_4OH en CH_3OH) en CH_2Cl_2 como eluyente (0,013 g, 20% de rendimiento). EM: MH^+ = 326; p.f.: 71-72°C.

EJEMPLO 302:



Siguiendo esencialmente el mismo procedimiento indicado en el Ejemplo 301 sustituyendo únicamente el compuesto del Ejemplo Preparativo 187, se preparó el compuesto anterior (0,049 g, 68% de rendimiento). EM: MH^+ = 344; p.f.: 69-71°C.

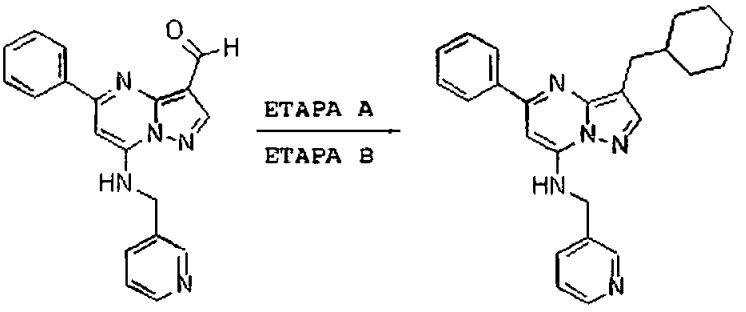
EJEMPLO 303:



A una solución del aducto 3-H del Ejemplo Preparativo 187,1 (0,70 g, 2,32 mmoles) en DMF (4,2 mL) a 0°C se agregó $POCl_3$ (0,67 mL, 7,2 mmoles) por goteo. La mezcla se agitó durante 14 horas a temperatura ambiente, se enfrío a 0°C, y se apagó por adición de hielo. Se agregó cuidadosamente NaOH 1N para ajustar el pH a 8 y la mezcla se extrajo con CH_2Cl_2 (3 x 25 mL). Las capas orgánicas se combinaron, se secaron (Na_2SO_4), se filtraron, y se concentraron bajo presión reducida. El producto crudo se recristalizó a partir de EtOAc para proporcionar 0,43 g (56%) de un sólido de color amarillo. P.f.: 181-183°C; M+H = 330.

216

EJEMPLO 304:



ETAPA A:

A una solución de aldehído (100 mg, 0,30 mmoles) del Ejemplo 303 en THF (1 mL) a 0°C se agregó bromuro de ciclohexil magnesio (0,46 mL, 2,0M en Et_2O) por goteo en 5 minutos. La mezcla resultante se agitó a 0°C durante 2 horas y a temperatura ambiente durante 12 horas. La mezcla se enfrió a 0°C y luego se trató con NH_4Cl acuoso saturado (3 mL) y CH_2Cl_2 (5 mL). Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (2 x 5 mL). Las capas orgánicas se combinaron, se lavaron con salmuera (1 x 5 mL), se secaron (Na_2SO_4), se filtraron y se concentraron bajo presión reducida para proporcionar 110 mg (89%) de un semisólido de color amarillo claro. M+H = 414. Este material se llevó en crudo a la Etapa B sin purificación adicional.

ETAPA B:

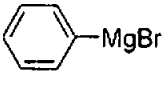
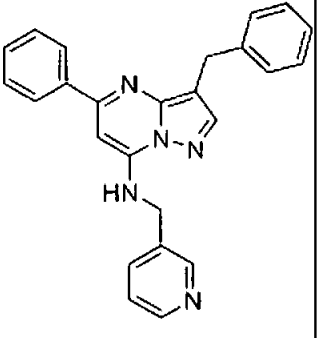
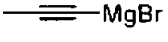
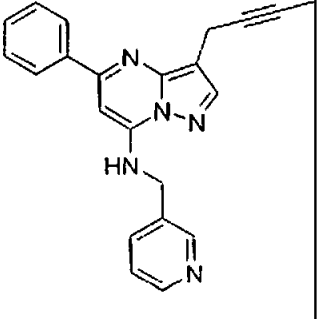
A una solución de alcohol (53 mg, 0,13 mmoles) en CH_2Cl_2 (0,5 mL) a 0°C se agregó Et_3SiH (24 µL, 0,15 mmoles) seguido de TFA (24 µL, 0,30 mmoles). La mezcla se agitó durante 2 horas a 0°C y a temperatura ambiente durante 2 horas después de lo cual se agregaron porciones adicionales de Et_3SiH (24 µL, 0,15 mmoles) y TFA (24 µL, 0,30 mmoles) y la mezcla se agitó durante 3 horas a temperatura ambiente (hasta completarla por TLC). La mezcla se concentró bajo presión reducida y el residuo crudo se dividió entre CH_2Cl_2 (5 mL) y $NaHCO_3$ acuoso saturado (2,5 mL). Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (2 x 5 mL). Las capas orgánicas se combinaron, se lavaron con salmuera (1 x 5 mL), se secaron (Na_2SO4), se filtraron y se concentraron bajo

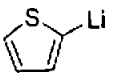
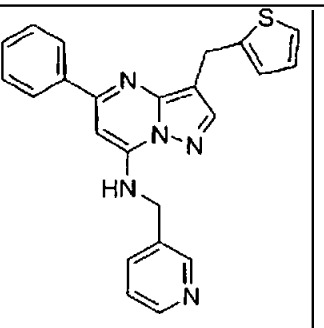
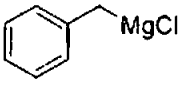
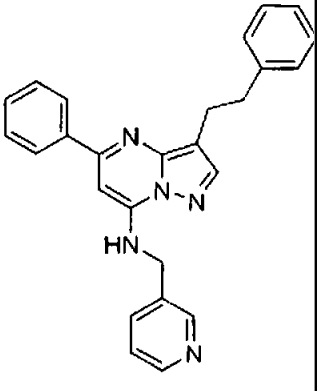
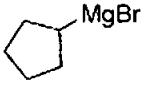
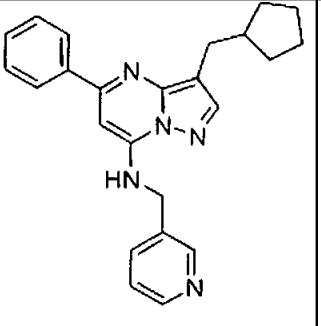
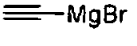
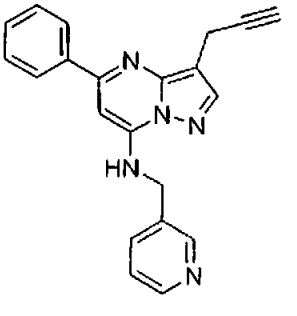
presión reducida. El producto crudo se purificó por TLC Preparativo (8 x 1000 mM) eluyendo con CH_2Cl_2/MeOH (22:1) para proporcionar 29 mg (56%) de un semisólido amarillo. M+H = 398.

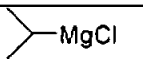
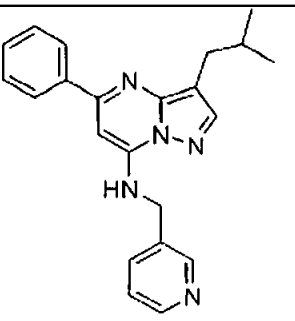
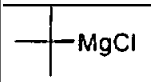
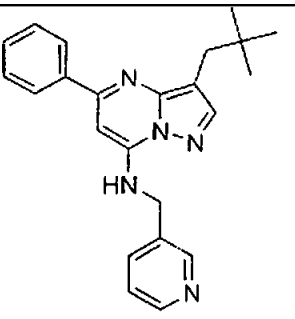
EJEMPLOS 305-312:

Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo 304, utilizando el aldehído del Ejemplo 303 y sustituyendo los reactivos de Grignard o de organolitio que se muestran en la Columna 2 de la Tabla 28, se prepararon los compuestos de la Columna 3 de la Tabla 28:

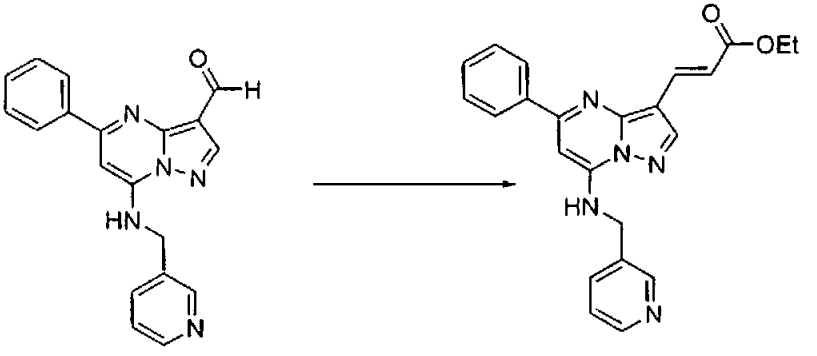
TABLA 28

Ej.	Columna 2 (Organométalica)	Columna 3 (Estructura final)	COMP. 1. p.f.: (°C) 2. M+H
305			1. aceite amarillo 2. M+H = 392
306			1. aceite rojo 2. M+H = 353

307			1. aceite rojo 2. M+H = 398
308			1. aceite amarillo 2. M+H = 406
309			1. semisólido amarillo 2. M+H = 384
310			1. semisólido 2. M+H = 340

311			1. P.f.: 141-143 2. M+H = 358
312			1. P.f.: 148-150 2. M+H = 372

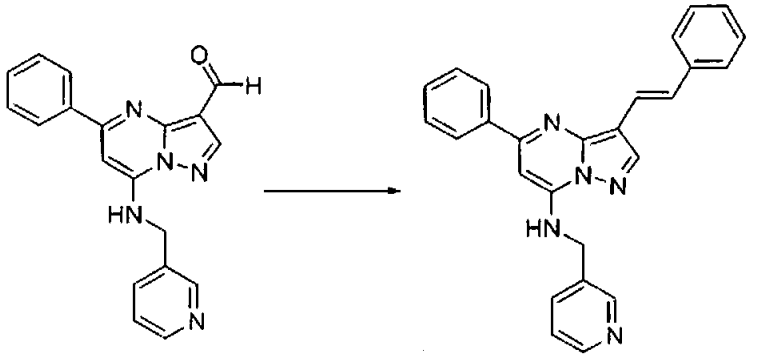
EJEMPLO 313:



A una solución de aldehído (81 mg, 0,25 mmoles) del Ejemplo 303 en benceno (2,5 mL) se agregó carboetoximetilentrifenilfosforano (0,12 g, 0,33 mmoles) en una porción. La mezcla se calentó a reflujo durante 24 horas, se enfrío a temperatura ambiente y se concentró bajo presión reducida. La mezcla de CH_2Cl_2 diluido (5 mL), se agregó salmuera (2 mL), y las capas se separaron. La capa acuosa se extrajo con CH_2Cl_2 (2 x 4 mL). Las capas orgánicas se combinaron, se secaron (Na_2SO_4), se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por TLC Preparativo (8 x 1000 μM)

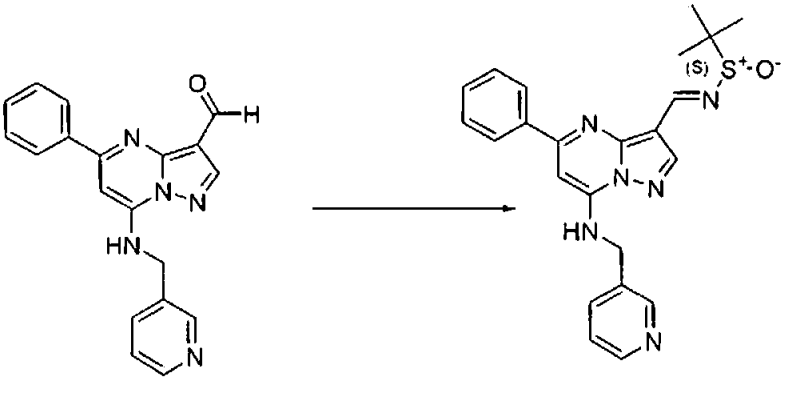
eluyendo con CH_2Cl_2/MeOH (20:1) para proporcionar 98 mg (100%) de un sólido blanco. P.f.: 151-153°C; M+H = 400.

EJEMPLO 314:



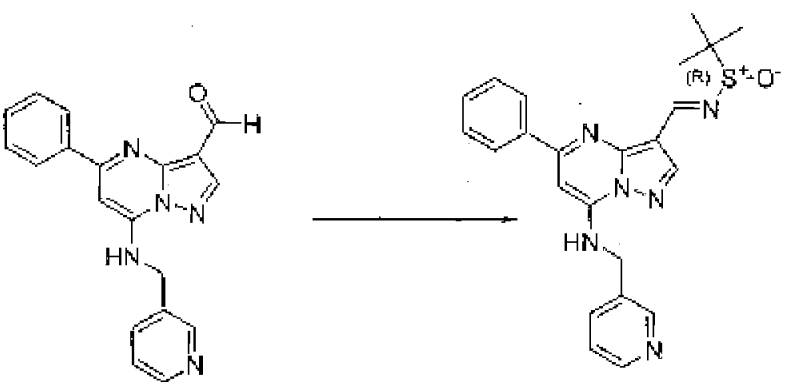
A una mezcla de bromuro de benciltrifenilfosfonio (0,59 g, 1,37 mmoles) en THF (3 mL) se agregó NaH (55 mg, 1,37 mmoles) y la mezcla se agitó durante 30 minutos. El aldehído (0,15 g, 0,46 mmoles) del Ejemplo 303 se agregó en una sola porción y la mezcla se calentó a reflujo durante 36 horas. La mezcla se enfrió a temperatura ambiente y se concentró bajo presión reducida. La mezcla era de CH_2Cl_2 diluido (5 mL), se agregó salmuera (2 mL), y las capas se separaron. La capa acuosa se extrajo con CH_2Cl_2 (2 x 4 mL). Las capas orgánicas se combinaron, se secaron (Na_2SO_4), se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por TLC Preparativo (8 x 1000 μM) eluyendo con CH_2Cl_2/MeOH (20:1) para proporcionar 58 mg (32%) de un sólido de color amarillo. P.f.: 138-141°C; M+H = 404.

EJEMPLO 315:



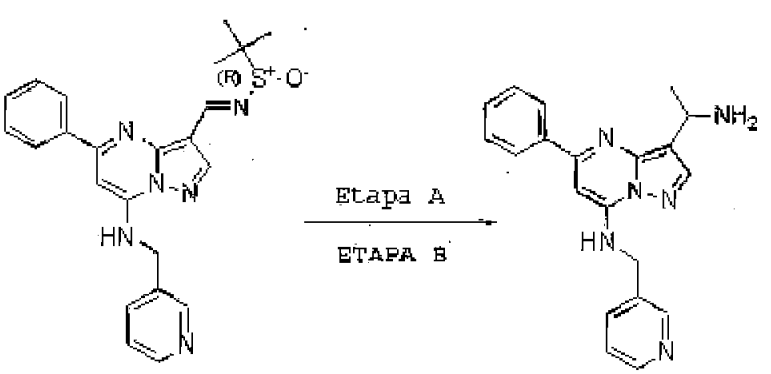
A una solución de aldehído (0,20 g, 0,60 mmoles) del Ejemplo 303 en THF (3 mL) se agregó Ti (i-OPr)$_4$ (0,36 mL, 1.21 mmoles) por goteo seguido de adición de (*S*)-(-)-2-metil-2-propansulfinamida (74 mg, 0,61 mmoles). La mezcla resultante se agitó durante 18 horas a reflujo, se enfrío a temperatura ambiente, y se apagó con salmuera (2 mL). La mezcla se filtró a través de una almohadilla de Celite la cual se lavó con EtOAc (2 x 2 mL). Las capas se separaron y la capa acuosa se extrajo con EtOAc (2 x 4 mL). Las capas orgánicas se combinaron, se secaron (Na_2SO_4), se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por TLC Preparativo (8 x 1000 μM) eluyendo con CH_2Cl_2/MeOH (20:1) para proporcionar 0,21 g (80%) de un sólido de color amarillo. P.f.: 108-110°C; M+H = 433.

EJEMPLO 316:



Se preparó de la misma manera que el Ejemplo 315, excepto que se sustituyó (*R*)-(-)-2-metil-2-propansulfinamida para proporcionar 0,25 g (94%) en forma de un sólido de color amarillo. P.f.: 107-109°C; M+H = 433.

EJEMPLO 317:



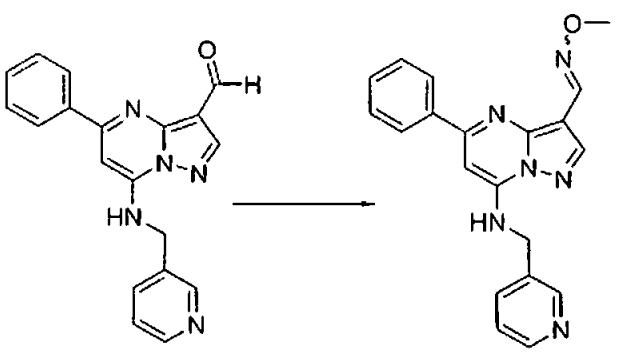
ETAPA A:

A una solución de sulfinimina (50 mg, 0,12 mmoles) del Ejemplo 316 en CH_2Cl_2 (2,5 mL) a -40 °C se agregó MeMgBr (96 mL, 0,29 mmoles) por goteo. La mezcla se agitó durante 5 horas a -40°C y se agitó a temperatura ambiente durante 12 horas. Una porción adicional de MeMgBr (96 mL, 0,29 mmoles) y la mezcla se agitaron durante 12 horas. Se agregó NH_4Cl acuoso saturado (2 mL) y la mezcla se extrajo con EtOAc (3 x 4 mL). Las capas orgánicas se combinaron, se secaron (Na_2SO_4), se filtraron, y se concentraron bajo presión reducida para proporcionar 30 mg (58%) de un residuo crudo. Este material se recogió en la etapa siguiente sin purificación.

ETAPA B:

Al material crudo de la Etapa A (30 mg, 0,067 mmoles) en MeOH (2 mL) se le agregó HCl concentrado (2 mL). La mezcla se agitó a temperatura ambiente durante 12 horas y luego la mezcla se concentró hasta sequedad. El material crudo se dividió entre CH_2Cl_2 (3 mL) y $NaHCO_3$ acuoso saturado (2 mL) y las capas se separaron. La capa acuosa se extrajo con CH_2Cl_2 (2 x 3 mL) y las capas orgánicas se combinaron. La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida para proporcionar 6 mg (24%) del compuesto del título en forma de un sólido de color amarillo claro. P.f.: 100-102 °C; M + H = 345.

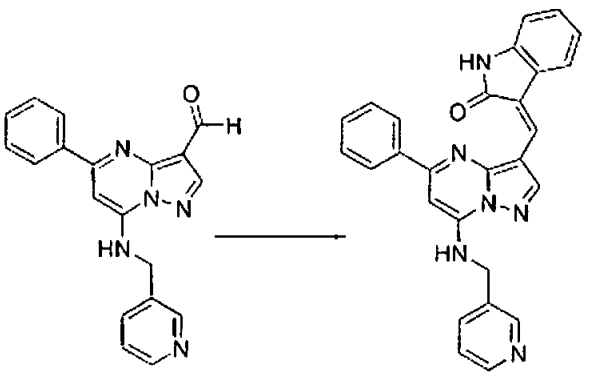
EJEMPLO 318:



A una solución de aldehído (75 mg, 0,23 mmoles) del Ejemplo 300 en THF/CH_2Cl_2 (5 mL/1 mL) a temperatura ambiente se agregó $MeONH_2$·HCl (38 mg, 0,46 mmoles) seguido de adición por goteo de piridina (46 µL, 0,57 mmoles). La

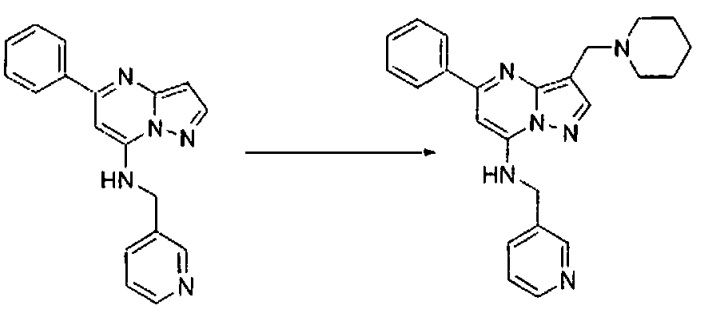
mezcla se agitó durante 72 horas a temperatura ambiente después de lo cual la mezcla se concentró hasta sequedad. El material crudo se dividió entre CH_2Cl_2 (3 mL) y $NaHCO_3$ acuoso saturado (2 mL) y las capas se separaron. La capa acuosa se extrajo con CH_2Cl_2 (2 x 3 mL) y las capas orgánicas se combinaron. La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida. El producto crudo se purificó por TLC Preparativo (3 x 1000 μM) eluyendo con CH_2Cl_2/MeOH (22:1) para proporcionar 90 mg (100%) de un sólido de color amarillo claro. P.f.: 173-175 °C; M + H = 359.

EJEMPLO 319:



A una solución de aldehído (60 mg, 0,18 mmoles) del Ejemplo 303 a EtOH (2,5 mL) se agregó oxindol (48 mg, 0,37 mmoles) seguido de piperidina (3 gotas). La mezcla se calentó a reflujo durante 14 horas y luego la mezcla se enfrío a temperatura ambiente. El precipitado resultante se filtró y lavó con EtOH (2 x 2 mL). El producto se secó bajo alto vacío para proporcionar 81 mg (100%) del compuesto del título en forma de un sólido de color anaranjado/castaño. P.f.: 182-185°C; M+H = 445.

EJEMPLO 320:



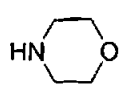
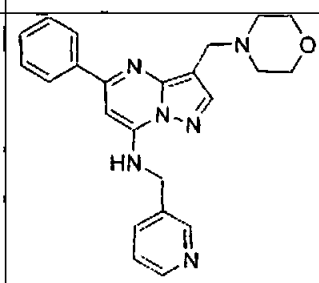
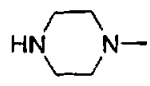
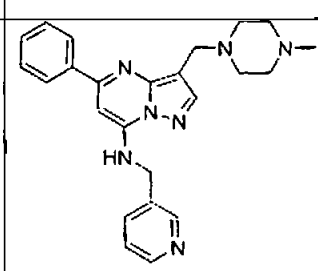
926

A una solución del análogo 3-H (106 mg, 0,35 mmoles) del Ejemplo Preparativo 187,10 en AcOH (2 mL) se agregó formaldehído acuoso al 37% (1,5 ml; 1,40 mmoles) seguido de piperidina (100 µL; 0,37 mmoles). La mezcla resultante se agitó a temperatura ambiente durante 24 horas y se removió el AcOH bajo presión reducida. La mezcla se diluyó con agua (2 mL) y se neutralizó con NaOH 2M hasta pH = 8. La capa acuosa se extrajo con CH_2Cl_2 (3 x 7 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 se concentró bajo presión reducida para proporcionar 96 mg (69%) de un sólido blancuzco. P.f.: 88-90°C; M+H 399.

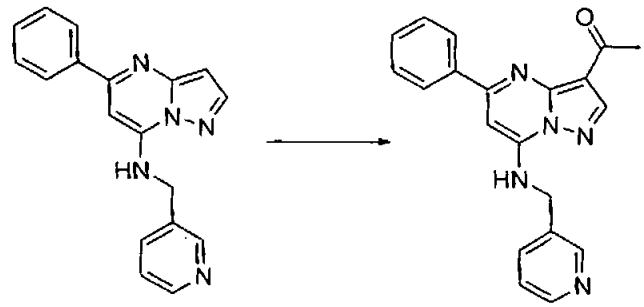
EJEMPLOS 321-322:

Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo 320 sustituyendo únicamente las aminas de la Columna 2 de la Tabla 29 y empleando el aducto 3-H del Ejemplo Preparativo 187.10, se prepararon los compuestos en la Columna 3 de la Tabla 29:

TABLA 29

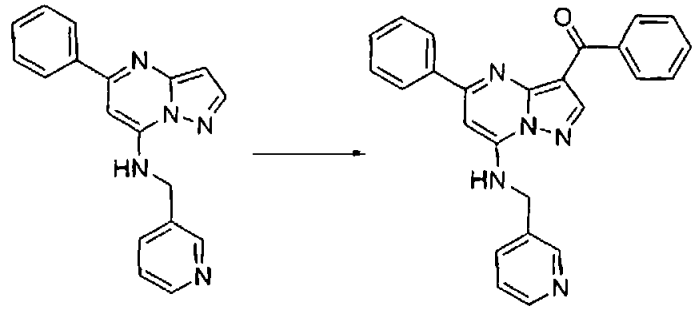
Ej.	Columna 2 (Amina)	Columna 3 (Estructura Final)	COMP. 1. P.f.: (°C) 2. M+H
321			1. P.f.: 178-180 2. M+H = 401
322			1. P.f.: 102-104 2. M+H = 414

EJEMPLO 323:



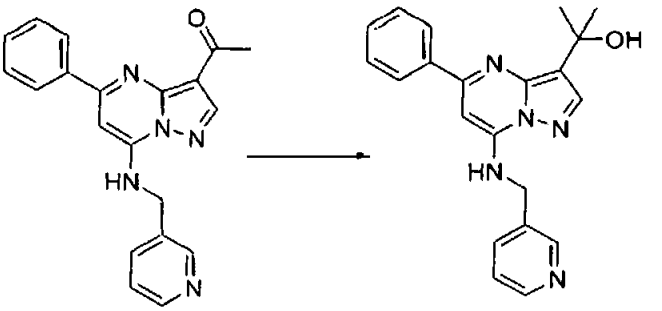
A una solución del análogo 3-H (113 mg, 0,38 mmoles) del Ejemplo Preparativo 187,10 en CH_2Cl_2 (5 mL) a temperatura ambiente se agregó $AlCl_3$ (215 mg, 1,61 mmoles) seguido de AcCl (100 mL, 1,40 mmoles). La mezcla se calentó a reflujo durante 12 horas y se enfrío a temperatura ambiente. La mezcla se trató consecutivamente con HCl 3M (3 mL) seguido de $NaHCO_3$ acuoso saturado (hasta pH = 8). Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (2 x 5 mL). Las capas orgánicas se combinaron, se secaron (Na_2SO_4), se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por TLC Preparativo (8 x 1000 mM) eluyendo con CH_2Cl_2/MeOH (20:1) para proporcionar 68 mg (52%) de un sólido blanco. P.f.: 220-221°C; M+H = 344.

EJEMPLO 324:



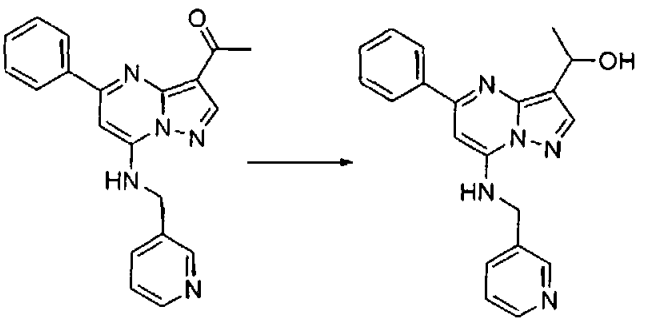
Utilizando el método descripto en el Ejemplo 323, excepto que se empleó cloruro de benzoilo, se preparó el compuesto del título con un rendimiento del 61% en forma de un sólido blanco. P.f.: 172-175°C; M+H = 406.

EJEMPLO 325:



A una solución de cetona (100 mg, 0,29 mmoles) del Ejemplo 323 en CH_2Cl_2 (2.5 mL) a 0°C se agregó MeMgBr (0,35 mL, 3,0M en Et_2O) por goteo. La mezcla resultante se agitó durante 18 horas a temperatura ambiente y se apagó cuidadosamente por adición de NH_4Cl acuoso saturado (2 mL) y se agregó CH_2Cl_2 (2 mL). Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (2 x 4 mL). Las capas orgánicas se combinaron, se secaron (Na_2SO_4), se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por TLC Preparativo (8 x 1000 μM) eluyendo con CH_2Cl_2/MeOH (10:1) para proporcionar 68 mg (52%) de un sólido de color amarillo. P.f.: 160-162 °C; M+H = 360.

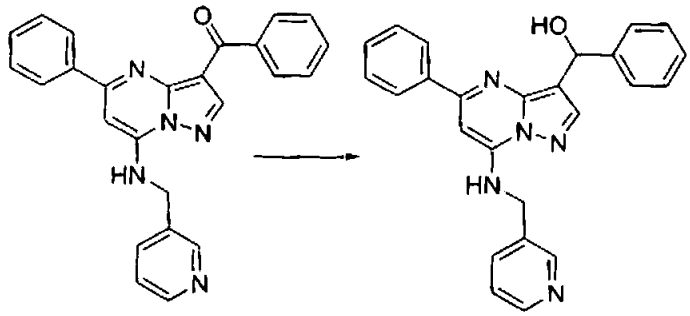
EJEMPLO 326:



A una solución de cetona (84 mg, 0,24 mmoles) del Ejemplo 323 en MeOH/THF (1:1; 2 mL total) a 0°C se agregó $NaBH_4$ (12 mg, 0,30 mmoles) en una porción. La mezcla resultante se agitó durante 18 horas a temperatura ambiente después de los cual se agregó una porción adicional de $NaBH_4$ (12 mg, 0.30 mmoles). La mezcla se agitó durante 12 horas después de lo cual la mezcla se apagó con hielo seguido de adición de NaOH 1M para ajustar el pH = 9. La mezcla se diluyó con CH_2Cl_2 (5 mL). Las capas se separaron y la capa acuosa se

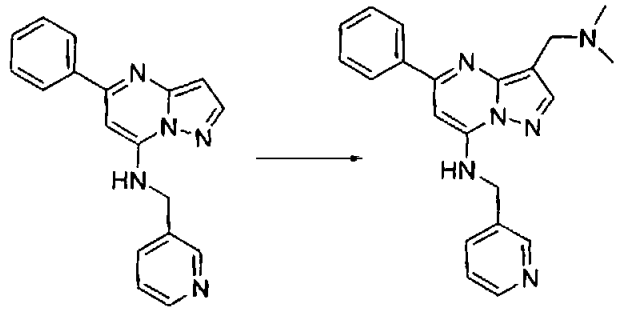
extrajo con CH_2Cl_2 (2 x 4 mL). Las capas orgánicas se combinaron, se secaron (Na_2SO_4), se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por TLC Preparativo (8 x 1000 μM) eluyendo con CH_2Cl_2/MeOH (10:1) para proporcionar 25 mg (30%) de un sólido de color amarillo. P.f.: 148-150°C; M+H = 346.

EJEMPLO 327:



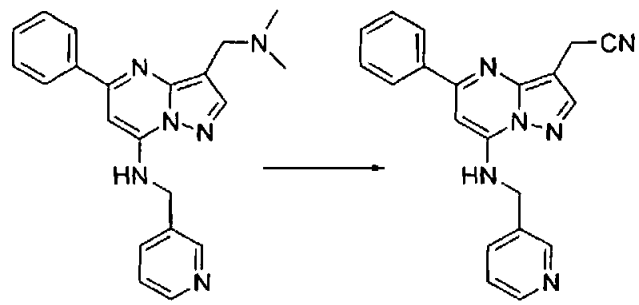
Usando el mismo procedimiento señalado en el Ejemplo 326, la cetona (84 mg, 0,21 mmoles) se convirtió a 53 mg (62%) en forma de un sólido de color amarillo claro. P.f.: 78-80°C; M+H = 408.

EJEMPLO 328:



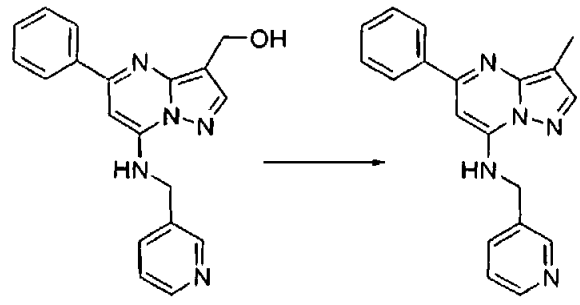
A una solución del aducto 3-H (1,3 g, 4,31 mmoles) del Ejemplo Preparativo 187,10 en CH_2Cl_2 (50 mL) se le agregó una sal de Eschenmoser's (0,79 g, 4,31 mmoles) seguido de adición por goteo de TFA (0,56 mL, 7,33 mmoles). La mezcla se agitó a temperatura ambiente durante 48 horas y luego se diluyó con CH_2Cl_2 (250 mL). La capa orgánica se lavó con $NaHCO_3$ acuoso saturado (2 x 125 mL) para proporcionar 1,41 horas (92%) de un sólido de color amarillo. P.f.: 231-233°C; M+H = 359.

EJEMPLO 329:



A una solución de un aducto de amina terciaria (100 mg, 0,28 mmoles) del Ejemplo 328 en 50% de DMF acuoso (5 mL) en un tubo de presión se agregó KCN (0,15 g, 2,32 mmoles). El tubo se tapó y se calentó a 100°C durante 96 horas. La mezcla se enfrío a temperatura ambiente y se diluyó con EtOAc (25 mL). La capa orgánica se lavó con salmuera (1 x 5 mL) y agua (1 x 5 mL). Las capas orgánicas se secaron (Na_2SO_4), se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por TLC Preparativo (4 x 1000 μM) eluyendo con EtOAc para proporcionar 21 mg (30%) de un sólido de color castaño. P.f.: 152-155°C; M+H = 341.

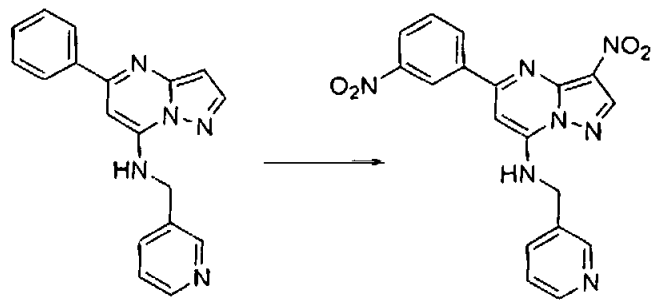
EJEMPLO 330:



A una solución de alcohol (45 mg, 0,14 mmoles) del Ejemplo 17,10 en CH_2Cl_2 (0,7 mL) a 0°C se agregó Et_3SiH (26 μL, 0.16 mmoles) seguido de TFA (25 μL, 0,33 mmoles). La mezcla se agitó durante 2 horas a 0°C y a temperatura ambiente durante 2 horas después de lo cual se agregaron porciones adicionales de Et_3SiH (26 μL, 0.16 mmoles) y TFA (25 μL, 0,33 mmoles) y la mezcla se agitó durante 4 horas a temperatura ambiente (hasta completarla por TLC). La mezcla se concentró bajo presión reducida y el residuo crudo se dividió entre CH_2Cl_2 (3 mL) y $NaHCO_3$ acuoso saturado (1,5 mL). Las capas se separaron, y la capa

acuosa se extrajo con CH_2Cl_2 (2 x 4 mL). Las capas orgánicas se combinaron, se lavaron con salmuera (1 x 5 mL), se secaron (Na_2SO_4), se filtraron y se concentraron bajo presión reducida. El producto crudo se purificó por TLC preparativa (4 x 1000 mM) eluyendo con CH_2Cl_2/MeOH (20:1) para proporcionar 21 mg (48%) de un sólido de color amarillo. P.f.: 146-148°C; M+H = 316.

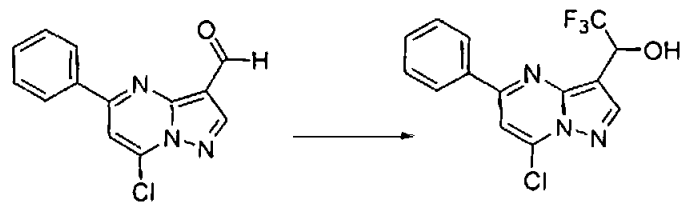
EJEMPLO 331:



A una solución del aducto 3-H (90 mg, 0,30 mmoles) del Ejemplo Preparativo 187,10 H_2SO_4 concentrado (2 mL) a 0°C se agregó HNO_3 fumante (30 µL, 0,72 mmoles) por goteo. La mezcla resultante se agitó durante 1 hora a 0°C después de lo cual se agregó hielo (~1g) a la mezcla. El precipitado resultante se recogió y se lavó con agua (2 x 2 mL) y CH_2Cl_2 (2 x 2 mL). El producto crudo se secó bajo alto vacío para proporcionar 67 mg (60%) de la sal de monosulfato en forma de un sólido de color amarillo/anaranjado sólido. P.f.: 250°C; M+H (base libre) = 392.

EJEMPLO 332:

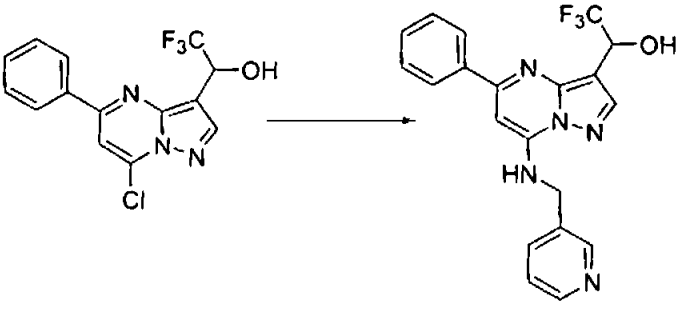
Etapa A:



A una solución de aldehído (0,10 g, 0,39 mmoles) del Ejemplo Preparativo 168 en THF (2,5 mL) a 0°C se agregó CF_3TMS (64 mL, 0,43 mmoles) seguido de CsF (10 mg). La mezcla resultante se agitó durante 2 horas a 0°C y 2 horas a temperatura ambiente. Se agregó HCl 1M (5 mL) y la mezcla se diluyó con CH_2Cl_2

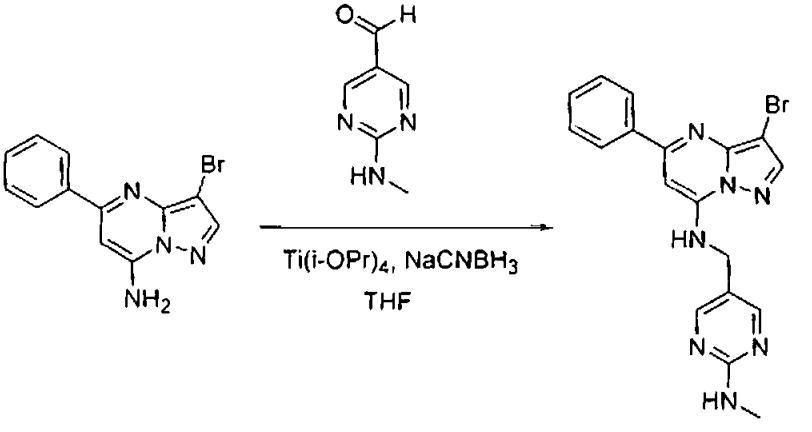
(10 mL). Las capas se separaron, la capa acuosa se extrajo con CH_2Cl_2 (2 x 10 mL), y las capas orgánicas se combinaron. La capa orgánica se lavó con salmuera (1 x 10 mL), se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida para proporcionar 127 mg (99%) de un semisólido amarillo. M+H =328. El producto crudo se llevó sin purificación adicional.

Etapa B:



Utilizando el procedimiento general que se indica en el Ejemplo 1, el aducto 7-Cl (127 mg, 0,39 mmoles) del Ejemplo 332, Etapa A se hizo reaccionar con 3-(aminometil)piridina (73 µL, 0,43 mmoles) para proporcionar 80 mg (51%) del compuesto del título en forma de un sólido de color amarillo claro. P.f.: 68-72°C; M+H = 400.

EJEMPLO 333:



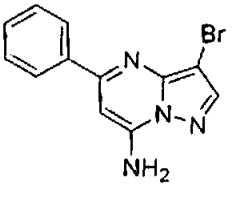
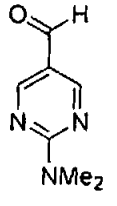
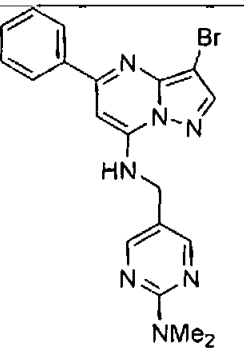
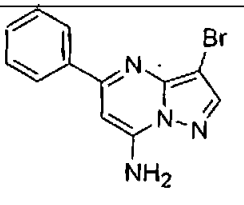
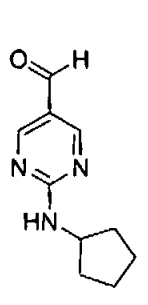
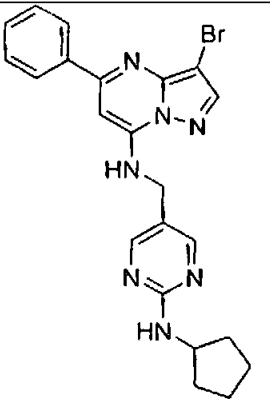
A una solución de anilina (200 mg, 0,69 mmoles) del Ejemplo Preparativo 174 en THF (6 mL) a temperatura ambiente se agregó aldehído (114 mg, 0,83 mmoles) a partir del Ejemplo Preparativo 256 seguido de adición por goteo de Ti(*i*-OPr)$_4$ (0,82 mL, 2,77 mmoles). La mezcla se agitó a reflujo durante 4 horas y se enfrío a temperatura ambiente. Se agregó $NaCNBH_3$ (347 mg, 5,53 mmoles) y la

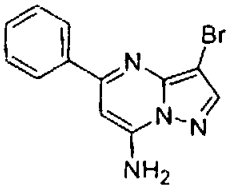
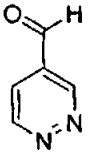
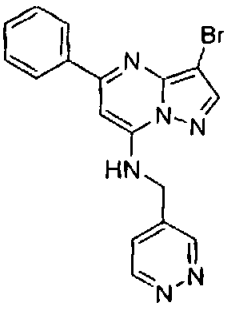
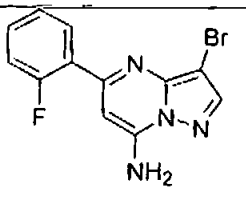
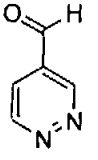
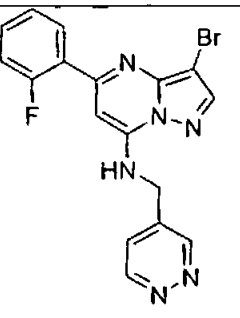
mezcla se agitó durante 2 horas a temperatura ambiente. La mezcla se enfrío a 0°C, se trató NaOH 1M (4 mL) y salmuera (1 mL) y se agitó durante 30 minutos. La mezcla se extrajo con CH_2Cl_2 (3 x 10 mL) y las capas orgánicas se combinaron. La capa orgánica se lavó con salmuera (1 x 7 mL), se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía de capa delgada preparativa (placas de 8 x 1000 µM) eluyendo con CH_2Cl_2/MeOH (25:1) para proporcionar 89 mg (31%) del compuesto del título en forma de un sólido amarillo. P.f.: 210-213°C; M+H = 411.

EJEMPLOS 334-337:

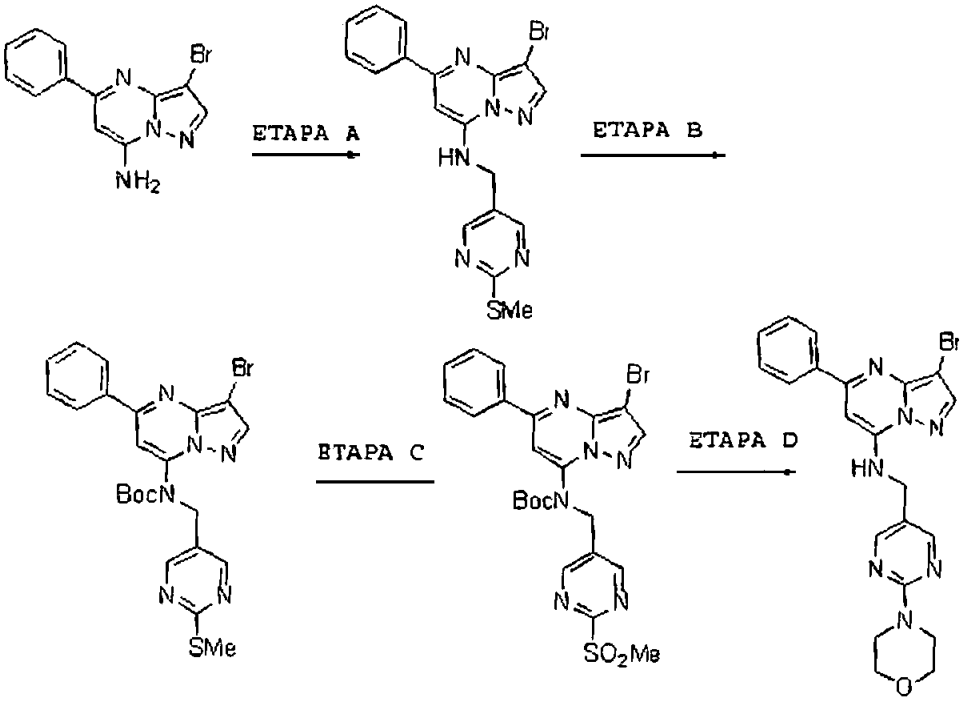
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo 333 utilizando únicamente las anilinas que se muestran en la Columna 2 de la Tabla 30 y los aldehídos que se muestran en la Columna 3 de la Tabla 30, se prepararon los compuestos de la Columna 4 de la Tabla 30:

TABLA 30

Ej.	Columna 2 (Anilina)	Columna 3 (Aldehído)	Columna 4 (Estructura Final)	COMP. 1. P.f.: (°C) 2. M+H
334				1. P.f.: 85-87 2. M+H = 425
335				1. P.f.: 160-162 2. M+H = 451

336				1. P.f.: 117-119 2. M+H = 382
337				1. P.f.: 171-175 2. M+H = 400

EJEMPLO 338:



ETAPA A:

La reacción de anilina (0,20 g, 0,69 mmoles) con aldehído (0,13 g, 0,83 mmoles) bajo las condiciones de reacción que se describen en el Ejemplo 333 proporcionaron 70 mg (23%) del derivado tiometilo en forma de un sólido de color amarillo. M+H = 428.

ETAPA B:

A una solución del derivado tiometilo (60 mg, 0,14 mmoles) del Ejemplo 338, Etapa A en dioxano (2 mL) se agregó Boc_2O (61 mg, 0,28 mmoles) seguido de DMAP (21 mg, 0,17 mmoles). La mezcla se agitó durante 14 horas a temperatura ambiente y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía de capa delgada preparativa (placas de 6 x 1000 μM) eluyendo con hexanos/EtOAc (4:1) para obtener 61 mg (83%) del compuesto del título en forma de un sólido amarillo. M+H = 528.

ETAPA C:

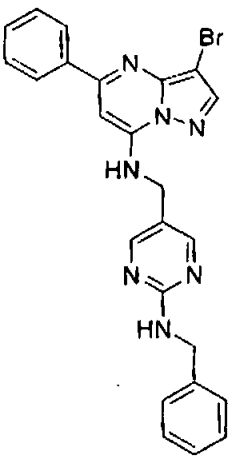
A una solución del derivado tiometilo del Ejemplo 338, Etapa B (41 mg, 0,078 mmoles) en CH_2Cl_2 (2 mL) se agregó MCPBA (33 mg, 0,19 mmoles) en una sola porción. La mezcla resultante se agitó durante 3 horas a temperatura ambiente y la mezcla se diluyó con CH_2Cl_2 (5 mL) y $NaHCO_3$ acuoso saturado (2,5 mL). Las capas se separaron, la capa acuosa se extrajo con CH_2Cl_2 (2 x 5 mL), y las capas orgánicas se combinaron. La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida para proporcionar 40 mg (92%) del aducto de sulfona en forma de un sólido de color amarillo claro. M+H = 560.

ETAPA D:

A un frasco cargado con la sulfona del Ejemplo 338, Etapa C (75 mg, 0,13 mmoles) y una barra agitadora se agregó morfolina (2 ml; 22 mmoles). La mezcla se calentó a reflujo durante 12 horas, se enfrío a temperatura ambiente, y se concentró hasta sequedad bajo alto vacío. El producto crudo se purificó por cromatografía de capa delgada preparativa (placas de 6 x 1000 μM) eluyendo con

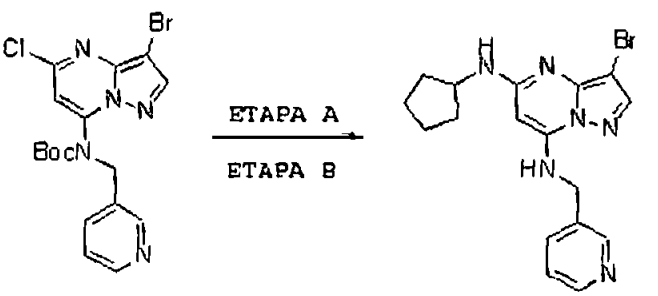
CH_2Cl_2/MeOH (40:1) para proporcionar 41 mg (68%) del compuesto del título en forma de un sólido amarillo. P.f.: 209-210°C; M+H = 466.

EJEMPLO 339:



Se preparó el compuesto del título de acuerdo con el procedimiento señalado en el Ejemplo 338 excepto que se usó bencilamina para proporcionar 12 mg (70%) de un sólido blanco. P.f.: 194-196; M+H = 487.

EJEMPLO 340:



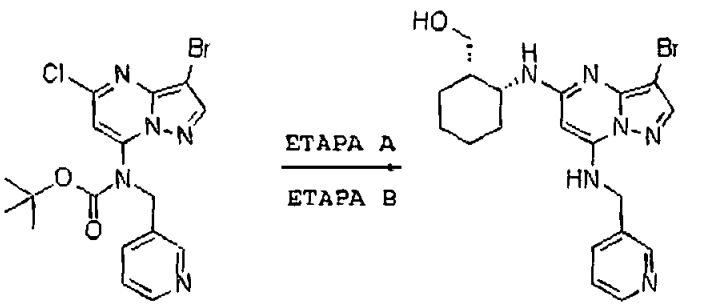
ETAPA A:

A una solución de aducto de 5-cloro (0,15 g, 0,34 mmoles) en dioxano/DIPEA (2,5 mL/1,0 mL) a temperatura ambiente se agregó ciclopentilamina (0,041 μL, 0,41 mmoles) por goteo. La solución resultante se agitó a reflujo durante 16 horas, se enfrío a temperatura ambiente, y se concentró bajo presión reducida. El material crudo se purificó por cromatografía de capa delgada preparativa (8 x 1000 μM) eluyendo con CH_2Cl_2/MeOH (25:1) para obtener 148 mg (89%) de un aceite amarillo. M+H = 489.

ETAPA B: Remoción del grupo protector t-butoxicarbonilo con TFA

A una solución del compuesto preparado en el Ejemplo 340, Etapa A (135 mg, 0,28 mmoles) en CH_2Cl_2 (2 mL) a temperatura ambiente se agregó TFA (0,54 mL, 7,0 mmoles) por goteo. La solución resultante se agitó durante 18 horas a temperatura ambiente y se concentró bajo presión reducida. El material crudo se re-disolvió en CH_2Cl_2 (5 mL) y la capa orgánica se lavó consecutivamente con $NaHCO_3$ acuoso saturado (2 x 2 mL) y salmuera (1 x 2 mL). La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida. El material crudo se purificó por cromatografía de capa delgada preparativa (8 x 1000 μM) eluyendo con CH_2Cl_2/MeOH (20:1) para obtener 105 mg (97%) de un sólido blanco. P.f.: 120-122°C; M+H = 389.

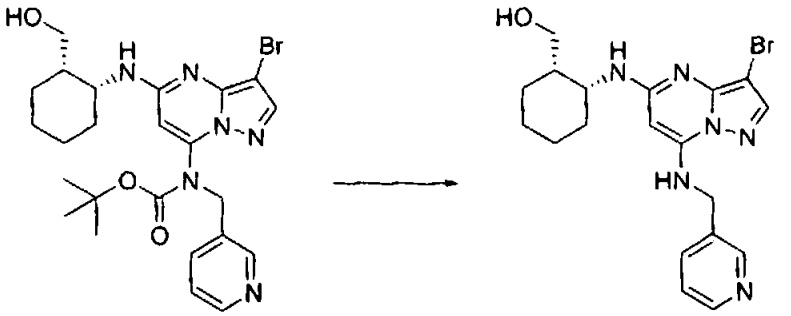
EJEMPLO 341:



Etapa A:

Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo 340 sustituyendo únicamente la amina apropiada, se preparó el compuesto anterior. EM: MH^+= 431.

Etapa B: Remoción del grupo protector t-butoxicarbonilo con KOH.



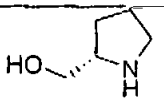
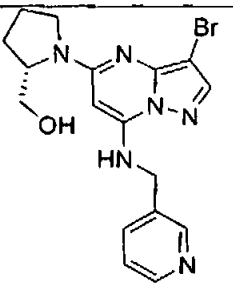
9/5
34063/08

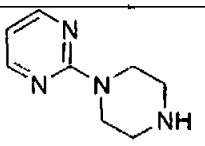
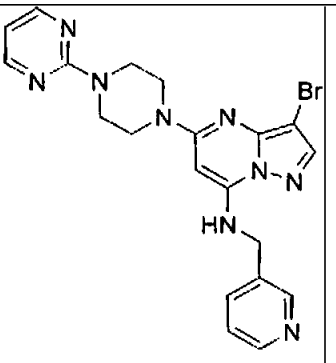
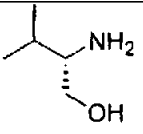
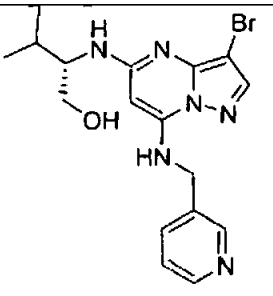
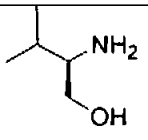
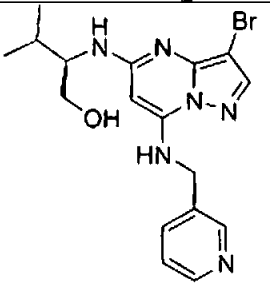
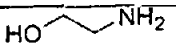
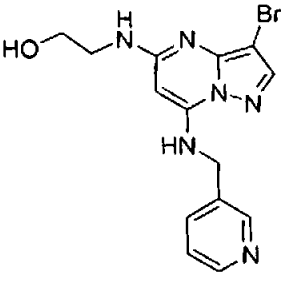
A una mezcla del compuesto preparado en el Ejemplo 341, Etapa A (0,14 g, 0,26 mmoles) en EtOH:H_2O (3 mL, 2:1) se agregó KOH (0,29 g, 20 eq.) en una sola porción. La solución resultante se agitó a reflujo durante 14 horas, se enfrío a temperatura ambiente, y se concentró bajo presión reducida. El residuo se recogió en CH_2Cl_2 (5 mL) y se diluyó con $NaHCO_3$ saturado (2 mL). Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (2 x 4 mL). Los orgánicos combinados se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por TLC Preparativo (8 x 1000 μM) eluyendo con 5% de MeOH en solución de CH_2Cl_2 (0,066 g, 59% de rendimiento). EM: MH^+ = 432; p.f.: 219-221°C.

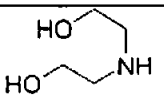
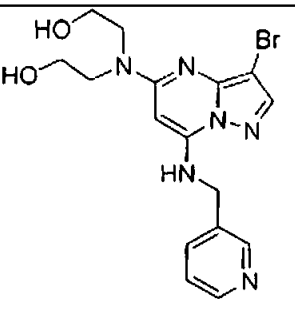
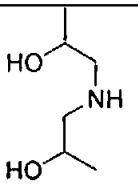
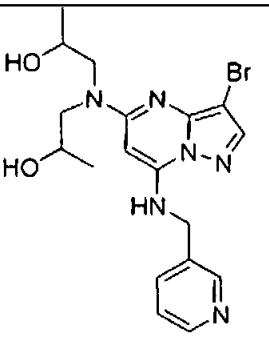
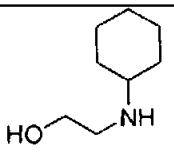
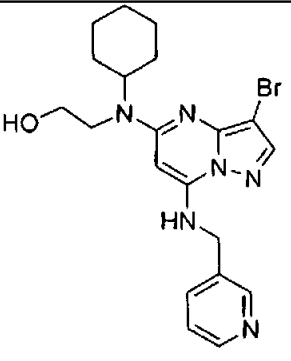
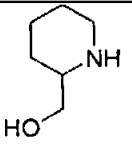
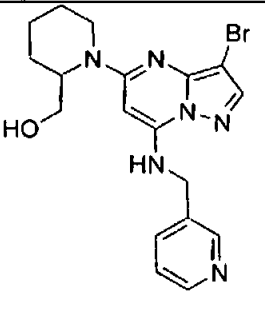
EJEMPLOS 342-397:

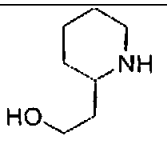
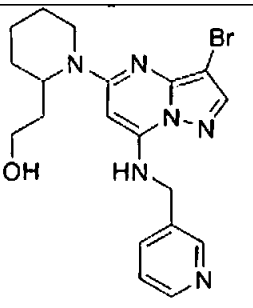
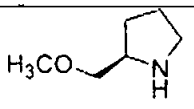
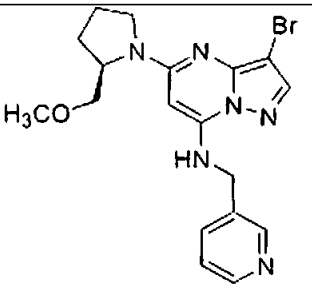
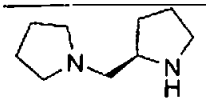
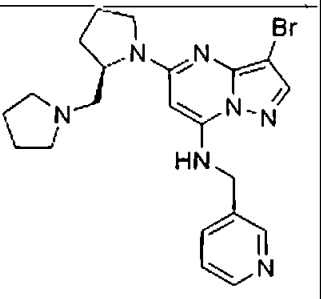
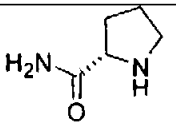
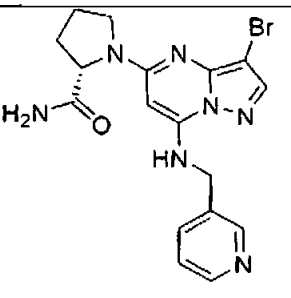
Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo 340 sustituyendo únicamente los cloruros en la Columna 2 de la Tabla 31 y removiendo el grupo protector t-butoxicarbonilo por el método que se muestra en la Columna 3 de la Tabla 31, se prepararon los compuestos que se muestra en la Columna 4 de la Tabla 31.

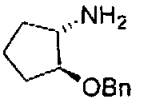
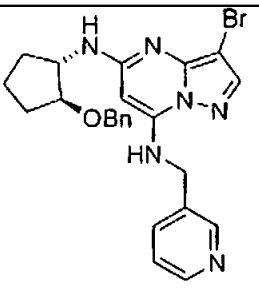
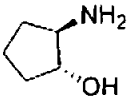
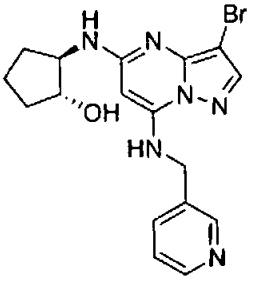
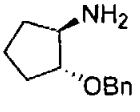
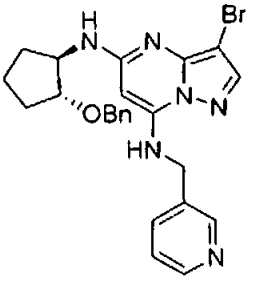
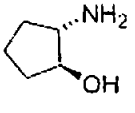
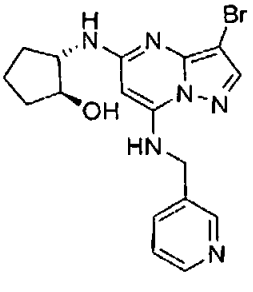
Tabla 31

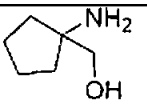
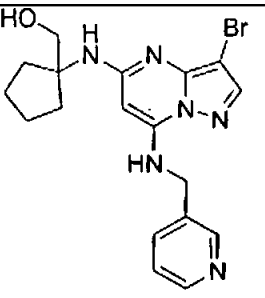
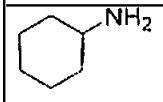
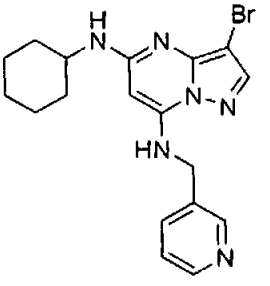
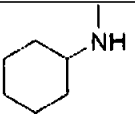
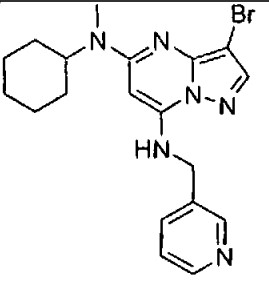
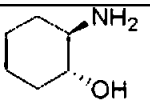
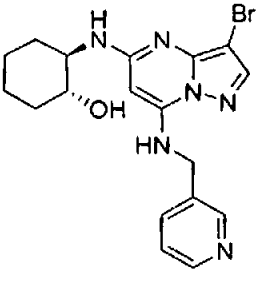
Ej.	Columna 2	Columna 3	Columna 4	COMP.
342		HCl		EM: MH^+ = 403 p.f.:151–157°C

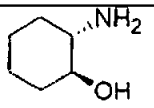
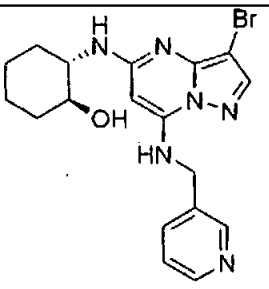
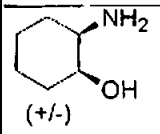
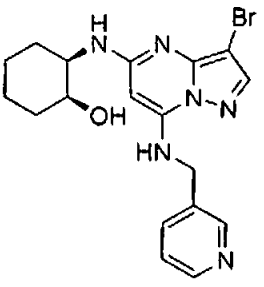
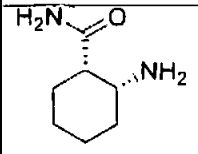
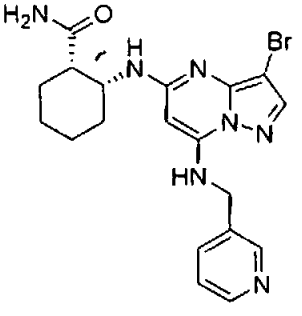
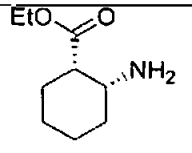
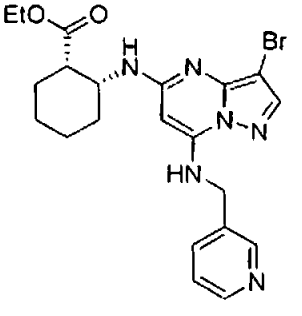
343		HCl		EM: MH^+ = 466 p.f.:212–217°C
344		HCl		EM: MH^+ = 405 p.f.:53–58°C
345		HCl		EM: MH^+ = 405 p.f.:63–69°C
346		HCl		EM: MH^+ = 363 p.f.:170–171°C

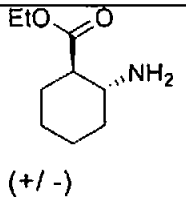
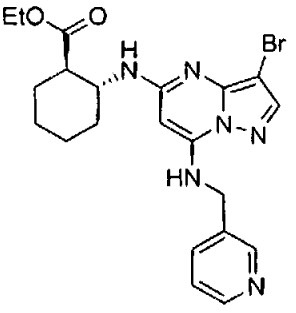
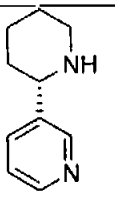
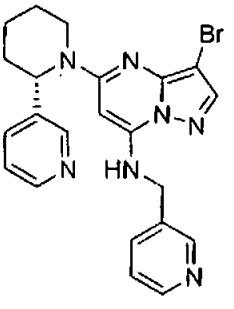
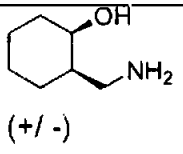
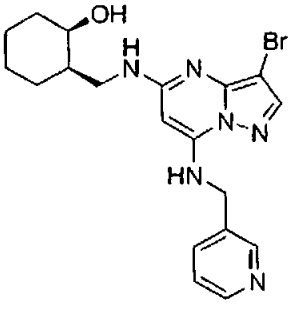
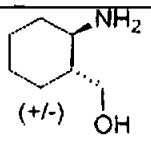
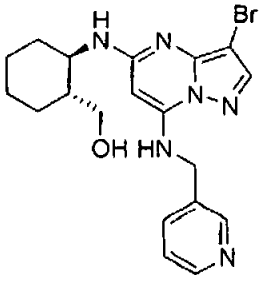
347		HCl		EM: MH$^+$ = 407 p.f.:148–151°C
348		HCl		EM: MH$^+$ = 435 p.f.:56–59°C
349		HCl		EM: MH$^+$ = 445 p.f.:66–68°C
350		KOH		EM: MH$^+$ = 417 p.f.:149–151°C

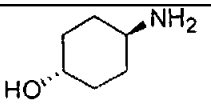
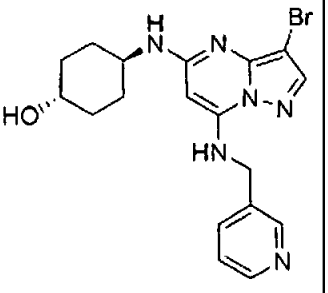
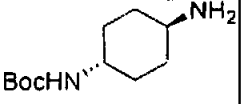
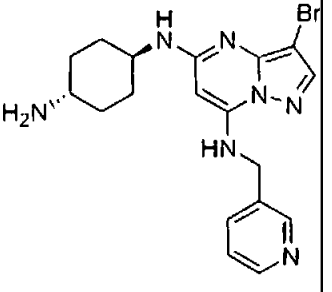
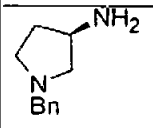
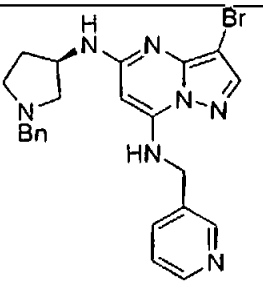
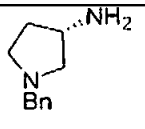
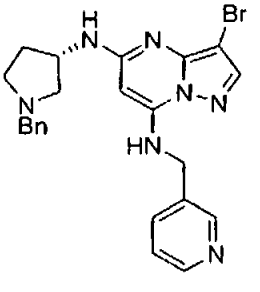
351		KOH		EM: MH^+ = 431 p.f.:111–114°C
352		KOH		EM: MH^+ = 417 p.f.:53–58°C
353		KOH		EM: MH^+ = 456 p.f.:186–189°C
354		KOH		EM: MH^+ = 416 p.f.:210–213°C

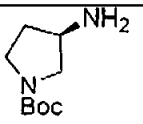
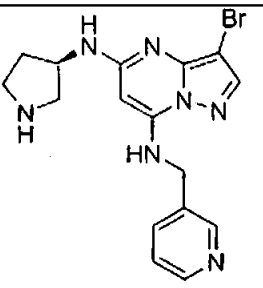
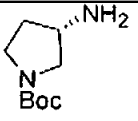
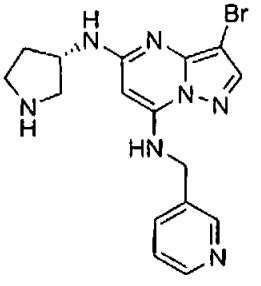
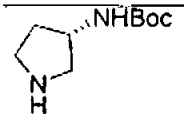
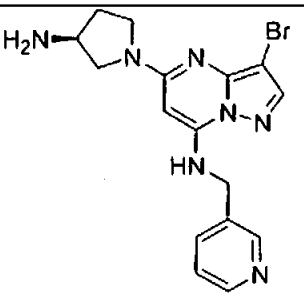
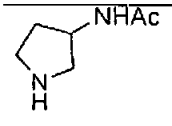
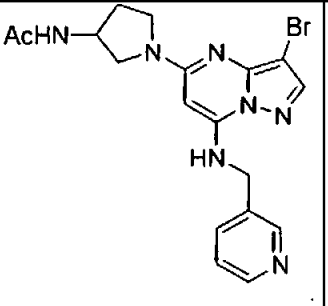
355		TFA		1. P.f.: 68 - 70 2. M+H = 494
356		KOH		1. P.f.: 181 - 183 2. M+H = 404
357		TFA		1. P.f.: 69 - 71 2. M+H = 494
358		KOH		1. P.f.: 182 - 184 2. M+H = 404

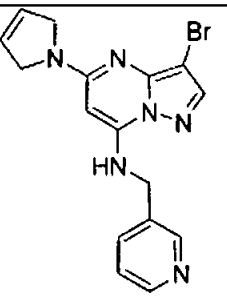
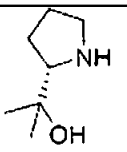
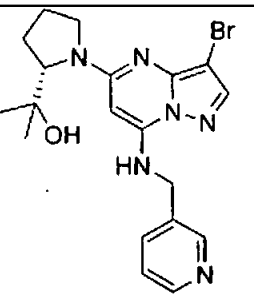
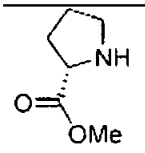
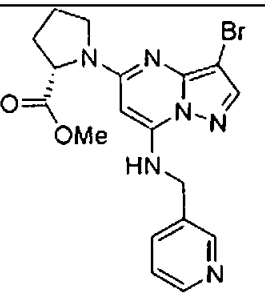
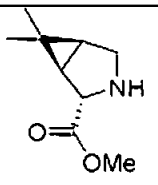
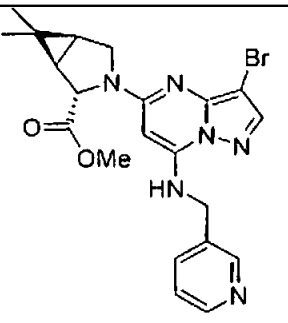
359		KOH		1. P.f.: 202 - 204 2. M+H = 418
360		TFA		1. P.f.: 160 - 162 2. M+H = 402
361		TFA		1. P.f.: 151 - 153 2. M+H = 416
362		KOH		1. P.f.: 140 - 143 2. M+H = 418

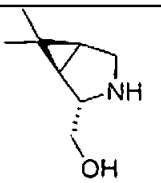
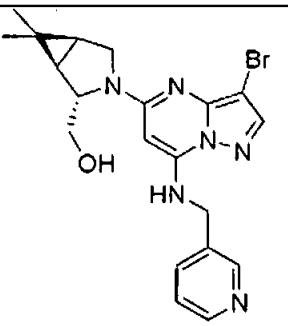
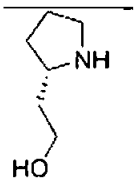
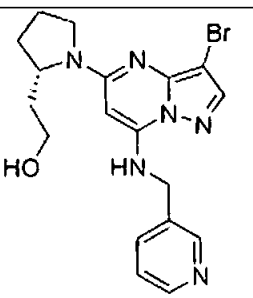
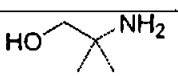
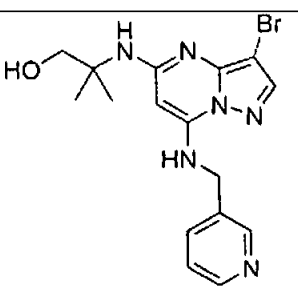
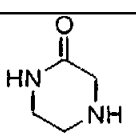
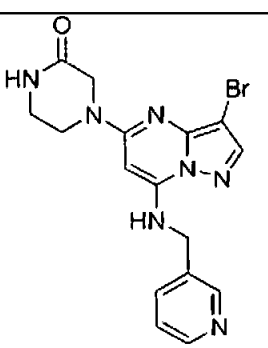
363		KOH		1. P.f.: 139 - 142 2. M+H = 418
364	 (+/-)	KOH		1. P.f.: 115 - 117 2. M+H = 418
366	 (+/ -)	TFA		1. P.f.: 102 - 104 2. M+H = 445
367	 (+/ -)	TFA		1. P.f.: 118 - 120 2. M+H = 474

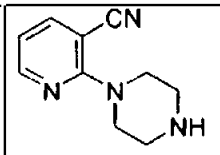
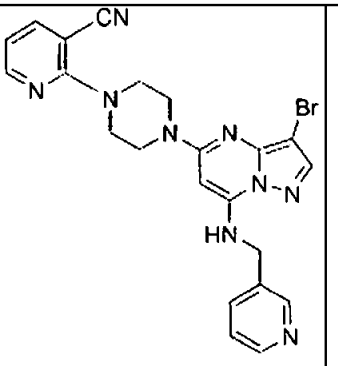
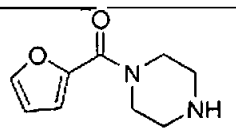
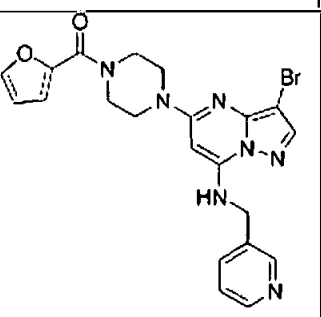
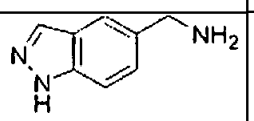
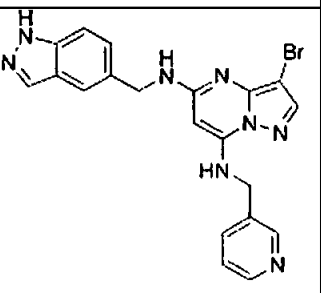
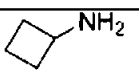
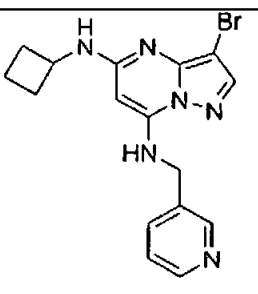
368	 (+/ -)	TFA		1. P.f.: 106 - 108 2. M+H = 474
369		TFA		1. P.f.: 160 - 161 2. M+H = 464
370	 (+/ -)	TFA		1. P.f.: 93 - 95 2. M+H = 432
371	 (+/-)	KOH		1. P.f.: 108 - 110 2. M+H = 432

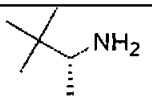
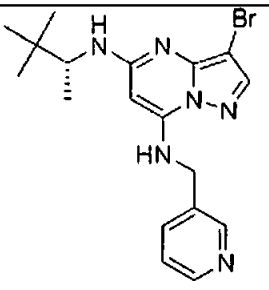
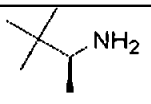
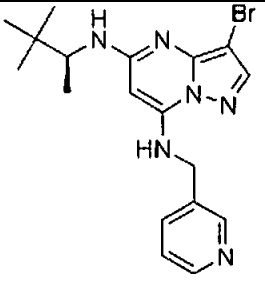
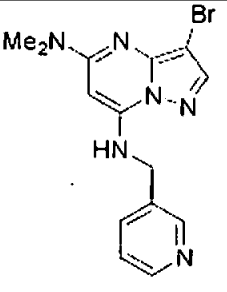
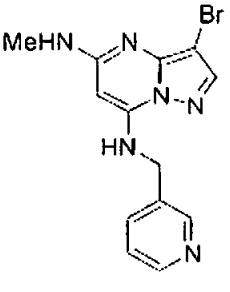
372		KOH		1. P.f.: 180 - 182 2. M+H = 418
373		TFA		1. P.f.: 169 - 170 2. M+H = 417
374		TFA		1. P.f.: 77 - 79 2. M+H = 479
375		TFA		1. P.f.: 76 - 79 2. M+H = 479

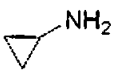
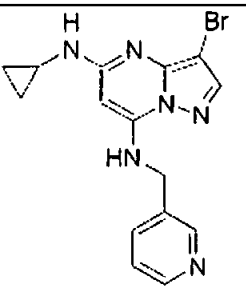
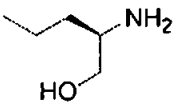
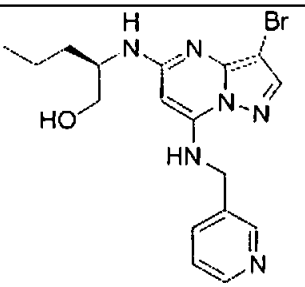
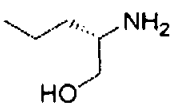
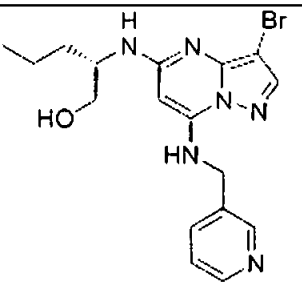
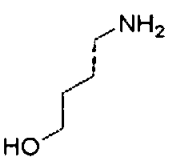
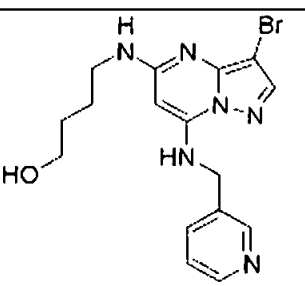
376		TFA		1. P.f.: 105 - 107 2. M+H = 389
377		TFA		1. P.f.: 105 - 107 2. M+H = 389
378		TFA		1. P.f.: 130 - 133 2. M+H = 389
379		TFA		1. P.f.: 132 - 135 2. M+H = 431

380		TFA		1. P.f.: 135 - 137 2. M+H = 372
381		KOH		1. P.f.: 78 - 82 2. M+H = 432
382		TFA		1. P.f.: 101 - 103 2. M+H = 432
383		TFA		1. P.f.: 92 - 95 2. M+H = 472

384		TFA		1. P.f.: 107 - 111 2. M+H = 444
384.10		TFA		1. P.f.: 2. M+H = 417
384.11		TFA		1. P.f.: 210 - 212 2. M+H = 391
385		TFA		1. P.f.: 122 - 124 2. M+H = 403

386		TFA		1. P.f.: 186 - 188 2. M+H = 491
387		TFA		1. P.f.: 173 - 175 2. M+H = 483
388		TFA		1. P.f.: 167 - 169 2. M+H = 450
389		TFA		1. P.f.: 90 - 92 2. M+H = 374

390		TFA		1. P.f.: 113 - 115 2. M+H = 404
391		TFA		1. P.f.: 114 - 116 2. M+H = 404
392	$HNMe_2$	TFA		LCEM: MH^+ = 347;
393	H_2NMe	TFA		LCEM: MH^+ = 333;

394		TFA		LCEM: MH^+ = 359;
395		TFA		LCEM: MH^+ = 405;
396		TFA		LCEM: MH^+ = 405;
397		TFA		LCEM: MH^+ = 391;

Datos adicionales para ejemplos seleccionados que se muestran a continuación:

Ejemplo 392: ^{1}H RMN (DMSO-d_6) δ 8,65 (s, 1H), 8,46 (d, J = 3,3 Hz, 1H), 8,21 (t, J = 6,6 Hz, 1H), 7,90 (s, 1H), 7,80 (d, J = 7,8 Hz, 1H), 7,35 (dd, J = 7,8, 4,8 Hz, 1H), 5,46 (s, 1H), 4,61 (d, J = 6,9 Hz, 2H), 3,01 (s, 6H).

Ejemplo 393: ^{1}H RMN ($CDCl_3$) δ 8,65 (s, 1H), 8,60 (d, J = 4,8 Hz, 1H), 7,76 (s, 1H), 7,70 (m, 1H), 7,32 (dd, J = 8,1, 4,8 Hz, 1H), 6,43 (t, J = 6,0 Hz, 1H), 5,08 (s, 1H), 4,80 (m, 1H), 4,56 (d, J = 6,0 Hz, 2H), 2,96 (d, J = 5,1 Hz, 3H).

Ejemplo 394: ^{1}H RMN ($CDCl_3$) δ 8,68 (s, 1H), 8,60 (d, J = 4,8 Hz, 1H), 7,76 (s, 1H), 7,72 (m, 1H), 7,32 (dd, J = 7,8, 5,4 Hz, 1H), 6,55 (t, J = 5,7 Hz, 1H), 5,53 (s, 1H), 5,35 (s, 1H), 4,62 (d, J = 5,7 Hz, 2H), 2,49 (m, 1H), 0,75 (m, 2H), 0,51 (m, 2H).

Ejemplo 395: ^{1}H RMN ($CDCl_3$) δ 8,65 (s, 1H), 8,60 (d, J = 4,0 Hz, 1H), 7,75 (s, 1H), 7,69 (m, 1H), 7,33 (dd, J = 8,1, 5,1 Hz, 1H), 6,45 (t, J = 6,0 Hz, 1H), 5,07 (s, 1H), 4,69 (m, 1H), 4,54 (d, J = 6,0 Hz, 2H), 3,98 (m, 1H), 3,79 (dd, J = 10,8, 2,4 Hz, 1H), 3,59 (dd, J = 11,1, 7,2 Hz, 1H), 1,59-1,36 (m, 4H), 0,94 (t, J = 6,9 Hz, 3H).

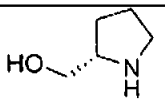
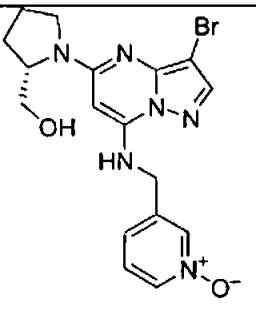
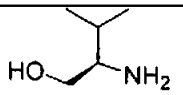
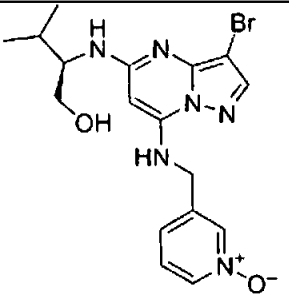
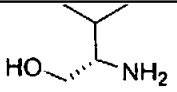
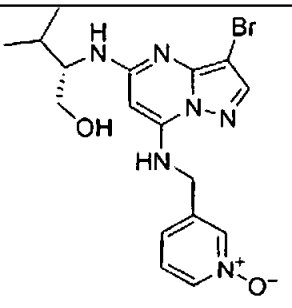
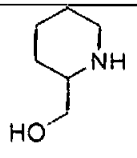
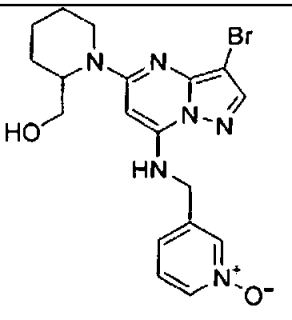
Ejemplo 396: ^{1}H RMN ($CDCl_3$) δ 8,60 (s, 1H), 8,56 (d, J = 4,2 Hz, 1H), 7,73 (s, 1H), 7,66 (m, 1H), 7,31 (dd, J = 7,8, 4,8 Hz, 1H), 6,51 (t, J = 6,0 Hz, 1H), 5,05 (s, 1H), 4,86 (d, J = 6,6 Hz, 1H), 4,50 (d, J = 6,0 Hz, 2H), 3,94 (m, 1H), 3,78 (dd, J = 11,1, 2,4 Hz, 1H), 3,57 (dd, J = 11,1, 7,2 Hz, 1H), 1,57-1,34 (m, 4H), 0,91 (t, J = 7,2 Hz, 3H).

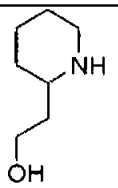
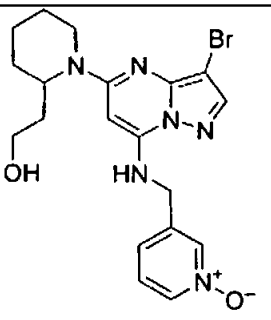
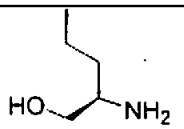
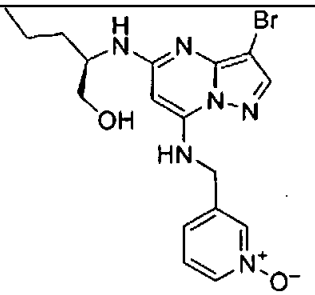
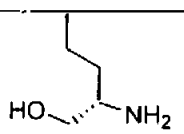
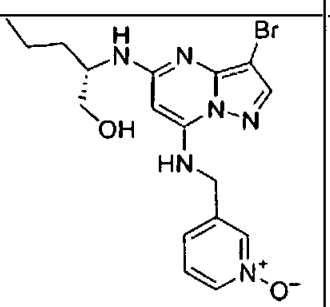
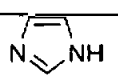
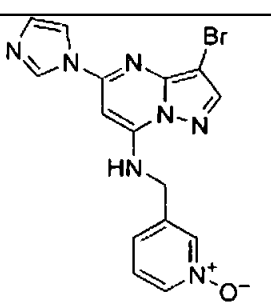
Ejemplo 397: ^{1}H RMN ($CDCl_3$) δ 8,65 (s, 1H), 8,59 (d, J = 4,5 Hz, 1H), 7,75 (s, 1H), 7,69 (m, 1H), 7,31 (m, 1H), 6,43 (t, J = 6,0 Hz, 1H), 5,06 (s, 1H), 4,88 (m, 1H), 4,55 (d, J = 6,0 Hz, 2H), 3,70 (m, 2H), 3,38 (m, 2H), 1,79-1,61 (m, 4H).

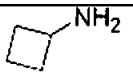
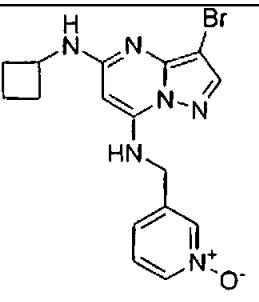
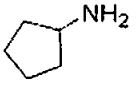
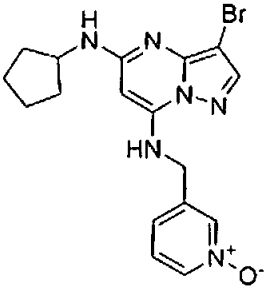
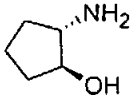
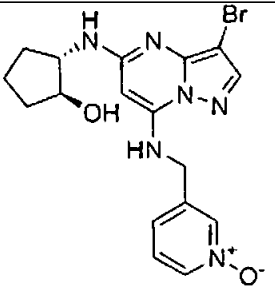
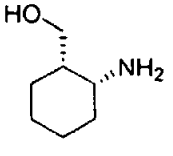
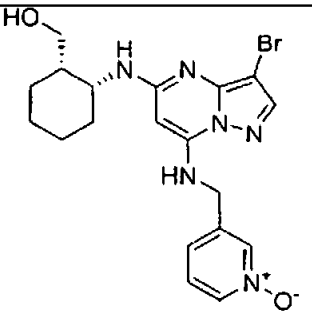
EJEMPLOS 398-416:

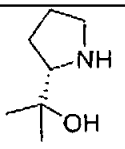
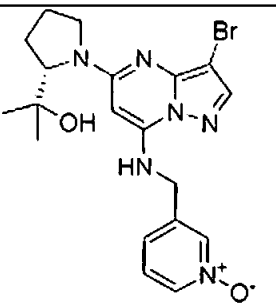
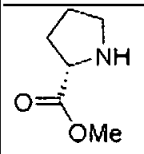
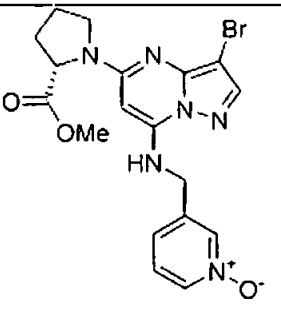
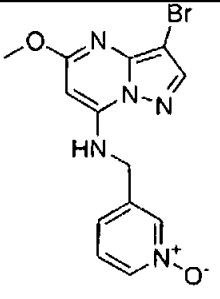
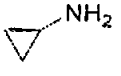
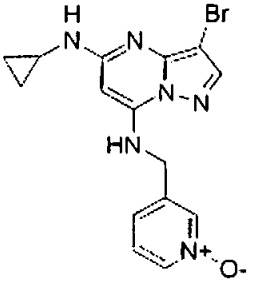
Siguiendo esencialmente las mismas condiciones que se indicaron en el Ejemplo 341, Etapas A y B sustituyendo únicamente el compuesto preparado en el Ejemplo Preparativo 193.10, se prepararon los compuestos de la Columna 4 de la Tabla 32.

Tabla 32

Ej.	Columna 2	Columna 3	Columna 4	COMP.
398				EM: MH^+ = 419 p.f.: 102–105°C
399				EM: MH^+ = 421 p.f.: 79–81°C
400				EM: MH^+ = 421 p.f.: 78–79°C
401				EM: MH^+ = 433 p.f.: 228 - 231°C

402				EM: MH^+ = 447 p.f.: 97 - 102°C
403				EM: MH^+ = 421 p.f.: °C
404				EM: MH^+ = 421 p.f.: °C
405				EM: MH^+ = 386 p.f.: °C

407		KOH		1.P.f.: 98 - 100 2.M+H = 390
408		TFA		1.P.f.: 170 - 173 2.M+H = 404
409		KOH		1.P.f.: 219 - 221 2.M+H = 420
410	 (+/ -)	KOH		1.P.f.: 110 - 112 2.M+H = 448

411		TFA		1.P.f.: 81 - 83 2.M+H = 448
412		TFA		1.P.f.: 136 - 138 2.M+H = 448
413	NaOMe	KOH		1.P.f.: 107 - 110 2.M+H = 351
414				LCEM: MH^+ = 375;

Datos adicionales para ejemplos seleccionados que se muestran a continuación:

258

Ejemplo 414: ^{1}H RMN (DMSO-d_6) δ 8,26 (s, 1H), 8,23 (m, 1H), 8,13 (m, 1H), 7,90 (s, 1H), 7,40-7,27 (m, 3H), 5,34 (s, 1H), 4,49 (d, J = 6,3 Hz, 2H), 2,56 (m, 1H), 0,67 (m, 2H), 0,35 (m, 2H).

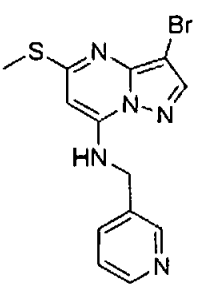
Ejemplo 403: ^{1}H RMN (DMSO-d_6+$CDCl_3$) δ 8,08 (s, 1H), 7,90 (d, J = 6,3 Hz, 1H), 7,49 (s, 1H), 7,34 (t, J = 6,3 Hz, 1H), 7,16-7,09 (m, 2H), 5,65 (d, J = 6,6 Hz, 1H), 4,97 (s, 1H), 4,90 (s, 1H), 4,29 (d, J = 6,3 Hz, 2H), 3,70 (m, 1H), 3,46 (m, 1H), 3,34 (m, 1H), 1,35-1,17 (m, 4H), 0,71 (t, J = 7,2 Hz, 3H).

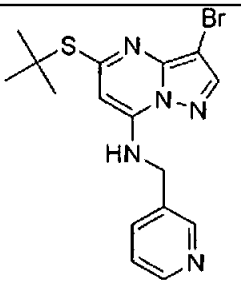
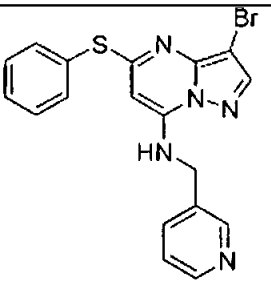
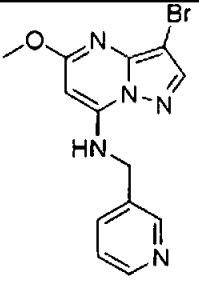
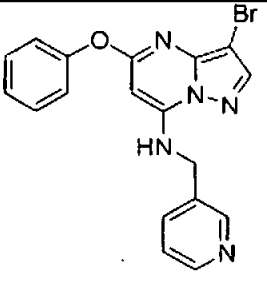
Ejemplo 404: ^{1}H RMN (DMSO-d_6) δ 8,21 (s, 1H), 8,12 (d, J = 6,6 Hz, 1H), 8,06 (m, 1H), 7,86 (s, 1H), 7,38 (t, J = 7,8 Hz, 1H), 7,30 (d, J = 7,5 Hz, 1H), 6,73 (d, J = 8,7 Hz, 1H), 5,28 (s, 1H), 4,70 (t, J = 5,1 Hz, 1H), 4,41 (d, J = 6,6 Hz, 2H), 4,00 (s, 1H), 3,39 (m, 1H), 1,53 (m, 1H), 1,36-1,25 (m, 3H), 0,86 (t, J = 7,0 Hz, 3H).

EJEMPLOS 417—421:

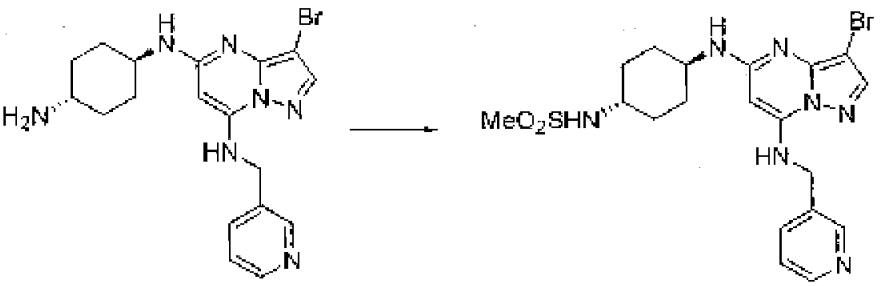
Mediante el procedimiento indicado en *Chem. Pharm. Bull.* **1999**, *47*, 928-938, utilizando los nucleófilos de oxígeno o azufre que se muestran en la Columna 2 descripta en la Tabla 33 y empleando el método de disociación enumerado en la Columna 3 de la Tabla 33, se prepararon los compuestos de la Columna 4 de la Tabla 33:

TABLA 33

Ej.	Columna 2 (Nucleófilo)	Columna 3 (método de disociación)	Columna 4 (Estructura Final)	COMP. 1. p.f. 2. M+H
417	NaSMe	TFA		1. P.f. = 172-175 2. M+H = 351

418	NaSt-Bu	TFA		1. P.f. = 165-168 2. M+H = 392
419	NaSPh	TFA		1. P.f. = 154-156 2. M+H = 412
420	NaOMe	TFA		1. P.f. = 161-163 2. M+H = 335
421	NaOPh	TFA		1. P.f. = 64-66 2. M+H = 397

EJEMPLO 422:

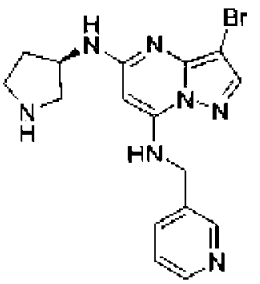
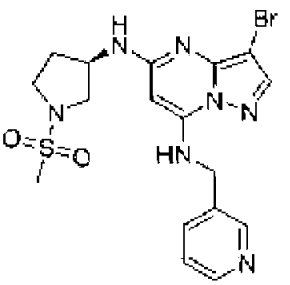
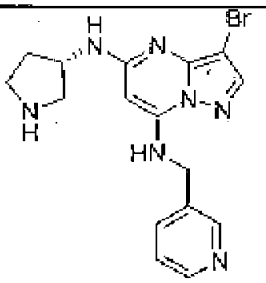
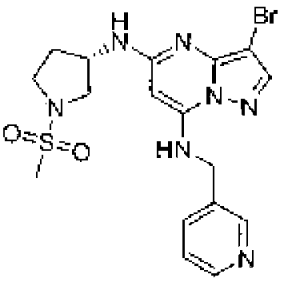


A una solución del compuesto amino (18 mg, 0,043 mmoles) del Ejemplo 373 en CH_2Cl_2 (1 mL) a temperatura ambiente se agregó DIPEA (10 µL, 0,056 mmoles) seguido de $MeSO_2Cl$ (4 mL, 0,052 mmoles). La mezcla se agitó a temperatura ambiente durante 12 horas y se diluyó con CH_2Cl_2 (2 mL) y $NaHCO_3$ acuoso saturado (2 mL). Las capas se separaron y la capa orgánica se extrajo con salmuera (1 x 2 mL). La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida. El material crudo se purificó por cromatografía de capa delgada preparativa (4 x 1000 µM) eluyendo con CH_2Cl_2/MeOH (20:1) para proporcionar 16 mg (75%) de un sólido blando. P.f. 152-154°C; M+H = 495.

EJEMPLOS 423-424:

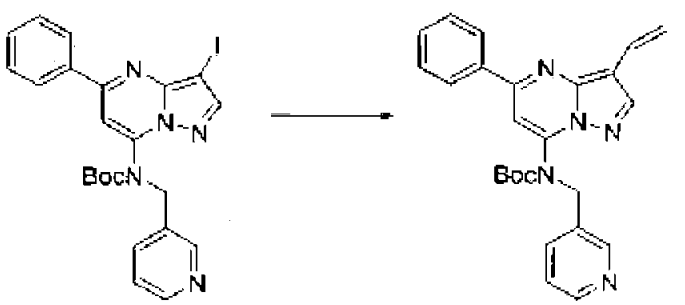
Utilizando el procedimiento señalado en el Ejemplo 422, los compuestos amino (Columna 2) se convirtieron a las metilsulfonamidas correspondientes (Columna 3) en la Tabla 34.

TABLA 34

Ej.	Columna 2 (Amina)	Columna 3 (Estructura Final)	COMP. 1. P.f. 2. M+H
423			1. P.f. = 166-168 2. M+H = 467
424			1. P.f. = 165-168 2. M+H = 467

EJEMPLO 425:

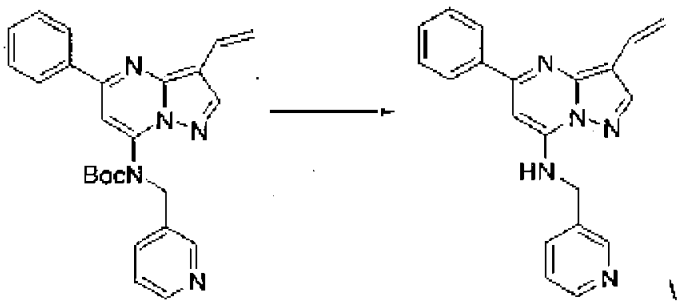
ETAPA A:



Una mezcla del compuesto del Ejemplo Preparativo 194 (132 mg, 0,25 mmoles), tributilvinilestaño (95 mg, 0,30 mmoles) y tetrakis(trifenilfosfina) paladio (29 mg, 0,025 mmoles) en dioxano anhidro (5 mL) se reflujaron bajo N_2 durante

24 horas. El solvente se evaporó y el residuo se purificó por cromatografía evaporativa usando 2:1 de CH_2Cl_2:EtOAc como eluyente para proporcionar un sólido amarillo ceroso (53 mg, 50%). LCMS: MH^+=428.

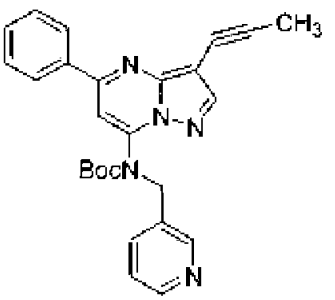
ETAPA B:



Una mezcla del compuesto preparado en el Ejemplo 425, Etapa A (50 mg, 0,12 mmoles) y KOH (100 mg, 1,80 mmoles) en etanol (3 mL) y H_2O (0,6 mL) se agitó a 70°C bajo N_2 durante 24 horas. Se agregaron $NaHCO_3$ (1,0 g), Na_2SO_4 (2,0 g), y CH_2Cl_2 (20 mL), la mezcla se agitó y luego se filtró. El solvente se evaporó y el residuo se purificó por cromatografía evaporativa usando 20:1:0,1 CH_2Cl_2:MeOH:NH_4OH concentrado como eluyente para proporcionar un sólido amarillo ceroso (17 mg, 45%). LCMS: MH^+=328. P.f.=48-51°C.

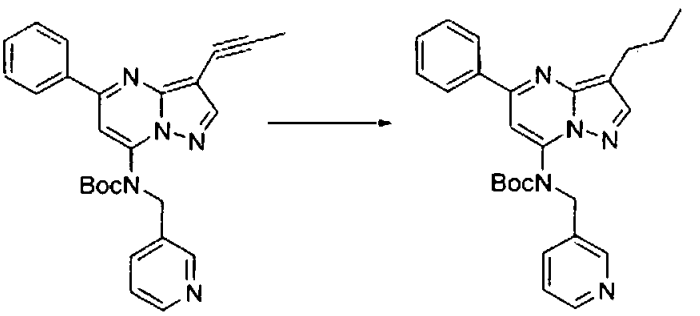
EJEMPLO 426:

ETAPA A:



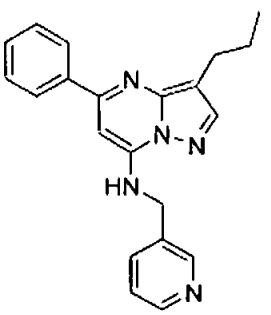
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo 425, Etapa A usando únicamente tributilmetiletinilestaño, se preparó el compuesto que se muestra anteriormente.

ETAPA B:



Una mezcla del compuesto preparado en el Ejemplo 426, Etapa A (150 mg, 0,34 mmoles) y PtO2 (30 mg, 0,13 mmoles) en ácido acético glacial (5 mL) se agito bajo 1 atmósfera de H_2 durante 20 horas. La mezcla se filtró, se agregó PtO2 fresco (30 mg, 0,13 mmoles) y la mezcla se agitó bajo 1 atmósfera de H_2 durante 2,5 horas. La mezcla se vertió sobre Na_2CO_3 (20 g) y H_2O (200 mL) y luego se extrajo con CH_2Cl_2 (4x20 mL). Los extractos combinados se secaron sobre Na_2SO_4 y se filtraron. El solvente se evaporó y el residuo se purificó por cromatografía evaporativa usando 1:1 de CH_2Cl_2:EtOAc como eluyente para proporcionar un sólido amarillo ceroso (68 mg, 45%).

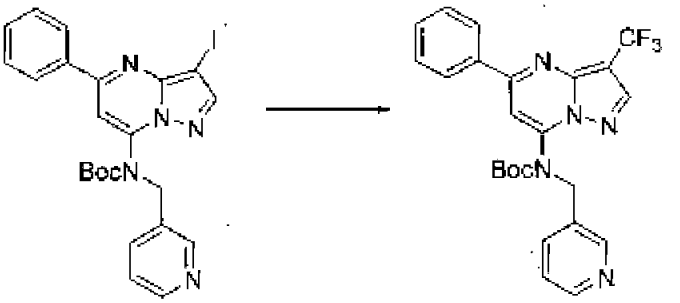
ETAPA C:



Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo 425, Etapa B sustituyendo únicamente el compuesto preparado en el Ejemplo 426, Etapa B, se preparó el compuesto que se muestra anteriormente, EM: MH^+=344. P.f. = 110-112°C.

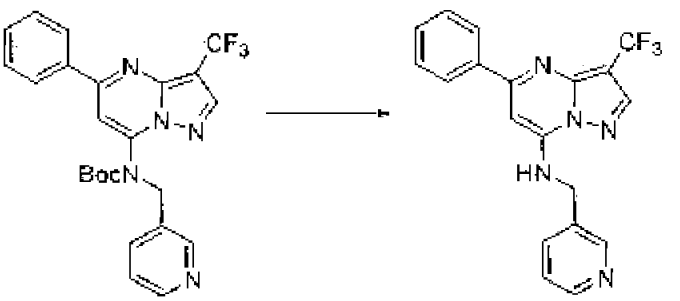
EJEMPLO 427:

ETAPA A:



Una mezcla del compuesto preparado en el Ejemplo Preparativo 194 (527 mg, 1,00 mmoles), trietil(trifluormetil)silano (666 mg, 3,60 mmoles), fluoruro de potasio (210 mg, 3,60 mmoles), y CuI (850 mg, 4,46 mmoles) en DMF anhidro (4 mL) se agitó en un recipiente cerrado bajo presión a 80°C durante 72 horas. Se agregó CH_2Cl_2 (80 mL) y la mezcla se filtró a través de Celite. El solvente se evaporó y el residuo se purificó por cromatografía evaporativa usando 2:1 de CH_2Cl_2: EtOAc como eluyente para proporcionar un sólido ceroso de color naranja pálido (70 mg, 15%). LCMS: M^+=470.

ETAPA B:

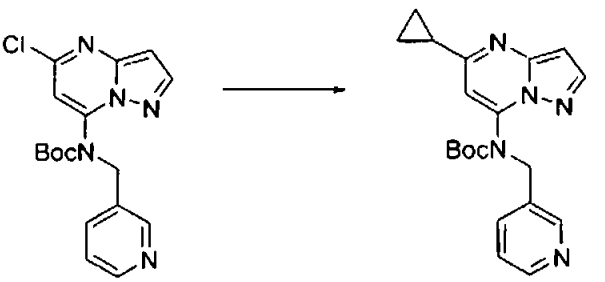


Se agregó TFA (0,70 mL) a 0°C bajo N_2 a una solución agitada del compuesto preparado en el Ejemplo 427, Etapa A (70 mg, 0,15 mmoles), en CH_2Cl_2 anhidro (3 mL). La mezcla se agitó a 0°C durante 10 minutos, y luego a 25°C durante 2 horas. Se vertió en Na_2CO_3 acuoso al 10% (50 mL), se extrajo con CH_2Cl_2 (3x15 mL), se secó sobre Na_2SO_4, y se filtró. El solvente se evaporó y el residuo se purificó por cromatografía evaporativa usando EtOAc como eluyente

para proporcionar un sólido blancuzco (40 mg, 73%). LCMS: M^+=370. P.f.=156-158°C.

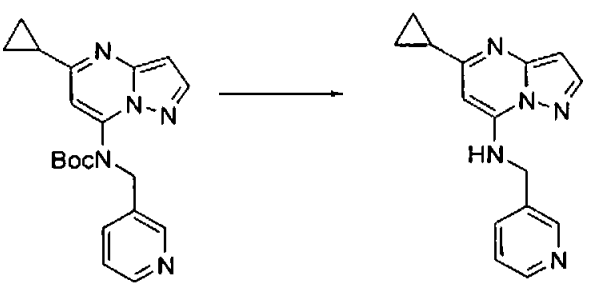
EJEMPLO 428:

ETAPA A:



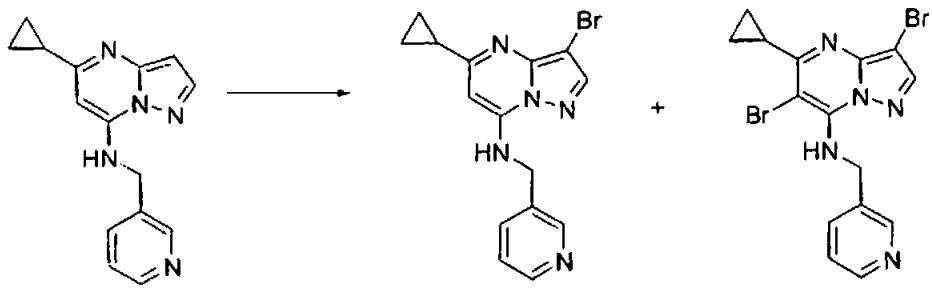
Una mezcla del compuesto preparado en el Ejemplo Preparativo 193 (100 mg, 0,28 mmoles), tetraciclopropilestaño (91 mg, 0,32 mmoles), Pd_2dba_3 (8,0 mg, 0,009 mmoles) y $Pd(Pt\text{-}Bu_3)_2$ (9,0 mg, 0,017 mmoles) en dioxano anhidro (3 mL) se reflujó bajo N_2 durante 27 horas. El solvente se evaporó y el residuo se purificó por cromatografía evaporativa usando 1:1 CH_2Cl_2:EtOAc como eluyente para proporcionar un sólido ceroso incoloro (38 mg, 38%). LCMS: MH^+=366.

ETAPA B:



Una mezcla del compuesto preparado en el Ejemplo 428, Etapa A (36 mg, 0,10 mmoles) y KOH (300 mg, 5,40 mmoles) en etanol (3 mL), 1,2-dimetoxietano (3,0 mL) y H_2O (0,8 mL) se reflujó bajo N_2 durante 4 horas. Se vertió en $NaHCO_3$ acuoso saturado (100 mL), se extrajo con CH_2Cl_2 (5x10 mL), se secó sobre Na_2SO_4, y se filtró. El solvente se evaporó y el residuo se purificó por cromatografía evaporativa usando 30:1 de EtOAc:MeOH como eluyente para proporcionar un sólido ceroso incoloro (18 mg, 69%). LCMS: MH^+=266.

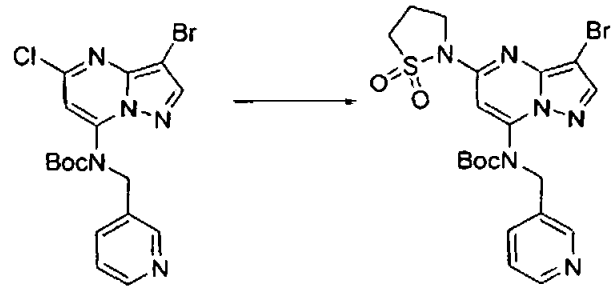
ETAPA C:



Se agregó N-bromosuccinimida (12 mg, 0,068 mmoles) CH_3CN anhidro (2 mL) bajo N_2 a una solución agitada del compuesto preparado en el Ejemplo 428, Etapa B (18 mg, 0,068 mmoles), CH_3CN anhidro (2 mL). La mezcla se agitó a 25°C durante 2 horas. El solvente se evaporó y el residuo se purificó por cromatografía evaporativa usando EtOAc como eluyente para proporcionar 5 mg (17%) del compuesto dibromo (sólido blanco, LCMS: MH^+=370, p.f.= 150-152°C) y 8 mg (34%) del compuesto monobromo (sólido incoloro, LCMS: M^+=344, p.f.= 196-198°C).

EJEMPLO 429:

ETAPA A:

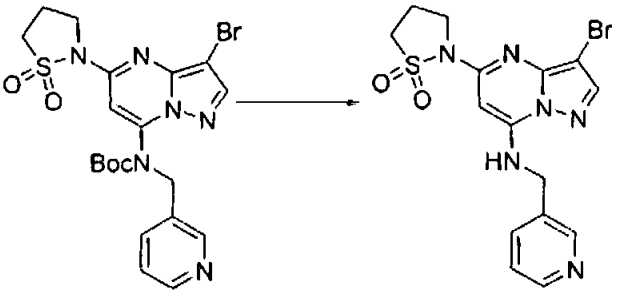


Se agregó 1,3-propansultam (72 mg, 0,60 mmoles) en DMF anhidro (3 mL) bajo N_2 a NaH al 60% en aceite mineral (36 mg, 0,90 mmoles). La mezcla se agitó durante 20 minutos, y luego se agregó el compuesto preparado en el Ejemplo Preparativo 196 (200 mg, 0,46 mmoles). La mezcla se agitó a 100°C durante 30 minutos, el solvente se evaporó y el residuo se purificó por cromatografía

196

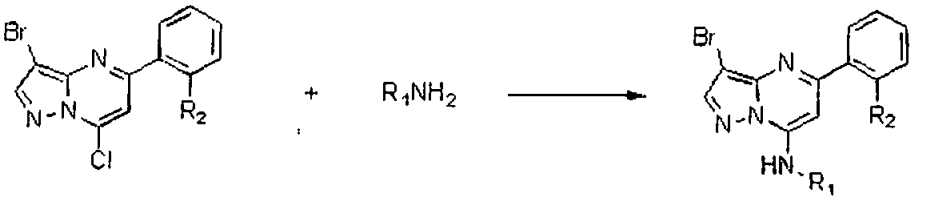
evaporativa usando EtOAc como eluyente para proporcionar un sólido incoloro (150 mg, 63%). LCMS: M^+=523.

ETAPA B:



Se agregó TFA (1,5 mL) a 0°C bajo N_2 a una solución agitada del compuesto preparado en el Ejemplo Preparativo 196 (140 mg, 0,27 mmoles), en CH_2Cl_2 anhidro (5 mL). La mezcla se agitó a 0°C durante 10 minutos, y luego a 25°C durante 2 horas. Se vertió sobre Na_2CO_3 (10 g), se extrajo con CH_2Cl_2 (3x50 mL), y se filtró. El solvente se evaporó y el residuo se purificó por cromatografía evaporativa usando 40:1 EtOAc:MeOH como eluyente para proporcionar un sólido blanco (32 mg, 28%). LCMS: M^+=423. P.f.=218-220°C.

EJEMPLO 430:



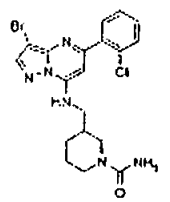
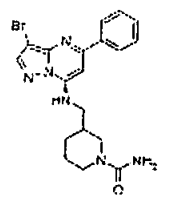
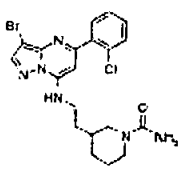
donde : R_2=H, o Cl

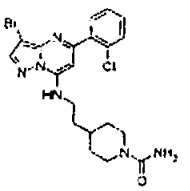
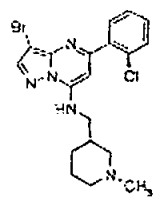
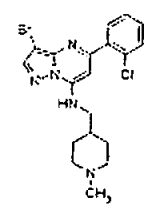
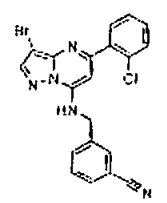
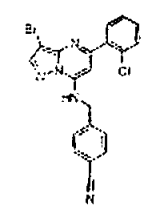
3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (1 equivalente) (preparado tal como se describió en el Ejemplo Preparativo 129), o 3-Bromo-7-cloro-5-fenilpirazolo[1,5-a]pirimidina (1 equivalente) (preparado tal como se describió en el Ejemplo Preparativo 127), R_1NH_2 (1,2 equivalentes) y diisopropiletilamina (2 equivalentes) se disolvieron en 1,4-dioxano anhidro y la mezcla se calentó a 75°C durante el tiempo que se da en la Tabla 97. La solución se evaporó hasta sequedad y el residuo se cromatografió sobre una Columna de

gel de sílice tal como se describió en la Tabla 97, para proporcionar el compuesto del título.

Usando los reactivos apropiados y esencialmente el mismo procedimiento que se describió anteriormente, se prepararon los productos de los Ejemplos 431 a 438. Las variaciones en las condiciones de reacción se señalan en la Tabla 35.

TABLA 35

Ej.	Estructura	MW	FABMS MH^+	Condiciones de la Reacción	Rendimiento	Datos Cromatográficos
431		463,8	463,0	75°C/26h	52%	15x2,5cm 0,5-2% (10% hidróxido de amonio concentrado, en metanol)-diclorometano
432		429,3	429,2	75°C/26h 25°C/39h	53%	15x5cm Diclorometano; 1,5% (10% hidróxido de amonio concentrado, en metanol)-diclorometano
433		477,8	477,1	75°C/26h	48%	15x5cm Diclorometano; 3,5-15% (10% hidróxido de amonio concentrado, en metanol)-diclorometano

434		477,8	477,0	75°C/26h	50%	15x5cm Diclorometano; 3,5-15% (10% hidróxido de amonio concentrado, en metanol)-diclorometano
435		434,8	434,1	75°C/24h 25°C/65h	53%	15x2,5cm 3% (10% hidróxido de amonio concentrado, en metanol)-diclorometano
436		434,8	434,2	75°C/27h	31%	15x2,5cm 3% (10% hidróxido de amonio concentrado, en metanol)-diclorometano
437		438,7	438,1	75°C/21h 25°C/46h	97%	15x2,5cm 0,25% (10% hidróxido de amonio concentrado, en metanol)-diclorometano
438		438,7	438,1	75°C/28h -20°C/72h	95%	60x2,5cm 20% Acetato de etilo en hexano

Los datos físicos adicionales para los compuestos se dan a continuación:

EJEMPLO 431: Reactivos: 3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (110 mg, 0,318 mmoles) (preparados tal como se describió en el

Ejemplo Preparativo 129); 3-(aminometil)piperidin-1-carboxamida (60 mg, 0,382 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 241 anterior); diisopropil etilamina (0,111 mL, 0,636 mmoles); 1,4-dioxano anhidro (2,5 mL). Propiedades físicas: HRFABMS: m/z 463,0628 (MH^+), Calc. para $C_{19}H_{21}N_6OBrCl$: m/z 463,0649: δ_H ($CDCl_3$) 1,38 (1H, m, CH_2), 1,52 (1H, m, CH_2), 1,73 (1H, m, CH), 1,93 (1H, m, CH_2), 2,02 (1H, m, CH_2), 2,98 (1H, m, CH_2), 3,06 (1H, m, CH_2), 3,37 (2H, m, CH_2), 3,58 (1H, m, CH_2), 3,82 (1H, m, CH_2), 4,87 (2H, bm, $CONH_2$), 6,28 (1H, s, H_6), 7,02 (1H, m, NH), 7,36 (2H, m, Ar-H), 7,45 (1H, m, Ar-H), 7,68 (1H, m, Ar-H) y 8,00 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 23,7, 28,1, 44,6, 45,5, 47,2; CH: 35,2, 87,4, 127,2, 130,1, 130,3, 131,6, 143,9: C: 83,1, 132,1, 138,6, 145,5, 146,5, 158,0, 158,4.

EJEMPLO 432: Reactivos: 3-Bromo-7-cloro-5-fenilpirazolo[1,5-a]pirimidina (500 mg, 1,62 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 127); 3-(aminometil)piperidin-1-carboxamida (306 mg, 1,944 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 241 anterior); diisopropil etilamina (0.566 mL, 3.24 mmoles); 1,4-dioxano anhidro (13 mL). Propiedades físicas: HRFABMS: m/z 429.1031 (MH^+). Calc. para $C_{19}H_{22}N_6OBr$: m/z 429,1038; δ_H ($CDCl_3$) 1,44 (1H, m, CH_2), 1,59 (1H, m, CH_2), 1,79 (1H, m, CH), 2,01 (1H, m, CH_2), 2,08 (1H, m, CH_2), 3,03 (1H, m, CH_2), 3,13 (1H, m, CH_2), 3,39 (1H, m, CH_2), 3,47 (1H, m, CH_2), 3,63 (1H, m, CH_2), 3,90 (1H, m, CH_2), 4,88 (2H, bm, $CONH_2$), 6,40 (1H, s, H_6), 6,90 (1H, m, NH), 7,53 (2H, m, Ar-H), 8,02 (1H, s, H_2) y 8,12 (1H, m, Ar-H); δ_C ($CDCl_3$) CH_2: 23,7, 28,2, 44,7, 45,5, 47,3; CH: 35,2, 82,9, 127,5, 127,5, 128,7, 128,7, 130,0, 143,9; C: 83,0, 138,5, 145,8, 147,1, 158,3, 158,5.

EJEMPLO 433: Reactivos: 3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (347 mg, 1,01 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 129); 3-(aminoetil)piperidin-1-carboxamida (208 mg, 1,21 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 242 anterior); diisopropil etilamina (0,393 mL, 2,02 mmoles); 1,4-dioxano anhidro (9 mL). Propiedades físicas: δ_H ($CDCl_3$) 1,24 (1H, m, CH_2), 1,55 (1H, m, CH), 1,72 (4H, m, CH_2), 1,93 (1H, m, CH_2), 2,69 (1H, m, CH_2), 2,94 (1H, m, CH_2), 3,55 (2H, m, CH_2), 3,73 (1H, m, CH_2), 3,98 (1H, m, CH_2), 4,83 (2H, bm, $CONH_2$), 6,55 (1H, s, H_6), 6,78 (1H, m, NH), 7,41 (2H, m, Ar-H), 7,50 (1H, m, Ar-H), 7,75 (1H, m, Ar-

H) y 8,04 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 24,6, 30,7, 32,6, 39,9, 45,3, 49,3; CH: 33,3, 87,5, 127,4, 130,1, 130,2, 131,6, 143,8; C: 83,2, 132,1, 138,8, 145,7, 146,2, 158,1, 158,1.

EJEMPLO 434: Reactivos: 3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (275 mg, 0,803 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 129); 4-(aminoetil)piperidin-1-carboxamida (165 mg, 0,963 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 243 anterior); diisopropil etilamina (0,311 mL, 0,963 mmoles); 1,4-dioxano anhidro (7,2 mL). Propiedades físicas: δ_H (d_6-DMSO) 1,00 (2H, m, CH_2), 1,50 (1H, m, CH), 1,59 (2H, m, CH_2), 1,67 (2H, m, CH_2), 2,60 (2H, m, CH_2), 3,48 (2H, m, CH_2), 3,70 (2H, m, CH_2), 5,84 (2H, bs, $CONH_2$), 6,43 (1H, s, H_6), 7,50 (2H, m, Ar-H), 7,62 (2H, m, Ar-H), 8,30 (1H, s, H_2) y 8,36 ppm (1H, m, NH); δ_C (d_6-DMSO) CH_2: 31,5, 31,5, 34,8, 43,5, 43,5, 43,5; CH: 32,8, 86,8, 127,1, 129,7, 130,3, 131,0, 143,3; CH: 81,3, 131,0, 138,7, 145,1, 146,4, 157,3, 157,8.

EJEMPLO 435: Reactivos: 3-Bromo-7-cloro-5-fenilpirazolo[1,5-a]pirimidina (174 mg, 0.507 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 129) y 3-(aminometil)-1-metilpiperidina (65 mg, 0,507 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 244 anterior); diisopropil etilamina (0,178 mL, 1,014 mmoles); 1,4-dioxano anhidro (2,5 mL). Propiedades físicas: HRFABMS: m/z 434.0742 (MH^+). Calc. para $C_{19}H_{22}N_5BrCl$: m/z 434,0747; δ_H ($CDCl_3$) 1,18 (1H, m, CH_2), 1,68 (1H, m, CH_2), 1,80 (1H, m, CH_2), 1,87 (1H, m, CH_2), 1,96 (1H, m, CH), 2,14 (2H, m, CH_2), 2,32 (3H, s, NCH_3), 2,75 (1H, m, CH_2), 2,29 (1H, m, CH_2), 3,42 (2H, m, -NHC$\underline{H}_2$CH), 6,36 (1H, s, H_6), 6,64 (1H, bm, NH), 7,41 (2H, m, Ar-H), 7,51 (1H, m, Ar-H), 7,74 (1H, m, Ar-H) y 8,06 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 46,6; CH_2: 24,4, 27,9, 46,1, 56,1, 59,6; CH: 36,0, 87,4, 127,1, 130,1, 130,2, 131,6, 143,8; C: 83,2, 132,1, 138,9, 145,6, 146,4, 158,2.

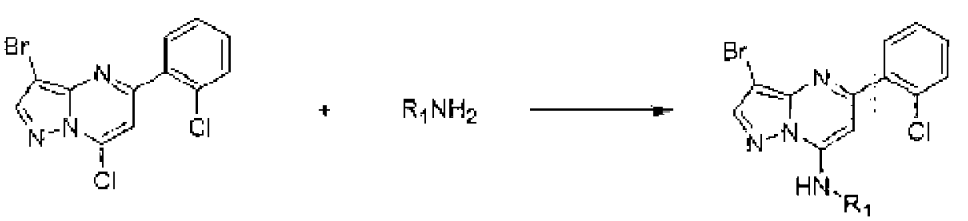
EJEMPLO 436: Reactivos: 3-Bromo-7-cloro-5-fenilpirazolo[1,5-a]pirimidina (111.4 mg, 0.325 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 129); 4-(aminometil)-1-metilpiperidina (50 mg, 0,39 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 245 anterior); diisopropil etilamina (0,1135 mL, 0,65 mmoles); 1,4-dioxano anhidro (1,5 mL). Datos físicos: HRFABMS: m/z 434.0735 (MH^+). Calc. para $C_{19}H_{22}N_5BrCl$: m/z 434,0747; δ_H ($CDCl_3$) 1,42 (2H, m,

CH_2), 1,72 (1H, m, CH), 1,82 (2H, m, CH_2), 1,93 (2H, m, CH_2), 2,20 (3H, s, NCH_3), 2,89 (2H, m, CH_2), 3,34 (2H, m, -NHC$\underline{H_2}$CH), 6,31 (1H, s, H_6), 6,46 (1H, m, NH), 7,36 (2H, m, Ar-H), 7,46 (1H, m, Ar-H), 7,70 (1H, m, Ar-H) y 8,00 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 46,4; CH_2: 30,2, 30,2, 48,0, 55,3, 55,3; CH: 35,4, 87,5, 127,2, 130,2, 130,2, 131,6, 143,8; C: 83,3, 132,2, 138,9, 145,7, 146,4, 158,1.

EJEMPLO 437: Reactivos: 3-Bromo-7-cloro-5-fenilpirazolo[1,5-a]pirimidina (191 mg, 0.557 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 129); 3-(aminometil)benzonitrilo (88,3 mg, 0,668 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 246 anterior); diisopropil etilamina (0,192 mL, 1,114 mmoles); 1,4-dioxano anhidro (4,5 mL). Datos físicos: HRFABMS: m/z 438.0125 (MH^+). Calc. para $C_{19}H_{12}N_5BrCl$: m/z 438,0121; δ_H ($CDCl_3$) 4,76 (2H, d, -C$\underline{H_2}$NH-), 6,32 (1H, s, H_6), 7,00 (1H, m, -CH_2N$\underline{H}$-), 7,40 (2H, m, Ar-H), 7,46 (1H, m, Ar-H), 7,55 (1H, m, Ar-H), 7,67 (2H, m, Ar-H), 7,71 (1H, m, Ar-H), 7,75 (1H, m Ar-H) y 8,10 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 45,5; CH: 88,2, 127,2, 130,0, 130,2, 130,4, 130,6, 131,4, 131,6, 131,9, 144,1; C: 83,8, 113,4, 118,3, 132,0, 137,8, 138,3, 145,6, 145,9, 158,0.

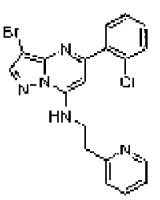
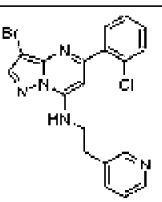
EJEMPLO 438: Reactivos: 3-Bromo-7-cloro-5-fenilpirazolo[1,5-a]pirimidina (233,5 mg, 0,681 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 129); 4-(aminometil)benzonitrilo (108 mg, 0,817 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 247 anterior); diisopropil etilamina (0,235 mL, 1,362 mmoles); 1,4-dioxano anhidro (5,3 mL). Datos físicos: HRFABMS: m/z 438,0117 (MH^+) Calc. para $C_{20}H_{14}N_5BrCl$: m/z 438,0121; δ_H ($CDCl_3$) 4,80 (2H, d, CH_2), 6,30 (1H, s, H_6), 7,01 (1H, m, NH), 7,40 (2H, m, Ar-H), 7,47 (1H, m, Ar-H), 7,70 (2H, m, Ar-H), 7,72 (2H, m, Ar-H), 7,80 (1H, m, Ar-H) y 8,10 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 45,8; CH: 88,2, 127,2, 127,7, 127,7, 130,2, 130,4, 131,6, 132,9, 132,9, 144,1; C: 83,8, 112,2, 118,4, 132,0, 138,2, 141,5, 145,5, 146,0, 158,0.

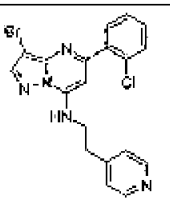
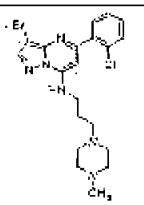
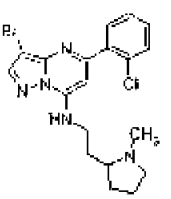
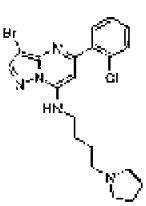
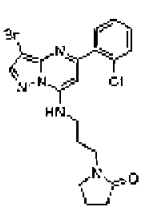
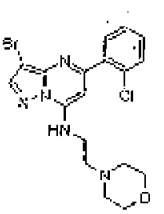
EJEMPLO 439:

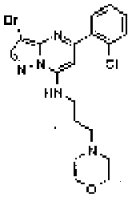
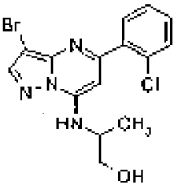


3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (50 mg, 0,146 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 129) se disolvió en 1,4-dioxano anhidro (5 mL) en un tubo de reacción GeneVac Technologies carousel. Se agregó a cada tubo resina de PS-diisopropil etilamina (161 mg, 0,5828 mmoles). Una solución 1M recientemente preparada de la amina R_1NH_2 apropiada en 1,4-dioxano anhidro (0,2185 mL, 0,2185 mmoles) se agregó a cada uno de los tubos y los tubos se sellaron y calentaron a 70°C durante 78 horas a agitación magnética en el bloque de reacción. Cada tubo se filtró y la resina se lavó con 1,4-dioxano anhidro y luego con diclorometano. Los filtrados individuales combinados de cada tubo se evaporaron hasta sequedad y cada uno de los residuos se re-disolvió en 1,4-dioxano anhidro (5 mL) y se colocó en tubos de reacción GeneVac. A cada tubo se agregó PS-resina de isocianato (594 mg, 0,8742 mmoles) y PS-resina de trisamina (129 mg, 0,4371 mmoles) y los tubos se agitaron a 25°C durante 20 horas en el bloque de reacción. Las resinas se separaron por filtración y se lavaron con 1,4-dioxano anhidro y diclorometano. Los filtrados de cada tubo se evaporaron hasta sequedad y cada uno de los residuos se cromatografió sobre una columna de gel de sílice usando el tamaño de columna y el eluyente que se muestran en la Tabla 36, para proporcionar los compuestos del título.

TABLA 36

Ej.	Estructura	MW	FABMS MH^+	Rendimiento	Datos Cromatográficos
440		428.7	428.0	81%	15x2.5cm. Diclorometano; 0,5% de metanol en diclorometano
441		428.7	428.0	48%	20x2cm Diclorometano; 1,5% Metanol en diclorometano

442		428.7	428.0	24%	15x2,5cm Diclorometano; 1,5% Metanol en diclorometano
443		463.8	463.0	44%	15x2,2cm Diclorometano; 5% Metanol en diclorometano
444		434.8	434.1	63%	15x2.5cm 5% Metanol en diclorometano
445		448.8	448.2	65%	15x2.5cm 5% Metanol en diclorometano
446		448.8	448.1	40%	15x2,5cm Diclorometano; 0,5% de metanol en diclorometano
447		436.7	436.1	72%	15x2.5cm 0,5% de metanol en diclorometano

448		450.8	450.0	53%	20x2cm Diclorometano; 0,5% de metanol en diclorometano
449		381.7	381.0	44%	20x2cm 1,5% Metanol en diclorometano

Los datos físicos adicionales para los compuestos se dan a continuación:

EJEMPLO 440: Propiedades físicas: HRFABMS: m/z 428.0272 (MH^+). Calc. para $C_{19}H_{16}N_5BrCl$: m/z 428,0278; δ_H ($CDCl_3$) 3,28 (2H, dd, $C_5H_4NC\underline{H_2}CH_2NH$-), 3,94 (2H, ddd, $C_5H_4NCH_2C\underline{H_2}NH$-), 6,40 (1H, s, H_6), 7,22-7,29 (3H, m, Ar-H), 7,38-7,44 (2H, m, Ar-H), 7,51 (1H, m, Ar-H), 7,68 (1H, ddd, Ar-H), 7,73 (1H, Ar-H), 8,18 (1H, s, H_2) y 8,68ppm (1H, NH); δ_C ($CDCl_3$) CH_2: 36,4, 41,5; CH: 87,3, 122,1, 123,6, 127,1, 130,1, 130,1, 131,6, 137,0, 143,8, 149,5; C: 83,1, 132,1, 138,9, 145,7, 146,3, 158,0, 158,1.

EJEMPLO 441: Propiedades físicas: HRFABMS: m/z 428,0272 (MH^+), Calc, para $C_{19}H_{16}N_5BrCl$: m/z 428,0278; δ_H ($CDCl_3$) 3,12 (2H, dd, $C_5H_4NC\underline{H_2}CH_2NH$-), 3,77 (2H, ddd, $C_5H_4NCH_2C\underline{H_2}NH$-), 6,40 (1H, s, H_6), 6,59 (1H, m, Ar-H), 7,34 (1H, bm, Ar-H), 7,39-7,45 (2H, m, Ar-H), 7,52 (1H, m, Ar-H), 7,62 (1H, m, Ar-H), 7,75 (1H, m, Ar-H), 8,05 (1H, s, H_2) y 8,63ppm (1H, m, NH); δ_C ($CDCl_3$) CH_2: 32,7, 43,1; CH: 87,5, 127,2, 130,2, 130,3, 131,6, 136,4, 142,9, 148,3, 149,8; C: 83,5, 132,0, 138,6, 145,6, 145,9, 158,1.

EJEMPLO 442: Propiedades físicas: HRFABMS: m/z 428,0275 (MH^+), Calc, para $C_{19}H_{16}N_5BrCl$: m/z 428,0278; δ_H ($CDCl_3$) 3,13 (2H, dd, $C_5H_4NC\underline{H_2}CH_2NH$-), 3,80 (2H, ddd, $C_5H_4NCH_2C\underline{H_2}NH$-), 6,42 (1H, s, H_6), 6,53 (1H, m, Ar-H), 7,23 (2H, m, Ar-H), 7,40-7,46 (2H, m, Ar-H), 7,62 (1H, m, Ar-H), 7,76 (1H, m, Ar-H), 8,07 (1H, s, H_2) y 8,63ppm (1H, m, NH); δ_C ($CDCl_3$) CH_2: 34,7, 42,5; CH: 87,4, 124,5, 124,5,

127,2, 130,2, 130,3, 131,6, 144,0, 150,2, 150,2; C: 83,5, 132,0, 138,6, 145,6, 145,9, 146,6, 158,1.

EJEMPLO 443: Propiedades físicas: HRFABMS: m/z 463.1003 (MH^+). Calc. para $C_{20}H_{25}N_6BrCl$: m/z 463.1013; δ_H ($CDCl_3$) 1.98 (2H, m, $=NCH_2C\underline{H}_2CH_2NH$-), 2,43 (3H, s, NCH_3), 2,67 (2H, m, $=NC\underline{H}_2CH_2CH_2NH$-), 2,70 (8H, piperazine CH_2), 3,58 (2H, m, $=NCH_2CH_2C\underline{H}_2NH$-), 6,32 (1H, s, H_6), 7,37-7,43 (2H, m, Ar-H), 7,50 (1H, m, Ar-H), 7,73 (1H, m, Ar-H), 8,06 (1H, s, H_2) y 8,60ppm (1H, m, NH); δ_C ($CDCl_3$) CH_3: 46,1; CH_2: 24,1, 42,8, 53,3, 54,6, 54,6, 57,5, 57,5; CH: 87,1, 127,0, 130,0, 130,1, 131,5, 143,4; C: 82,7, 132,1, 139,2, 145,7, 146,7, 158,0.

EJEMPLO 444: Propiedades físicas: HRFABMS: m/z 434,0742 (MH^+), Calc, para $C_{19}H_{22}N_5BrCl$: m/z 434,0747; δ_H ($CDCl_3$) 1,72 (1H, m, CH/CH_2), 1,78-1,90 (2H, m, CH/CH_2), 2,02 (3H, m, CH/CH_2), 2,50 (1H, m, CH/CH_2), 2,45 (3H, s, NCH_3), 2,51 (1H, m, CH/CH_2), 3,23 (1H, m, CH/CH_2), 3,54 (1H, m, CH/CH_2), 3,60 (1H, m, CH/CH_2), 6,32 (1H, s, H_6), 7,38-7,44 (2H, m, Ar-H), 7,51 (1H, m, Ar-H), 7,75 (1H, m, Ar-H), 7,96 (1H, bm, NH) y 8,05 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 40,7; CH_2: 22,7, 29,3, 30,1, 39,4, 57,0; CH: 64,2, 87,1, 127,1, 130,0, 130,1, 131,6, 143,8; C: 82,8, 132,1, 139,1, 145,7, 146,4, 158,0.

EJEMPLO 445: Propiedades físicas: HRFABMS: m/z 448,0910 (MH^+), Calc, para $C_{20}H_{24}N_5BrCl$: m/z 448,0904; δ_H ($CDCl_3$) 1,90 (4H, m, CH_2), 2,00 (4H, m, CH_2), 2,84 (2H, m, CH_2), 2,95 (4H, m, CH_2), 3,51 (2H, m, CH_2), 6,32 (1H, s, H_6), 7,05 (1H, bm, NH), 7,37-7,43 (2H, m, Ar-H), 7,50 (1H, m, Ar-H), 7,73 (1H, m, Ar-H) y 8,04 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 23,4, 23,4, 24,8, 26,4, 41,8, 53,9, 53,9, 55,2; CH: 87,3, 127,1, 130,1, 130,2, 131,6, 143,7; C: 83,0, 132,0, 138,9, 145,7, 146,3, 158,1.

EJEMPLO 446: Propiedades físicas: HRFABMS: m/z 448,0548 (MH^+), Calc, para $C_{19}H_{20}N_5OBrCl$: m/z 448,0540; δ_H ($CDCl_3$) 1,94 (2H, m, CH_2), 2,09 (2H, m, CH_2), 2,49 (2H, m, CH_2), 3,45 (2H, m, CH_2), 3,51 (4H, m, CH_2), 6,32 (1H, s, H_6), 7,37-7,44 (3H, m, Ar-H/NH), 7,51 (1H, m, Ar-H), 7,75 (1H, m, Ar-H) y 8,10 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 18,0, 26,3, 30,8, 39,2, 39,9, 47,5; CH: 87,0, 127,1, 130,1, 130,1, 131,6, 144,1; C: 82,9, 132,1, 138,9, 145,6, 146,2, 157,9, 176,2.

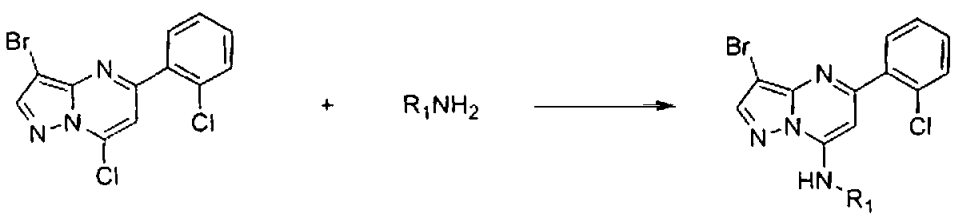
EJEMPLO 447: Propiedades físicas: HRFABMS: m/z 436,0532 (MH^+), Calc, para $C_{18}H_{20}N_5OBrCl$: m/z 436,0540; δ_H ($CDCl_3$) 2,60 (4H, bm, $-N(C\underline{H}_2CH_2)_2O$), 2,83

(2H, m, =NC$\underline{H}_2$CH$_2$NH-), 3,57 (2H, m, =NCH$_2$C$\underline{H}_2$NH-), 3,83 (4H, m, -N(CH$_2$C$\underline{H}_2$)$_2$O), 6,37 (1H, s, H$_6$), 6,99 (1H, bm, NH), 7,38-7,45 (2H, m, Ar-H), 7,51 (1H, m, Ar-H), 7,75 (1H, m, Ar-H) y 8,09 ppm (1H, s, H$_2$); δ_C ($CDCl_3$) CH$_2$: 38,2, 53,3, 53,3, 56,2, 66,9, 66,9; CH: 87,6, 127,1, 130,1, 130,2, 131,6, 143,9; C; 83,1, 132,1, 138,9, 145,7, 146,2, 158,1.

EJEMPLO 448: Propiedades físicas: HRFABMS: m/z 450,0688 (MH^+), Calc, para $C_{19}H_{22}N_5OBrCl$: m/z 450,0696; δ_H ($CDCl_3$) 1,98 (2H, m, =NCH$_2$C$\underline{H}_2$CH$_2$NH-), 2,58 (4H, m, -N(C$\underline{H}_2$CH$_2$)$_2$O), 2,67 (2H,m, =NC$\underline{H}_2$CH$_2$CH$_2$NH-), 3,59 (2H, m, =NCH$_2$CH$_2$C$\underline{H}_2$NH-), 3,94 (4H, m, -N(CH$_2$C$\underline{H}_2$)$_2$O), 6,31 (1H, s, H$_6$), 7,37-7,44 (2H, Ar-H), 7,51 (1H, m, Ar-H), 7,78 (1H, m, Ar-H), 8,08 (1H, s, H$_2$) y 8,60 ppm (1H, bm, NH); δ_C ($CDCl_3$) CH$_2$: 23,7, 42,7, 52,9, 52,9, 58,0, 66,6, 66,6; CH: 87,0, 127,1, 130,0, 130,1, 131,5, 143,6; C: 82,8, 132,1, 139,1, 145,7, 146,7, 158,0.

EJEMPLO 449: Propiedades físicas: HRFABMS: m/z 381,0114 (MH^+), Calc, para $C_{15}H_{15}N_4OBrCl$: m/z 381,0118; δ_H ($CDCl_3$) 1,39 (3H, d, CHC$\underline{H}_3$), 2,76 (1H, bm, -OH), 3,71 (1H, m, =CHC$\underline{H}_2$OH), 3,81 (1H, m, =CHC$\underline{H}_2$OH), 3,88 (1H, m, =C$\underline{H}$CH$_2$OH), 6,38 (1H, s, H$_6$), 7,38 (2H, m, Ar-H), 7,48 (1H, m, Ar-H), 7,68 (1H, m, Ar-H) y 8,02 ppm (1H, s, H$_2$); δ_C ($CDCl_3$) CH$_3$: 16,9; CH$_2$: 65,0; CH: 50,0, 88.0, 127.1, 130.1, 130.3, 131.4, 143.8; C: 83.0, 132.0, 138.5, 145.6, 146.0, 158.2.

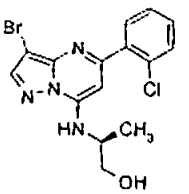
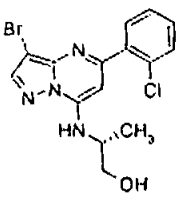
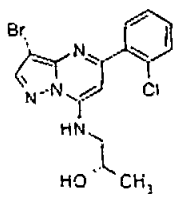
EJEMPLO 450:

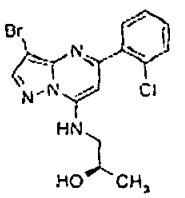
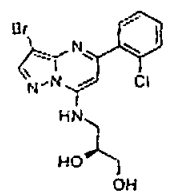
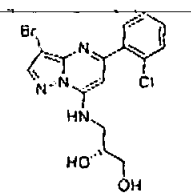
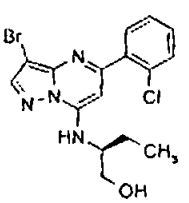
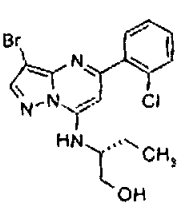
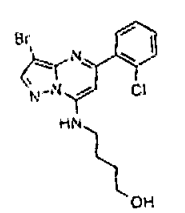


3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (50 mg, 0,146 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 129) se disolvió en 1,4-dioxano anhidro (5 mL) en un tubo de reacción GeneVac Technologies carousel. Se agregó a cada tubo PS-resina de diisopropil etilamina (161 mg, 0,5828 mmoles). Una solución recientemente preparada de la amina R_1NH_2 apropiada (0,219 mmoles) en 1,4-dioxano anhidro (0,3 mL) se agregó a

cada tubo, con excepción del Ejemplo 99-5 en el cual la amina se disolvió en 10% MeOH en 1,4-dioxano (0,3 mL), y los tubos se sellaron y calentaron a 70°C durante 74 horas con agitación magnética en el bloque de reacción. Cada tubo se filtró y la resina se lavó con 1,4-dioxano anhidro y luego con diclorometano. Los filtrados individuales combinados de cada tubo se evaporaron hasta sequedad y cada uno de los residuos se re-disolvió en 1,4-dioxano anhidro (5 mL) y se colocó en tubos de reacción GeneVac. Se agregó a cada tubo PS-resina de isocianato (594 mg, 0,8742 mmoles) y PS-resina de trisamina (129 mg, 0,4371 mmoles) y los tubos se agitaron a 25°C durante 20 horas en el bloque de reacción. Las resinas se separaron por filtración y se lavaron con 1,4-dioxano anhidro y diclorometano. Los filtrados de cada tubo se evaporaron hasta sequedad y cada uno de los residuos se cromatografió sobre columna de gel de sílice usando el tamaño de columna y el eluyente que se muestran en la Tabla 37, para proporcionar los compuestos del título.

TABLA 37

Ej.	Estructura	MW	FABMS MH^+	Rendimiento	Datos Cromatográficos
451		381.7	380.9	66%	15x2,5cm; 0,5% de metanol en diclorometano
452		381.7	380.9	60%	20x2cm; 0,5% de metanol en diclorometano
453		381.7	380.9	69%	15x2,5cm; 0,35% Metanol en diclorometano

454		381.7	380.9	75%	15x2,5cm; 0,35% Metanol en diclorometano
455		397.7	397.2	84%	15x2,5cm; 1,5% Metanol en diclorometano
456		397.7			
457		395.7	395.0	60%	15x2,5cm; 0,35% Metanol en diclorometano
458		395.7	396.3	50%	15x2,5cm; 0,35% Metanol en diclorometano
459		395.7	396.0	76%	15x2,5cm; 0,35% Metanol en diclorometano

Los datos físicos adicionales para los compuestos se dan a continuación:

EJEMPLO 451: Propiedades físicas: HRFABMS: m/z 381.0115 (MH^+). Calc. para $C_{15}H_{15}N_4OBrCl$: m/z 381,0118; $[\alpha]_D^{25°C}$ +1.4° (c=0,25 , MeOH); δ_H ($CDCl_3$) 1,44 (3H, d, -CHC<u>H</u>$_3$), 3,77 3,89 (1H, dd, CHC<u>H</u>$_2$OH), (1H, dd, CHC<u>H</u>$_2$OH), 3,94 (1H, m, C<u>H</u>CH$_2$OH), 6,41 (1H, s, H_6), 6,58 (1H, d, NH), 7,41 (2H, m, Ar-H), 7,51 (1H, m, Ar-H), 7,74 (1H, m, Ar-H) y 8,04 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 17,1; CH_2: 65,5; CH: 49,9, 88,0, 127,1, 130,1, 130,2, 131,6, 143,8; C: 83,2, 132,1, 138,7, 145,6, 145,8, 158,1.

EJEMPLO 452: Propiedades físicas: HRFABMS: m/z 381.0115 (MH^+). Calc. para $C_{15}H_{15}N_4OBrCl$: m/z 381,0118; $[\alpha]_D^{25°C}$ +6.5° (c=0,32 , MeOH); δ_H ($CDCl_3$) 1,44 (3H, d, -CHC<u>H</u>$_3$), 3,78 (1H, dd, CHC<u>H</u>$_2$OH), 3,89 (1H, dd, CHC<u>H</u>$_2$OH), 3,96 (1H, m, C<u>H</u>CH$_2$OH), 6,41 (1H, s, H_6), 6,58 (1H, d, NH), 7,41 (2H, m, Ar-H), 7,51 (1H, m, Ar-H), 7,75 (1H, m, Ar-H) y 8,04 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 17,1; CH_2: 65,5; CH: 49,9, 88,0, 127,1, 130,1, 130,3, 131,6, 143,8; C: 83,2, 132,1, 138,6, 145,6, 145,8, 158,1.

EJEMPLO 453: Propiedades físicas: HRFABMS: m/z 381.0115 (MH^+). Calc. para $C_{15}H_{15}N_4OBrCl$: m/z 381,0118; $[\alpha]_D^{25°C}$ +9,4° (c=0,27, MeOH); δ_H ($CDCl_3$) 1,33 (3H, d, CH_3), 2,25 (1H, bs, OH), 3,37 (1H, dd, CH_2), 3,51 (1H, m, CH_2), 4,16 (1H, m, C<u>H</u>OH), 6,35 (1H, s, H_6), 6,93 (1H, m, NH), 7,40 (2H, m, Ar-H), 7,50 (1H, m, Ar-H), 7,70 (1H, m, Ar-H) y 8,04 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 20,8; CH_2: 49,2; CH: 65,7, 87,8, 127,1, 130,1, 130,2, 131,2, 143,9; C: 83,1, 132,1, 138,5, 145,6, 146,6, 158,3.

EJEMPLO 454: Propiedades físicas: HRFABMS: m/z 381.0112 (MH^+). Calc. para $C_{15}H_{15}N_4OBrCl$: m/z 381,0118; $[\alpha]_D^{25°C}$ -3,2° (c=0,29 , MeOH); δ_H ($CDCl_3$) 1,32 (3H, d, CH_3), 2,48 (1H, bs, OH), 3,35 (1H, dd, CH_2), 3,49 (1H, m, CH_2), 4,15 (1H, m, C<u>H</u>OH), 6,34 (1H, s, H_6), 6,93 (1H, m, NH), 7,39 (2H, m, Ar-H), 7,49 (1H, m, Ar-H), 7,68 (1H, m, Ar-H) y 8,03 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 20,8; CH_2: 49,2; CH: 65,7, 87,7, 127,1, 130,1, 130,3, 131,4, 143,9; C: 83,0, 132,0, 138,6, 145,6, 146,6, 158,3.

EJEMPLO 455: Propiedades físicas: HRFABMS: m/z 397.0054 (MH^+). Calc. para $C_{15}H_{15}N_4O_2BrCl$: m/z 397,0067; $[\alpha]_D^{25°C}$ -9,5° (c= 0,28, MeOH); δ_H ($CDCl_3$) 3,18 (2H, bs, OH), 3,47 (1H, dd, CH_2), 3,58 (1H, dd, CH_2), 3,63 (1H, dd, C<u>H</u>$_2$OH), 3,70

(1H, dd, C$\underline{H}_2$OH), 3,98 (1H, m, CH), 6,35 (1H, s, H_6), 7,10 (1H, m, NH), 7,37 (2H, m, Ar-H), 7,46 (1H, m, Ar-H), 7,64 (1H, m, Ar-H) y 8,01 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 44,7, 64,0; CH: 69,7, 87,7, 127,0, 130,1, 130,3, 131,3, 143,9; C: 82,9, 132,0, 138,4, 145,4, 146,7, 158,3.

EJEMPLO 456: Este enantiómero puede prepararse esencialmente de la misma manera que se ha descripto anteriormente.

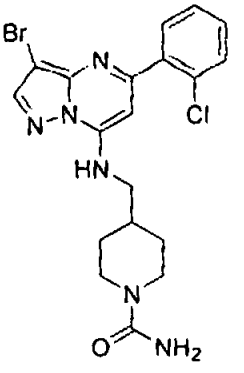
EJEMPLO 457: Propiedades físicas: HRFABMS: m/z 395.0260 (MH^+). Calc. para $C_{16}H_{17}N_4OBrCl$: m/z 395,0274; $[\alpha]_D^{25°C}$ -34,3° (c= 0,28, MeOH); δ_H ($CDCl_3$) 1,08 (3H, dd, CH_3), 1,78 (1H, m, CH_2), 1,86 (1H, m, CH_2), 2,35 (1H, bs, $CH_2O\underline{H}$), 3,71 (1H, m, C$\underline{H}$NH), 3,81 (1H, dd, C$\underline{H}_2$OH), 3,90 (1H, dd, C$\underline{H}_2$OH), 6,42 (1H, s, H_6), 6,53 (1H, m, NH), 7,41 (2H, m, Ar-H), 7,51 (1H, Ar-H), 7,75 (1H, m, Ar-H) y 8,04 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 10,5; CH_2: 24,5, 63,7; CH: 55,9, 88,0, 127,1, 130,1, 130,2, 131,6, 143,8; C: 83,2, 132,1, 138,6, 145,6, 146,3, 158,1.

EJEMPLO 458: Propiedades físicas: HRFABMS: m/z 395,0274 (MH^+). Calc. para $C_{16}H_{17}N_4OBrCl$: m/z 395,0274; $[\alpha]_D^{25°C}$ +27,5° (c= 0,25, MeOH); δ_H ($CDCl_3$) 1,05 (3H, dd, CH_3), 1,76 (1H, m, CH_2), 1,85 (1H, m, CH_2), 2,28 (1H, bs, $CH_2O\underline{H}$), 3,67 (1H, m, C$\underline{H}$NH), 3,77 (1H, dd, C$\underline{H}_2$OH), 3,84 (1H, dd, C$\underline{H}_2$OH), 6,49 (1H, s, H_6), 6,66 (1H, m, NH), 7,39 (2H, m, Ar-H), 7,49 (1H, Ar-H), 7,71 (1H, m, Ar-H) y 8,04 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 10,5; CH_2: 24,3, 63,3; CH: 56,1, 88,0, 127,1, 130,1, 130,3, 131,5, 143,8; C: 83,0, 132,1, 138,6, 145,6, 146,3, 158,2.

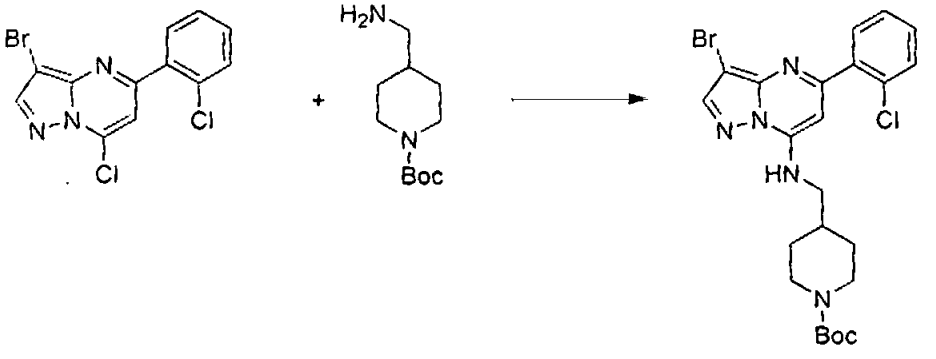
EJEMPLO 459: Propiedades físicas: HRFABMS: m/z 395.0264 (MH^+). Calc. para $C_{16}H_{17}N_4OBrCl$: m/z 395,0274; δ_H ($CDCl_3$) 1,77 (2H, m, -NHCH$_2$CH$_2$C$\underline{H}_2$CH$_2$OH), 1,90 (1H, bm, -NHCH$_2$CH$_2$CH$_2$CH$_2$O$\underline{H}$), 1,93 (2H, m, -NHCH$_2$C$\underline{H}_2$CH$_2$CH$_2$OH), 3,54 (2H, m, -NHC$\underline{H}_2$CH$_2$CH$_2$CH$_2$OH), 3,77 (2H, m, -NHCH$_2$CH$_2$CH$_2$C$\underline{H}_2$OH), 6,37 (1H, s, H_6), 6,72 (1H, m, -N$\underline{H}$CH$_2$CH$_2$CH$_2$CH$_2$OH), 7,41 (2H, m, Ar-H), 7,51 (1H, m, Ar-H), 7,75 (1H, m, Ar-H) y 8,06 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 25,7, 29,7, 42,2, 62,2; CH: 87,4, 127,1, 130,1, 130,2, 131,6, 143,8; C: 83,1, 132,1, 138,8, 145,6, 146,3, 158,1.

EJEMPLO 460:

AMIDA DE ÁCIDO 4-{[3-BROMO-5-(2-CLOROFENIL)PIRAZOLO[1,5-a]PIRIMIDIN-7-ILAMINO]METIL}PIPERIDIN-1-CARBOXÍLICO:



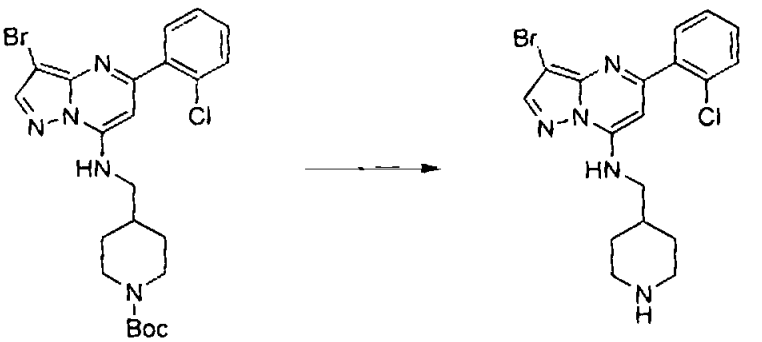
A. ÉSTER TER-BUTÍLICO DE ÁCIDO 4-{[3-BROMO-5-(2-CLOROFENIL)PIRAZOLO[1,5-a]PIRIMIDIN-7-ILAMINO]METIL}PIPERIDIN-1-CARBOXÍLICO



3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (300 mg, 0,875 mmoles) (preparada tal como se describió en el Ejemplo Preparativo 129) se disolvió en 1,4-dioxano anhidro (6,8 mL). Se agregaron éster ter-butílico de ácido 4-(aminometil)piperidin-1-carboxílico (225 mg, 1,05 mmoles) y diisopropil etilamina (0,3055 mL, 1,75 mmoles) y la mezcla se calentó a 75°C durante 24 horas. La solución se evaporó hasta sequedad y el residuo se cromatografió sobre una columna de gel de sílice (15 x 5cm) usando diclorometano como eluyente para proporcionar éster ter-butílico de ácido 4-{[3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-ilamino]metil}piperidin-1-carboxílico (461,2 mg, 100%): FABMS: m/z 520.1 (MH^+); HRFABMS: m/z 520,1111 (MH^+). Calc. para $C_{23}H_{28}N_5O_2BrCl$: m/z 520,1115; δ_H ($CDCl_3$) 1,30 (2H, m, CH_2), 1,51 (9H, s, -$COOC(CH_3)_3$), 1,85 (2H, d, CH_2), 1,95 (1H, m , CH), 2,76 (2H, m, CH_2), 3,40 (2H, m, CH_2), 6,37 (1H, s, H_6), 6,55 (1H, m, NH), 7,42 (2H, m, Ar-H), 7,52 (1H, m, Ar-H), 7,76 (1H, m, Ar-H) y 8,07 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 28,5, 28,5, 28,5; CH_2: 29,1, 29,1, 43,5, 43,5,

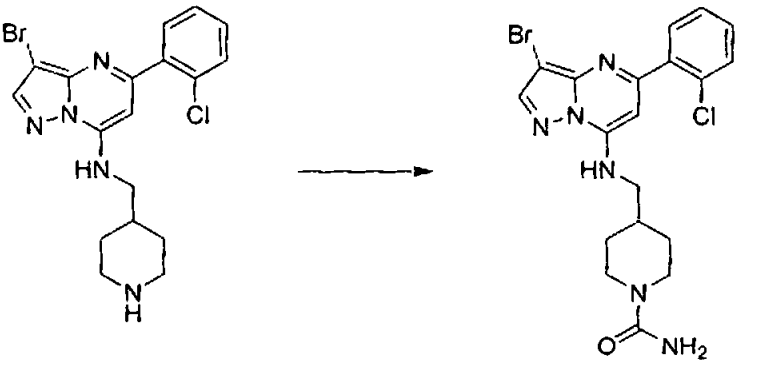
47,9; CH: 36,3, 87,5, 127,2, 130,2, 130,3, 131,6, 143,9; C: 79,7, 83,3, 132,1, 138,6, 145,4, 146,3, 154,7, 158,1.

B. [3-BROMO-5-(2-CLOROFENILPIRAZOLO[1,5-a]PIRIMIDIN-7-IL]PIPERIDIN-4-ILMETILAMINA:



Éster ter-butílico de ácido 4-{[3-Bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-ilamino]metil}piperidin-1-carboxílico (441 mg, 0,847 mmoles) (preparado tal como se describió en el Ejemplo 460, Etapa A anterior) se disolvió en metanol (4,5 mL) y se agregaron 10% (v/v) de ácido sulfúrico concentrado en 1,4-dioxano (11,46 mL). La mezcla se agitó a 25°C durante 0,5 horas. El producto se elaboró tal como se describió en el Ejemplo Preparativo 241, etapa B y se cromatografió sobre una columna de gel de sílice (15x5cm) usando 8% (hidróxido de amonio concentrado al cromatografió sobre una columna de gel de sílice en metanol)-diclorometano como eluyente para proporcionar [3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-il]piperidin-4-ilmetilamina (314,4 mg, 88%): FABMS: m/z 420,0 (MH^+); HRFABMS: m/z 420,0585 (MH^+). Calc. para $C_{18}H_{20}N_5BrCl$: m/z 420,0591; δ_H ($CDCl_3$) 1.34 (2H, m, CH_2), 1,86 (2H, m, CH_2), 1,91 (1H, m, CH), 2,10 (1H, bm, piperidin-NH), 2,67 (2H, m, CH_2), 3,18 (2H, m, CH_2), 3,38 (2H, m, CH_2), 6,37 (1H, s, H_6), 6,53 (1H, m, NH), 7,42 (2H, m, Ar-H), 7,52 (1H, m, Ar-H), 7,76 (1H, m, Ar-H) y 8,06 ppm (1H, s Ar-H); δ_C ($CDCl_3$) CH_2: 31,2, 31,2, 46,2, 46,2, 48,4; CH: 36,4, 89,5, 127,1, 130,1, 130,5, 131,6, 143,8; C: 83,2, 132,1, 138,9, 145,6, 146,4, 158,1.

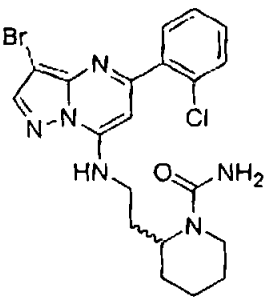
C. AMIDA DE ÁCIDO 4-{[3-BROMO-5-(2-CLOROFENIL)PIRAZOLO[1,5-a]PIRIMIDIN-7-ILAMINO]METIL}PIPERIDIN-1-CARBOXÍLICO:



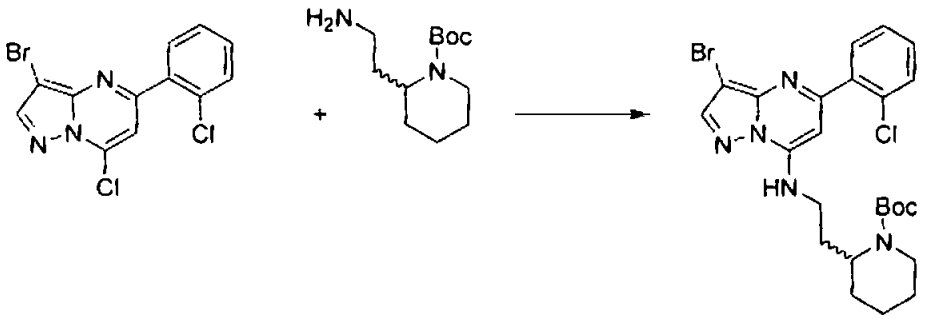
[3-Bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-il]piperidin-4-ilmetilamina (57 mg, 0.136 mmoles) (preparado tal como se describió en el Ejemplo 460, Etapa B anterior) se disolvió en diclorometano anhidro (1,2 mL) y se agregó trimetilsililisocianato (0,091 mL, 0,679 mmoles). La mezcla se agitó a 25°C durante 2,5 horas. La mezcla se diluyó con diclorometano y se lavó con bicarbonato de sodio acuoso saturado. La capa orgánica se secó ($MgSO_4$), se secó y se evaporó hasta sequedad. El residuo se cromatografió sobre una columna de gel de sílice (30x2,5cm) usando 3% (hidróxido de amonio concentrado al 10% en metanol)-diclorometano como eluyente para proporcionar la amida de ácido 4-{[3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-ilamino]metil}piperidin-1-carboxílico (53,7 mg, 86%): FABMS: m/z 463,1 (MH^+); HRFABMS: m/z 463,0647 (MH^+). Calc. para $C_{19}H_{21}N_6OBrCl$: m/z 463,0649; δ_H (d_6-DMSO) 1.09 (2H, m, CH_2), 1,63 (2H, m, CH_2), 1,87 (1H, m, CH), 2,60 (2H, m, CH_2), 3,53 (2H, bm, $CONH_2$), 3,91 (2H, d, CH_2), 6,52 (1H, s, H_6), 7,50 (2H, m, Ar-H), 7,62 (2H, m, Ar-H), 8,33 (1H, s, H_2) y 8,52 ppm (1H, m, NH); δ_C (d_6-DMSO) CH_2: 30,1, 30,1, 44,2, 44,2, 47,7; CH: 36,4, 88,2, 128,1, 130,7, 131,4, 132,1, 147,9; C: 82,1, 132,1, 139,4, 145,7, 147,9, 158,1, 158,8.

EJEMPLO 461:

AMIDA DE ÁCIDO 2-{2-[3-BROMO-5-(2-CLOROFENIL)PIRAZOLO[1,5-a]PIRIMIDIN-7-ILAMINO]ETIL}PIPERIDIN-1-CARBOXÍLICO:



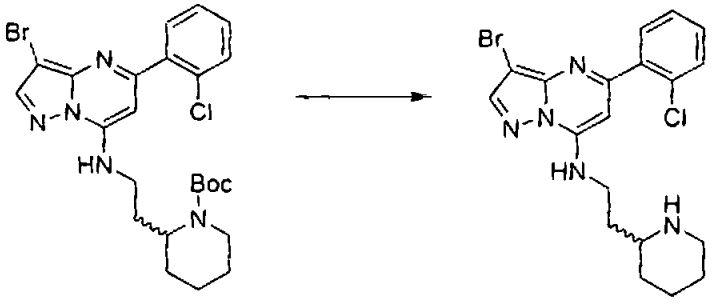
A. ÉSTER TER-BUTÍLICO DE ÁCIDO 2-{2-[3-BROMO-5-(2-CLOROFENIL)PIRAZOLO[1,5-a]PIRIMIDIN-7-ILAMINO]ETIL}PIPERIDIN-1-CARBOXÍLICO:



3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (400 mg, 1,166 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 129) se disolvió en 1,4-dioxano anhidro (5,7 mL). Se agregaron éster ter-butílico de ácido 2-aminoetilpiperidin-1-carboxílico (266 mg, 1,166 mmoles) y diisopropil etilamina (0,409 mL, 2,33 mmoles) y la mezcla se calentó a 75°C durante 48 horas. Se agregó diisopropil etilamina adicional (0,204 mL, 1,166 mmoles) y el calentamiento se continuó por un total de 58 horas. La solución se evaporó hasta sequedad y el residuo se cromatografió sobre una columna de gel de sílice (15x5cm) usando diclorometano seguido de 0,3% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente para proporcionar éster ter-butílico de ácido 2-{[3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-ilamino]etil}piperidin-1-carboxílico (491,1 mg, 79%): FABMS: m/z 534,1 (MH^+); HRESIMS: m/z 534.12797 (MH^+). Calc. para $C_{24}H_{30}N_5O_2BrCl$: m/z 534,12714; δ_H ($CDCl_3$) 1,50 (1H, m, CH_2), 1,51 (9H, s, $COOC(CH_3)_3$), 1,57 (2H, m, CH_2), 1,68 (2H, m, CH_2), 1,76 (2H, m, CH_2), 2,24 (1H, bm, CH_2), 2,82/3,40/3,54/4,08/4,51 (5H, m, CH/CH_2), 6,34 (1H, s, H_6), 7,41 (2H, m, Ar-H), 7,51 (1H, m, Ar-H), 7,76

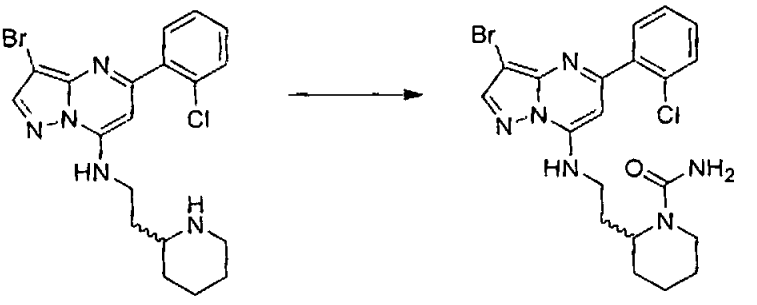
(1H, m, Ar-H) y 8,08 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 28,5, 28,5, 28,5; CH_2: 19,2, 25,5, 29,2, 29,2, 39,2, 67,1; CH: ~47,4, 87,1, 127,1, 130,1, 130,1, 131,6, 143,9; C: 80,0, 83,0, 132,1, 138,9, 145,7, 146,2, 158,0.

B. [3-BROMO-5-(2-CLOROFENIL)PIRAZOLO[1,5-a]PIRIMIDIN-7-IL]-(2-PIPERIDIN-2-ILETIL)AMINA:



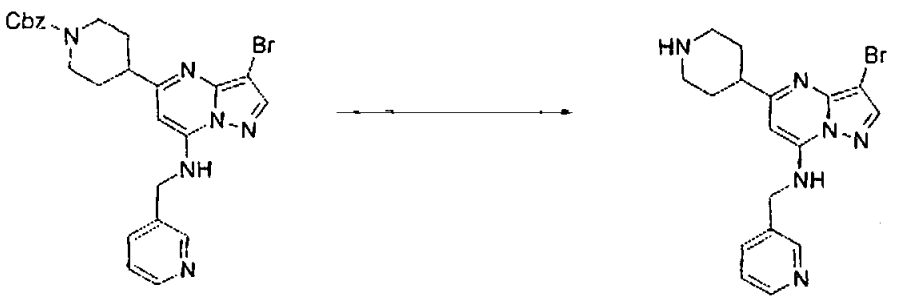
Éster ter-butílico de ácido 2-{[3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-ilamino]etil}piperidin-1-carboxílico (465 mg, 0,869 mmoles) (preparado tal como se describió en el Ejemplo 461, Etapa A anterior) se disolvió en metanol (4,5 mL) y se agregó 10% (v/v) de ácido sulfúrico concentrado en 1,4-dioxano (11,76 mL). La mezcla se agitó a 25°C durante 1,5 horas. El producto se elaboró tal como se describió en el Ejemplo Preparativo 241, Etapa B y se cromatografió sobre una columna de gel de sílice (15x5cm) usando 3,5% (hidróxido de amonio concentrado al 10% en metanol)-diclorometano como eluyente para proporcionar [3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-il]piperidin-2-iletil)amina (365,6 mg, 97%): FABMS: m/z 434,1 (MH^+); HRFABMS: m/z 434,0726 (MH^+). Calc. para $C_{19}H_{22}N_5BrCl$: m/z 434,0747; δ_H ($CDCl_3$) 1,24 (1H, m, CH_2), 1,41 (1H, m, CH_2), 1,49 (1H, m, CH_2), 1,66 (1H, m, CH_2), 1,73 (1H, m, CH_2), 1,81 (1H, m, CH_2), 1,88 (2H, m, CH_2), 2,68 (1H, m, CH_2), 2,78 (1H, m, CH_2), 3,20 (1H,m, CH), 3,55 (1H, m, CH_2), 3,60 (1H, m, CH_2), 6,32 (1H, s, H_6), 7,41 (2H, m, Ar-H), 7,51 (1H, m, Ar-H), 7,74 (1H, m, Ar-H), 7,78 (1H, m, NH) y 8,05 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 24,7, 26,8, 33,1, 35,2, 40,3, 47,0; CH: 55,7, 87,2, 127,1, 130,0, 130,1, 131,5, 143,8; C: 82,9, 132,1, 139,0, 145,7, 146,5, 158,1.

C. AMIDA DE ÁCIDO 2-{2-[3-BROMO-5-(2-CLOROFENIL)PIRAZOLO[1,5-a]PIRIMIDIN-7-ILAMINO]ETIL}PIPERIDIN-1-CARBOXÍLICO:



[3-Bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-il]piperidin-2-iletil)amina (200 mg, 0,46 mmoles) (preparado tal como se describió en el Ejemplo 461, Etapa B anterior) se disolvió en diclorometano anhidro (2 mL) y trimetilsililisocianato (0,31 mL, 2,3 mmoles). La mezcla se agitó a 25°C durante 1,25 horas. Se agregó trimetilsililisocianato adicional (0,155 mL, 1,15 mmoles) y la agitación se continuó por un total de 3 horas. La mezcla se diluyó con diclorometano y se lavó con bicarbonato de sodio acuoso saturado. La capa orgánica se secó ($MgSO_4$), se filtró y evaporó hasta sequedad. El residuo se cromatografió sobre una columna de gel de sílice (30x2,5cm) usando 2% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente para proporcionar amida de ácido 2-{2-[3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-ilamino]etil}piperidin-1-carboxílico (106,3 mg, 48%): FABMS: m/z 477,0 (MH^+); HRFABMS: m/z 477,0804 (MH^+). Calc. para $C_{20}H_{23}N_6OBrCl$: m/z 477,0805; δ_H (d_6-DMSO) 1,29 (1H, m, CH_2), 1,52 (5H, m, CH_2), 1,72 (1H, m, CH_2), 2,05 (1H, m, CH_2), 2,51 (2H, s, $CONH_2$), 2,79 (1H, dd, CH), 3,31 (1H, m, CH_2), 3,34 (1H, m, CH_2), 3,76 (1H, m, CH_2), 4,30 (1H, bm, CH_2), 6,42 (1H, s, H_6), 7,50 (2H, m, Ar-H), 7,60 (1H, m, Ar-H), 7,63 (1H, m, Ar-H), 8,29 (1H, s, H_2) y 8,38 ppm (1H, dd, NH); δ_C (d_6-DMSO) CH_2: 18,6, 25,2, 28,2, 38,4, 38,6, 54,8; CH: 46,7, 86,6, 127,1, 129,7, 130,3, 131,0, 143,4; C: 81,2, 131,0, 138,7, 145,1, 146,4, 158,2.

EJEMPLO 462:

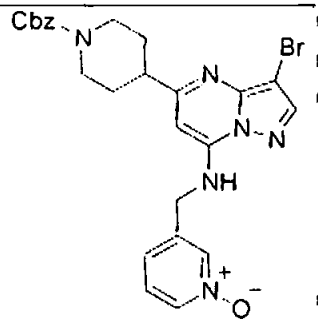
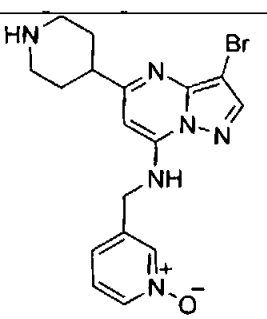


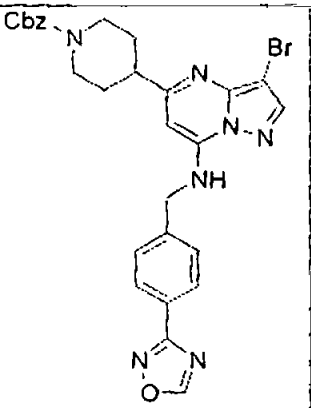
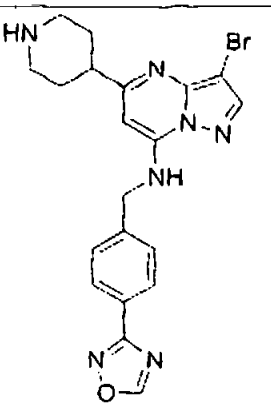
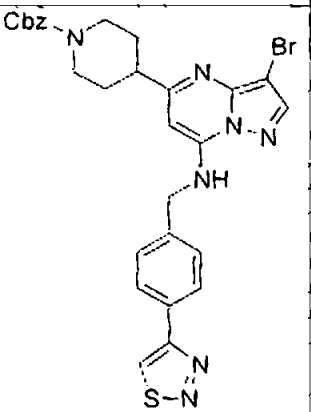
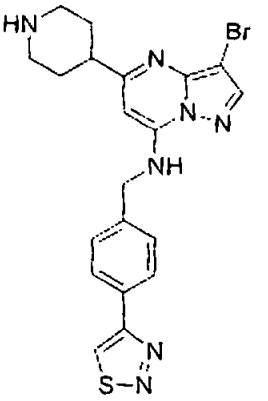
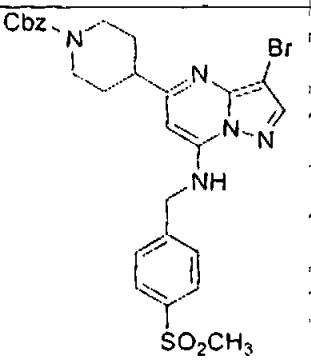
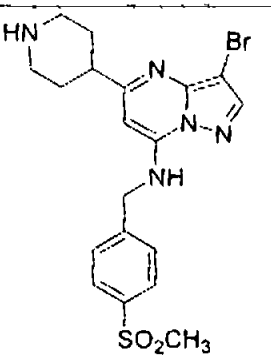
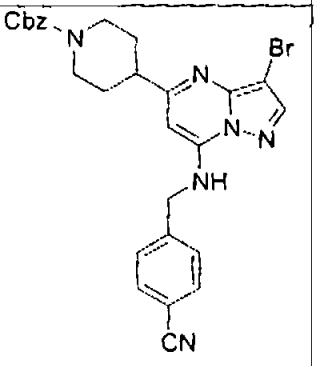
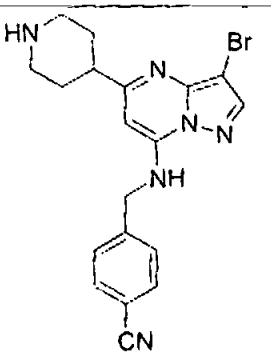
A una solución del compuesto preparado en el Ejemplo 204 (1,11 g, 2,12 mmoles) en acetonitrilo anhidro (20 mL) se agregó TMSI (1,70 g, 8,52 mmoles), por goteo a temperatura ambiente. Después de 10 minutos se extrajo el acetonitrilo *al vacío*. La espuma de color amarillo resultantes se trató con una solución de HCl 2N (7 mL) y luego se lavó inmediatamente con Et_2O (5X). El pH de la fase acuosa se ajustó a 10 con 50% de NaOH (acuosa y el producto se aisló por saturación de la solución con NaCl (s) seguido de extracción con CH_2Cl_2 (5X) para proporcionar el producto cristalino (733 mg, 89% de rendimiento). MH^+ = 387; p. f. = 207,5°C

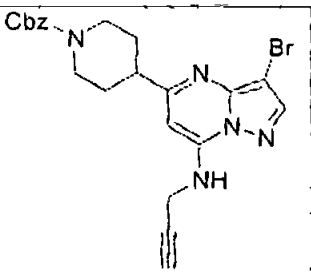
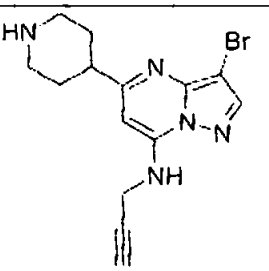
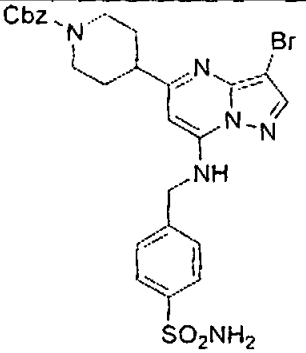
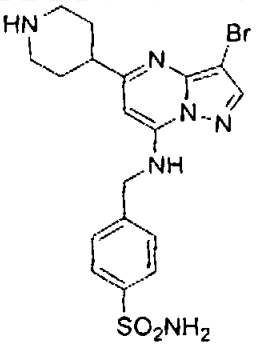
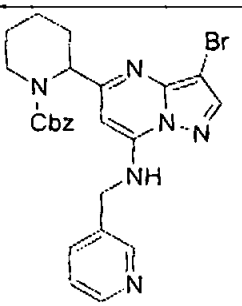
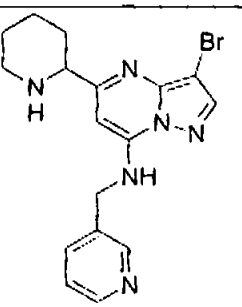
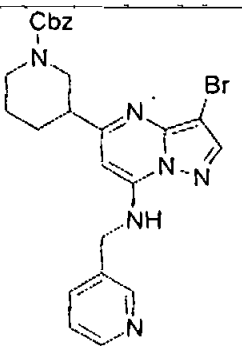
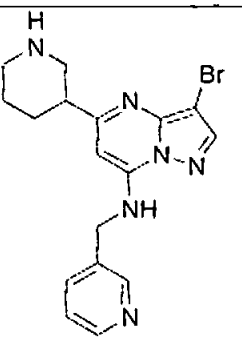
EJEMPLOS 463-472:

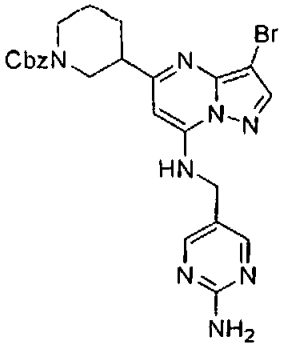
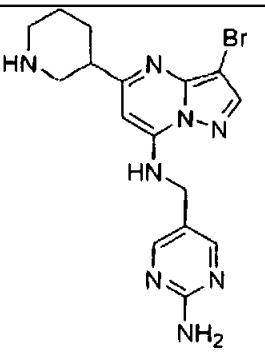
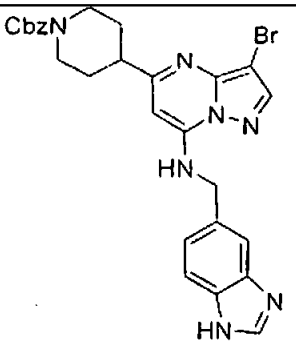
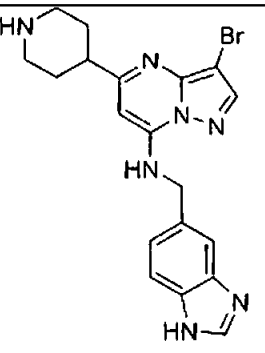
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo 462, sustituyendo únicamente los compuestos que se muestran en la Columna 2 de la Tabla 38, se prepararon los compuestos que se muestran en la Columna 3 de Tabla 38.

TABLA 38

Ej.	Columna 2	Columna 3	COMP.
463			MH^+ = 403 ^1H RMN (300MHz, $CDCl_3$) δ 8,52 (s, 1H), 8,38 (d, 1H), 8,04 (s, 1H), 7,78 (d, 1H), 7,65 (t, 1H), 6,18 (s, 1H), 4,89 (s, 2H), 3,26 –3,21 (d, 2H), 2,96 – 2,70 (m, 3H), 2,05 –1,78 (m, 4H)

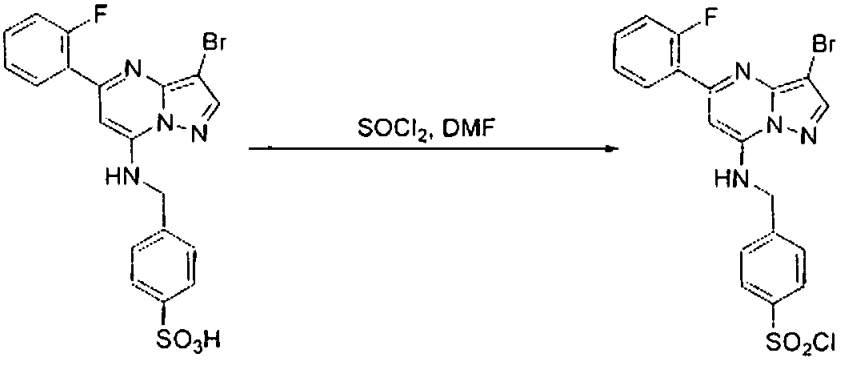
464			MH^+ = 454 p. f. = 175,4°C
465			Rendimiento = 87 MH^+ = 470 p. f. = 220°C p.f. (sal de clorhidrato de) = 164,3°C
466			MH^+ = 464 p. f. = 206°C
467			MH^+ = 411 p. f. = 169,5°C

468			MH^+ = 334 p. f. = 176,2°C
469			MH^+ = 465 p. f. = 250,4°C
470			MH^+ = 387 p. f. = 68,5°C
471			MH^+ = 387 p. f. = 59,4°C

472			1. P.f. = 230-232 2. M+H = 396
472.10			1. P.f. = 157-160 2. M+H = 427

EJEMPLO 473:

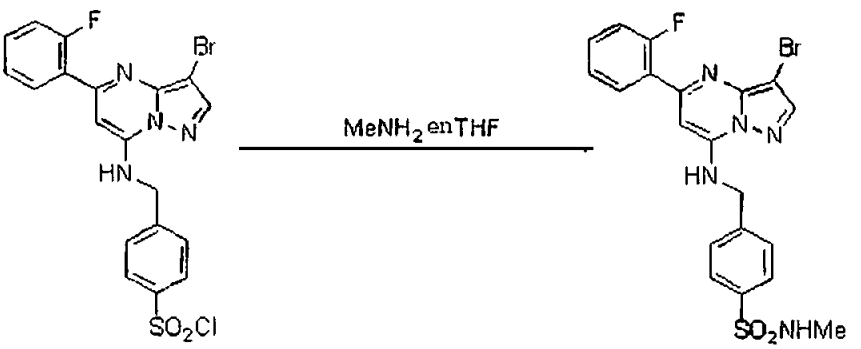
Etapa A:



Una solución de ácido sulfónico (560 mg, 1,17 mmoles) en 5 mL de DMF secó se enfrío a 0°C y se agregó $SOCl_2$ (278 mg, 2,34 mmoles). La mezcla de reacción se llevó a temperatura ambiente y se agitó durante la noche. Al día siguiente se vertieron los contenidos en hielo y el pH se ajustó cuidadosamente a 8. El producto se extrajo en EtOAc y el solvente se extrajo después de secar

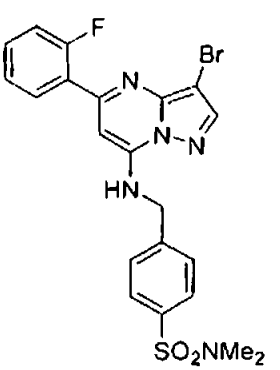
(Na_2SO_4) para proporcionar 240 mg (41%) del cloruro de sulfonilo crudo que se uso para la etapa siguiente sin purificación adicional. ^{1}H RMN ($CDCl_3$) δ 8,20-8,10 (m,1H), 8,10-7,95 (m, 3H), 7,65 (d, 2H), 7,45-7,35 (m, 1H), 7,35-7,20 (m, 1H), 7,15-7,05 (m, 1H), 6,95 (t, 1H), 4,85 (d, 2H).

Etapa B:



Una solución del compuesto preparado en el Ejemplo 473, Etapa A (120 mg, 0,24 mmoles) en 10 mL de THF se trató con 2 mL de 1 M $MeNH_2$ (2,00 mmoles) en THF a temperatura ambiente durante la noche. El solvente se extrajo y el residuo se purificó por cromatografía (sílice, hexano:EtOAc (4:1→1:1)) para proporcionar 56 mg (48%) de la sulfonamida. ^{1}H RMN (DMSO-d6) δ 9,05 (t, J = 9 Hz, 1H), 8,35 (s, 1H), 7,90 (t, J = 7,5 Hz, 1H), 7,75 (d, J = 9 Hz, 2H), 7,62 (d, J = 9 Hz, 2H), 7,55-7,46 (m, 1H), 7,45-7,38 (m, 1H), 7,38-7,25 (m, 1H), 6,50 (s, 1H), 4,80 (d, 2H), 3,30 (s, 3H)
LCMS: MH^+ = 492,1

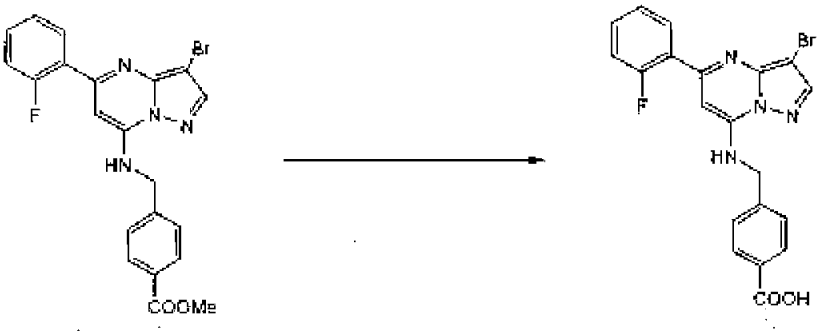
EJEMPLO 474:



Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo 473, sustituyendo únicamente dimetilamina, se preparó el compuesto anterior. ^{1}H RMN ($CDCl_3$) δ 8,14 (t, J = 9 Hz, 1H), 8,00 (s, 1H), 7,76 (d, J = 9 Hz,

2H), 7,54 (d, J = 9 Hz, 2H), 7,34-7,44 (m, 1H), 7,26 (t, J = 9 Hz, 1H), 7,14-7,04 (m, 1H), 6,93 (t, J= 6 Hz, 1H), 6,45 (s, 1H), 4,75 (d, 2H), 2,70 (s, 6H)
LCMS: MH^+ = 504,2

EJEMPLO 475:

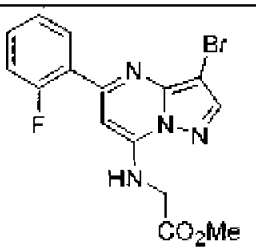
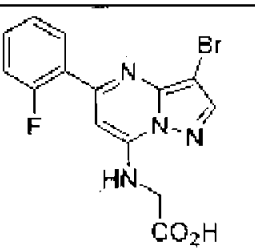
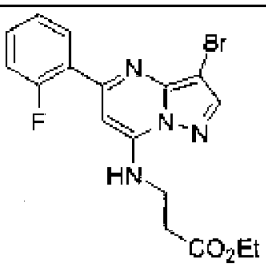
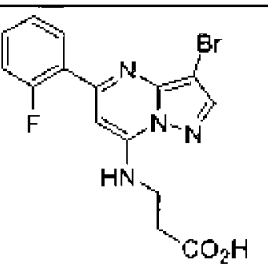
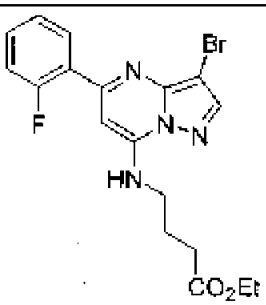
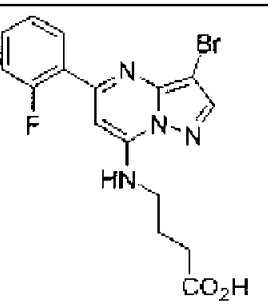
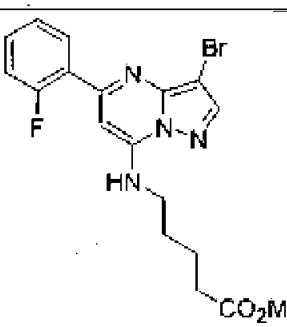
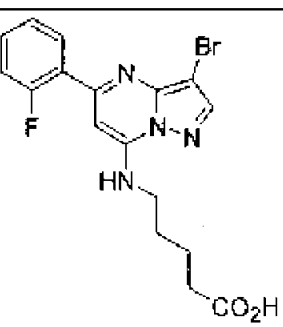


Una mezcla del compuesto preparado en el Ejemplo 129 (300 mg, 0,66 mmoles), NaOH (5 g), CH_3OH –H_2O (100 mL, 90:10) se agitó a 25°C durante aproximadamente 15 horas. Se controló el progreso de la hidrólisis por TLC. La mezcla de reacción se concentró para remover el metanol. El concentrado se diluyó con 50 mL de agua, y se extrajo con éter para remover cualquier éster no reaccionado. La solución acuosa, así obtenida, se neutralizó con HCl 3N a pH 4 para obtener el ácido libre, se filtró y se lavó repetidamente con agua. El ácido se secó bajo al vacío (270 mg, 93%) y se usó sin purificación adicional.

Ejemplo 476-479:

Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo 475 sustituyendo únicamente los compuestos de la Columna 2 de la Tabla 39, se prepararon los compuestos en la Columna 3 de la Tabla 39.

Tabla 39

Ej.	Columna 2	Columna 3	COMP.
476			Rendimiento = 82% LCMS: MH^+ = 365
477			Rendimiento = 82% LCMS: MH^+ = 379
478			Rendimiento = 72% LCMS: MH^+ = 393
479			Rendimiento = 70% LCMS: MH^+ = 407

Los datos adicionales para los ejemplos seleccionados se muestran a continuación:

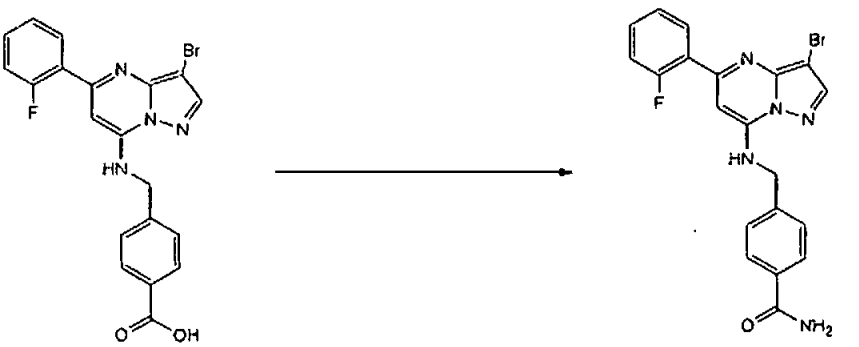
Ejemplo 476: ^{1}H RMN ($CDCl_3$) δ 8,15 (m, 2H), 8,0 (m, 1H), 7,6 (m, 1H), 7,3 (m, 2H), 6,6 (s, 1H), 4,2 (d, 2H).

Ejemplo 477: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,4 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 7,0 (t, 1H), 6,5 (s, 1H), 3,8 (dt, 2H), 2,6 (t, 2H).

686

Ejemplo 479: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,4 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 6,8 (t, 1H), 3,5 (dt, 2H), 2,4 (t, 2H), 1,8 (m, 4H).

EJEMPLO 480:

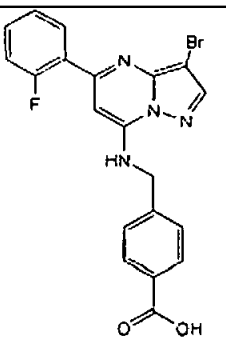
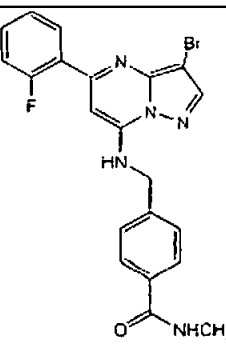


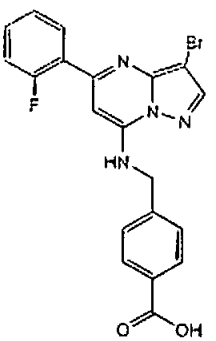
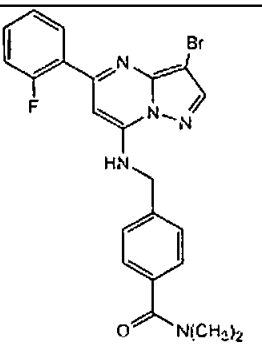
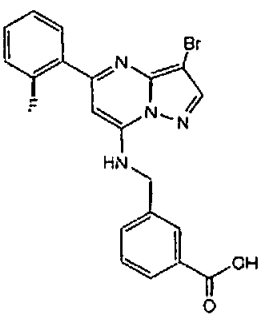
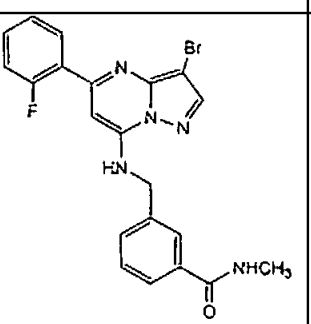
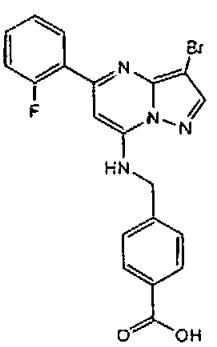
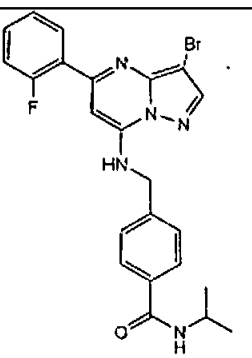
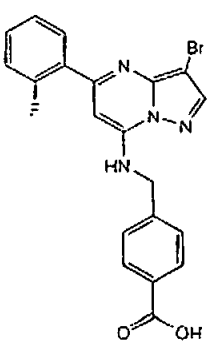
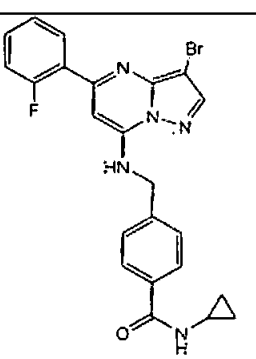
Una mezcla del Ejemplo 475 (85 mg, 0.193 mmoles) y Et_3N (20 mg, 0,193 mmoles) en THF (20 mL) se agitó a 25°C durante 15 minutos. Se agregó cloroformiato de isobutirilo (28 mg, 0,205 mmoles) y se agregó a la mezcla de reacción y se agitó durante 10 minutos seguido de adición de una solución de NH4OH (0,5 mL). La mezcla de reacción se agitó durante 1 hora y se concentró hasta sequedad. La masa seca se purificó por cromatografía en columna.

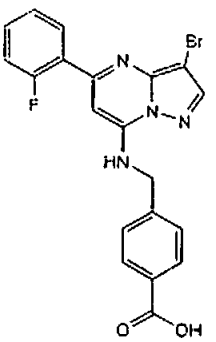
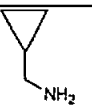
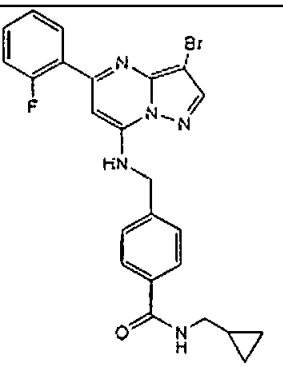
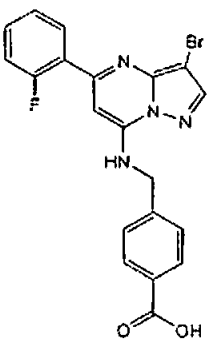
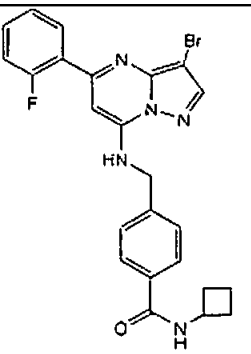
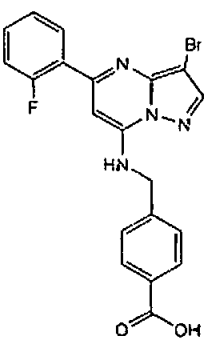
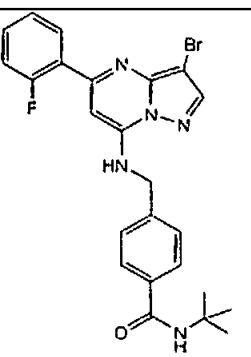
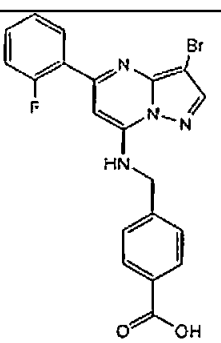
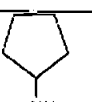
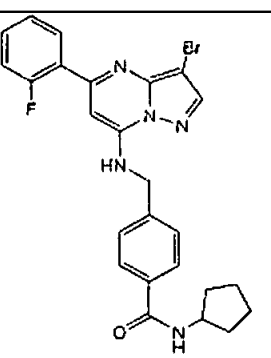
EJEMPLOS 481-509:

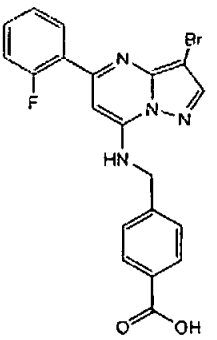
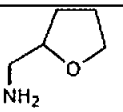
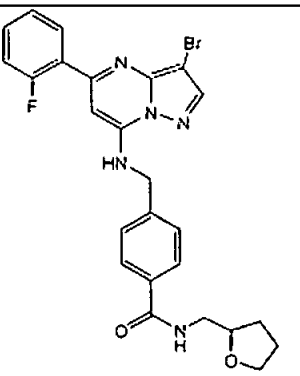
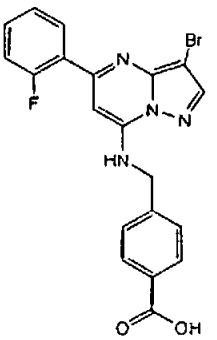
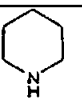
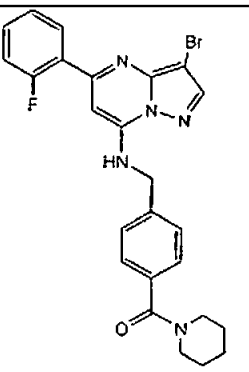
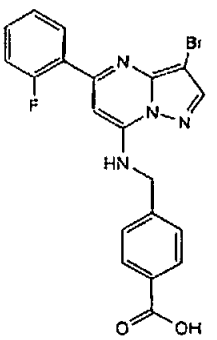
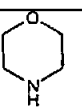
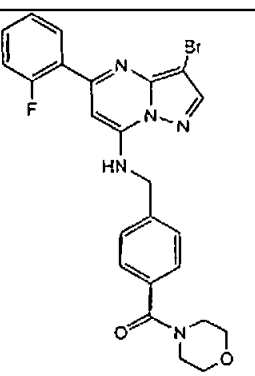
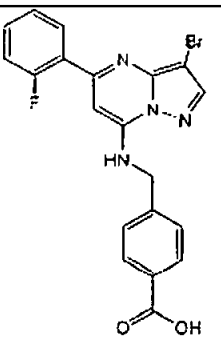
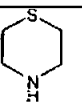
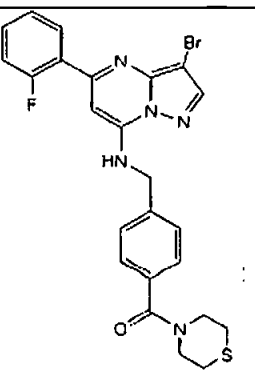
Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo 480, sustituyendo únicamente el ácido carboxílico que se muestra en la Columna 2 de la Tabla 40 y la amina que se muestra en la Columna 3 de la Tabla 40, se prepararon los compuestos que se muestran en la Columna 4 de la Tabla 40.

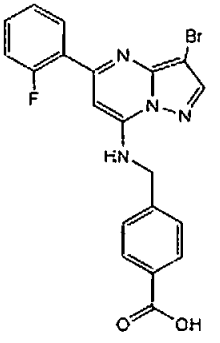
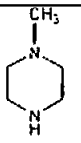
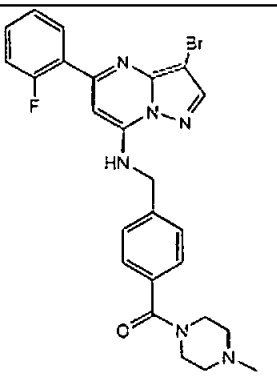
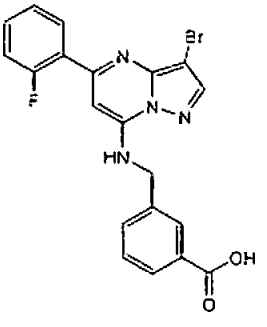
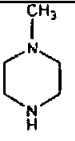
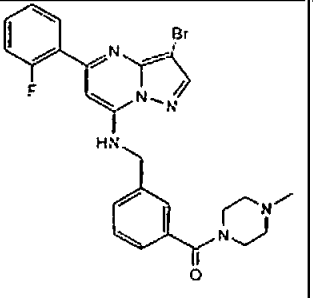
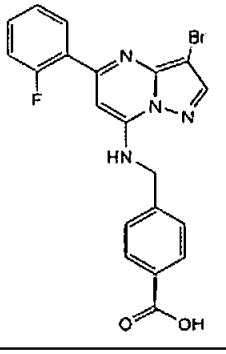
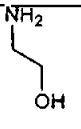
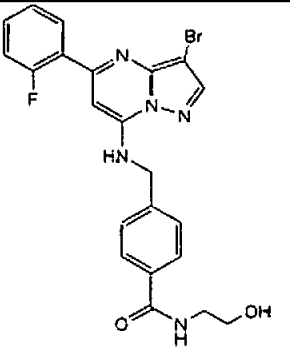
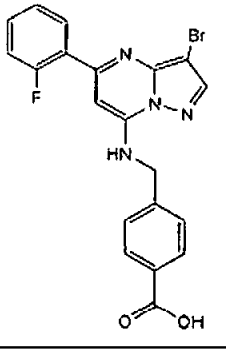
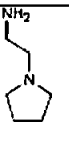
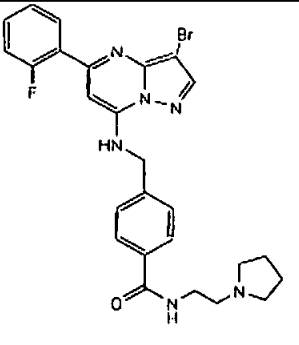
Tabla 40

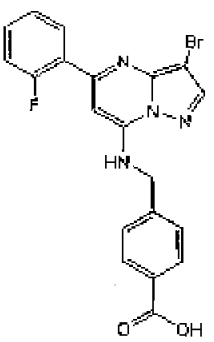
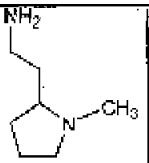
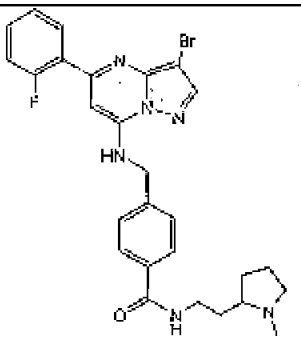
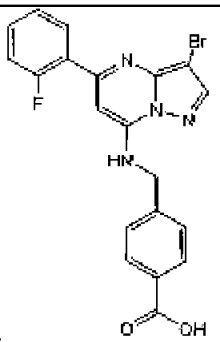
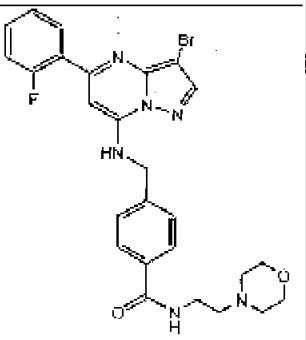
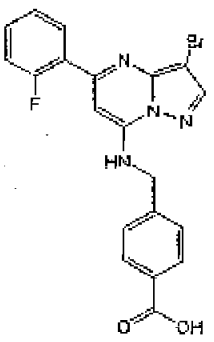
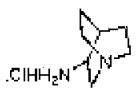
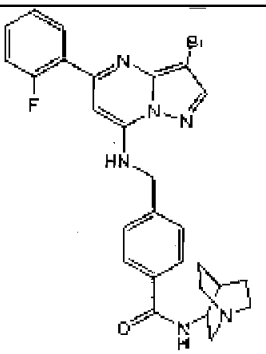
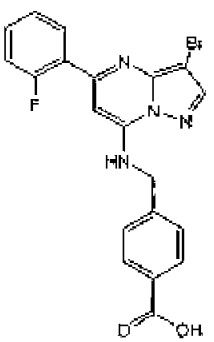
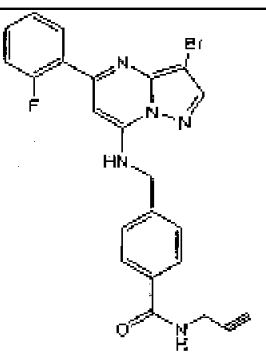
Ej.	Columna 2	Columna 3	Columna 4	COMP.
481		CH_3NH_2		Rendimiento = 88% LCMS: MH^+ = 454

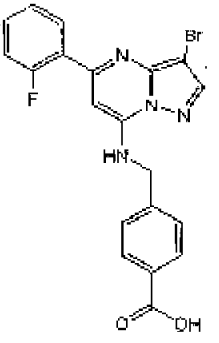
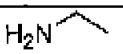
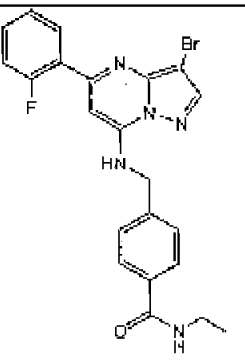
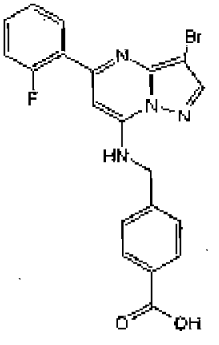
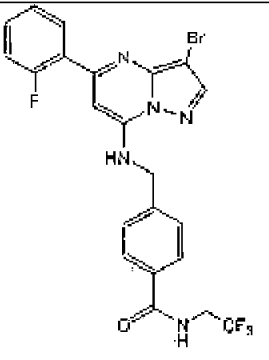
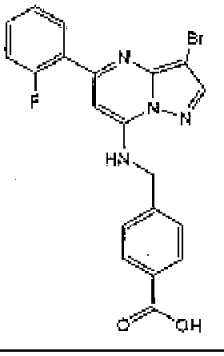
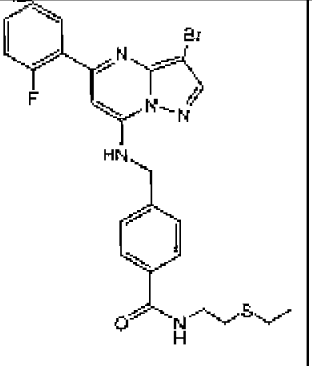
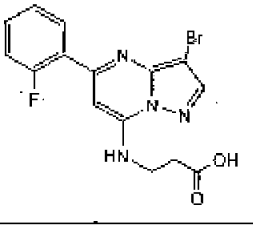
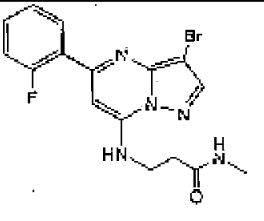
482		$(CH_3)_2NH$		Rendimiento= 80% LCMS MH^+ = 468
483		CH_3NH_2		Rendimiento= 70% LCMS MH^+ = 454
484				Rendimiento= 75% LCMS MH^+ = 482,1
485				Rendimiento= 71% LCMS MH^+ = 480,1

486				Rendimiento= 75% LCMS MH^+ = 494,1
487				Rendimiento= 75% MH^+ = 494,1
488				Rendimiento= 75% MH^+ = 496,1
489				Rendimiento= 75% LCMS MH^+ = 508,1

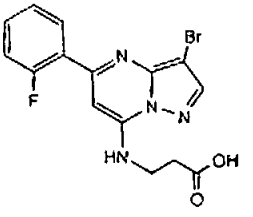
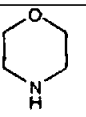
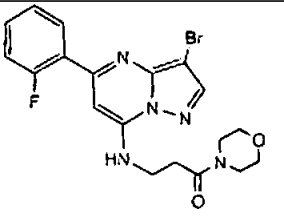
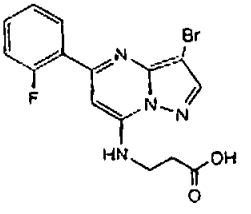
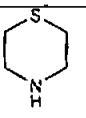
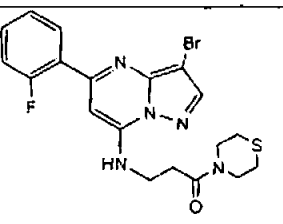
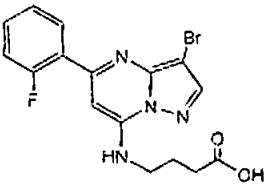
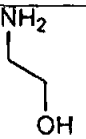
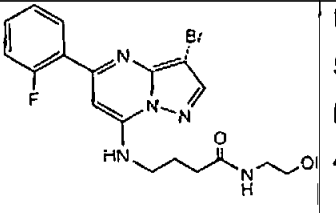
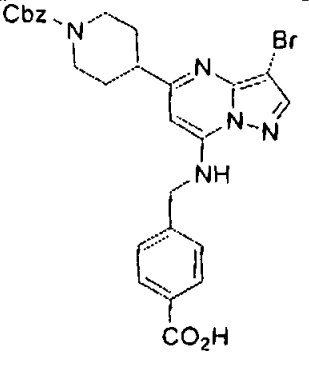
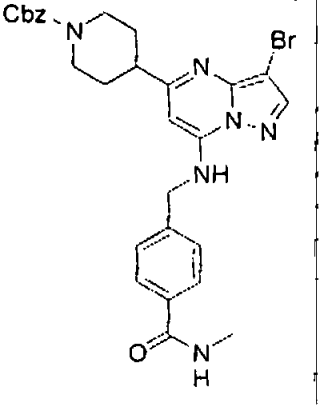
490				Rendimiento= 78% LCMS MH^+ = 524,1
491				Rendimiento= 73% LCMS MH^+ = 508,1
492				Rendimiento= 73% LCMS MH^+ = 510,1
493				Rendimiento= 76% LCMS MH^+ = 526,1

494				Rendimiento= 76% MH^+ = 523,1
495				Rendimiento= 76% MH^+ = 523,1
496				Rendimiento= 51% LCMS MH^+ = 484,1
497				Rendimiento= 66% MH^+ = 537,1

498				Rendimiento= 76% LCMS MH^+ = 551,2
499				Rendimiento= 79% LCMS MH^+ = 552,1
500				Rendimiento= 80% MH^+ = 549,1
501				Rendimiento= 80% LCMS MH^+ = 478,1

502				Rendimiento= 80% LCMH$^+$ = 468,1
503				Rendimiento= 80% MH$^+$ = 522,1
504				Rendimiento= 82% LCMS MH$^+$ = 528,1
505		CH_3NH_2		Rendimiento= 60% MH$^+$ = 392

516

506				Rendimiento= 60% LCMH$^+$ = 448,1
507				Rendimiento= 70% MH$^+$ = 464,1
508				Rendimiento= 50% LCMS MH$^+$ = 436,1
508 .10		CH_3NH_2		Rendimiento = 92 MH$^+$ = 577

Los datos adicionales para los ejemplos seleccionados se dan a continuación:

Ejemplo 481: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,7 (d, 2H), 7,4 (s, 1H), 7,35 (d, 2H), 7,25 (dd, 1H), 7,1 (dd, 1H), 6,95 (t, 1H), 6,5 (s, 1H), 6,25 (bs, 1H), 4,7 (d, 2H), 3,0 (d, 3H).

Ejemplo 482: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H),8,0 (s, 1H), 7,45 – 7,35 (m, 4H), 7,25 (d, 2H), 7,15 (dd, 1H), 6,7 (t, 1H), 6,5 (s, 1H), 4,7 (d, 2H), 3,1 (s, 3H), 3,0 (s, 3H).

Ejemplo 483: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,8 (bs, 1H), 7,7 (d, 1H), 7,5 – 7,3 (m, 3H), 7,25 (d, 1H), 7,15 (dd, 1H), 6,75 (t, 1H), 6,5 (s, 1H), 6,2 (bs, 1H), 4,7 (d, 2H), 3,0 (d, 3H).

Ejemplo 484: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,7 (d, 2H), 7,4 (d, 2H), 7,35 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 6,8 (t, 1H), 6,5 (s, 1H), 6,0 bs, 1H), 4,7 (d, 2H), 4,25 (m, 1H), 1,2 (d, 6H).

Ejemplo 485: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,7 (d, 2H), 7,4 (d, 2H), 7,35 (s, 1H), 7,25 (dd, 1H), 7,1 (dd, 1H), 6,9 (t, 1H), 6,5 (s, 1H), 6,3 (t, 1H), 4,7 (d, 2H), 2,9 (m, 1H), 0,8 (bt, 2H), 0,6 (bt, 2H).

Ejemplo 486: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,8 (d, 2H), 7,4 (d, 2H), 7,35 (d, 1H), 7,25 (dd, 1H), 7,1 (dd, 1H), 6,9 (t, 1H), 6,5 (s, 1H), 6,2 (t, 1H), 4,7 (d, 2H), 3,3 (dd, 2H), 1,05 (m, 1H), 0,5 (m, 2H), 0,25 (m, 2H).

Ejemplo 487: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,7 (d, 2H), 7,4 (d, 2H), 7,35 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 6,85 (t, 1H), 6,5 (s, 1H), 6,2 (bs, 1H), 4,7 (d, 2H), 4,6 (m, 1H), 2,4 (m, 2H), 1,95 (m, 1H), 1,75 (m, 2H).

Ejemplo 488: ^{1}H RMN ($CDCl_3$) δ 8,5 (t, 1H), 8,15 (dt, 1H), 8,0 (s, 1H), 7,7 (d, 2H), 7,4 (d, 2H), 7,35 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 6,8 (t, 1H), 6,5 (s, 1H), 5,9 (bs, 1H), 4,7 (d, 2H), 1,4 (s, 9H).

Ejemplo 489: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,7 (d, 2H), 7,4 (d, 2H), 7,35 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 6,8 (t, 1H), 6,5 (s, 1H), 6,0 bs, 1H), 4,7 (d, 2H), 4,4 (m, 1H), 2,05 (m, 2H), 1,7 (m, 4H), 1,4 (m, 2H).

Ejemplo 490: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,7 (d, 2H), 7,4 (d, 2H), 7,35 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 6,8 (t, 1H), 6,5 (s, 1H), 6,5 (bs, 2H), 4,7 (d, 2H), 4,1 (m, 1H), 3,9 – 3,7 (m, 3H), 3,3 (m, 1H), 2,0 – 1,9 (m, 4H).

Ejemplo 491: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,45 – 7,35 (m, 5H), 7,25 (dd, 1H), 7,1 (dd, 1H), 6,8 (t, 1H), 6,5 (s, 1H), 4,7 (d, 2H), 3,7 (bs, 2H),3,3 (bs, 2H), 1,7 (bs, 4H), 1,5 (bs, 2H).

Ejemplo 492: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,45 – 7,35 (m, 5H), 7,25 (dd, 1H), 7,1 (dd, 1H), 6,85 (t, 1H), 6,5 (s, 1H), 4,7 (d, 2H), 3,8 – 3,4 (bm, 8H).

Ejemplo 493: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,45 – 7,35 (m, 5H), 7,25 (dd, 1H), 7,1 (dd, 1H), 6,80 (t, 1H), 6,5 (s, 1H), 4,7 (d, 2H), 4,0 (m, 2H), 3,6 (m, 2H), 2,8 – 2,45 (m, 4H).

Ejemplo 494: ^{1}H RMN (CH3OD) δ 8,15 (s, 1H), 8,0 (dt, 1H), 7,45 – 7,35 (m, 5H), 7,25 (dd, 1H), 7,1 (dd, 1H), 6,80 (t, 1H), 6,5 (s, 1H), 4,7 (d, 2H), 3,7 (bs, 2H), 3,4 (bs, 2H), 2,5 – 2,4 (m, 4H), 2,2 (s, 3H).

Ejemplo 495: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,45 – 7,35 (m, 5H), 7,25 (dd, 1H), 7,1 (dd, 1H), 6,80 (t, 1H), 6,5 (s, 1H), 4,7 (d, 2H), 3,75 (bs, 2H), 3,35 (bs, 2H), 2,4 (bs, 2H), 2,3 (s, 3H), 2,2 (bs, 2H).

Ejemplo 496: ^{1}H RMN ($CDCl_3$) δ 7,95 (s, 1H), 7,9 (dt, 1H), 7,8 (t, 1H), 7,7 (d, 2H), 7,15 (m, 4H), 7,05 (dd,1H), 6,9 (dd, 1H), 6,2 (s,1H), 4,5 (d, 2H), 3,6 (t, 2H), 3,3 (dt, 2H).

Ejemplo 497: ^{1}H RMN (CH3OD) δ 8,1 (s, 1H), 7,9 (dt, 1H), 7,8 (d, 2H), 7,5 (d, 2H), 7,4 (m, 1H), 7,3 (dd, 1H), 7,2 (dd, 1H), 6,4 (s, 1H), 4,7 (d, 2H), 3,5 (t, 2H), 2,7 (m, 2H), 2,6 (bs, 4H), 1,8 (bs, 4H).

Ejemplo 498: ^{1}H RMN ($CDCl_3$) δ 8,5 (t, 1H), 8,15 (dt, 1H), 8,0 (s, 1H), 7,8 (d, 2H), 7,4 (d, 2H), 7,35 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 6,8 (t, 1H), 6,5 (s, 1H), 4,7 (d, 2H), 3,7 – 2,5 (m, 4H), 2,35 (s, 3H), 2,2 (m, 1H), 1,9 – 1,6 (m, 6H).

Ejemplo 499: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,8 (d, 2H), 7,4 (d, 2H), 7,35 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 6,8 (t, 1H), 6,5 (s, 1H), 4,7 (d, 2H), 3,7 (m, 4H), 3,5 (dt, 2H), 2,6 (t, 2H), 2,5 (m, 4H).

Ejemplo 500: ^{1}H RMN (CH3OD) δ 8,15 (s, 1H), 7,9 (dt, 1H), 7,8 (d, 2H), 7,45 (d, 2H), 7,4 (m, 1H),7,25 (dd, 1H), 7,15 (dd, 1H), 6,4 (s, 1H), 4,75 (d, 2H), 4,2 (m, 1H), 3,4 – 2,8 (m, 7H), 1,9 – 1,6 (m, 4H).

Ejemplo: ^{1}H RMN ($CDCl_3$) δ 8,05 (dt, 1H), 8,0 (s, 1H), 7,6 (d, 2H), 7,4 (s, 1H), 7,35 (d, 2H), 7,25 (dd, 1H), 7,1 (dd, 1H), 6,9 (t, 1H), 6,5 (s, 1H), 6,4 (t,1H), 4,7 (d, 2H), 4,2 (d, 2H), 2,3 (bs, 1H).

Ejemplo 502: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,75 (d, 2H), 7,45 (s, 1H), 7,4 (d, 2H), 7,3 (dd, 1H), 7,1(dd, 1H), 6,8 (t, 1H), 6,5 (s, 1H), 6,1(bs, 1H), 4,7 (d, 2H), 3,5 (dq, 2H), 1,2 (t, 3H).

Ejemplo 503: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,8 (d, 2H), 7,4 (d, 2H), 7,35 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 6,9 (t, 1H), 6,5 (s, 1H), 6,4 (t, 1H), 4,75 (d, 2H), 4,1 (m, 2H).

Ejemplo 504: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,8 (d, 2H), 7,45 (d, 2H), 7,4 (m, 1H), 7,25 (dd, 1H), 7,1 (dd, 1H), 6,8 (t, 1H), 6,6 (t, 1H), 6,5 (s, 1H), 4,7 (d, 1H), 3,6 (m, 2H), 2,8 (t, 2H), 2,6 (q, 2H), 1,3 (t, 3H).

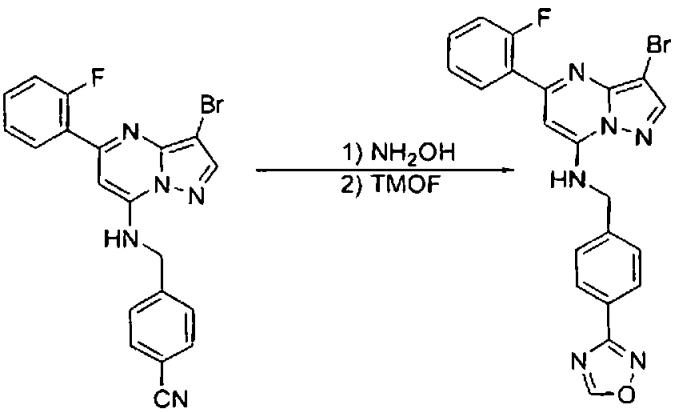
Ejemplo 505: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,4 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 7,0 (t, 1H), 6,5 (s, 1H), 3,8 (m, 2H), 2,7 (t, 2H), 3,0 (d, 3H).

Ejemplo 506: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,4 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 7,0 (t, 1H), 6,5 (s, 1H), 3,8 (m, 2H), 3,6 (m, 6H), 3,4 (m, 2H), 2,7 (t, 2H).

Ejemplo 507: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,4 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 7,0 (t, 1H), 6,5 (s, 1H), 3,9 (t, 2H), 3,8 (dt, 2H), 3,7 (t, 2H), 2,7 (t, 2H), 2,6 (m, 4H).

Ejemplo 508: ^{1}H RMN (CH_3OD) δ 8,1 (s, 1H), 7,95 (dt, 1H), 7,5 (m, 1H), 7,35 – 7,2 (m, 2H), 6,5 (s, 1H),3,6 (m, 4H), 3,25 (m, 4H), 2.4 (t, 2H), 2.05 (dt, 2H).

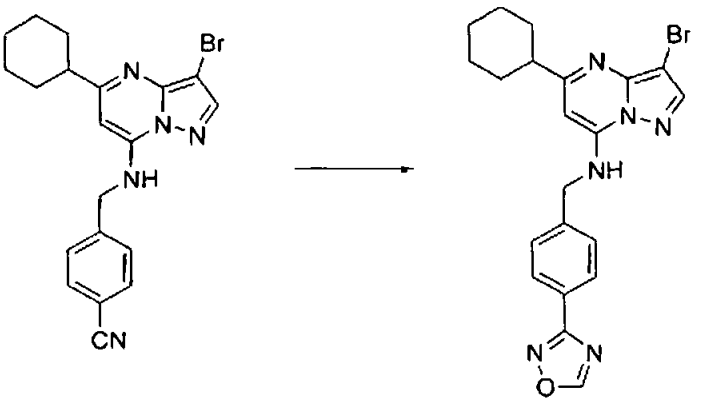
EJEMPLO 509:



Una solución de NaOH (59 mg, 1,47 mmoles) en 1 mL de agua, se agregó a una suspensión de $NH_2OH.HCl$ (102 mg, 1,47 mmoles) en 10 mL de metanol a 0°C. Después de 5 minutos, se agregó el compuesto preparado en el Ejemplo 210.10 (208 mg, 0,49 mmoles) y la mezcla de reacción se reflujó durante la noche. El solvente se removió *al vacío* y el residuo se dividió entre agua y EtOAc. La capa de EtOAc se secó (Na_2SO_4) y el solvente se evaporó. La amidoxima cruda resultante se suspendió en ortoformiato de trimetilo que contenía una cantidad catalítica de ácido PTS y se reflujó durante la noche. El solvente se

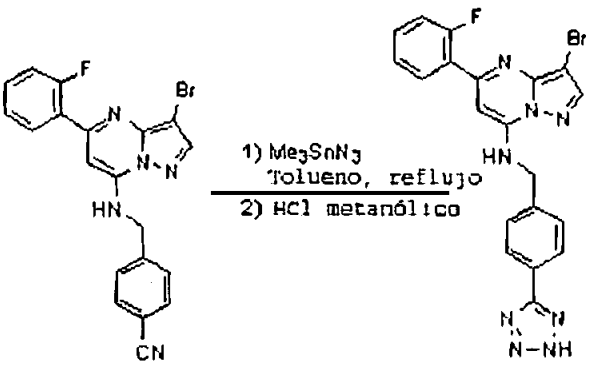
removió y el residuo se recogió en EtOAc. La capa de EtOAc se lavó con $NaHCO_3$ acuoso, seguido de agua y salmuera. El solvente se evaporó y el residuo se purificó por cromatografía (sílice, hexano:EtOAc (1:1)) para proporcionar 80 mg (35%) del oxadiazol. ^1H RMN ($CDCl_3$) δ 8,75 (s, 1H), 8.20-8.10 (m, 3H), 8.03 (s, 1H), 7.53 (d, J = 9 Hz, 2H), 7.45-7.36 (m, 1H), 7.30-7.22 (m, 2H), 7.16-7.08 (m, 1H), 6.80 (t, J = 5 Hz, 1H), 6.56 (s, 1H).
LCMS: MH^+ = 465,2

EJEMPLO 510:



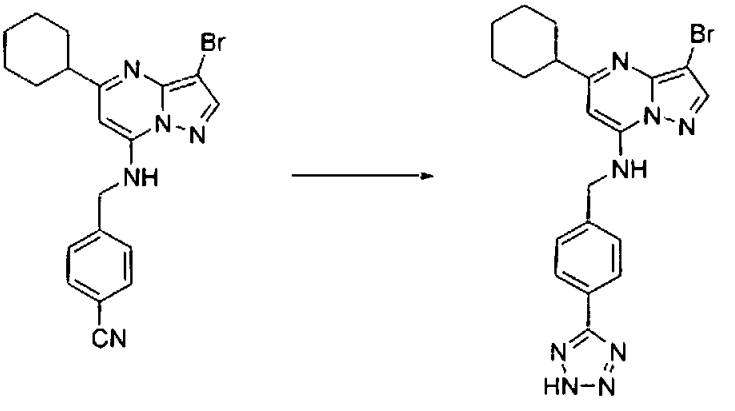
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo 509, sustituyendo únicamente el compuesto preparado en el Ejemplo Preparativo 192, se preparó el compuesto anterior. Rendimiento = 75; MH^+ = 453; p. f. = 79,3°C.

EJEMPLO 511:



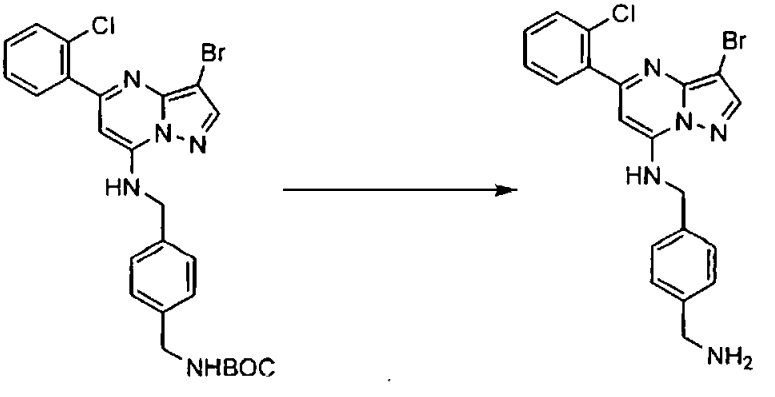
Una mezcla de nitrilo (235 mg, 0,56 mmoles) y Me_3SnN_3 (343 mg, 1,67 mmoles) en 20 mL de tolueno seco se reflujó durante 2 días bajo Ar. El solvente se extrajo *al vacío* y el residuo se disolvió en metanol seco. Se hizo burbujear gas HCl a través de la solución durante 15 minutos y la mezcla de reacción se dejó reposar durante la noche a temperatura ambiente. Al día siguiente, se extrajo el solvente, se recogió el residuo en agua y se ajustó el pH a 5. El producto precipitado se extrajo con EtOAc. La evaporación de la capa de EtOAc después del secado (Na_2SO_4) proporcionó el residuo el cual se purificó por cromatografía (sílice, DCM:MeOH (98:2→95:5)) para proporcionar 50 mg (19%) del tetrazol puro. ^1H RMN (CD_3OD) δ 8,10 (s, 1H), 8,00 (d, J = 9 Hz, 2H), 7,90 (t, J = 7 Hz, 1H), 7,65 (d, J = 9 Hz, 2H), 7,50-7,40 (m, 1H), 7,30-7,10 (m, 2H), 6,45 (s, 1H), 4,80 (s, 2H); LCMS: MH^+ = 465,0

EJEMPLO 512:



Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo 511 sustituyendo únicamente el compuesto preparado en el Ejemplo 192, se preparó el compuesto anterior. Rendimiento = 64; MH^+ = 453; p. f. = 238,9°C.

EJEMPLO 513:

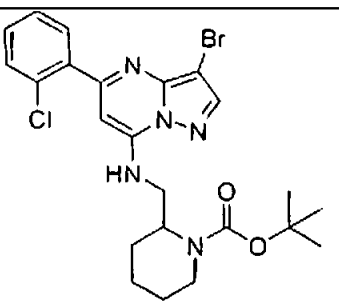
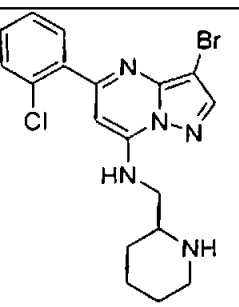
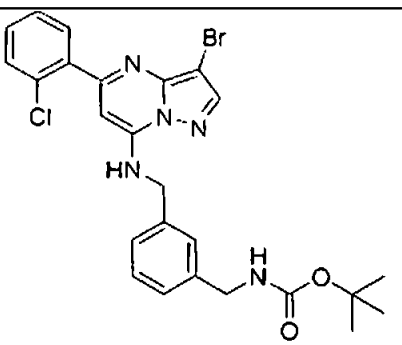
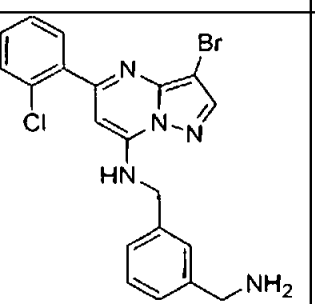


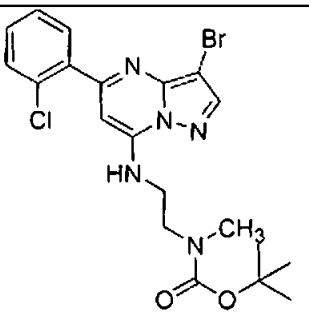
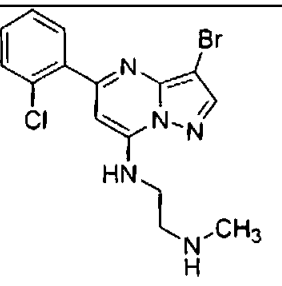
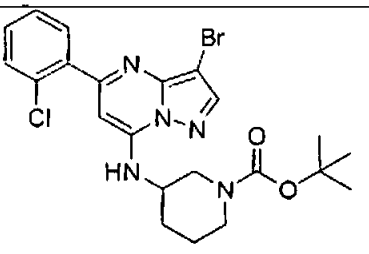
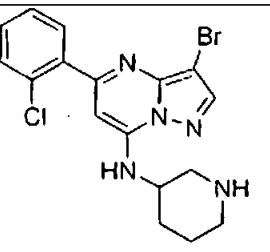
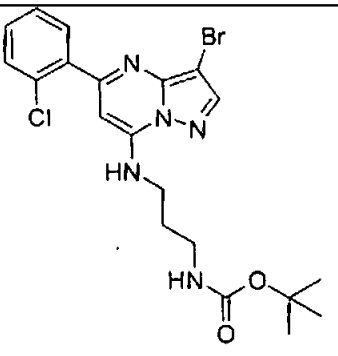
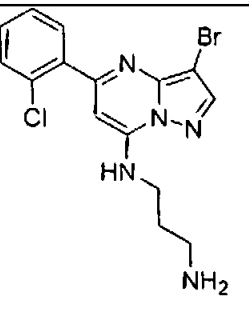
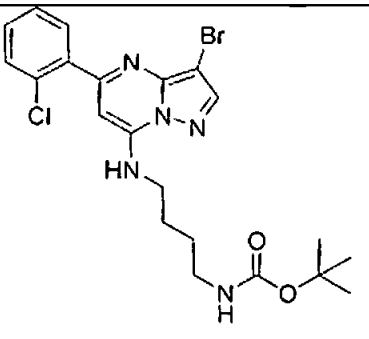
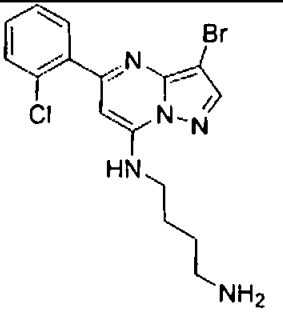
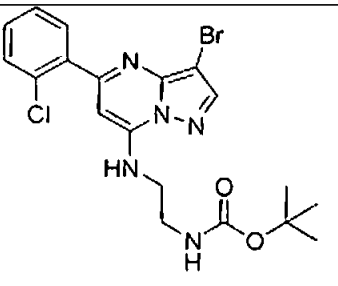
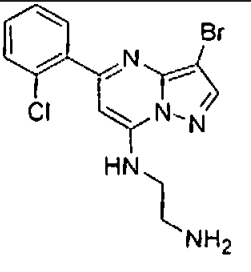
El compuesto preparado en el Ejemplo 157 se disolvió en dioxano (30 mL) y se agregó una solución de HCl-dioxano (4 M, 30 mL). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se evaporó bajo presión reducida y se agregó acetato de etilo (200 mL). La solución orgánica se lavó con hidróxido de sodio 1 N seguido de salmuera saturada. La capa orgánica se secó sobre sulfato de sodio anhidro y se evaporó bajo presión reducida. MH^+ = 442,1

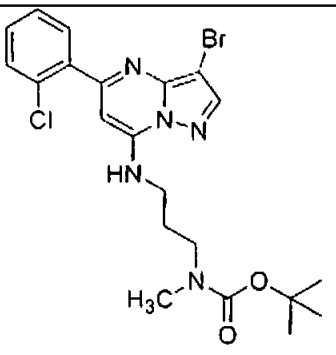
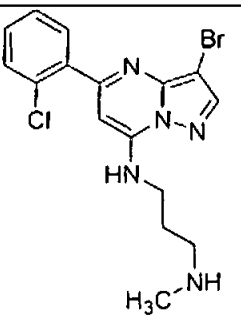
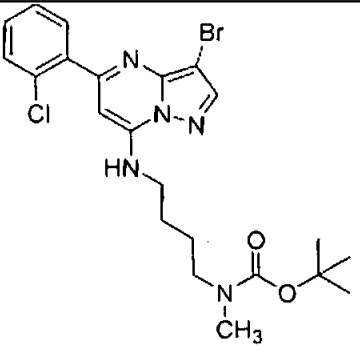
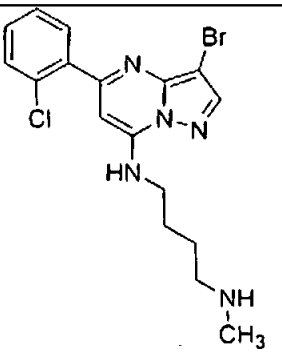
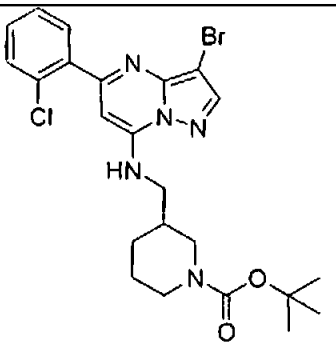
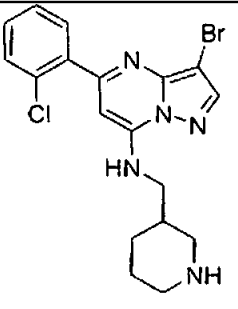
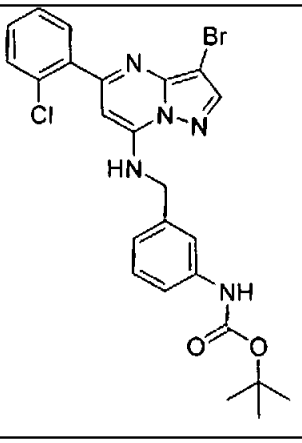
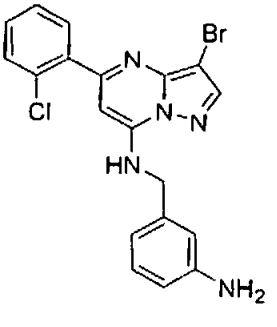
EJEMPLO 514-526:

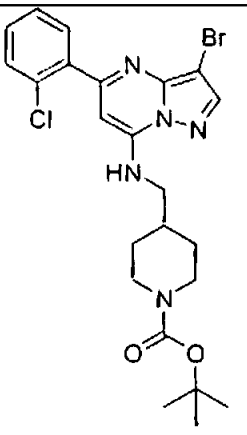
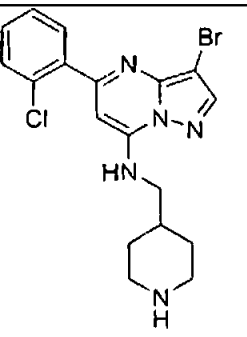
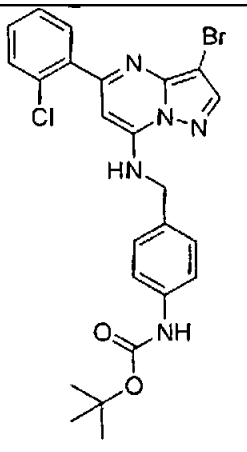
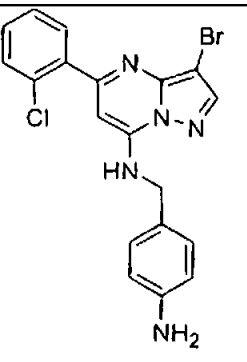
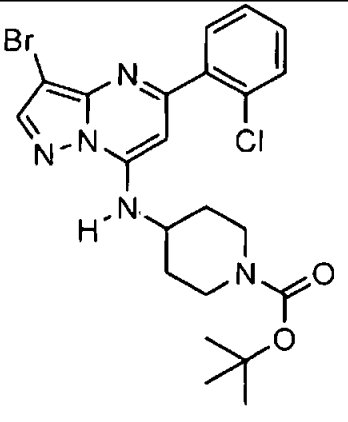
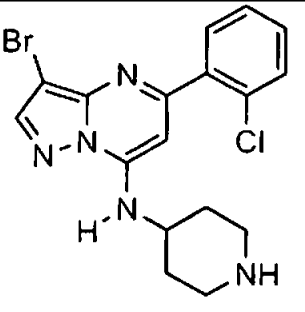
Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo 513, sustituyendo únicamente los compuestos que se muestran en la Columna 2 de la Tabla 41, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 41.

TABLA 41

Ej.	Columna 2	Columna 3	COMP.
514			MH^+ = 420,1
515			MH^- = 442,1

516			MH^+ = 380,1
517			MH^+ = 406,1
518			MH^+ = 380,1
519			MH^+ = 394,1
520			MH^+ = 366

521			MH^+ = 394
522			MH^+ = 408,1
523			MH^+ = 420,1
524			

525			MH^+ = 420,1
526			MH^+ = 428,1
526.10			

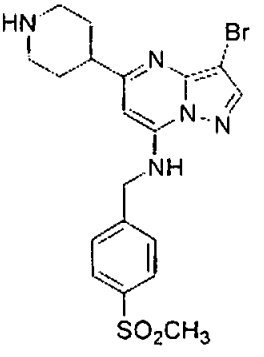
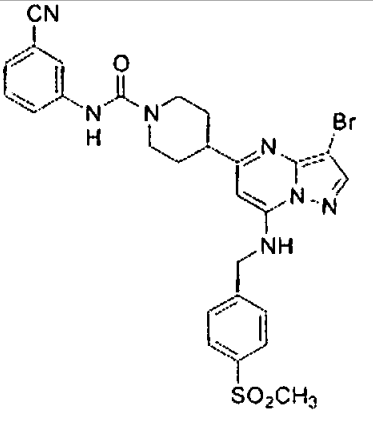
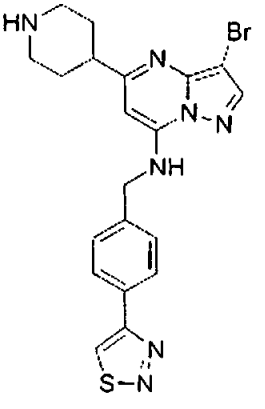
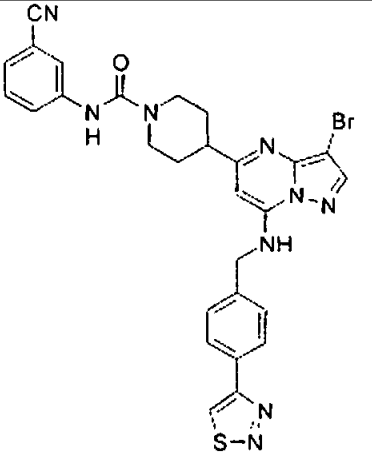
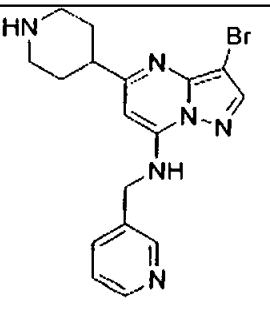
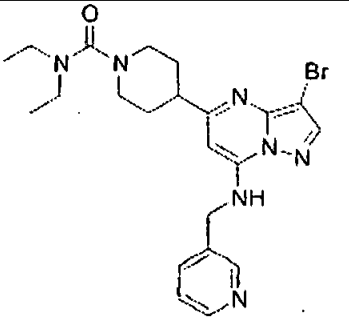
EJEMPLOS 528-564:

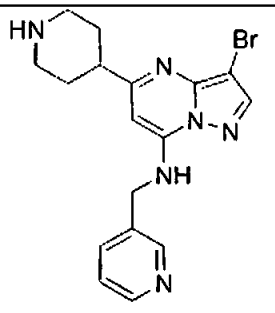
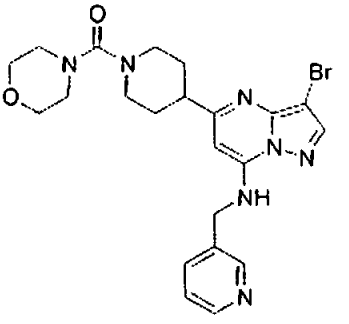
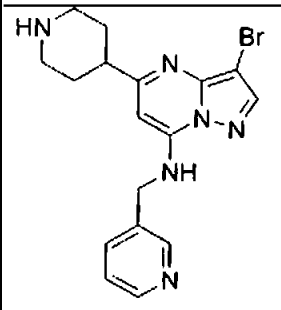
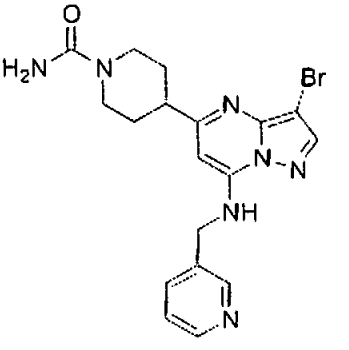
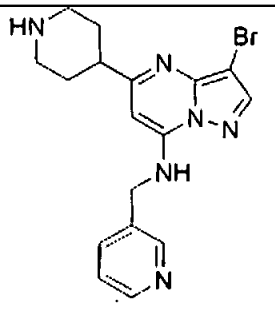
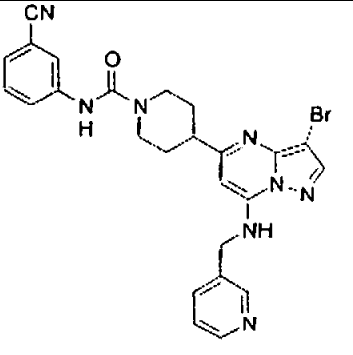
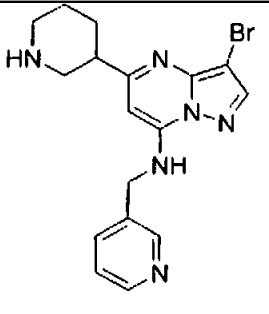
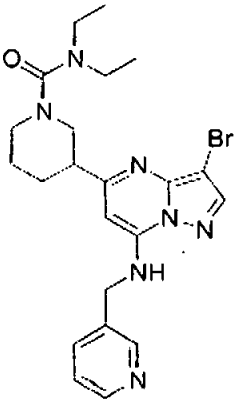
Procedimiento general para la formación de una colección paralela de 5-piperidinilo:

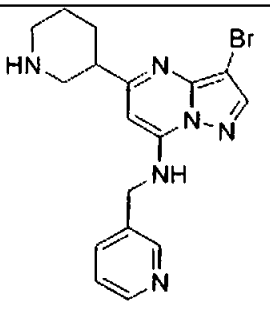
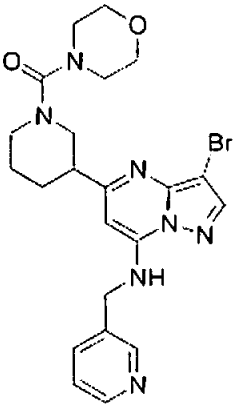
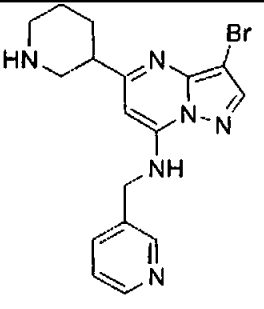
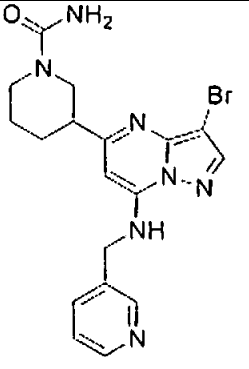
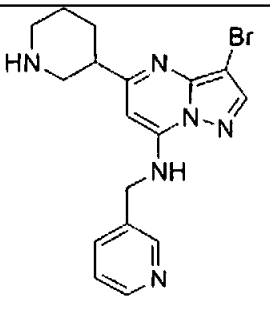
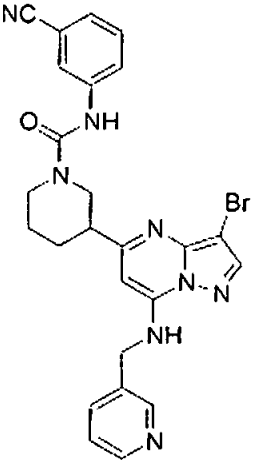
A una mezcla del material de partida (80 mg, 0,21 mmoles) que se muestra en la Columna 2 de la Tabla 42 en CH_2Cl_2 anhidro (1,5 mL) se agregó DIPEA (75 µL, 0,42 mmoles) y el reactivo de taponamiento apropiado (1.1 equiv., 0,23

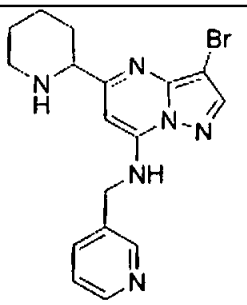
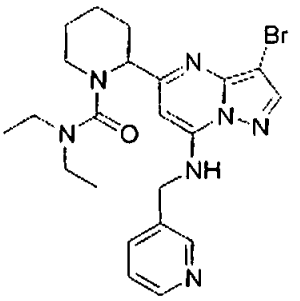
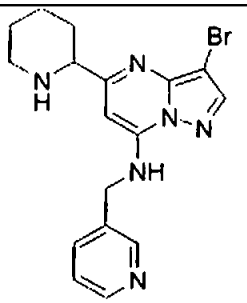
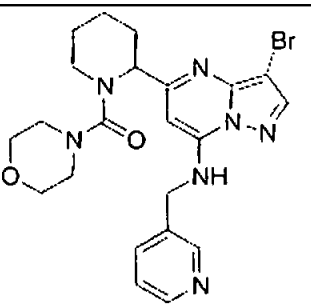
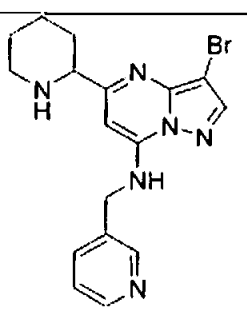
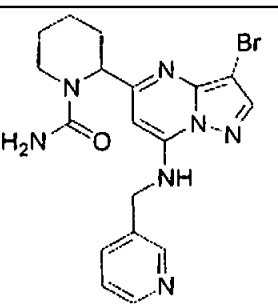
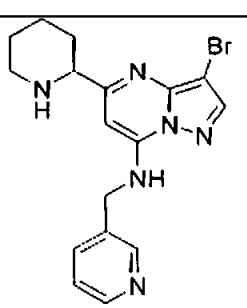
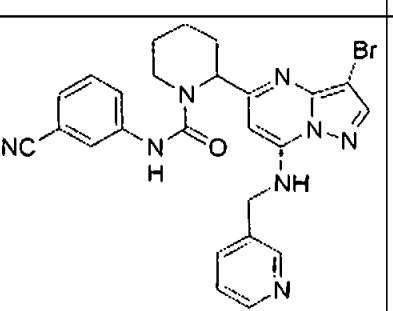
mmoles). Después de 1 a 2 horas, la mezcla de reacción se aplicó a una placa de TLC preparatoria de 1000 micrones y subsiguientemente se reveló usando EtOH – CH_2Cl_2 a 8 – 10% como eluyente para proporcionar los compuestos que se muestran en la Columna 3 de la Tabla 42.

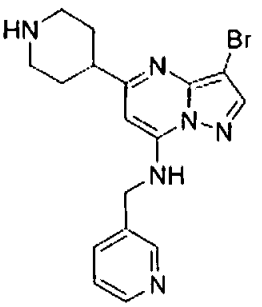
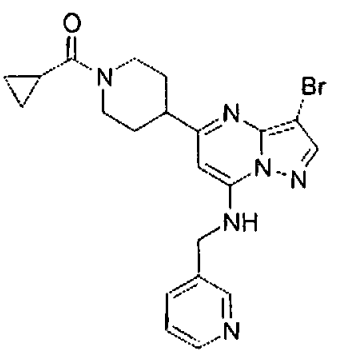
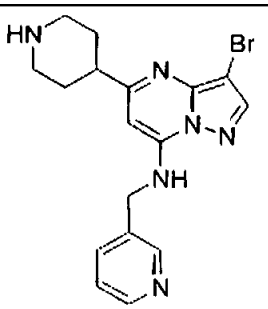
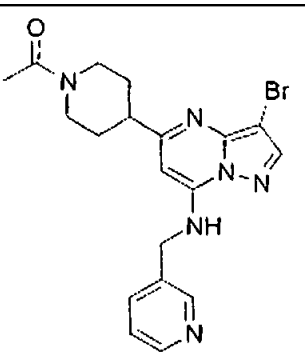
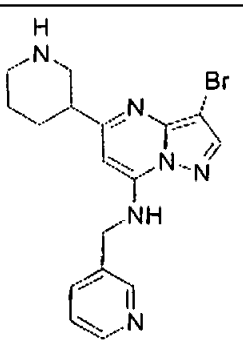
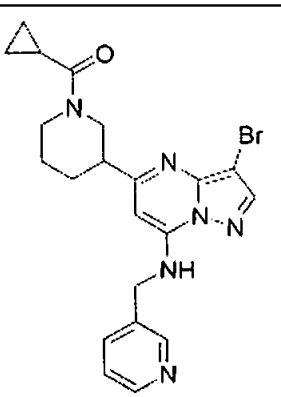
TABLA 42

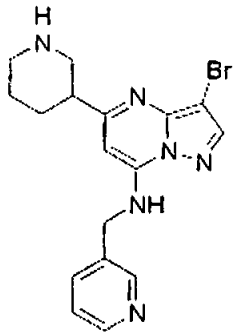
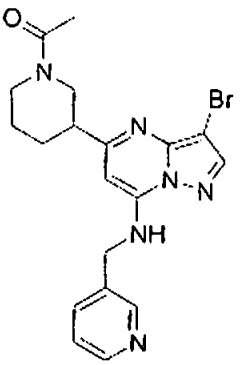
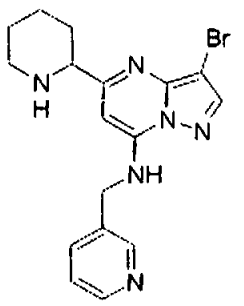
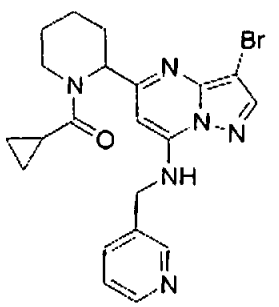
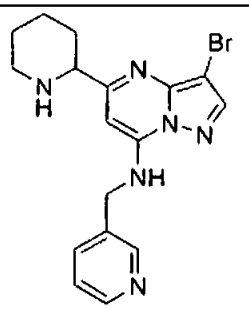
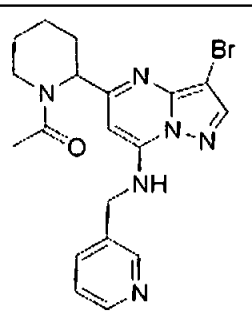
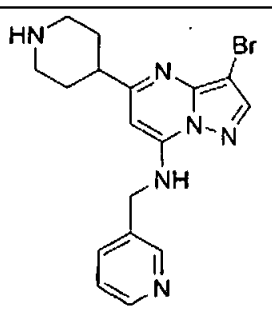
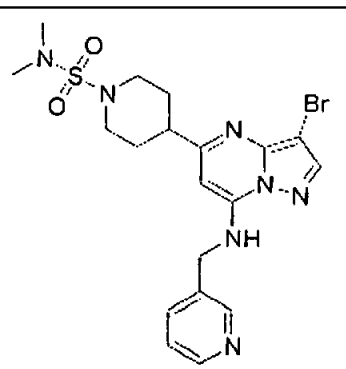
Ej.	Columna 2	Columna 3	COMP.
528			MH^+ = 608 p. f. = 230,1°C
529			Rendimiento = 82 MH^+ = 614 p. f. = 235,4°C
530			MH^+ = 486 p. f. = 60,5°C

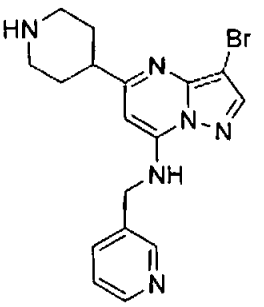
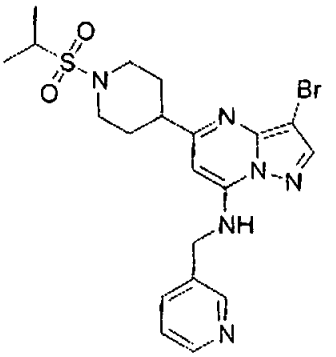
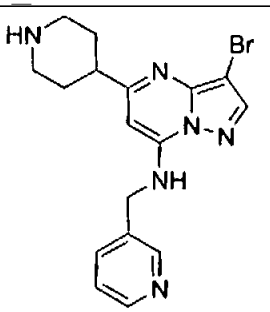
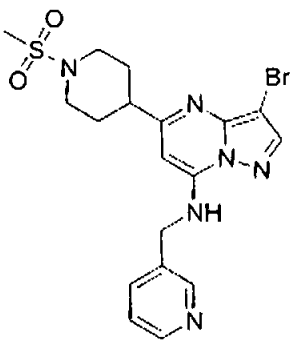
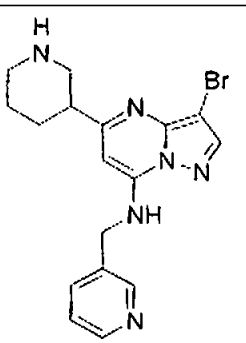
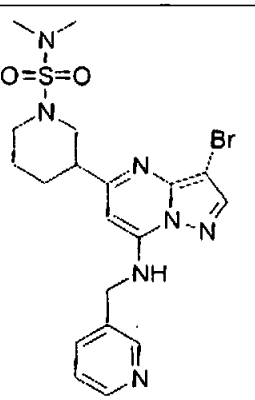
531			MH^+ = 500 p. f. = 113,6°C
532			MH^+ = 430 p. f. = 158,3 – 159,2°C
533			MH^+ = 531 p. f. =105,9°C
534			MH^+ = 486

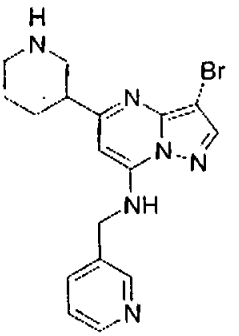
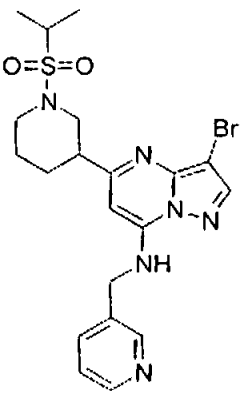
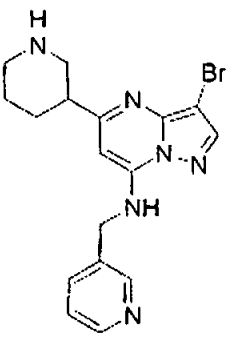
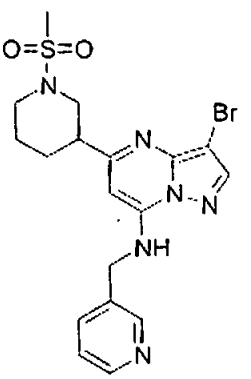
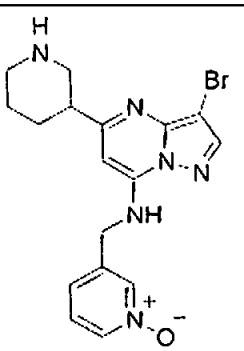
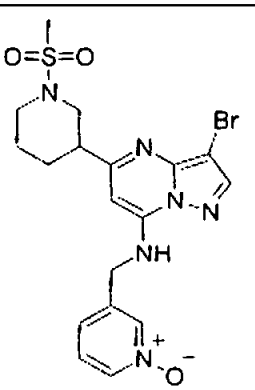
535			MH^+ = 500
536			MH^+ = 430
537			MH^+ = 531

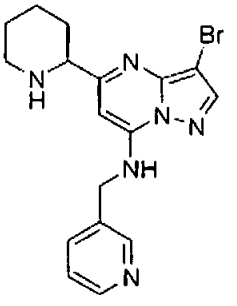
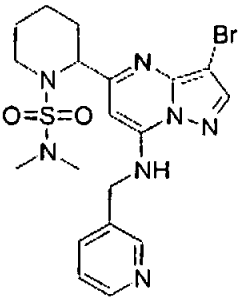
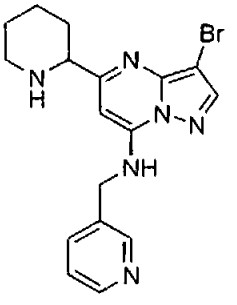
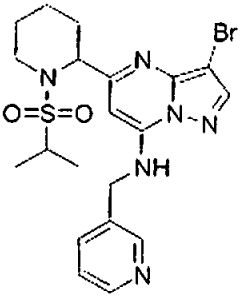
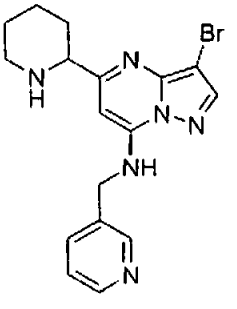
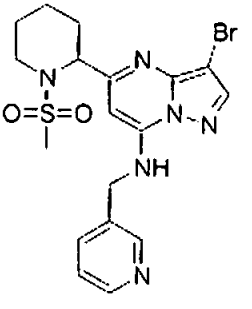
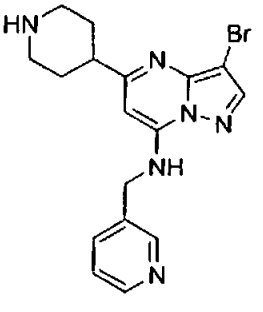
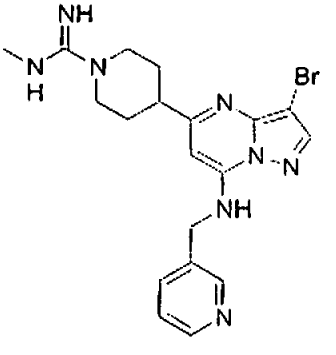
538			MH^+ = 486 p. f. = 69,6°C
539			MH^- = 500 p. f. = 82,3°C
540			MH^+ = 430 p. f. = 223,6°C
541			MH^+ = 531 p. f. = 118,1°C

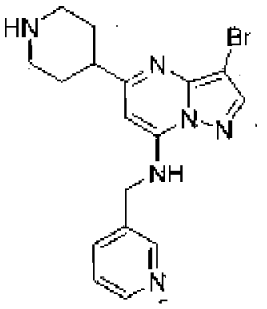
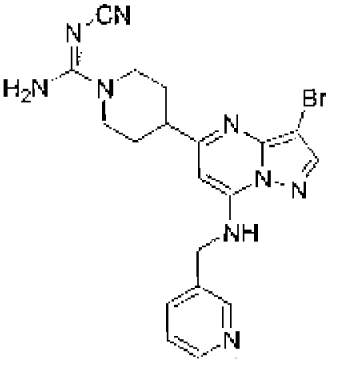
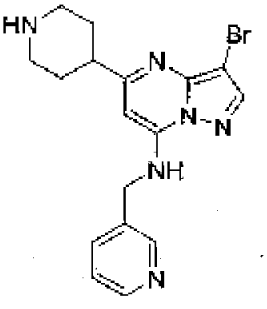
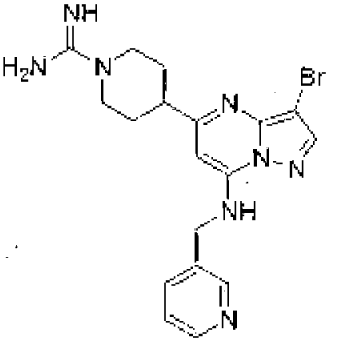
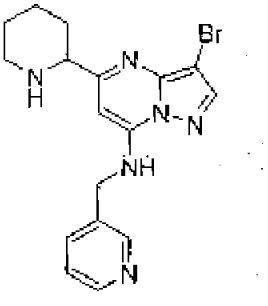
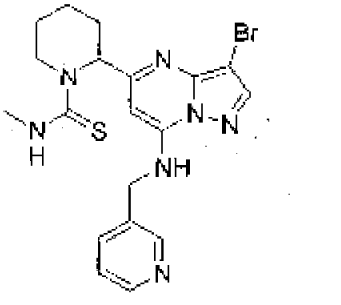
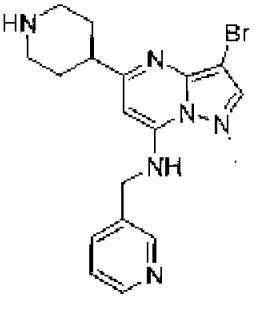
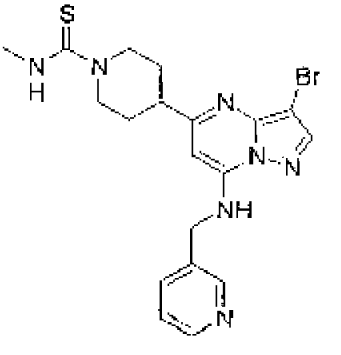
542			MH^+ = 455 p. f. = 109 – 110°C
543			MH^+ = 429 p. f. = 111,5°C
544			MH^+ = 455

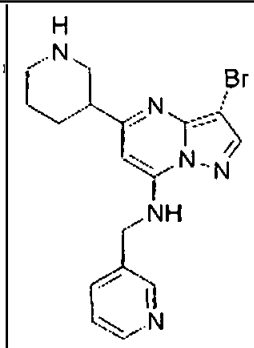
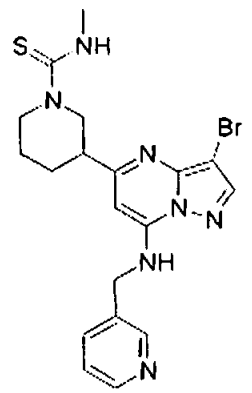
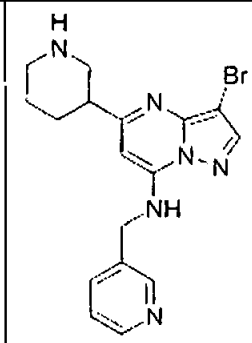
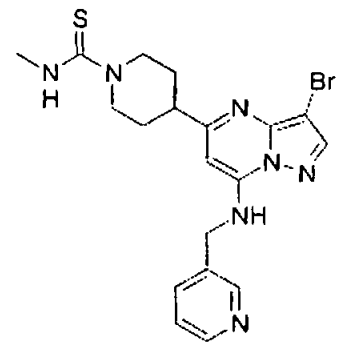
545			MH^+ = 429
546			MH^+ = 455 p. f. =80,1°C
547			MH^+ = 429 p. f. = 64,7°C
548			MH^+ = 494 p. f. = 76,5°C

549			MH^+ = 493 p. f. = 83,6°C
550			MH^+ = 465 p. f. =207,5°C
551			MH^+ = 494

552			MH^+ = 493
553			MH^+ = 465
554			MH^+ = 481 p. f. = 102,7°C

555			MH^+ = 494 p. f. = 85,3°C
556			MH^+ = 493 p. f. = 89,1°C
557			MH^+ = 465 p. f. = 83,8°C
558			Rendimiento = quant. MH^+ = 443 p. f. = 98,3°C (sal HCl)

559			MH^+ = 454
560			Rendimiento = cuant. MH^+ = 429 p. f. = 111,5 – 112,6°C
561			MH^+ = 460 p. f. = 122,7°C
562			MH^+ = 460 p. f. = 95,4°C

563			MH^+ = 460
564			MH^+ = 460 p. f. = 95,4°C

Los datos adicionales para los ejemplos que se dan a continuación:

Ejemplo 534: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,66 – 8,62 (s, 1H), 8,62 – 8,58 (d, 1H), 7,95 (s, 1H), 7,72 – 7,68 (d, 1H), 7,36 – 7,31 (dd, 1H), 6,66 – 6,62 (t, 1H), 5,93 (s, 1H), 4,65 – 4,62 (d, 2H), 3,86 – 3,82 (d, 1H), 3,65 – 3,58 (m, 1H), 3,26 – 3,12 (dd, 4H), 3,02 – 2,80 (m, 3H), 2,10 – 2,00 (m, 1H), 1,67 – 1,57 (m, 3H).

Ejemplo 535: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,66 – 8,62 (s, 1H), 8,62 – 8,58 (d, 1H), 7,95 (s, 1H), 7,72 – 7,67 (d, 1H), 7,36 – 7,30 (dd, 1H), 6,70 – 6,64 (t, 1H), 5,90 (s, 1H), 4,63 – 4,61 (d, 2H), 3,93 – 3,86 (m, 1H), 3,69 – 3,61 (m, 4H), 3,27 – 3,23 (m, 4H), 3,10 – 3,01 (dd, 1H), 2,93 – 2,84 (m, 2H), 2,08 – 2,03 (m, 1H), 1,90 – 1,57 (m, 4H).

Ejemplo 536: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,67 (s, 1H), 8,62 – 8,58 (d, 1H), 7,96 (s, 1H), 7,72 – 7,68 (d, 1H), 7,36 – 7,30 (dd, 1H), 6,79 – 6,72 (t, 1H), 5,96 (s, 1H), 4,86 (br s, 2H), 4,66 – 4,63 (d, 2H), 3,89 – 3,73 (m, 2H), 3,55 – 3,32 (m, 2H), 3,00 – 2,89 (m, 1H), 2,10 – 1,97 (m, 2H), 1,70 – 1,53 (m, 2H).

1017

Ejemplo 537: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,66 (s, 1H), 8,62 – 8,58 (d, 1H), 7,98 (s, 1H), 7,77 – 7,76 (t, 1H), 7,72 – 7,69 (d, 1H), 7,63 – 7,59 (m, 1H), 7,56 (s, 1H), 7,36 – 7,29 (dd, 1H), 6,83 – 6,79 (t, 1H), 5,96 (s, 1H), 4,67 – 4,64 (d, 2H), 3,98 – 3,93 (dd, 1H), 3,79 – 3,68 (m, 2H), 3,37 – 3,28 (m, 1H), 3,03 – 2,94 (m, 1H), 2,12 – 1,99 (m, 1H), 1,76 – 1,56 (m, 3H).

Ejemplo 544: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,66 – 8,62 (d, 1H), 8,61 – 8,58 (dd, 1H), 7,95 (s, 1H), 7,72 – 7,67 (d, 1H), 7,36 – 7,30 (dd, 1H), 6,80 – 6,62 (br s, 1H), 5,88 (s, 1H), 4,63 (s, 2H), 3,08 – 2,95 (m, 2H), 2,87 – 2,80 (m, 2H), 2,04 (m, 1H), 1,85 – 1,78 (m, 4H), 1,52 – 1,44 (m, 1H), 0,87 – 0,82 (m, 2H), 0,72 – 0,66 (m, 2H).

Ejemplo 545: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,66 (s, 1H), 8,62 – 8,58 (br t, 1H), 7,97 (s, 1H), 7,73 – 7,68 (d, 1H), 7,36 – 7,30 (br t, 1H), 6,79 – 6,72 (br t, 1H), 5,96 (s, 1H), 4,64 (br s, 2H), 4,59 – 4,46 (br d, 1H), 3,95 – 3,74 (br m, 1H), 3,57 – 3,49 (dd, 1H), 3,10 – 3,01 (dd, 1H), 2,86 – 2,70 (m, 2H), 2,13 (s, 3H), 2,06 – 2,00 (m, 2H), 1,65 – 1,48 (m, 2H).

Ejemplo 551: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,67 (s, 1H), 8,63 – 8,59 (d, 1H), 7,96 (s, 1H), 7,74 – 7,69 (d, 1H), 7,36 – 7,30 (dd, 1H), 6,69 – 6,64 (t, 1H), 5,95 (s, 1H), 4,67 – 4,63 (d, 2H), 3,85 3,65 (m,1H), 3,75 – 3,65 (m, 1H), 3,25 – 3,18 (dd, 1H), 3,03 – 2,90 (m, 2H), 2,81 (s, 6H), 2,03 – 1,95 (m, 1H), 1,89 – 1,68 (m, 3H).

Ejemplo 552: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,67 (s, 1H), 8,62 – 8,59 (d, 1H), 7,95 (s, 1H), 7,74 – 7,69 (d, 1H), 7,36 – 7,31 (dd, 1H), 6,67 – 6,60 (t, 1H), 5,98 (s, 1H), 4,67 – 4,63 (d, 2H), 3,92 – 3,86 (m, 1H), 3,85 – 3,75 (m, 1H), 3,40 – 3,30 (dd, 1H), 3,27 – 3,16 (m, 1H), 3,10 – 2,86 (m, 2H), 2,10 – 1,78(m, 3H), 1,40– 1,30 (d, 6H).

Ejemplo 553: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,67 (s, 1H), 8,62 (br s, 1H), 7,96 (s, 1H), 7,74 – 7,69 (d, 1H), 7,36 – 7,31 (dd, 1H), 6,70 – 6,66 (t, 1H), 5,98 (s, 1H), 4,67 – 4,63 (d, 2H), 3,88 – 3,81 (m, 1H), 3,71 – 3,65 (m, 1H), 3,20 – 3,11 (dd, 1H), 3,02 – 2,91 (m, 1H), 2,90 – 2,80 (m, 4H), 2,01 – 1,80 (m, 3H).

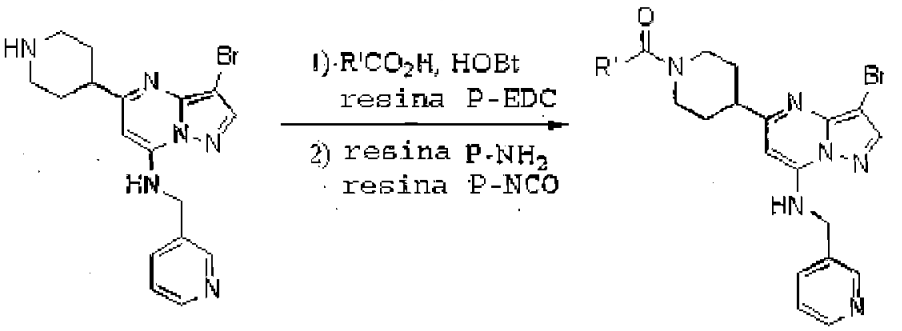
Ejemplo 559: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,66 –8,60 (d, 1H), 8,50 – 8,44 (dd, 1H), 8,01 (s, 1H), 7,93 (m, 1H), 7,48 – 7,40 (dd, 1H), 6,08 (s, 1H), 4,80 – 7,74 (s, 2H), 4,32 –4,19 (br d, 2H), 3,10 – 2,86 (m, 2H), 1,95 – 1,68 (m, 4H).

Ejemplo 563: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,66 (s, 1H), 8,62 – 8,58 (d, 1H), 7,96 (s, 1H), 7,73 – 7,68 (d, 1H), 7,36 – 7,30 (dd, 1H), 6,96 – 6,86 (br s, 1H), 6,79 – 6,74 (t, 1H), 6,00 (s, 1H), 4,67 – 4,64 (d, 2H), 4,37 – 4,30 (dd, 1H), 4,22 – 4,13 (m,

1018

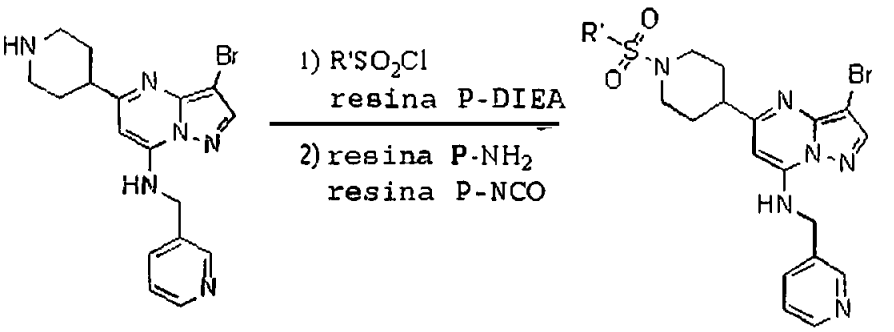
1H), 3,97 – 3,86 (dd, 1H), 3,73 – 3,64 (m, 1H), 3,17 – 3,14 (d, 3H), 3,07 – 2,99 (m, 1H), 2,20 – 1,97 (m, 2H); 1,68 – 1,48 (m, 2H).

PROCEDIMIENTO GENERAL 1: Procedimiento para la síntesis paralela de formación de amida:



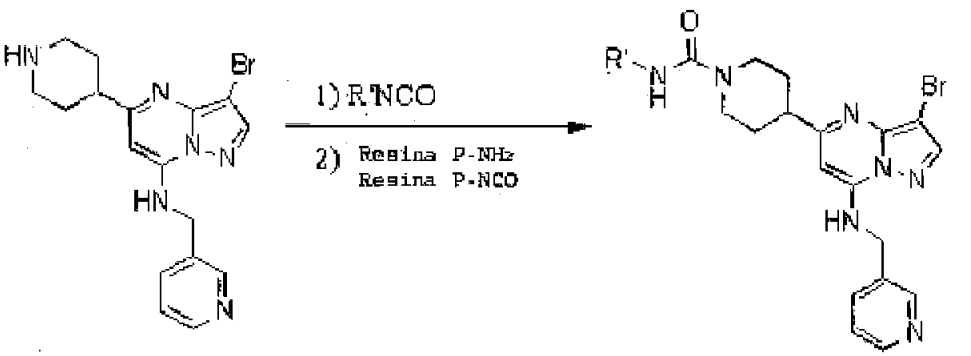
La síntesis paralela se llevó a cabo en bloques de reacción de 96 receptáculos de polipropileno, con un sellamiento removible en la parte superior y con un sellamiento fijo en la parte inferior. Cada receptáculo de reacción estaba provisto de un fondo fritado de polipropileno de 20 micrones y el volumen máximo fue de 3 mL. El bloque de recolección no estaba provisto de fritado en la parte inferior. A cada receptáculo de reacción se agregó una solución de una amina (0,021 mmoles) disuelta en una mezcla de DMF-THF-MeCN (4:3:3 v/v, 0,95 mL), resina EDC (P-EDC, Polymer Laboratories Ltd., 43 mg, 0,063 mmoles), 1-hidroxibenzotriazol (HOBt, 5,67 mg, 0,042 mmoles) y una solución de un ácido carboxílico en dimetilformamida (1 M, 0,0315 mL, 0,0315 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 16 horas. La solución del producto crudo se filtro en un recipiente de reacción cargado con resina trisamina (P-NH2, Argonaut Tech. Inc., 30 mg, 0,126 mmoles) y resina de isocianato (P-NCO, Argonaut Tech. Inc., 35 mg, 0,063 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 16 horas y se filtró en un bloque de recolección. La solución del producto se evaporó bajo presión reducida para proporcionar el producto amida deseado.

PROCEDIMIENTO GENERAL 2: Procedimiento de la síntesis paralela de formación de sulfonamida



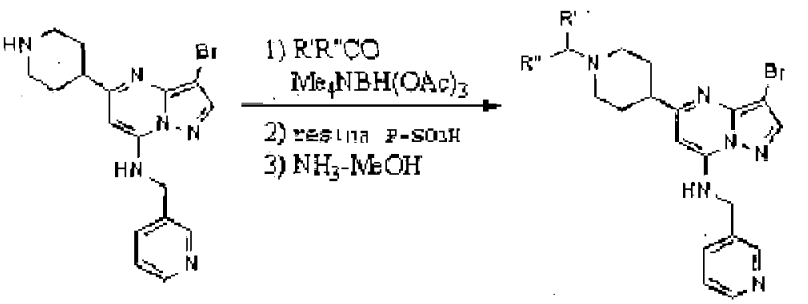
La síntesis paralela se llevó a cabo en bloques de reacción de 96 receptáculos de polipropileno con un sellamiento removible en la parte superior y con un sellamiento fijo en la parte inferior. Cada recipiente de reacción estaba provisto con un fondo fritado de polipropileno de 20 micrones y el volumen máximo fue de 3 mL. El bloque de recolección no estaba provisto de fritado en la parte inferior. A cada uno de los recipientes de reacción se agregó una solución de una amina (0,021 mmoles) disuelta en una mezcla de DMF-THF-MeCN (3:2:2 v/v, 0,95 mL), resina de DIEA (**P**-DIEA, Argonaut Tech. Inc., 18 mg, 0,063 mmoles) y una solución de un cloruro de sulfonilo en dimetilformamida (1 M, 0,0315 mL, 0,0315 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 16 horas. La solución de producto crudo se filtró en un recipiente de reacción cargado con una resina de trisamina (**P**-NH2, Argonaut Tech. Inc., 30 mg, 0,126 mmoles) y con resina de isocianato (**P**-NCO, Argonaut Tech. Inc., 35 mg, 0,063 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 16 horas y se filtró en un bloque de recolección. La solución del producto se evaporó bajo presión reducida para proporcionar el producto sulfonamida deseado.

PROCEDIMIENTO GENERAL 3: Procedimiento para la síntesis paralela de formación de urea



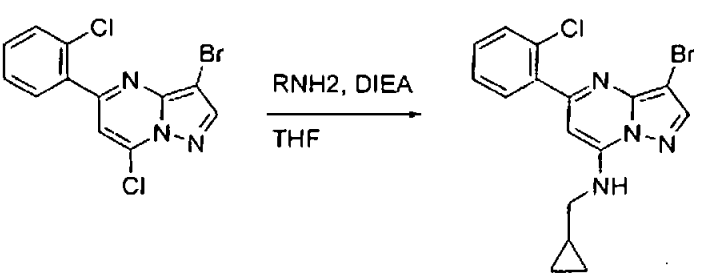
La síntesis paralela se llevó a cabo en bloques de reacción de 96 receptáculos de polipropileno con un sellamiento removible en la parte superior y un sellamiento fijo en la parte inferior. Cada recipiente de reacción estaba provisto de un fritado de polipropileno en la parte inferior de 20 micrones, y el volumen máximo fue de 3 mL. El bloque de recolección no estaba provisto de fritado en la parte inferior. A cada recipiente de reacción se agregó una solución de una amina (0,021 mmoles) disuelto en una mezcla de DMF-MeCN (1:1 v/v, 0,95 mL) y una solución de un isocianato en diclorometano (0,33 M, 0,126 mL, 0,042 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 16 horas. La solución de producto crudo se filtró en un recipiente de reacción cargado con una resina de trisamina (P-NH2, Argonaut Tech. Inc., 30 mg, 0,126 mmoles) y resina de isocianato (P-NCO, Argonaut Tech. Inc., 35 mg, 0,063 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 16 horas y se filtró en un bloque de recolección. La solución de producto se evaporó bajo presión reducida para proporcionar el producto de urea deseado.

PROCEDIMIENTO GENERAL 4: Procedimiento para la síntesis paralela de alquilación reductiva



La síntesis paralela se llevó a cabo en bloques de reacción de 96-receptáculos de polipropileno con sellamiento removible en la parte superior y sellamiento fijo en la parte inferior. Cada recipiente de reacción estaba provisto de un fritado en la parte inferior de polipropileno de 20 micrones, y el volumen máximo era de 3 mL. El bloque de recolección no estaba provisto de fritado en la parte inferior. A cada uno de los recipientes de reacción se agregó una solución de una amina (0,021 mmoles) disuelta en una mezcla de AcOH-DCE (1:99 v/v, 0,5 mL), una solución de un aldehído o cetona en dicloroetano (1 M, 0,147 mL, 0,147 mmoles), y una solución de triacetoxiborohidruro de tetrametilamonio (11 mg, 0,042 mmoles) disuelto en una mezcla de AcOH-DCE 1:99 v/v, 0,5 mL). La mezcla de reacción se agitó a temperatura ambiente durante 3 días. La solución de producto crudo se filtró en un receptáculo de reacción cargado con resina de ácido sulfónico Lanterns (P-SO_3H, MimotopesPty Ltd., 0,3 mmoles). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas y se decantó. El producto de resina Lanterns se lavó con metanol (1 mL) tres veces. Se agregó una solución de amoníaco en metanol (2 M, 1,2 mL). La mezcla de reacción se agitó a temperatura ambiente durante 30 minutos y se filtró en un bloque de recolección. La solución del producto se evaporó bajo presión reducida para proporcionar el producto de amina terciaria deseado.

PROCEDIMIENTO GENERAL 5: Procedimiento para la síntesis paralela de pirazolo [1,5a] pirimidinas 7,N-sustituidas



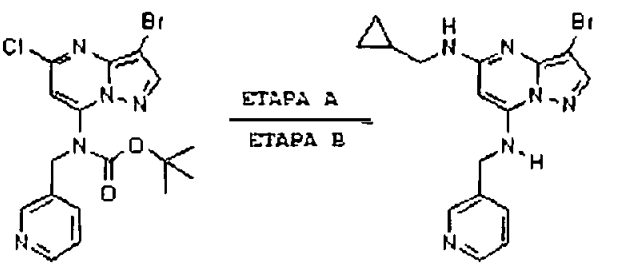
A 3-bromo-7-cloro-5-(2-cloro-fenil)-pirazolo[1,5-a]pirimidina (9,0 mg, 0,03 mmoles) en tetrahidrofurano se agregó di-*iso*-propiletilamina (12 µL, 0,07), seguido de ciclopropilmetilamina (70 µL, .07 mmol; solución 1M en DMF). La

mezcla de reacción se calentó a 70°C durante 36 horas y luego se enfrió a temperatura ambiente. La mezcla se trató con (**P**-NCO, Argonaut Tech. Inc 70 mg, 0,12 mmoles), y **P**-CO_3^- (Argonaut Tech. Inc 70 mg, 0,24 mmoles) y se agitó a temperatura ambiente durante 12-18 horas. La solución se filtró y evaporó hasta sequedad para proporcionar el producto. e/z observado m/z 375.21.

PROCEDIMIENTO GENERAL 6: Procedimiento para la síntesis paralela de pirazolo[1,5a]pirimidinas de 5,N-sustituidas

Protocolos Generales:

La síntesis paralela se llevó a cabo en bloques de polipropileno de 96 receptáculos tal como se describió en otra parte. En el caso de ser necesario calentamiento, las reacciones se efectuaron en tubos de vidrio de 2,5 mL sellados individualmente con una esterilla de polipropileno y el calentamiento se logró mediante un bloque de transferencia de calor a los 96 receptáculos.



ETAPA A:

A la 3-bromo-5-cloro-7-N-Boc-alquilamino-pirazolo[1,5-a]pirimidina (17 mg, 0,04 mmoles) en *p*-dioxano se agregó DIEA (9 μL, 0,05), seguido de ciclopropil-metilamina (80 μL, .08 mmol; solución 1M en isopropanol). La mezcla de reacción se calentó a 90 °C durante 36 horas y luego se enfrió a temperatura ambiente. La mezcla se trató con **P**-NCO (Argonaut Tech. Inc. 70 mg, 0,12 mmoles) y **P**-CO_3^- (Argonaut Tech. Inc. 70 mg, 0,24 mmoles) y se agitó a temperatura ambiente durante 12-18 horas. La solución se filtró y evaporó hasta sequedad para proporcionar el producto.

ETAPA B(ácida):

El producto de la ETAPA A se recogió en 35% de TFA/DCM y se agitó durante 4 horas seguido de concentración bajo alto vacío. El residuo se trató con

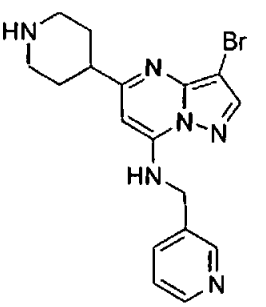
10% de HCl(acuoso) en MeOH agitado durante 2 horas y luego se concentró para proporcionar el producto deseado. observado m/z 375.21.

ETAPA B(básica):

El producto de la etapa A se recogió en EtOH y se trató con una resina de intercambio iónico con Ambersep® 900-OH (Acros, 100mg), calentada a reflujo durante 48 horas con agitación suave. La mezcla de reacción se enfrió a temperatura ambiente, se filtró y se concentró para proporcionar el producto deseado.

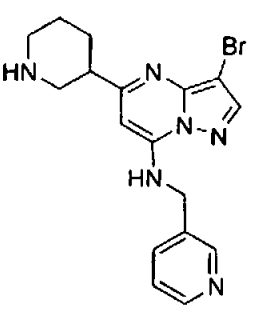
EJEMPLO 565:

Utilizando el procedimiento que se indica en el Procedimiento General 1 y el compuesto del Ejemplo 462 que se muestra a continuación, se prepararon los compuestos con las m/z observadas en la Tabla 43.



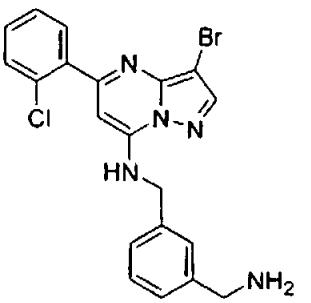
EJEMPLO 566:

Utilizando el procedimiento que se indica en el Procedimiento General 1 y el compuesto del Ejemplo 471 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 44 con la m/z observada.



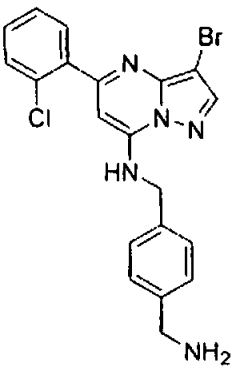
EJEMPLO 567:

Utilizando el procedimiento que se indica en el Procedimiento General 1 y el compuesto del Ejemplo 515 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 45 con la m/z observada.



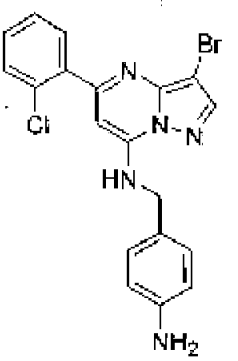
EJEMPLO 568:

Utilizando el procedimiento que se indica en el Procedimiento General 1 y el compuesto del Ejemplo 513 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 46 con la m/z observada.



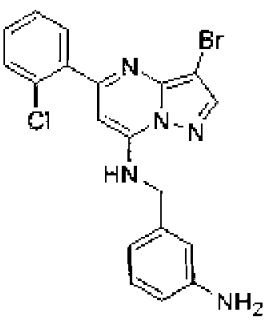
EJEMPLO 569:

Utilizando el procedimiento que se indica en el Procedimiento General 1 y el compuesto del Ejemplo 526 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 47 con la m/z observada.



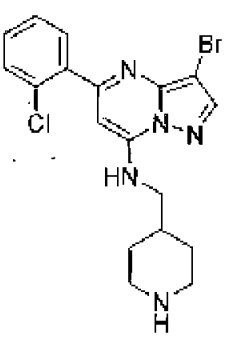
EJEMPLO 570:

Utilizando el procedimiento que se indica en el Procedimiento General 1 y el compuesto del Ejemplo 524 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 48 con la m/z observada.



EJEMPLO 571:

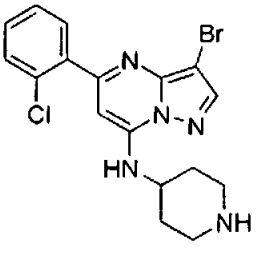
Utilizando el procedimiento que se indica en el Procedimiento General 1 y el compuesto del Ejemplo 525 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 49 con la m/z observada.



1025

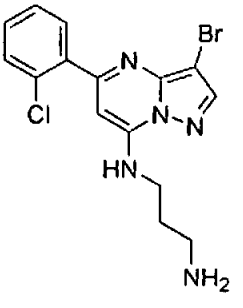
EJEMPLO 572:

Utilizando el procedimiento que se indica en el Procedimiento General 1 y el compuesto del Ejemplo 526.10 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 50 con la m/z observada.



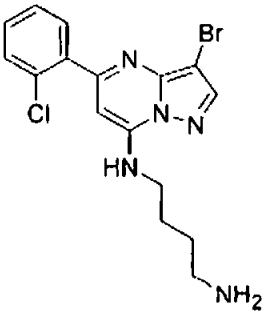
EJEMPLO 573:

Utilizando el procedimiento que se indica en el Procedimiento General 1 y el compuesto del Ejemplo 518 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 51 con la m/z observada.



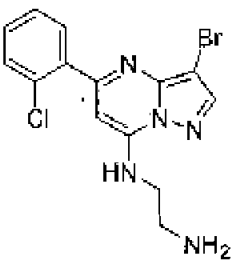
EJEMPLO 574:

Utilizando el procedimiento que se indica en el Procedimiento General 1 y el compuesto del Ejemplo 519 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 52 con la m/z observada.



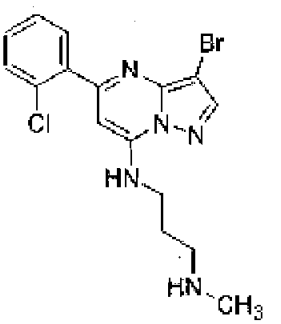
EJEMPLO 575:

Utilizando el procedimiento que se indica en el Procedimiento General 1 y el compuesto del Ejemplo 520 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 53 con la m/z observada.



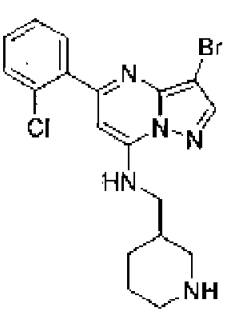
EJEMPLO 576:

Utilizando el procedimiento que se indica en el Procedimiento General 1 y el compuesto del Ejemplo 522 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 54 con la m/z observada.



EJEMPLO 577:

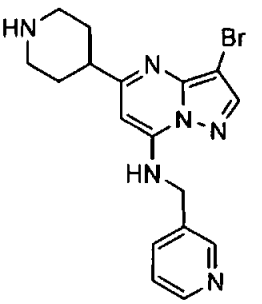
Utilizando el procedimiento que se indica en el Procedimiento General 1 y el compuesto del Ejemplo 523 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 55 con la m/z observada.



1027

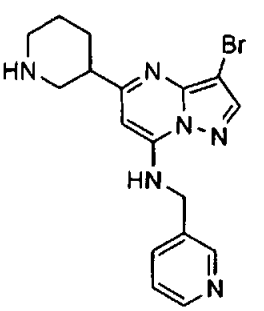
EJEMPLO 578:

Utilizando el procedimiento que se indica en el Procedimiento General 2 y el compuesto del Ejemplo 462 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 56 con la m/z observada.



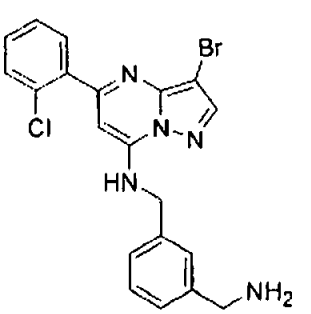
EJEMPLO 579:

Utilizando el procedimiento que se indica en el Procedimiento General 2 y el compuesto del Ejemplo 471 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 57 con la m/z observada.



EJEMPLO 580:

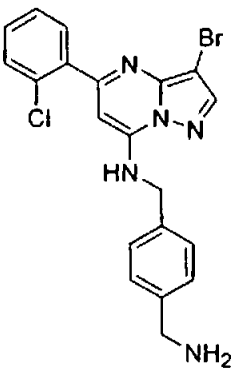
Utilizando el procedimiento que se indica en el Procedimiento General 2 y el compuesto del Ejemplo 515 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 58 con la m/z observada.



82901

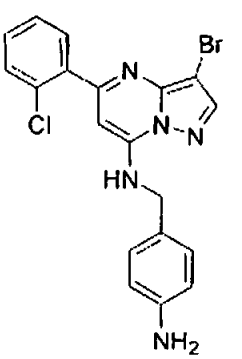
EJEMPLO 581:

Utilizando el procedimiento que se indica en el Procedimiento General 2 y el compuesto del Ejemplo 513 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 59 con la m/z observada.



EJEMPLO 582:

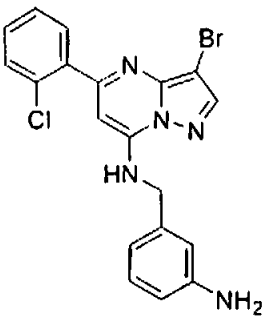
Utilizando el procedimiento que se indica en el Procedimiento General 2 y el compuesto del Ejemplo 513 que se muestra a continuación se prepararon los compuestos que se muestran en la Tabla 60 con la m/z observada.



EJEMPLO 583:

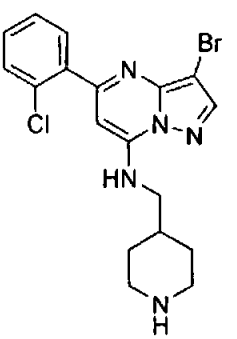
Utilizando el procedimiento que se indica en el Procedimiento General 2 y el compuesto del Ejemplo 524 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 61 con la m/z observada.

b291



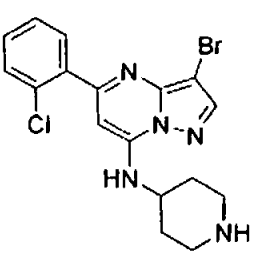
EJEMPLO 584:

Utilizando el procedimiento que se indica en el Procedimiento General 2 y el compuesto del Ejemplo 525 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 62 con la m/z observada.



EJEMPLO 585:

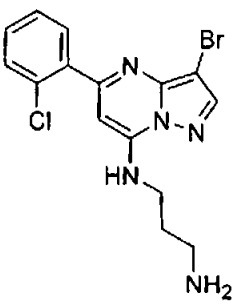
Utilizando el procedimiento que se indica en el Procedimiento General 2 y el compuesto del Ejemplo 526.10 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 63 con la m/z observada.



1030

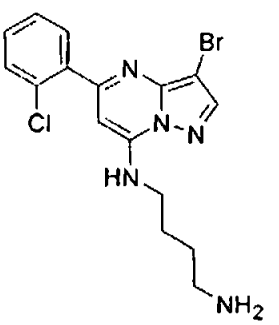
EJEMPLO 586:

Utilizando el procedimiento que se indica en el Procedimiento General 2 y el compuesto del Ejemplo 518 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 64 con la m/z observada.



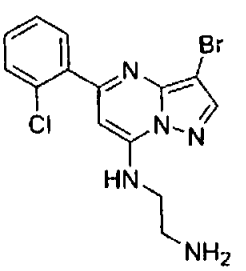
EJEMPLO 587:

Utilizando el procedimiento que se indica en el Procedimiento General 2 y el compuesto del Ejemplo 519 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 65 con la m/z observada.



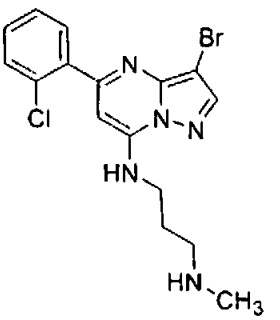
EJEMPLO 588:

Utilizando el procedimiento que se indica en el Procedimiento General 2 y el compuesto del Ejemplo 520 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 67 con la m/z observada.



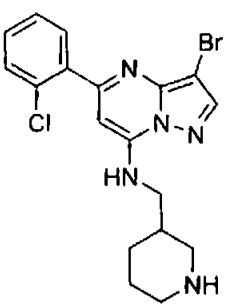
EJEMPLO 589:

Utilizando el procedimiento que se indica en el Procedimiento General 2 y el compuesto del Ejemplo 521 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 68 con la m/z observada.



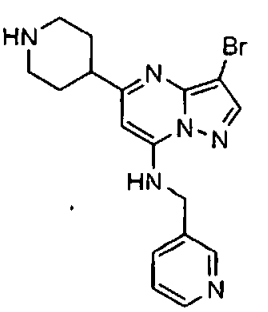
EJEMPLO 590:

Utilizando el procedimiento que se indica en el Procedimiento General 2 y el compuesto del Ejemplo 523 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 69 con la m/z observada.



EJEMPLO 591:

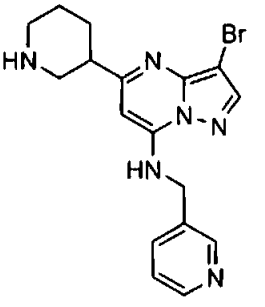
Utilizando el procedimiento que se indica en el Procedimiento General 3 y el compuesto del Ejemplo 462 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 70 con la m/z observada.



289

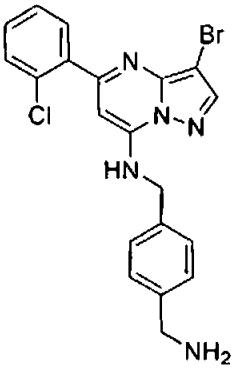
EJEMPLO 592:

Utilizando el procedimiento que se indica en el Procedimiento General 3 y el compuesto del Ejemplo 471 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 71 con la m/z observada.



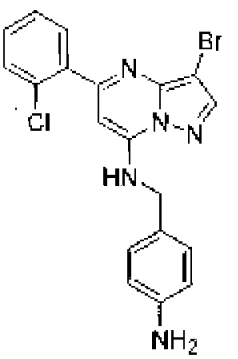
EJEMPLO 593:

Utilizando el procedimiento que se indica en el Procedimiento General 3 y el compuesto del Ejemplo 513 que se muestra a continuación se prepararon los compuestos que se muestran en la Tabla 72 con la m/z observada.



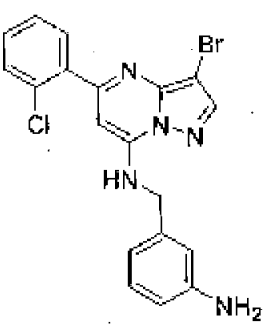
EJEMPLO 594:

Utilizando el procedimiento que se indica en el Procedimiento General 3 y el compuesto del Ejemplo 524 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 73 con la m/z observada.



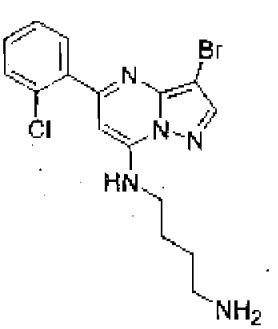
EJEMPLO 595:

Utilizando el procedimiento que se indica en el Procedimiento General 3 y el compuesto del Ejemplo 524 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 74 con la m/z observada.



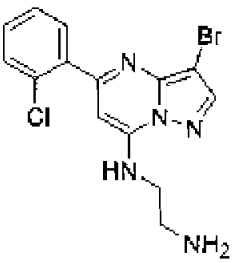
EJEMPLO 596:

Utilizando el procedimiento que se indica en el Procedimiento General 3 y el compuesto del Ejemplo 519 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 75 con la m/z observada.



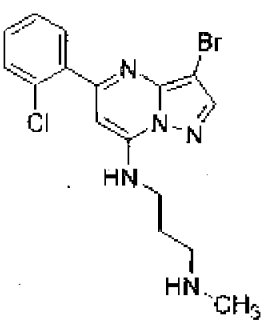
EJEMPLO 597:

Utilizando el procedimiento que se indica en el Procedimiento General 3 y el compuesto del Ejemplo 520 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 76 con la m/z observada.



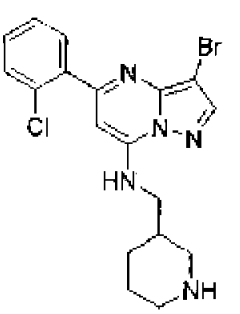
EJEMPLO 598:

Utilizando el procedimiento que se indica en el Procedimiento General 3 y el compuesto del Ejemplo 521 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 77 con la m/z observada.



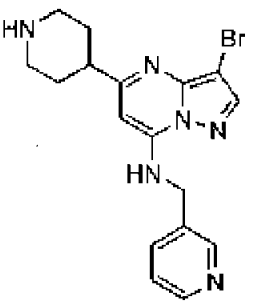
EJEMPLO 599:

Utilizando el procedimiento que se indica en el Procedimiento General 3 y el compuesto del Ejemplo 523 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 78 con la m/z observada.



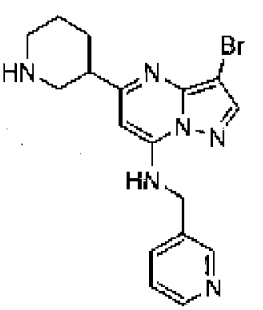
EJEMPLO 600:

Utilizando el procedimiento que se indica en el Procedimiento General 4 y el compuesto del Ejemplo 462 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 79 con la m/z observada.



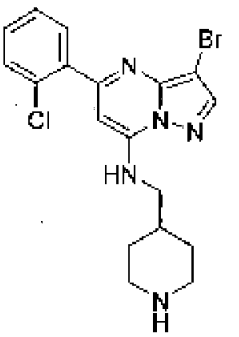
EJEMPLO 601:

Utilizando el procedimiento que se indica en el Procedimiento General 4 y el compuesto del Ejemplo 471 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 80 con la m/z observada.



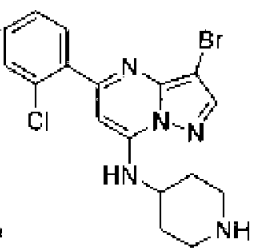
EJEMPLO 602:

Utilizando el procedimiento que se indica en el Procedimiento General 4 y el compuesto del Ejemplo 525 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 81 con la m/z observada.



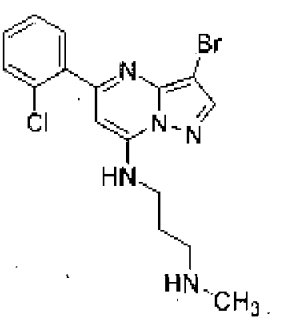
EJEMPLO 603:

Utilizando el procedimiento que se indica en el Procedimiento General 4 y el compuesto del Ejemplo 526.10 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 82 con la m/z observada.



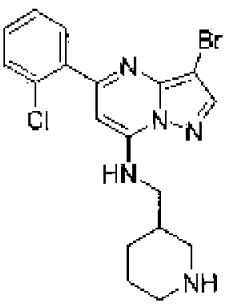
EJEMPLO 604:

Utilizando el procedimiento que se indica en el Procedimiento General 4 y el compuesto del Ejemplo 521 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 83 con la m/z observada.



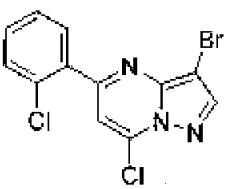
EJEMPLO 605:

Utilizando el procedimiento que se indica en el Procedimiento General 4 y el compuesto del Ejemplo 523 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 84 con la m/z observada.



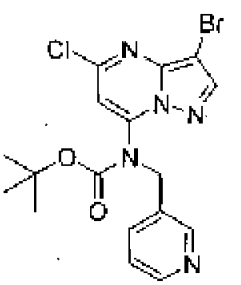
EJEMPLO 606:

Utilizando el procedimiento que se indica en el Procedimiento General 5 y el compuesto del Ejemplo 81 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 85 con la m/z observada.

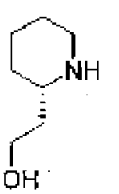


EJEMPLO 607:

Utilizando el procedimiento que se indica en el Procedimiento General 6 y el compuesto del Ejemplo 196 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 86 con la m/z observada.



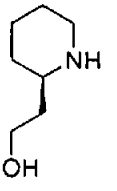
EJEMPLO PREPARATIVO 500



Se agregó piperidin-2-etanol (127 g, 980 mmoles) en 95% de EtOH (260 mL) a ácido *(S)*-(+)-alcanforsulfónico (228,7 g, 1,0 eq.) en 95% EtOH (150 mL) y la solución resultante se calentó a reflujo. Se agregó Et_2O (600 mL) y la solución caliente y la solución se enfrió a temperatura ambiente y se dejó en reposo

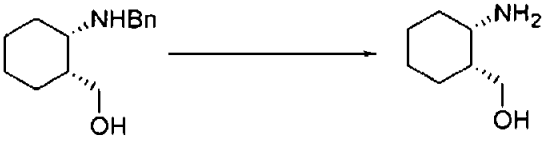
durante 3 días. Los cristales resultantes se filtraron y se secaron al vacío (25 g): p.f. 173-173°C (lit. 168°C). Luego la sal se disolvió en NaOH (3M, 100 mL) y se agito durante 2 horas y la solución resultante se extrajo con CH_2Cl_2 (5 x 100 mL). Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, filtraron y concentraron bajo presión reducida para proporcionar *(S)*-piperidin-2-etanol (7,8 g) una porción del cual se recristalizó a partir de Et_2O: p.f. = 69-70°C (lit. 68-69°C); $[\alpha]_D$ = 14,09° ($CHCl_3$, c=0,2).

EJEMPLO PREPARATIVO 501



Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo preparativo 500 sustituyendo únicamente ácido *(R)*-(-)-alcanforsulfónico, se preparó *(R)*-piperidin-2-etanol. (1,27 g): $[\alpha]_D$ = 11.3° ($CHCl_3$, c=0,2).

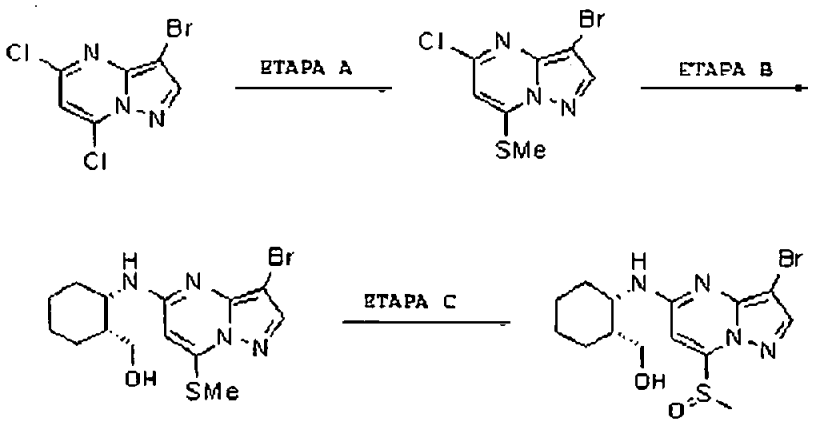
EJEMPLO PREPARATIVO 502



A una botella de presión cargada con una solución de *cis*-(1*R*,2*S*)-(+)-2-(bencilamino) ciclohexanmetanol (1 g, 4,57 mmoles) en MeOH (35 mL) se agregó 20% en peso de $Pd(OH)_2$ (0,3 g, >50% en húmedo) en una sola porción. La mezcla se agitó bajo 344,5 kPa (50 psi) de H_2 en un aparato de hidrogenación Parr durante 12 horas. La mezcla se purgó con N_2 y se filtró a través de una almohadilla de Celite. La almohadilla se lavó generosamente con MeOH (2 x 25 mL) y el filtrado resultante se concentró bajo presión reducida para proporcionar 0,57g (97%) de un sólido blanco. M+H = 130.

102

EJEMPLO PREPARATIVO 503



Etapa A:

A una solución del aducto 3-Br (1,1 g, 4,1 mmoles) del Ejemplo preparativo 142 en THF (40 mL) a 0°C se agregó CH_3SNa (0,32 g, 4,53 mmoles) en una sola porción. La mezcla heterogénea se agitó durante 72 horas a temperatura ambiente y luego la mezcla se concentró bajo presión reducida. El producto crudo se dividió entre agua (10 mL) y EtOAc (30 mL) y las capas se separaron. La capa orgánica se lavó con salmuera (1 x 10 mL) y se secó (Na_2SO_4). La capa orgánica se filtró y se concentró bajo presión reducida para proporcionar 1,0 g (88%) de un sólido amarillo. P.f. 150-152°C; M+H = 280. Este material se recogió sobre la Etapa B sin purificación adicional.

Etapa B:

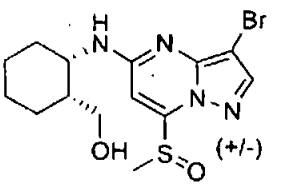
A una solución del derivado tiometilo (1,5 g, 5,37 mmoles) de la Etapa A en dioxano/DIPEA (15 mL/4 mL) a temperatura ambiente se agregó amino alcohol (1,3 g, 8,06 mmoles) del Ejemplo Preparativo 10. La mezcla se calentó a reflujo durante 48 horas, se enfrió a temperatura ambiente y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía evaporativa usando CH_2Cl_2/MeOH (30:1) como eluyente para proporcionar 1,8 g del producto (90%) en forma de un sólido amarillo cristalino. P.f. 167-169 °C; M+H = 373.

Etapa C:

A una solución del derivado tiometilo (2,2 g, 5,92 mmoles) de la Etapa B en CH_2Cl_2 (20 mL) a 0°C se agregó MCPBA (1,53 g, 8,9 mmoles) en una porción. La

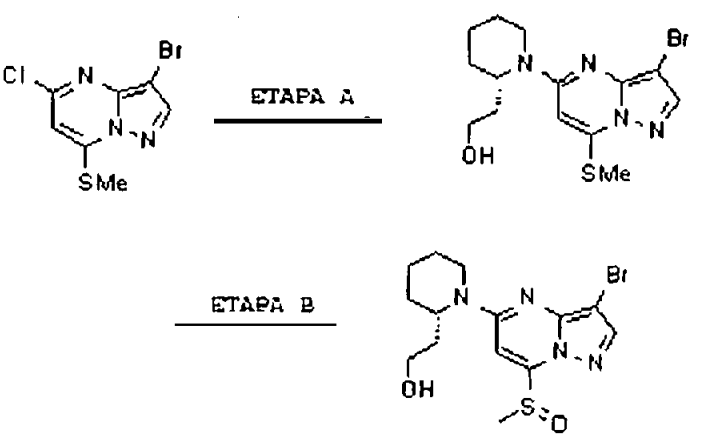
mezcla resultante se agitó durante 2 horas a 0°C después de lo cual la mezcla se diluyó con CH_2Cl_2 (20 mL) y $NaHCO_3$ acuoso saturado (15 mL). Las capas se separaron y la capa orgánica se lavó con $NaHCO_3$ acuoso saturado (15 mL) y salmuera (1 x 15 mL). La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida para proporcionar 2,0 g de un sólido de color castaño (87%). P.f. 181-183°C; M+H = 388.

EJEMPLO PREPARATIVO 504



Se preparó el compuesto del título (racémico) de acuerdo con el procedimiento que se indica en el Ejemplo preparativo 503 excepto que se sustituyó el clorhidrato de *cis*-hidroximetil-1-ciclohexilamina comercialmente obtenible en la Etapa B.

EJEMPLO PREPARATIVO 505



Etapa A:

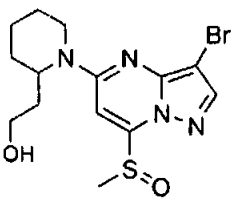
El tratamiento del derivado tiometilo (2,0 g, 7,2 mmoles) de la Etapa A del Ejemplo preparativo 503 con (*S*)-piperidin-2-etanol (1,2 g, 9,3 mmoles) del Ejemplo preparativo 500 bajo condiciones idénticas a las descritas en la Etapa B

del Ejemplo preparativo 503, proporcionó 0,90 g (34%) del compuesto del título en forma de un semisólido. P.f. 173-175°C. M+H = 372.

Etapa B:

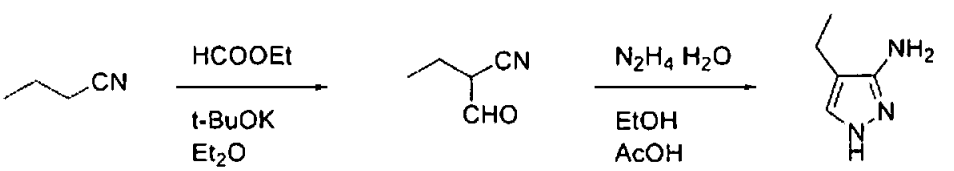
Siguiendo el procedimiento de la Etapa C en el Ejemplo Preparativo 503, se trató el derivado tiometilo (0,30 g, 0,81 mmoles) con MCPBA (0,21 g, 1,2 mmoles) para proporcionar 0,31 g (99%) del compuesto del título en forma de un aceite amarillo viscoso. M+H = 388.

EJEMPLO PREPARATIVO 506



Se preparó el compuesto del título (racémico) de acuerdo con el procedimiento que se indica en el Ejemplo Preparativo 505 excepto que se sustituyó el piperidin-2-etanol comercialmente obtenible. M+H = 388.

EJEMPLO PREPARATIVO 507



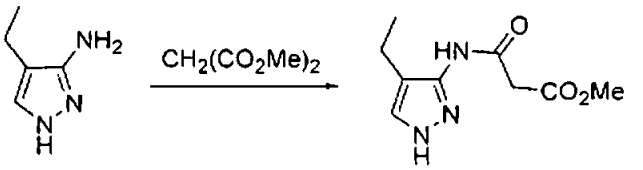
Se agitó t-BuOK (112,0 g, 1,00 mol) bajo N_2 en Et_2O seco (3,0 L) en un frasco de 5 L equipado con un embudo de adición. Se agregó por goteo una mezcla de butironitrilo (69,0 g, 1,00 mol) y formiato de etilo (77,7 g, 1,05 moles) se agregó por goteo durante 3 horas, y luego se agitó la mezcla de reacción durante la noche a temperatura ambiente. La mezcla se enfrió a 0°C, se agregó AcOH (57 mL), y la mezcla se filtró, y el sólido se lavó con Et_2O (500 mL). Los filtrados combinados se evaporaron a temperatura ambiente en un rotoevaporador para proporcionar un aceite de color amarillo pálido (95,1g).

El aceite se disolvió en EtOH seco (100 mL), se agregó 99% de monohidrato de hidrazina (48 mL), y luego se agregó AcOH (14 mL), y la mezcla se reflujó bajo N_2 durante la noche. Los solventes se evaporaron y el aceite

2701

resultante se cromatografió sobre gel de sílice con CH_2Cl_2:7N NH_3 en MeOH. Se obtuvo 22,4 g (20%) de 3-amino-4-etilpirazol en forma de un aceite claro que se solidificó por reposo.

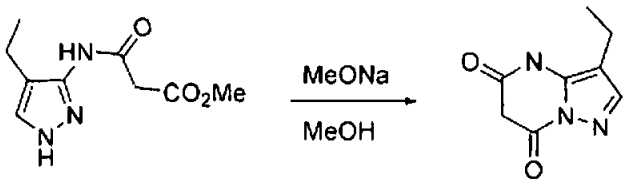
EJEMPLO PREPARATIVO 508



Etapa A:

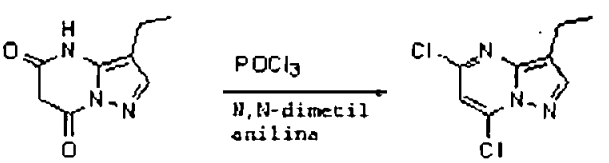
El pirazol del Ejemplo Preparativo 507 (9,80g) y malonato de dimetilo (45 mL) se agitaron y reflujaron bajo N_2 durante 3 horas. El exceso de malonato de dimetilo se evaporó al vacío y el residuo se cromatografió con 15:1 de CH_2Cl_2:MeOH para proporcionar un sólido de color amarillo pálido (10,6 g, 57%). LCMS: MH^+ = 212.

Etapa B:



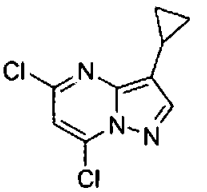
Se agregó MeOH seco (200 mL) bajo N_2 a una mezcla de la amida de la Etapa A (11,9 g, 56,4 mmoles) y metóxido de sodio (4,57 g, 84,6 mmoles). La mezcla se agitó y reflujó bajo N_2 durante 5 horas, se enfrió a temperatura ambiente, y se agregó HCl concentrado (20 mL). Los solventes se evaporaron y el residuo se suspendió en H_2O (300 mL). El sólido se separó por filtración, se lavó en un filtro con 2x300 mL de H_2O, y se secó al vacío a 100°C. Se obtuvieron 7,40g (73%) de un sólido color crema. LCMS: MH^+ = 180.

Etapa C:



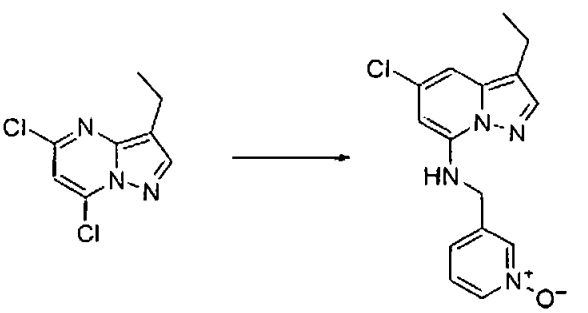
Se agregaron $POCl_3$ (100 mL) y N, N-dimetilanilina (20 mL) bajo N_2 a la dicetona de la Etapa B (7,70 g), y la mezcla se agitó y reflujó durante 20 horas bajo N_2. Luego se enfrió a temperatura ambiente, se vertió cuidadosamente en un litro de hielo triturado y se extrajo con EtOAc (2x500 mL). Los extractos se lavaron con H_2O (500 mL), se secaron sobre Na_2SO_4, se filtraron, y el solvente se evaporó. El residuo se cromatografió con CH_2Cl_2 para proporcionar un sólido de color amarillo pálido (8,20 g, 90%). LCMS: MH^+ = 216.

EJEMPLO PREPARATIVO 508.10



Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo Preparativo 508, sustituyendo únicamente el compuesto del Ejemplo Preparativo 1, se preparó el compuesto anterior. LCMS: MH^+ = 228.

EJEMPLO PREPARATIVO 509

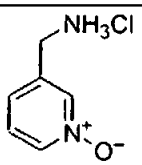
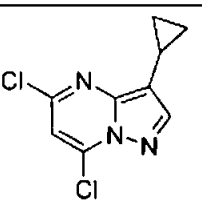
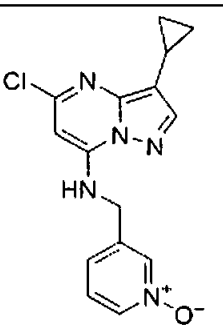
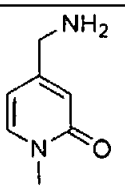
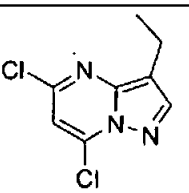
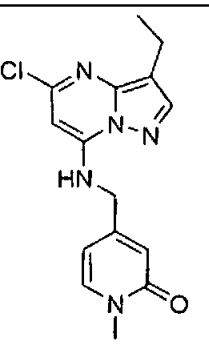
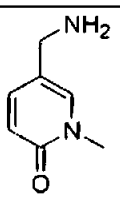
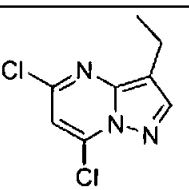
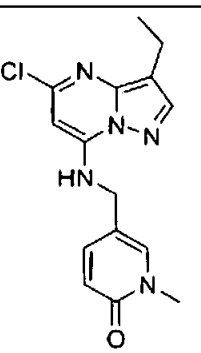


Una mezcla de dicloruro del Ejemplo Preparativo 508 (3,13 g, 14,5 mmoles), la amina.HCl del Ejemplo Preparativo (3,00 g, 18,9 mmoles), DIPEA (7,5 mL), y NMP seco (40 mL) más dioxano seco (40 mL) se agitó a 60°C durante 4 días bajo N_2. Luego los solventes se separaron por destilación al vacío y el residuo se cromatografió con 6:1 de EtOAc: MeOH y luego se recromatografió con 12:1 de CH_2Cl_2:MeOH. El sólido así obtenido se suspendió en H_2O (100 mL), se filtró, se lavó sobre filtro con H_2O (2x100 mL), y se secó al vacío. Se obtuvo un sólido de color rosa pálido (2,37 g, 54%). M+H = 304.

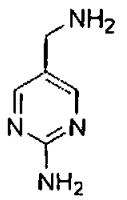
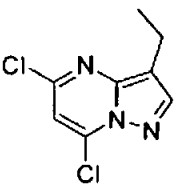
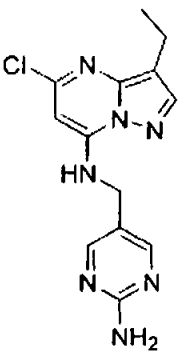
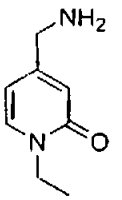
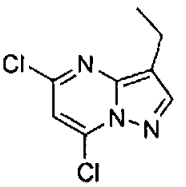
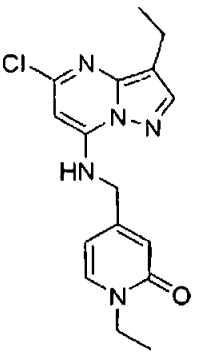
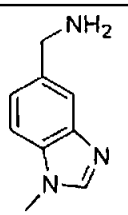
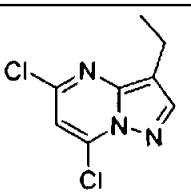
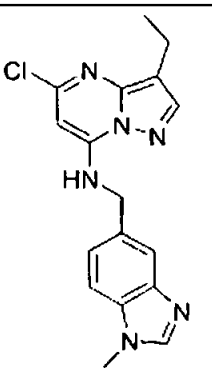
EJEMPLOS PREPARATIVOS 510-516

Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo Preparativo 509 sustituyendo únicamente las aminas en la Columna 2 de la Tabla 500 y los cloruros que se muestran en la Columna 3 de la Tabla 500, se prepararon los compuestos que se muestran en la Columna 4 de la Tabla 500.

TABLA 500

Ej. Prep.	Columna 2	Columna 3	Columna 4	COMP.
510				M+H = 316
512				M+H = 318
513				M+H = 318

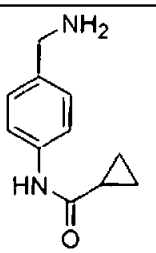
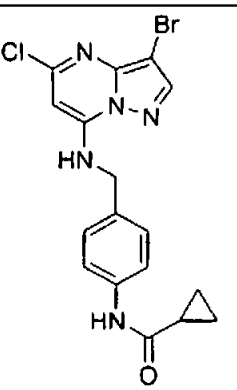
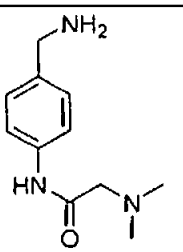
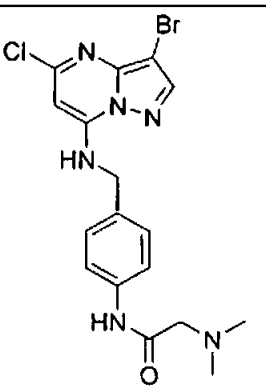
193

514				
515				M+H = 332
516				

EJEMPLO PREPARATIVO 517:

Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo Preparativo 184 sustituyendo únicamente las aminas de la Columna 2 de la Tabla 501, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 501.

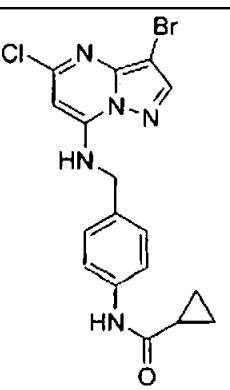
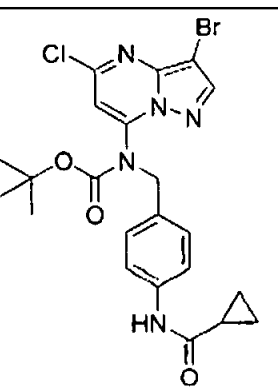
TABLA 501

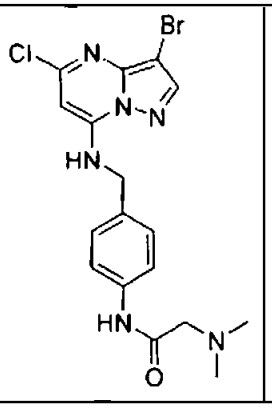
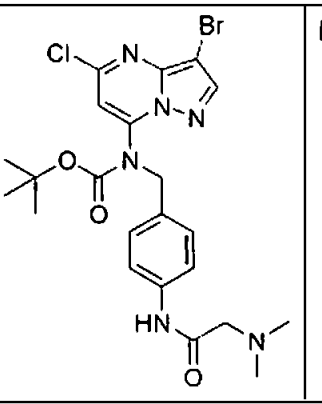
Ej. Prep.	Columna 2	Columna 3	COMP.
518			M+H= 422.1
519			

EJEMPLOS PREPARATIVOS 520-521:

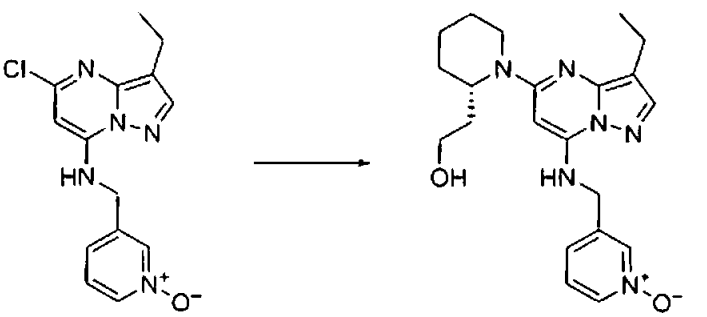
Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo Preparativo 192 sustituyendo únicamente los compuestos de la Columna 2 de la Tabla 502, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 502.

TABLA 502

Ej. Prep.	Columna 2	Columna 3	COMP.
520			M+H= 522,1

521			M+H= 539,1

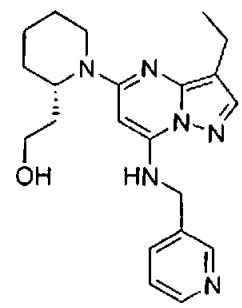
EJEMPLO 1000:



Una mezcla del compuesto preparado en el Ejemplo Preparativo 509 (1,50g, 4,94 mmoles) con el aminoalcohol del Ejemplo Preparativo 500 (1,91 g, 14,8 mmoles) en NMP seco (3 mL) se agitó bajo N_2 a 160°C durante 48 horas. El NMP se separó por destilación al vacío y el residuo se cromatografió primero con 5:1 EtOAc:MeOH, luego el producto crudo se recromatografió con 10:1 de CH_2Cl_2:MeOH. Se obtuvo un sólido blanco (460 mg, 24%). LCSM: MH^+ = 397; P.f. = 113-115°C.

EJEMPLO 1001:

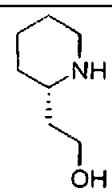
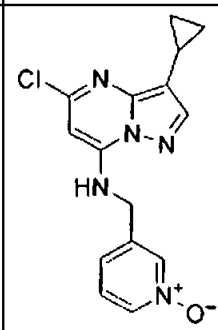
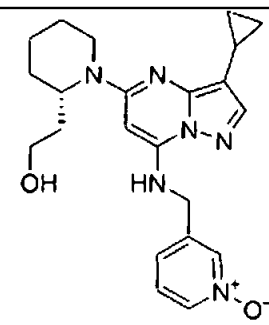
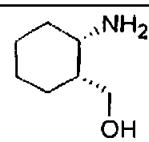
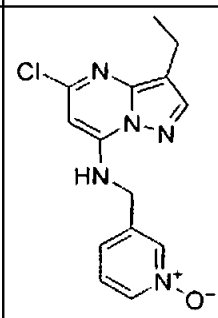
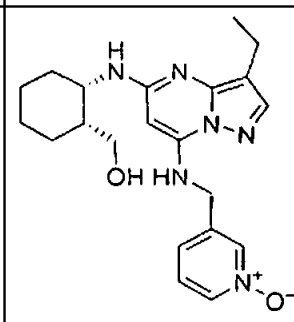
El producto secundario principal aislado (540 mg, 29%) fue un producto desoxigenado (LCMS: MH^+ = 381; P.f. = 49-52 °C.

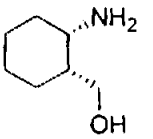
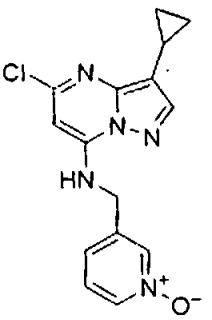
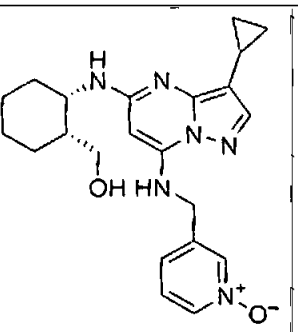
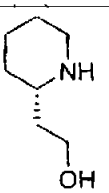
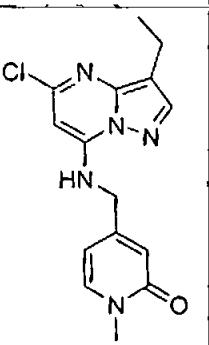
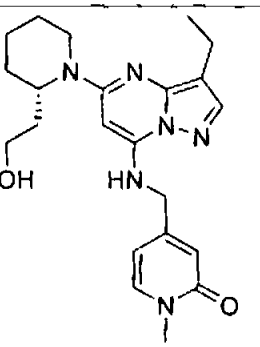
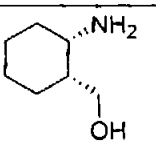
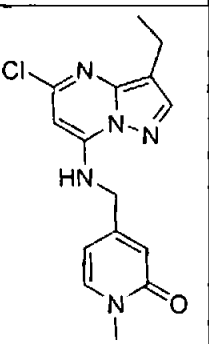
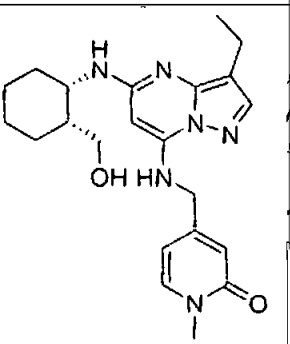
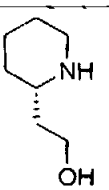
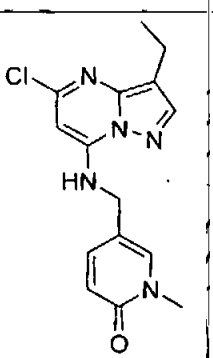
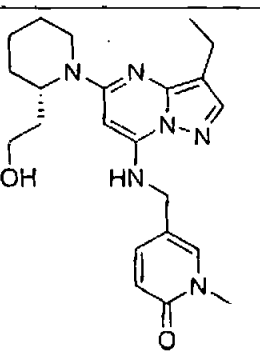


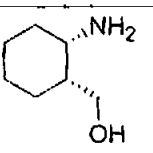
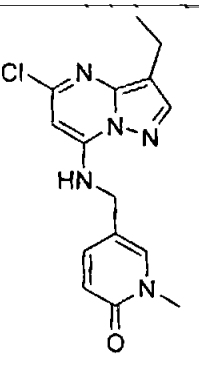
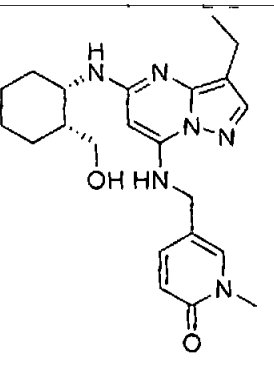
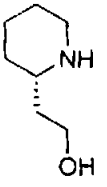
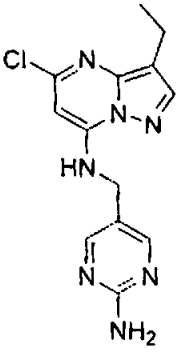
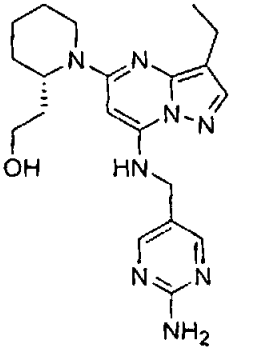
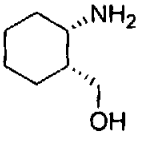
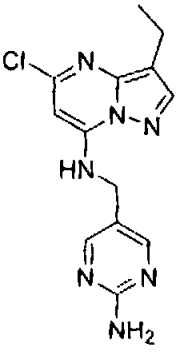
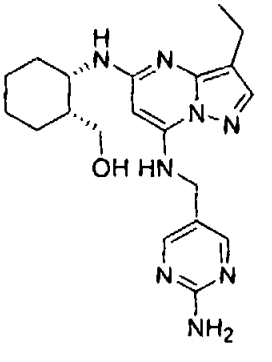
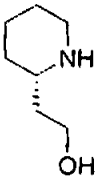
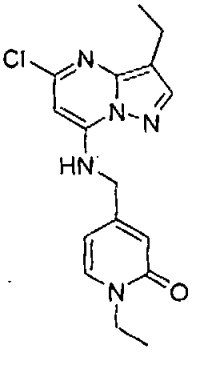
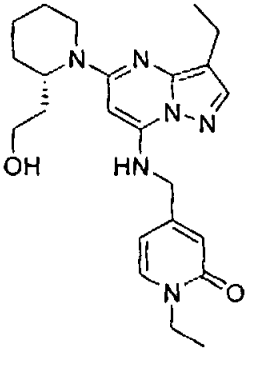
EJEMPLOS 1002 – 1014:

Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo 1000 sustituyendo únicamente las aminas de la Columna 2 de la Tabla 1000 y los cloruros en la Columna 3 de la Tabla 1000, se prepararon los compuestos de la Columna 4 de la Tabla 1000.

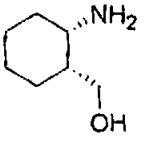
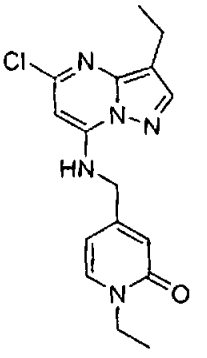
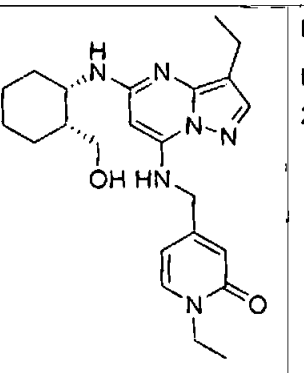
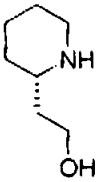
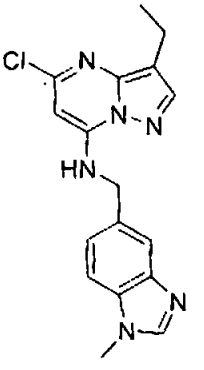
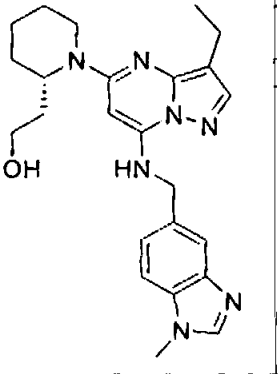
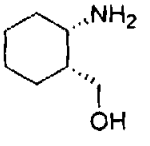
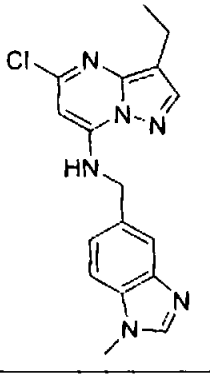
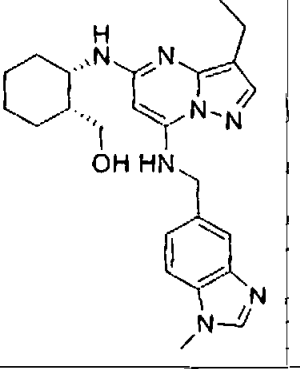
TABLA 1000

Ej.	Columna 2	Columna 3	Columna 4	COMP.
1002				MH^+ = 409; p.f. = 165-171°C
1003				MH^+ = 397; p.f. = 219-221°C

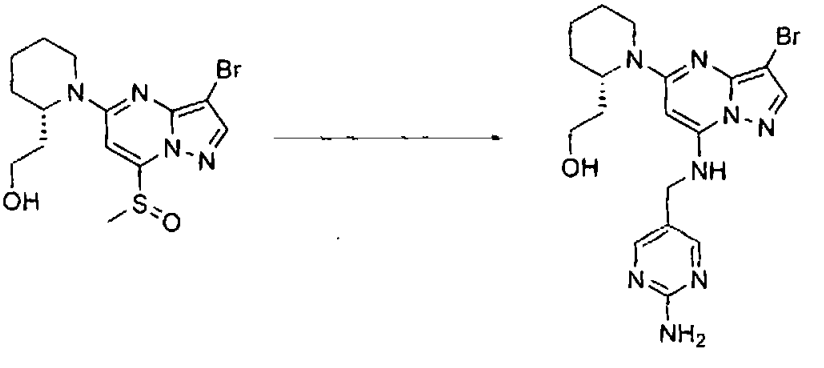
1004				MH^+ = 409; p.f. = 138-142°C
1005				MH^+ = 411; p.f. = 194-196°C
1006				MH^+ = 411; p.f. = 118-120°C
1007				MH^+ = 411; p.f. = 85-87°C

1008				MH^+ = 411; p.f. = 105-108°C
1009				MH^+ = 397; p.f. = 173-177°C
1010				MH^+ = 397; p.f. = 169-173°C
1011				MH^+ = 425

151

1012				MH^+ = 425; p.f. = 232-234°C
1013				
1014				

EJEMPLO 1015:



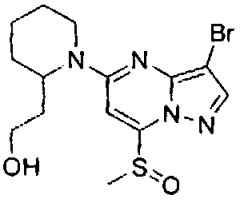
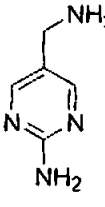
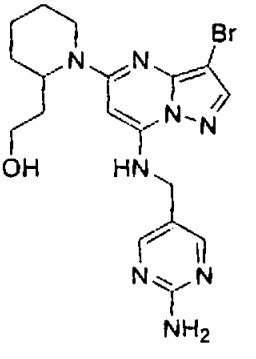
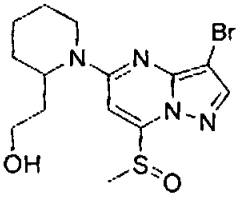
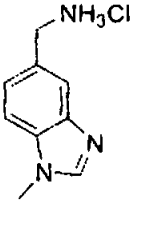
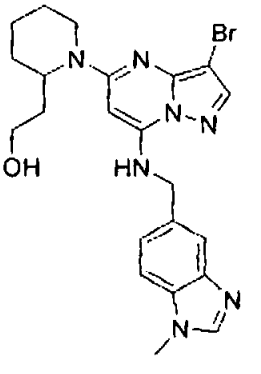
1052

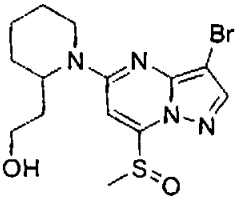
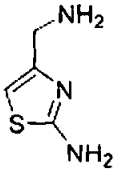
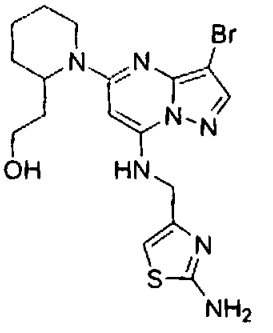
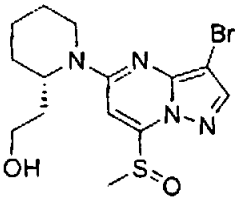
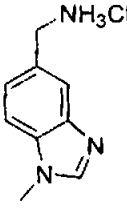
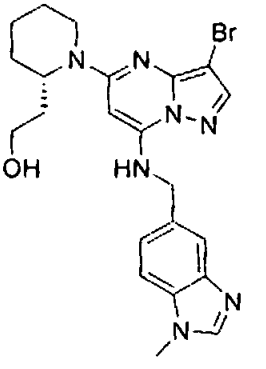
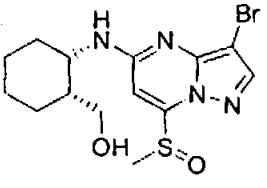
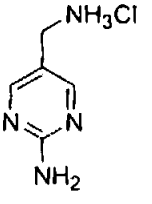
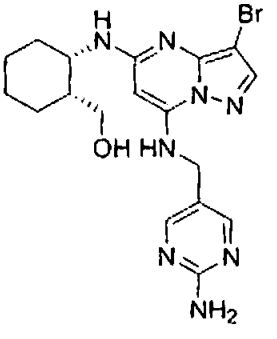
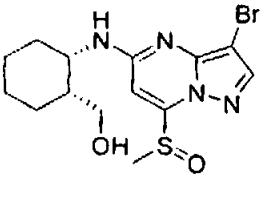
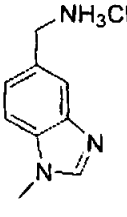
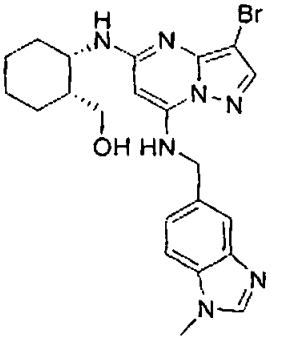
A una solución del sulfóxido del Ejemplo Preparativo 505 (0,10 g, 0,28 mmoles) en *n*-BuOH en un tubo sellado se agregó Et_3N (0,13 mL, 1,0 mmoles) seguido del diclorhidrato de amina (0,13 g, 0,65 mmoles) del Ejemplo Preparativo 216. El tubo se selló y luego se calentó a 100°C, se enfrió a temperatura ambiente, y se concentró bajo presión reducida. El residuo crudo se purificó por TLC preparativa (6 x 1000 μM) se eluyó con CH_2Cl_2/MeOH (20:1) para proporcionar 50 mg (40 %) de un sólido de color blanco pálido. P.f. 182-185 °C; M+H = 446.

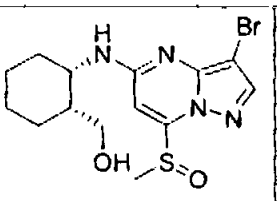
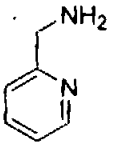
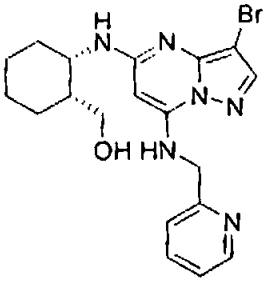
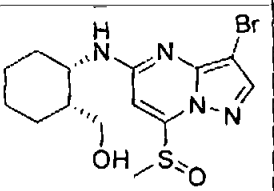
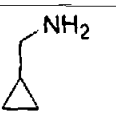
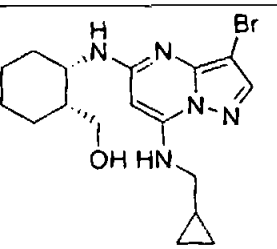
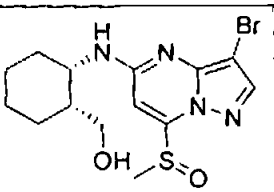
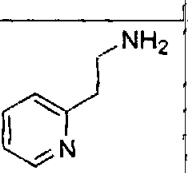
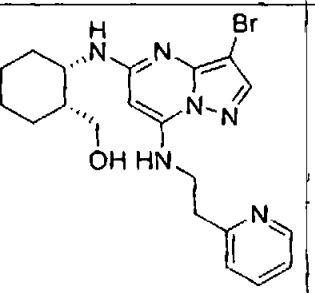
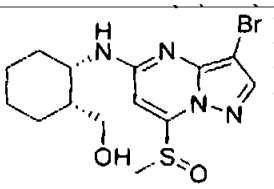
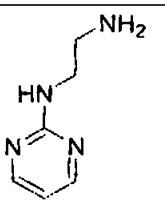
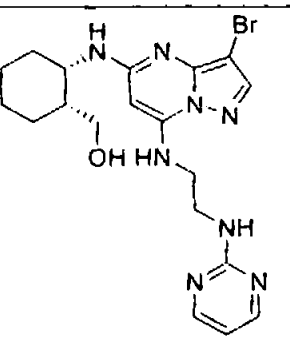
EJEMPLOS 1016-1026:

Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo 1015 sustituyendo únicamente el sulfóxido que se mostró en la Columna 2 de la Tabla 1001 y la amina en la Columna 3 de la Tabla 1001, se prepararon los compuestos que se muestran en la Columna 4 de la Tabla 1001.

TABLA 1001

Ej.	Columna 2	Columna 3	Columna 4	COMP.
1016				p.f. = 182-185 °C; M+H = 448
1017				p.f. = 187-189 °C; M+H = 445

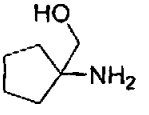
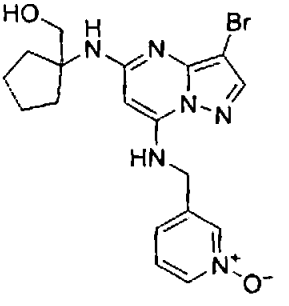
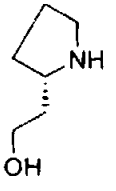
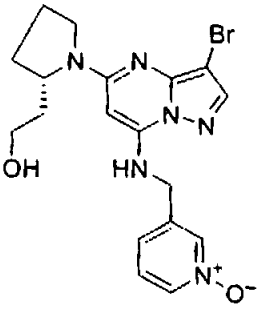
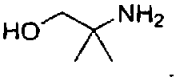
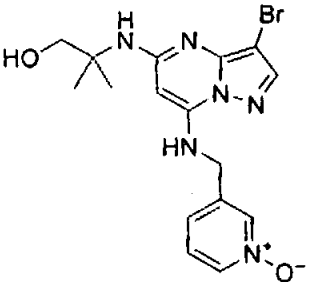
1018				p.f. = 139-143 °C; M+H = 453
1020				p.f. = 186-189 °C; M+H = 485
1021				p.f. = 154-157 °C; M+H = 448
1022				p.f. = 103-105 °C; M+H = 485

1023	 (±)		 (±)	p.f. = 203-205 °C; M+H = 432
1024	 (±)		 (±)	p.f. = 210-212 °C; M+H = 395
1025	 (±)		 (±)	p.f. = 82-84 °C; M+H = 446
1026	 (±)		 (±)	p.f. = 86-90 °C; M+H = 462

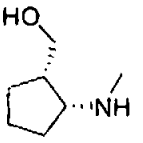
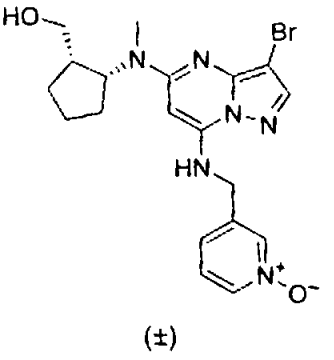
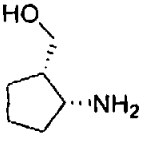
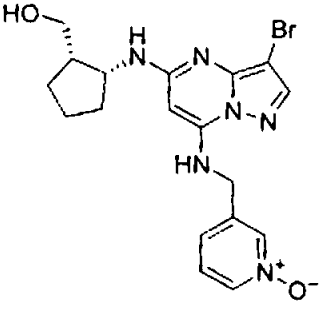
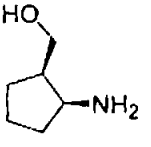
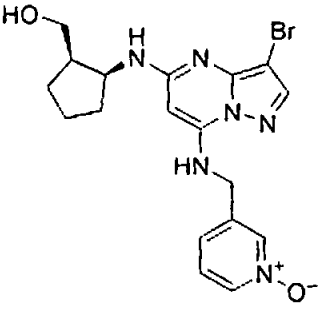
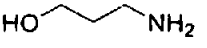
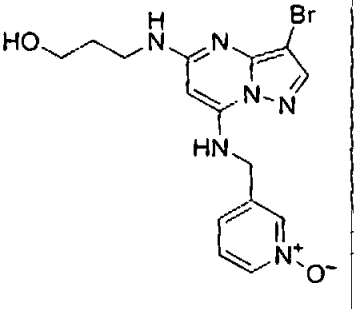
EJEMPLOS 1027-1038:

Siguiendo esencialmente las mismas condiciones que se indican en el Ejemplo 341, Etapas A y B sustituyendo únicamente las aminas en la Columna 2 de la Tabla 1002 y el compuesto preparado en el Ejemplo Preparativo 193.10, se prepararon los compuestos de la Columna 4 de la Tabla 1002.

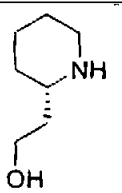
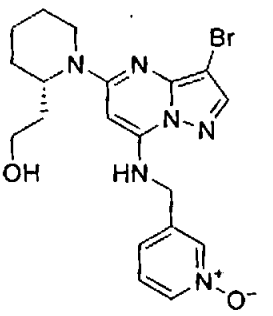
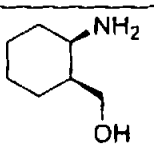
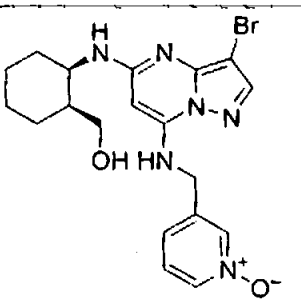
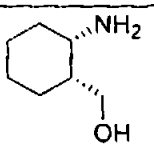
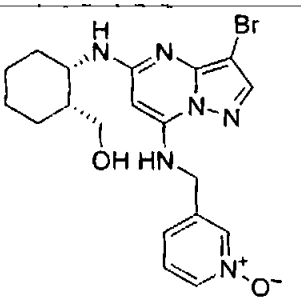
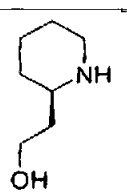
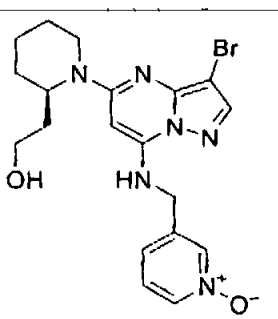
TABLA 1002

Ej.	Columna 2	Columna 4	COMP.
1027			p.f. = 160-163 °C; M+H = 434
1028			p.f. = 122-124 °C; M+H = 434
1029			p.f. = 153-156 °C; M+H = 408

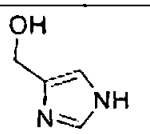
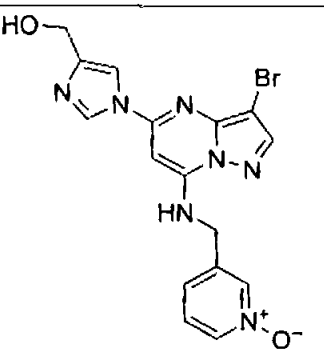
2686

1030	 (±)	 (±)	p.f. = 170-174 °C; M+H = 448
1031			p.f. = 166-169 °C; M+H = 434
1032			p.f. = 167-168 °C; M+H = 434
1033			MH^+ = 393

1691

1034			p.f. = 157-160 °C; M+H = 447
1035			p.f. = 164-168 °C; M+H = 448
1036			p.f. = 165-168 °C; M+H = 448
1037			p.f. = 131-135 °C; M+H = 447

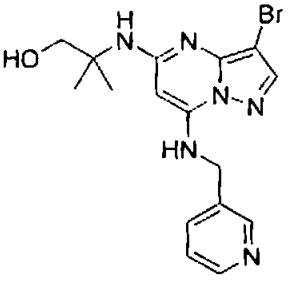
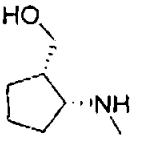
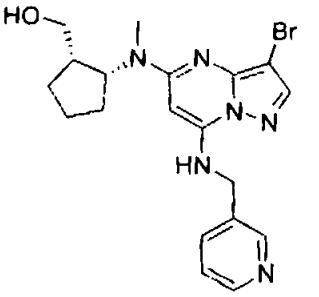
1058

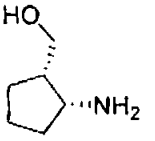
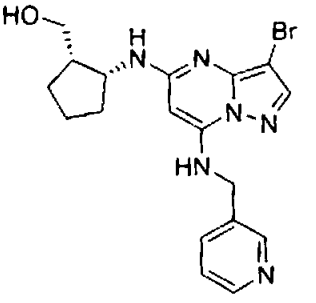
1038			

EJEMPLOS 1039-1041:

Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo 340 sustituyendo únicamente las aminas de la Columna 2 de la Tabla 1003, se prepararon los compuestos que se muestran en la Columna 4 de la Tabla 1003.

TABLA 1003

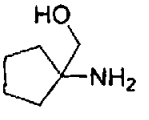
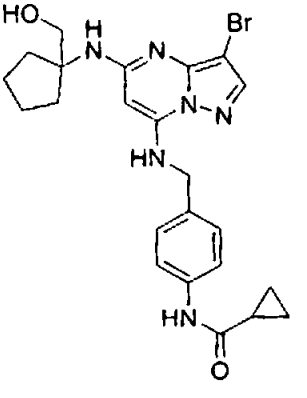
Ej.	Columna 2	Columna 4	COMP.
1039			p.f. = 210-212°C; M+H = 392
1040	 (±)	 (±)	p.f. = 128-130°C; M+H = 432

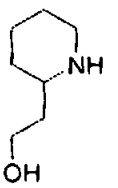
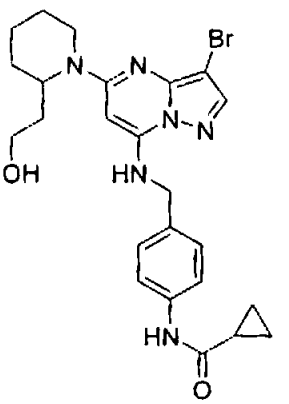
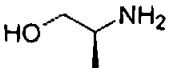
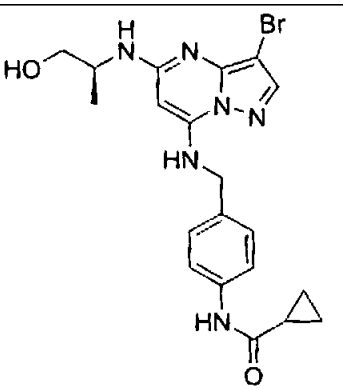
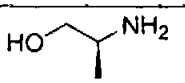
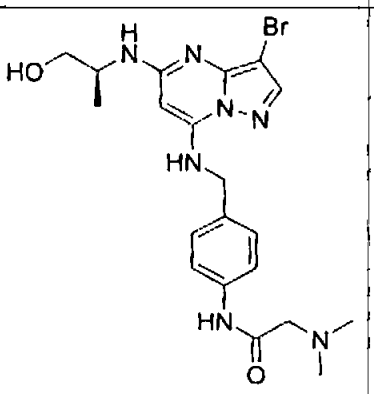
1041			p.f. = 148-151°C; M+H = 18

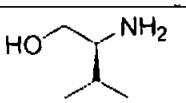
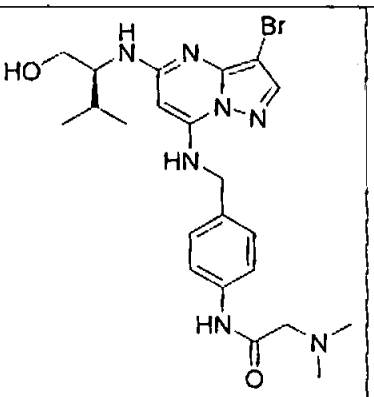
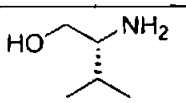
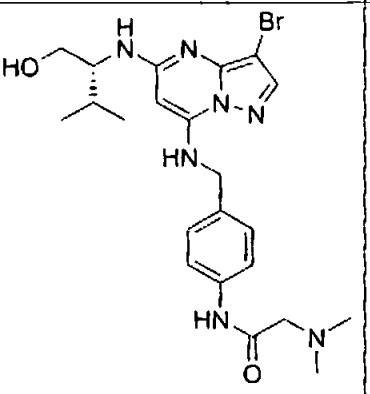
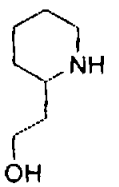
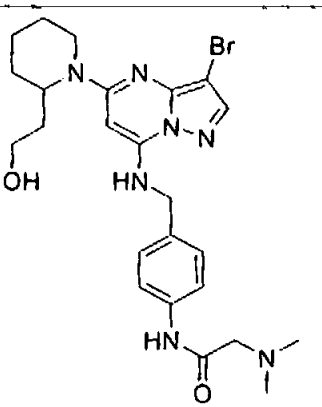
EJEMPLOS 1042-1057:

Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo 340 usando únicamente el derivado 5-cloro apropiado y sustituyendo las aminas en la Columna 2 de la Tabla 1004, se prepararon los compuestos que se muestran en la Columna 4 de la Tabla 1004.

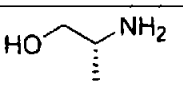
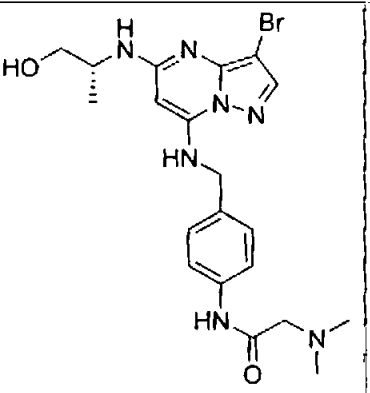
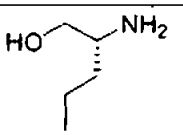
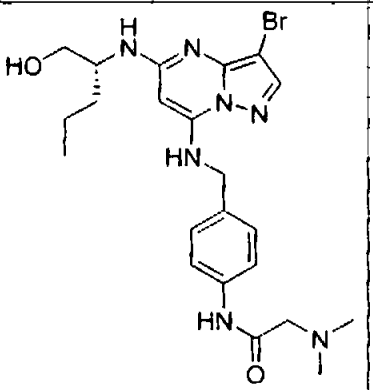
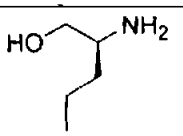
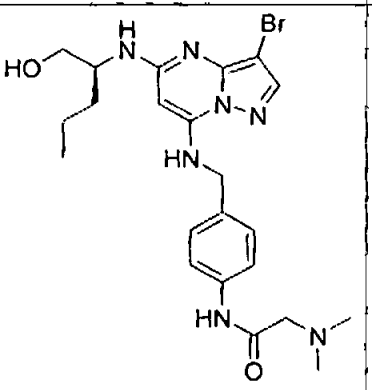
TABLA 1004

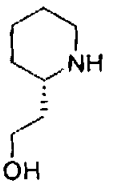
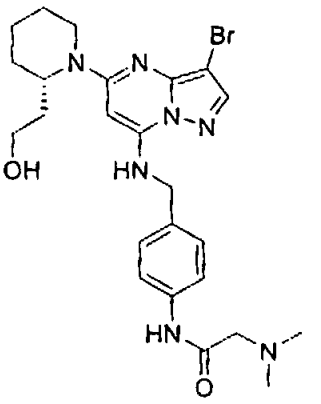
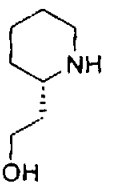
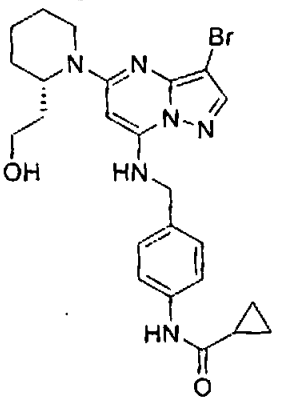
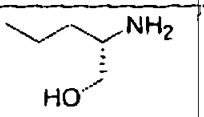
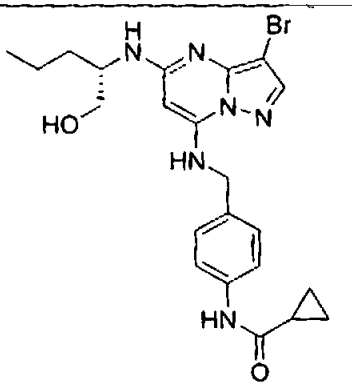
Ej.	Columna 2	Columna 4	COMP.
1042			M+H= 500.3

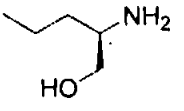
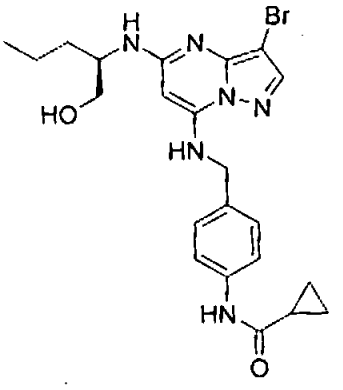
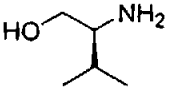
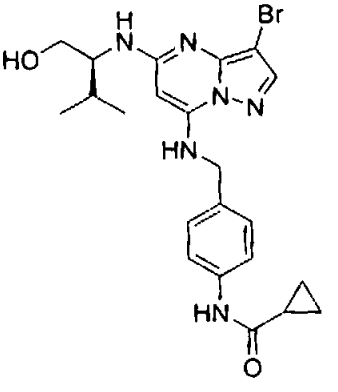
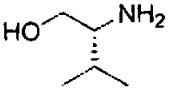
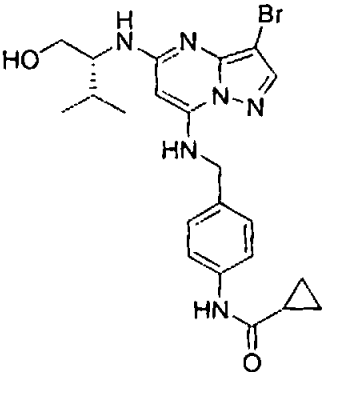
1043			M+H= 514,1
1044			M+H= 460,3
1045			M+H= 477,1

1046			M+H= 505,1
1047			M+H= 505,1
1048			M+H=531,1

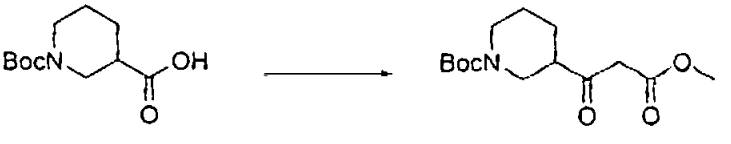
2201

1049			M+H= 477,1
1050			M+H= 505,1
1051			M+H= 505,1

1052			M+H= 531,1
1053			M+H= 514,1
1054			M+H= 488,3

1055			M+H= 488,3
1056			M+H= 488,1
1057			M+H= 488,1

EJEMPLO PREPARATIVO 10-K:



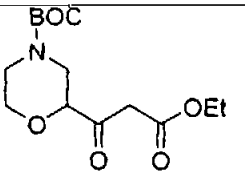
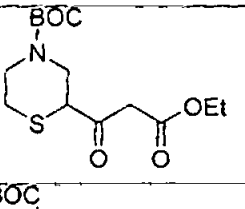
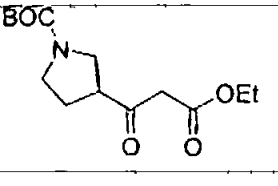
Se agregó $SOCl_2$ (18,5 mL) lentamente bajo N_2 a una mezcla agitada del ácido (50,0 g, 218 mmoles) y piridina (44,0 mL) en CH_2Cl_2 anhidro (60 mL). La

mezcla se agitó a 25°C durante 20 minutos, y luego se agregaron ácido de Meldrum's (35,0 g, 243 mmoles) y DMAP (66,6 g, 546 mmoles) y la mezcla se agitó bajo N_2 durante 1 hora. Luego se agregó Et_2O (2 L), la mezcla se lavó con HCl 1M (3x500 mL), salmuera (500 mL), y la capa orgánica se secó sobre Na_2SO_4, se filtró, y el solvente se evaporó. El residuo se disolvió en MeOH (580 mL), y la mezcla se reflujó durante 4 horas. El solvente se evaporó y el residuo se purificó por cromatografía en columna sobre gel de sílice con 10:1 de CH_2Cl_2/EtOAc como eluyente. Se obtuvo un aceite de color amarillo pálido (26,5 g, 43 %).

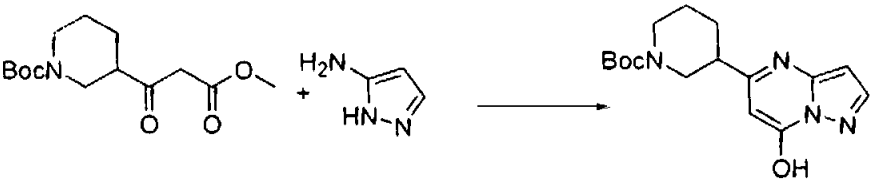
EJEMPLOS PREPARATIVOS 10-K-40-K:

Siguiendo esencialmente el mismo procedimiento del Ejemplo Preparativo 10-K, se prepararon los compuestos que se dan en la Columna 2 de la Tabla 10-K.

TABLA 10-K

Ej. Prep.	Columna 2
20-K	
30-K	
40-K	

EJEMPLO PREPARATIVO 100-K:

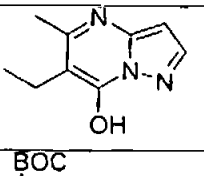
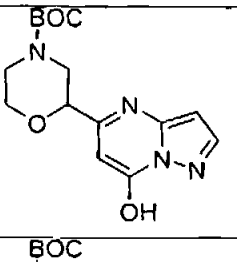
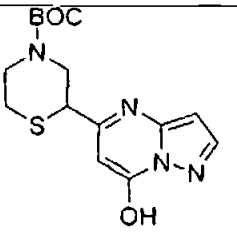


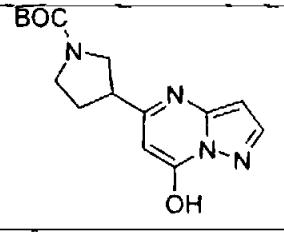
Una mezcla del b-cetoéster del Ejemplo Preparativo 10-K (20,0 g, 70,1 mmoles) y 3-aminopirazol (5,40 g, 65,0 mmoles) en tolueno anhidro (60 mL) se agitaron y reflujaron bajo N_2 durante 24 horas. El solvente se evaporó y el residuo se purificó por cromatografía en columna sobre gel de sílice con 20:1 de CH_2Cl_2/MeOH como eluyente. Se obtuvo un sólido blanco (15,0 g, 73 %). LC-EM: 319 [M+H].

EJEMPLO PREPARATIVO 101-K – 104-K:

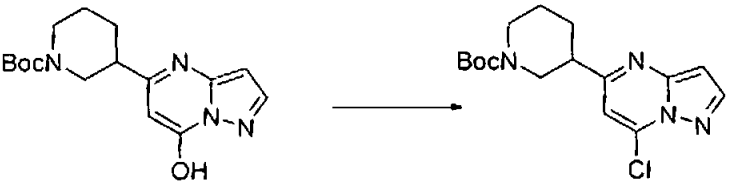
Siguiendo esencialmente el mismo procedimiento del Ejemplo Preparativo 100-K, combinando 3-aminopirazol con los β-cetoésteres correspondientes, se prepararon los compuestos que se dan en la Columna 2 de la Tabla 100-K.

TABLA 100-K

Ej. Prep.	Columna 2
101-K	
102-K	
103-K	

104-K	

EJEMPLO PREPARATIVO 200-K:

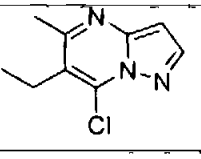


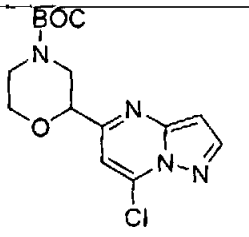
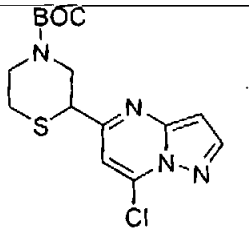
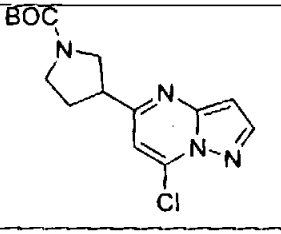
Una mezcla del producto del Ejemplo Preparativo 100-K (12,50 g, 39,3 mmoles), N,N-dimetilanilina (15,5 mL), y $POCl_3$ (125 mL) se agitó a 25°C durante 4 días. El exceso de $POCl_3$ se evaporó y el residuo se vertió en $NaHCO_3$ acuoso saturado (600 mL). La mezcla se extrajo con CH_2Cl_2 (3x200 mL), los extractos combinados se secaron sobre Na_2SO_4, se filtraron, y el solvente se evaporó. El residuo se purificó por cromatografía en columna sobre gel de sílice con 8:1 de CH_2Cl_2/EtOAc como eluyente. Se obtuvo una cera de color amarillo pálido (9,41 g, 71 %). LC-EM: 337 [M+].

EJEMPLO PREPARATIVO 201-K – 204-K:

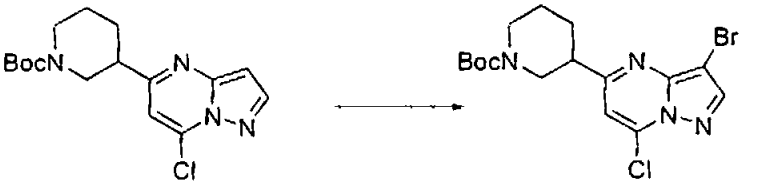
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo Preparativo 200-K, se prepararon los compuestos que se dan en la Columna 2 de la Tabla 200-K.

TABLA 200-K

Ej. Prep.	Columna 2
201-K	

202-K	
203-K	
204-K	

EJEMPLO PREPARATIVO 300-K:

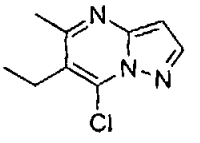
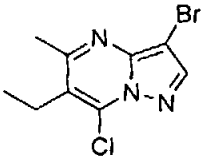
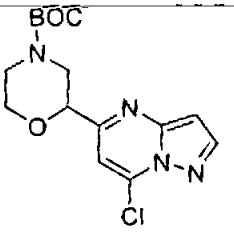
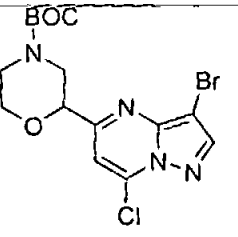
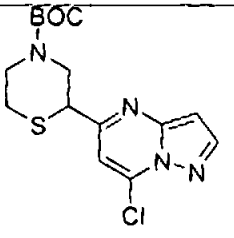
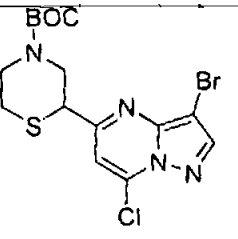
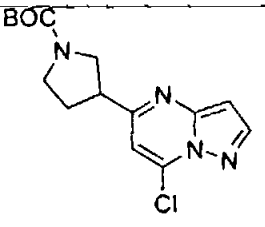
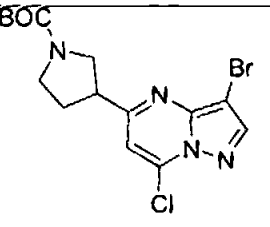


Una solución de NBS (4,03 g, 22,7 mmoles) en CH_3CN anhidro (40 mL) se agregó bajo N_2 a una solución agitada del producto del Ejemplo Preparativo 200-K (7,63 g, 22,7 mmoles) en CH_3CN anhidro (60 mL) y CH_2Cl_2 (20 mL). La mezcla se agitó durante 2 horas, los solventes se evaporaron, y el residuo se purificó por cromatografía en columna sobre gel de sílice con 20:1 de CH_2Cl_2/EtOAc como eluyente. Se obtuvo un sólido de color amarillo pálido (9,20 g, 97%). LC-EM: 417 [M+H].

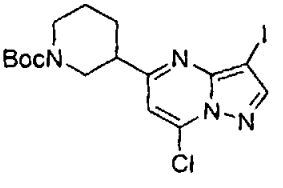
EJEMPLO PREPARATIVO 301-K – 304-K:

Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo Preparativo 300-K sustituyendo únicamente los compuestos que se muestran en la Columna 2 de la Tabla 300-K, se prepararon los compuestos que se dan en la Columna 3 de la Tabla 300-K.

TABLA 300-K

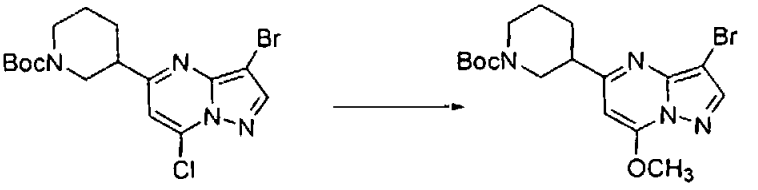
Ej. Prep.	Columna 2	Columna 3
301-K		
302-K		
303-K		
304-K		

EJEMPLO PREPARATIVO 303-K:



Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo Preparativo 300-K sustituyendo únicamente N-iodosuccinimida se preparó el compuesto anterior.

EJEMPLO PREPARATIVO 400-K:

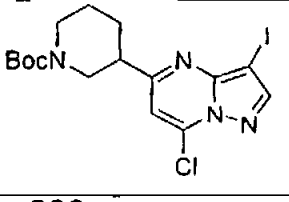
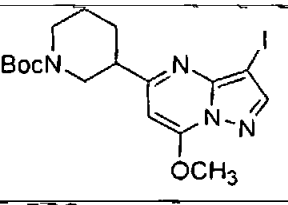
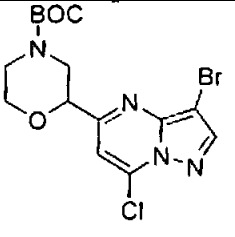
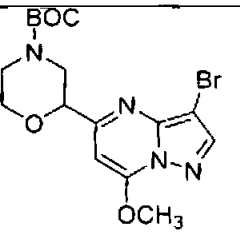


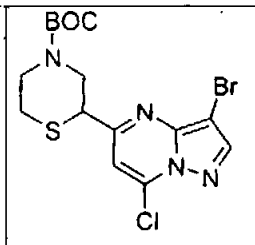
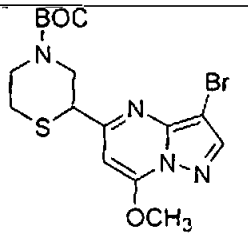
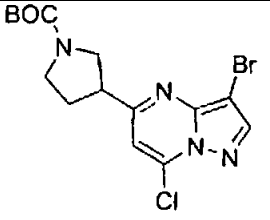
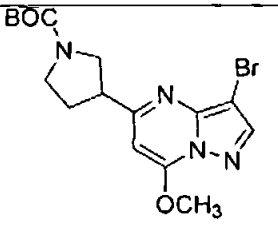
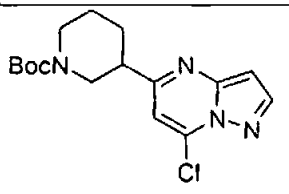
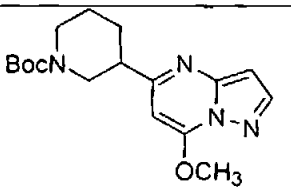
Una mezcla del producto del Ejemplo Preparativo 300-K (8,00 g, 19,3 mmoles) y MeONa (2,16 g, 40,0 mmoles) en MeOH anhidro (100mL) se agitó durante 20 horas. Se agregó CH_2Cl_2 (200mL), la mezcla se filtró a través de Celite, el solvente se evaporó, y el residuo se purificó por cromatografía en columna sobre gel de sílice con 2:1 de CH_2Cl_2/EtOAc como eluyente. Se obtuvo un sólido blanco (7,75 g, 98%).

EJEMPLO PREPARATIVOS 401-K – 405-K:

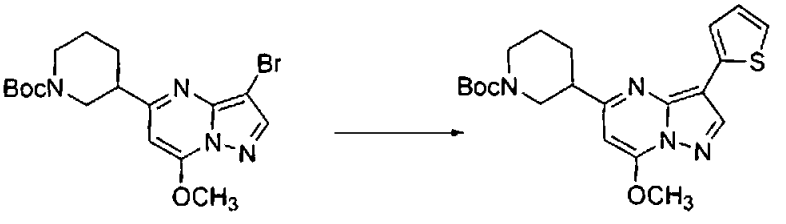
Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo Preparativo 400-K, sustituyendo únicamente el compuesto que se muestra en la Columna 2 de la Tabla 400-K, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 400-K.

TABLA 400-K

Ej. Prep.	Columna 2	Columna 3
401-K		
402-K		

403-K		
404-K		
405-K		

EJEMPLO PREPARATIVO 500-K:

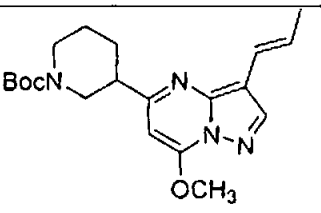
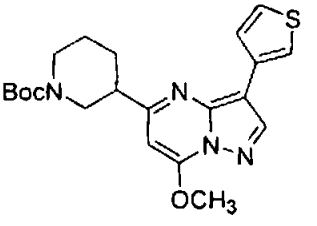
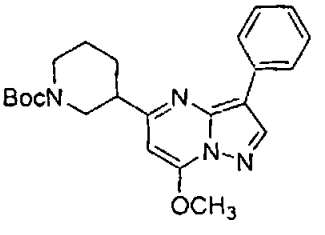
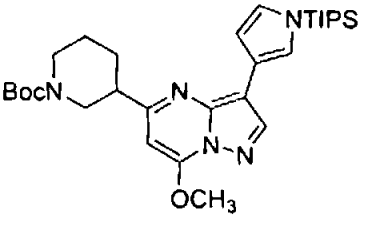
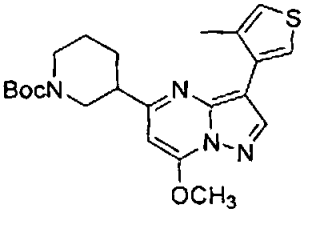
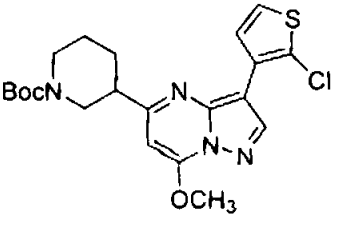


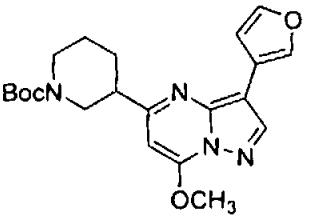
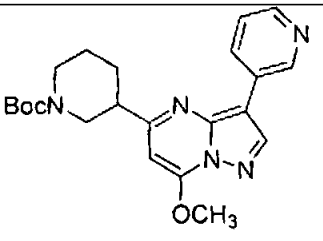
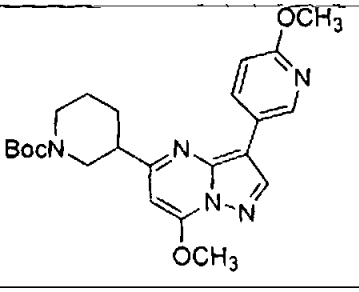
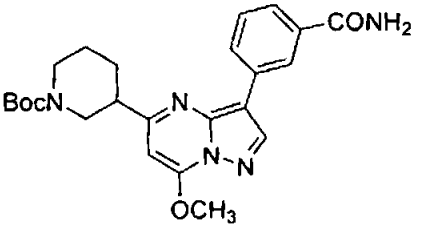
Una mezcla del producto del Ejemplo Preparativo 400-K (600 mg, 1,46 mmoles), ácido 2-tienilborónico (230 mg, 1,80 mmoles), $Pd[PPh_3]_4$ (160 mg, 0,14 mmoles), y Na_2CO_3 (466 mg, 4,40 mmoles) en 1,2-dimetoxietano (20 mL) y H_2O (4 mL) se agitó y reflujó bajo N_2 durante 20 horas. Los solventes se evaporaron y el residuo se purificó por cromatografía en columna sobre gel de sílice con 2:1 de CH_2Cl_2/EtOAc como eluyente. Se obtuvo un sólido de color amarillo pálido (355 mg, 59 %). LC-EM: 415 [M+].

EJEMPLOS PREPARATIVOS 501-511-K:

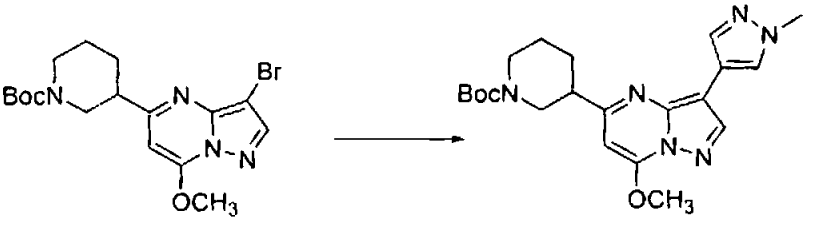
Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo Preparativo 500-K sustituyendo únicamente el ácido borónico apropiado se prepararon los compuestos que se dan en la Columna 2 de la Tabla 500-K.

TABLA 500-K

Ej. Prep.	Columna 2	Datos
501-K		LCMS: MH^+=373
502-K		LCMS: MH^+=415
503-K		LCMS: MH^+=409
504-K		LCMS: MH^+=555
505-K		LCMS: MH^+=429
506-K		

507-K		LCMS: MH^+=399
508-K		LCMS: MH^+=410
510-K		LCMS: MH^+=425
511-K		LCMS: MH^+=452

EJEMPLO PREPARATIVO 520-K:



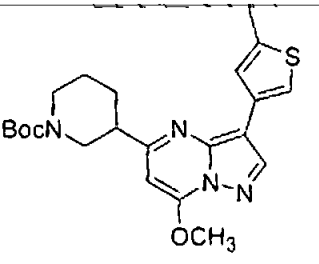
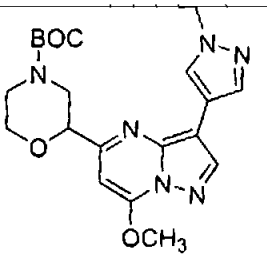
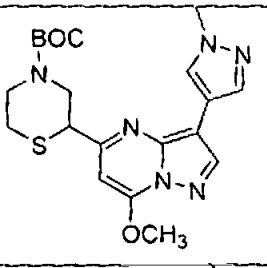
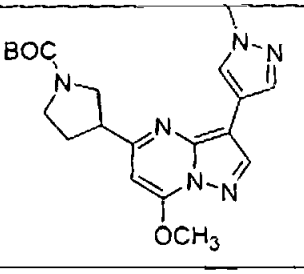
Una mezcla del producto del Ejemplo Preparativo 400-K (1,23 g, 3,00 mmoles), 1-metil-4-(4,4,5,5-tetrametil-1,3,2-dioxaborolan-2il)1-H-pirazol (850 mg, 4,00 mmoles), $Pd[PPh_3]_4$ (348 mg, 0,30 mmoles), y Na_2CO_3 (1,27 g, 12,0 mmoles) en 1,2-dimetoxietano (36 mL) y H_2O (7,5 mL) se agitó y reflujó bajo N_2 durante 20 horas. Los solventes se evaporaron y el residuo se purificó por cromatografía en columna sobre gel de sílice con 20:1 de EtOAc/MeOH como

eluyente. Se obtuvo un sólido de color naranja pálido (740 mg, 60 %). LC-EM: 413 [M+H].

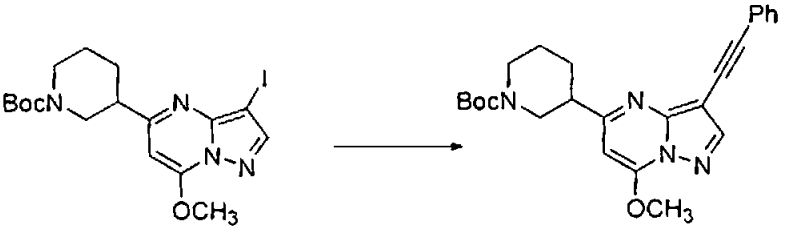
EJEMPLO PREPARATIVO 530-K – 533-K:

Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo Preparativo 520-K, se prepararon los compuestos que se muestran en la Columna 2 de la Tabla 530-K.

TABLA 530-K

Ej. Prep.	Columna 2	Datos
530-K		LC-EM: 429 [M+H].
531-K		
532-K		
533-K		

EJEMPLO PREPARATIVO 550-K:

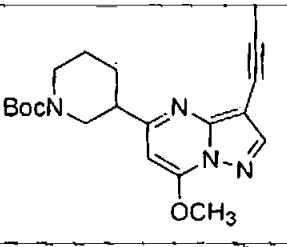
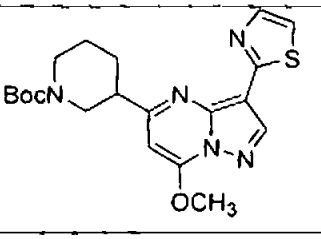


Una mezcla del compuesto del Ejemplo Preparativo 512-K (230 mg, 0,50 mmoles), tributilfenil estaño (235 mg, 0,60 mmoles), y Pd[PPh3]4 (58 mg, 0,05 mmoles) en dioxano anhidro (5 mL) se agitó bajo N_2 a 90°C durante 3 horas. El solvente se evaporó y el residuo se purificó por cromatografía en columna sobre gel de sílice con 20:1 de CH_2Cl_2/EtOAc como eluyente. Se obtuvo una cera de color amarillo pálido (46 mg, 21 %). LC-EM: 433 [M+].

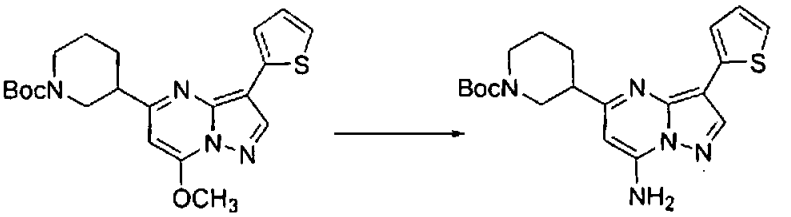
EJEMPLOS PREPARATIVOS 551-K -552-K:

Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo Preparativo 550-K, sustituyendo únicamente el reactivo de tributil estaño, se prepararon los compuestos que se dan en la Columna 2 de la Tabla 550-K.

TABLA 550-K

Ej. Prep.	Columna 2	Datos
551-K		LCMS: MH^+=371
552-K		LCMS: MH^+=416

EJEMPLO PREPARATIVO 600-K:

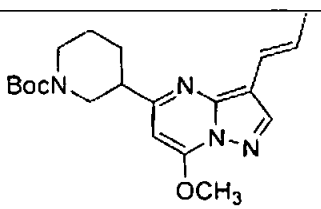
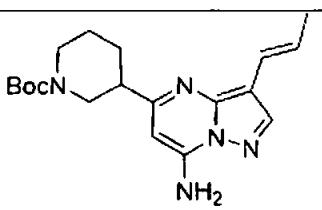
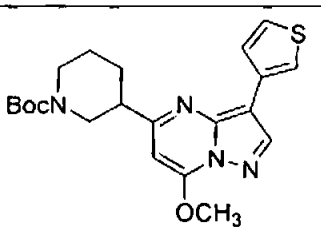
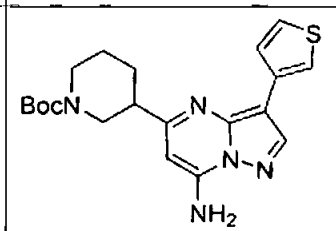


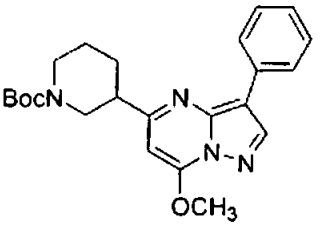
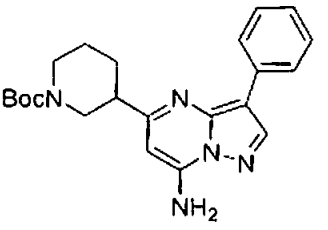
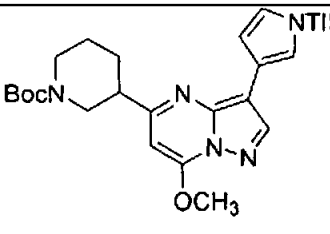
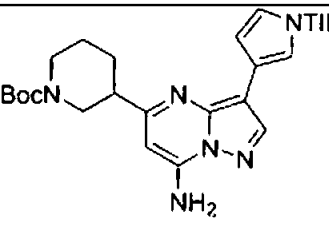
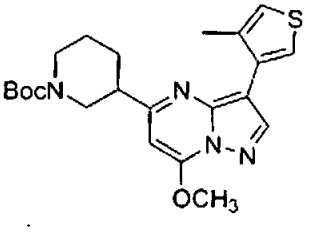
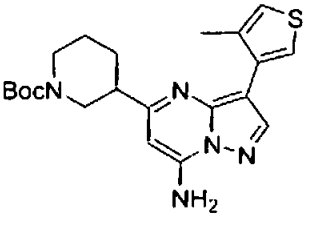
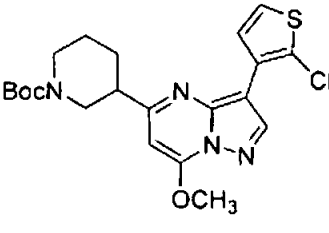
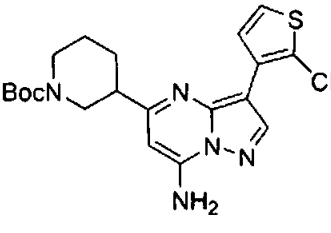
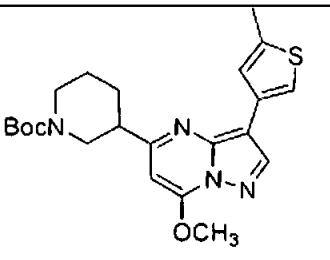
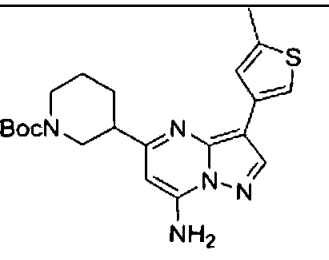
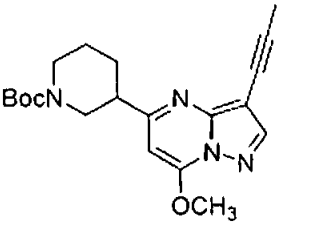
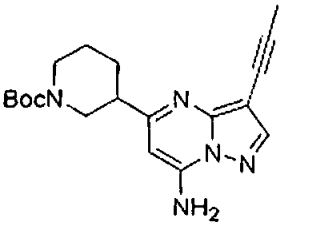
Una mezcla del producto del Ejemplo Preparativo 500-K (350 mg, 0,85 mmoles), 2,0 M NH_3 en 2-propanol (7,5 mL), y NH_4OH (0,75 mL) acuoso concentrado se agitó en un recipiente de presión cerrado a 75°C durante 3 días. Los solventes se evaporaron y el residuo se purificó por cromatografía en columna sobre gel de sílice con 50:1 de CH_2Cl_2/MeOH como eluyente. Se obtuvo un sólido de color amarillo pálido (143 mg, 42 %). LC-EM: 400 [M+].

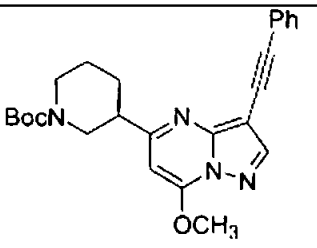
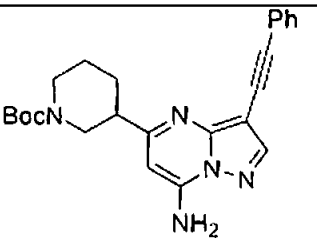
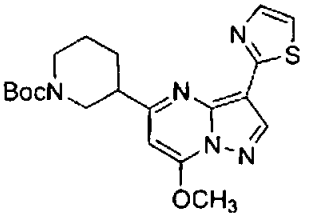
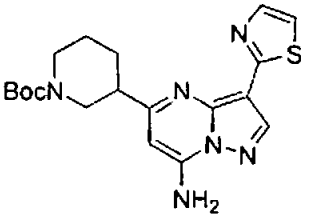
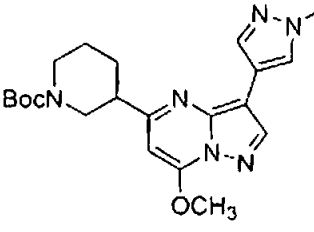
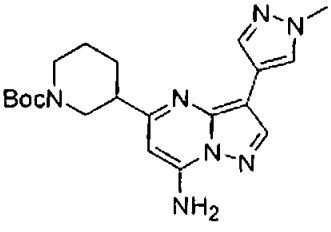
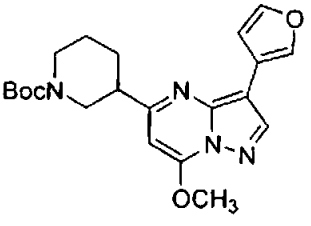
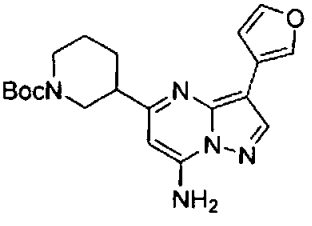
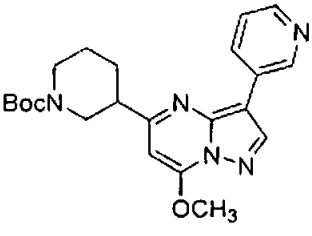
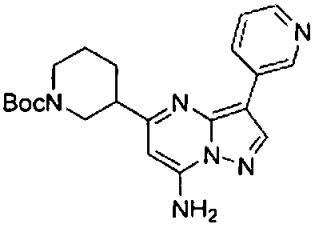
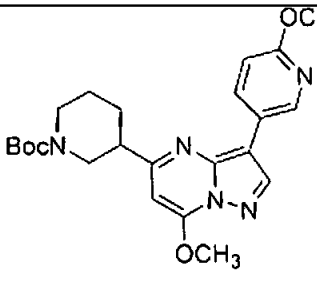
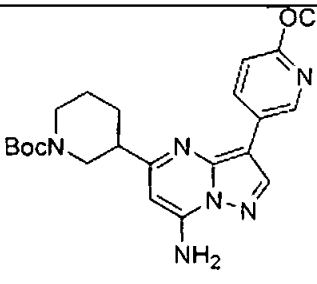
EJEMPLO PREPARATIVO 601-K -615-K:

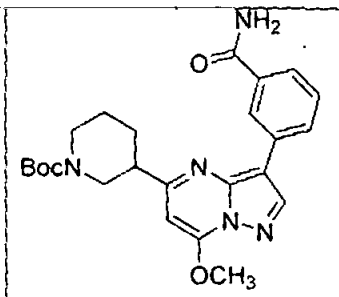
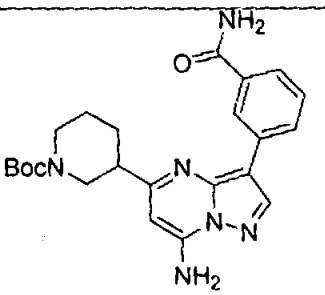
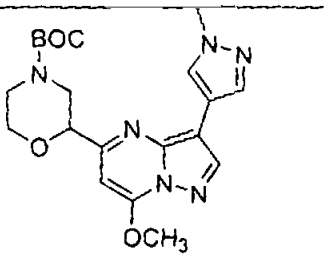
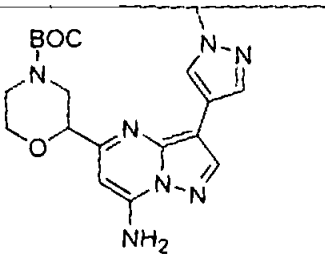
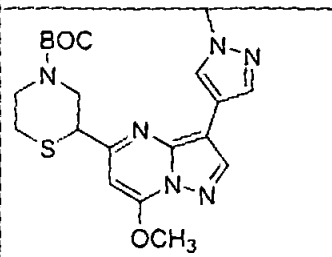
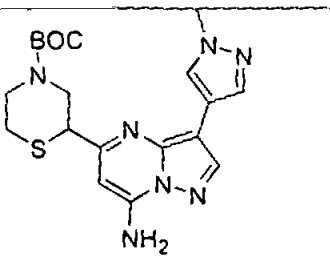
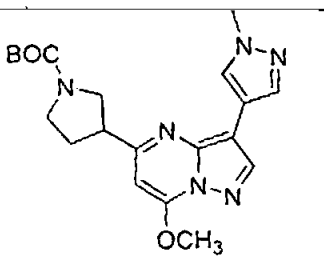
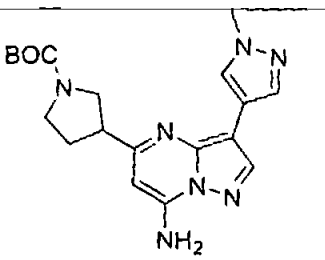
Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo Preparativo 600-K sustituyendo únicamente los compuestos de la Columna 2 de la Tabla 600-K, se prepararon los compuestos que se dan en la Columna 3 de la Tabla 600-K.

TABLA 600-K

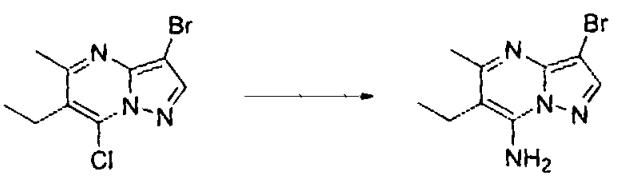
Ej. Prep.	Columna 2	Columna 3	Datos
601-K			LCMS: MH^+=359
602-K			LCMS: MH^+=400

603-K			
604-K			LCMS: MH^+=540
605-K			LCMS: MH^+=414
606-K			LCMS: M^+=434
607-K			LCMS: MH^+=414
608-K			LCMS: MH^+=356

609-K			LCMS: MH^+=418
610-K			LCMS: MH^+=401
611-K			LCMS: MH^+=398
612-K			LCMS: MH^+=384
613-K			LCMS: MH^+=395
614-K			LCMS: MH^+=425

615-K			LCMS: MH^+=437
616-K			
617-K			
618-K			

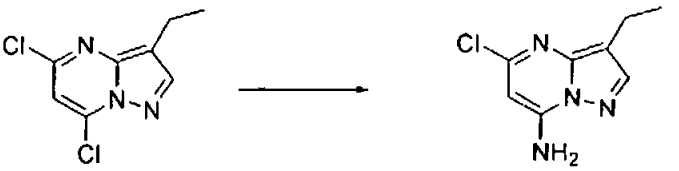
EJEMPLO PREPARATIVO 650-K:



Una mezcla del producto del Ejemplo Preparativo 201-K (100 mg, 0,37 mmoles), 2,0 M NH_3 en 2-propanol (2,0 mL), y NH_4OH (0,2 mL) acuoso concentrado se agitó en un recipiente cerrado bajo presión a 50°C durante 2 días. Los solventes se evaporaron y el residuo se purificó por cromatografía en columna sobre gel de sílice con 30:1 de CH_2Cl_2/MeOH como eluyente. Se obtuvo un sólido blanco (38 mg, 41 %). LC-EM: 257 [M+2H].

QSO)

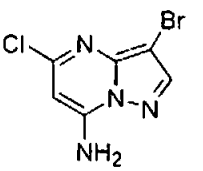
EJEMPLO PREPARATIVO 660-K:



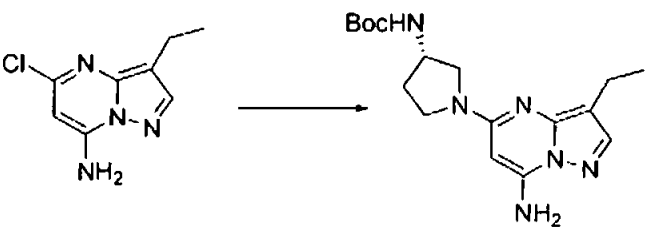
Una mezcla del material de partida (2,16 g, 10,0 mmoles), 2,0 M NH_3 en 2-propanol (50,0 mL), y NH_4OH (10,0 mL) acuoso concentrado se agitó en un recipiente cerrado bajo presión a 50°C durante 2 días. Los solventes se evaporaron, el sólido se suspendió en H_2O (100 mL), se filtró, se lavó en un filtro con H_2O (100 mL), y se secó al vacío a 100°C. Se obtuvo un sólido de color ligeramente beige (1,80 g, 91 %).

EJEMPLO PREPARATIVO 661-K:

Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo Preparativo 660-K, se preparó el compuesto que da a continuación.



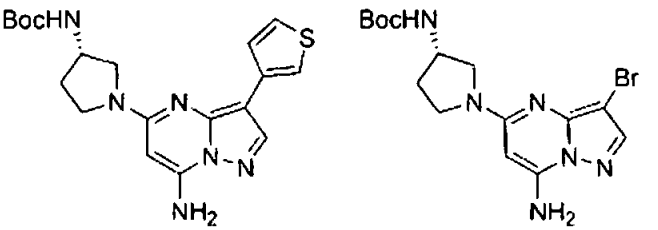
EJEMPLO PREPARATIVO 662-K:



Una mezcla del producto del Ejemplo Preparativo 660-K (600 mg, 3,05 mmoles), la amina (837 mg, 4,50 mmoles), y $NaHCO_3$ (756 mg, 9,00 mmoles) en N-metilpirrolidona anhidra (4 mL) se agitó bajo N_2 a 140°C durante 18 horas. La mezcla se enfrió a 25°C, se agregó CH_2Cl_2 (15 mL) y la mezcla se filtró. Los solventes del filtrado se separaron por destilación y el residuo se purificó por cromatografía en columna sobre gel de sílice con 2:1 CH_2Cl_2/EtOAc como eluyente. Se obtuvo un sólido blanco (1,01g, 95 %).

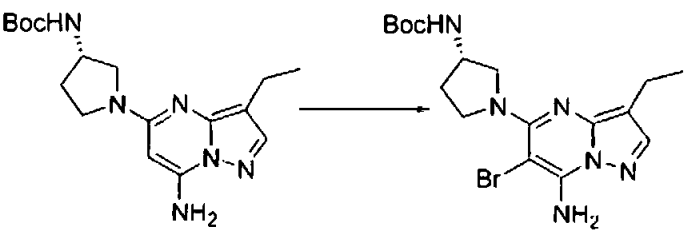
EJEMPLO PREPARATIVO 663-K:

Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo Preparativo 662-K, se prepararon los compuestos que se dan a continuación.



LC-EM: 401 [M+H].

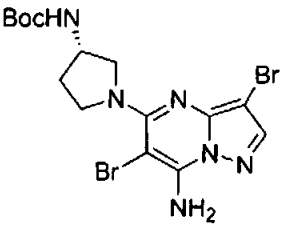
EJEMPLO PREPARATIVO 664-K:



Una solución de NBS (142 mg, 0,80 mmoles) en CH_3CN anhidro (5 mL) se agregó bajo N_2 a una solución agitada del producto del Ejemplo Preparativo 662-K (400 mg, 0,90 mmoles) en CH_3CN anhidro (5 mL) y CH_2Cl_2 (5 mL). La mezcla se agitó durante 18 horas, los solventes se evaporaron, y el residuo se purificó por cromatografía en columna sobre gel de sílice con 3:1 de CH_2Cl_2/EtOAc como eluyente. Se obtuvo un sólido blanco (330 mg, 67 %).

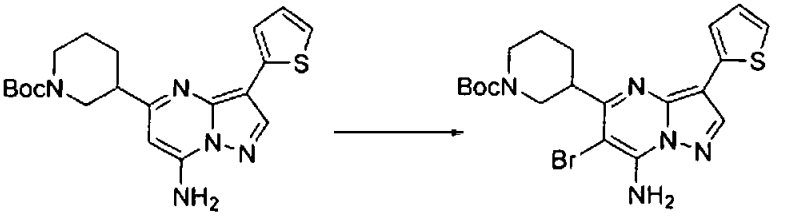
EJEMPLO PREPARATIVO 665-K:

Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo Preparativo 664-K, se preparó el compuesto que se da a continuación.



2801

EJEMPLO PREPARATIVO 700-K:

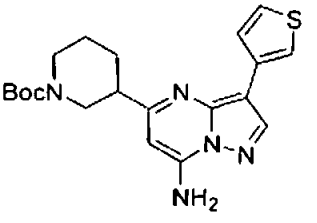
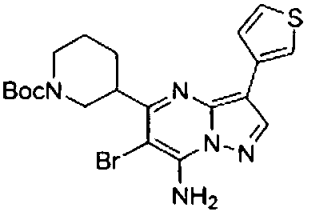
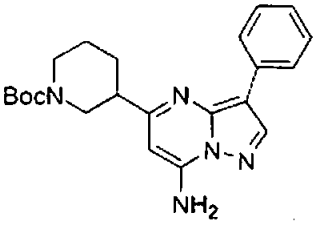
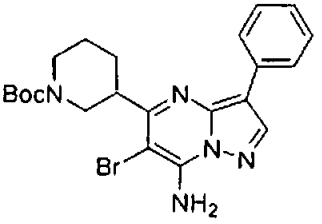


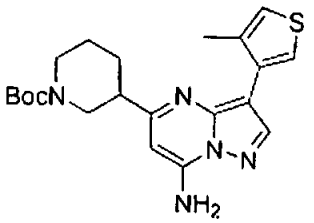
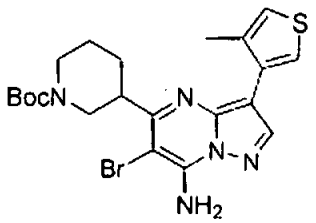
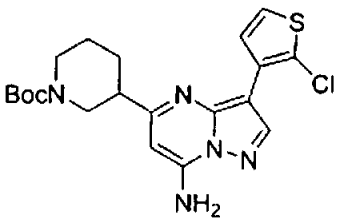
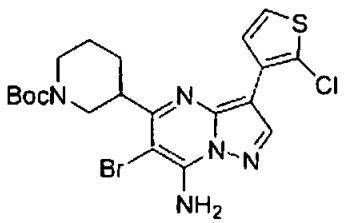
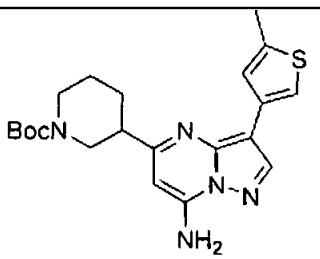
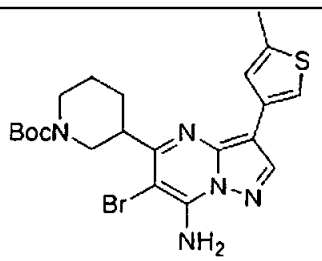
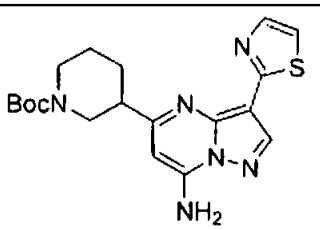
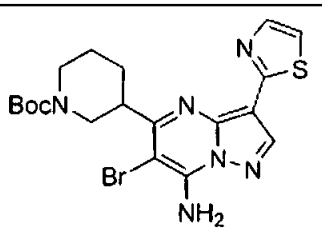
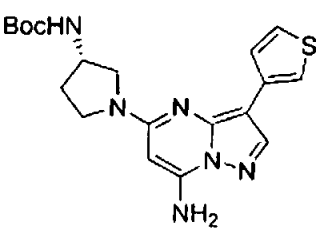
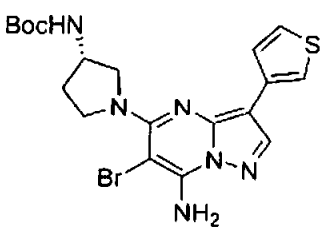
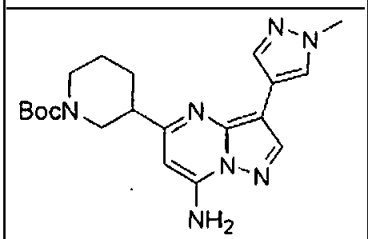
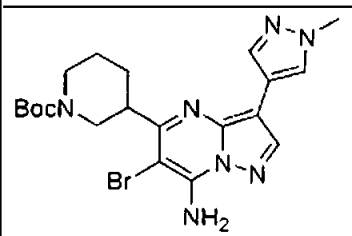
Una solución de Br_2 (16 mg) en CH_2Cl_2 (0,5 mL) se agregó bajo N_2 a una solución agitada del producto del Ejemplo Preparativo 600-K (40 mg, 0,10 mmoles) en t-BuNH_2 (2,0 mL). La mezcla se agitó durante 1 hora, los solventes se evaporaron, y el residuo se purificó por cromatografía en columna sobre gel de sílice con 10:1 de CH_2Cl_2/EtOAc como eluyente. Se obtuvo un sólido blancuzco (18 mg, 38 %). LC-EM: 480 [M+H].

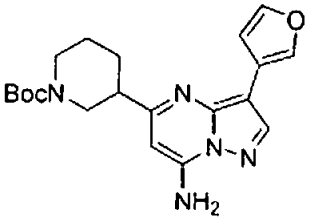
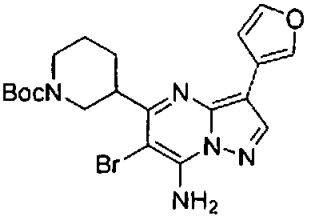
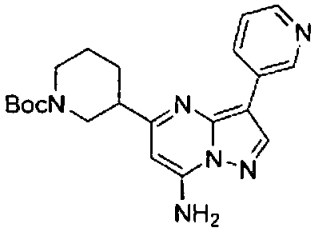
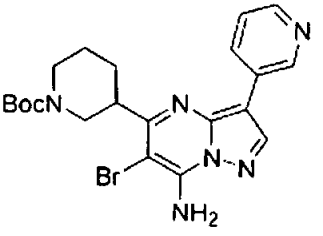
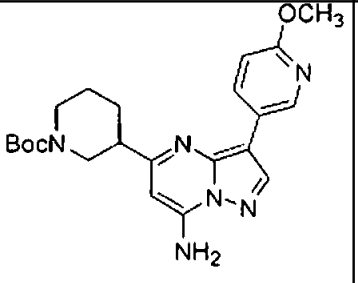
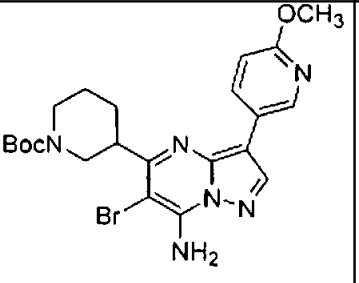
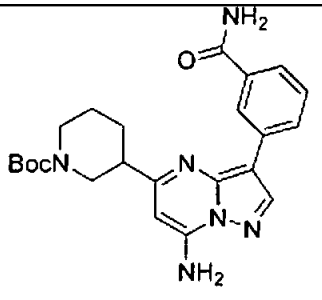
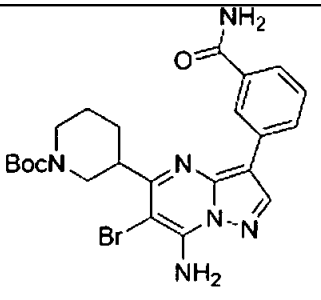
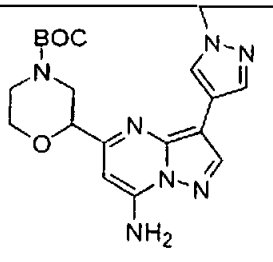
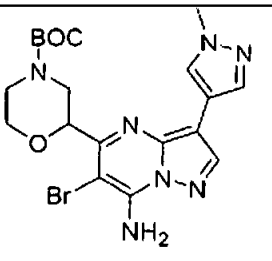
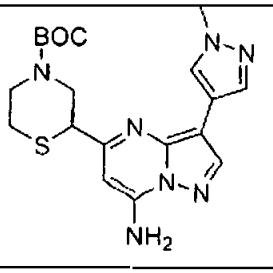
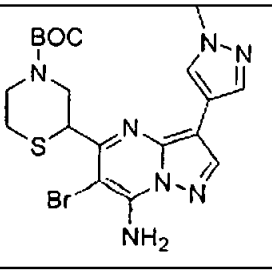
EJEMPLO PREPARATIVO 701-712-K:

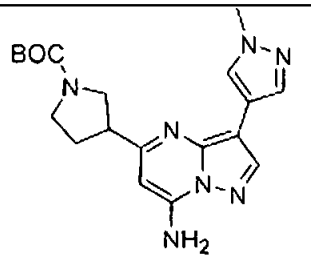
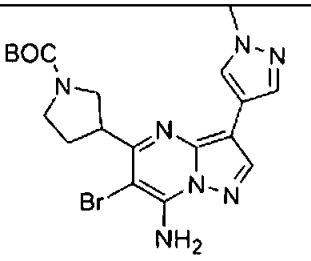
Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo Preparativo 700-K sustituyendo únicamente los compuestos de la Columna 2 de la Tabla 700-K, se prepararon los compuestos de la Columna 3 de la Tabla 700-K.

TABLE 700-K

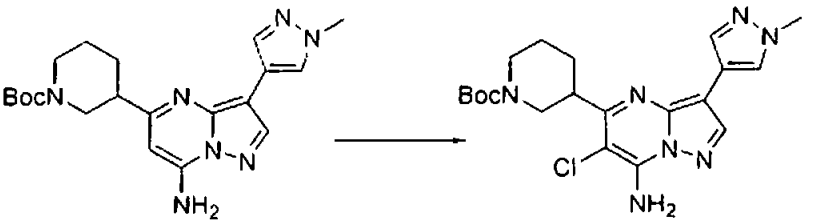
Ej. Prep.	Columna 2	Columna 3	Datos
701-K			LCMS: MH^+=
702-K			

703-K			LCMS: MH^+=
704-K			LCMS: M^+=
705-K			LCMS: MH^+=
706-K			LCMS: MH^+=
707-K			LCMS: M^+=479
708-K			LCMS: M^+=476

709-K			LCMS: M^+=462
710-K			LCMS: M^+=473
711-K			LCMS: M^+ = 503
712-K			LCMS: M^+H = 517
713-K			
714-K			

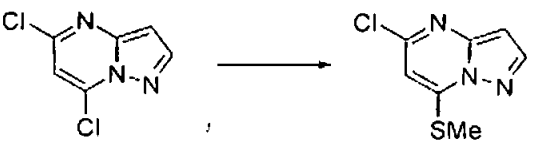
715-K			

EJEMPLO PREPARATIVO 750-K:



Una solución de N-clorosuccinimida (23 mg, 0,17 mmoles) en CH_3CN anhidro (2 mL) se agregó bajo N_2 a una solución agitada del producto del Ejemplo Preparativo 611-K (73 mg, 0,17 mmoles) en CH_3CN anhidro (2 mL). La mezcla se agitó durante 24 horas, los solventes se evaporaron, y el residuo se purificó por cromatografía en columna sobre gel de sílice con 1:1 de CH_2Cl_2/EtOAc como eluyente. Se obtuvo un sólido blanco (54 mg, 68 %). LC-EM: 432 [M+].

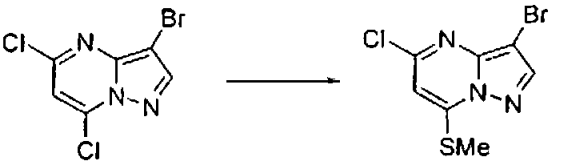
EJEMPLO PREPARATIVO 800-K:



A una solución del dicloruro (3,0 g, 16,0 mmoles) preparado tal como se describió anteriormente en THF (25 mL) se agregó NaSMe (1,1 g, 16,0 mmoles) en una porción. La mezcla resultante se agitó durante 12 horas a temperatura ambiente y se concentró bajo presión reducida. El producto crudo se dividió entre EtOAc (150 mL) y H_2O (30 mL) y las capas se separaron. La capa orgánica se lavó consecutivamente con H_2O (2 x 30 mL) y salmuera (1 x 30 mL). La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida para proporcionar 3,0 g (94 % de rendimiento) de un sólido de color castaño. LC-EM: 200.1 [M+H], pureza 99%.

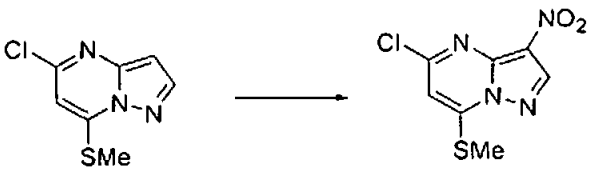
16886

EJEMPLO PREPARATIVO 900-K:



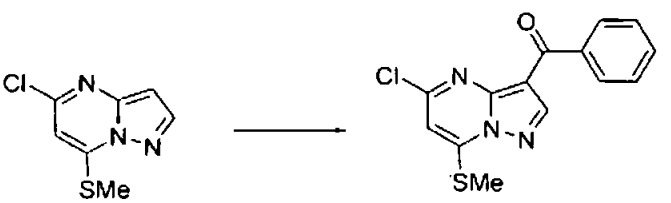
Se preparó el procedimiento señalado en el Ejemplo Preparativo 800-K excepto que se partió del dicloruro que se muestra anteriormente (7,4 g, 27,7 mmoles) preparado tal como se describió anteriormente y NaSMe (2,1 g, 30,5 mmoles) proporcionó 7,4 g (96% de rendimiento) del compuesto del titulo en forma de un sólido de color naranja claro. LC-EM: 278.1 [M+H], pureza 95%.

EJEMPLO PREPARATIVO 1000-K:



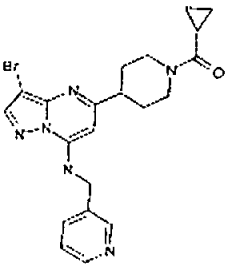
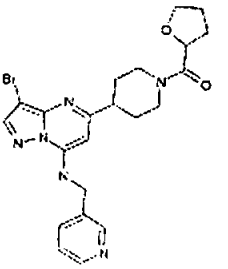
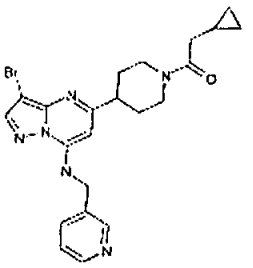
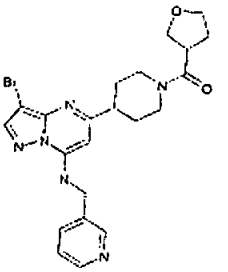
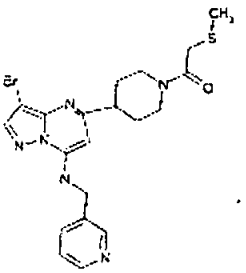
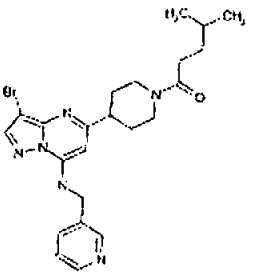
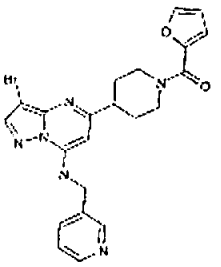
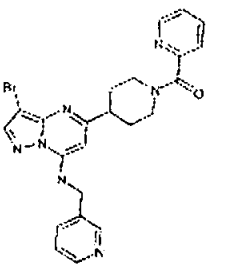
A una solución del derivado tiometilo del Ejemplo Preparativo 800-K (1,5 g, 7,5 mmoles) en H_2SO_4 (9 mL) a 0°C se agregó 60% de HNO_3 (4,5 mL) por goteo. La solución resultante se agitó durante 2 horas a 0°C y 2 horas a temperatura ambiente. La mezcla de reacción se vertió en un frasco que contenía hielo (~15 g) y la mezcla heterogénea se agitó durante 45 minutos. El ppt resultante se recogió por filtración y se lavó consecutivamente con H_2O (2 x 3 mL) y Et_2O (2 x 3 mL). El ppt se colocó bajo alto vacío para remover los residuos volátiles para proporcionar 1,1 g (60%) de un sólido de color naranja. LC-EM: 245.0 [M+H], pureza 90%.

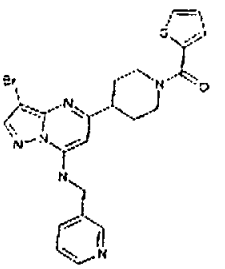
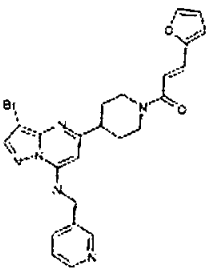
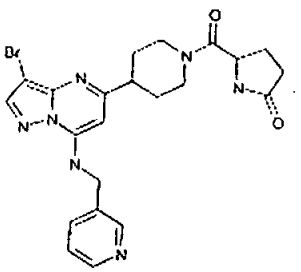
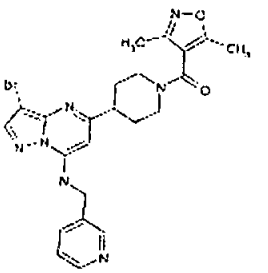
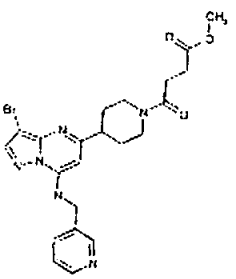
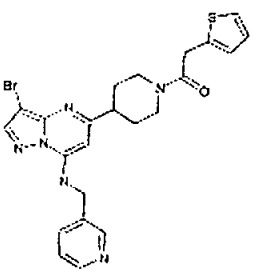
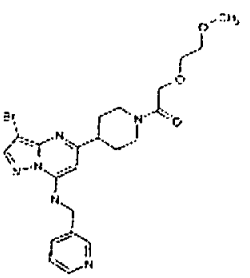
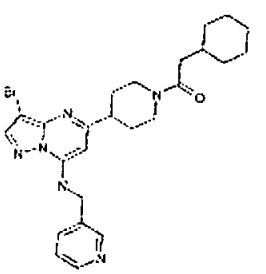
EJEMPLO PREPARATIVO 1100-K:

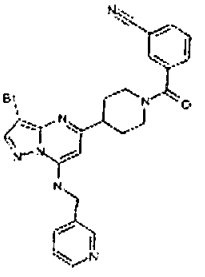
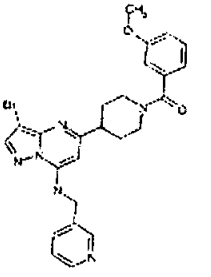
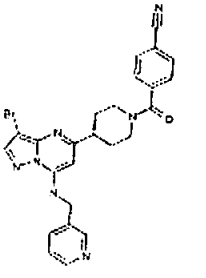
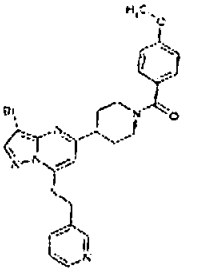
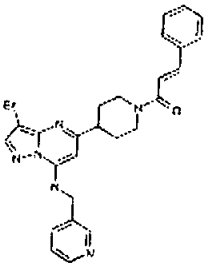
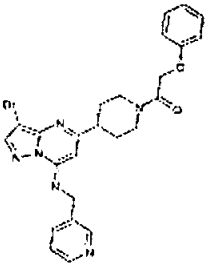
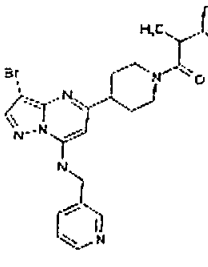
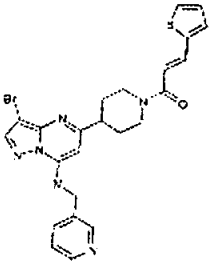


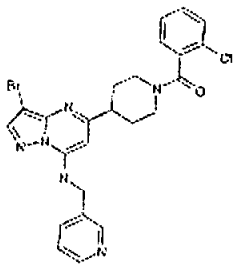
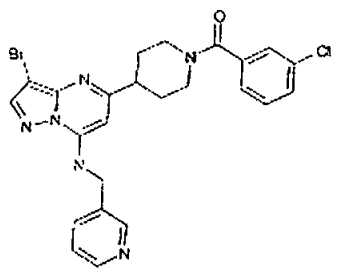
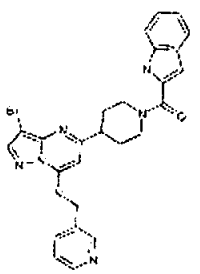
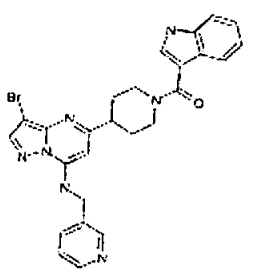
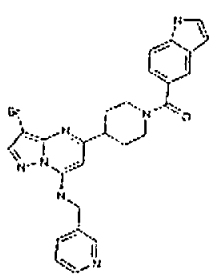
A una solución del derivado tiometilo (0,20 g, 1,0 mmoles) del Ejemplo Preparativo 800-K en CH_2Cl_2 (5 mL) a 0°C se agregó $AlCl_3$ (0,70 g, 5,3 mmoles) seguido de cloruro de benzoilo (0,40 mL, 3,5 mmoles). La mezcla se calentó a reflujo durante 12 horas a temperatura ambiente después de lo cual la mezcla se apagó cuidadosamente a 0°C con $NaHCO_3$ acuoso saturado (3 mL). Se agregó CH_2Cl_2 (5 mL), las capas se separaron, y la capa acuosa se extrajo con CH_2Cl_2 (2

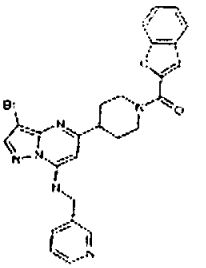
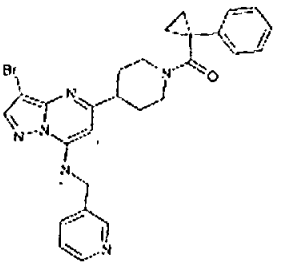
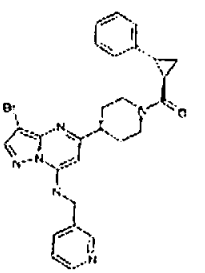
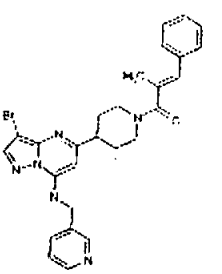
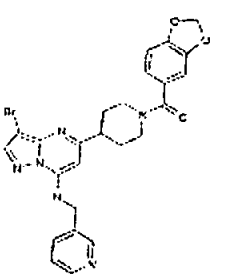
TABLA 43

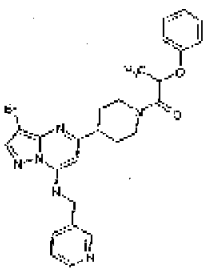
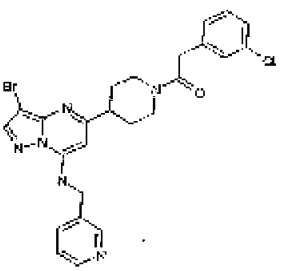
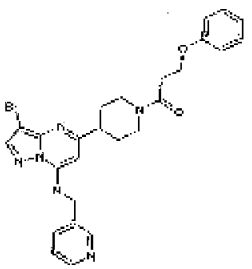
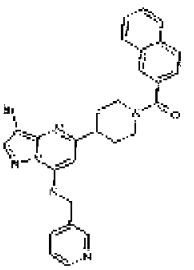
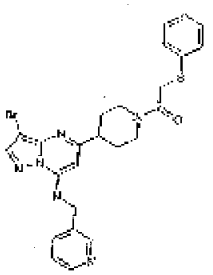
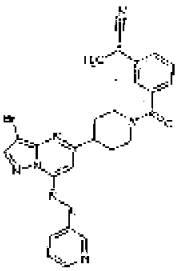
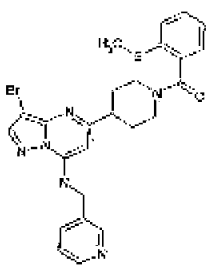
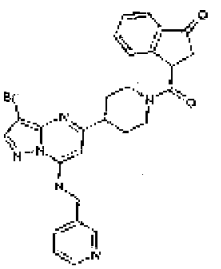
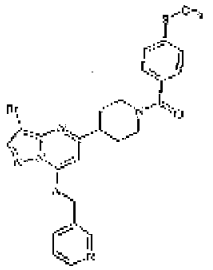
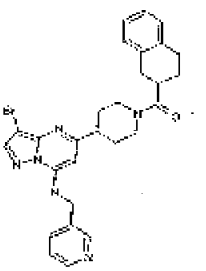
Ej.	Compuesto	m/z	Ej.	Compuesto	m/z
4301		457,25	4305		487,27
4302		471,26	4306		487,27
4303		477,26	4307		487,27
4304		483,27	4308		494,27

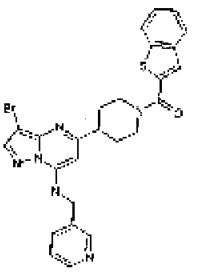
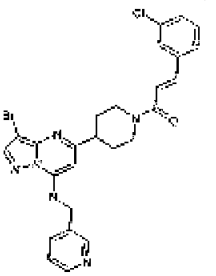
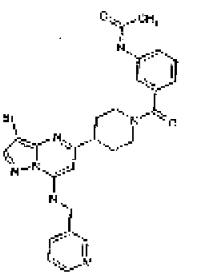
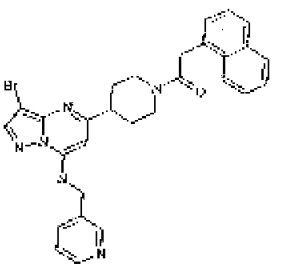
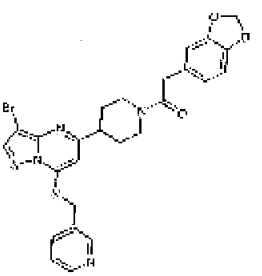
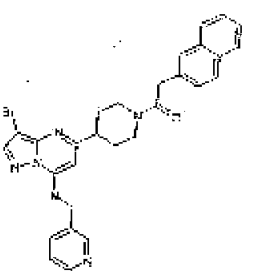
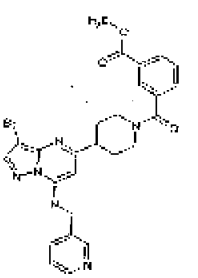
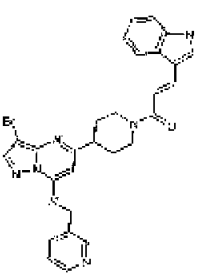
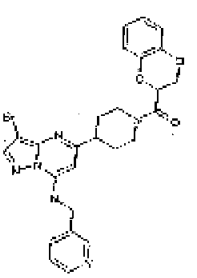
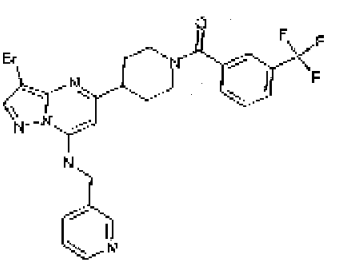
Ej.	Producto	m/z	Ej.	Producto	m/z
4309		499,27	4313		509,28
4310		500,27	4314		512,28
4311		503,28	4315		513,28
4312		505,28	4316		513,28

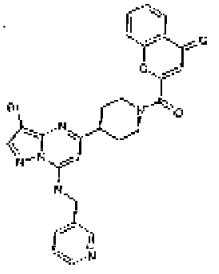
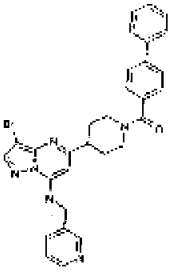
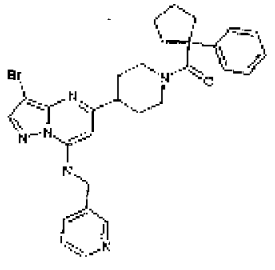
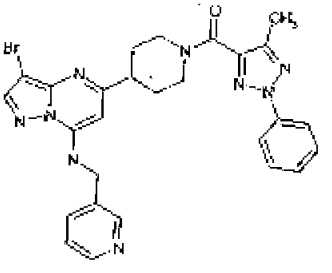
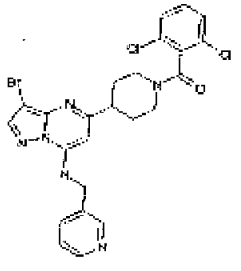
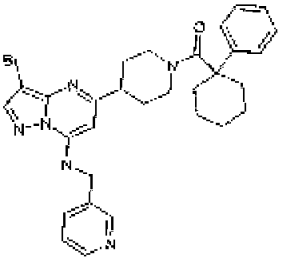
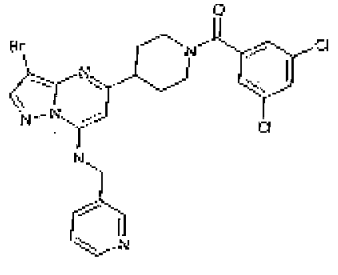
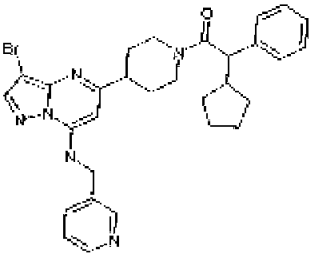
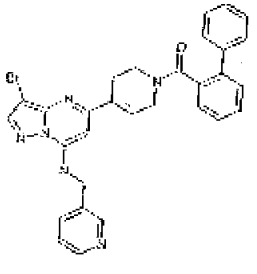
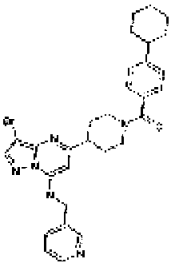
Ej.	Producto	m/z	Ej.	Producto	m/z
4317		518,28	4321		523,29
4318		518,28	4322		523,29
4319		519,29	4323		523,29
4320		521,29	4324		525,29

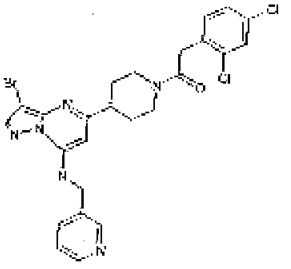
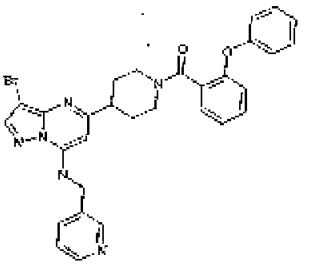
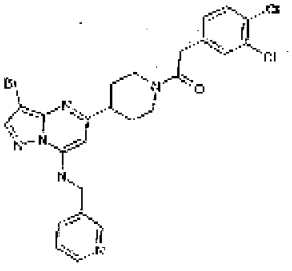
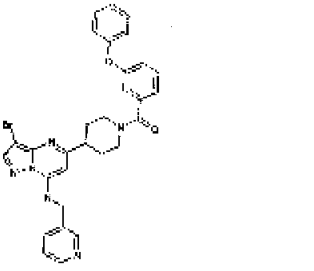
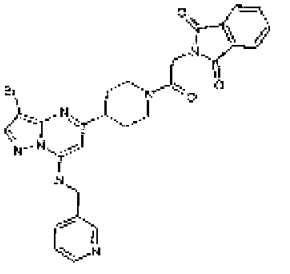
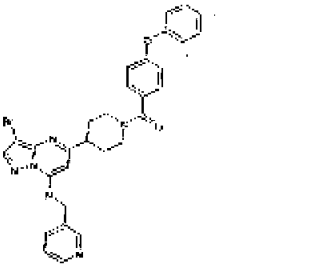
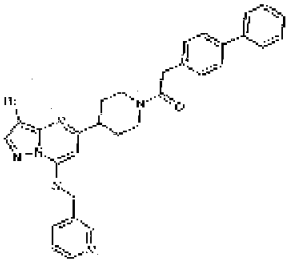
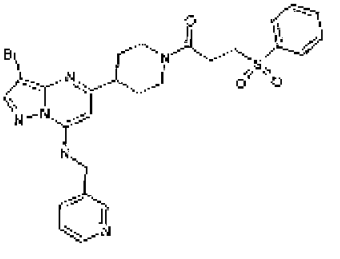
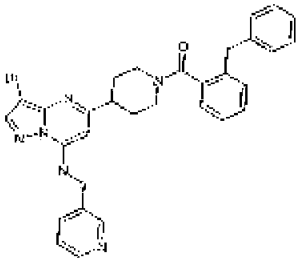
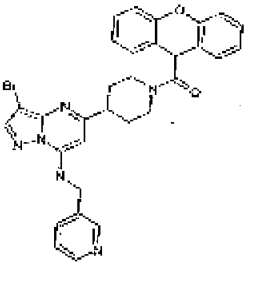
Producto	1. Ej. 2. m/z
	1. 4325 2. 527.29
	1. 4326 2. 527.29
	1. 4327 2. 532.29
	1. 4328 2. 532.29
	1. 4329 2. 532.29

Producto	1. Ej. 2. m/z
	1. 4330 2. 533.29
	4331
	1. 4332 2. 533.29
	1. 4333 2. 533.29
	1. 4334 2. 537.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4335 2. 537.3		1. 4340 2. 541.3
	1. 4336 2. 537.3		1. 4341 2. 543.3
	1. 4337. 2. 539.3		1. 4342 2. 546.3
	1. 4338 2. 539.3		1. 4343 2. 547.3
	1. 4339 2. 539.3		1. 4344 2. 547.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4345 2. 549.3		1. 4350 2. 553.3
	1. 4346 2. 550.3		1. 4351 2. 557.31
	1. 4347 2. 551.3		1. 4352 2. 557.31
	1. 4348 2. 551.3		1. 4353 2. 558.31
	1. 4349 2. 551.3		1. 4354 2. 561.31

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4355 2. 561.31		1. 4360 2. 569.31
	1. 4356 2. 561.31		1. 4361 2. 574.32
	1. 4357 2. 561.31		1. 4362 2. 573.32
	1. 4358 2. 561.31		1. 4363 2. 573.32
	1. 4359 2. 569.31		1. 4364 2. 575.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4365 2. 575.32		1. 43700 2. 585.32
	1. 43666 2. 575.32		1. 4371 2. 583.32
	1. 4367 2. 574.32		1. 4372 2. 585.32
	1. 43668 2. 583.32		1. 4373 2. 585.32
	1. 4369 2. 583.32		1. 4374 2. 597.33

b31

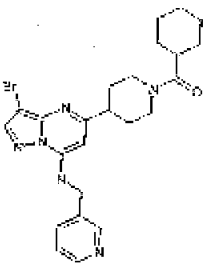
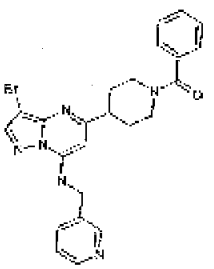
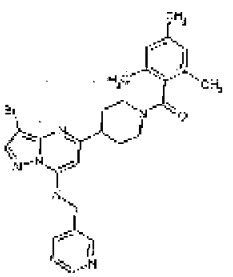
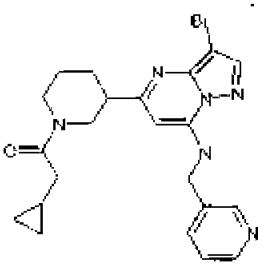
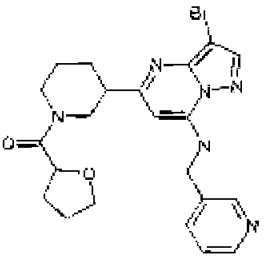
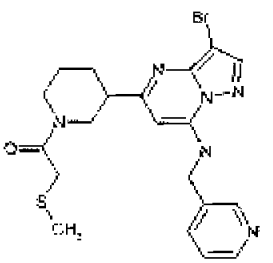
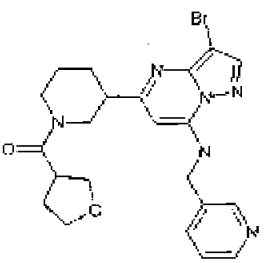
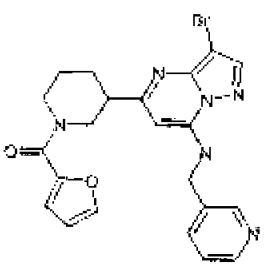
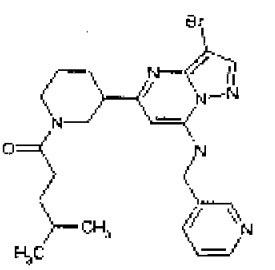
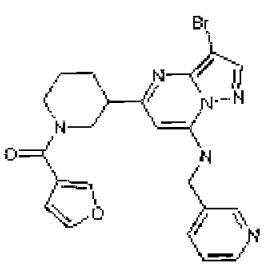
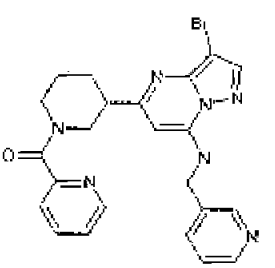
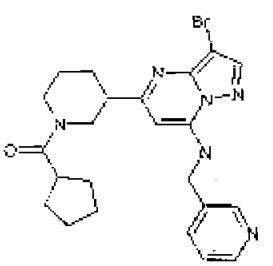
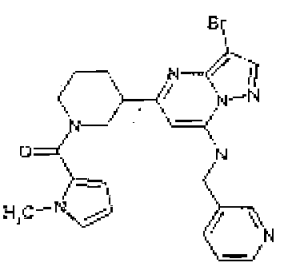
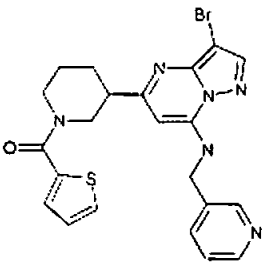
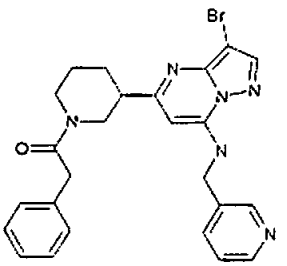
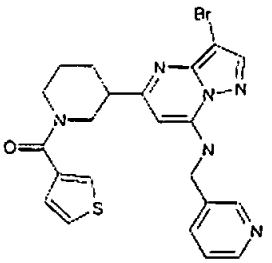
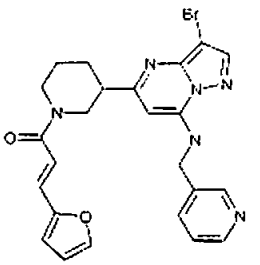
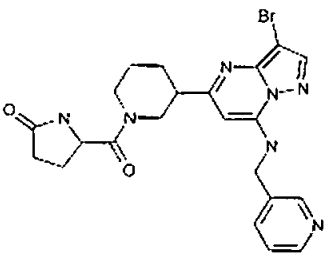
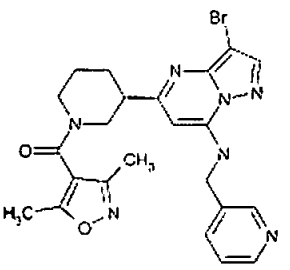
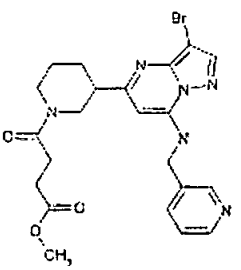
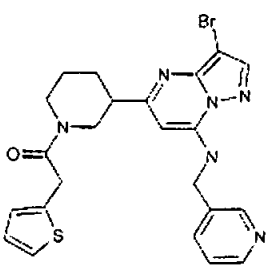
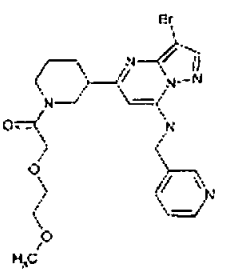
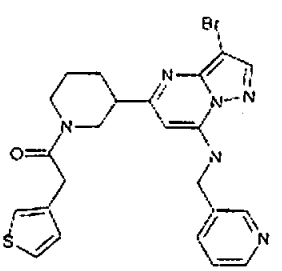
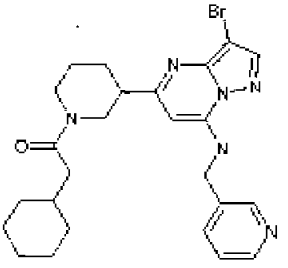
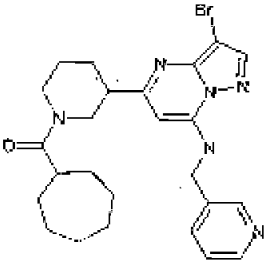
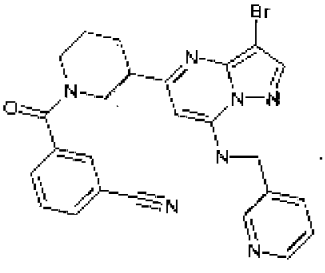
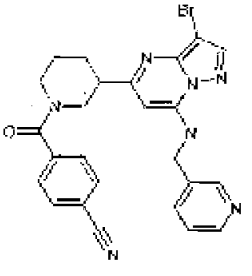
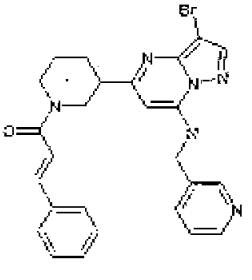
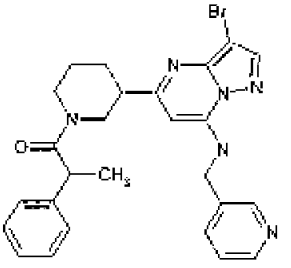
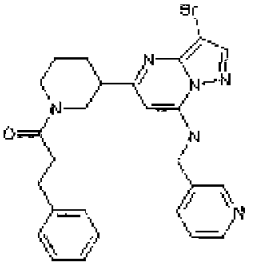
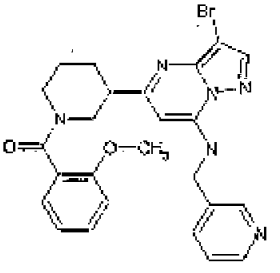
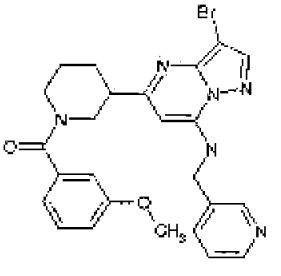
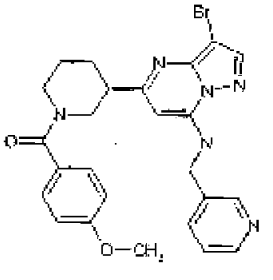
Producto	1. Ej. 2. m/z
	1. 4375 2. 498.27
	1. 4376 2. 493.27
	1. 4377 2. 535.29

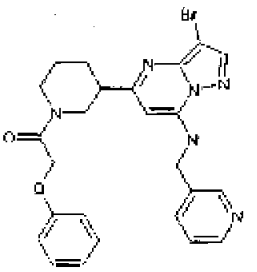
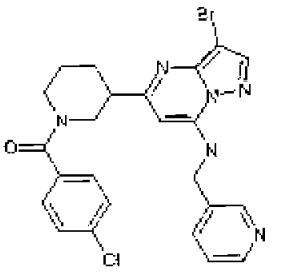
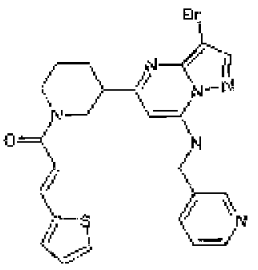
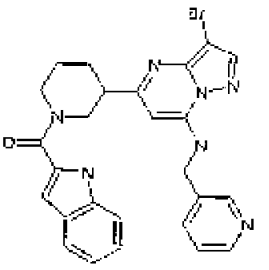
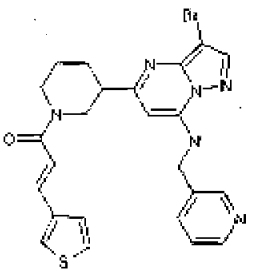
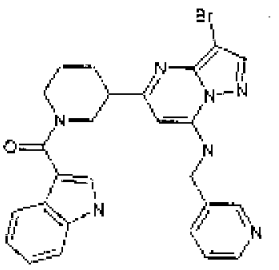
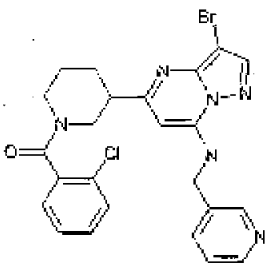
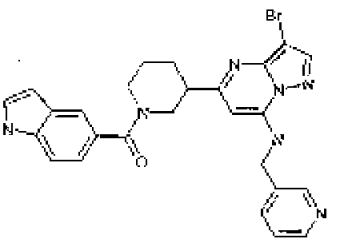
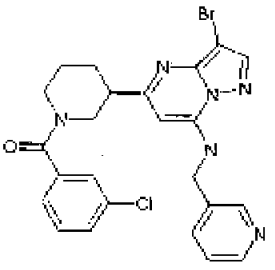
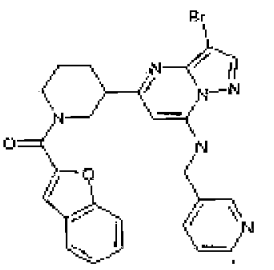
TABLA 44

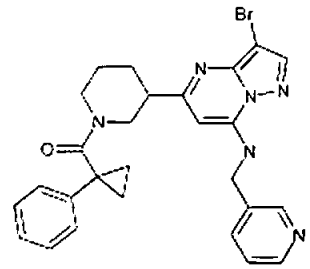
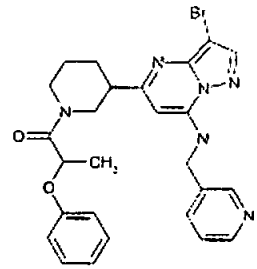
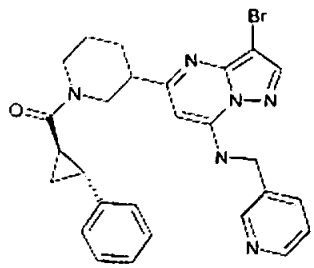
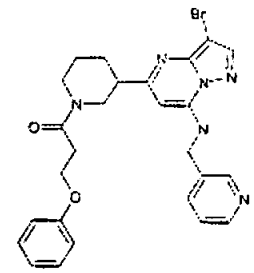
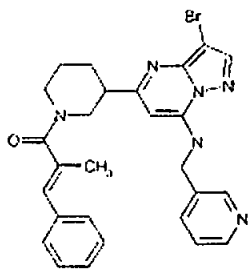
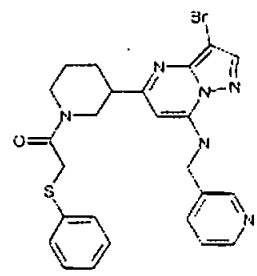
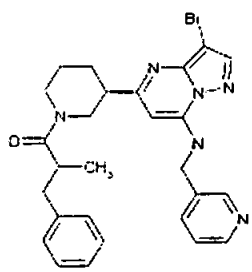
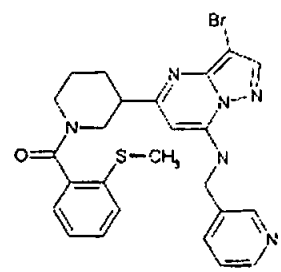
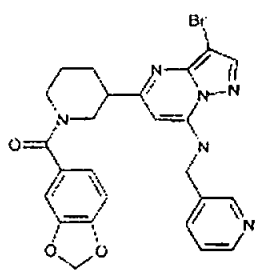
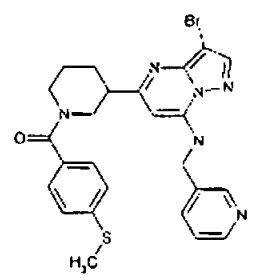
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4401 2. 471.3		1. 4406 2. 487.27
	1. 4402 2. 475.26		1. 4407 2. 487.27
	1. 4403 2. 483.27		1. 4408 2. 487.27
	1. 4404 2. 481.26		1. 4409 2. 494.3
	1. 4405 2. 485.27		1. 4410 2. 496.27

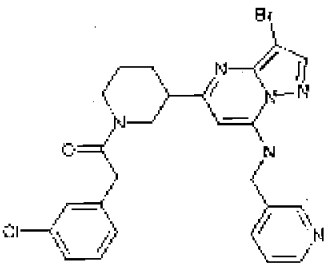
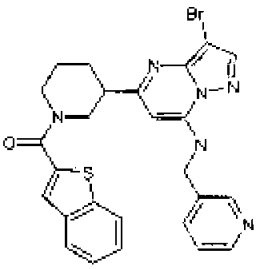
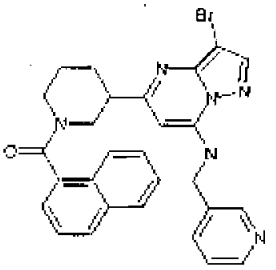
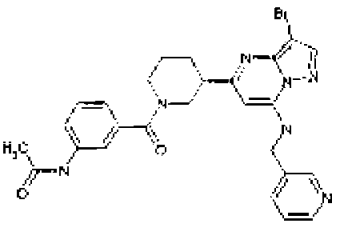
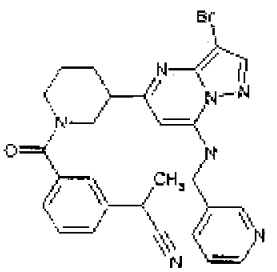
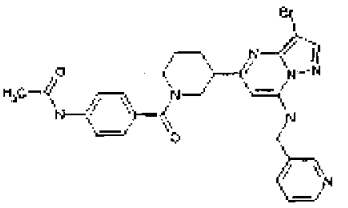
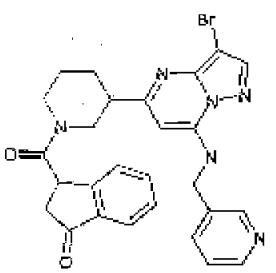
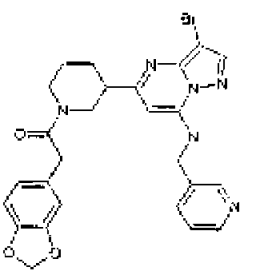
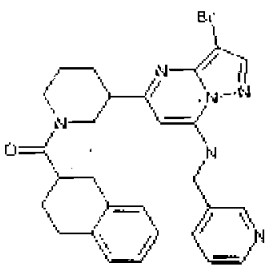
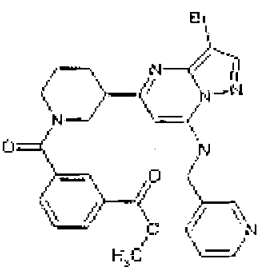
Producto	1. Ej 2. m/z	Producto	1. Ej. 2. m/z
	1. 4411 2. 499.27		1. 4416 2. 507.28
	2. 4412 2. 499.27		1. 4417 2. 509.3
	1. 4413 2. 500.27		1. 4418 2. 512.28
	1. 4414 2. 503.28		1. 4419 2. 513.28
	1. 4415 2. 505.28		1. 4420 2. 513.28

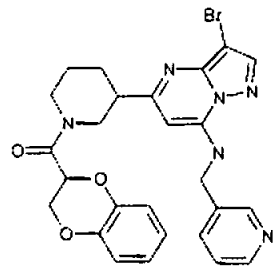
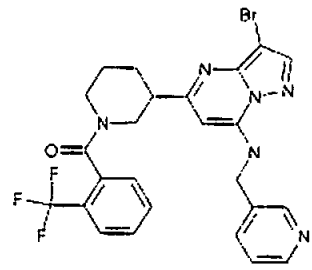
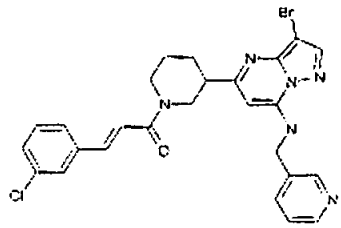
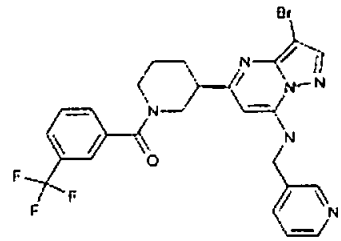
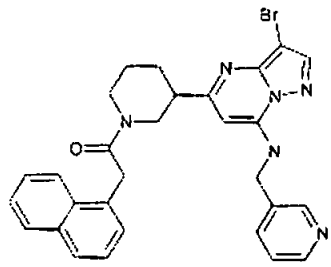
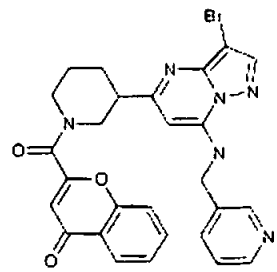
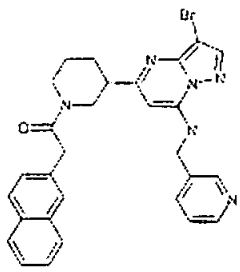
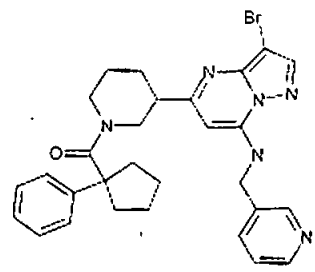
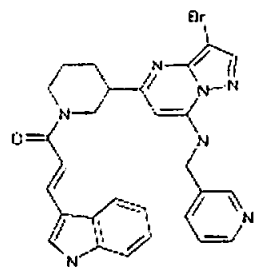
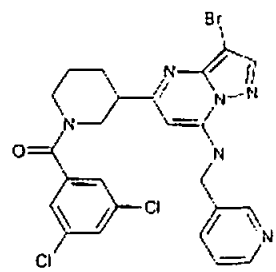
Producto	1. Ej. 2. m/z
	1. 4421 2. 513.28
	1. 4422 2. 513.28
	1. 4423 2. 518.28
	1. 4424 2. 518.28
	1. 4425 2. 519.3

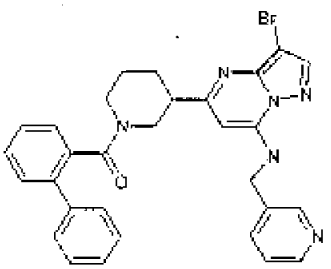
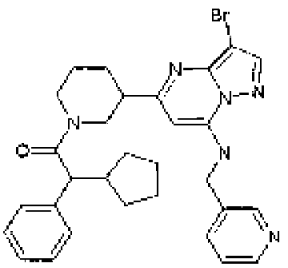
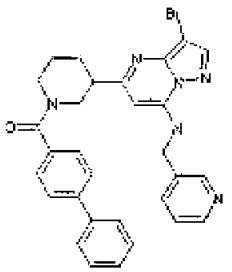
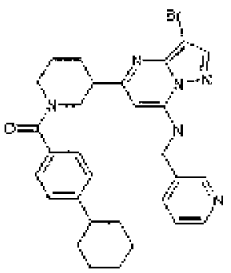
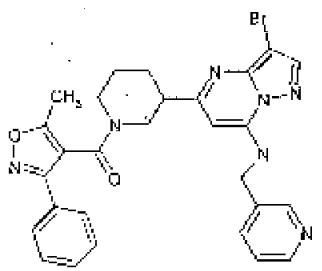
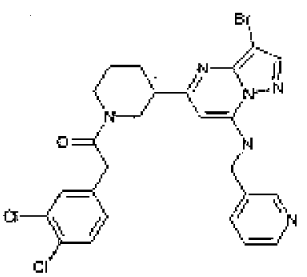
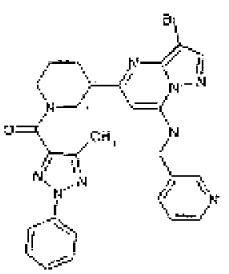
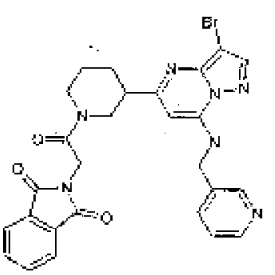
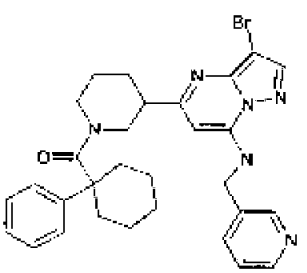
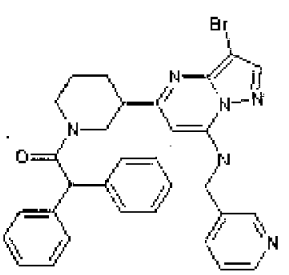
Producto	1. Ej. 2. m/z
	1. 4426 2. 521.29
	1. 4428 2. 521.29
	1. 4428 2. 523.29
	1. 4429 2. 523.29
	1. 4430 2. 523.29

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4431 2. 523.29		1. 4436 2. 527.29
	1. 4432 2. 526.29		1. 4437 2. 532.29
	1. 4433 2. 526.3		1. 4438 2. 532.29
	1. 4434 2. 527.29		1. 4439 2. 532.29
	1. 4435 2. 527.29		1. 4440 2. 531.29

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4441 2. 533.3		1. 4446 2. 537.3
	1. 4442 2. 531.29		1. 4447 2. 537.3
	1. 4443 2. 533.29		1. 4448 2. 539.3
	1. 4444 2. 535.29		1. 4449 2.539.3
	1. 4445 2. 537.3		1. 4450 2.539.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4451 2. 541.3		1. 4456 2. 549.3
	1. 4451 2. 543.3		1. 4457 2. 550.3
	1. 4453 2. 546.3		1. 4458 2. 550.3
	1. 4454 2.547.3		1. 4459 2. 551.3
	1. 4455 2.547.3		1. 4460 2. 551.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4461 2. 549.3		1. 4466 2. 561.31
	1. 4462 2. 553.3		1. 4467 2. 561.31
	1. 4463 2. 557.3		1. 4468 2. 561.31
	1. 4464 2. 557.31		1. 4469 2. 561.31
	1. 4465 2. 558.31		1. 4470 2. 562.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4471 2. 569.31		1. 4476 2.572.31
	1. 4472 2. 569.31		1. 4477 2. 573.32
	1. 4473 2. 572.31		1. 4478 2. 574.32
	1. 4474 2. 572.31		1. 4479 2. 576.32
	1. 4475 2. 575.32		1. 4480 2. 583.32

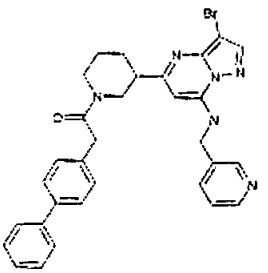
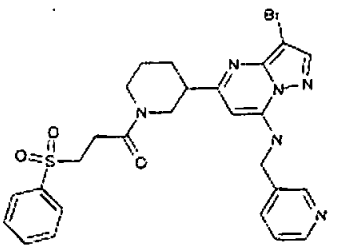
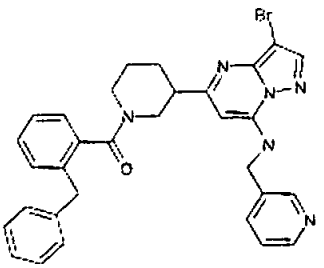
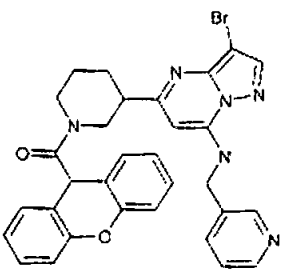
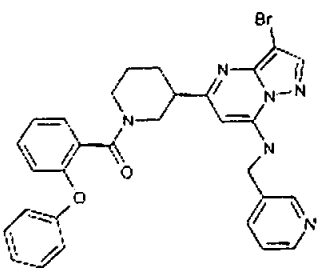
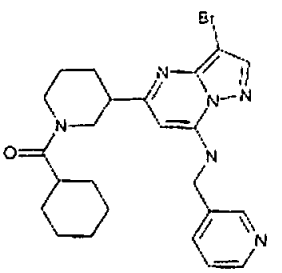
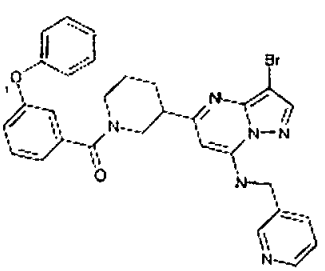
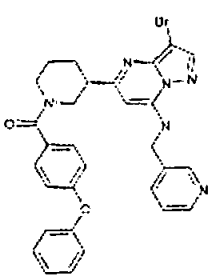
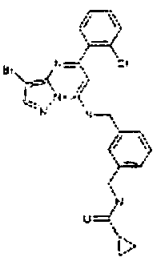
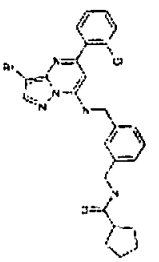
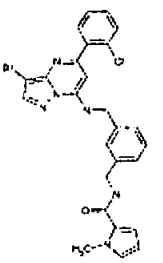
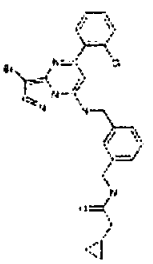
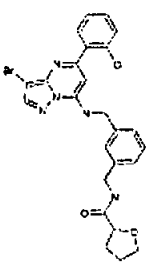
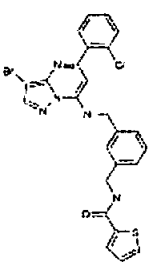
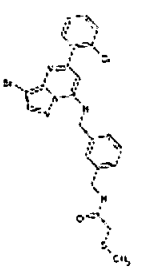
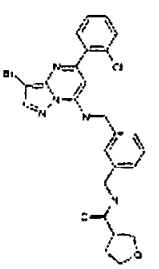
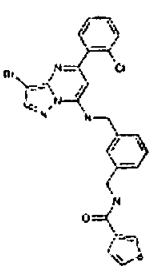
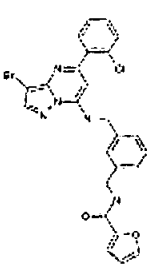
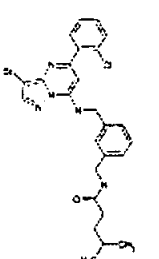
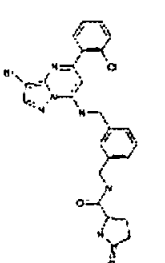
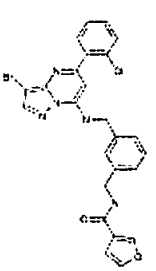
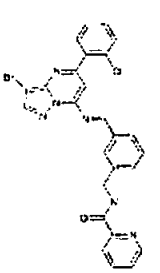
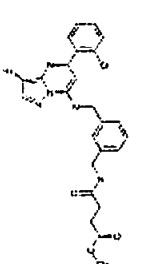
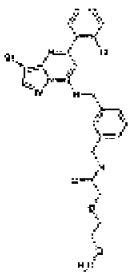
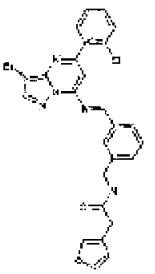
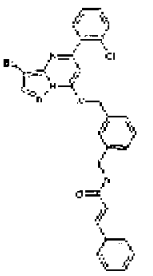
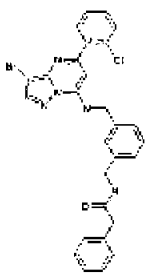
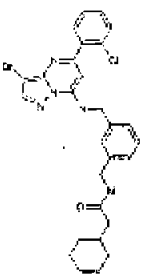
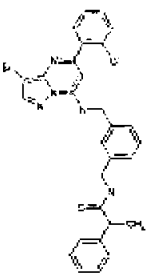
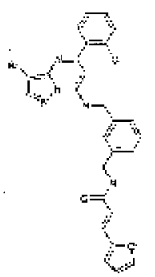
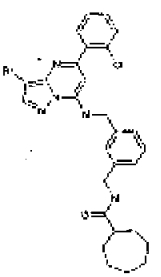
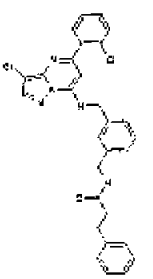
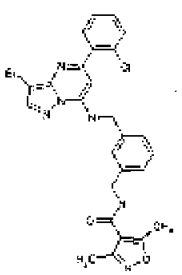
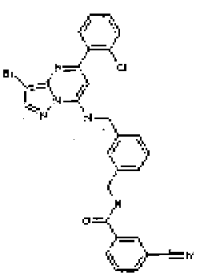
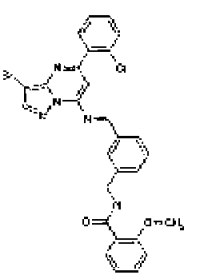
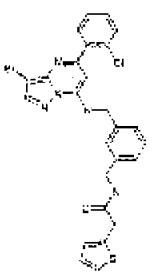
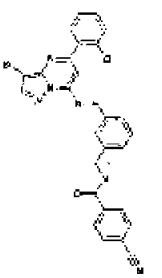
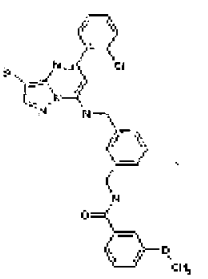
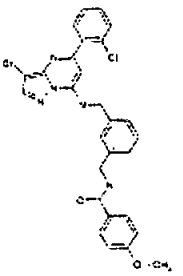
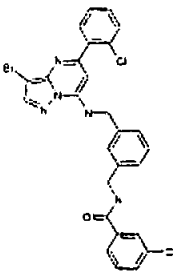
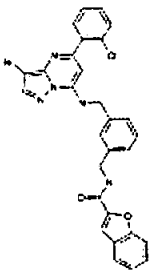
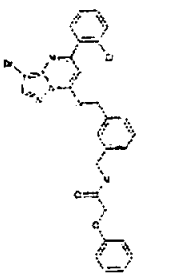
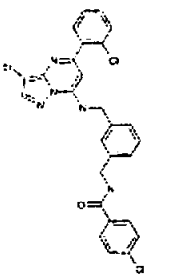
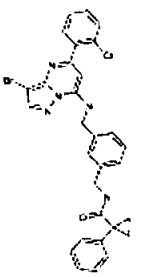
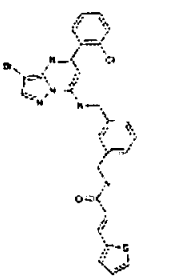
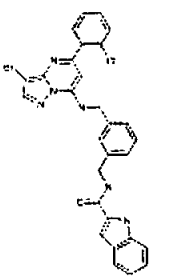
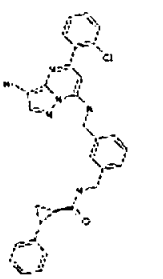
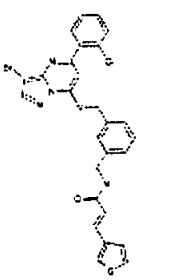
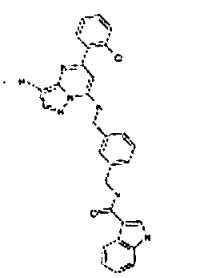
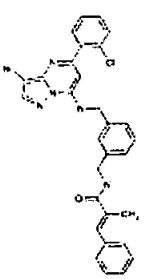
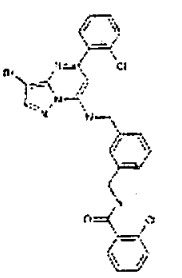
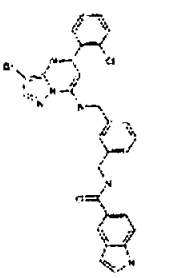
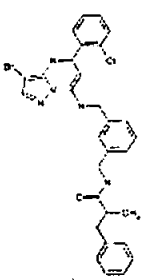
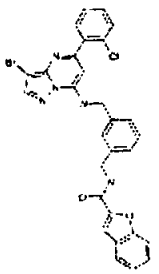
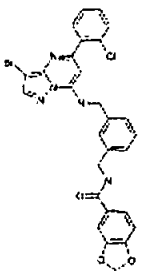
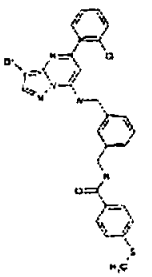
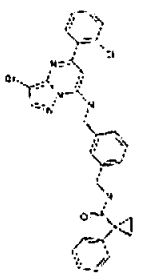
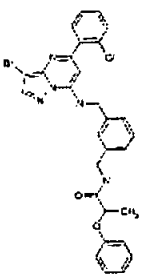
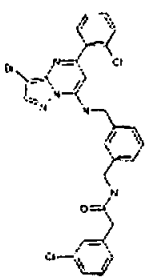
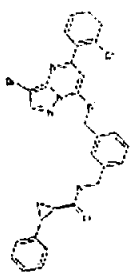
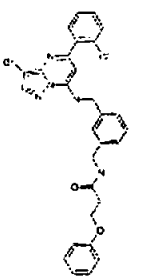
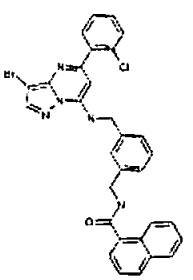
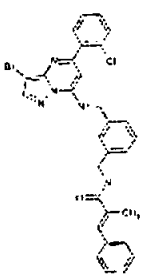
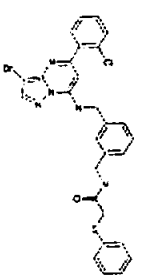
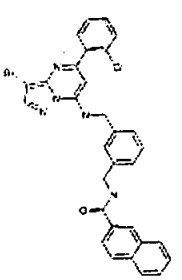
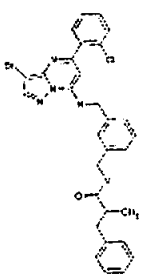
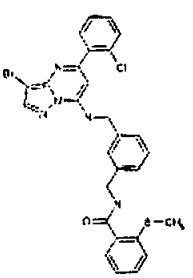
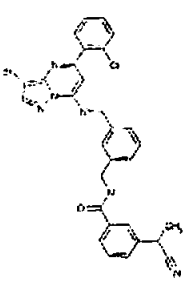
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4481 2. 583.32		1. 4486 2. 585.32
	1. 4482 2. 583.32		1. 4487 2. 597.33
	1. 4483 2. 585.32		1. 4488 2. 499.27
	1. 4484 2. 585.32		
	1. 4485 2. 585.3		

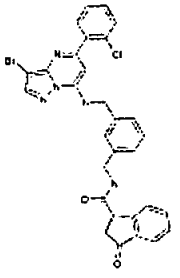
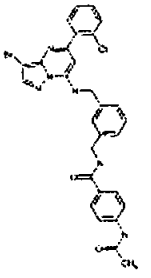
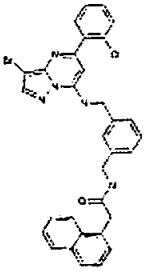
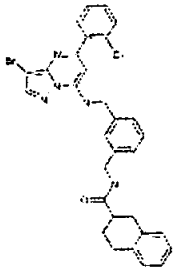
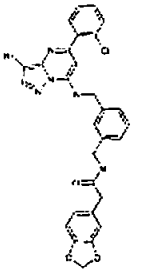
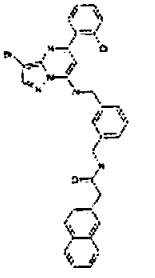
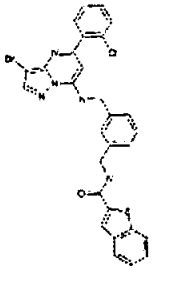
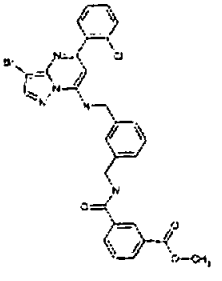
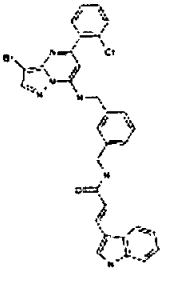
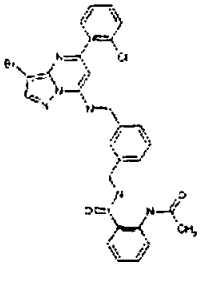
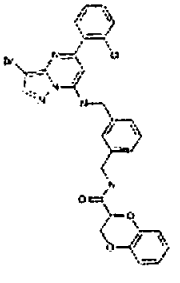
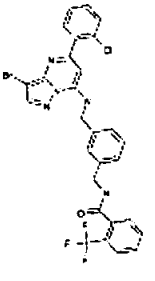
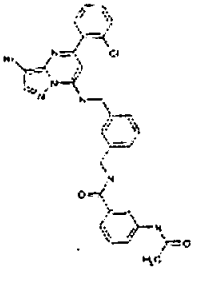
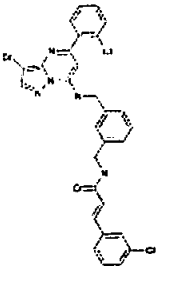
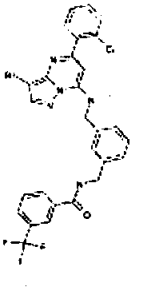
TABLA 45

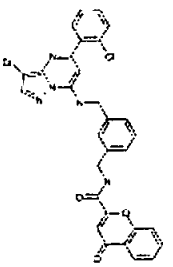
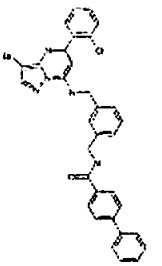
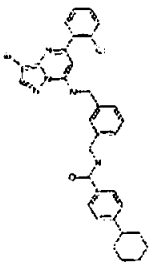
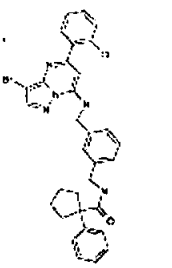
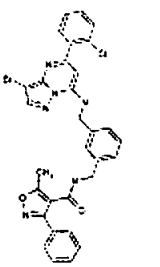
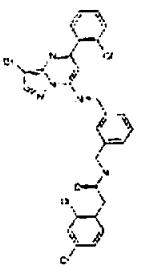
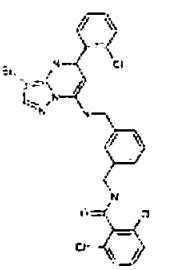
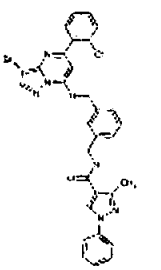
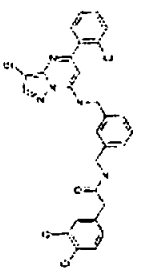
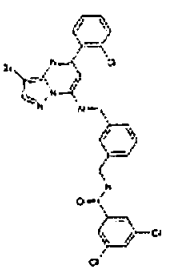
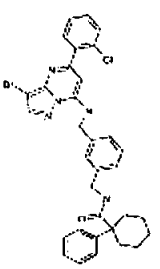
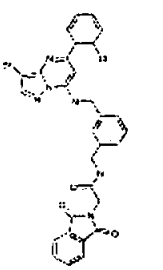
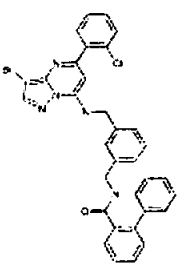
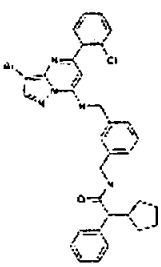
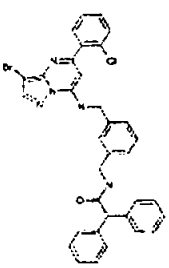
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4501 2. 512.28		1. 4506 2. 540.3		1. 4511 2. 551.3
	1. 4502 2. 526.29		1. 4507 2. 542.3		1. 4512 2. 554.3
	1. 4503 2. 532.29		1. 4508 2. 542.3		1. 4513 2. 554.3
	1. 4504 2. 538.3		1. 4509 2. 542.3		1. 4514. 2. 555.31
	1. 4505 2. 538.3		1. 4510 2. 549.3		1. 4515 2. 558.31

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4516 2. 560.31		1. 4521 2. 568.31		1. 4526 2. 574.32
	1. 4517 2. 562.31		1. 4522 2. 568.31		1. 4527 2. 576.32
	1. 4518 2. 564.31		1. 4523 2. 568.31		1. 4528 2. 576.32
	1. 4519 2. 567.31		1. 4524 2. 573.32		1. 4529 2. 578.32
	1. 4520 2. 568.31		1. 4525 2. 573.32		1. 4530 2. 578.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4531 2. 578.32		1. 4536 2. 582.32		1. 4541 2. 588.32
	1. 4532 2. 578.32		1. 4537 2. 582.32		1. 4542 2. 588.32
	1. 4533 2. 580.32		1. 4538 2. 587.32		1. 4543 2. 588.32
	1. 4534 2. 580.32		1. 4539 2. 587.32		1. 4544 2. 588.32
	1. 4535 2. 582.32		1. 4540 2. 587.32		1. 4545 2. 590.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4546 2. 588.32		1. 4551 2. 592.33		1. 4556 2. 593.33
	1. 4547 2. 588.32		1. 4552 2. 592.33		1. 4557 2. 596.33
	1. 4548 2. 588.32		1. 4553 2. 592.33		1. 4558 2. 596.33
	1. 4549 2. 588.32		1. 4554 2. 594.33		1. 4559 2. 598.33
	1. 4550 2. 590.32		1. 4555 2. 594.33		1. 4560 2. 601.33

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4561 2. 602.33		1. 4665 2. 605.33		1. 4571 2. 612.34
	1. 4562 2. 602.33		1. 4567 2. 606.33		1. 4572 2. 612.34
	1. 4563 2. 604.33		1. 4568 2. 606.33		1. 4573 2. 613.34
	1. 4564 2. 603.3		1. 4569 2. 606.33		1. 4574 2. 616.34
	1. 4565 2. 605.33		1. 4570 2. 608.33		1. 4575 2. 616.34

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4576 2. 616.34		1. 4581 2. 624.34		1. 4586 2. 630.35
	1. 4577 2. 616.34		1. 4582 2. 629.35		1. 4587 2. 630.35
	1. 4578 2. 616.34		1. 4583 2. 629.35		1. 4588 2. 630.35
	1. 4579 2. 616.34		1. 4584 2. 630.35		1. 4589 2. 631.35
	1. 4580 2. 624.34		1. 4585 2. 630.35		1. 4590 2. 638.35

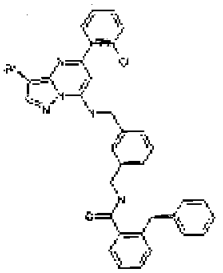
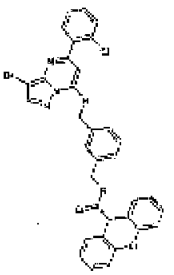
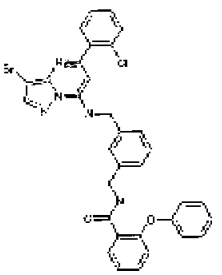
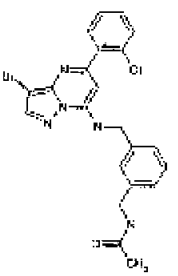
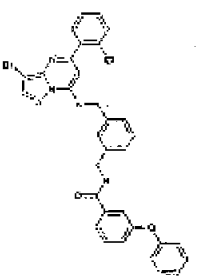
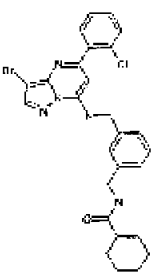
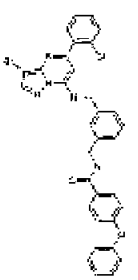
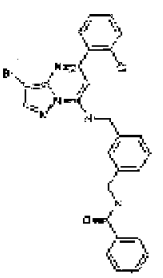
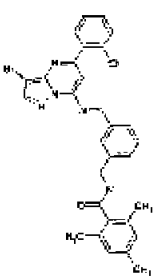
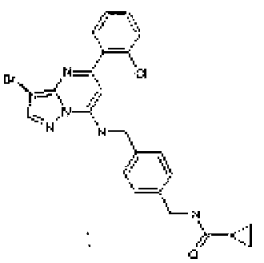
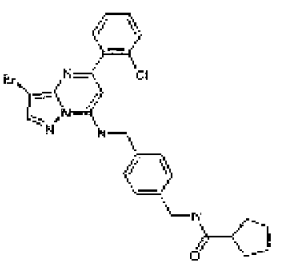
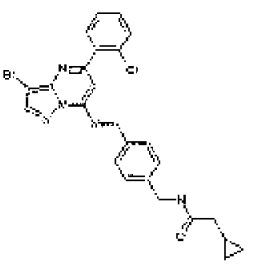
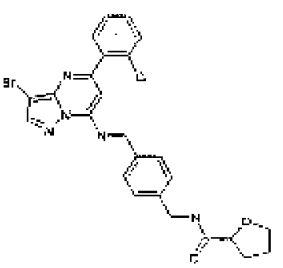
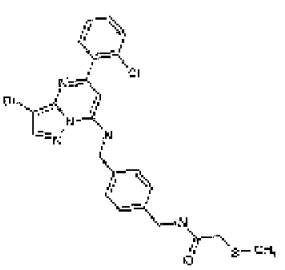
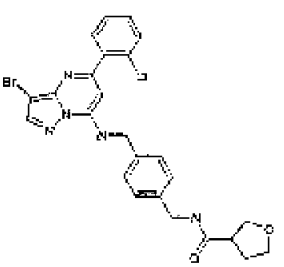
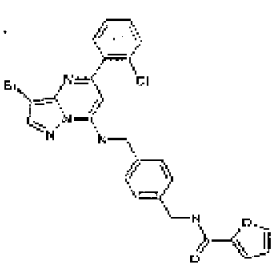
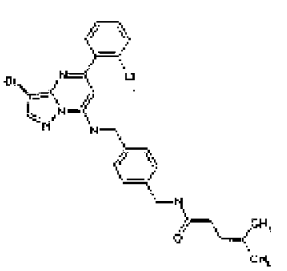
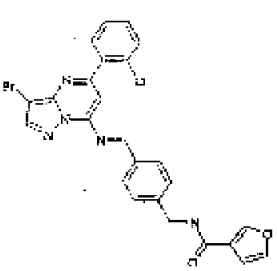
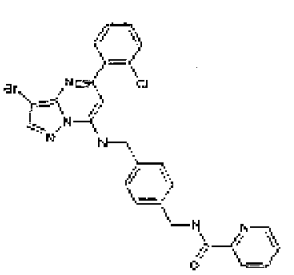
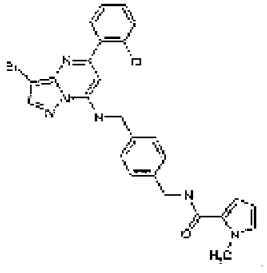
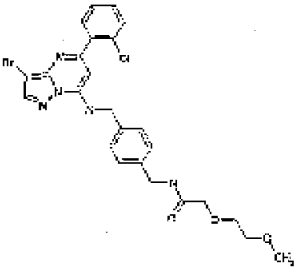
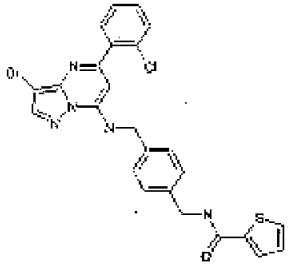
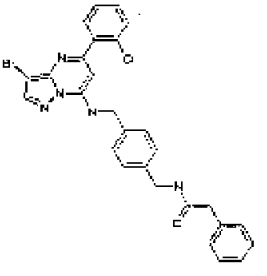
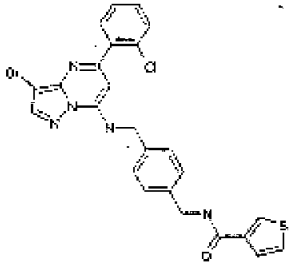
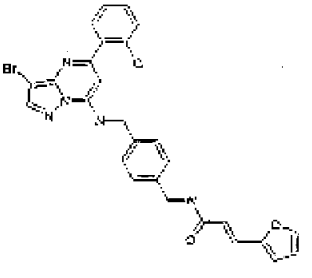
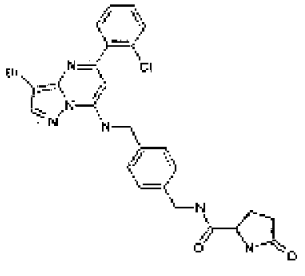
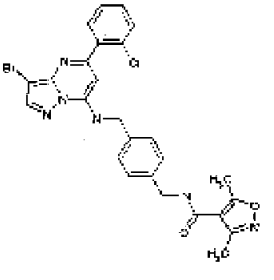
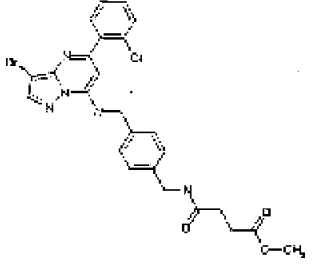
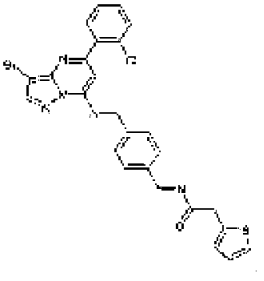
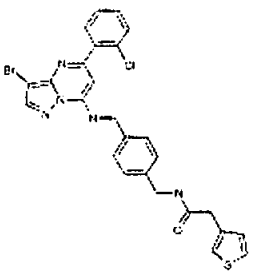
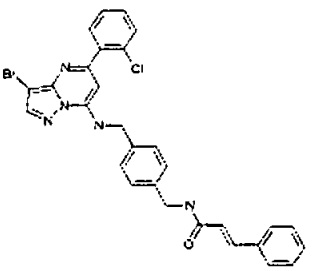
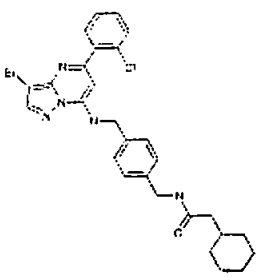
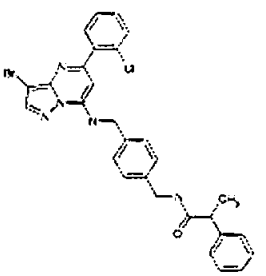
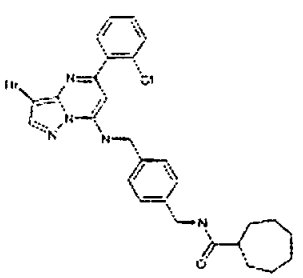
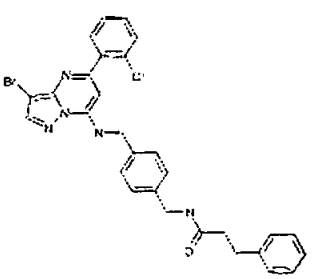
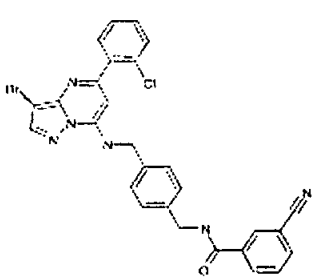
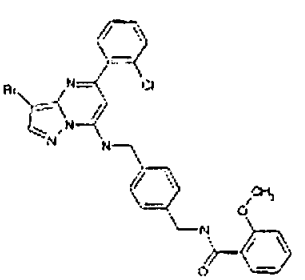
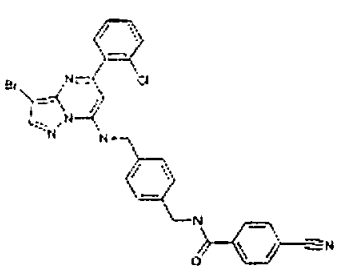
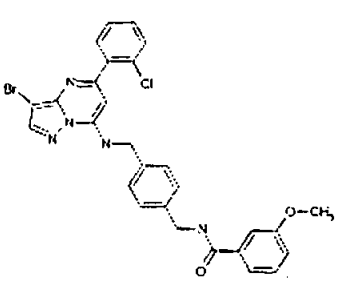
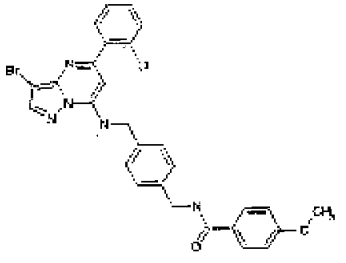
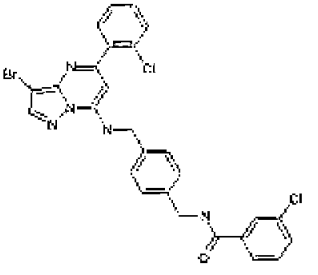
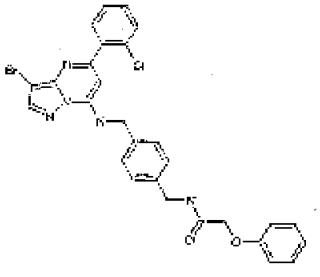
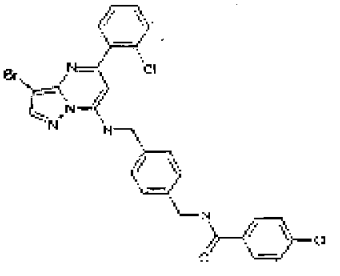
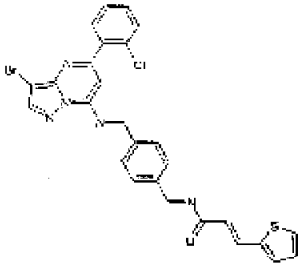
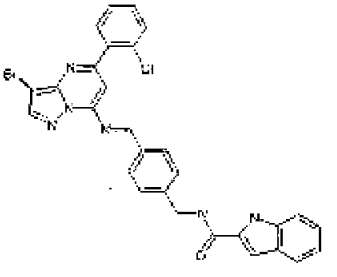
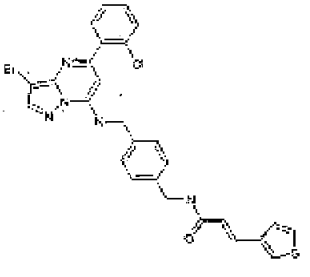
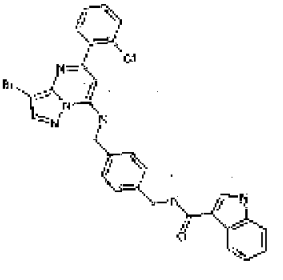
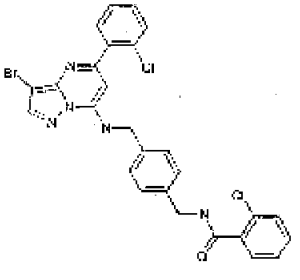
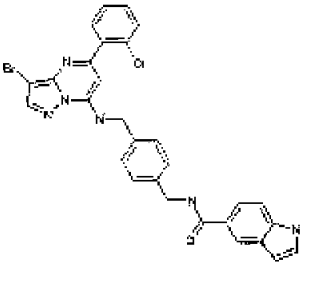
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4591 2. 638.35		1. 4596 2. 652.36
	1. 4592 2. 640.35		1. 4597 2. 486.27
	1. 4593 2. 640.35		1. 4598 2. 554.3
	1. 4594 2. 640.35		1. 4599 2. 548.3
	1. 4595 2. 640.35		1. 45100 2.

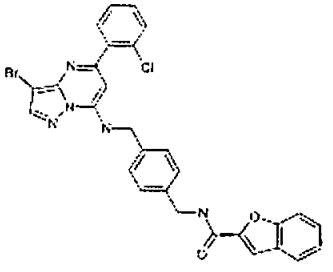
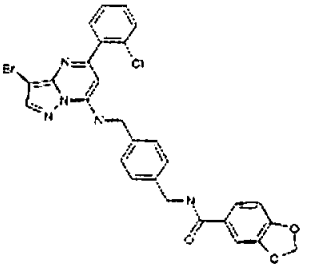
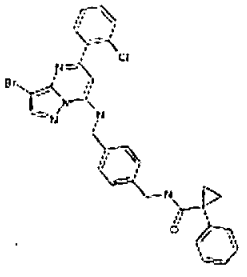
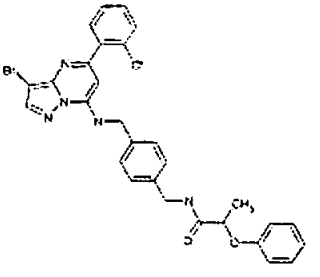
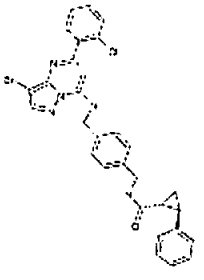
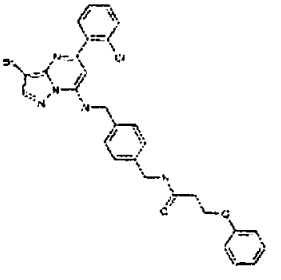
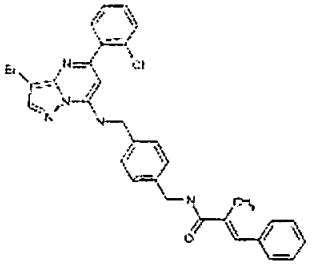
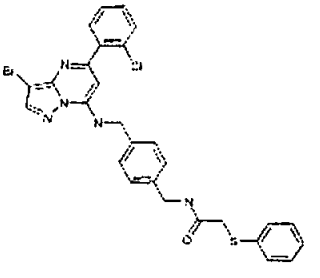
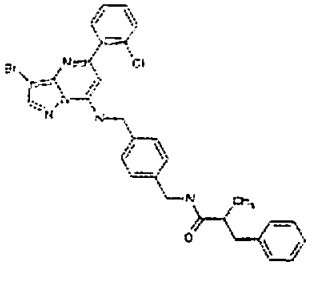
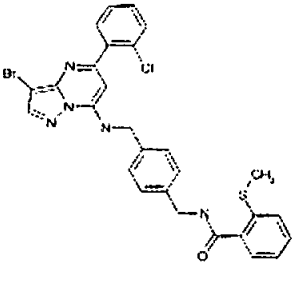
TABLA 46

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4601 2. 512.28		1. 4606 2. 540.3
	1. 4602 2. 526.29		1. 4607 2. 542.3
	1. 4603 2. 532.29		1. 4608 2. 542.3
	1. 4604 2. 538.3		1. 4609 2. 542.3
	1. 4605 2. 536.3		1. 4610 2. 547.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4611 2. 551.3		1. 4616 2. 560.31
	1. 4612 2. 552.3		1. 4617 2. 562.31
	1. 4613 2. 552.3		1. 4618 2. 562.3
	1. 4614 2. 555.31		1. 4619 2. 567.31
	1. 4615 2. 558.31		1. 4620 2. 568.31

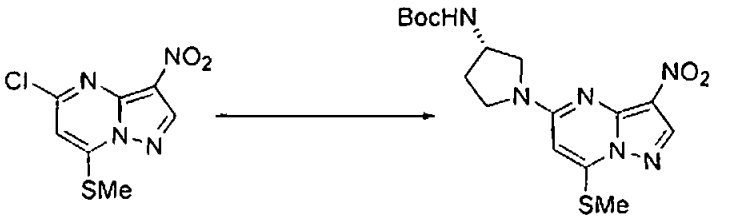
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4621 2. 568.31		1. 4626 2. 574.32
	1. 4622 2. 568.31		1. 4627 2. 576.32
	1. 4623 2. 568.31		1. 4628 2. 576.32
	1. 4624 2. 573.32		1. 4629 2. 578.32
	1. 4625 2. 573.32		1. 4630 2. 578.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4631 2. 578.32		1. 4636 2. 582.32
	1. 4632 2. 578.32		1. 4637 2. 582.32
	1. 4633 2. 580.32		1. 4638 2. 587.32
	1. 4634 2. 580.32		1. 4639 2. 585.3
	1. 4635 2. 582.32		1. 4640 2. 585.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4641 2. 588.32		1. 4646 2. 592.33
	1. 4642 2. 588.32		1. 4647 2. 592.33
	1. 4643 2. 588.32		1. 4648 2. 592.33
	1. 4644 2,. 588.32		1. 4649 2.
	1. 4645 2. 590.32		1. 4650 2. 594.33

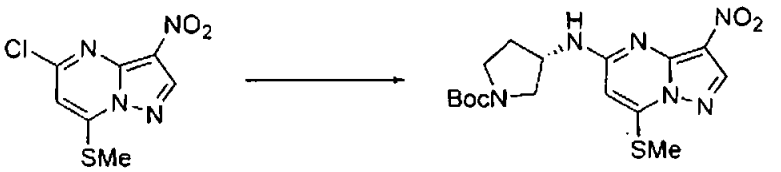
x 5 mL). Las capas orgánicas se combinaron, se lavaron con salmuera (1 x 5 mL), se secaron (Na_2SO_4), se filtraron, y se concentraron bajo presión reducida para proporcionar 0,27 g (88% de rendimiento crudo) de un sólido de color castaño. LC-EM: 304.0 [M+H], pureza 85%.

EJEMPLO PREPARATIVO 1200-K:



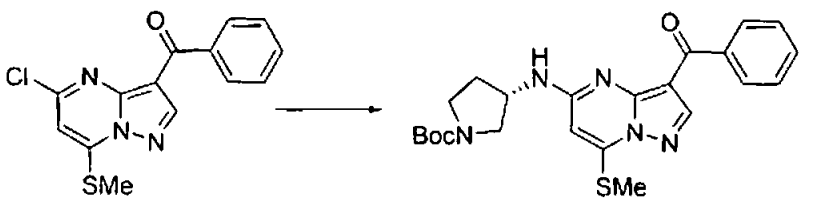
A una solución de un derivado tiometilo (0,4 g, 1,63 mmoles) del Ejemplo Preparativo 1000-K en dioxano/DIPEA (7 ml/2 mL) a temperatura ambiente se agregó (*S*)-(-)-3-(Boc-amino)pirrolidina (0,36 g, 1,96 mmoles) en una sola porción. La mezcla se agitó a reflujo durante 12 horas y luego se enfrió a temperatura ambiente. La mezcla se filtró y se lavó con CH_2Cl_2 (2 x 2 mL) y Et_2O (2 x 2 mL). El ppt resultante se secó al vacío para proporcionar 0,57 g (90% de rendimiento) de un sólido de color amarillo. LC-EM: 395.1 [M+H], pureza 90%.

EJEMPLO PREPARATIVO 1300-K:



Se preparó el compuesto anterior de acuerdo con el procedimiento señalado en el Ejemplo Preparativo 1200-K utilizando el derivado tiometilo del Ejemplo Preparativo 1000 (66 mg, 0,27 mmoles) y (*S*)-(-)-1-(Boc-amino)pirrolidina (65 mg, 0,35 mmoles) para proporcionar 83 mg (77% de rendimiento) de un sólido amarillo. LC-EM: 395.1 [M+H], pureza 99%.

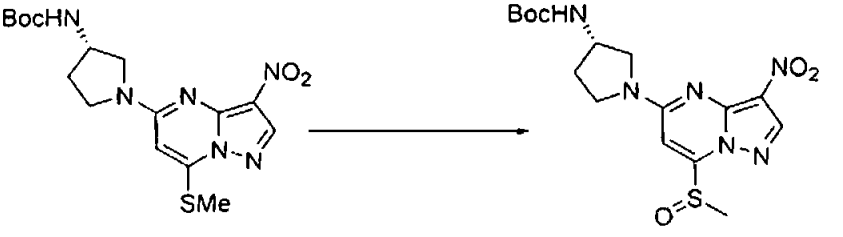
EJEMPLO PREPARATIVO 1400-K:



Se preparó el compuesto del título de acuerdo con el procedimiento señalado en el Ejemplo preparativo 1200-K utilizando el derivado tiometilo (0,30 g,

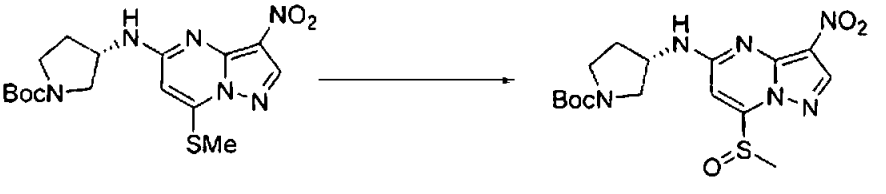
1 mmoles) del Ejemplo Preparativo 1100-K y (*S*)-(-)-1-(Boc-amino)pirrolidina (0,24 g, 1,3 mmoles) para proporcionar 160 mg (35% de rendimiento) de un sólido de color amarillo. LC-EM: 454.1 [M+H], pureza 60%.

EJEMPLO PREPARATIVO 1500-K:



A una solución del aducto de tiometilo (0,17 g, 0,42 mmoles) del Ejemplo Preparativo 1200-K en CH_2Cl_2 (2 mL) a 0°C se agregó MCPBA (0,11 g, 0,63 mmoles) en una porción. La mezcla se agitó durante 2 horas a 0°C y 1 hora a temperatura ambiente después de lo cual se agregó una porción adicional de MCPBA (54 mg, 0,32 mmoles). La mezcla se agitó durante 2 horas a temperatura ambiente después de lo cual se agregaron CH_2Cl_2 (3 mL) y $NaHCO_3$ (3 mL) acuoso saturado. Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (2 x 5 mL). Las capas orgánicas se combinaron y se lavaron con salmuera (1 x 3mL). La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida para proporcionar 0,17 (98% de rendimiento crudo) de un sólido de color amarillo. Este material se usó directamente sin purificación adicional. LC-EM: 411.1 [M+H], pureza 85%.

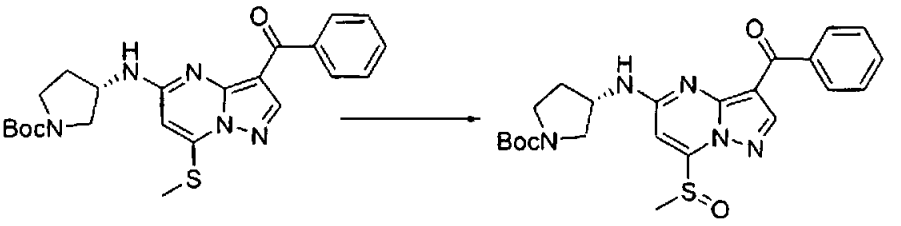
EJEMPLO PREPARATIVO 1600-K:



El compuesto del título se preparó de acuerdo con el procedimiento señalado en el Ejemplo Preparativo 1500-K utilizando el derivado tiometilo (82 mg, 0,21 mmoles) del Ejemplo Preparativo 1300-K para proporcionar 84 mg (98% de rendimiento) de un sólido amarillo. Este material se usó directamente sin purificación adicional. LC-EM: 411.1 [M+H], pureza 89%.

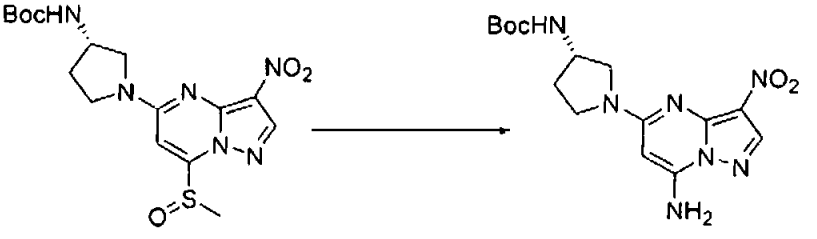
2801

EJEMPLO PREPARATIVO 1700:



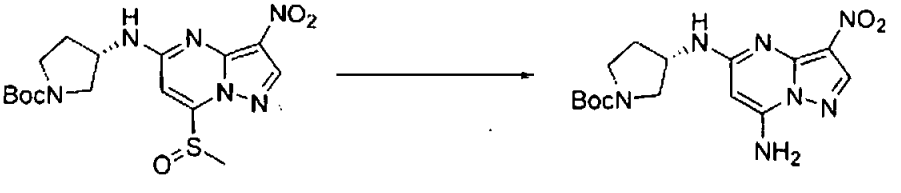
El compuesto del título se preparó de acuerdo con el procedimiento señalado en el Ejemplo preparativo 1500-K utilizando el derivado tiometilo (0,15 g, 0,33 mmoles) del Ejemplo preparativo 1400-K para proporcionar 152 mg (98% de rendimiento) de un sólido amarillo. Este material se usó directamente sin purificación adicional. LC-EM: 470.1 [M+H], pureza 40%.

EJEMPLO PREPARATIVO 1800-K:



A un tubo bajo presión provisto de una barra agitadora se agregó sulfóxido (0,15 g, 0,36 mmoles) del Ejemplo Preparativo 1500-K seguido de NH_3 eM en IPA (4 mL) y NH_4OH concentrado (1 mL). El tubo se tapó y se calentó a 85°C y se agitó durante 14 horas. La mezcla se enfrió a temperatura ambiente y se concentró bajo presión reducida y se colocó bajo alto vacío para eliminar los residuos volátiles. El producto crudo se purificó en placas de cromatografía de capa delgada preparativa (4 x 1000 μM) usando una mezclad de 20:1 de CH_2Cl_2/MeOH como eluyente para proporcionar 105 mg (80% de rendimiento) de un sólido de color amarillo anaranjado. LC-EM: 364.2 [M+H], pureza 99%.

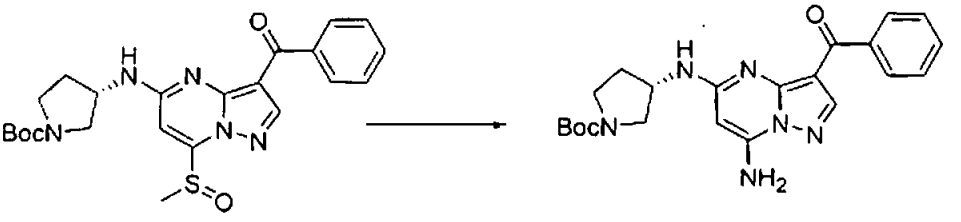
EJEMPLO PREPARATIVO 1900-K:



Se preparó el compuesto del título de acuerdo con el procedimiento señalado en el Ejemplo Preparativo 1800-K utilizando el derivado tiometilo (60

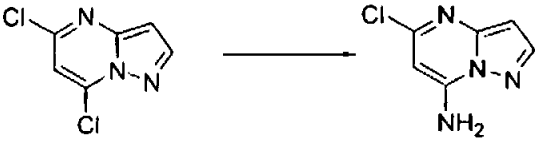
mg, 0,15 mmoles) del Ejemplo Preparativo 1600-K para proporcionar 21 mg (39% de rendimiento) de un sólido blancuzco. LC-EM: 364.1 [M+H], pureza 90%.

EJEMPLO PREPARATIVO 2000-K:



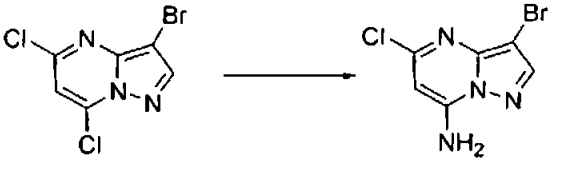
Se preparó el compuesto del título de acuerdo con el procedimiento señalado en el Ejemplo Preparativo 1800-K utilizando el derivado tiometilo (140 mg, 0,30 mmoles) del Ejemplo Preparativo 1700-K para proporcionar 30 mg (24% de rendimiento) de un sólido cristalino amarillo. LC-EM: 423.1 [M+H], pureza 93%.

EJEMPLO PREPARATIVO 2100-K:



A un tubo bajo presión cargado con dicloruro (5 g, 26,7 mmoles) y una barra agitadora se agregó NH_4OH concentrado (110 mL). El tubo se selló y se calentó a 70°C. La mezcla se agitó durante 5 horas, se enfrió a temperatura ambiente, y se concentró hasta sequedad bajo presión reducida. El sólido resultante se suspendió en H_2O (70 mL), se filtró, y el sólido se lavó con Et_2O (100 mL). El material crudo se secó bajo presión reducida para proporcionar 4,2 g (93% de rendimiento) de un sólido amarillo que se usó sin purificación. LC-EM: 169.0 [M+H], pureza 99%.

EJEMPLO PREPARATIVO 2200-K:



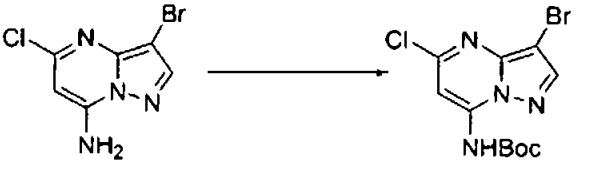
Se preparó el compuesto del título de acuerdo con el procedimiento señalado en el Ejemplo Preparativo 2100-K excepto que se utilizó el derivado 3-bromo (2,0 g, 7,5 mmoles) para proporcionar 1,7 g (92% de rendimiento) de un sólido blanco. P.f. >215 °C; LC-EM: 249.0 [M+H], pureza 99%.

EJEMPLO PREPARATIVO 2300-K:



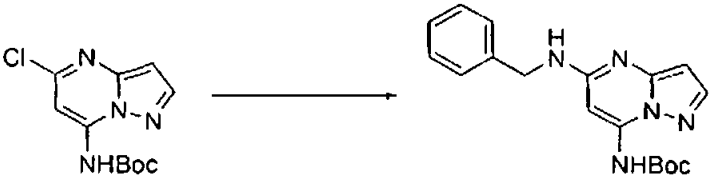
A una solución del aducto 7-amino (4,2 g, 24,8 mmoles) del Ejemplo Preparativo 2100-K wn CH_2Cl_2 (50 mL) a temperatura ambiente se agregó Boc_2O (5,9 g, 27,3 mmoles) y DMAP (3,3 g, 27,3 mmoles). La solución resultante se agitó durante 12 horas a temperatura ambiente y se diluyó con CH_2Cl_2 (50 mL) y $NaHCO_3$ acuoso saturado (25 mL). Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (2 x 30 mL). Las capas orgánicas combinadas se lavaron con salmuera (1 x 30 mL), se secaron (Na_2SO_4), se filtraron y se concentraron bajo presión reducida. El producto crudo se purificó por 40M Flash Elute usando un gradiente (1L de CH_2Cl_2 a 2,5L de 1% MeOH (7M NH_3):CH_2Cl_2 para proporcionar 6,3 g (95% de rendimiento) de un sólido blanco. LC-EM: 269.0 [M+H], pureza 99%.

EJEMPLO PREPARATIVO 2400-K:



Se preparó el compuesto del título de acuerdo con el procedimiento señalado en el in Ejemplo Preparativo 2300-K excepto que se utilizó el derivado 3-bromo (2,0 g, 8,1 mmoles) del Ejemplo preparativo 2200-K para proporcionar 2,5 g (89% de rendimiento) de un sólido blanco; LC-EM: 349.1 [M+H], pureza 95%.

EJEMPLO PREPARATIVO 2500-K:



A una solución del derivado Boc (0,10 g, 0,37 mmoles) del Ejemplo Preparativo 2300-K en dioxano/DIPEA (3 ml/0,5 mL) a temperatura ambiente se agregó bencilamina (61 µL ,0,56 mmoles) por goteo. La mezcla se agitó a reflujo durante 12 horas, se enfrió a temperatura ambiente, y se concentró bajo presión

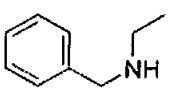
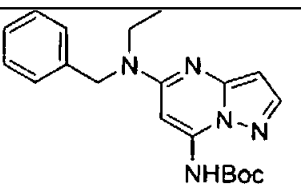
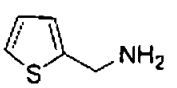
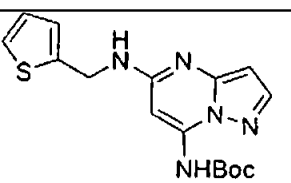
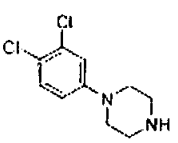
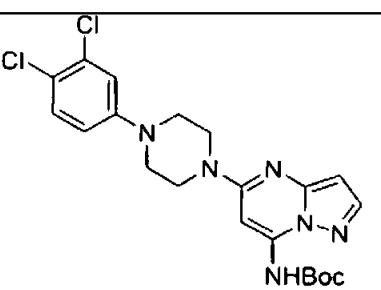
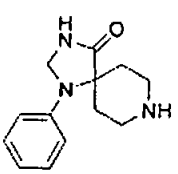
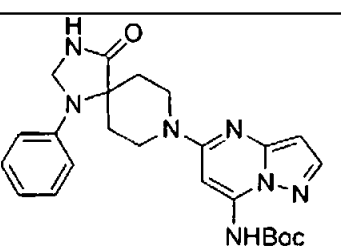
2601

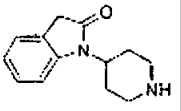
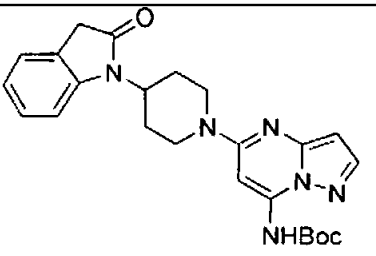
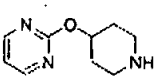
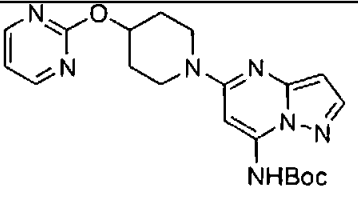
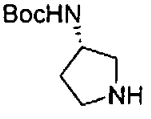
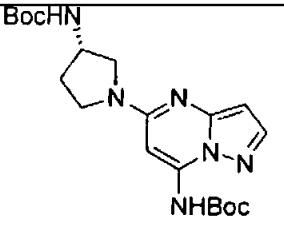
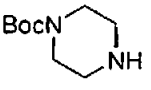
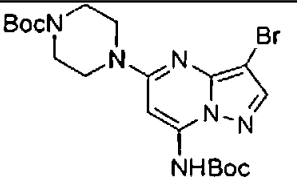
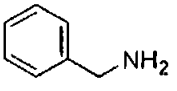
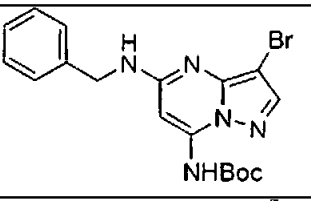
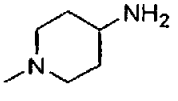
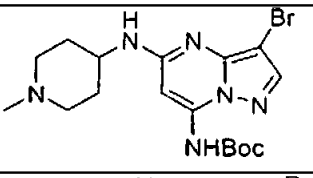
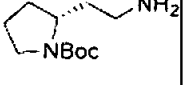
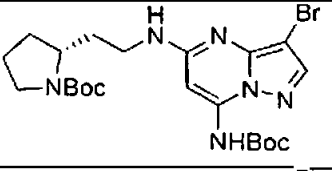
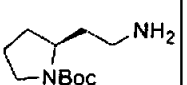
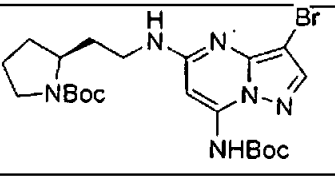
reducida. El producto crudo se purificó por cromatografía de capa delgada preparativa (placas 4 x 1000 μM) usando una mezcla de 30:1 de CH_2Cl_2/MeOH como eluyente para proporcionar 65 mg (52% de rendimiento) de un sólido amarillo. LC-EM: 340.1 [M+H], pureza 99%.

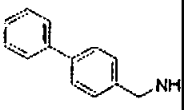
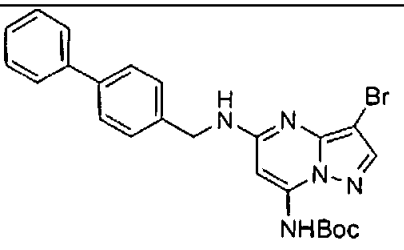
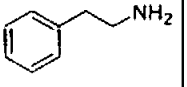
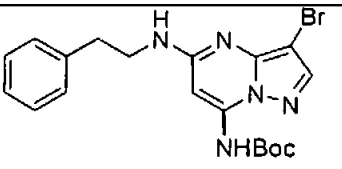
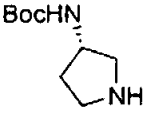
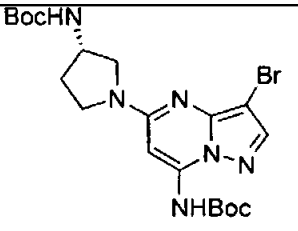
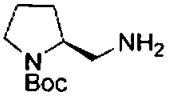
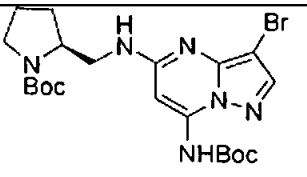
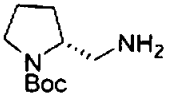
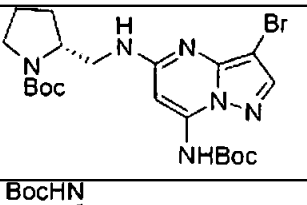
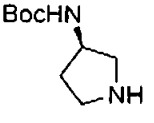
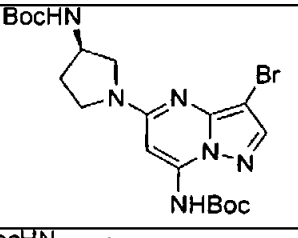
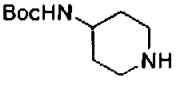
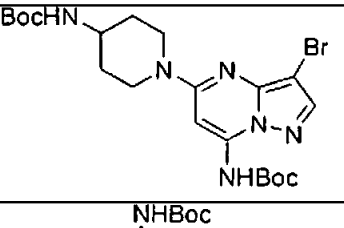
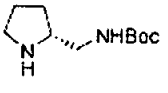
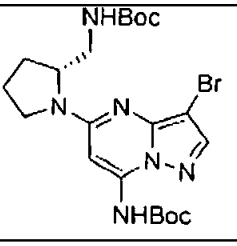
EJEMPLOS PREPARATIVOS 2501-K -2525-K:

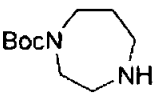
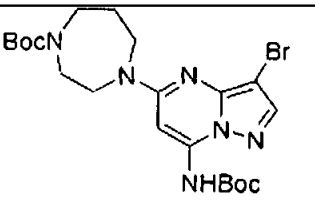
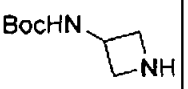
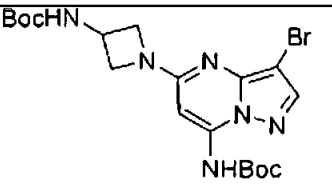
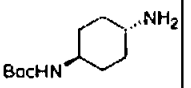
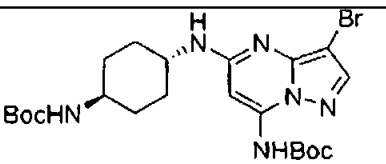
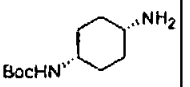
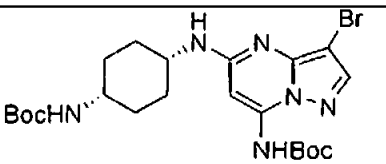
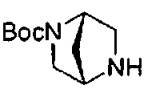
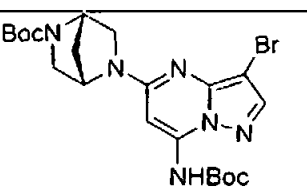
Siguiendo el procedimiento que se indica en el Ejemplo Preparativo 2500-K pero sustituyendo las aminas comercialmente obtenibles, se obtuvieron los compuestos de la Columna 3 de la Tabla 2500-K.

TABLA 2500-K

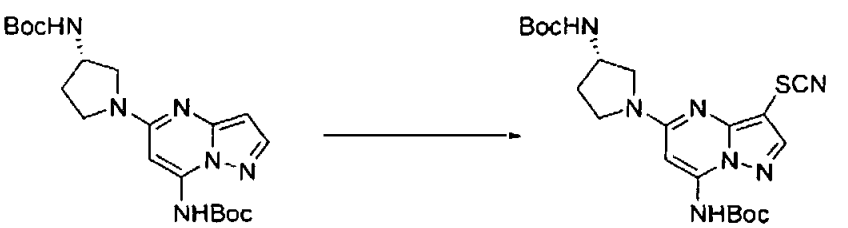
Ej. Prep.	**Columna 2**	**Columna 3**	1. Rendimiento (%) 2. LC-EM
2501-K			1. 12 2. 368.1
2502-K			1. 30 2. 346.1
2503-K			1. 69 2. 463.1
2504-K			1. 98 2. 464.1

2505-K			1. 46 2. 449.1
2506-K			1. 72 2. 412.1
2507-K			1. 94 2. 419.2
2508-K			1. 90 2. 499.1
2509-K			1. 47 2. 420.1
2510-K			1. 57 2. 427.1
2511-K			1. 85 2. 525,1
2512-K			1. 80 2. 525,1

2513-K			1. 53 2. 494,1
2514-K			1. 49 2. 434,1
2515-K			1. 95 2. 499,1
2516-K			1. 54 2. 513,1
2517-K			1. 84 2. 513,1
2618-K			1. 79 2. 499,1
2519-K			1. 78 2. 513,1
2520-K			1. 82 2. 513,1

2521-K			1. 92 2. 513,1
2522-K			1. 12 2. 485,3
2523-K			1. 28 2. 525,1
2524-K			1. 30 2. 525,1
2525-K			1. 89 2. 511,3

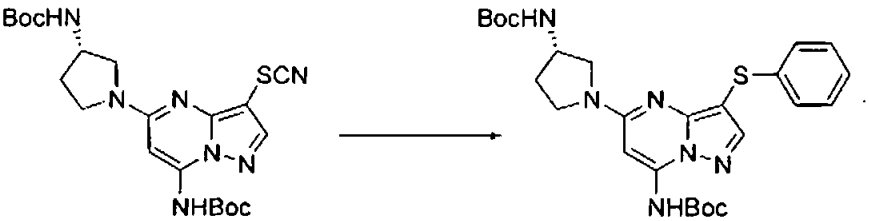
EJEMPLO PREPARATIVO 2600-K:



A una solución del derivado Boc (0,53 g, 1,27 mmoles) del Ejemplo Preparativo 2507-K en MeOH (4 mL) a 0°C se agregó KSCN (0,15 g, 1,52 mmoles) seguido de Br_2 (75 µL, 1,52 mmoles). La mezcla se dejó calentar a temperatura ambiente, se agitó durante 12 horas, y se concentró bajo presión reducida. El residuo crudo se suspendió en EtOAc (7 mL) y $NaHCO_3$ acuoso saturado (2 mL) y las capas se separaron. La capa acuosa se extrajo con EtOAc (2 x 7 mL) y las capas orgánicas se combinaron. La capa orgánica se lavó con

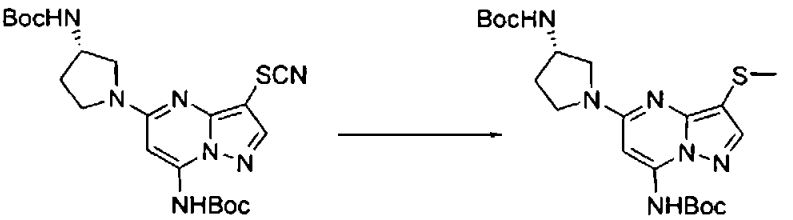
salmuera (1 x 5 mL), se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía en columna usando una mezcla de 20:1 de CH_2Cl_2/MeOH como eluyente para proporcionar 0,37g (65% de rendimiento) como un sólido de color amarillo claro. LCMS: 476.3 {M+H} 99% pureza.

EJEMPLO PREPARATIVO 2700-K:



A una solución de tiocianato (100 mg, 0,21 mmoles) del Ejemplo Preparativo 2600-K en THF (2 mL) a 0°C se agregó $Pd(PPh_3)_4$ (24 mg, 0,021 mmoles) seguido de adición por goteo de PhMgBr (1,0 M en THF, 1,26 mL). La mezcla se agitó durante 12 horas y se trató con NH_4Cl acuoso saturado (2 mL) y CH_2Cl_2 (5 mL). Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (2 x 5 mL). Las capas orgánicas se combinaron, se lavaron con salmuera (1 x 3 mL), se secaron (Na_2SO_4), se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por cromatografía de capa delgada preparativa (placas 4 x 1000 μM) usando una mezcla de 3:1 de hexanos/EtOAc como eluyente para proporcionar 66 mg (60% de rendimiento) de un semisólido amarillo. LC-EM: 527.1 [M+H], pureza 99%.

EJEMPLO PREPARATIVO 2800-K:

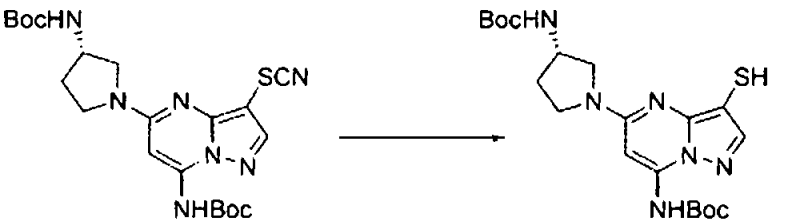


A una solución de tiocianato (100 mg, 0,21 mmoles) del Ejemplo Preparativo 2600-K en MeOH (1,5 mL) a temperatura ambiente se agregó PPh_3 (55 mg, 0,21 mmoles) en una sola porción. La mezcla se calentó a reflujo, se agito durante 12 horas, se enfrió y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía de capa delgada preparativa (placas de 4 x

1691

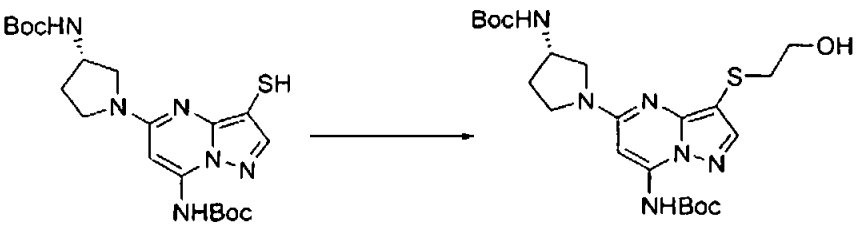
1000 μM) usando una mezcla de 3:1 de hexanos/EtOAc como eluyente para proporcionar 66 mg (68% de rendimiento) de un sólido blanco. LC-EM: 465,3 [M+H], pureza 99%.

EJEMPLO PREPARATIVO 2900-K:



A una solución de tiocianato (0,15 g, 0,32 mmoles) del Ejemplo Preparativo 2600-K en EtOH (2,5 mL) a temperatura ambiente, se agregó una solución 0,1 M de KH_2PO_4 (0,1 mL) seguido de DTT (0,19 g, 1,26 mmoles). La mezcla resultante se agitó durante 12 hs. a temperatura ambiente y se concentró bajo presión reducida. El semisólido resultante se disolvió en CH_2Cl_2 (5 mL) y se lavó consecutivamente con H_2O (3 x 2 mL) y salmuera (3 x 2 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se concentró bajo presión reducida para proporcionar 0,13 g (90% de rendimiento crudo) de un semisólido de color amarillo claro. Este material se recogió en crudo sin purificación.

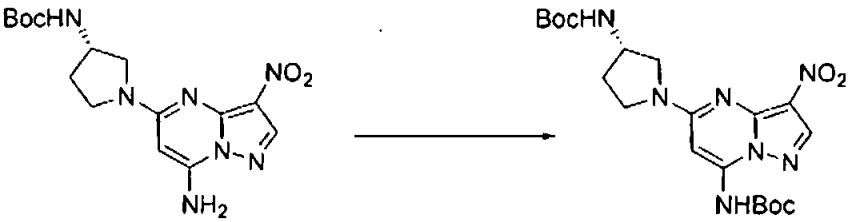
EJEMPLO PREPARATIVO 3000-K:



A una solución del derivado sulfhidrilo crudo (80 mg, 0,18 mmoles) del Ejemplo Preparativo 2900-K en DMF (1,5 mL) a 0°C, se agregó K_2CO_3 (73 mg, 0,53 mmoles) seguido de bromoetanol (37 μL, 0,53 mmoles). La mezcla resultante se agitó durante 72 hs. a temperatura ambiente después de la cual la mezcla se diluyó con EtOAc (5 mL) y agua (2 mL). Las capas se separaron, y la capa orgánica se lavó con H_2O (3 x 2 mL) y salmuera (3 x 2 mL). La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida para proporcionar

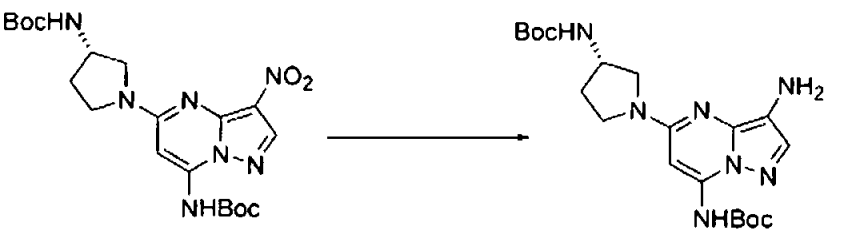
un semisólido amarillo. El producto crudo se purificó por cromatografía de capa delgada preparativa (placas de 4 x 1000 μM) usando una mezcla de 1:1 de hexanos/EtOAc como eluyente para proporcionar 37 mg (rendimiento 41%) de un semisólido de color castaño claro. LC-EM: 495,1 [M+H], pureza 99%.

EJEMPLO PREPARATIVO 3100-K:



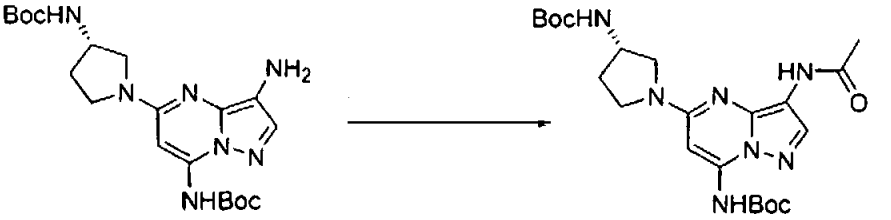
Se preparó el compuesto del título de acuerdo con el procedimiento señalado en el Ejemplo Preparativo 2300-K excepto que se utilizó el derivado 3-nitro (0,20 g, 0,55 mmoles) del Ejemplo Preparativo 1800-K para proporcionar 0,25 g (rendimiento 97%) de un semisólido amarillo. LC-EM: 464,3 [M+H], pureza 99%.

EJEMPLO PREPARATIVO 3200-K:



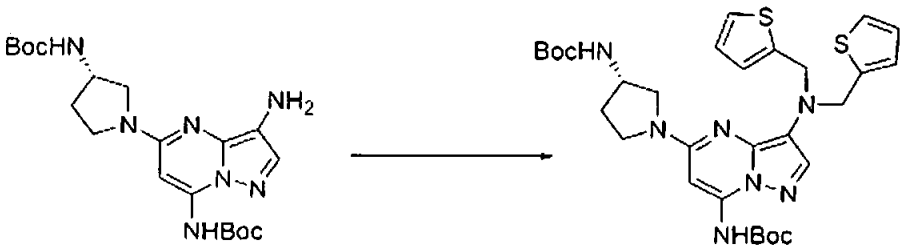
A una solución del aducto 3-nitro (70 mg, 0,15 mmoles) del Ejemplo Preparativo 3100-K en MeOH (2 mL) a temperatura ambiente se agregó Pd/C (10%, 25 mg en seco). La mezcla se agitó bajo H_2 (1 atmósfera) durante 12 horas después de lo cual se filtró a través de una almohadilla de Celite. La almohadilla se lavó generosamente con MeOH (2 x 4 mL) y el filtrado se concentró bajo presión reducida para proporcionar 64 mg (98% de rendimiento) de un sólido de color rosado. LC-EM: 434,1 [M+H], pureza 90%.

EJEMPLO PREPARATIVO 3300-K:



A una solución del aducto 3-amino (60 mg, 0,14 mmoles) del Ejemplo Preparativo 3200-K en CH_2Cl_2 (3 mL) a 0°C se agregó Et_3N (29 µL, 0,21 mmoles) seguido de AcCl (12 µL, 0,17 mmoles). La mezcla resultante se agitó a temperatura ambiente durante 12 hs. y luego se diluyó con salmuera (3 mL) y CH_2Cl_2 (3 mL). Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (2 x 3 mL). Las capas orgánicas se combinaron, se secaron (Na_2SO_4), se filtraron y se concentraron bajo presión reducida. El producto crudo se purificó por cromatografía de capa delgada preparativa (placas de 2 x 1000 µM) usando una mezcla de 20:1 de CH_2Cl_2/MeOH como eluyente para proporcionar 65 mg (68% de rendimiento) de un semisólido rosado. LC-EM: 476,1 [M+H], pureza 99%.

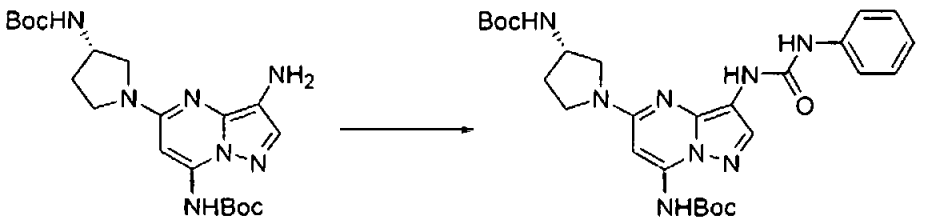
EJEMPLO PREPARATIVO 3400-K:



A una solución del aducto 3-amino (69 mg, 0,16 mmoles) del Ejemplo Preparativo 3200-K en CH_2Cl_2 (1 mL)/AcOH (0,1 mL) a 0°C se agregó 2-tiofencarboxaldehido (18 µL, 0,19 mmoles) seguido de $NaB(OAc)_3H$ (41 mg, 0,19 mmoles). La mezcla resultante se agitó a temperatura ambiente durante 12 horas y se diluyó con NaOH 1N (1 mL) y CH_2Cl_2 (3 mL). Las capas se separaron, y la capa acuosa se extrajo con CH_2Cl_2 (2 x 3 mL). Las capas orgánicas se combinaron, se secaron (Na_2SO_4), se filtraron y se concentraron bajo presión reducida. El producto crudo se purificó por cromatografía de capa delgada preparativo (placas 2 x 1000 µM) usando una mezcla de 30:1 de CH_2Cl_2/MeOH

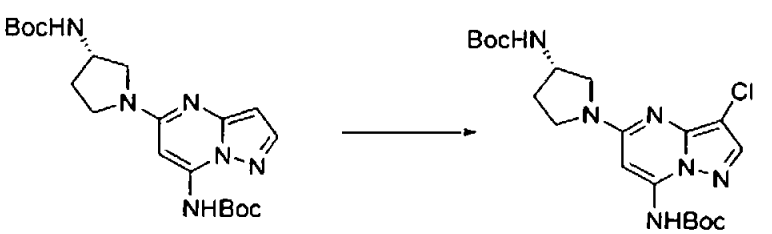
como eluyente para proporcionar 97 mg (rendimiento 96%) de un aceite de color castaño anaranjado. LC-EM: 626,1 [M+H], pureza 96%.

EJEMPLO PREPARATIVO 3500-K:



A una solución del aducto 3-amino (90 mg, 0,21 mmoles) del Ejemplo Preparativo 3200-K en CH_2Cl_2 (1,5 mL) a 0°C se agregó Et_3N (32 µL, 0,31 mmoles) seguido de FNCO (27 µL, 0,25 mmoles). La mezcla resultante se agitó a temperatura ambiente durante 12 hs. y se diluyó con $NaHCO_3$ acuoso saturado (2 mL) y CH_2Cl_2 (5 mL). Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (2 x 3 mL). Las capas orgánicas se combinaron, se lavaron con salmuera (1 x 3 mL), se secaron (Na_2SO_4), se filtraron y se concentraron bajo presión reducida. El producto crudo se purificó por cromatografía de capa delgada preparativa (placas de 2 x 1000 µM) usando una mezcla de 20:1 de CH_2Cl_2/MeOH como eluyente para proporcionar 110 mg (95% de rendimiento) de un sólido blanco. LC-EM: 553,1 [M+H], pureza 99%.

EJEMPLO PREPARATIVO 3600-K:

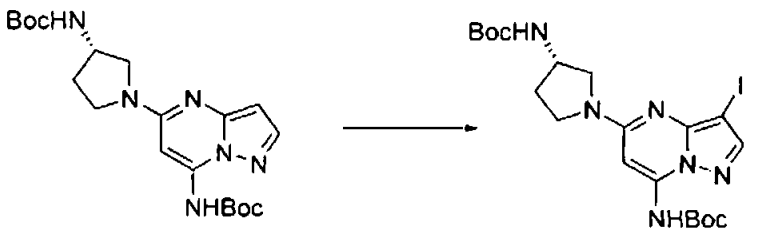


Para una solución del aducto 3-H (0,15 g, 0,36 mmoles) del Ejemplo Preparativo 2507-K en CH_3CN (2 mL) a 0°C se agregó NCS (48 mg, 0,36 mmoles) en una sola porción. La mezcla se agitó durante 3 horas a 0°C después de lo cual la mezcla se concentró bajo presión reducida. El producto crudo se purificó por cromatografía de capa delgada preparativa (placas de 4 x 1000 µM) usando una mezcla de 2:1 de hexanos/EtOAc como eluyente para proporcionar 0,16 g (98%

1011

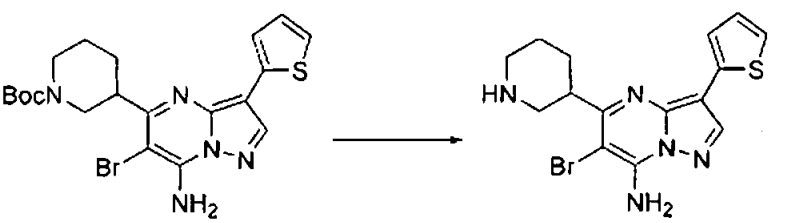
de rendimiento) de un semisólido de color amarillo claro. LC-EM: 453,1 [M+H], pureza 83%.

EJEMPLO PREPARATIVO 3700-K:



Se preparó el compuesto del título de acuerdo con el procedimiento señalado en el Ejemplo Preparativo 3600-K utilizando el derivado 3-H (0,20 g, 0,55 mmoles) del Ejemplo Preparativo 2507-K y NIS (0,13 g, 0,60 mmoles) para proporcionar 0,25 g (97% de rendimiento) de un semisólido amarillo. LC-EM: 464,3 [M+H], pureza 99%.

EJEMPLO 100-K:



Se agregó TFA (0,3 mL) bajo N_2 a una solución agitada del producto del Ejemplo Preparativo 700-K (18 mg, 0,04 mmoles) en CH_2Cl_2 (1,5 mL). La mezcla se agitó durante 1 hora, el solvente se evaporó y el residuo se mezcló con Na_2CO_3 sólido (100 mg) y 10:1 de CH_2Cl_2/MeOH (2,0 mL). La mezcla se agitó bajo N_2 durante 10 minutos, la solución se retiró y se cargó sobre una placa de TLC preparativa de gel de sílice, la cual se reveló con 10:1 CH_2Cl_2/7N NH_3 en MeOH. Se obtuvo un sólido de color amarillo pálido (5 mg, 35%). LC-EM: 380 [M+H]. P.f. = 106-109°C. SCH 773943

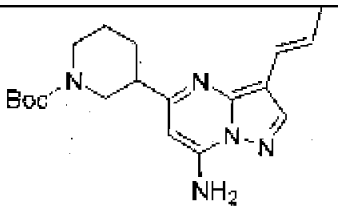
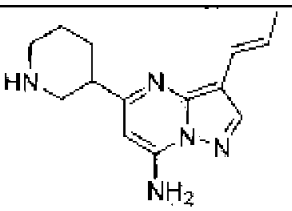
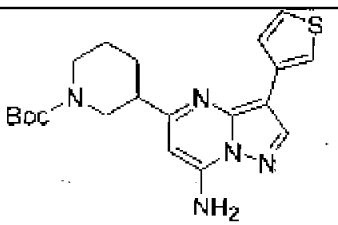
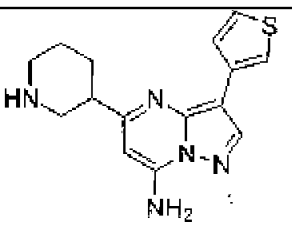
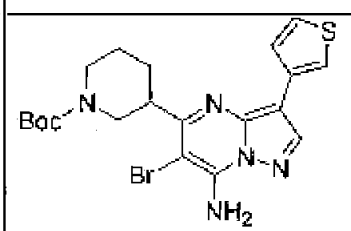
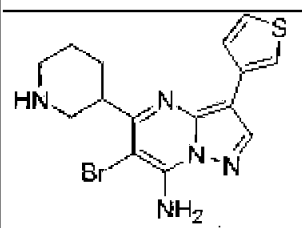
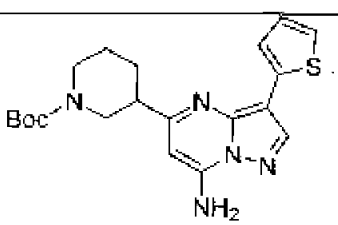
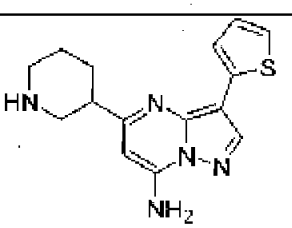
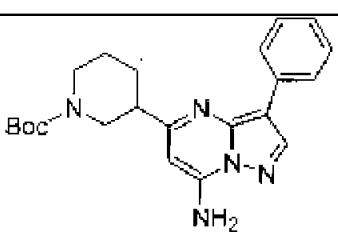
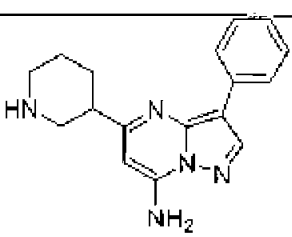
EJEMPLOS 101-K -123-K:

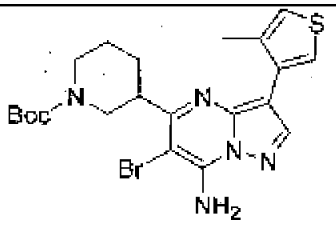
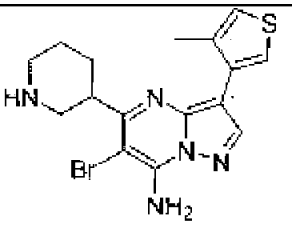
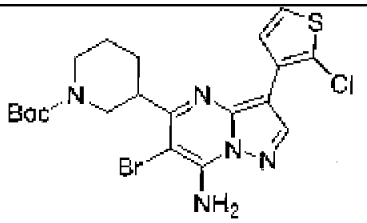
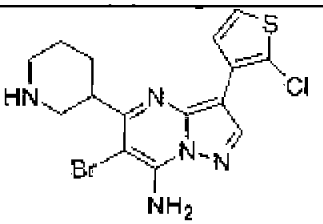
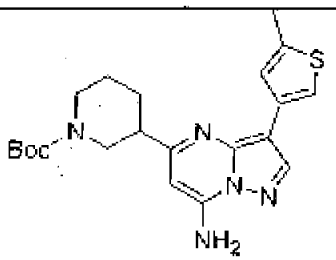
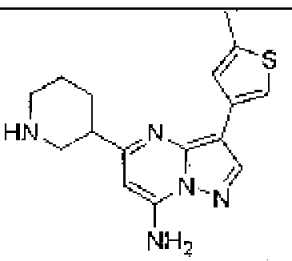
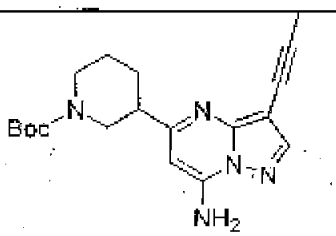
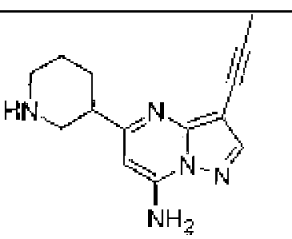
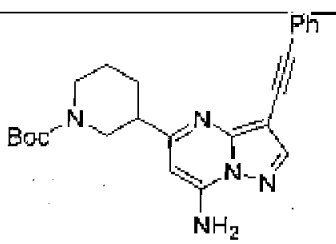
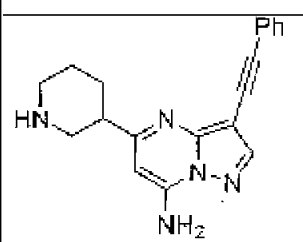
Siguiendo esencialmente el mismo procedimiento que se indicó en el ejemplo 100-K sustituyendo únicamente los compuestos que se muestran en la

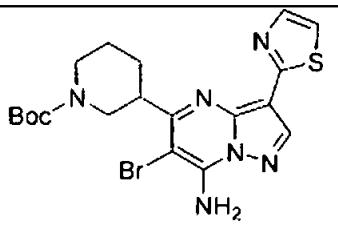
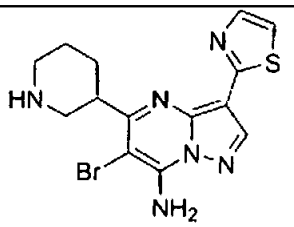
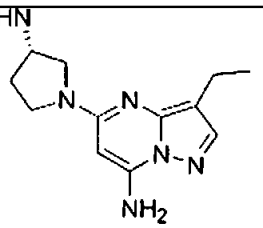
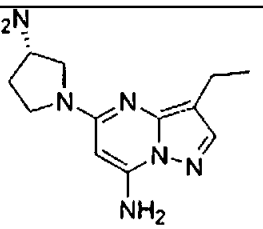
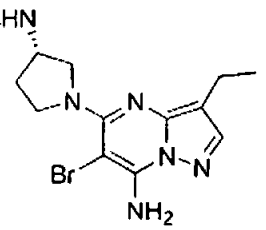
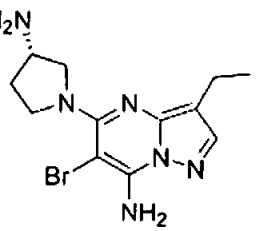
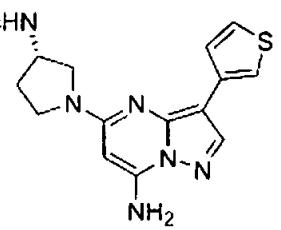
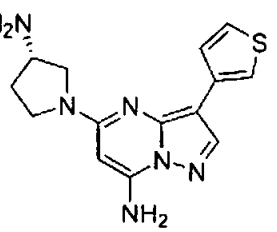
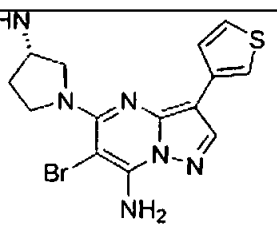
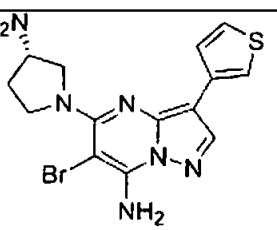
2911

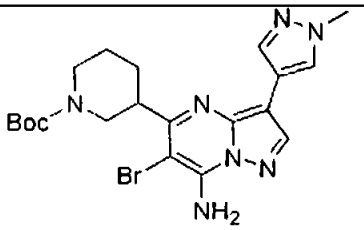
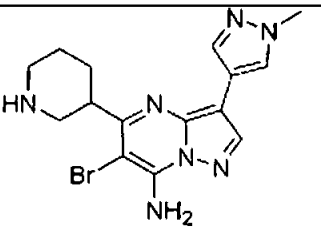
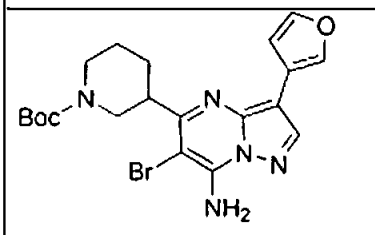
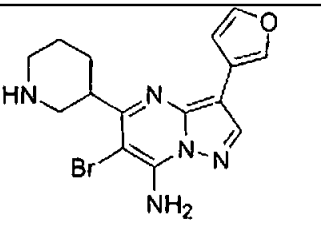
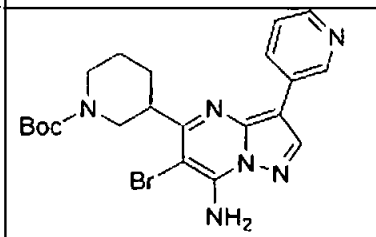
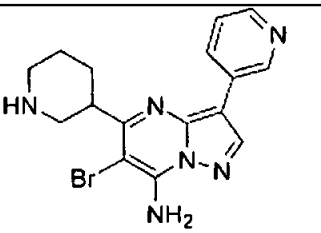
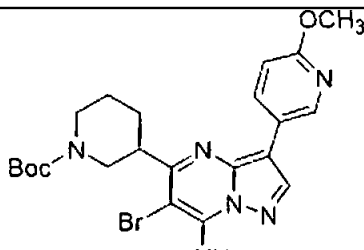
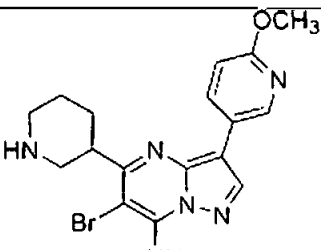
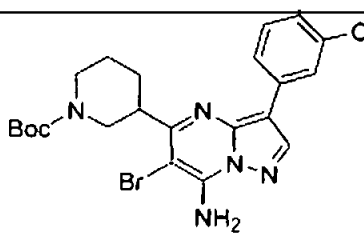
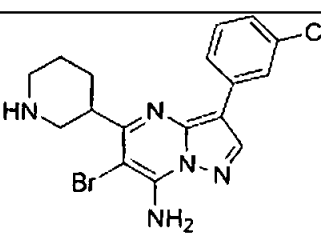
Columna 2 de la Tabla 800-K, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 800-K:

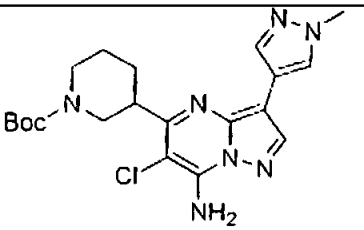
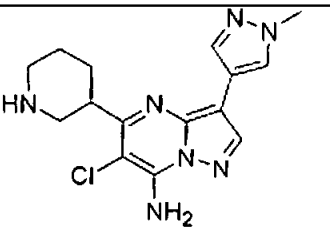
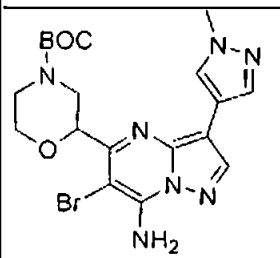
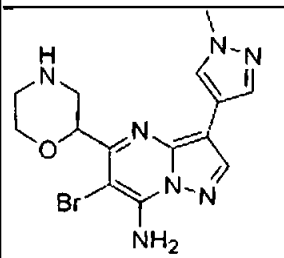
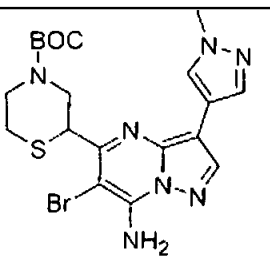
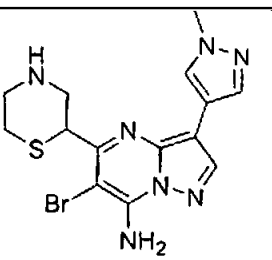
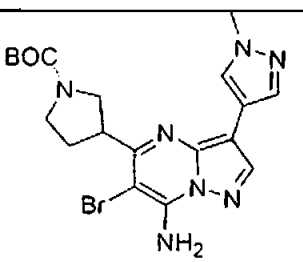
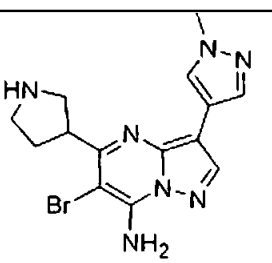
TABLA 800-K

Ej.	Columna 2	Columna 2	Datos
101-K			LCMS: MH^+=258 p.f. = 200-202°C
102-K			LCMS: MH^+=300 p.f. = 104-106°C
103-K			LCMS: MH^+=380
104-K			LCMS: MH^+=300 p.f. = 191-193°C
105-K			

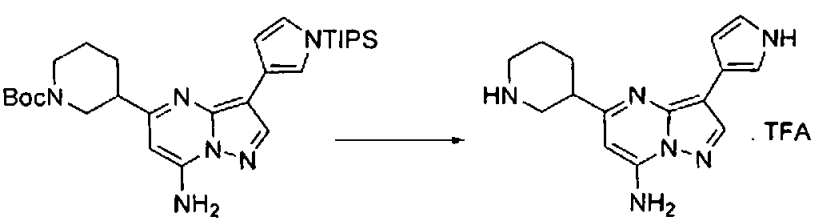
106-K			p.f. = 157-159°C
107-K			LCMS: MH^+=414 p.f. = 96-99°C
108-K			LCMS: $M2H^+$=394
109-K			LCMS: MH^+=256 cera
110-K			LCMS: MH^+=318 cera

111-K			LCMS: M^+=379 p.f. = 247-249°C
112-K			LCMS: MH^+=247 p.f. = 148-150°C
113-K			LCMS: MH^+=327 p.f. = 114-116°C
114-K			LCMS: MH^+=301 p.f. = 227-229°C
115-K			LCMS: MH^+=379 p.f. = 156-158°C

118-K			LCMS: M^+=376 p.f. = 95-98°C
119-K			LCMS: M^+=362 p.f. = 161-163°C
120-K			LCMS: M^+=373 p.f. = 220-222°C
121-K			LCMS: M^+=403 p.f. = 95-98°C
122-K			LCMS: M^+=415 p.f. = 90-93°C

123-K			LCMS: M^+=332 p.f. = 200-203°C
124-K			
125-K			
126-K			

EJEMPLO 200-K:

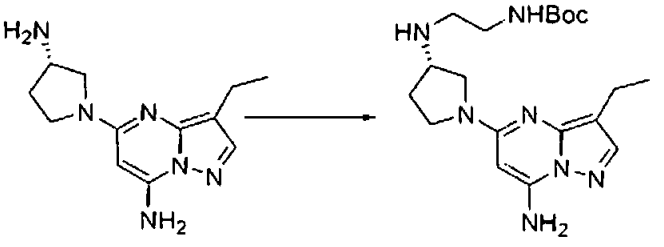


Se agregó TFA (0,5 mL) bajo N_2 a una solución agitada del producto del Ejemplo Preparativo 604-K (30 mg, 0,056 mmoles) en CH_2Cl_2 (1,0 mL). La mezcla se agitó durante 4 horas, el solvente se evaporó, y el residuo se mezclo con NaHCO3 (200 mg) y 4:1 CH_2Cl_2/MeOH (5 mL). La mezcla se agitó bajo N_2 durante 30 minutos, luego se agregó CH_2Cl_2 adicional (5 mL), la mezcla se filtró a

1102

través de Celite, y el solvente se evaporó. Se obtuvo una cera de color castaño pálido (31 g). LC-EM: 284 [M+2H].

EJEMPLO 300-K:

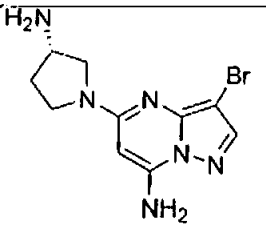
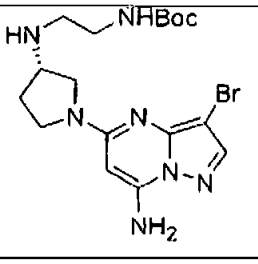


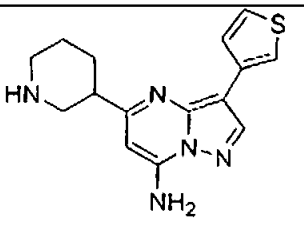
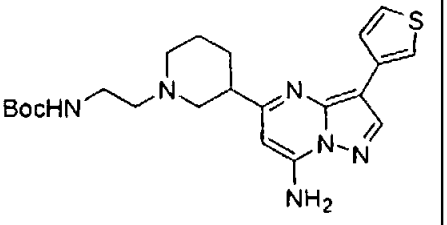
Una mezcla del producto del ejemplo 112-K (70 mg, 0,29 mmoles) y N-(2-oxoetil) carbamato de ter-butilo (45 mg, 0,29 mmoles) en CH_2Cl_2 anhidro (2 mL) se agitó bajo N_2 a 25°C durante 1 hora. Luego se agregó $NaBH(OAc)_3$ (106 mg, 0,50 mmoles), la mezcla se agitó durante 1 hora, y luego se apagó con MeOH (2 mL). Los solventes se evaporaron y el residuo se purificó por cromatografía en columna sobre gel de sílice con 20:1 de CH_2Cl_2/ 7 N NH_3 en MeOH como eluyente. Se obtuvo un sólido blanco (84 mg, 76 %). LC-EM: 390 [M+H]. P.f. = 75-78°C.

EJEMPLO 401-K - 402-K:

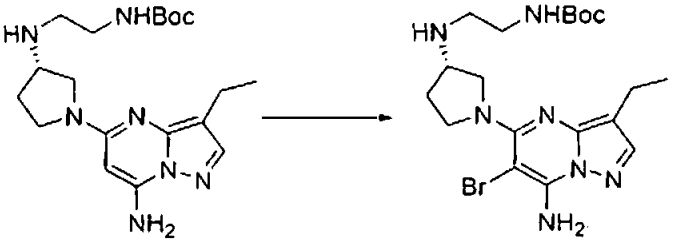
Siguiendo esencialmente el mismo procedimiento indicado en el Ejemplo 300-K sustituyendo únicamente los compuestos que se muestran en la Columna 2 de la Tabla 900-K, se prepararon los compuestos que se muestran en la Columna de la Tabla 900-K.

TABLA 900-K

Ej.	Columna 2	Columna 3	Datos
401-K			sólido blanco LC-EM: 440 [M+].

402-K			cera amarillo pálido . LC-EM: 443 [M+H].

EJEMPLO 500-K:

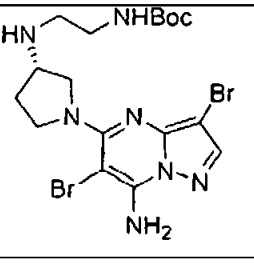


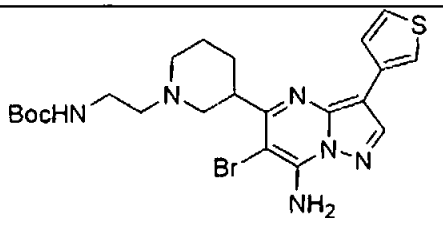
Una solución de NBS (23 mg, 0,13 mmoles) en CH_3CN anhidro (1,0 mL) se agregó bajo N_2 a una solución agitada del producto del Ejemplo 300-K (50 mg, 0,13 mmoles) en CH_3CN anhidro (2,0 mL) y CH_2Cl_2 (1,0 mL). La mezcla se agitó durante 20 hs., los solventes se evaporaron, y el residuo se purificó por cromatografía en columna sobre gel de sílice con 20:1 de CH_2Cl_2/MeOH como eluyente. Se obtuvo un sólido blanco (38 mg, 63 %). LC-EM: 468 [M+]. p.f. = 150-152°C.

EJEMPLO 500-K - 502-K:

Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo 500-K, se prepararon los compuestos que se muestran en la Columna 2 de la Tabla 930-K.

TABLA 930-K

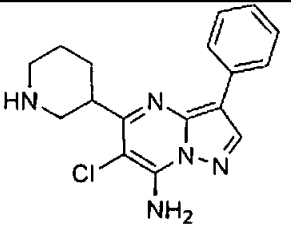
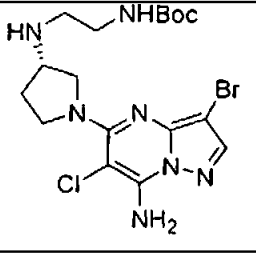
Ej.	Columna 2	Datos
501-K		sólido incoloro LC-EM: 520 [M+H].

502-K		cera amarillo pálido LC-EM: 523 [M+H]. SCH 785438

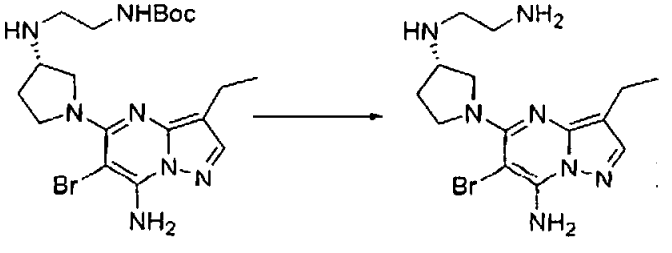
EJEMPLO 701-K - 702-K:

Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo 500-K, sustituyendo únicamente la N-clorosuccinimida, se prepararon los compuestos que se muestran en la Columna 2 de la Tabla 940-K.

TABLA 940-K

Ej.	Columna 2	Datos
701-K		LCMS: M^+= p.f =
702-K		sólido blanco LC-EM: 476 [M+H].

EJEMPLO 800-K:



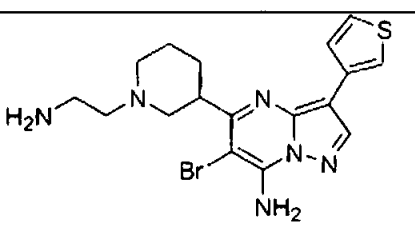
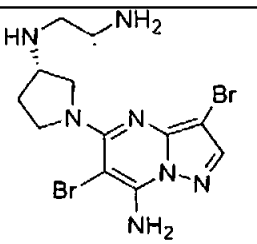
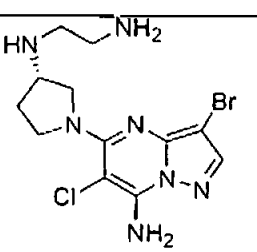
Se agregó TFA (0,4 mL) bajo N_2 a una solución agitada del producto del ejemplo 500-K (30 mg, 0,064 mmoles) en CH_2Cl_2 (2,0 mL). La mezcla se agitó

durante 1 hora, el solvente se evaporó, y el residuo se mezcló con Na_2CO_3 (200 mg) y 10:1 en CH_2Cl_2/MeOH (2,0 mL). La mezcla se agitó bajo N_2 durante 10 minutos, la solución se extrajo y cargó sobre una placa de TLC preparativa de gel de sílice, la cual se reveló con 10:1 CH_2Cl_2/7N NH_3 en MeOH. Se obtuvo un sólido blanco (10 mg, 42%). LC-EM: 368 [M+]. P.f = 132-135°C.

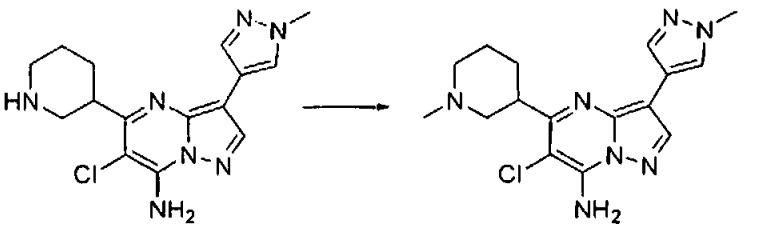
EJEMPLOS 801-K - 803-K:

Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo 800-K, se prepararon los compuestos que se muestran en la Columna 2 de la Tabla 950-K:

TABLA 950-K

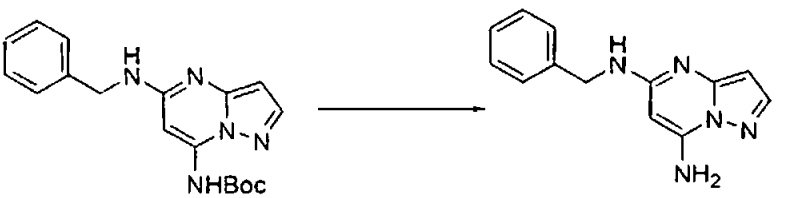
Ej.	Columna 2	Datos
801-K		sólido amarillo pálido LC-EM: 421 [M+H]. P.f = 148-150°C.
802-K		sólido blanco LC-EM: 420 [M+H]. P.f = 92-95°C.
803-K		sólido amarillo pálido LC-EM: 376 [M+H]. P.f = 138-140°C.

EJEMPLO 900-K:



Una solución de 37% de HCHO (0,002 mL) en H_2O (0,02 mL) se agregó bajo N_2 a una solución agitada del producto del Ejemplo Preparativo 823-K (9 mg, 0,027 mmoles) en THF anhidro (1 mL) y MeOH (0,3 mL) y luego la mezcla se agitó bajo N_2 a 25°C durante 5 hs. Luego se agregó $NaBH(OAc)_3$ (8 mg, 0,038 mmoles) y el residuo se purificó por TLC preparativo sobre gel de sílice con 10:1 de CH_2Cl_2/NH_3 7N en MeOH como eluyente. Se obtuvieron 8 mg de sólido blanco, (85 %). LC-EM: 346 [M+]. P.f = 92-95°C.

EJEMPLO PREPARATIVO 3800-K:

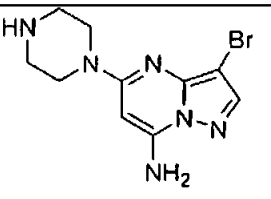
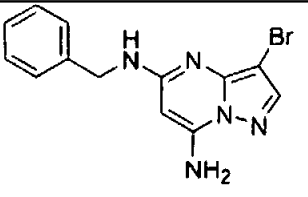
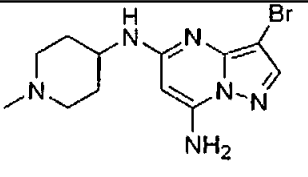
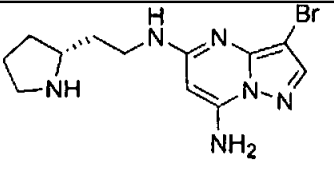
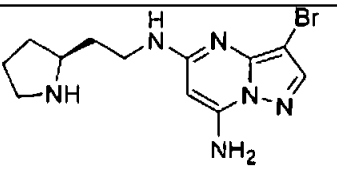


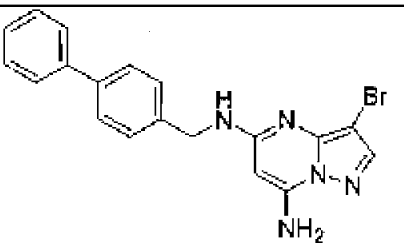
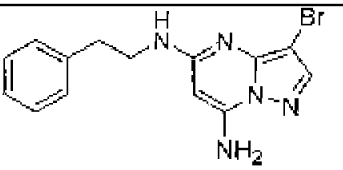
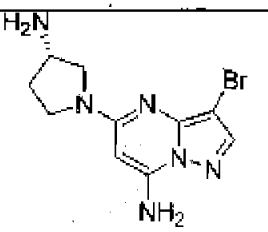
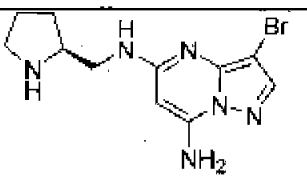
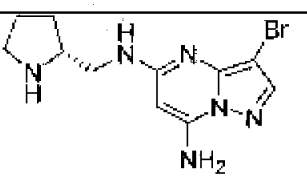
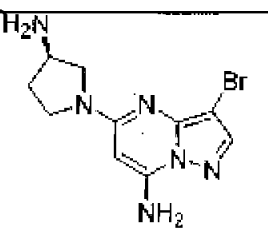
A una mezcla de un aducto 7-amino (65 mg, 0,19 mmoles) del Ejemplo Preparativo 2500-K en CH_2Cl_2 (2 mL) a 0°C se agregó TFA (1 mL) por goteo. La mezcla resultante se agitó por 12 horas a temperatura ambiente y se concentró bajo presión reducida. El material crudo se dividió entre EtOAc (5 mL) y Na_2CO_3 acuoso saturado (2 mL) y las capas se separaron. La capa acuosa se extrajo con EtOAc (2 x 5 mL) y las capas orgánicas se combinaron. La capa orgánica se lavó con salmuera (1 x 3 mL), se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía de capa delgada preparativa (placas de 4 x 1000 μM) usando una mezcla de 20:1 en CH_2Cl_2/MeOH (NH_3 7M) como eluyente para proporcionar 41 mg (rendimiento 89%) en forma de un sólido de color castaño. P.f.: 111-113°C; LC-EM: 240,0 [M+H], pureza 98%.

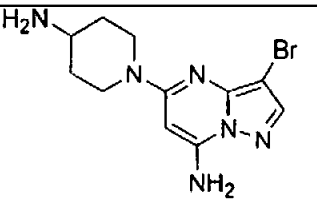
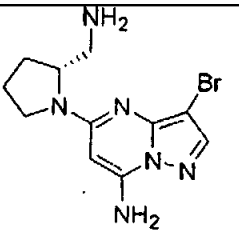
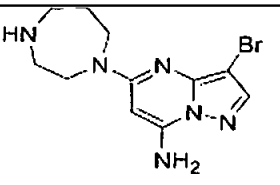
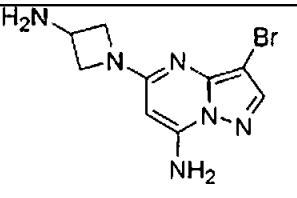
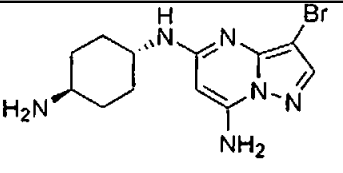
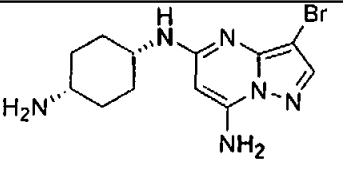
EJEMPLOS 1000-1025-K:

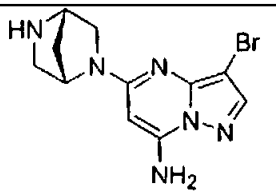
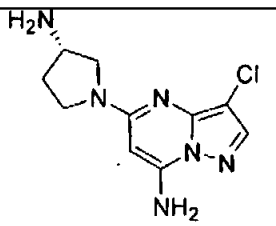
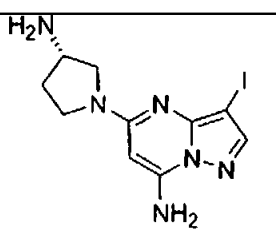
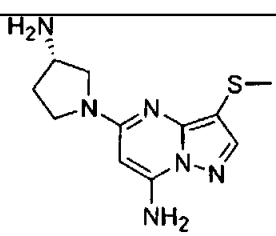
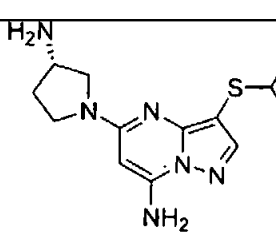
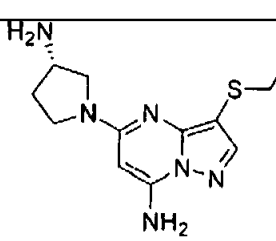
Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo Preparativo 3800-K pero utilizando los derivados Boc apropiados, se prepararon los compuestos de la Columna 2 de la Tabla 1000-K.

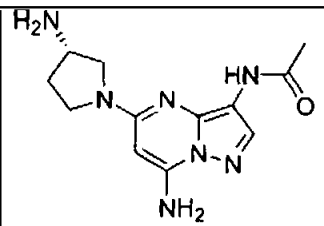
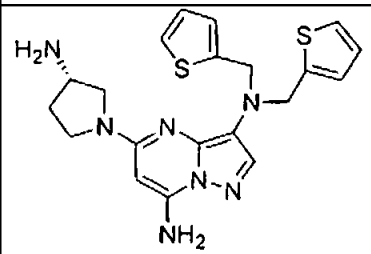
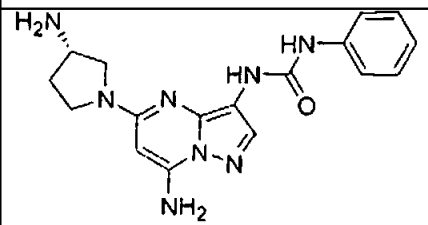
TABLA 1000-K

Ej.	**Columna 2**	1. Rendimiento (%) 2. LC-EM 3. p.f.
1000-K		1. 10 2. 297.1 3. 138-141
1001-K		1. 95 2. 320.1 3. 115-117
1002-K		1. 70 2. 327.1 3. 110-113
1003-K		1. 26 2. 325.1 3. 114-117
1004-K		1. 46 2. 325.1 3. 105-107

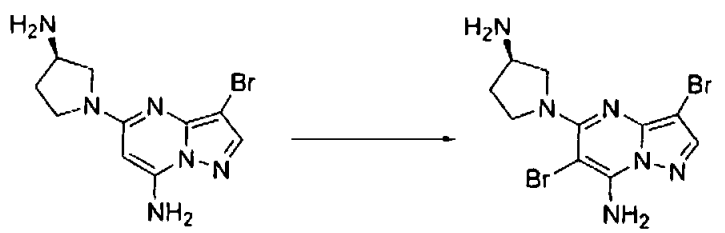
1005-K		1. 81 2. 394.1 3. 166-168
1006-K		1. 90 2. 334.1 3. 43-45
1007-K		1. 45 2. 299.1 3. 115-117
1008-K		1. 73 2. 313.1 3. 131-133
1009-K		1. 62 2. 313.1 3. 130-134
1010-K		1. 88 2. 299.1 3. 114-117

1011-K		1. 67 2. 313.1 3. 169-171
1012-K		1. 36 2. 313.1 3. 90-93
1013-K		1. 89 2. 313.1 3. 154-156
1014-K		1. 30 2. 285.3
1015-K		1. 83 2. 325.1 3. 115-117
1016-K		1. 80 2. 325.1 3. 105-107

1017-K		1. 64 2. 311.1 3. 98-102
1018-K		1. 79 2. 253.1 3. 188-190
1019-K		1. 20 2. 345.2 3. 127-129
1020-K		1. 70 2. 265.1 3. 120-122
1021-K		1. 87 2. 327.1 3. xxx-xxx
1022-K		1. 21 2. 295.1 3. xxx-xxx

1023-K		1. 17 2. 276.1
1024-K		1. 21 2. 295.1 3. xxx-xxx
1025-K		1. 20 2. 353.2 3. >200

EJEMPLO 1100-K:



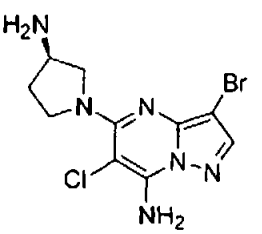
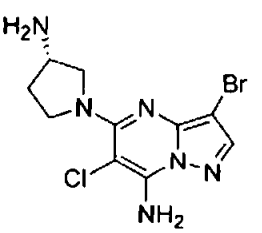
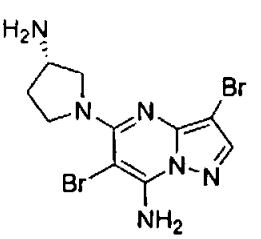
A una solución del aducto 7-amino (20 mg, 0,067 mmoles) del Ejemplo 1010-K en CH_3CN a 0°C se agregó NBS (12 mg, 0,067 mmoles) en una sola porción. La mezcla se agitó durante 2 horas a temperatura ambiente y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía de capa delgada preparativa (placas de 2 x 1000 μM) usando una mezcla de 10:1 de CH_2Cl_2/MeOH(7M NH_3) como eluyente para proporcionar 20 mg (79% de

rendimiento) en forma de un sólido anaranjado claro. P.f.: 159-161°C. LC-EM: 377,1 [M+H], pureza 99%.

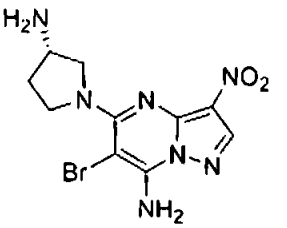
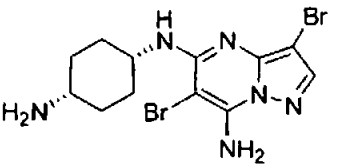
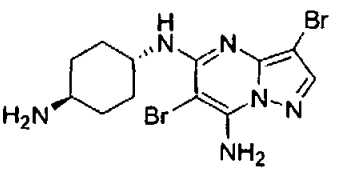
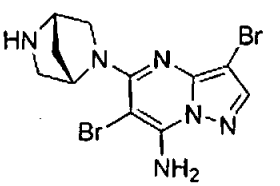
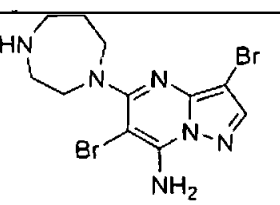
EJEMPLOS 1101-K - 1112-K:

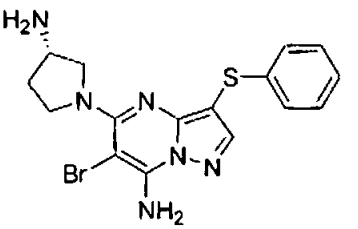
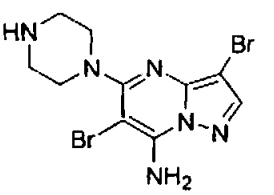
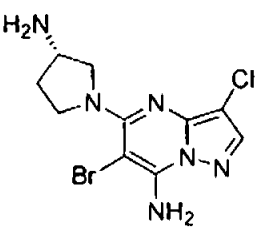
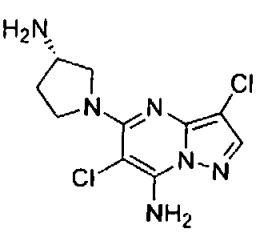
Siguiendo esencialmente el mismo procedimiento que se indicó en el Ejemplo 1100-K y utilizando cualquiera de NBS, NCS, o NIS se preparó los compuestos de la Columna 3 de la Tabla 1100-K.

TABLA 1100-K

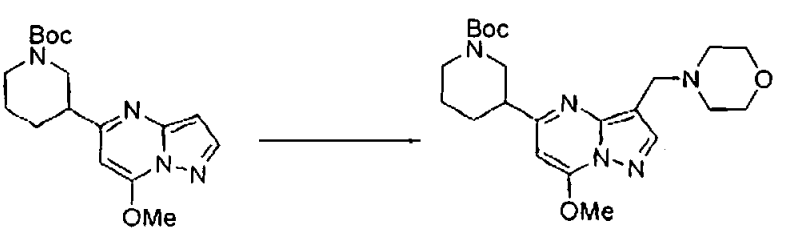
Prep. Ej.	**Columna 2**	**Columna 3**	1. Rendimiento (%) 2. LC-EM 3. p.f. (°C)
1101-K	NCS		1. 41 2. 333.2 3. 123-125
1102-K	NCS		1. 64 2. 333.2 3. 122-125
1103-K	NBS		1. 66 2. 377.2 3. 159-161

8112

1104-K	NBS		1. 38 2. 344.1 3. xxx-xxx
1105-K	NBS		1. 89 2. 403.1 3. 66-68
1106-K	NBS		1. 90 2. 403.1 3. 170-172
1107-K	NBS		1. 53 2. 389.1 3. xxx-xxx
1108-K	NBS		1. 48 2. 391.1 3. 142-144

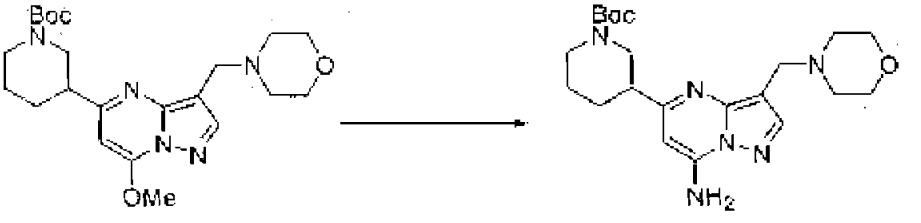
1109-K	NBS		1. 59 2. 407.2 3. 156-158
1110-K	NBS		1. 75 2. 375.1 3. 134-136
1111-K	NBS		1. 63 2. 333.1 3. 153-155
1112-K	NCS		1. 15 2. 287.1 3. >200

EJEMPLO PREPARATIVO 3900-K:



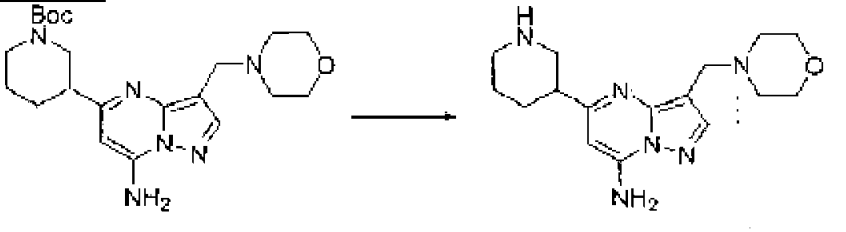
A una solución del aducto 7-metoxi (0,10 g, 0,30 mmoles) del Ejemplo Preparativo 402-K en AcOH a temperatura ambiente se agregó morfolina (29 µL, 0,33 mmoles) seguido de 40% de formaldehido en H_2O (1 mL). La mezcla resultante se agitó a temperatura ambiente durante 12 hs, después de lo cual la mezcla se concentró bajo presión reducida. El semisólido crudo se dividió entre CH_2Cl_2 (5 mL) y $NaHCO_3$ acuoso saturado (3 mL) y las capas se separaron. La capa acuosa se extrajo con CH_2Cl_2 (2 x 5 mL) y las capas orgánicas se combinaron. La capa orgánica se lavó con salmuera (1 x 3 mL), se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida para proporcionar 0,11 g (84% de rendimiento crudo) de un semisólido de color amarillo claro. LC-EM: 432,1 [M+H], pureza 94%.

EJEMPLO PREPARATIVO 4000-K:



A un tubo de presión cargado con una barra agitadora se agregó 7-metoxi (96 mg, 0,22 mmoles) del Ejemplo Preparativo 3900-K seguido de NH_3 2M en IPA (2 mL) y NH_4OH concentrado (2 mL). El tubo se tapó y se calentó a 85°C y se agitó durante 14 horas. La mezcla se enfrió a temperatura ambiente, se concentró bajo presión reducida y se colocó bajo alto vacío para eliminar los residuos volátiles. El producto crudo se purificó por cromatografía de capa delgada preparativa (placas de 4 x 1000 µM) usando una mezcla de 10:1 de CH_2Cl_2/MeOH como eluyente para proporcionar 40 mg (43% de rendimiento) de un semisólido amarillo. LC-EM: 417,1 [M+H], pureza 89%.

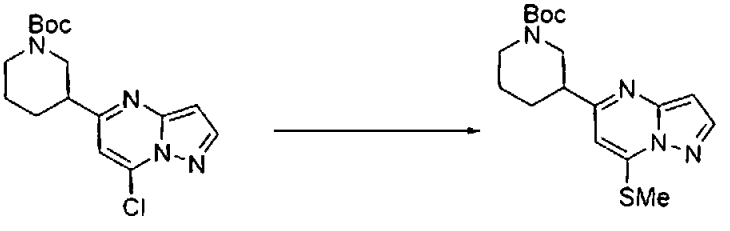
EJEMPLO 1200-K:



217

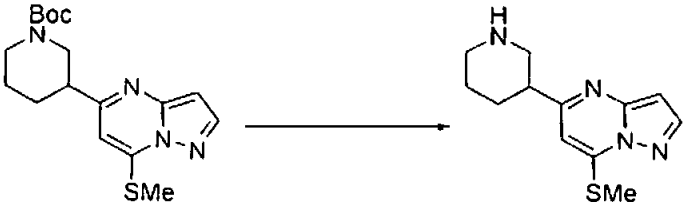
A una mezcla del aducto 7-amino (40 mg, 0,096 mmol) del Ejemplo Preparativo 4000-K se agregó HCl 4N/dioxano (3 mL) por goteo. La mezcla resultante se agitó durante 12 horas a temperatura ambiente y se concentró bajo presión reducida. El material crudo se recogió en CH_2Cl_2 (5 mL) y se concentró bajo presión reducida y este procedimiento se repitió tres veces. El sólido resultante se trituró con Et2O (3 x 3 m) y se concentró bajo presión reducida para proporcionar 26 mg (75% de rendimiento) de un sólido de color amarillo claro. P.f. 190-193°C; LC-EM: 317,1 [M+H], pureza >90%.

EJEMPLO PREPARATIVO 4100-K:



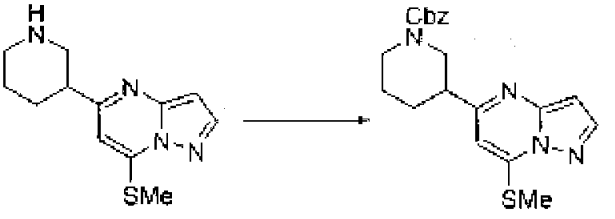
Se preparó el compuesto del título a partir del aducto 7-cloro (2,6 g, 7,7 mmoles) del Ejemplo Preparativo 200-K y NaSMe (0,65 g, 9,3 mmoles) de acuerdo con el procedimiento señalado en el Ejemplo Preparativo 1 para proporcionar 2,6 g (rendimiento 98%) de un sólido de color blanco pálido. LC-EM: 349,1 [M+H], pureza 98%.

EJEMPLO PREPARATIVO 4200-K:



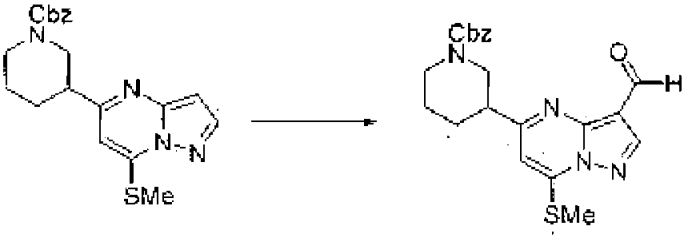
Se preparó el compuesto anterior a partir del aducto 7-tiometilo (1,1 g, 3,1 mmoles) del Ejemplo Preparativo 4100-K de acuerdo con el procedimiento señalado en el Ejemplo 1 para proporcionar 0,70 g (rendimiento 90%) de un semisólido amarillo. LC-EM: 249,1 [M+H], pureza 98%.

EJEMPLO PREPARATIVO 4300-K:



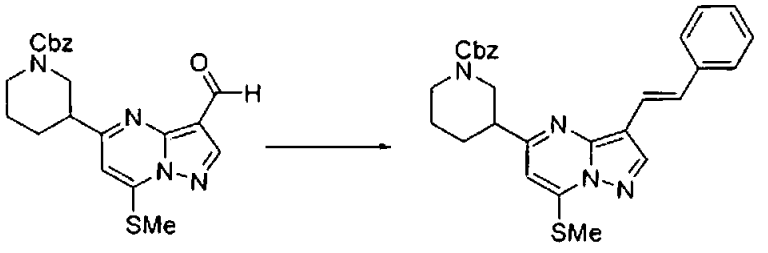
A una solución del aducto tiometilo (1,3 g, 3,13 mmoles) del Ejemplo Preparativo 4200-K en CH_2Cl_2 (20 mL) a 0°C se agregó Et_3N (0,65 mL, 4,7 mmoles) seguido de CbzCl (0,48 mL, 3,4 mmoles). La mezcla resultante se agitó durante 12 horas a temperatura ambiente y la mezcla se diluyó con CH_2Cl_2 (15 mL) y $NaHCO_3$ acuoso saturado (5 mL) y 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 5 mL), se secó (Na_2SO_4), se filtró y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía evaporativa usando CH_2Cl_2 como eluyente para obtener 0,96 g (rendimiento 80%) de un aceite amarillo. LC-EM: 383,1 [M+H], pureza 91%.

EJEMPLO PREPARATIVO 4400-K:



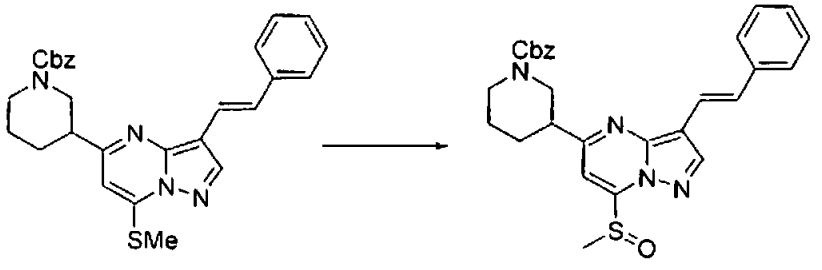
A una solución del aducto 7-tiometilo (0,29 g, 0,75 mmol) del Ejemplo Preparativo 4300-K en DMF (3 ml) a 0°C se agregó $POCl_3$ (0,10 mL, 1,1 mmoles). La mezcla resultante se dejó calentar a temperatura ambiente y se agitó durante 12 horas. La mezcla se enfrió a 0°C y se trató con agua helada (2 ml) y CH_2Cl_2 (5 mL). Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (2 x 5 mL). Las capas orgánicas se combinaron, se lavaron con salmuera (1 x 5 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se concentró bajo presión reducida para proporcionar 0,28 g (rendimiento 91%) de un sólido de color amarillo. LC-EM: 433,2 [M+H], pureza 84%.

EJEMPLO PREPARATIVO 4500-K:



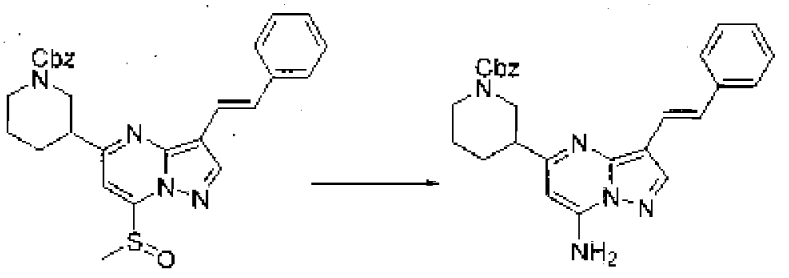
A una mezcla de bromuro de benciltrifenilfosfonio (0,64 g, 1,48 mmoles) y NaH (59 mg, 1,48 mmoles) en THF seco (3 mL) a temperatura ambiente se agregó un aducto de tiometilo (0,21 g, 0,50 mmol) del Ejemplo Preparativo 4400-K. La mezcla se calentó a reflujo durante 12 horas, se enfrió a temperatura ambiente y se diluyó con CH_2Cl_2 (5 mL) y salmuera (2 mL). Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (2 x 5 mL). Las capas orgánicas se combinaron, se lavaron con salmuera (1 x 5 mL). La capa orgánica se secó (Na_2SO_4), se filtró y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía de capa delgada preparativa (placas de 2 x 1000 μM) usando una mezcla de 1:1 de hexanos/EtOAc como eluyente para proporcionar 100 mg (rendimiento 42%) en forma de un sólido de color naranja claro.

EJEMPLO PREPARATIVO 4600-K:



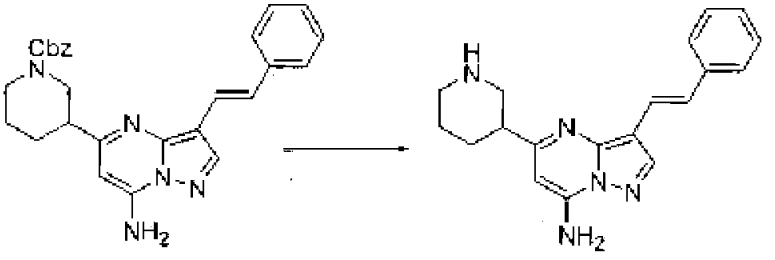
El compuesto del título se preparó a partir del aducto de 7-tiometilo (0,10 g, 0,21 mmol) del Ejemplo Preparativo 4500-K de acuerdo con el procedimiento señalado en el Ejemplo Preparativo 1500-K para proporcionar 0,11 g (rendimiento cuantitativo) de un sólido de color amarillo. LC-EM: 501,3 [M+H], pureza 63%.

EJEMPLO PREPARATIVO 4700-K:



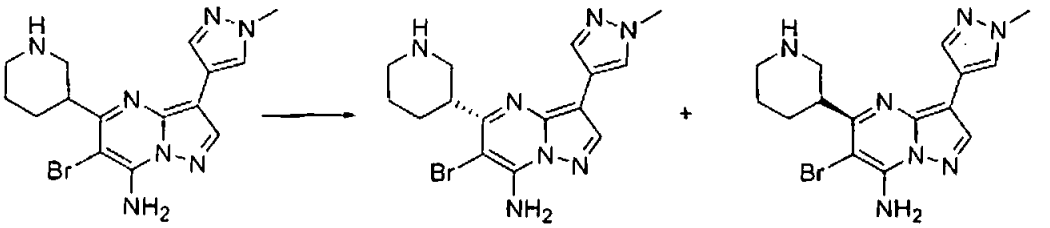
Se preparó el compuesto del título a partir del aducto 7-sulfóxido (0,11 g, 0,21 mmol) del Ejemplo Preparativo 4600-K de acuerdo con el procedimiento señalado en el Ejemplo Preparativo 1800-K para proporcionar 83 mg (rendimiento 40%) de un sólido de color amarillo. LC-EM: 454,1 [M+H], pureza 90%.

EJEMPLO 1300-K:



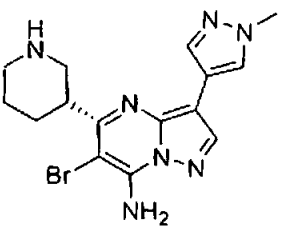
A una solución del aducto 7-amino (38 mg, 0,083 mmol) del Ejemplo Preparativo 4700-K en CH_3CN (3 mL) a 0°C se agregó TMSI (0,12 mL, 0,83 mmol) por goteo. La mezcla se agitó durante 12 horas a temperatura ambiente después de lo cual se agregó NaOH 1N (2 mL). La mezcla se extrajo con EtOAc (5 x 5 mL) y las capas orgánicas se combinaron. La capa orgánica se lavó con salmuera (1 x 3 mL), se secó (Na_2SO_4), se filtró y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía de capa delgada preparativa (placas de 2 x 1000 μM) usando una mezcla de 10:1 de CH_2Cl_2/MeOH(7M NH_3) como eluyente para obtener 15 mg (rendimiento 56%) de un sólido de color amarillo claro. P.f. 144-146°C. LCMS: 319,4 [M+H] 90% pureza.

EJEMPLO 1400-K - 1500-K:

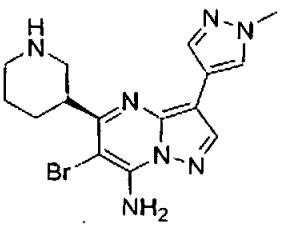


El compuesto preparado en el Ejemplo 118-K se separó en enantiómeros individuales por HPLC semi-preparativa usando una columna ChiralPak OD (régimen de flujo = 9 mL/min) y un gradiente de 85 : 15 de hexanos : isopropanol con 0,2% de dietilamina a una solución de 75 : 25 de hexanos : isopropanol con 0,2% de dietilamina como eluyente.

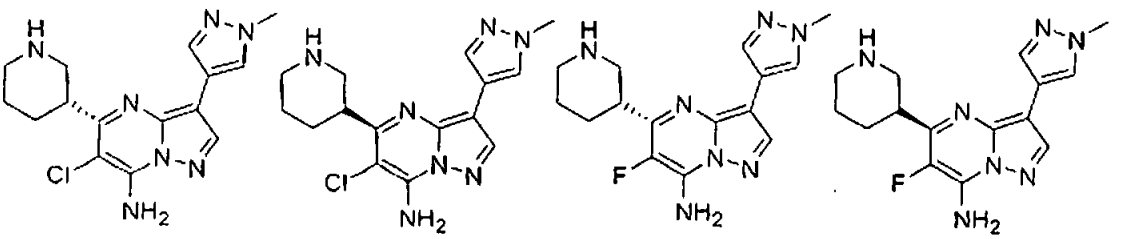
EJEMPLO 1400-K (primer isómero de elución, (R)): LCMS: M^+ = 376.



EJEMPLO 1500-K (segundo isómero de elución, (S)): M^+ = LCMS: 376:



EJEMPLO 1600K-, EJEMPLO 1700-K, EJEMPLO 1800-K Y EJEMPLO 1900-K:
Mediante un procedimiento similar, pueden prepararse también los compuestos siguientes:



1600-K 1700-K 1800-K 1900-K

ENSAYO:

CONSTRUCCIONES DE BACULOVIRUS: Las ciclinas A y E se clonaron en pFASTBAC (Invitrogen) por PCR, con adición de una secuencia GluTAG (EYMPME) en el extremo amino-terminal para permitir la purificación sobre columnas de afinidad anti-GluTAG. Las proteínas expresadas eran de un tamaño de aproximadamente 46kDa (ciclina E) y 50kDa (ciclina A). También se clonó la CDK2 en pFASTBAC por PCR, con adición de un marbete epitopo de hemaglutinina en el extremo carboxi-terminal (YDVPDYAS). La proteína expresada era de un tamaño de aproximadamente 34kDa.

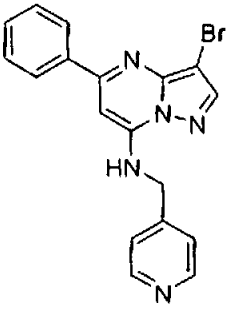
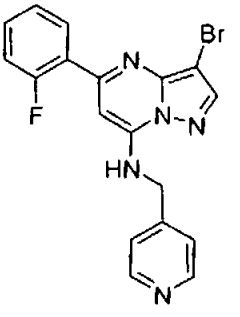
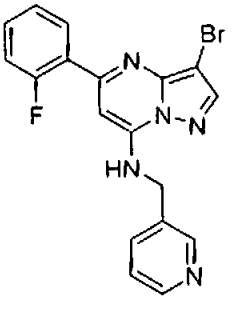
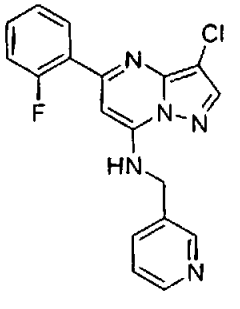
PRODUCCIÓN DE ENZIMA: Las ciclinas A, E que expresan báculovirus recombinantes y CDK2 se infestaron en células SF9 a una multiplicidad de infección (MOI) de 5, durante 48 hrs. Las células se cosecharon por centrifugación a 1000 RPM durante 10 minutos. El granulado que contenía ciclina (E o A) se combinó con un granulado de células que contenían CDK2 y se lisaron en hielo durante 30 minutos en cinco veces el volumen del granulado de buffer de lisis que contenía 50mM Tris pH 8,0, 0,5% NP40, 1mM DTT e inhibidores de proteasa/fosfatasa (Roche Diagnostics GmbH, Mannheim, Alemania). Las mezclas se agitaron durante 30-60 minutos para promover la formación del complejo ciclina-CDK2. Los lisados mixtos se centrifugaron luego a 15000 RPM durante 10 minutos y el sobrenadante se retuvo. Luego se usaron 5 ml de granos anti-GluTAG (para un litro de células SF9) para capturar los complejos de ciclina-CDK2. Los granos adheridos se lavaron tres veces en buffer de lisis. Las proteínas se eluyeron competitivamente en buffer de lisis que contenía 100-200 ug/mL del péptido GluTAG. El eluato se dializó durante la noche en 2 litros de buffer de quinasa que contenía 50mM de Tris pH 8,0, 1mM de DTT, 10mM de MgCl2, 100uM de ortovanadato de sodio y 20% de glicerol. La enzima se almacenó en alícuotas a -70°C.

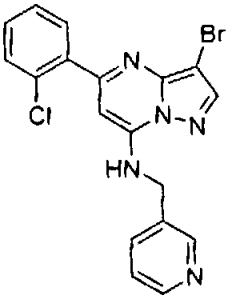
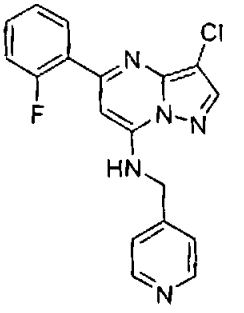
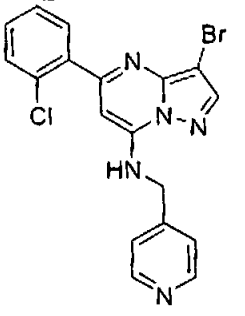
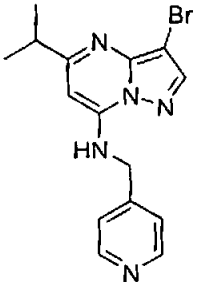
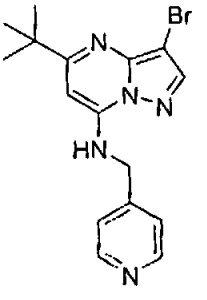
ENSAYO DE QUINASA IN VITRO: Los ensayos de quinasa CDK2 (de cualquier ciclina A o E-dependiente) se llevaron a cabo en placas de 96 receptáculos de baja adhesión de proteína (Corning Inc, Corning, New York). La enzima se diluyó hasta una concentración final de 50 µg/ml en buffer de quinasa que contenía

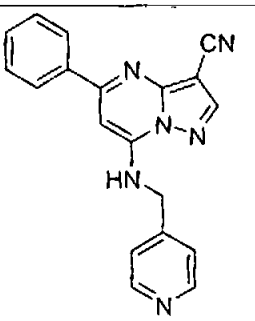
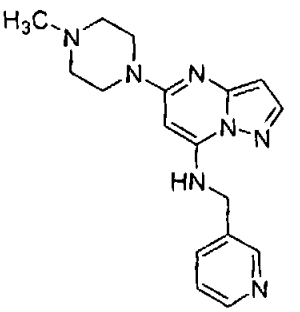
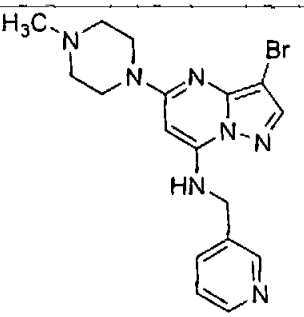
50mM Tris pH 8,0, 10mM $MgCl_2$, 1mM DTT, y 0,1mM de ortovanadato de sodio. El sustrato que se usó en estas reacciones era un péptido biotinilado derivado de Histona H1 (de Amersham, UK). El sustrato se descongeló en hielo y se diluyó a 2 μM en buffer de quinasa. Los compuestos se diluyeron en 10% de DMSO a las concentraciones deseables. Para cada reacción de quinasa se mezclaron 20 μl de la solución de sustrato de 50 μg/ml (1 μg de enzima) y 20 μl de la solución de sustrato 1 μM y luego se combinaron con 10 μl del compuesto diluido en cada receptáculo para ensayo. La reacción de quinasa se inició por adición de 50 μl de 4 μM de ATP y 1 μCi de 33P-ATP (de Amersham, UK). La reacción se dejó proseguir durante 1 hora a temperatura ambiente. La reacción se interrumpió por agregado de 200 μl de buffer de stop que contenía 0,1% Triton X-100, 1mM ATP, 5mM EDTA, y 5 mg/ml de granos de SPA recubiertos con estreptavidina (de Amersham, UK) durante 15 minutos. Los granos SPA fueron luego capturados en una placa de filtro GF/B de 96 receptáculos (Packard/Perkin Elmer Life Sciences) usando una cosechadora universal Filtermate (Packard/Perkin Elmer Life Sciences.). Se eliminaron las señales no específicas por lavado de los granos dos veces con NaCl 2M y luego dos veces con NaCl 2M con 1% de ácido fosfórico. Luego se midió la señal radioactiva usando un contador de centelleo líquido TopCount de 96 receptáculos (de Packard/Perkin Elmer Life Sciences).

DETERMINACIÓN DE LA CI_{50}: Se graficaron las curvas en respuesta a la dosis a partir de los datos de inhibición generados, cada uno por duplicado, a partir de diluciones seriadas de 8 puntos de los compuestos inhibidores. La concentración del compuesto se graficó contra el porcentaje de actividad de quinasa, calculado por CPM de las muestras tratadas dividido por el CPM de las muestras no tratadas. Para generar los valores de la CI_{50}, las curvas de respuesta a la dosis fueron luego ajustadas a una curva sigmoidal convencional y los valores de CI_{50} fueron derivados por análisis de regresión no lineal. Los valores de CI_{50} obtenidos de esta manera para los compuestos de la invención se muestran en la **Tabla 87.** Estas actividades de quinasa se generaron mediante el uso de ciclina A o ciclina E usando el ensayo descripto anteriormente.

TABLA 87

COMP	Ejemplo	CI_{50} (μM)
	1	0,020 0,029
	3	0,032 0,024
	4	0,011
	5	0.021

	8	0,003
	6	0,064 0,029
	7	0,01 0,006
	10	0,042
	12	0,17

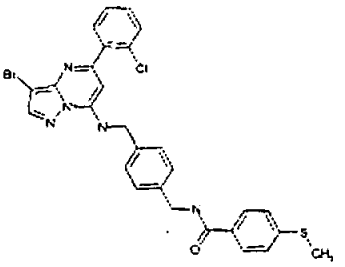
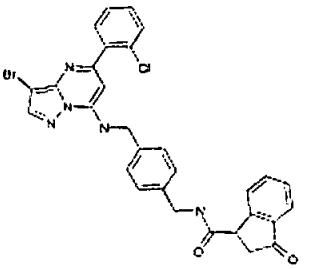
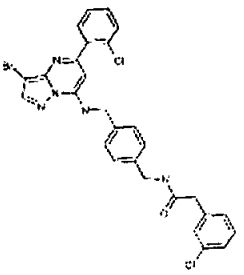
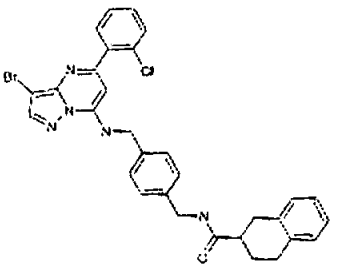
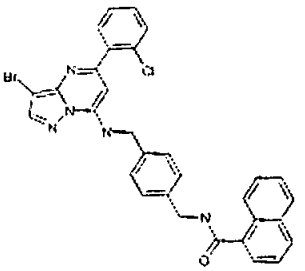
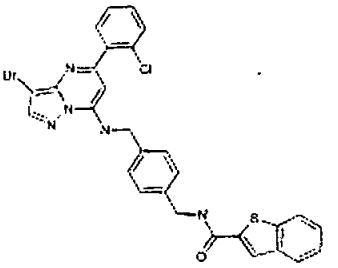
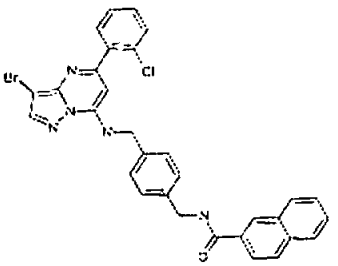
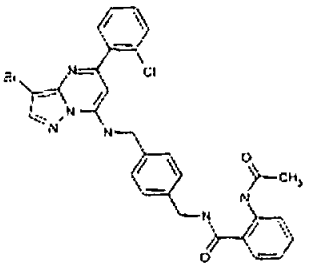
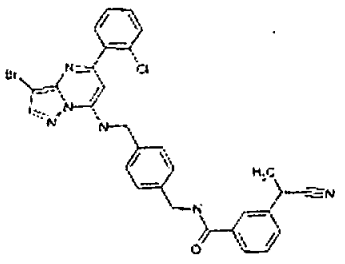
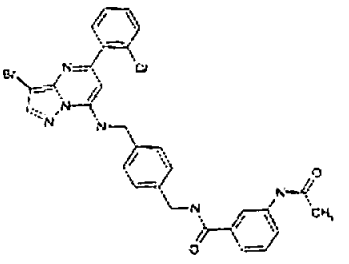
	16	0,62
	1	5,6
	3	0,14

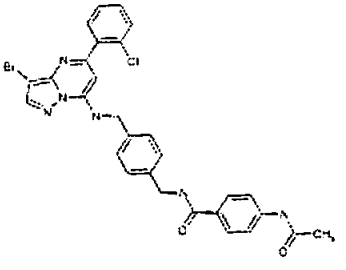
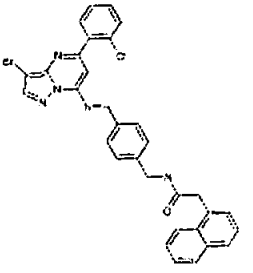
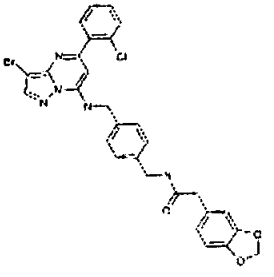
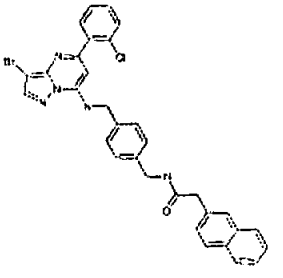
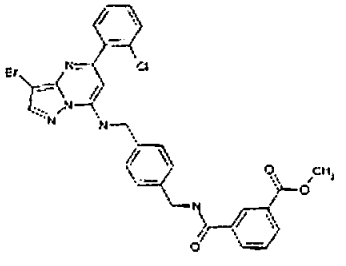
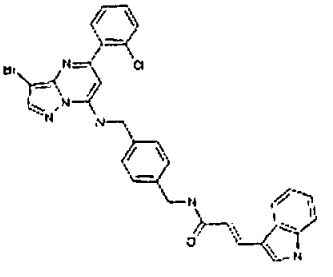
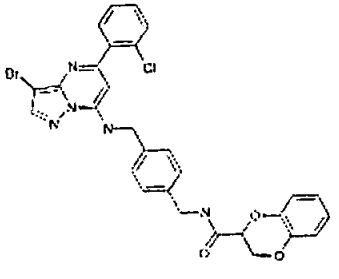
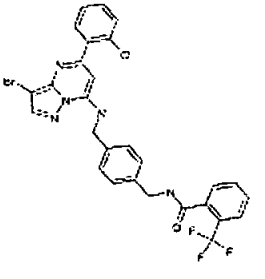
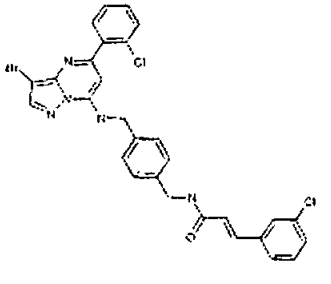
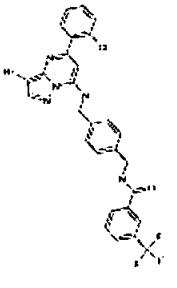
Tal como se demostró anteriormente por los valores de ensayo, los compuestos de la presente invención exhiben excelentes propiedades inhibidoras de CDK.

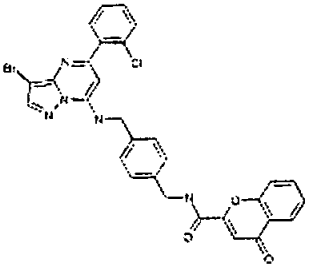
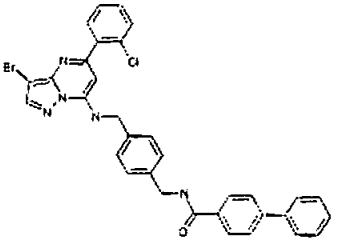
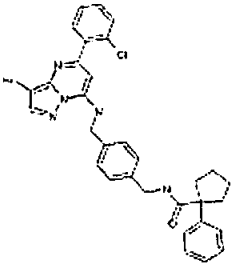
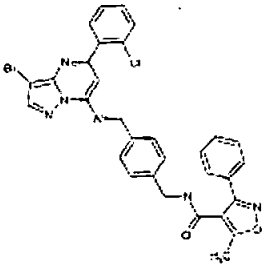
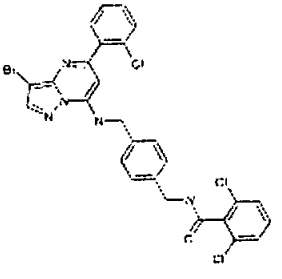
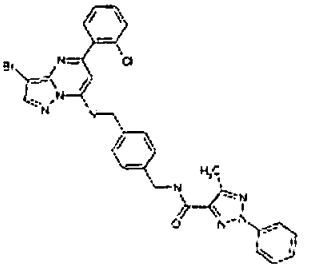
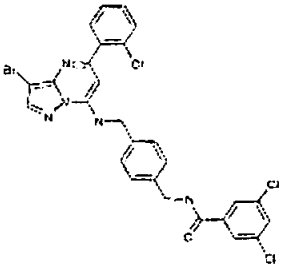
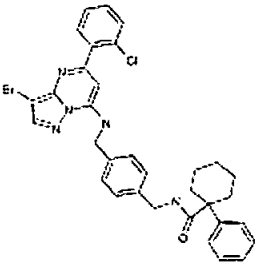
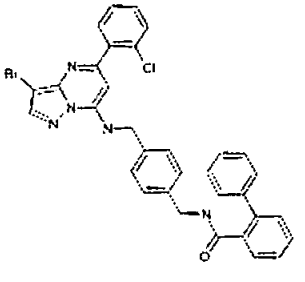
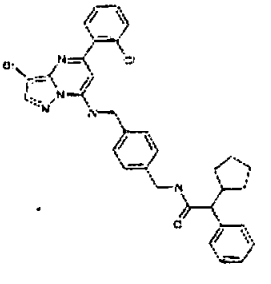
Aunque la presente invención ha sido descripta conjuntamente con realizaciones específicas tal como las que se indicaron anteriormente, muchas alternativas, modificaciones y otras variaciones de estas resultarán aparentes para los expertos en la materia. Todas dichas alternativas, modificaciones y variaciones están dentro del espíritu y alcance de la presente invención.

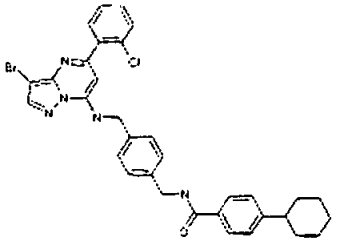
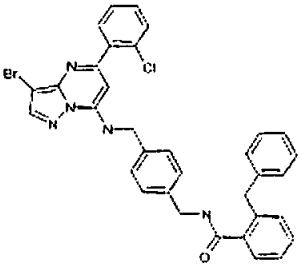
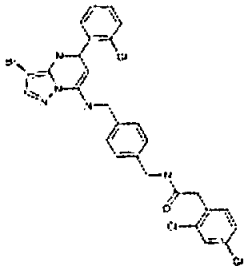
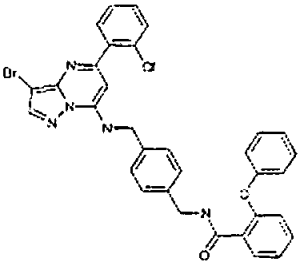
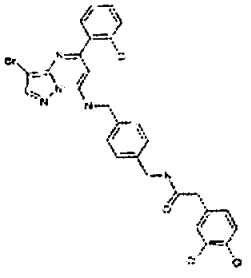
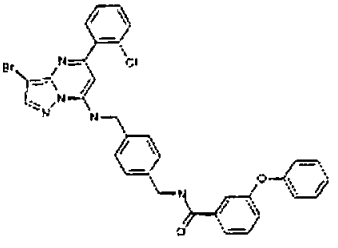
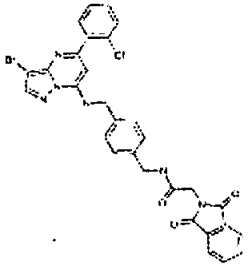
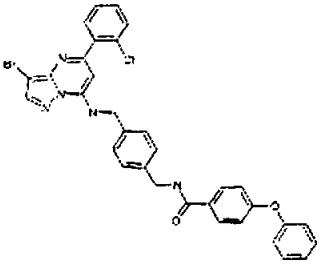
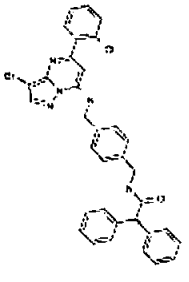
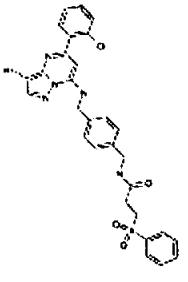
5/5 1162

34665/bf

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4651 2. 594.33		1. 4656 2. 602.33
	1. 4652 2. 596.33		1. 4657 2. 602.33
	1. 4653 2. 596.3		1. 4658 2. 604.33
	1. 4654 2. 598.33		1. 4659 2. 603.3
	1. 4655 2. 601.33		1. 4660 2. 605.33

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4661 2. 605.33		1. 4666 2. 612.34
	1. 4662 2. 606.33		1. 4667 2. 612.34
	1. 4663 2. 606.33		1. 4668 2. 613.34
	1. 4664 2. 606.33		1. 4669 2. 616.34
	1. 4665 2. 608.33		1. 4670 2. 616.34

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4671 2. 616.34		1. 4676 2. 624.34
	1. 4672 2. 616.34		1. 4677 2. 629.35
	1. 4673 2. 616.34		1. 4678 2. 629.35
	1. 4674 2. 616.34		1. 4679 2. 630.35
	1. 4675 2. 624.34		1. 4680 2. 630.35

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4681 2. 630.35		1. 4686 2. 638.35
	1. 4682 2. 630.35		1. 4687 2. 640.35
	1. 4683 2. 630.35		1. 4688 2. 640.35
	1. 4684 2. 631.35		4689 2.
	1. 4685 2. 638.35		1. 4690 2. 640.35

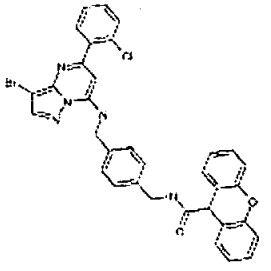
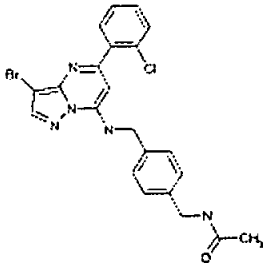
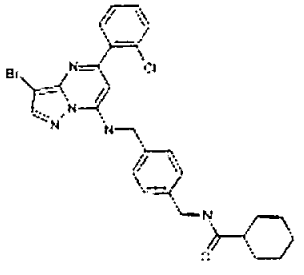
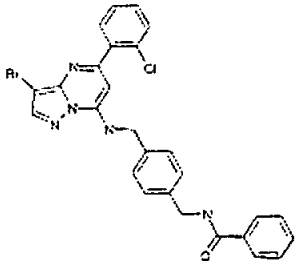
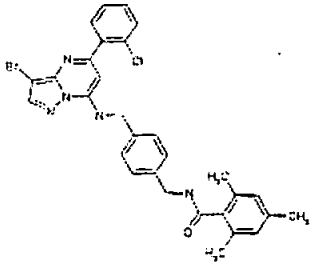
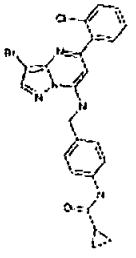
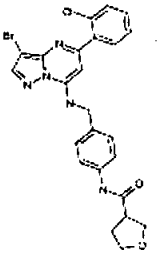
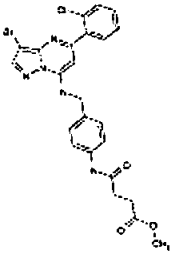
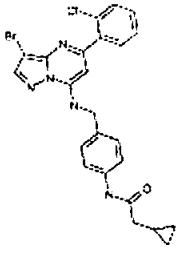
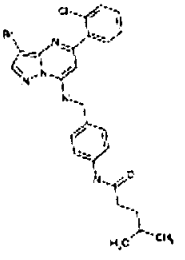
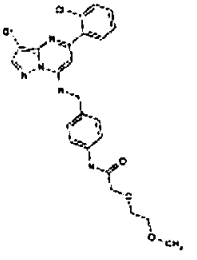
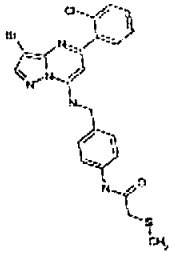
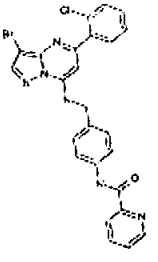
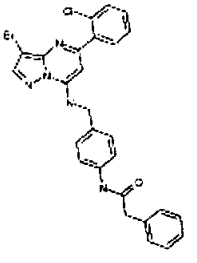
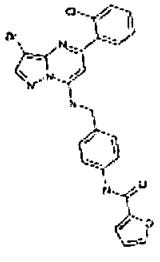
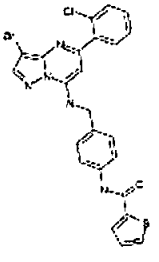
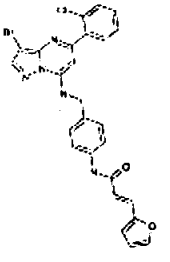
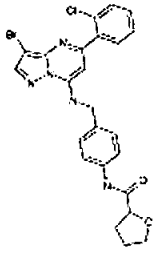
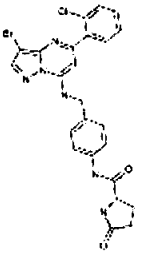
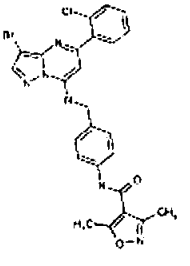
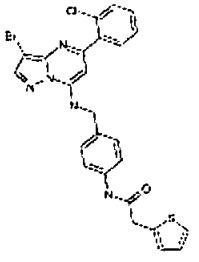
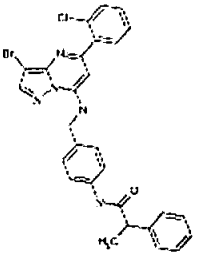
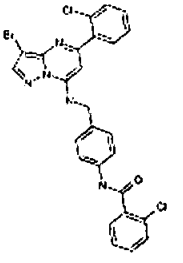
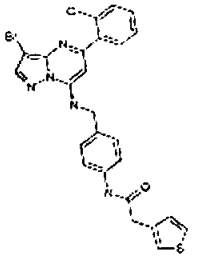
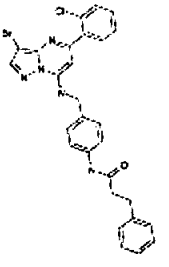
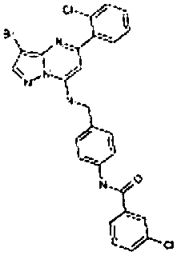
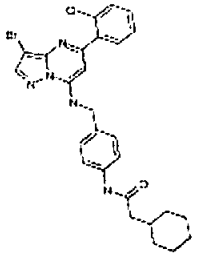
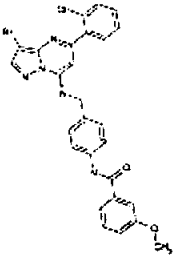
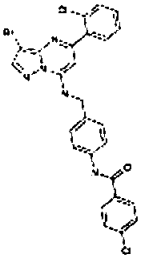
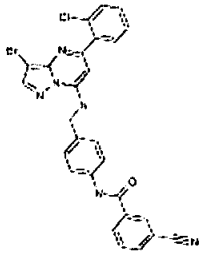
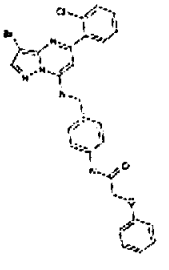
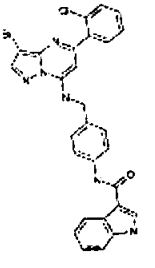
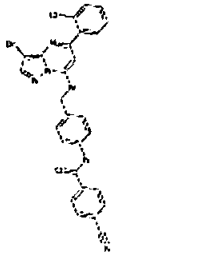
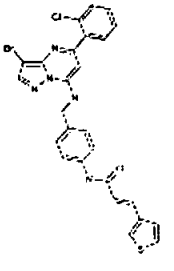
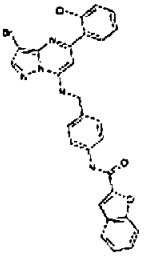
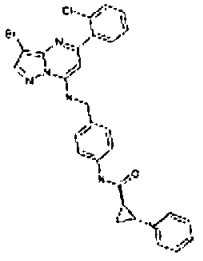
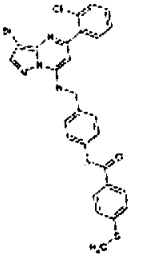
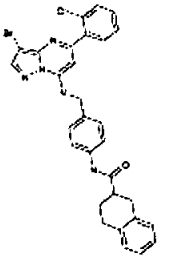
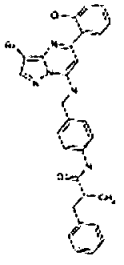
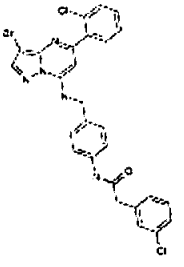
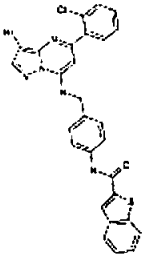
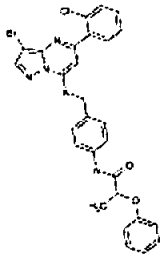
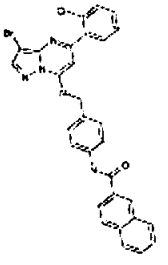
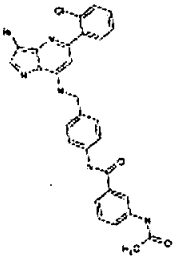
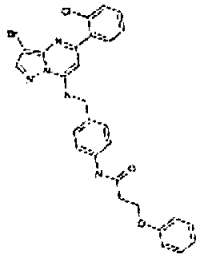
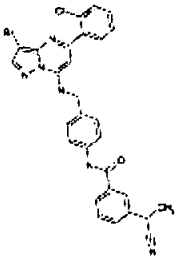
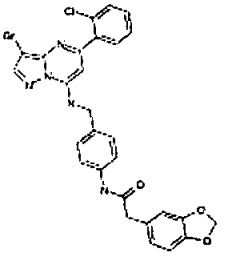
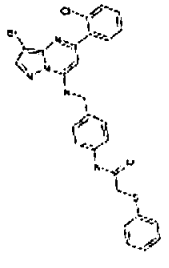
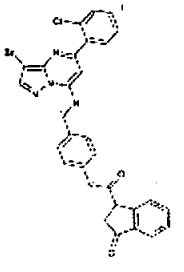
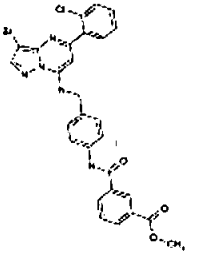
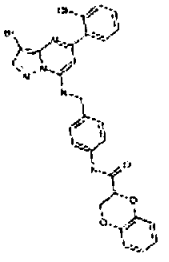
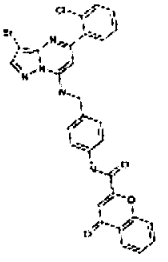
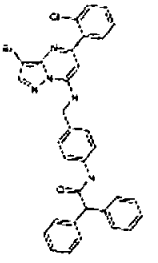
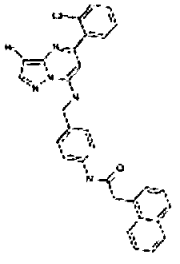
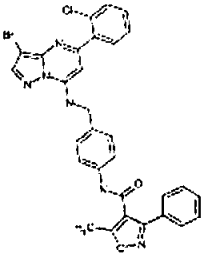
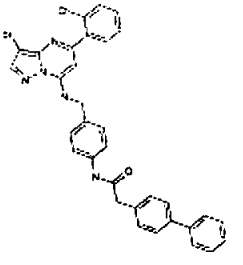
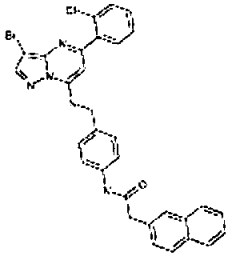
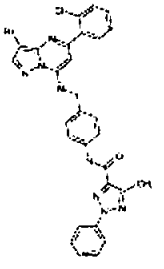
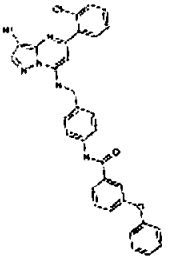
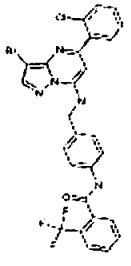
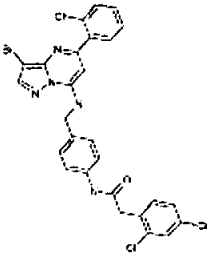
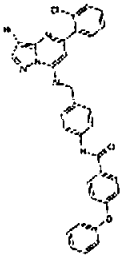
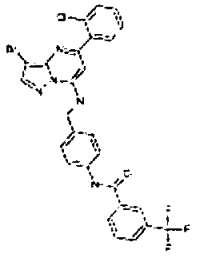
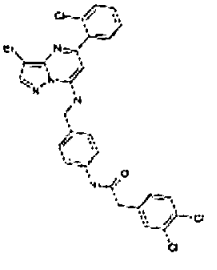
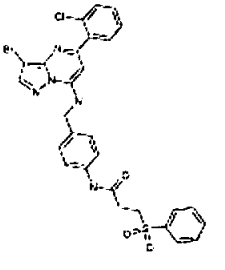
Producto	1. Ej. 2. m/z
	1. 4691 2. 652.36
	1. 4692 2. 484.3
	1. 4693 2. 554.3
	1. 4694 2. 548.3
	1. 4695 2. 590.32

TABLA 47

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4701 2. 498.27		1. 4706 2. 528.29		1. 4711 2. 544.3
	1. 4702 2. 512.28		1. 4707 2. 528.29		1. 4712 2. 546.3
	1. 4703 2. 518.28		1. 4708 2. 535.29		1. 4713 2. 548.3
	1. 4704 2. 524.29		1. 4709 2. 540.3		1. 4714 2. 550.3
	1. 4705 2. 528.29		1. 4710 2. 541.3		1. 4715 2. 553.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4716 2. 554.3		1. 4721 2. 562.31		1. 4726 2. 568.31
	1. 4717 2. 554.3		1. 4722 2. 562.31		1. 4727 2. 568.31
	1. 4718 2. 554.3		1. 4723. 2 564.31		1. 4728 2. 568.31
	1. 4719 2. 559.31		1. 4724 2. 564.31		1. 4729 2. 573.32
	1. 4720 2. 559.31		1. 4725 2. 566.31		1. 4730 2. 574.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4731 2. 574.32		1. 4736 2. 580.32		1. 4741 2. 588.32
	1. 4732 2. 576.32		1. 4737 2. 582.32		1. 4742 2. 590.32
	1. 4733 2. 578.32		1. 4738 2. 584.32		1. 4743 2. 591.33
	1. 4734 2. 578.32		1. 4739 2. 585.32		1. 4744 2. 592.33
	1. 4735 2. 580.32		1. 4740 2. 588.32		1. 4745 2. 592.33

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4746 2. 592.33		1. 4751 2. 602.33		1. 4756 2. 624.34
	1. 4747 2. 598.33		1. 4752 2. 615.34		1. 4757 2. 624.34
	1. 4748 2. 598.33		1. 4753 2. 615.34		1. 4758 2. 626.34
	1. 4749 2. 602.33		1. 4754 2. 616.34		1. 4759 2. 624.34
	1. 4750 2. 602.33		1. 4755 2. 616.34		1. 4760 2. 626.34

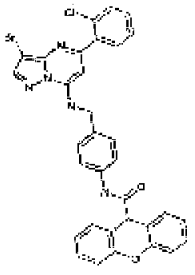
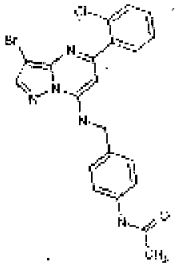
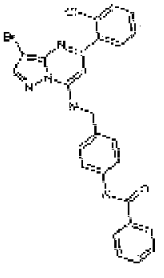
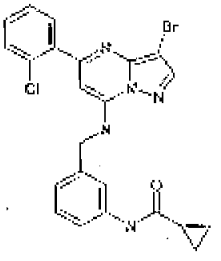
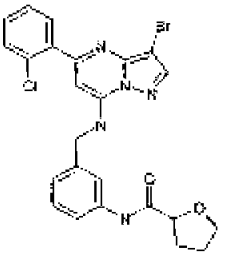
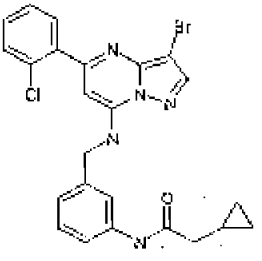
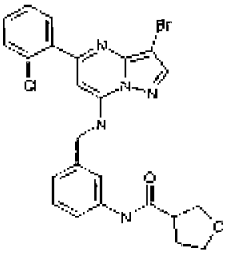
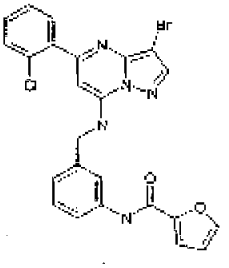
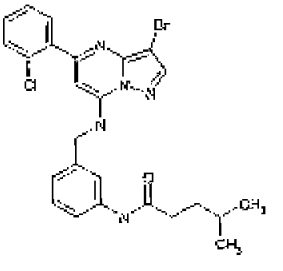
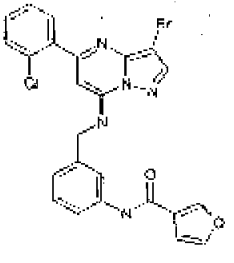
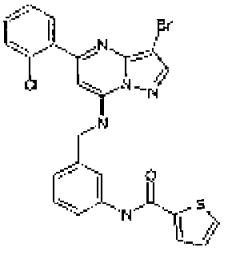
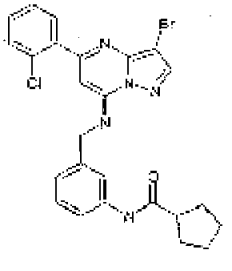
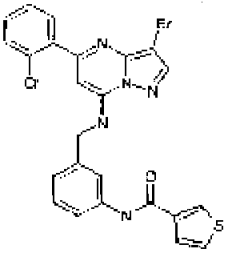
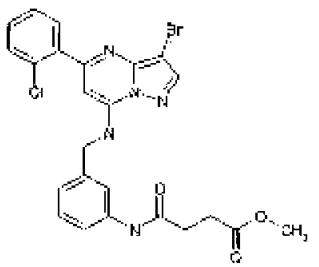
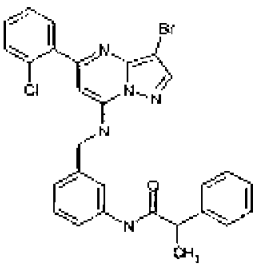
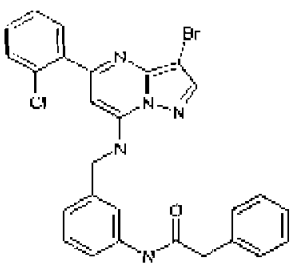
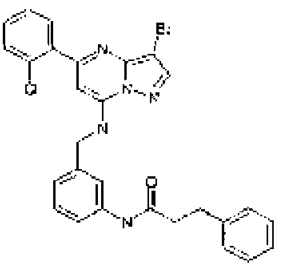
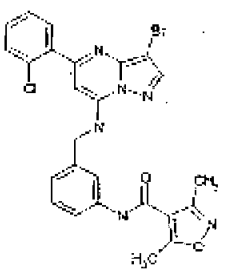
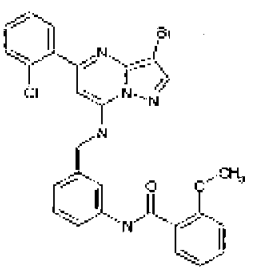
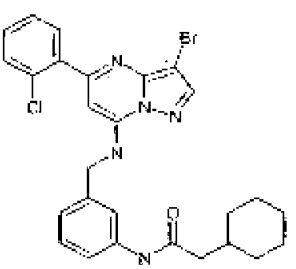
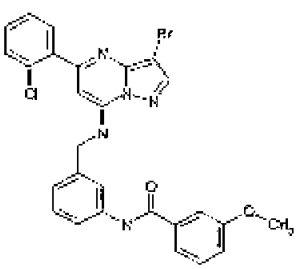
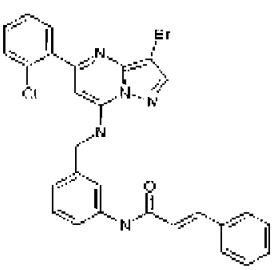
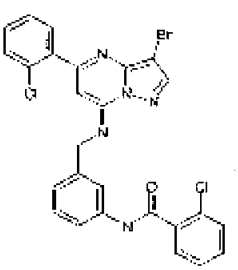
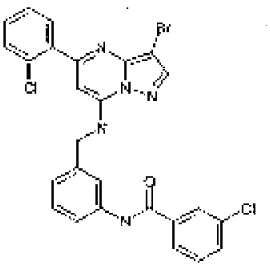
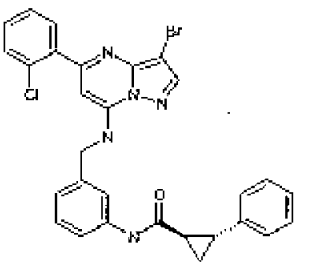
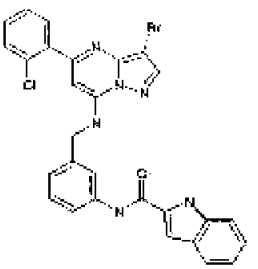
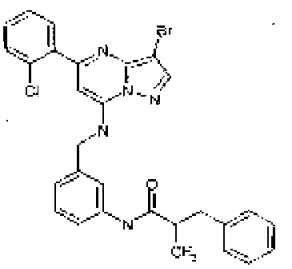
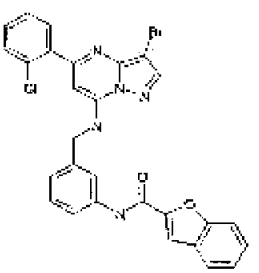
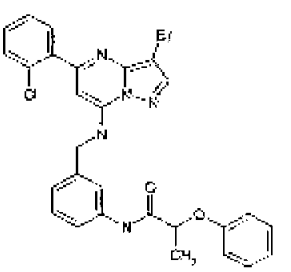
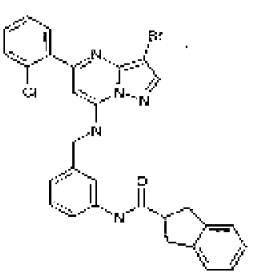
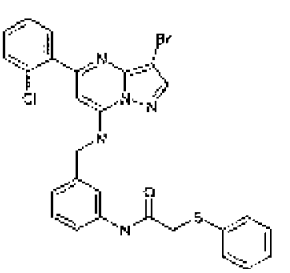
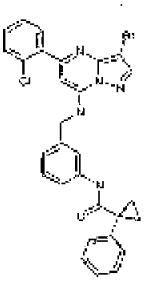
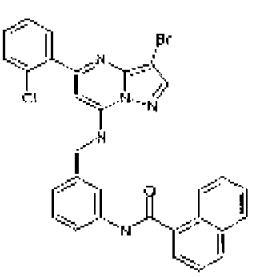
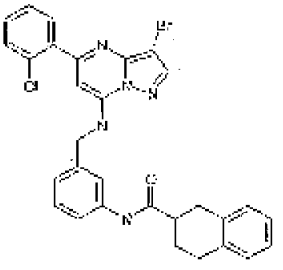
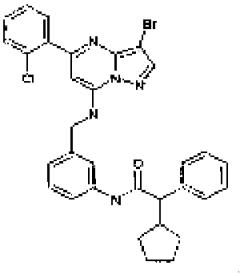
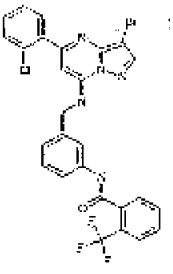
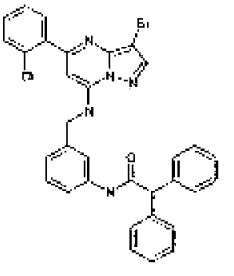
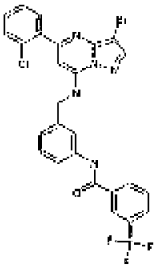
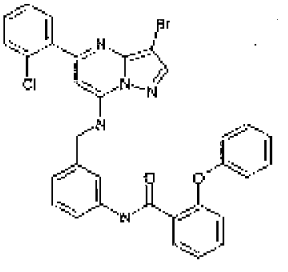
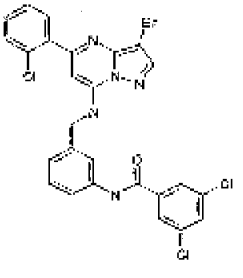
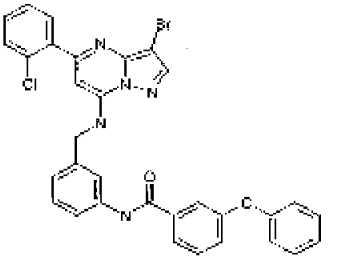
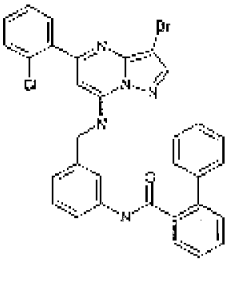
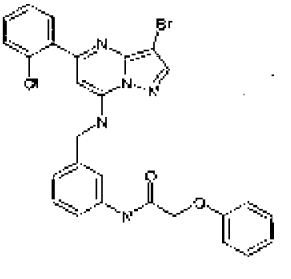
Producto	1. Ej. 2. m/z
	1. 4761 2. 638.35
	1. 4762 2. 472.26
	1. 4763 2. 534.29

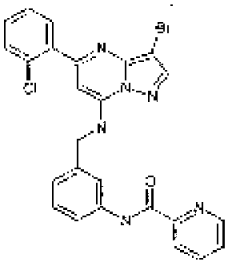
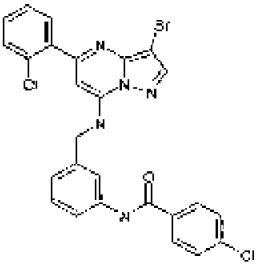
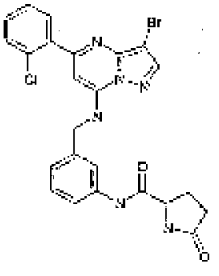
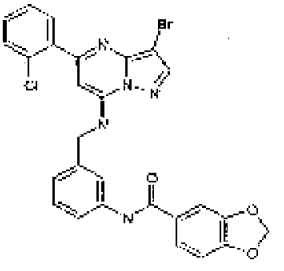
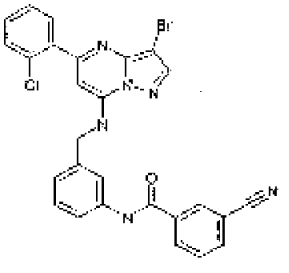
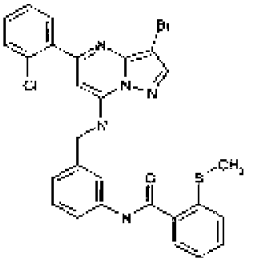
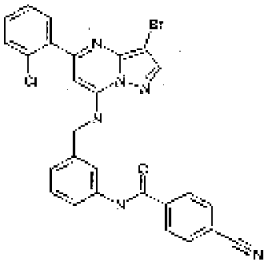
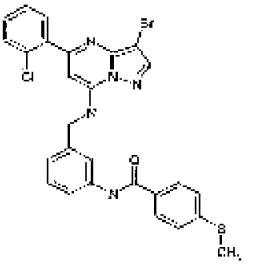
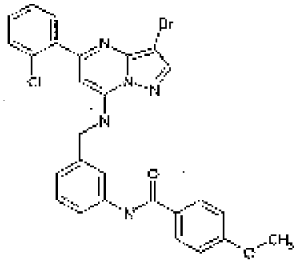
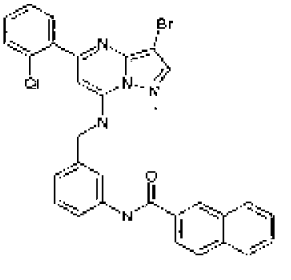
TABLA 48

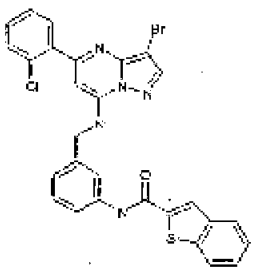
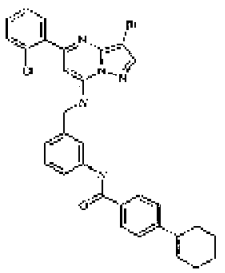
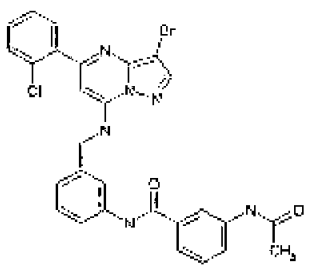
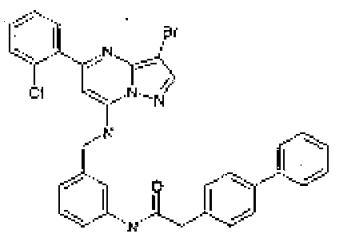
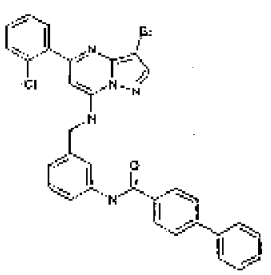
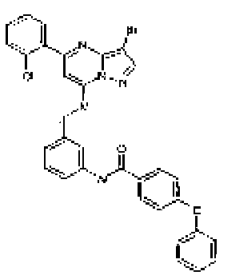
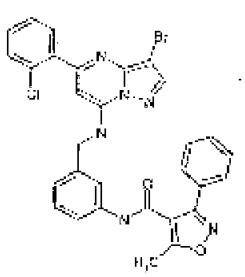
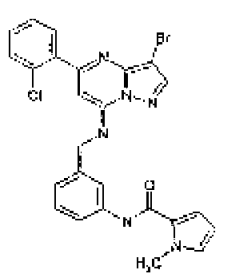
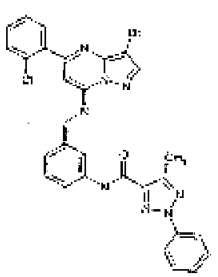
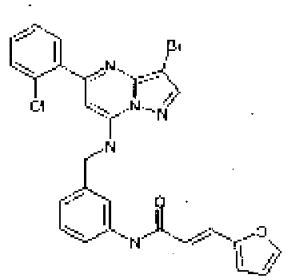
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4801 2. 498.27		1.4806 2. 526.29
	1. 4802 2. 512.28		1.. 4807 2. 528.29
	1. 4803 2. 524.29		1. 4808 2. 528.29
	1. 4804 2. 524.29		1. 4809 2. 540.3
	1. 4805 2. 526.29		1. 4810 2. 540.3

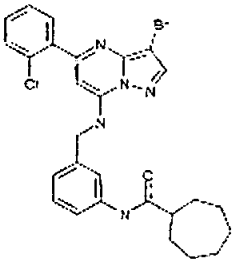
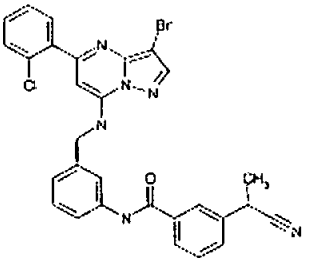
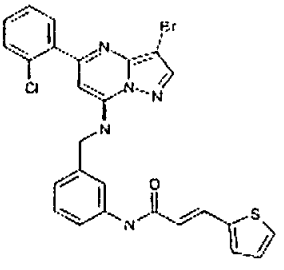
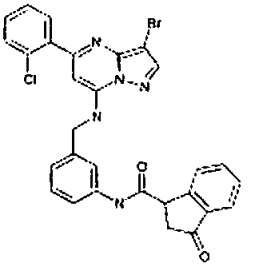
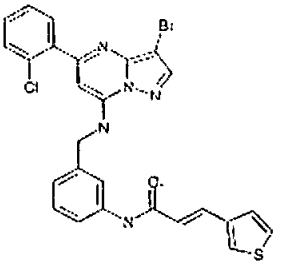
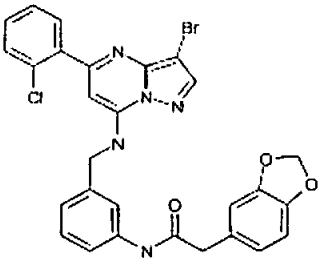
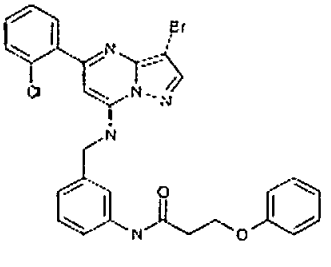
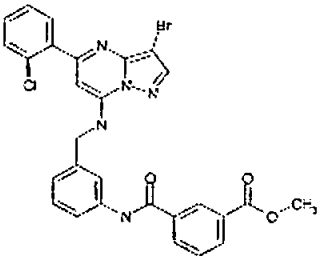
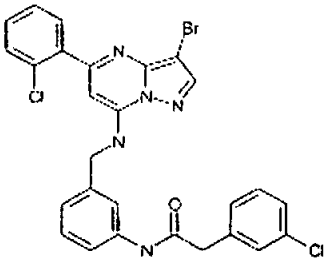
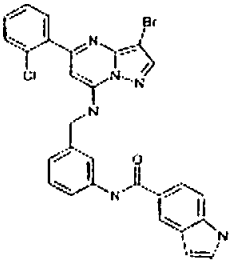
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4811 2. 544.3		1. 4816 2. 562.31
	1. 4812 2. 548.3		1. 4817 2. 562.31
	1. 4813 2. 553.3		1. 4818 2. 564.31
	1. 4814 2. 554.3		1. 4819 2. 564.31
	1. 4815 2. 560.31		1. 4820 2. 568.31

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4821 2. 568.31		1. 4826 2. 574.32
	1. 4822 2. 573.32		1. 4828 2. 576.32
	1. 4821 2. 574.32		1. 4829 2. 578.32
	1. 4824 2. 574.32		1. 4829 2. 580.32
	1. 4825 2. 574.32		1. 4830 2. 584.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4831 2. 588.32		1. 4836 2. 616.34
	1. 4832 2. 602.33		1. 4837 2. 624.34
	1. 4833 2. 602.33		1. 4838 2. 626.34
	1. 4834 2. 602.33		1. 4839 2. 626.34
	1. 4835 2. 610.34		1. 4840 2. 564.31

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4841 2. 535.29		1. 4846 2. 568.31
	1. 4842 2. 541.3		1. 4847 2. 578.32
	1. 4843 2. 559.31		1. 4848 2. 580.32
	1. 4844 2. 559.31		1. 4849 2. 580.32
	1. 4845 2. 564.31		1. 4850 2. 584.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4851 2. 590.32		1. 4856 2. 616.34
	1. 4852 2. 591.33		1. 4857 2. 624.34
	1. 4853 2. 610.34		1. 4858 2. 626.34
	1. 4854 2. 615.34		1. 4859 2. 537.3
	1. 4855 2. 615.34		1. 4860 2. 550.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4861 2. 554.3		1. 4866 2. 587.32
	1. 4862 2. 566.31		1. 4867 2. 588.32
	1. 4863 2. 566.31		1. 4868 2. 592.33
	1. 4864 2. 578.32		1. 4869 2. 592.33
	1. 4865 2. 582.32		1. 4870 2. 573.32

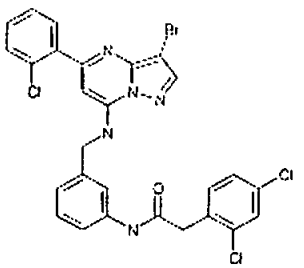
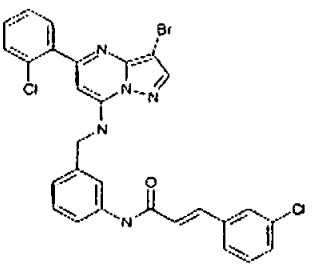
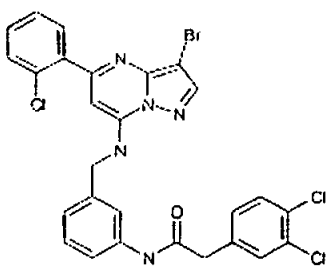
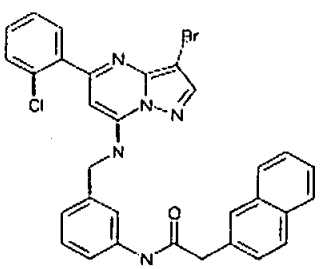
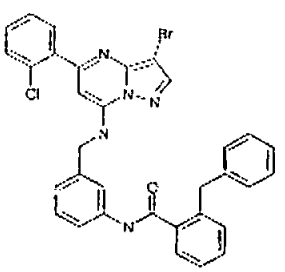
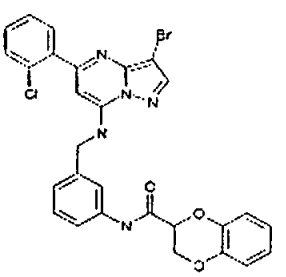
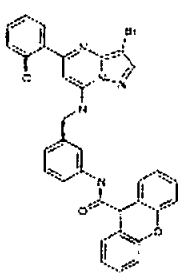
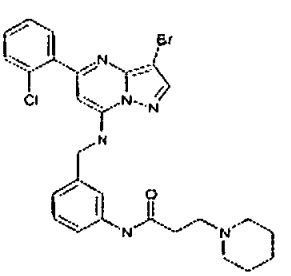
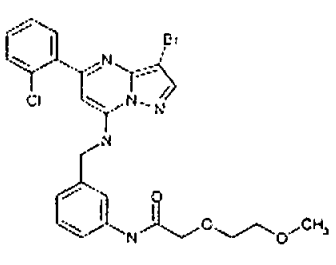
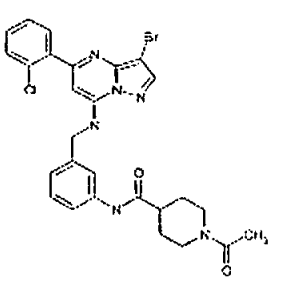
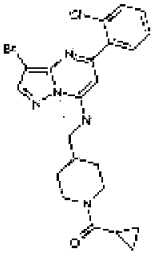
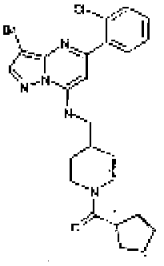
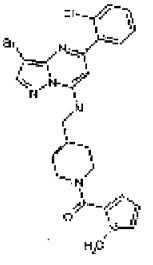
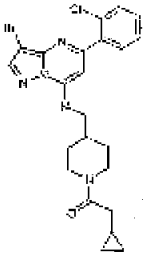
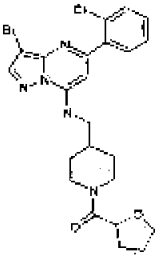
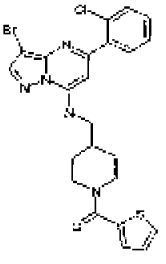
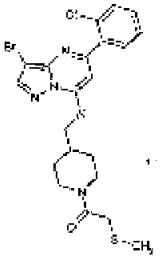
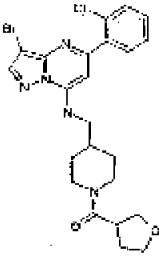
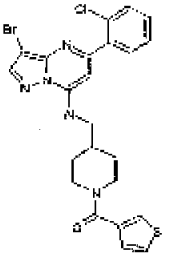
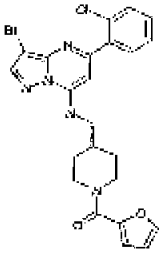
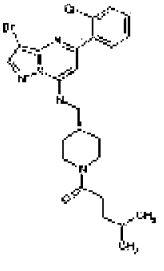
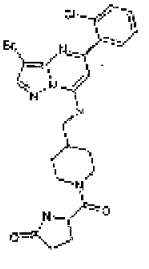
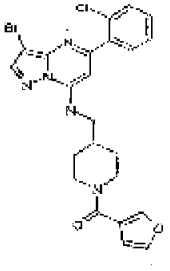
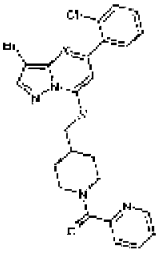
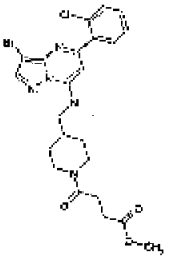
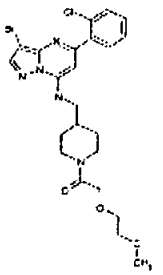
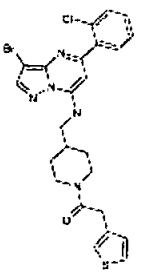
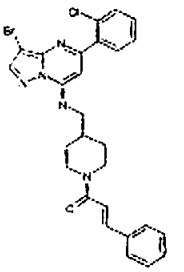
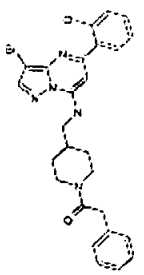
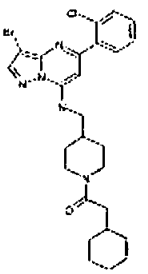
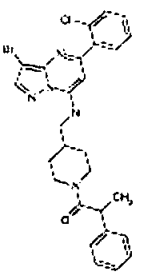
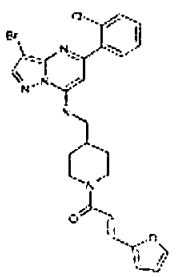
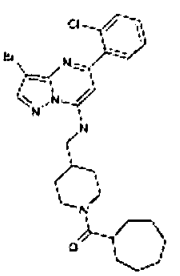
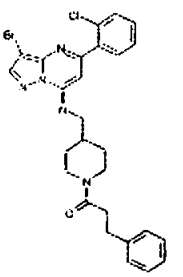
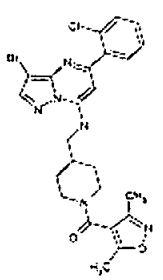
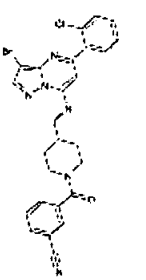
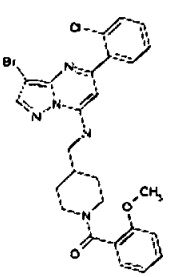
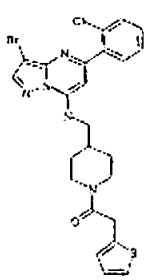
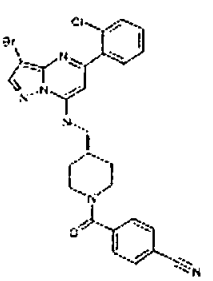
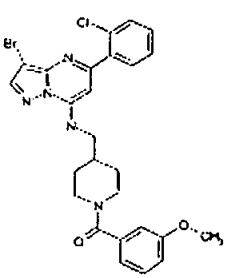
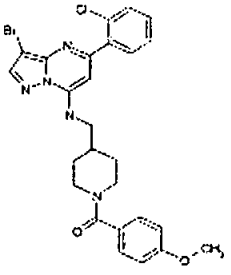
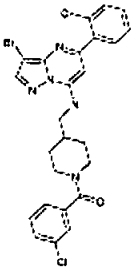
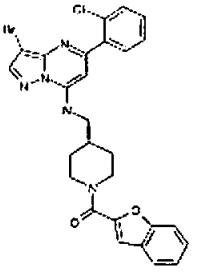
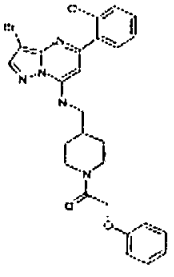
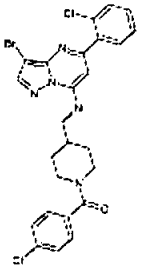
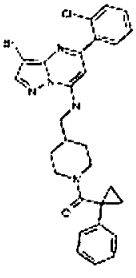
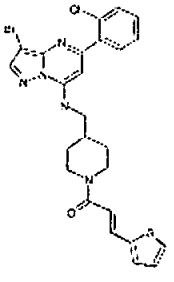
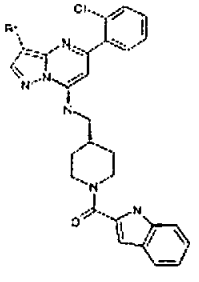
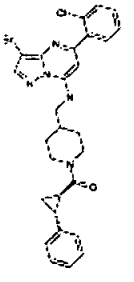
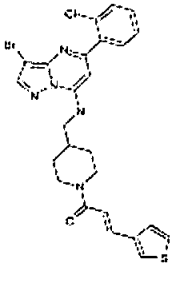
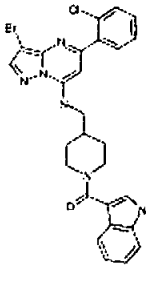
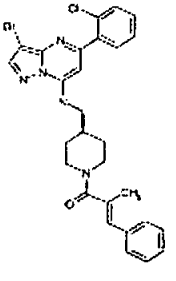
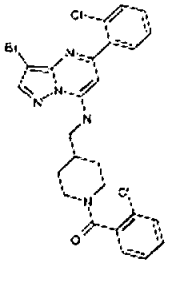
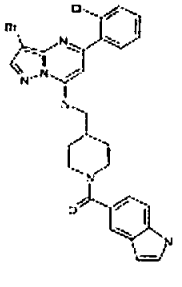
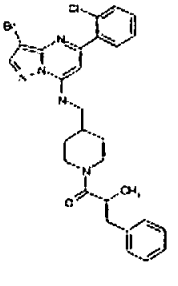
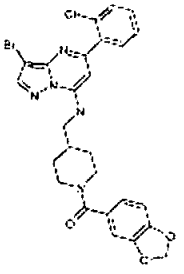
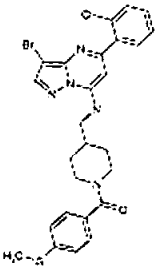
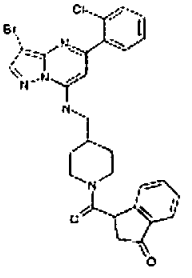
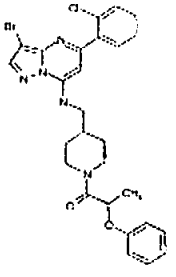
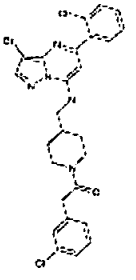
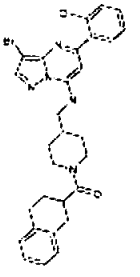
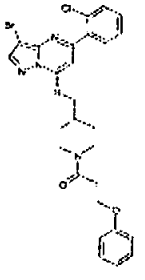
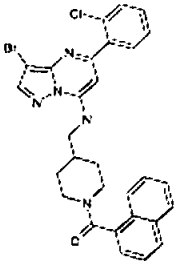
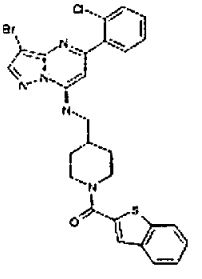
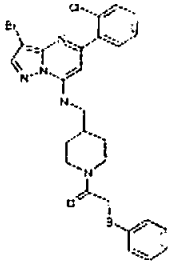
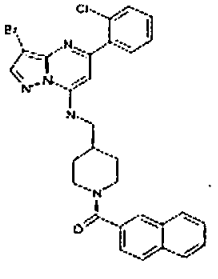
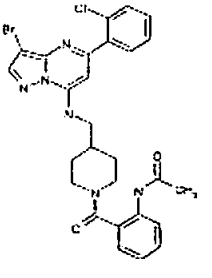
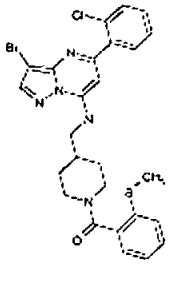
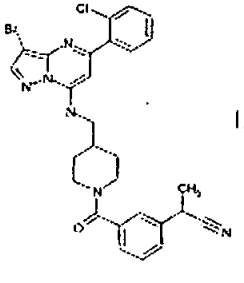
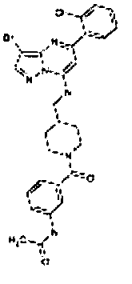
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4871 2. 616.34		1. 4876 2. 594.33
	1. 4872 2. 616.34		1. 4877 2. 598.33
	1. 4873 2. 624.34		1. 4878 2. 592.33
	1. 4874 2. 638.35		1. 4879 2. 569.31
	1. 4875 2. 546.3		1. 4880 2. 583.32

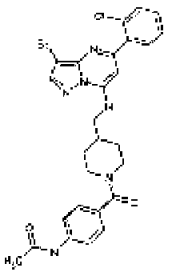
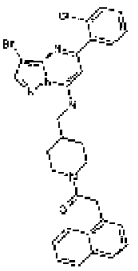
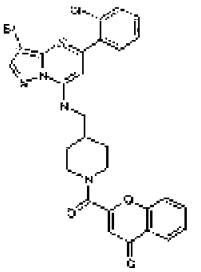
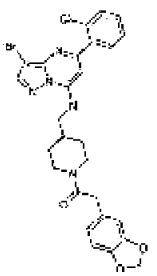
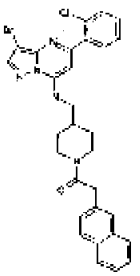
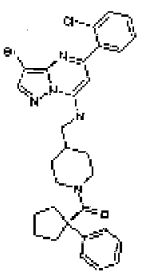
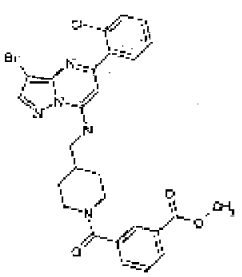
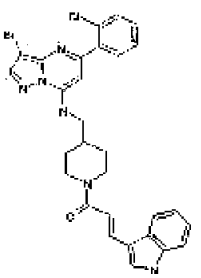
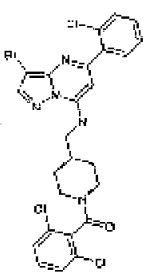
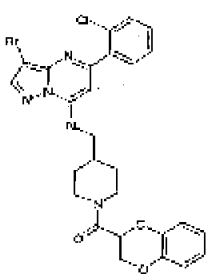
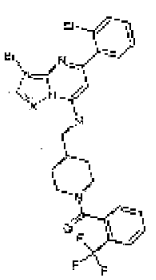
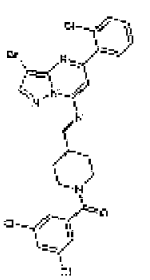
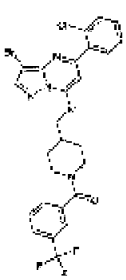
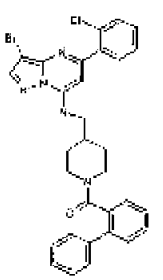
TABLA 49

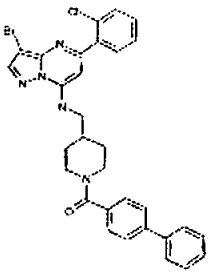
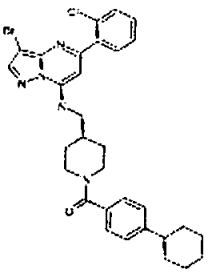
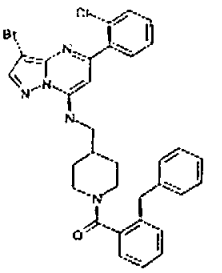
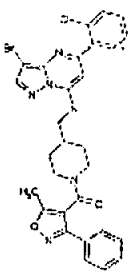
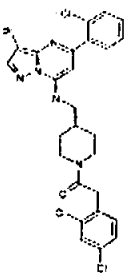
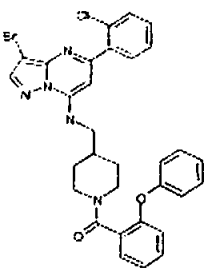
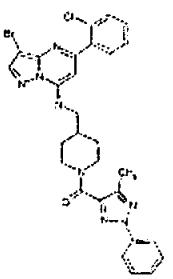
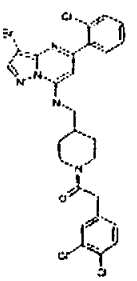
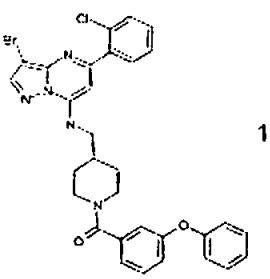
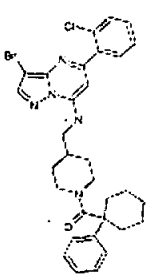
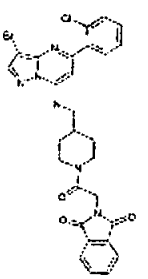
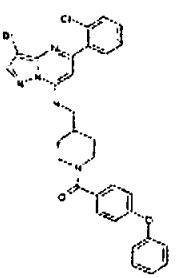
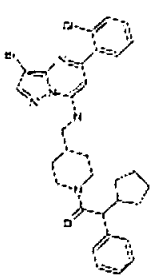
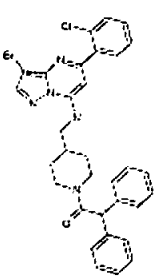
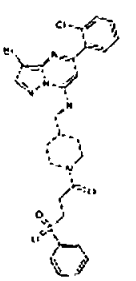
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4901 2. 490.27		1. 4906 2. 518.28		1. 4911 2. 529.29
	1. 4902 2. 504.28		1. 4907 2. 520.29		1. 4912 2. 532.29
	1. 4903 2. 510.28		1. 4908 2. 520.29		1. 4913 2. 532.29
	1. 4904 2. 516.28		1. 4909 2. 520.29		1. 4914 2. 533.29
	1. 4905 2. 516.28		1. 4910 2. 527.29		1. 4915 2. 536.29

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4916 2. 538.3		1. 4921 2. 546.3		1. 4926 2. 552.3
	1. 4917 2 .540.3		1. 4922 2. 546.3		1. 4927 2. 554.3
	1. 4918 2. 542.3		1. 4923 2. 546.3		1. 4928 2. 554.3
	1. 4919 2. 545.3		1. 4924 2. 551.3		1. 4929 2. 556.31
	1. 4920 2. 546.3		1. 4925 2. 551.3		1. 4930 2. 556.31

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4931 2. 556.31		1. 4936 2. 560.31		1. 4941 2. 566.31
	1. 4932 2. 556.31		1. 4937 2. 560.31		1. 4942 2. 566.31
	1. 4933 2. 558.31		1. 4938 2. 565.31		1. 4943 2. 566.31
	1. 4934 3. 558.31		1. 4939 2. 565.3		1. 4944 2. 566.31
	1. 4935 2. 560.31		1. 4940 2. 565.31		1. 4945 2. 568.31

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4946 2. 570.31		1. 4951 2. 571.31		1. 4956 2. 580.32
	1. 4947 2. 570.31		1. 4952 2. 574.32		1. 4957 2. 580.32
	1. 4948 2. 570.31		1. 4953 2. 576.32		1. 4958 2. 582.32
	1. 4949 2. 572.31		1. 4954 2. 576.32		1. 4959 2. 583.32
	1. 4950 2. 572.31		I. 4955 2. 579.32		1. 4960 2. 583.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4961 2. 583.32		1. 4966 2. 590.32		1. 4971 2. 594.33
	1. 4962 2. 584.32		1. 4967 2. 590.32		1. 4972 2. 594.33
	1. 4963 2. 584.32		1. 4968 2. 591.3		1. 4973 2. 594.33
	1. 4964 2. 584.32		1. 4969 2. 594.33		1. 4974 2. 594.33
	1. 4965 2. 586.32		1. 4970 2. 594.33		1. 4975 2. 602.33

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4976 2. 602.33		1. 4981 2. 608.33		1. 4986 2. 616.34
	1. 4977 2. 607.33		1. 4982 2. 608.33		1. 4987 2. 618.34
	1. 4978 2. 607.33		1. 4983 2. 608.33		1. 4988 2. 618.34
	1. 4979 2. 605.33		1. 4984 2. 609.33		1. 4089 2. 618.34
	1. 4980 2. 608.33		1. 4985 2. 616.34		1. 4990 2. 618.34

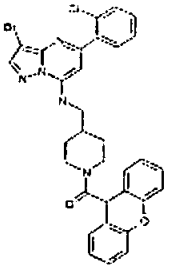
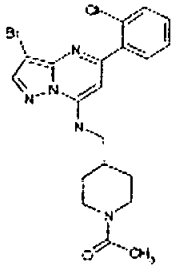
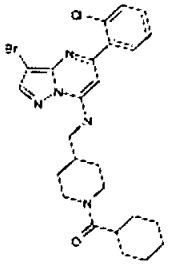
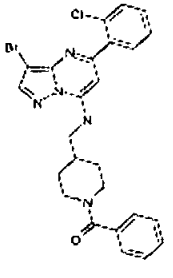
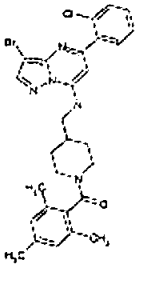
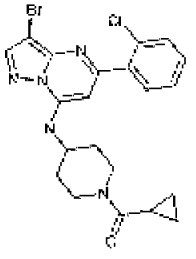
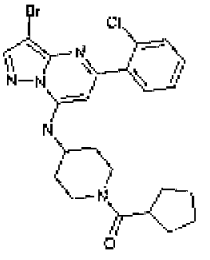
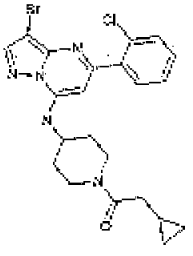
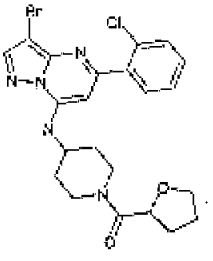
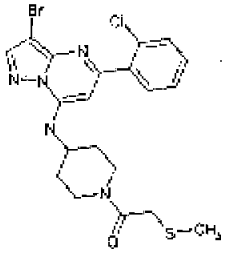
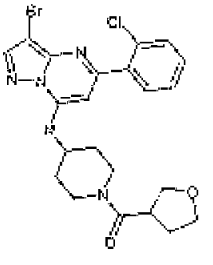
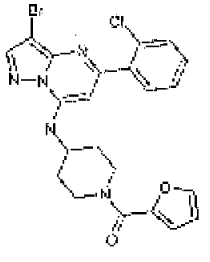
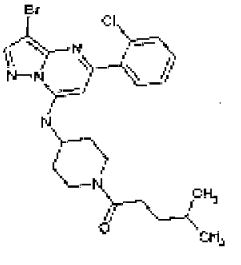
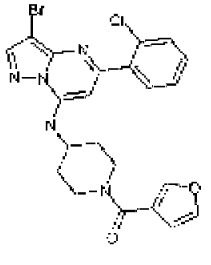
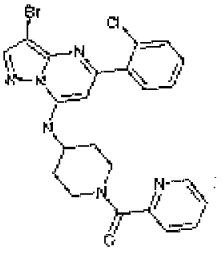
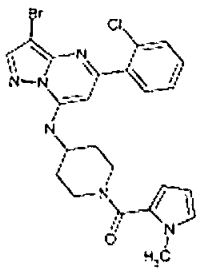
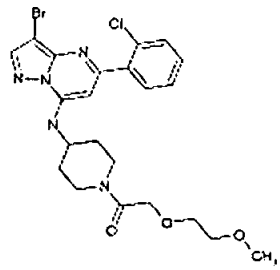
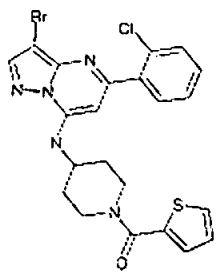
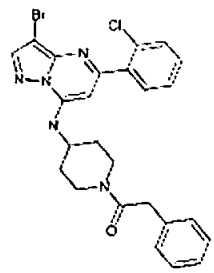
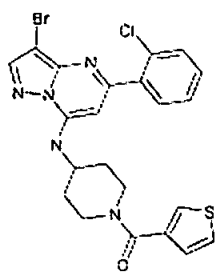
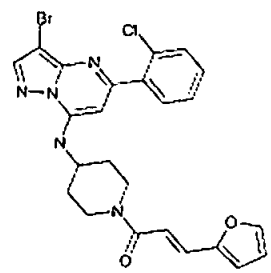
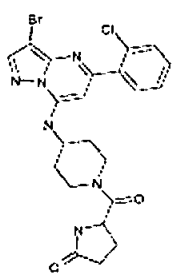
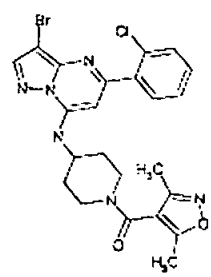
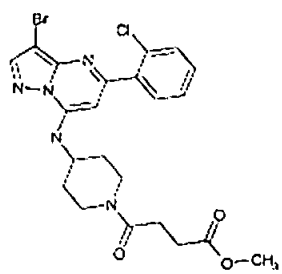
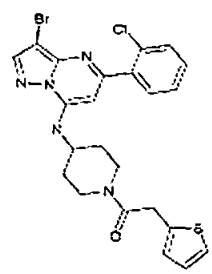
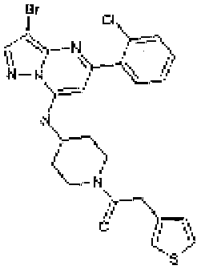
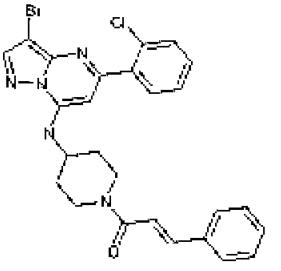
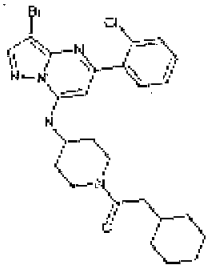
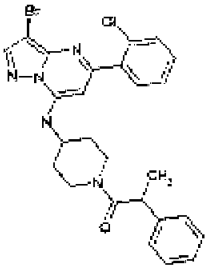
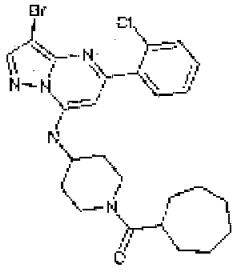
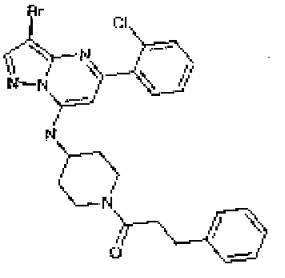
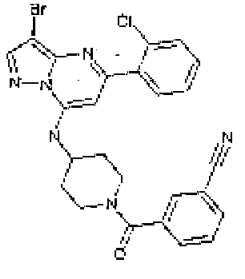
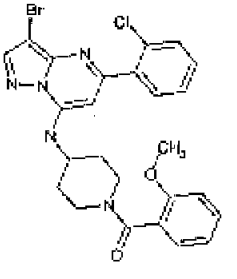
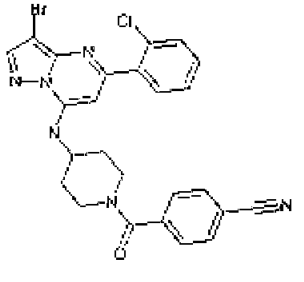
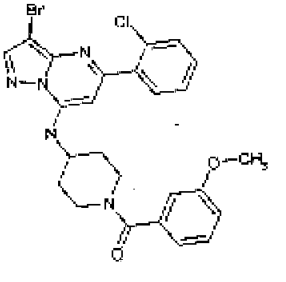
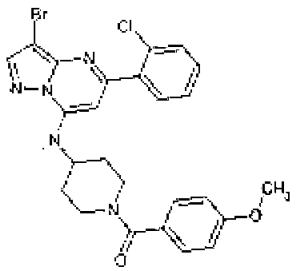
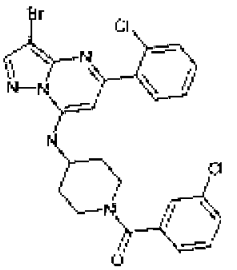
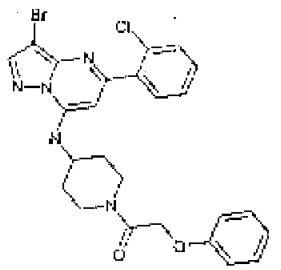
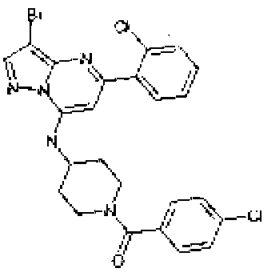
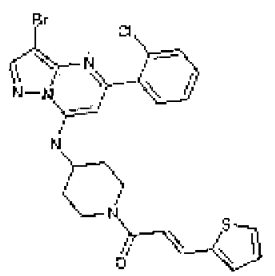
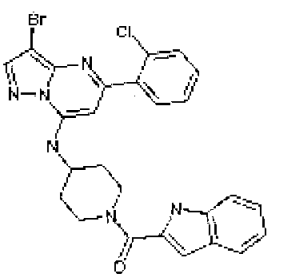
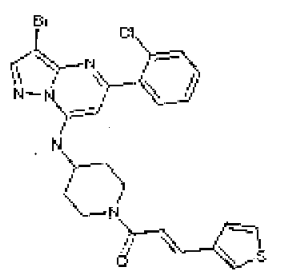
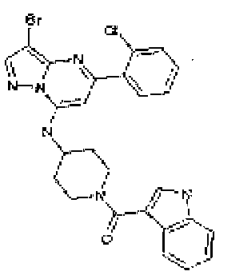
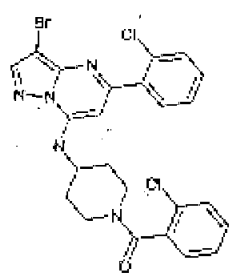
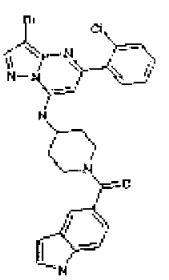
Producto	1. Ej. 2. m/z
	1. 4991 2. 630.35
	1. 4992 2. 464.26
	1. 4993 2. 532.29
	1. 4994 2. 526.29
	1. 4995 2. 568.31

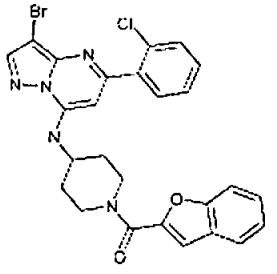
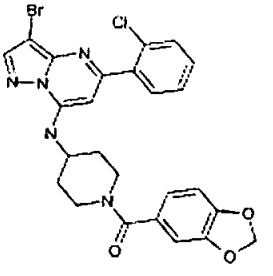
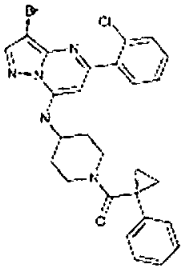
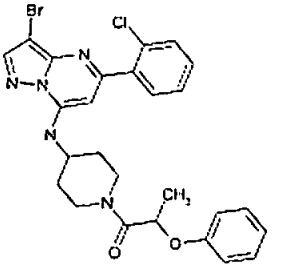
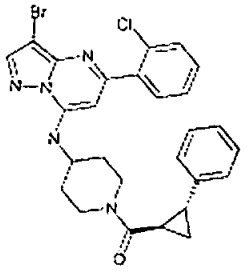
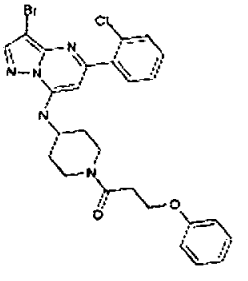
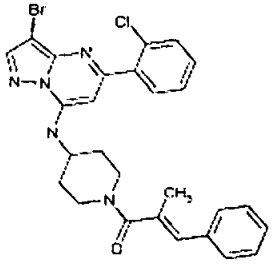
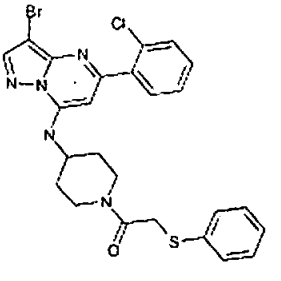
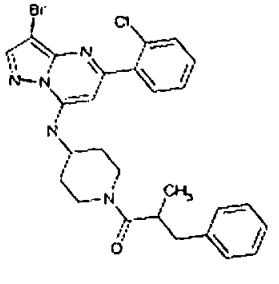
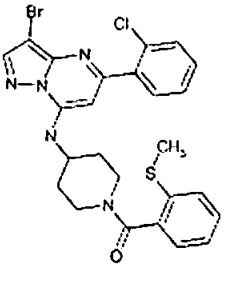
TABLA 50

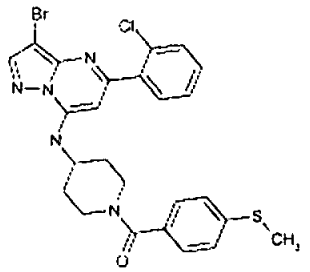
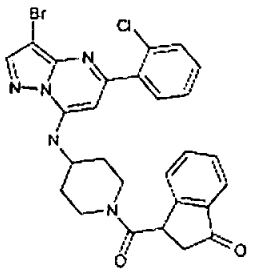
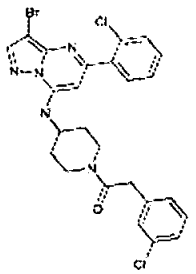
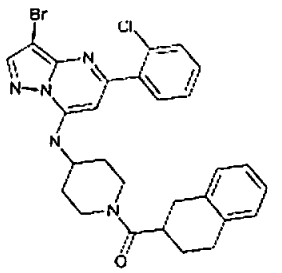
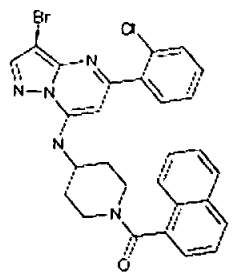
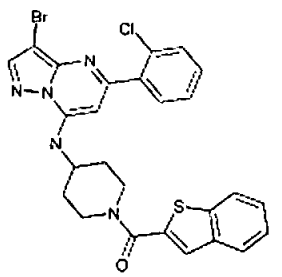
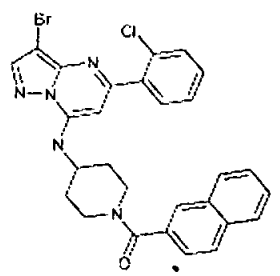
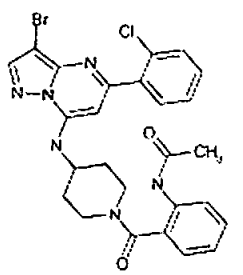
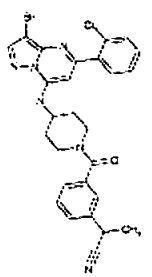
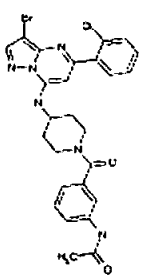
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5001 2. 476.26		1. 5006 2. 504.28
	1. 5002 2. 490.27		1. 5007 2. 506.28
	1. 5003 2. 496.27		1. 5008 2. 506.28
	1. 5004 2. 502.28		1. 5009 2. 506.28
	1. 5005 2. 502.28		1. 5010 2. 513.28

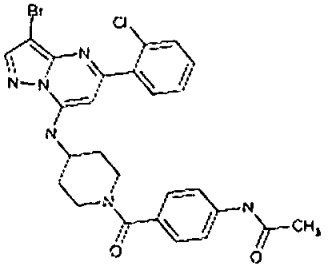
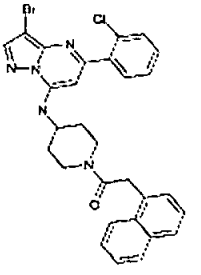
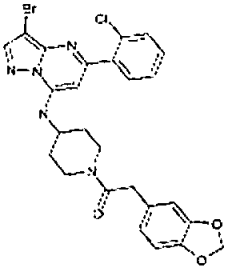
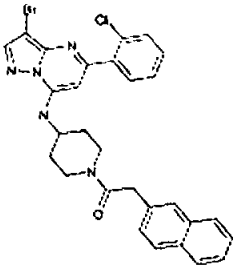
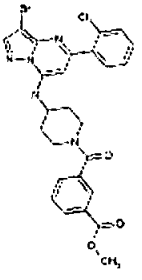
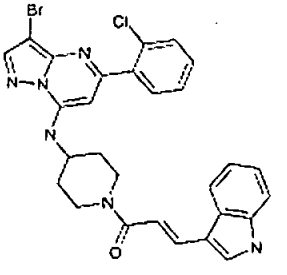
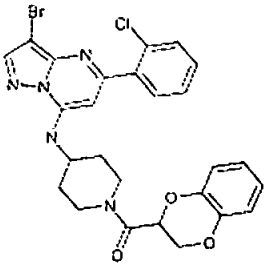
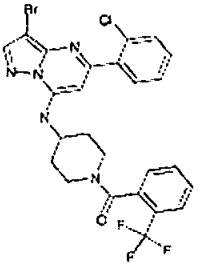
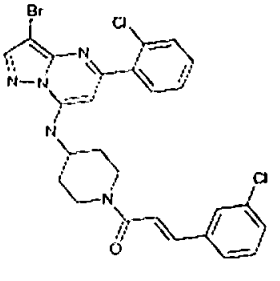
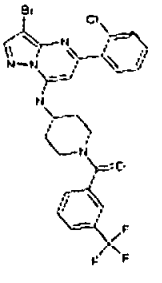
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5011 2. 515.28		1. 5016 2. 524.29
	1. 5012 2. 518.28		1. 5017 2. 526.29
	1. 5013 2. 518.28		1. 5018 2. 528.29
	1. 5014 2. 519.29		1. 5019 2. 531.29
	1. 5015 2. 522.29		1. 5020 2. 532.29

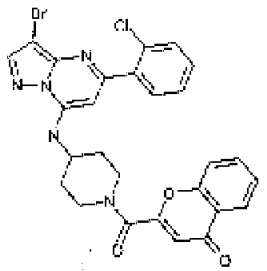
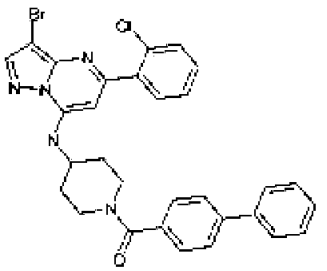
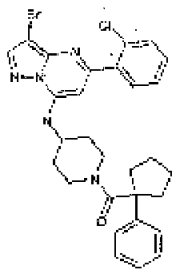
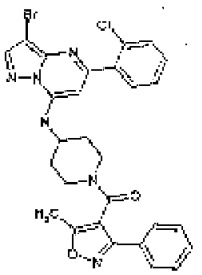
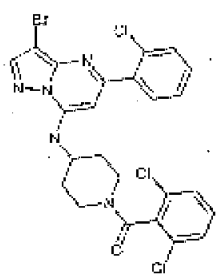
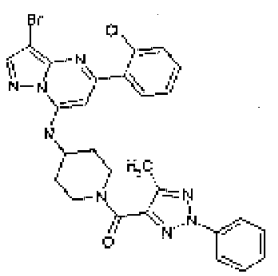
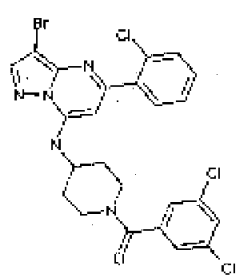
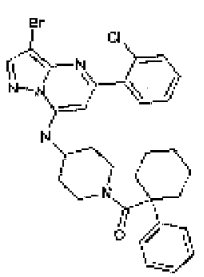
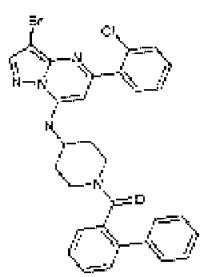
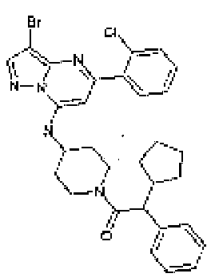
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5021 2. 532.29		1. 5026 2. 538.3
	1. 5022 2. 532.29		1. 5027 2. 540.3
	1. 5023 2. 532.29		1. 5028 2. 540.3
	1. 5024 2. 537.3		1. 5029 2. 542.3
	1. 5025 2. 537.3		1. 5030 2. 542.3

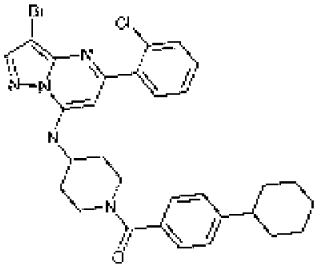
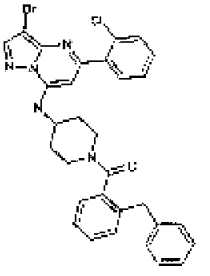
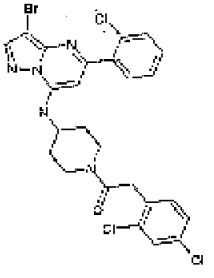
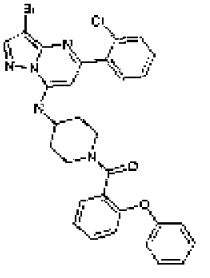
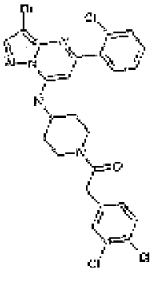
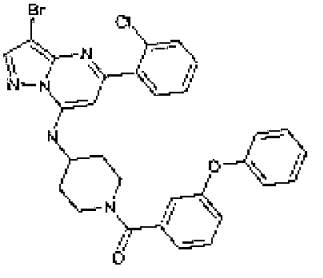
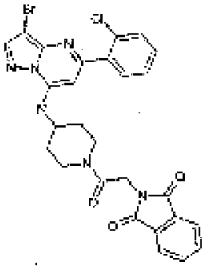
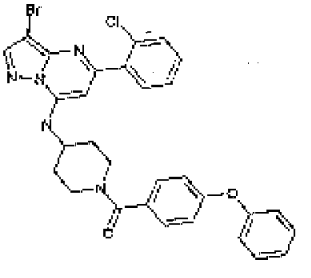
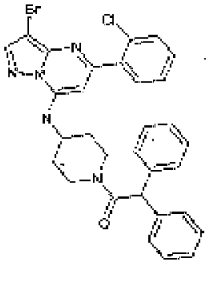
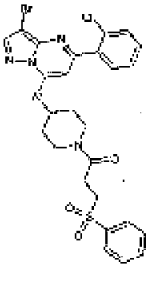
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5031 2. 542.3		1. 5036 2. 546.3
	1. 5032 2. 542.3		1. 5037 2 .546.3
	1. 5033 2. 544.3		1. 5038 2. 551.3
	1. 5034 2. 544.3		1. 5039 2. 551.3
	1. 5035 2 .546.3		1. 5040

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5041 2. 552.3		1. 5046 2. 556.31
	1. 5042 2. 552.3		1. 5047 2. 556.31
	1. 5043 2. 552.3		1. 5048 2. 556.31
	1. 5044 2. 552.3		1. 5049 2. 558.31
	1. 5045 2. 554.3		1. 5050 2. 558.31

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5051 2. 558.31		1. 5056 2. 566.31
	1. 5052 2. 560.31		1. 5057 2. 566.31
	1. 5053 2. 562.31		1. 5058 2. 568.31
	1. 5054 2. 562.31		1. 5059 2. 569.31
	1. 5055 2. 565.31		1. 5060 2. 569.31

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5061		1. 5066 2. 576.32
	1. 5062 2. 570.31		1. 5067 2. 576.32
	1. 5063 2. 570.31		1. 5068 2. 577.32
	1. 5064 2. 570.31		1. 5069 2. 580.32
	1. 5065 572.31		1. 5070 2. 580.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5071 2. 580.32		1 5076 2. 588.32
	1. 5072 2. 580.32		1. 5077 2. 593.33
	1 5073 2. 580.32		1 5078 2. 593.33
	1 5074 2. 580.32		1. 5079 2. 594.33
	1 5075 2. 588.32		1. 5080 2. 594.33

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5081 2. 594.33		1. 5086 2. 602.33
	1. 5082 2. 594.33		1.5087 2. 604.33
	1. 5083 2. 594.33		1. 5088 2. 604.33
	1. 5084 2. 595.33		1. 5089 2. 604.33
	1.5085 2. 602.33		1. 5090 2. 604.33

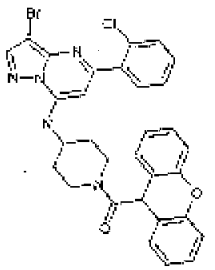
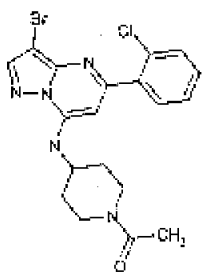
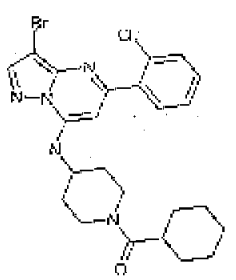
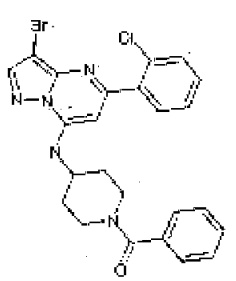
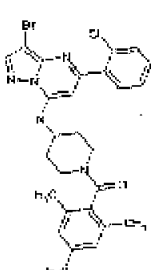
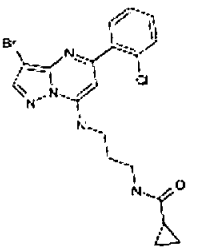
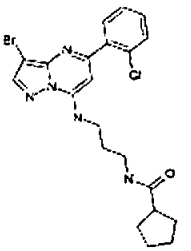
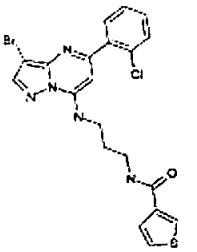
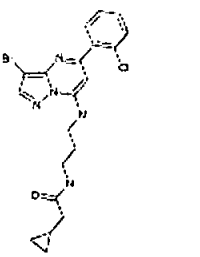
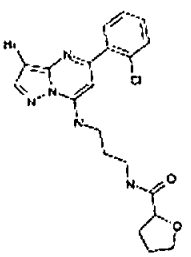
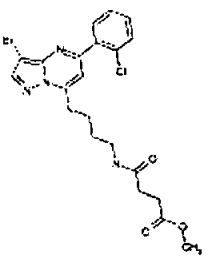
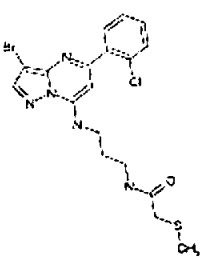
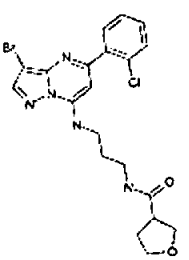
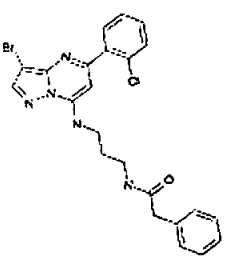
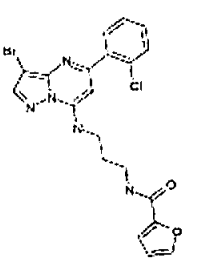
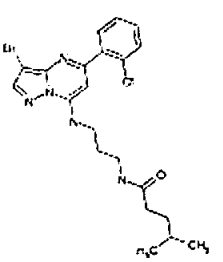
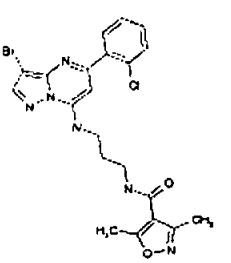
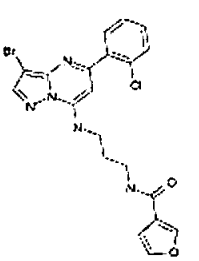
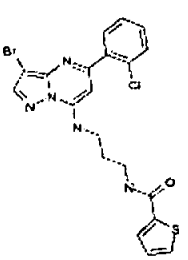
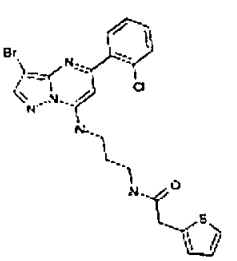
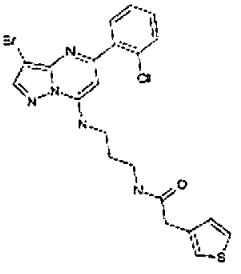
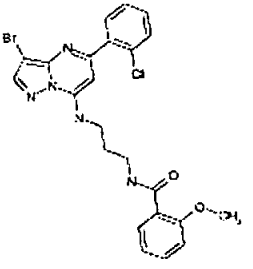
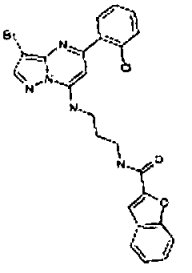
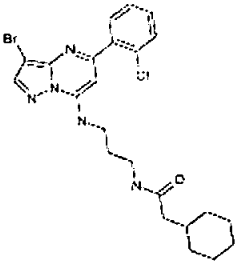
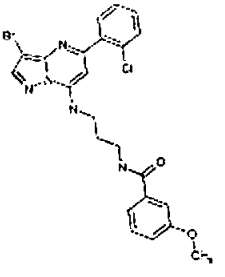
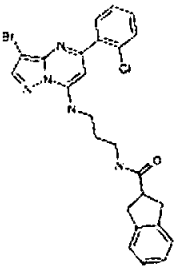
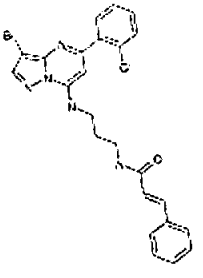
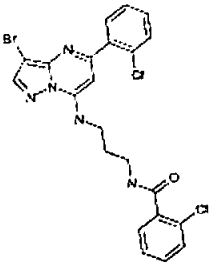
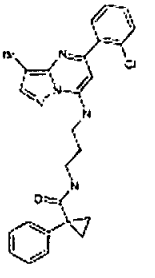
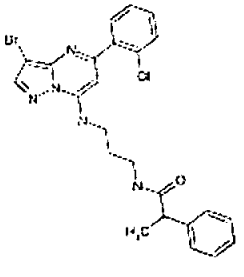
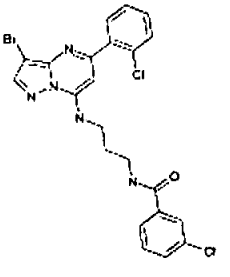
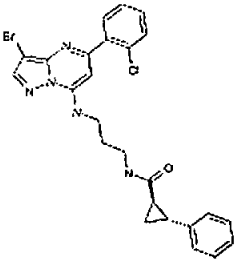
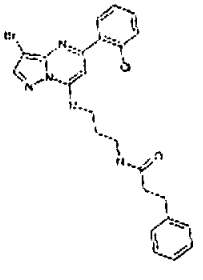
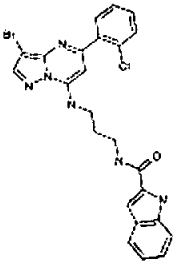
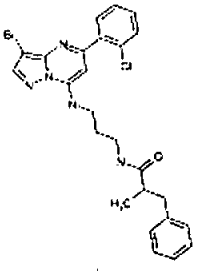
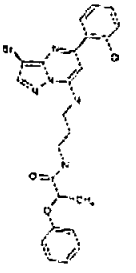
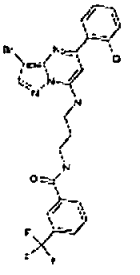
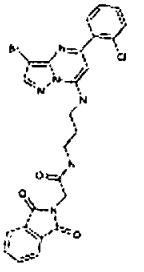
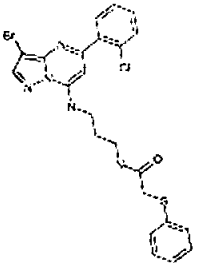
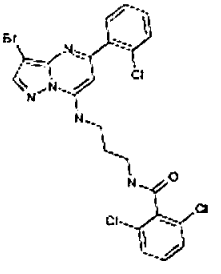
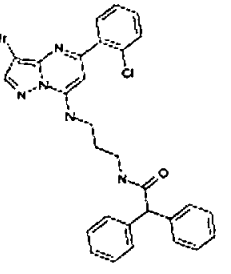
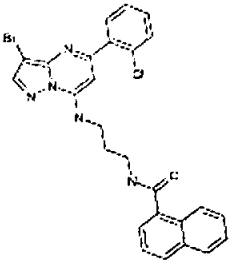
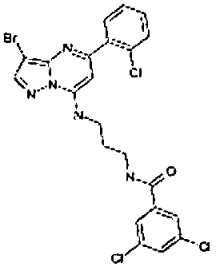
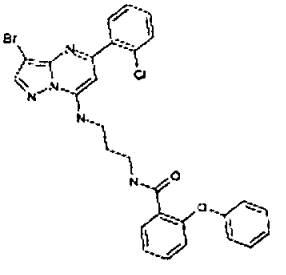
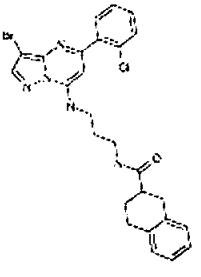
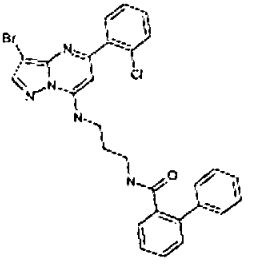
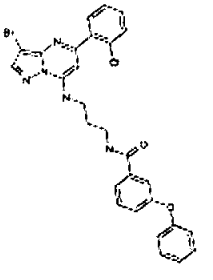
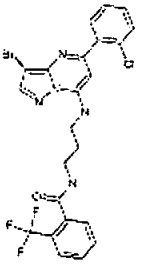
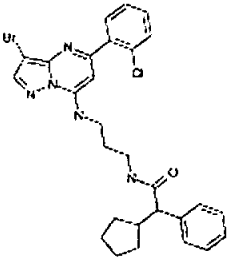
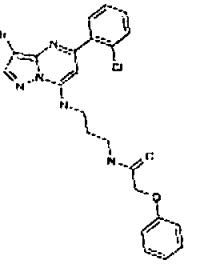
Producto	1. Ej. 2. m/z
	1. 5091 2. 616.34
	1. 5092 2. 450.25
	1. 5093 2. 518.28
	1. 5094 2. 512.28
	1. 5095 2.554.3

TABLA 51

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5101 2. 448.8		1. 5106 2. 476.8		1. 5111 2. 490.8
	1. 5102 2. 462.8		1. 5107 2. 478.8		1. 5112 2. 494.8
	1. 5103 2. 468.8		1. 5108 2. 478.8		1. 5113 2. 498.8
	1. 5104 2. 474.7		1. 5109 2. 478.8		1. 5114 2. 503.8
	1. 5105 2. 474.7		1. 5110 2. 490.8		1. 5115 2. 504.8

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5116 2. 504.8		1. 5121 2. 514.8		1. 5126 2. 524.8
	1. 5117 2. 504.9		1. 5122 2. 514.8		1. 5127 2. 524.9
	1. 5118 2. 510.8		1. 5123 2. 519.2		1. 5128 2 . 524.9
	1. 5119 2. 512.8		1. 5124 2. 519.2		1. 5129 2. 524.9
	1. 5120 2. 512.8		1. 5125 2. 523.8		1. 5130 2. 526.9

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5131 2. 528.8		1. 5136 2. 552.8		1. 5141 2. 567.8
	1. 5132 2. 530.9		1. 5137 2. 553.7		1. 5142 2. 574.9
	1. 5133 2. 534.8		1. 5138 2. 553.7		1. 5143 2. 576.9
	1. 5134 2. 538.9		1. 5139 2. 560.9		1. 5144 2. 576.9
	1. 5135 2. 552.8		1. 5140 2. 566.9		1. 5145 2. 514.8

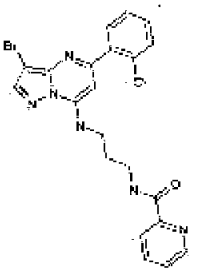
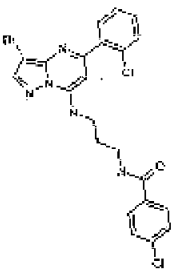
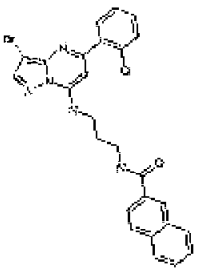
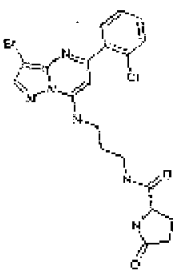
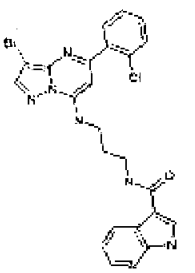
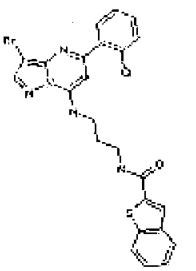
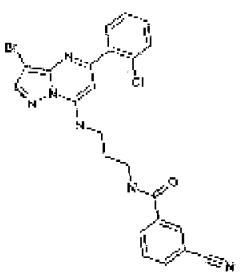
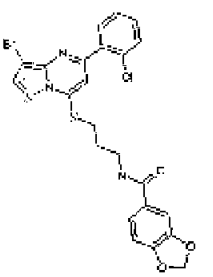
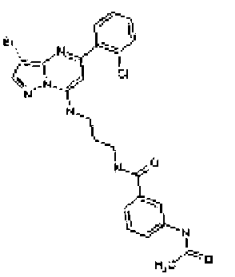
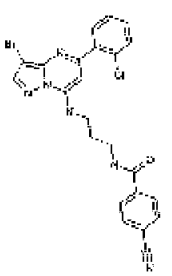
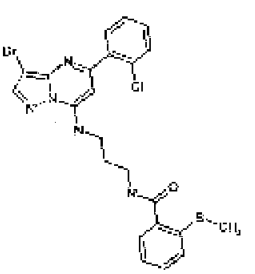
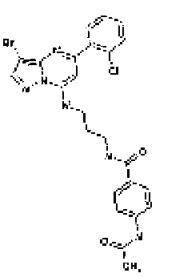
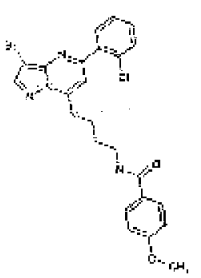
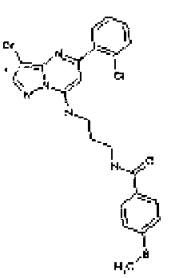
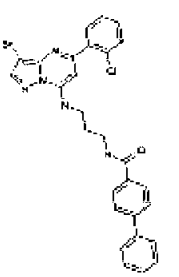
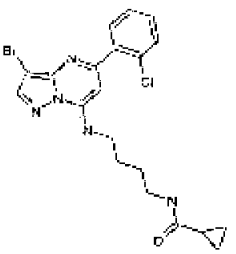
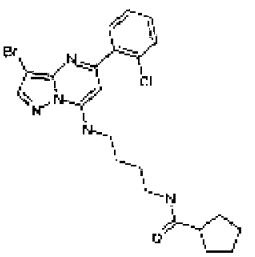
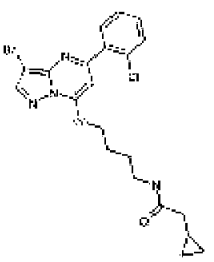
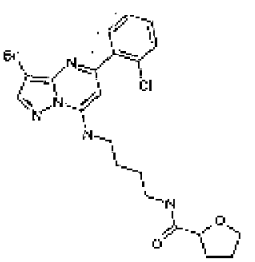
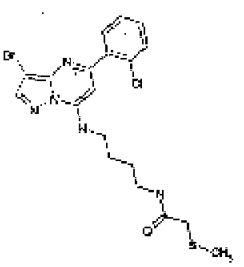
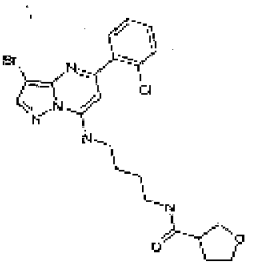
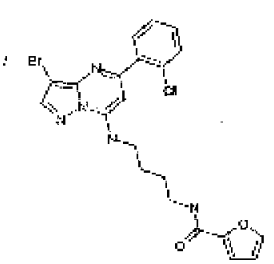
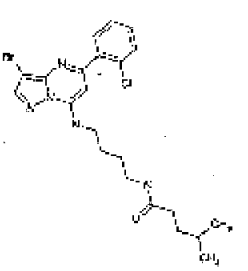
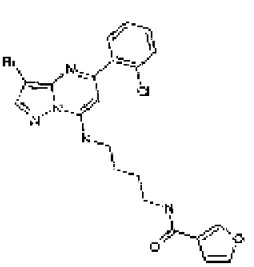
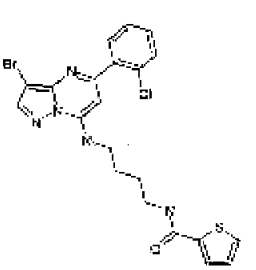
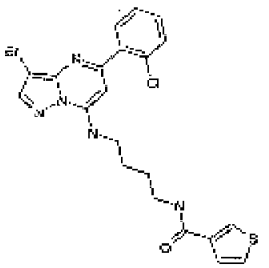
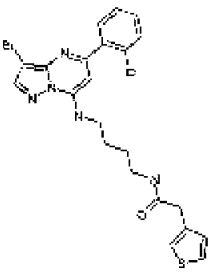
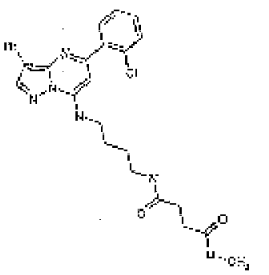
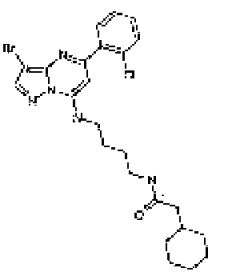
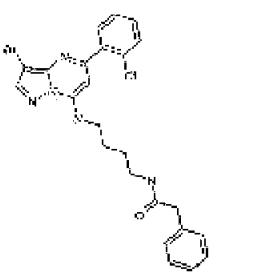
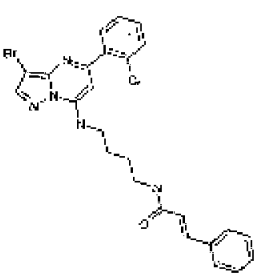
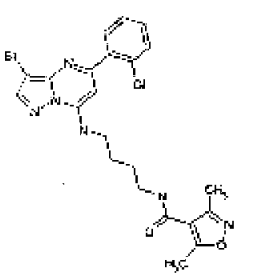
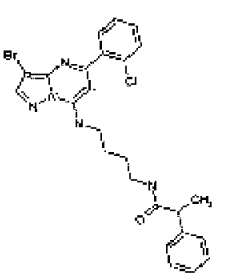
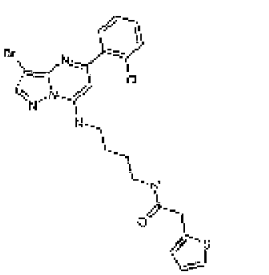
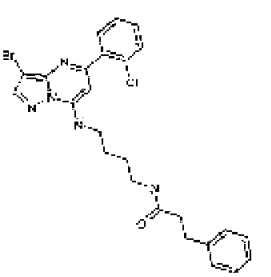
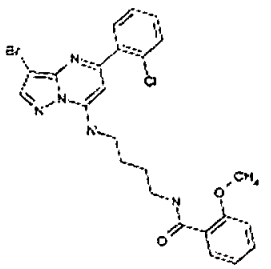
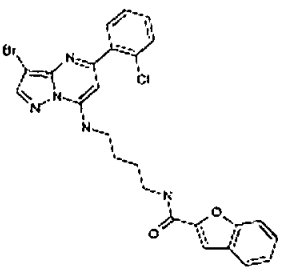
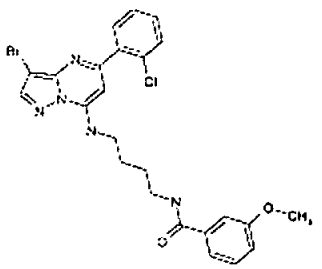
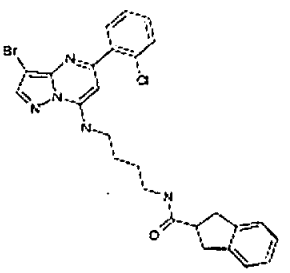
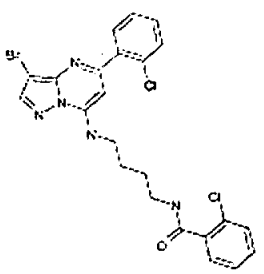
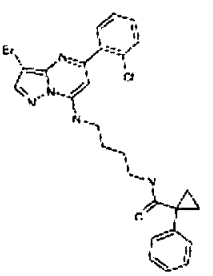
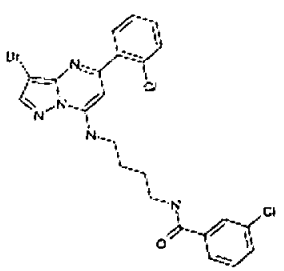
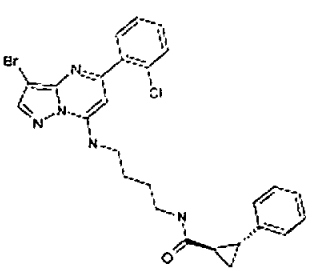
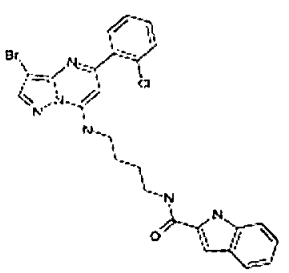
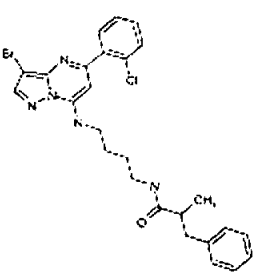
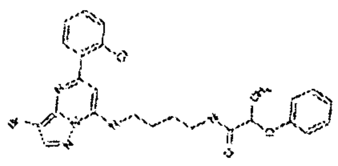
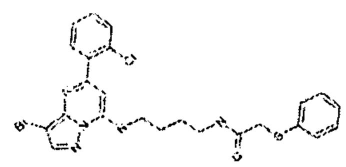
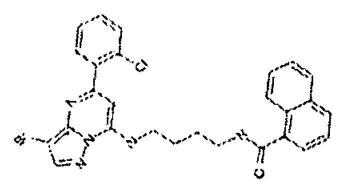
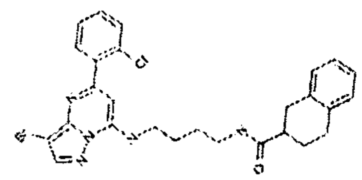
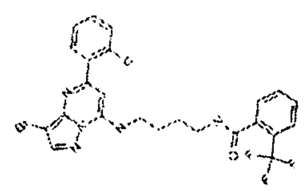
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5146 2. 485.8		1. 5151 2. 519.2		1. 5156 2. 534.8
	1. 5147 2. 491.8		1. 5152 2. 523.8		1. 5157 2. 540.9
	1. 5148 2. 509.8		1. 5153 2. 528.8		1. 5158 2. 541.8
	1. 5149 2. 509.8		1. 5154 2. 530.9		1. 5159 2. 541.8
	1. 5150 2. 514.8		1. 5155 2. 530.9		1. 5160 2. 560.9

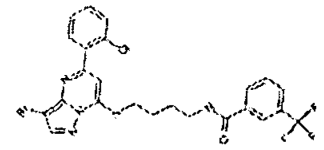
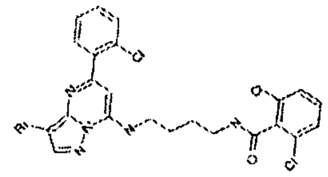
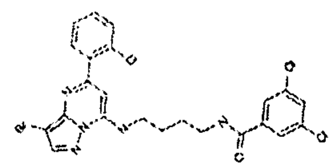
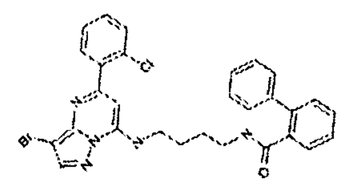
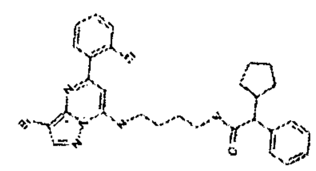
TABLA 52

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5201 2. 462.8		1. 5206 2. 490.8
	1. 5202 2. 476.8		1. 5207 2. 492.8
	1. 5203 2. 482.8		1. 5208 2. 492.8
	1. 5204 2. 488.8		1. 52009 2. 492.9
	1. 5205 2. 488.8		1. 5210 2. 504.8

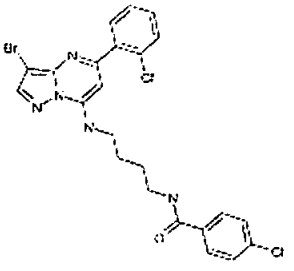
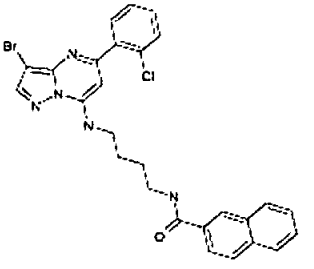
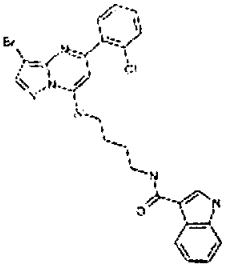
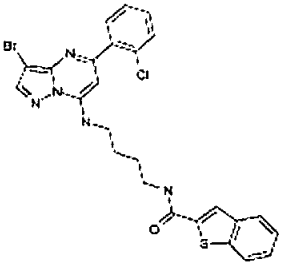
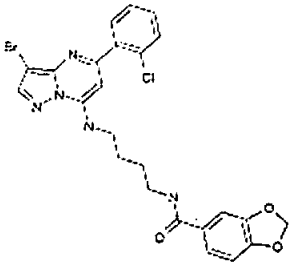
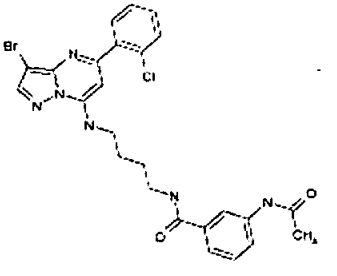
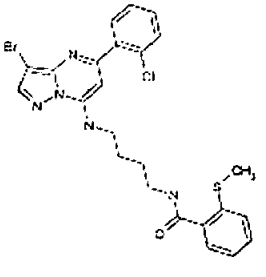
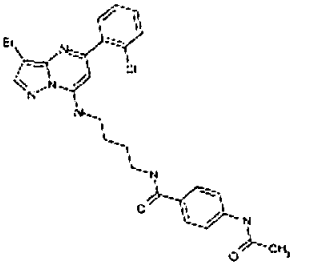
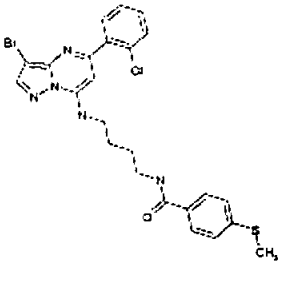
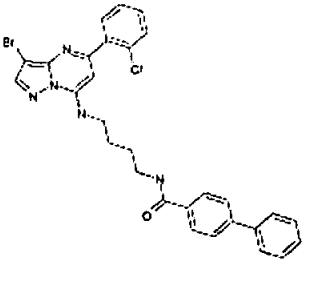
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5211 2. 504.8		1. 5216 2. 518.9
	2. 5212 2. 508.8		1. 5217 2. 518.9
	1. 5213 2. 512.8		1. 5218 2. 524.9
	1. 5214 2. 517.8		1. 5219 2. 526.9
	1. 5215 2. 518.9		1. 5220 2. 526.9

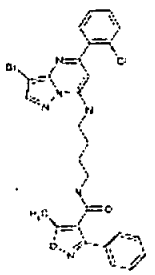
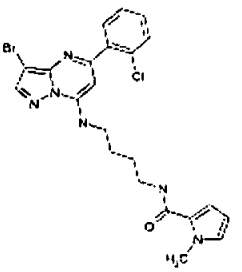
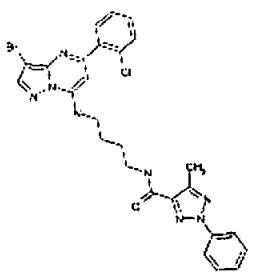
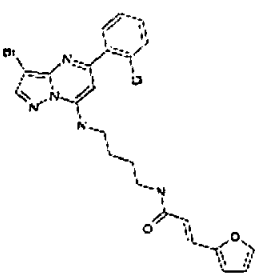
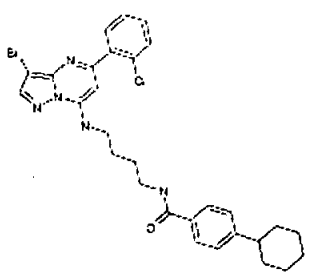
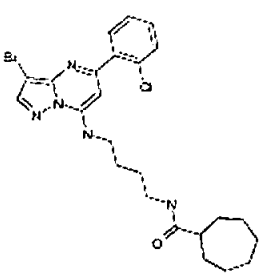
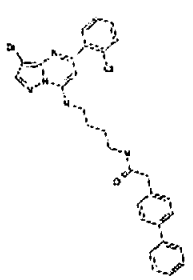
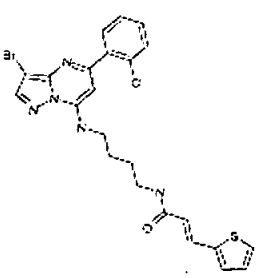
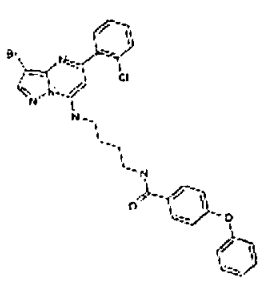
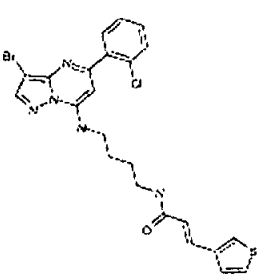
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5221 2. 528.8		1. 5226 2. 538.8
	1. 5222 2. 528.8		1. 5227 2. 538.9
	1. 5223 2. 533.3		1. 5228 2. 538.9
	1. 5224 2. 533.3		1. 5229 2. 538.9
	1. 5225 2. 537.9		1. 5230 2. 540.9

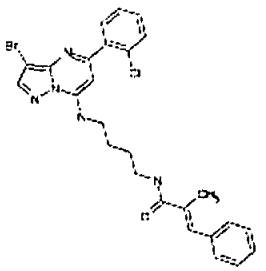
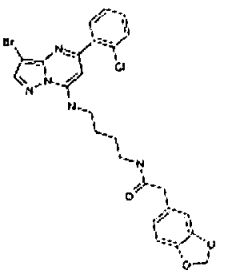
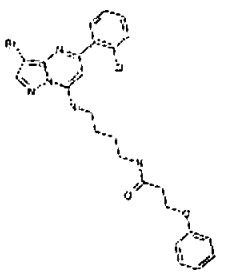
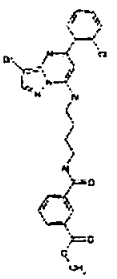
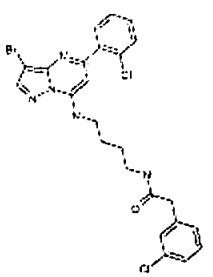
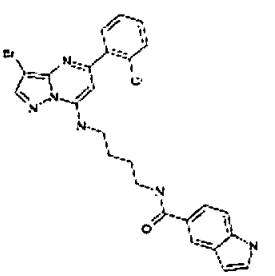
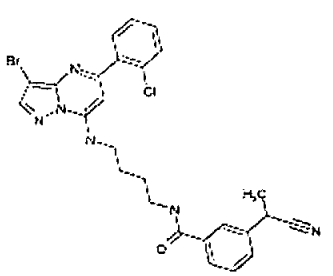
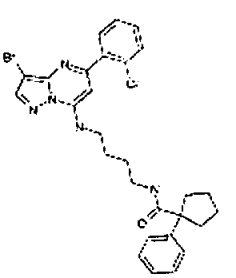
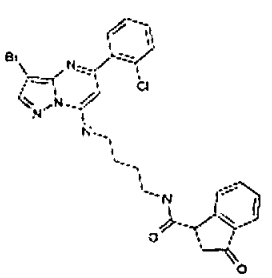
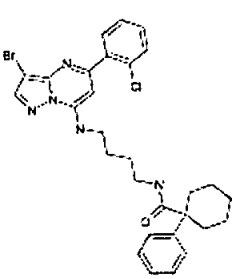
Producto	1. Ej. 2. m/z
	1. 5231 2. 542.9
	1. 5232 2. 544.9
	1. 5233 2. 548.9
	1. 5234 2. 552.9
	1. 5235 2. 566.8

Producto	1. Ej. 2. m/z
	1. 5236 2. 566.8
	1. 5237 2. 567.7
	1. 5238 2. 567.7
	1. 5239 2. 574.9
	1. 5240 2. 581

1205

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5241 2. 533.3		1. 5246 2. 548.9
	1. 5242 2. 537.9		1. 5247 2. 554.9
	1. 5243 2. 542.8		1. 5248 2. 555.9
	1. 5244 2. 544.9		1. 5249 2. 555.9
	1. 5245 2. 544.9		1. 5250 2. 574.9

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5251 2. 579.9		1. 5256 2. 501.8
	1. 5252 2. 579.9		1. 5257 2. 514.8
	1. 5253 2. 581		1. 5258 2. 518.9
	1. 5254 2. 588.9		1. 5259 2. 530.9
	1. 5255 2. 590.9		1. 5260 2. 530.9

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5261 2. 538.9		1. 5266 2. 556.9
	1. 5262 2. 542.9		1. 5267 2. 556.9
	1. 5263 2. 547.3		1. 5268 2. 537.9
	1. 5264 2. 551.9		1. 5269 2. 566.9
	1. 5265 2. 552.9		1. 5270 2. 581

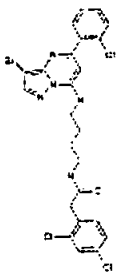
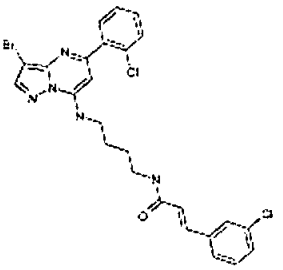
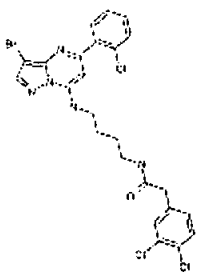
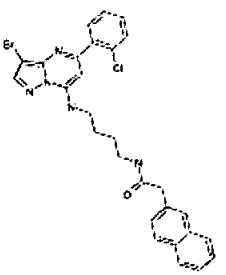
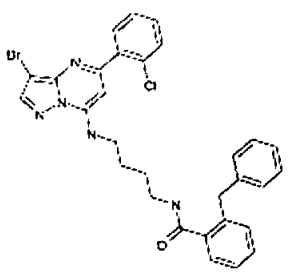
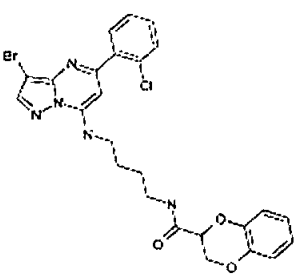
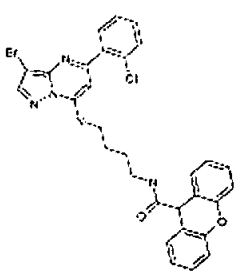
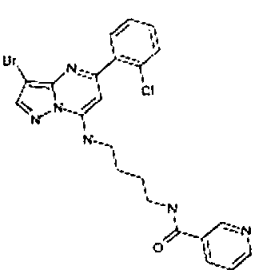
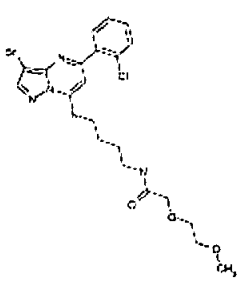
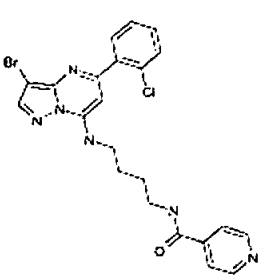
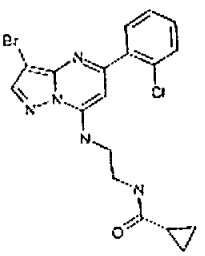
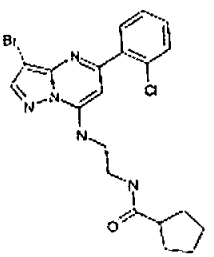
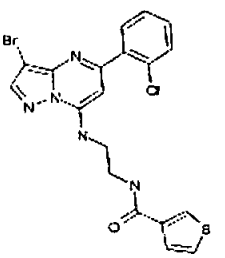
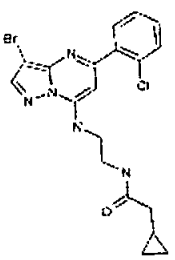
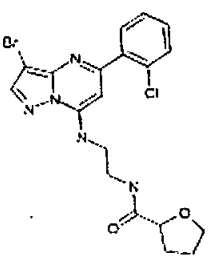
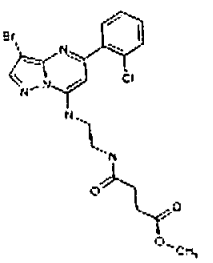
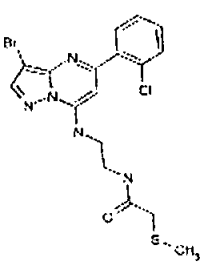
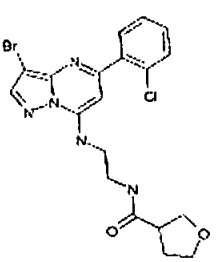
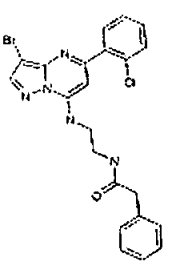
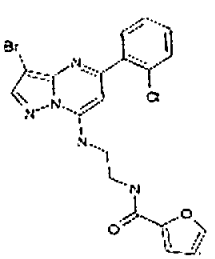
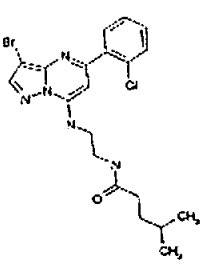
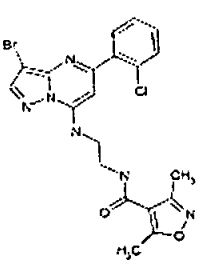
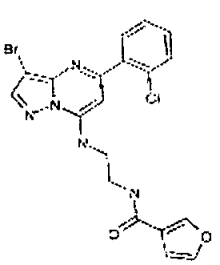
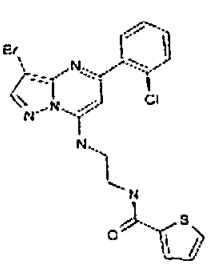
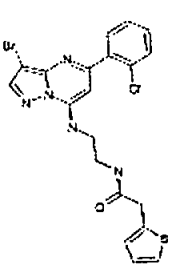
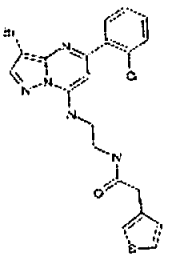
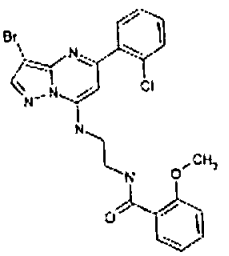
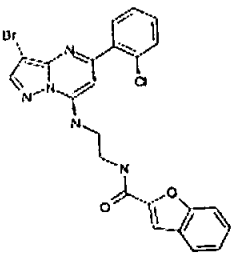
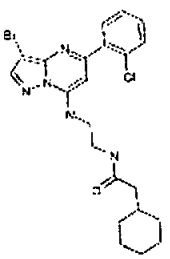
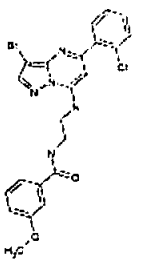
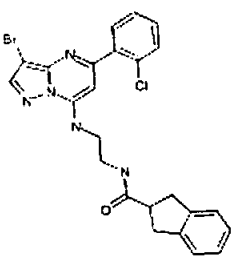
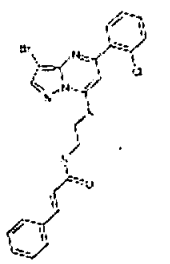
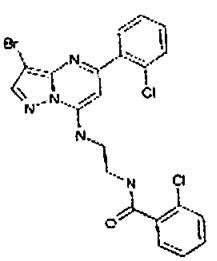
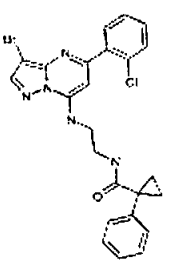
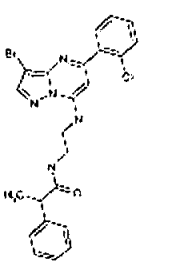
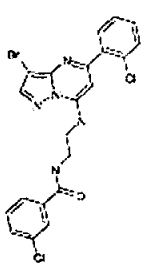
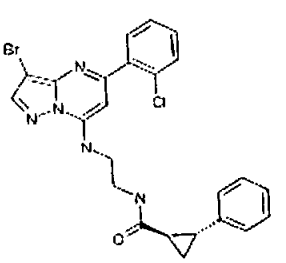
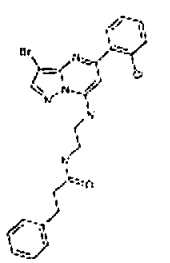
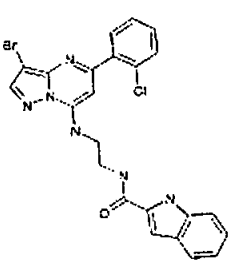
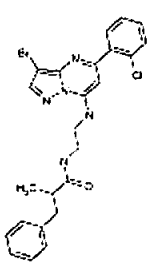
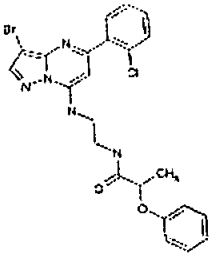
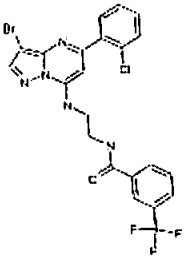
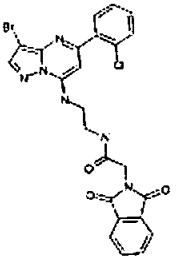
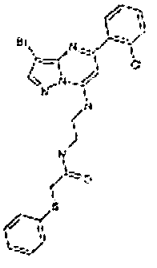
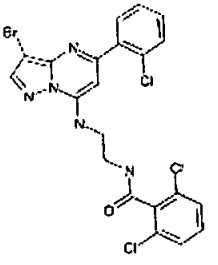
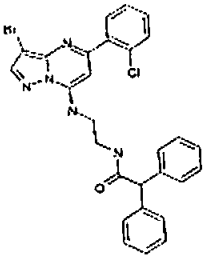
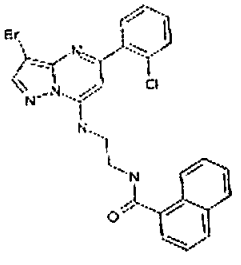
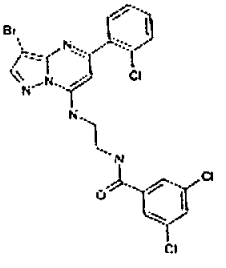
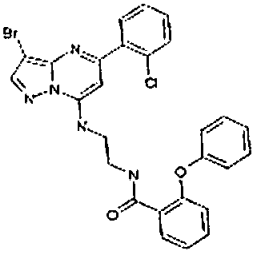
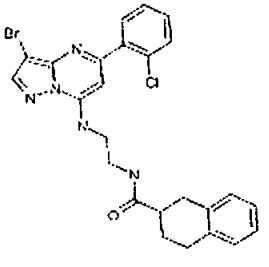
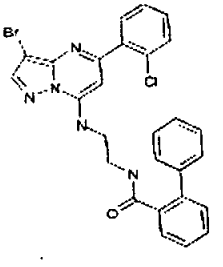
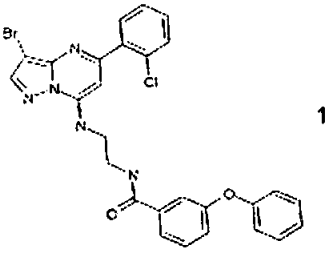
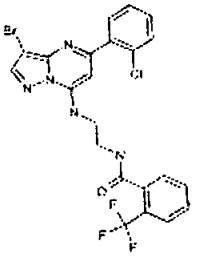
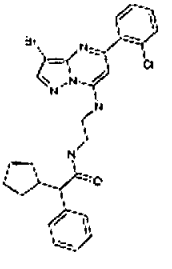
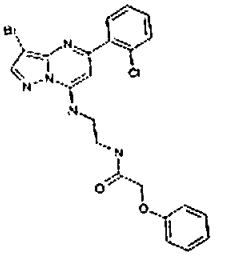
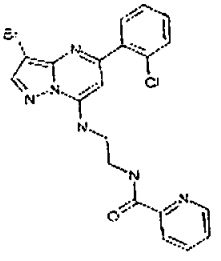
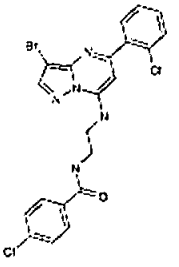
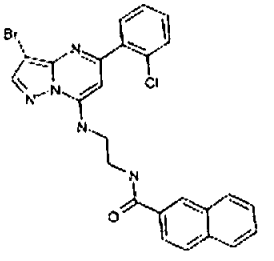
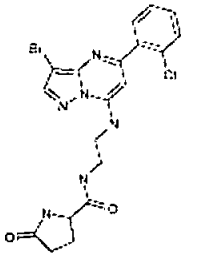
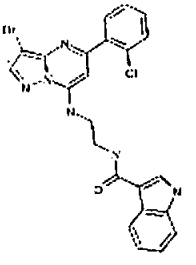
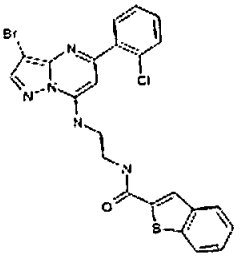
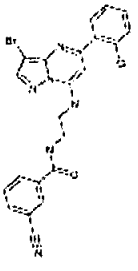
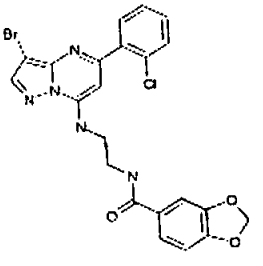
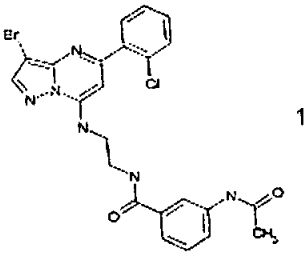
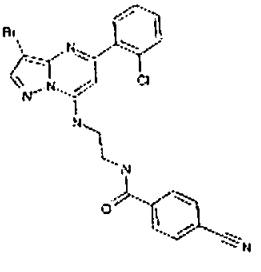
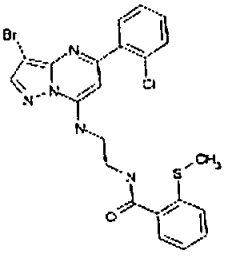
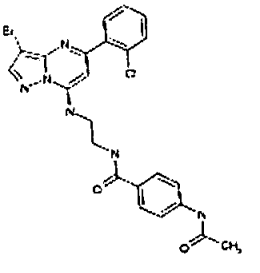
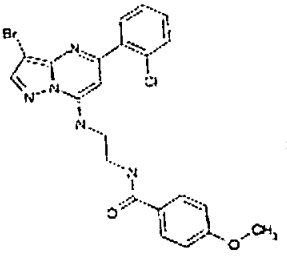
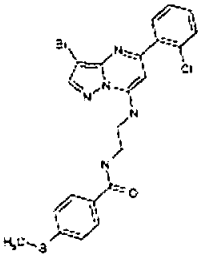
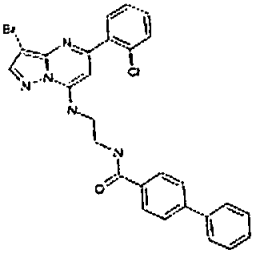
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5271 2. 581.7		1. 5276 2. 559.3
	1. 5272 2. 581.7		1. 5277 2. 562.9
	1. 5273 2. 588.9		1. 5278 2. 556.9
	1. 5274 2. 602.9		1. 5279 2. 499.8
	1. 5275 2. 510.8		1. 5280 2. 499.8

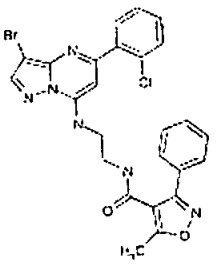
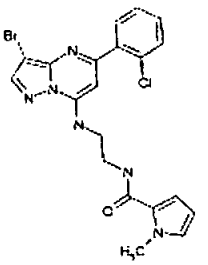
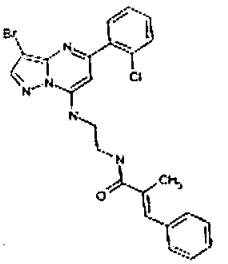
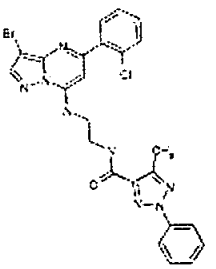
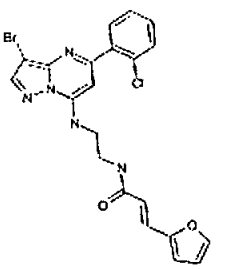
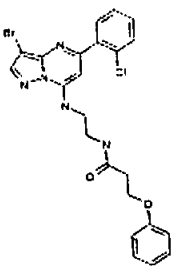
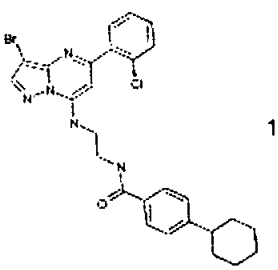
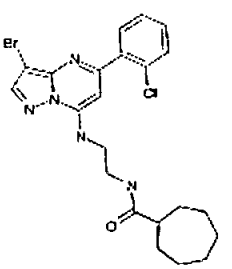
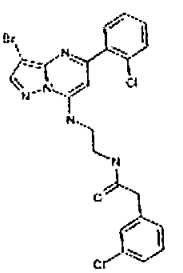
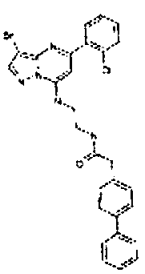
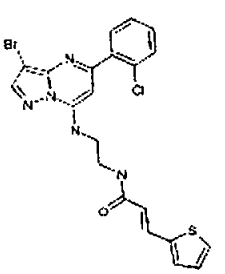
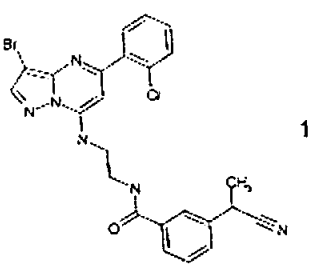
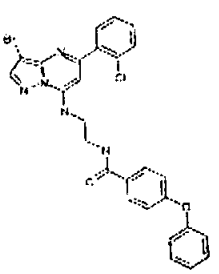
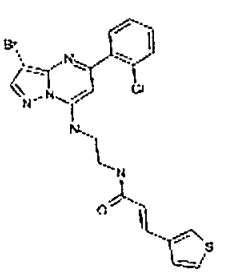
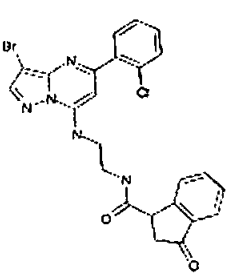
TABLA 53

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5301 2. 434.7		1. 5306 2. 462.8		1. 5311 2. 476.8
	1. 5302 2. 448.8		1. 5307 2. 464.8		1. 5312 2. 480.8
	1. 5303 2. 454.8		1. 5308 2. 464.8		1. 5313 2. 484.8
	1. 5304 2. 460.7		1. 5309 2. 464.8		1. 5314 2. 489.8
	1. 5305 2. 460.7		1. 5310 2. 476.8		1. 5315 2. 490.8

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5316 2. 490.8		1. 5321 2. 500.8		1. 5326 2. 510.8
	1. 5317 2. 490.8		1. 5322 2. 500.8		1. 5327 2. 510.8
	1. 5318 2. 496.8		1. 5323 2. 505.2		1. 5328 2. 510.8
	1. 5319 2. 498.8		1. 5324 2. 505.2		1. 5329 2. 510.8
	1. 5320 2. 498.8		1. 5325 2. 509.8		1. 5330 2. 512.8

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5331 2. 514.8		1. 5336 2. 538.8		1. 5341 2. 553.8
	1. 5332 2. 516.9		1. 5337 2. 539.6		1. 5342 2. 560.9
	1. 5333 2. 520.8		1. 5338 2. 539.6		1. 5343 2. 562.9
	1. 5334 2. 524.9		1. 5339 2. 546.9		1. 5344 2. 562.9
	1. 5335 2. 538.8		1.5340 2. 552.9		1. 5345 2. 500.8

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5346 2. 471.7		1. 5351 2. 505.2		1. 5356 2. 520.8
	1. 5347 2. 477.8		1. 5352 2. 509.8		1. 5357 2. 526.8
	1. 5348 2. 495.8		1. 5353 2. 514.8		1. 5358 2. 527.8
	1. 5349 2. 495.8		1. 5355 2. 516.9		1. 5359 2. 527.8
	5350 2. 500.8		1. 5356 2. 516.9		1. 5360 2. 546.9

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5361 2. 551.8		1. 5366 2. 473.8		1. 5371 2.510.8
	1. 5362 2. 551.8		1. 5367 2. 486.8		1. 5372 2. 514.8
	1. 5363 2. 552.9		1. 5368 2. 490.8		1. 5373 2. 519.2
	1. 5364 2. 560.9		1. 5369 2. 502.8		1. 5374 2. 523.8
	1. 5365 2. 562.9		1. 5370 2. 502.8		1. 5375 2. 524.8

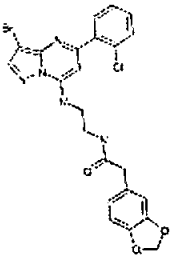
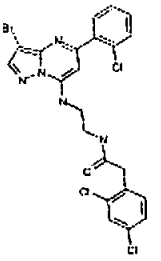
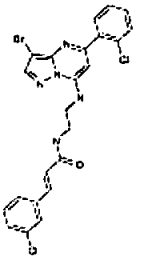
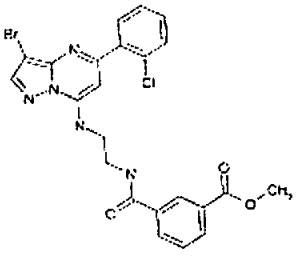
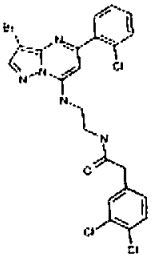
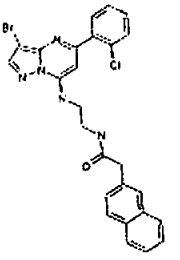
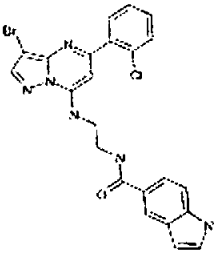
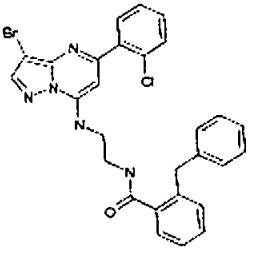
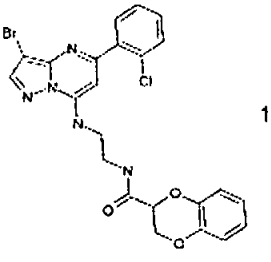
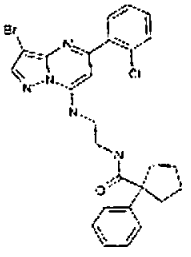
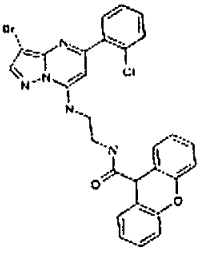
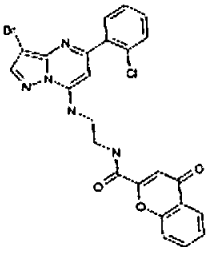
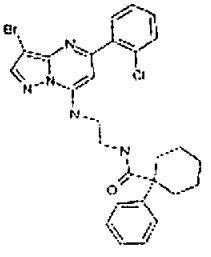
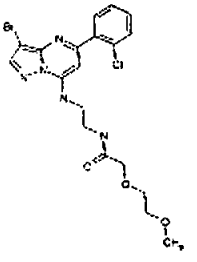
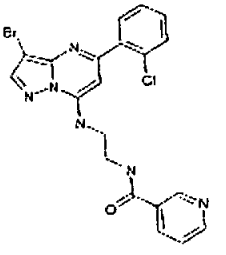
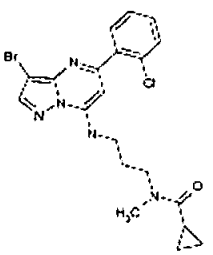
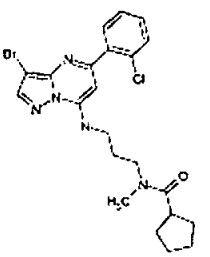
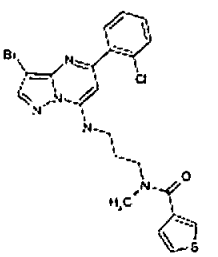
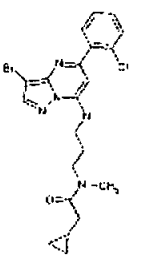
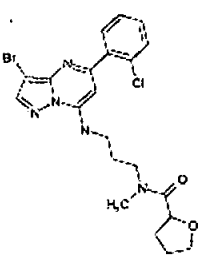
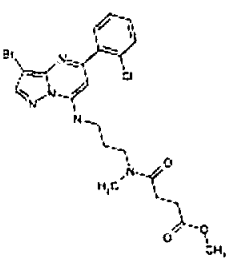
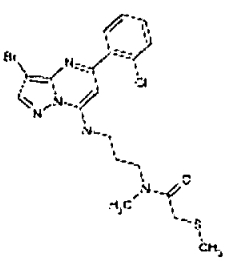
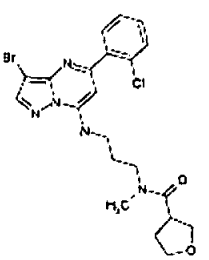
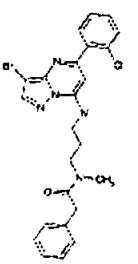
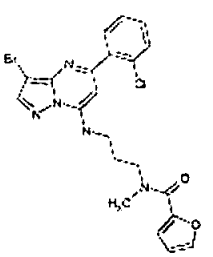
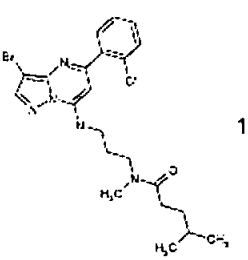
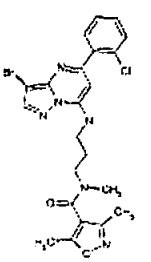
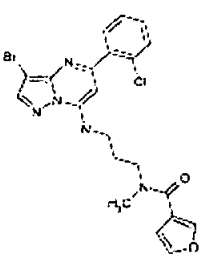
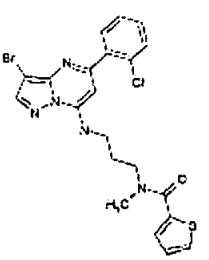
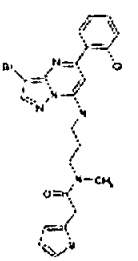
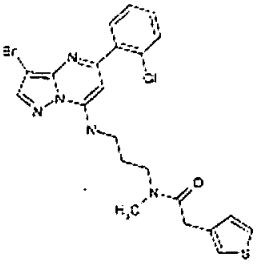
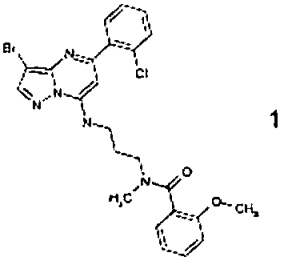
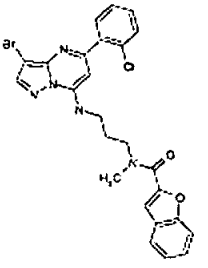
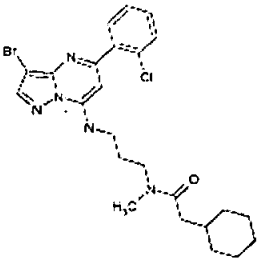
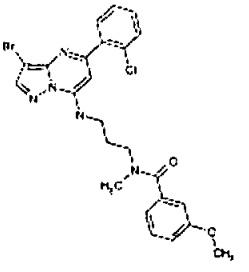
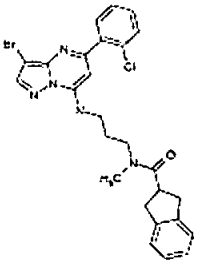
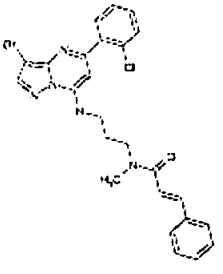
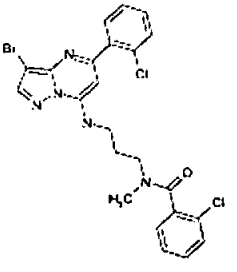
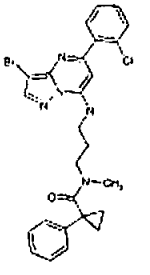
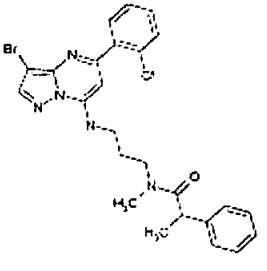
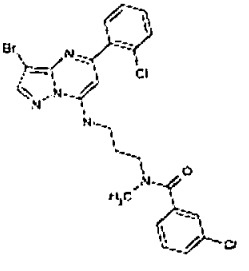
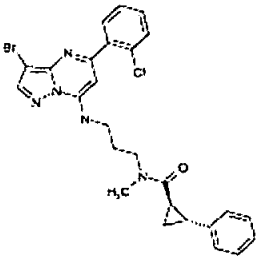
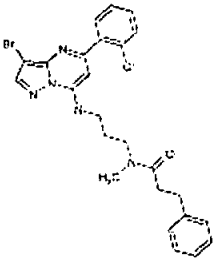
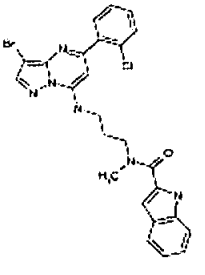
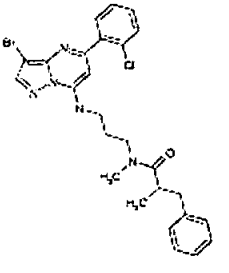
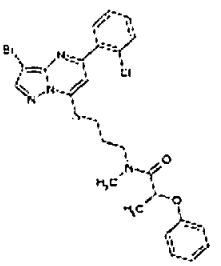
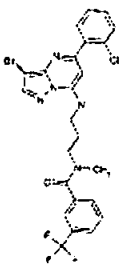
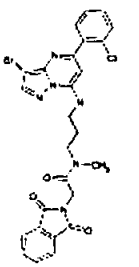
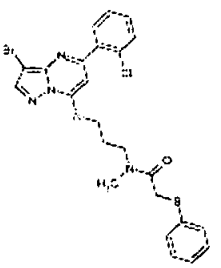
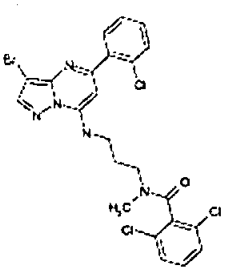
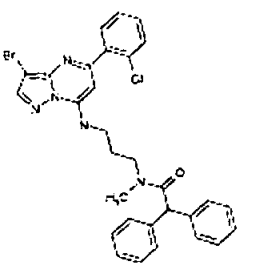
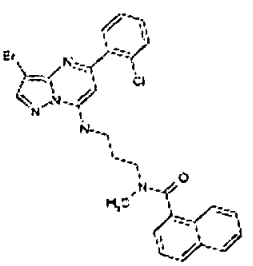
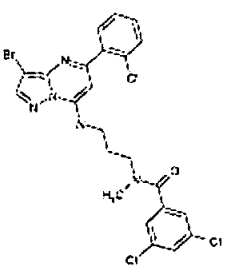
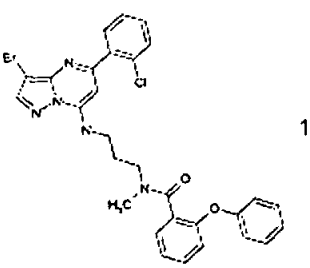
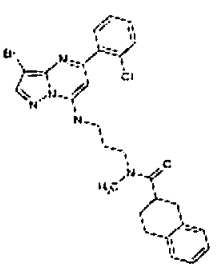
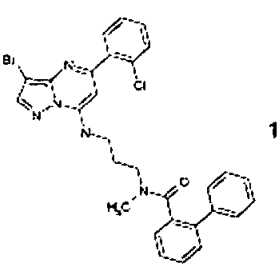
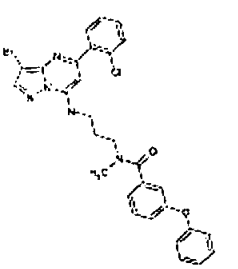
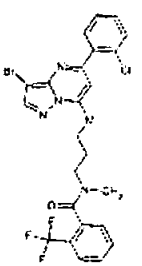
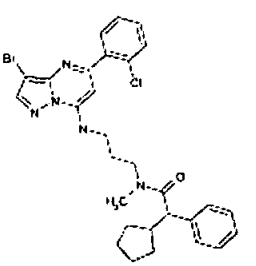
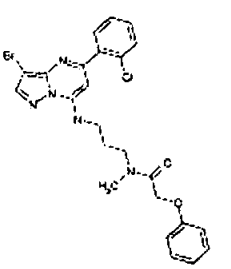
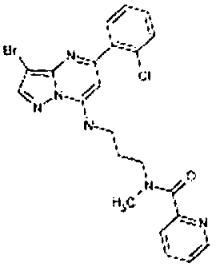
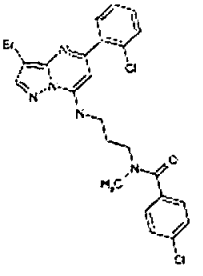
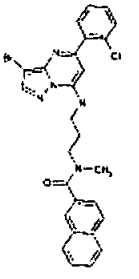
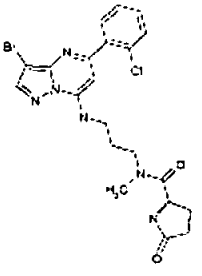
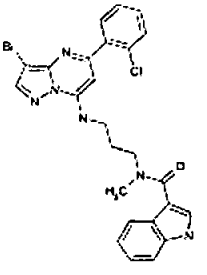
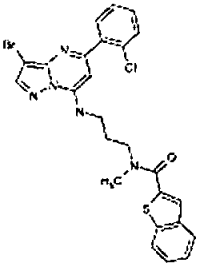
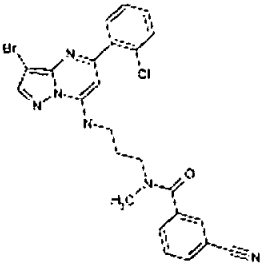
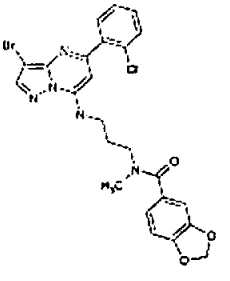
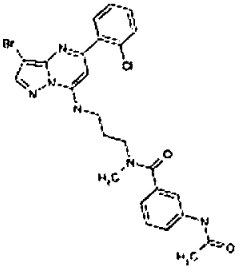
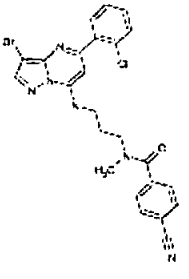
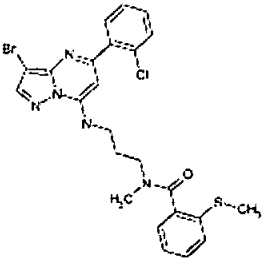
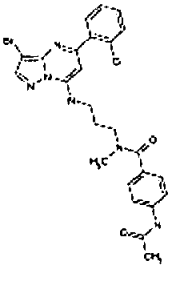
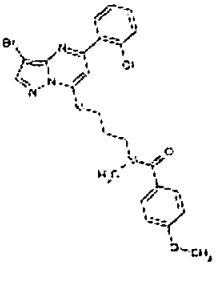
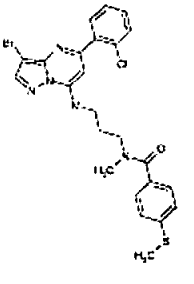
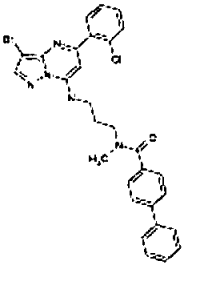
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5376 2. 528.8		1. 5381 2. 553.7		1. 5386 2. 531.2
	1. 5377 2. 528.8		1. 5382 2. 553.7		1. 5387 2. 534.8
	1. 5378 2. 509.8		1. 5383 2. 560.9		1. 5388 2. 528.8
	1. 5379 2. 538.9		1. 5384 2. 574.9		1. 5389 2. 538.8
	1. 5380 2. 552.9		1. 5385 2. 482.8		1. 5390 2. 471.7

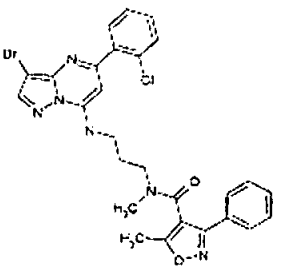
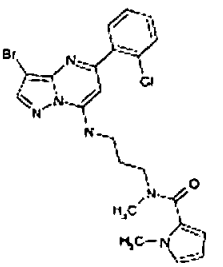
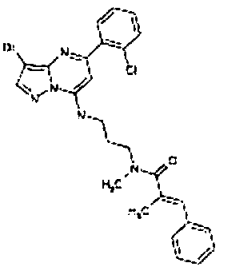
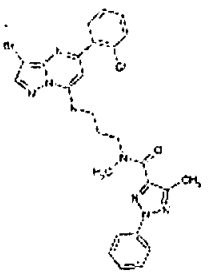
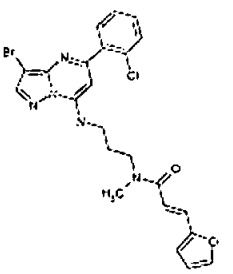
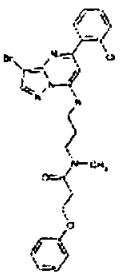
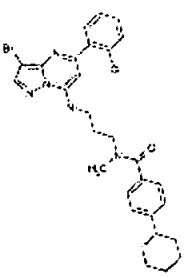
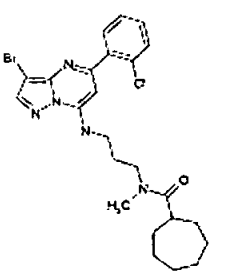
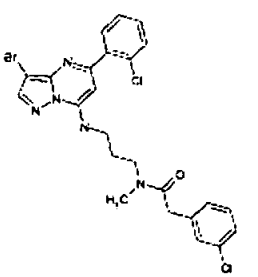
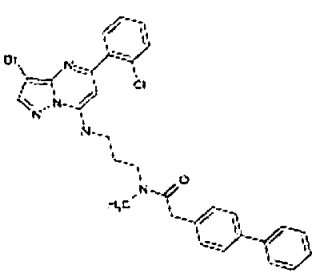
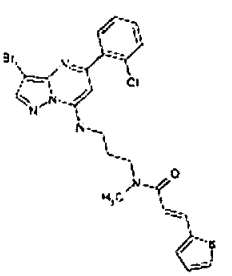
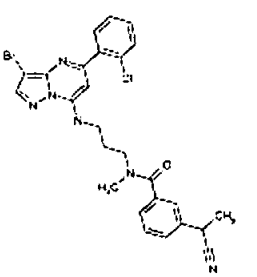
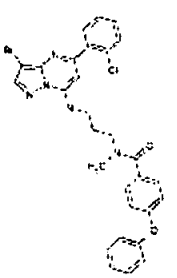
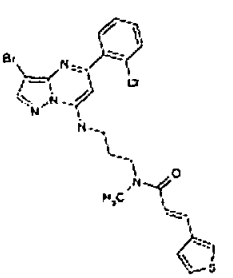
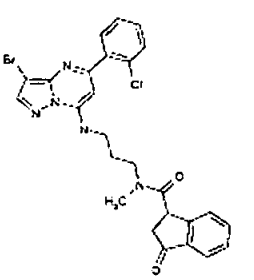
TABLA 54

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5401 2. 463.3		1. 5406 2. 491.3		1. 5411 2. 505.3
	1. 5402 2. 477.3		1. 5407 2. 493.3		1. 5412 2. 509.3
	1. 5403 2. 483.3		1. 5408 2. 493.3		1. 5413 2. 513.3
	1. 5404 2. 489.3		1. 5409 2. 493.3		1. 5414 2. 518.3
	1. 5405 2. 489.3		1. 5410 2. 505.3		1. 5415 2. 519.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5416 2. 519.3		1. 5121 2. 529.3		1. 5426 2. 539.3
	1. 5417 2. 519.3		1. 5422 2. 529.3		1. 5427 2. 539.3
	1. 5418 2. 525.3		1. 5423 2. 533.3		1. 5428 2. 539.3
	1. 5419 2. 527.3		1. 5424 2. 533.3		1. 5429 2. 539.3
	1. 5420 2. 527.3		1. 5425 2. 538.3		1. 5430 2. 541.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5431 2. 543.3		1. 5436 2. 567.3		1. 5441 2. 582.3
	1. 5432 2. 545.3		1. 5437 2. 567.3		1. 5442 2. 589.3
	1. 5433 2. 549.3		1. 5438 2. 567.3		1. 5443 2. 591.3
	1. 5434 2. 553.3		1. 5439 2. 575.3		1. 5444 2. 591.3
	1. 5435 2. 567.3		1. 5440 2. 581.3		1. 5445 2. 529.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5446 2. 500.3		1. 5451 2. 533.3		1. 5456 2. 549.3
	1. 5447 2. 830.5		1. 54525 2. 719.4		1. 5457 2. 555.3
	1. 5448 2. 524.3		1. 5453 2. 543.3		1. 5458 2. 556.3
	1. 5449 2. 524.3		1. 5454 2. 545.3		1.5459 2. 556.3
	1. 5450 2. 529.3		1. 5455 2. 545.3		1. 5460 2. 575.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5461 2. 580.3		1. 5466 2. 502.3		1. 5471 2. 539.3
	1. 5462 2. 580.3		1. 5467 2. 515.3		1. 5472 2. 543.3
	1. 5463 2. 581.3		1. 5468 2. 519.3		1. 5473 2. 547.3
	1. 5464 2. 589.3		1. 5469 2. 531.3		1. 5474 2. 552.3
	1. 5465 2. 591.3		1. 5470 2. 531.3		1. 5475 2. 553.3

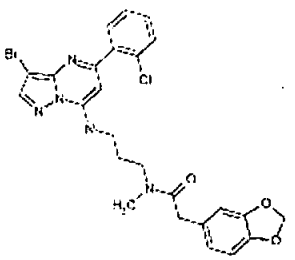
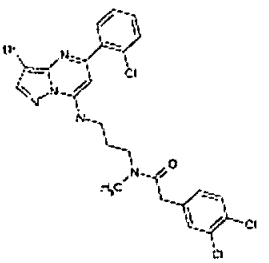
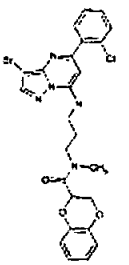
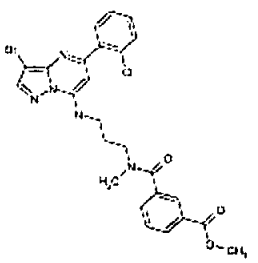
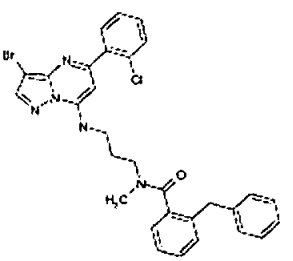
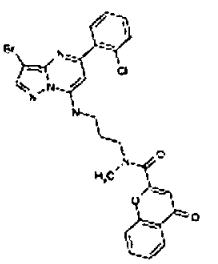
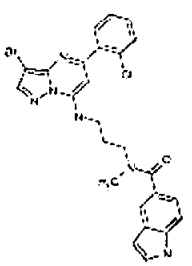
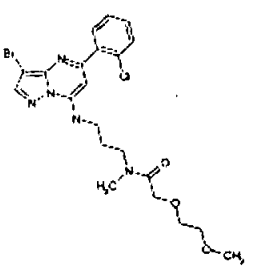
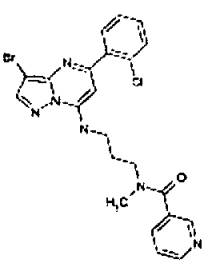
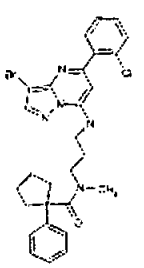
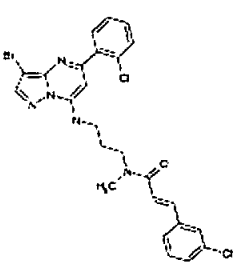
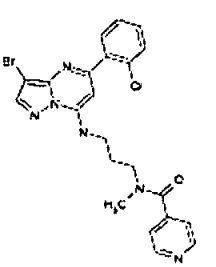
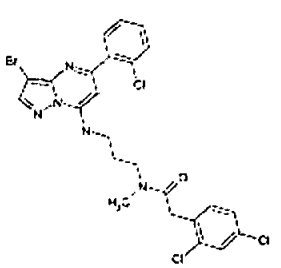
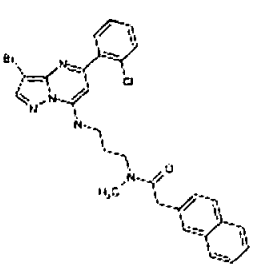
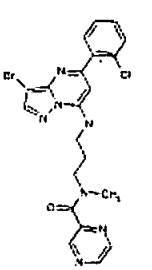
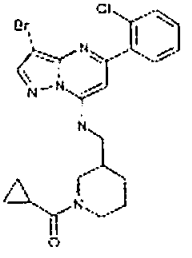
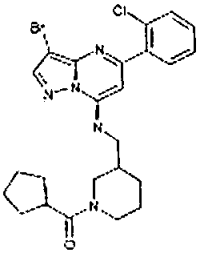
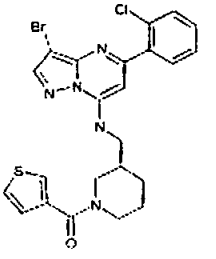
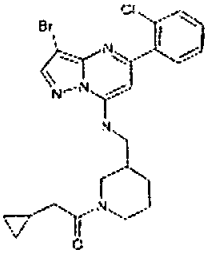
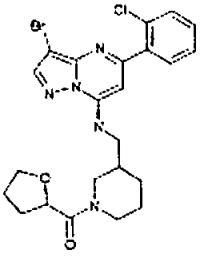
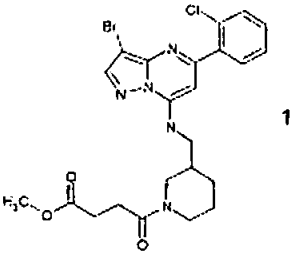
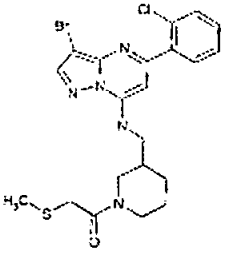
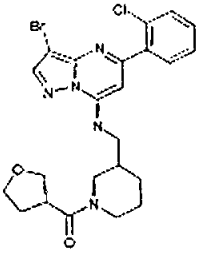
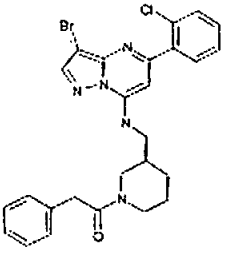
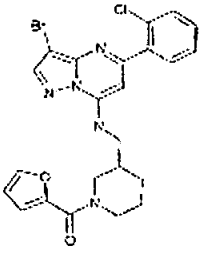
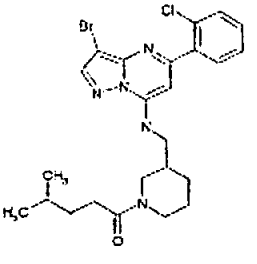
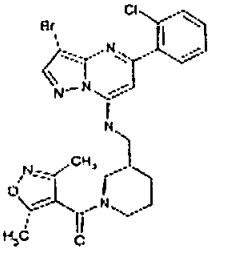
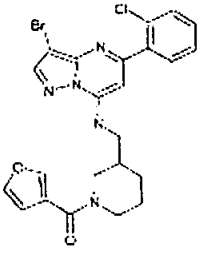
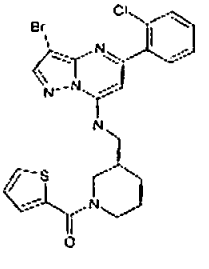
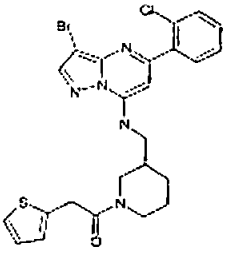
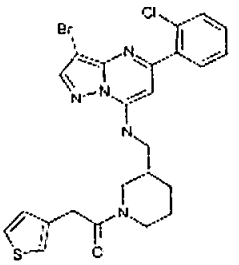
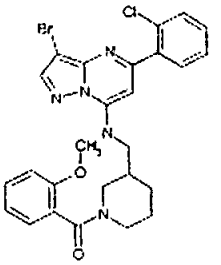
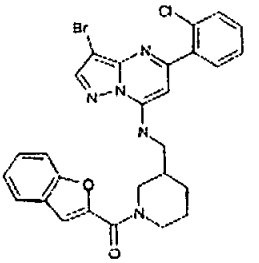
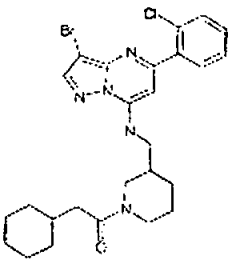
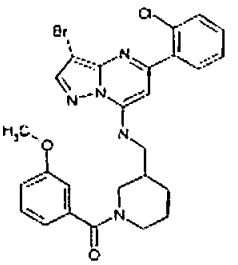
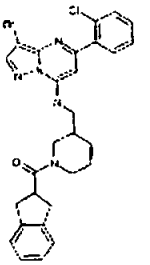
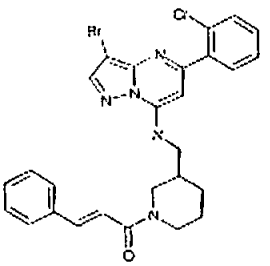
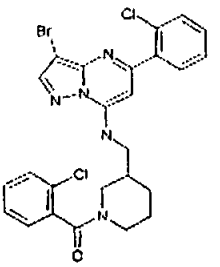
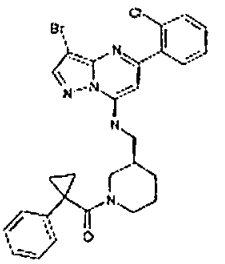
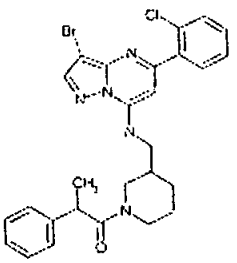
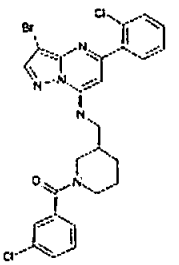
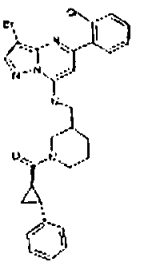
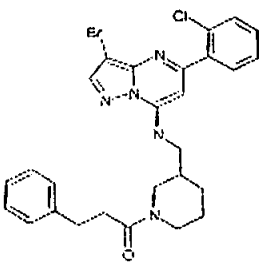
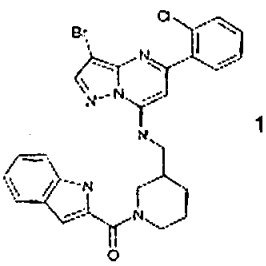
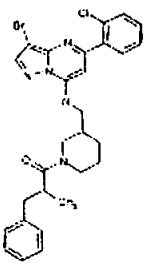
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5476 2. 557.3		1. 5481 2. 581.3		. 5486 2.
	1. 5477 2. 557.3		1. 5482 2. 589.3		1. 5487 2. 891.5
	1. 5478 2. 538.3		1. 5483 2. 511.3		1. 5488 2. 500.3
	1. 5479 2. 567.3		1. 5484 2. 559.3		1. 5489 2. 500.3
	1. 5480 2. 581.3		1. 5485 2. 563.3		1. 5490 2. 501.3

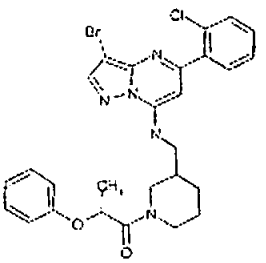
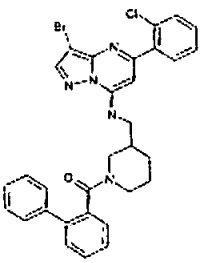
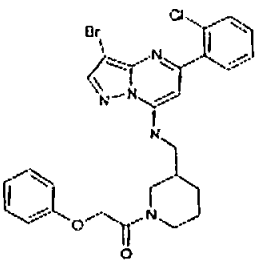
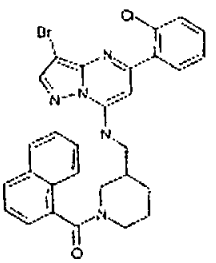
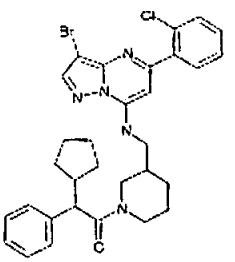
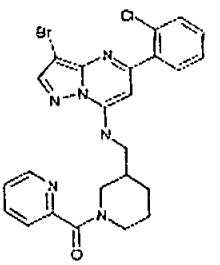
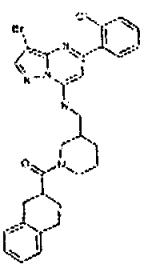
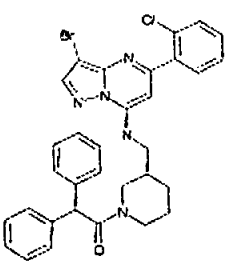
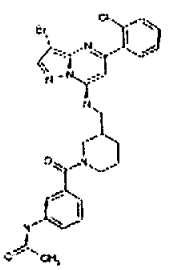
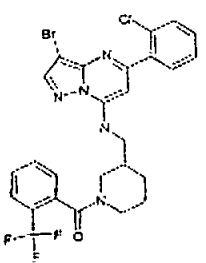
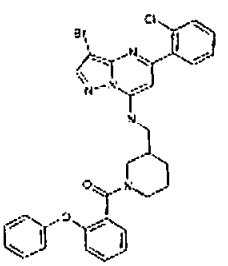
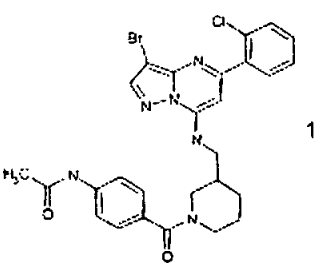
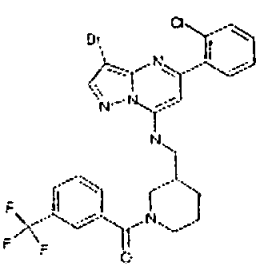
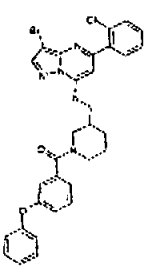
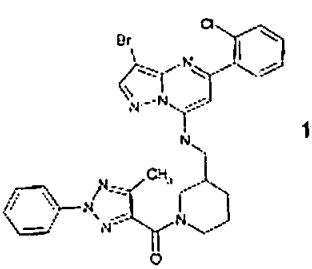
TABLA 55

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5501 2. 488.81		1. 5506 2. 516.87		1. 5511 2. 530.87
	1. 5502 2. 502.84		1. 5507 2. 518.84		1. 5512 2. 534.84
	1. 5503 2. 508.87		1. 5508 2. 518.84		1. 5513 2. 538.87
	1. 5504 2. 514.81		1. 5509 2. 518.88		1. 5514 2. 543.85
	1. 5505 2. 514.81		1. 5510 2. 530.87		1. 5515 2. 544.9

1222

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5516 2. 544.9		1. 5521 2. 554.87		1. 5526 2. 564.87
	1. 5517 2. 544.92		1. 5522 2. 554.87		1. 5527 2. 564.91
	1. 5518 2. 550.89		1. 5523 2. 559.29		1. 5528 2. 564.91
	1. 5519 2. 552.9		1. 5524 2. 559.29		1. 5529 2. 564.91
	1. 5520 2. 552.9		1. 5525 2. 563.88		1. 5530 2. 566.93

1223

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5531 2. 568.9		1. 5536 2. 600.95		1. 5541
	1. 5532 2. 574.91		1. 5537 2. 606.99		1. 5542 2. 525.83
	1. 5533 2. 578.94		1. 5538 2. 614.97		1. 5543 2. 581.9
	1. 5534 2. 592.85		1. 5539 2. 616.95		1. 5544 2. 581.9
	1. 5535 2. 592.85		1. 5540 2. 616.95		1. 5545 2. 605.92

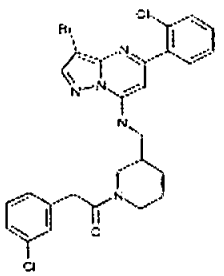
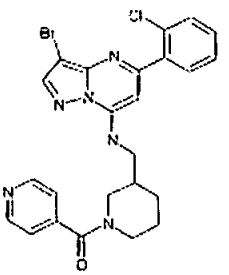
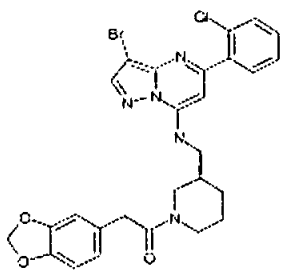
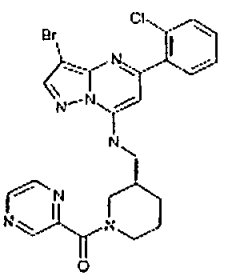
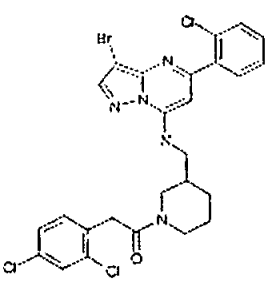
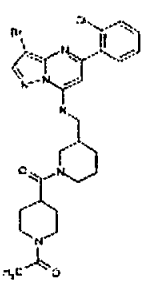
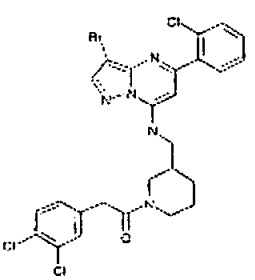
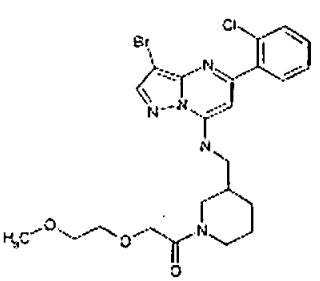
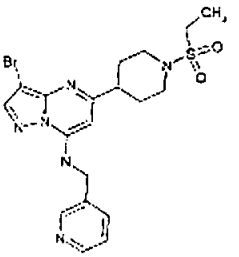
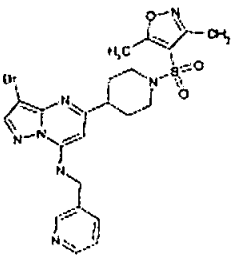
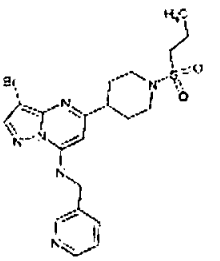
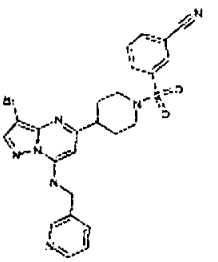
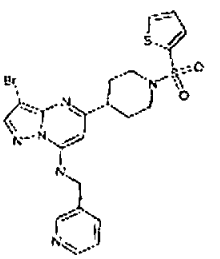
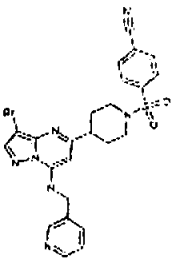
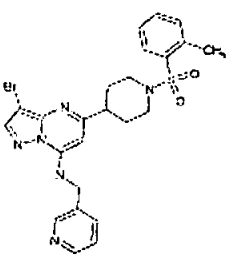
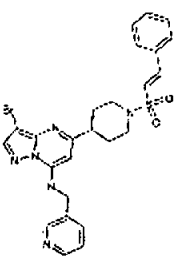
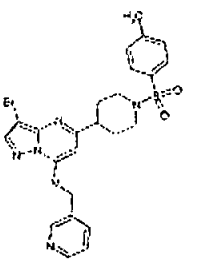
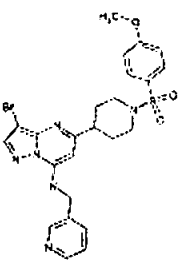
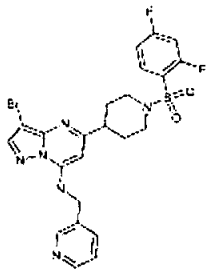
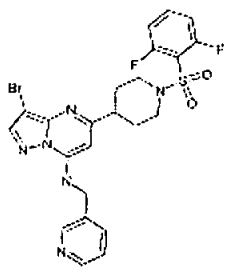
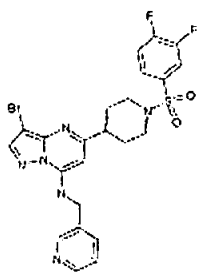
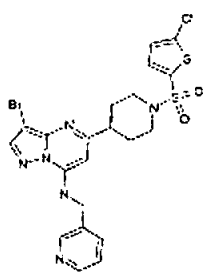
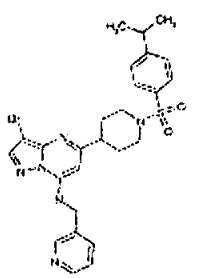
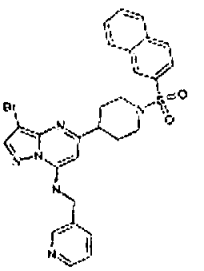
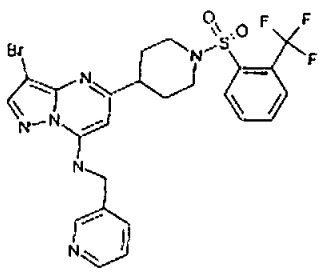
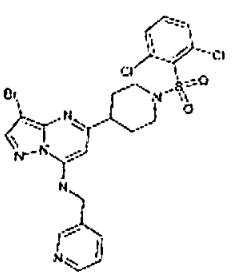
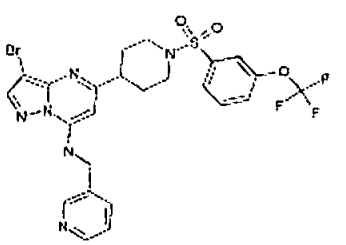
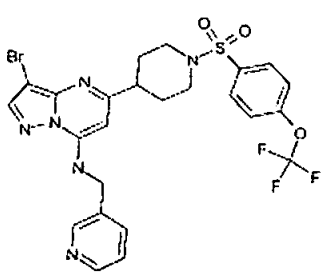
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5546 2. 573.32		1. 5551 2. 525.83
	1. 5547 2. 582.88		1. 5552 2. 526.82
	1. 5548 2. 607.76		1. 5553 2. 573.92
	1. 5549 2. 607.76		
	1. 5550 2. 536.86		

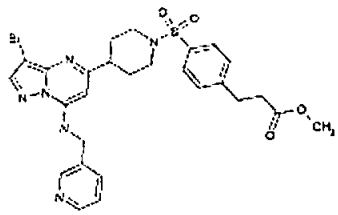
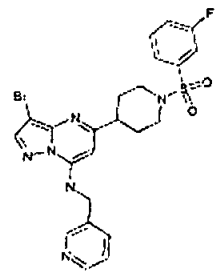
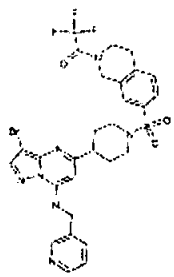
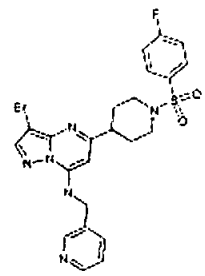
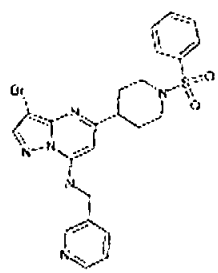
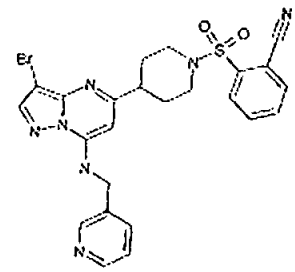
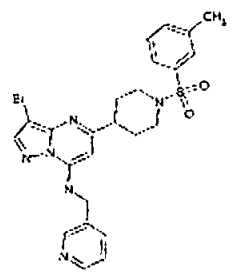
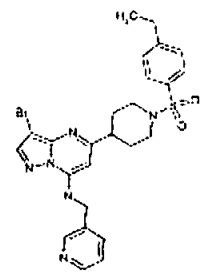
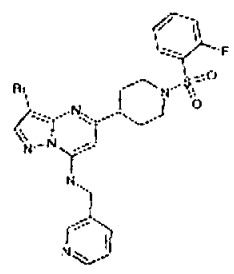
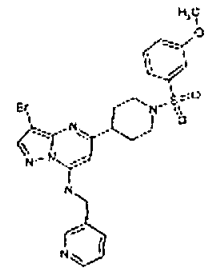
TABLA 56

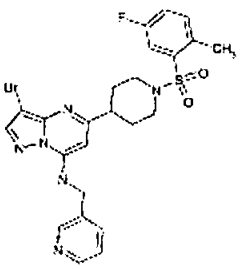
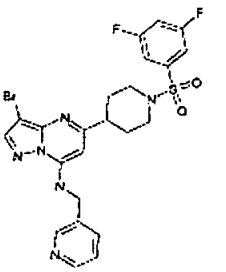
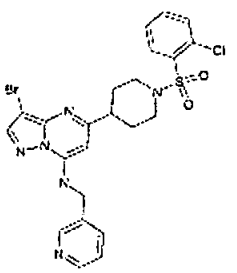
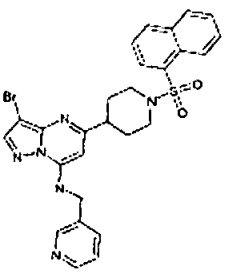
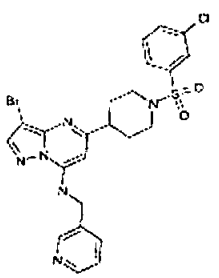
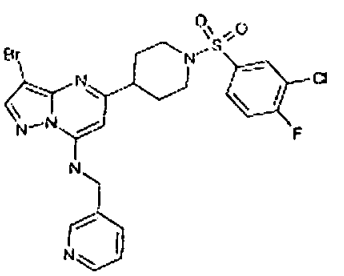
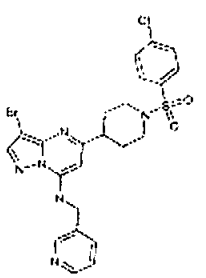
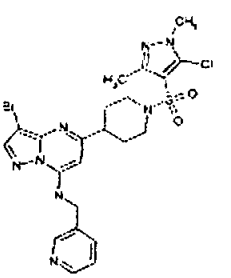
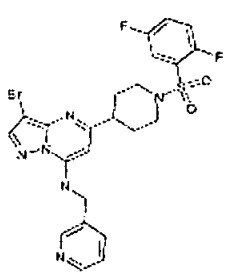
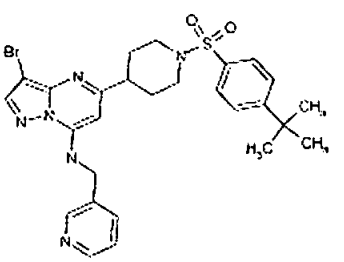
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5601 2. 481.26		1. 5606 2. 548.3
	1. 5602 2. 495.27		1. 5607 2. 554.3
	1. 5603 2. 535.29		1. 5608 2. 554.3
	1. 5604 2. 543.3		1. 5609 2. 555.31
	1. 5605 2. 543.3		1. 5610 2. 559.31

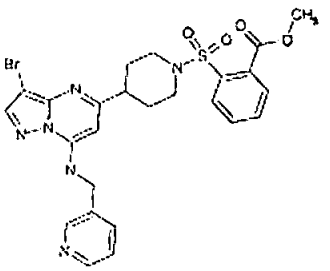
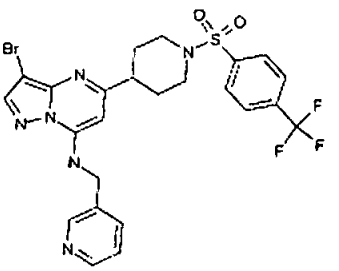
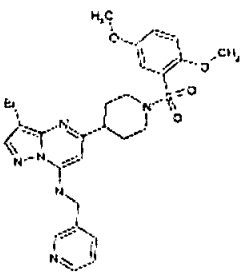
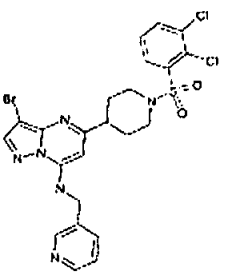
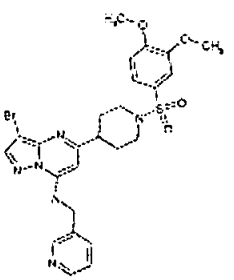
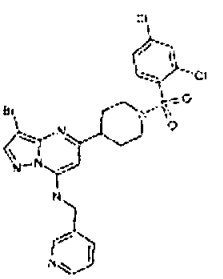
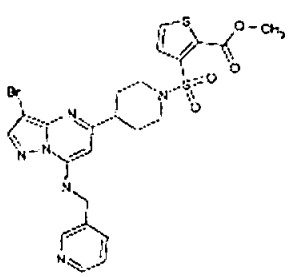
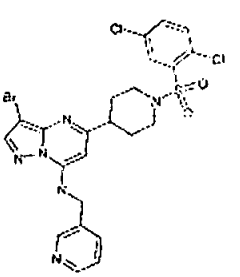
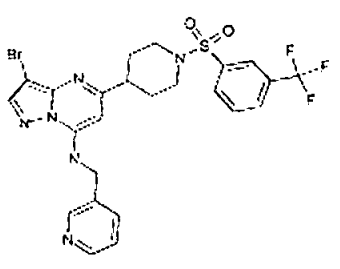
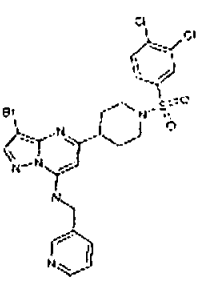
1226

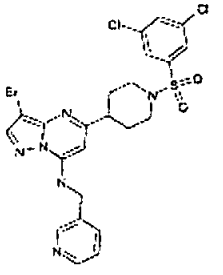
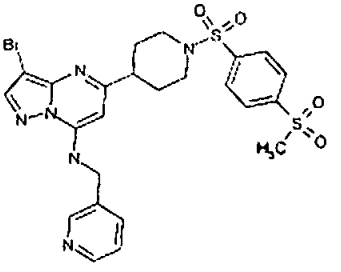
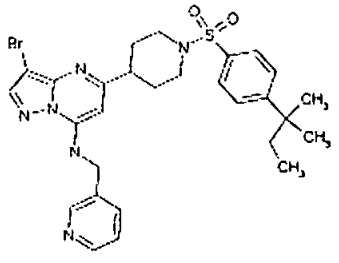
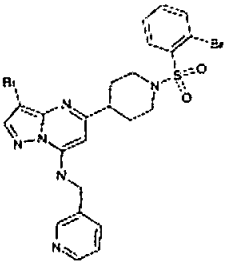
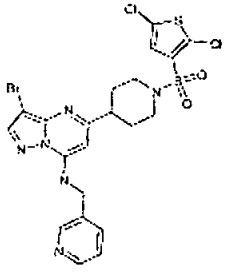
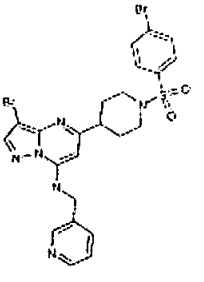
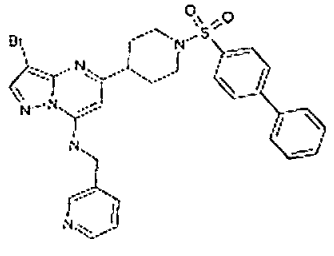
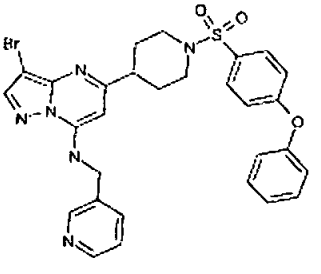
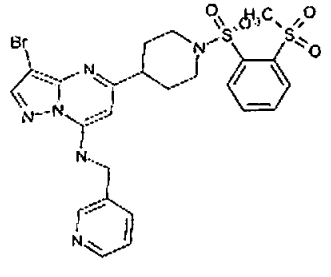
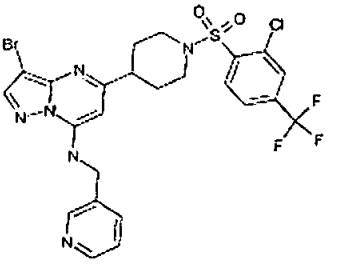
Producto	1. Ej. 2. m/z
	1. 5611 2. 565.31
	1. 5612 2. 565.31
	1. 5613 2. 565.31
	1. 5614 2. 569.31
	1. 5615 2. 571.31

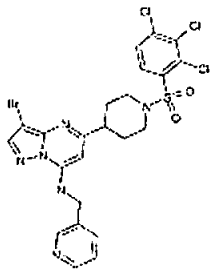
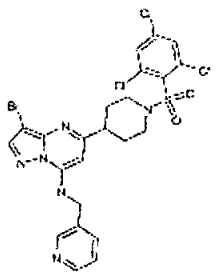
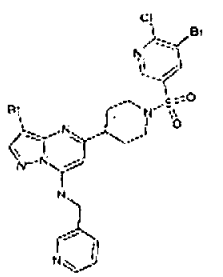
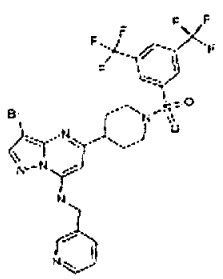
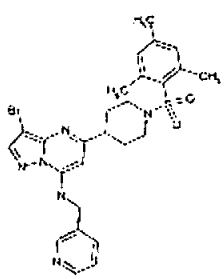
Producto	1. Ej. 2. m/z
	1 .5616 2. 579.32
	1. 5617
	1. 5618
	1. 5619
	1. 5620

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5621 2. 615.34		1. 5626 2. 547.3
	2. 5622 2. 680.37		1. 5627 2. 547.3
	1. 5623 2. 529.29		1. 5628 2. 554.3
	1. 5624 2. 543.3		1. 5629 2. 555.31
	1. 5625 2. 547.3		1. 5630 2. 559.31

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5631 2. 561.31		1. 5636 2. 565.31
	1. 5632 2. 563.31		1. 5637 2. 579.32
	1. 5633 2. 563.31		1. 5638 2. 581.32
	1. 5634 2. 563.31		1. 5639 2. 581.32
	1. 5635 2. 563.31		1. 5640 2. 585.32

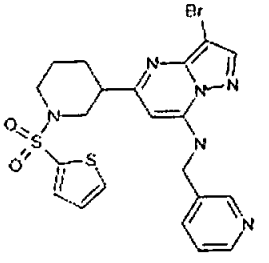
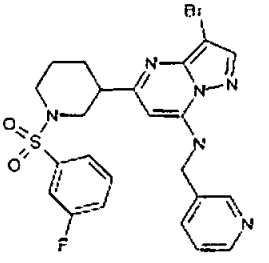
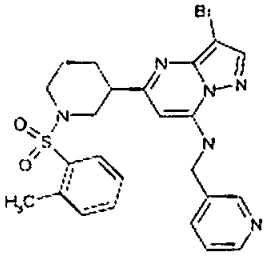
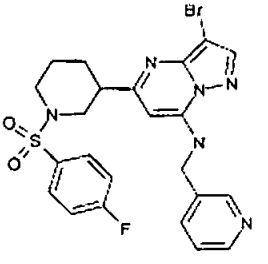
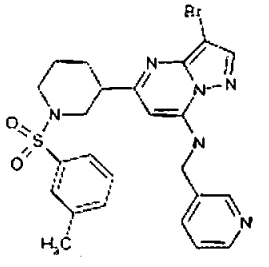
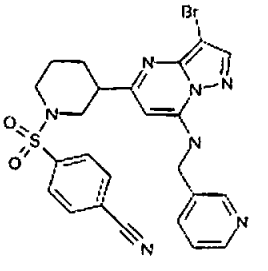
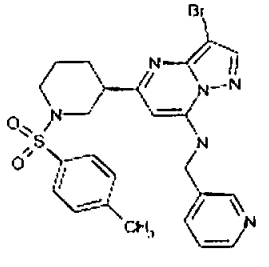
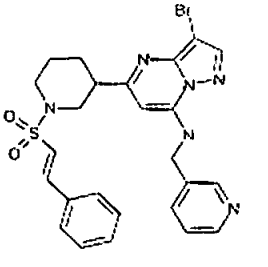
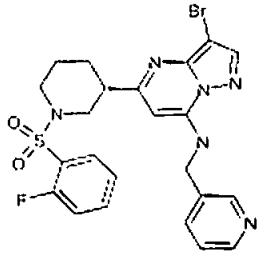
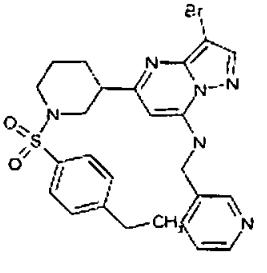
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5641 2. 587.32		1. 5646
	1. 5642 2. 589.32		1. 5647 2. 597.33
	1. 5643 2. 589.32		1. 5648 2. 597.33
	1. 5644 2. 593.33		1. 5649 2. 597.33
	1. 5645 2. 597.33		1. 5650 2. 597.33

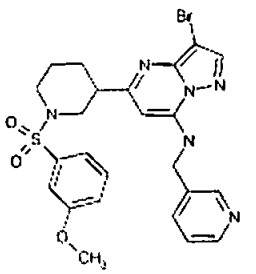
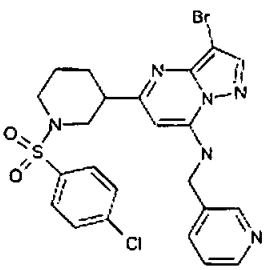
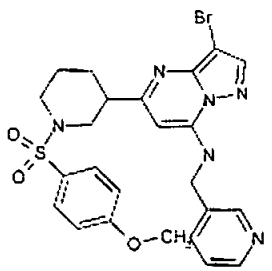
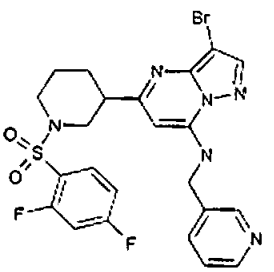
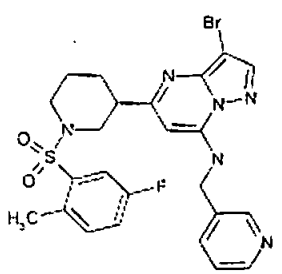
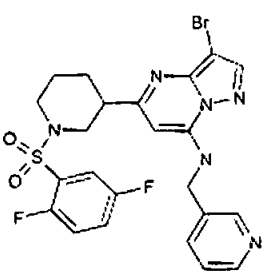
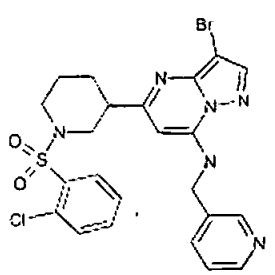
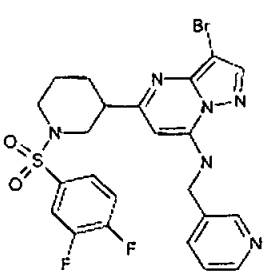
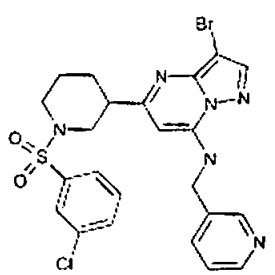
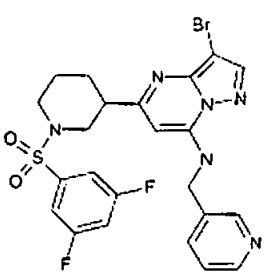
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5651 2. 597.33		1. 5656 2. 607.33
	1. 5652 2. 599.33		1. 5657 2. 607.33
	1. 5653 2. 603.33		1. 5658 2. 607.33
	1. 5654 2. 605.33		1. 5659 2. 621.34
	1. 5655 2. 607.33		1. 5660 2. 631.35

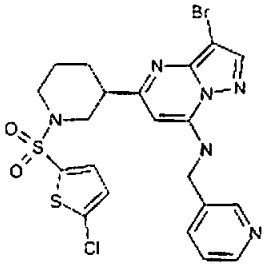
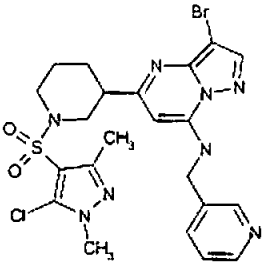
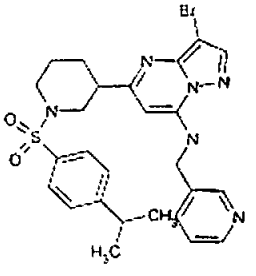
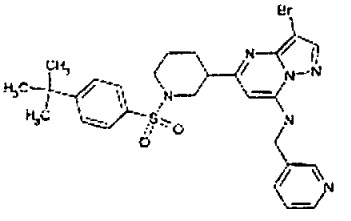
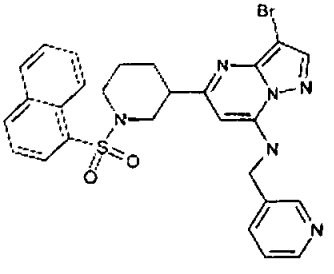
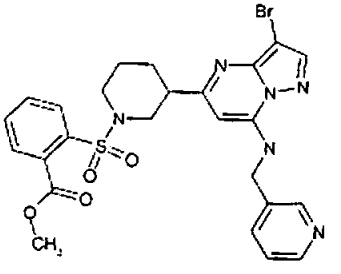
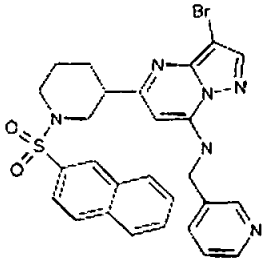
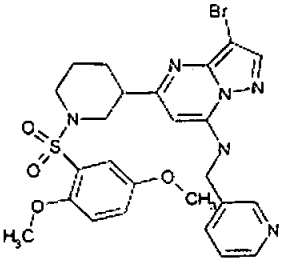
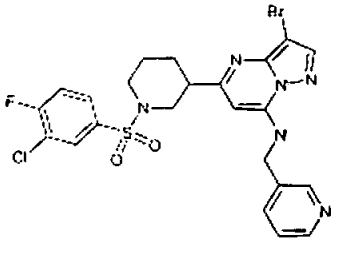
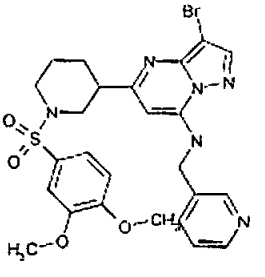
Producto	1. Ej. 2. m/z
	1. 5661 2. 631.35
	1. 5662 2. 631.35
	1. 5663 2. 642.35
	1. 5664 2. 665.37
	1. 5665 2. 571.31

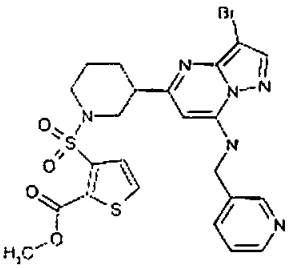
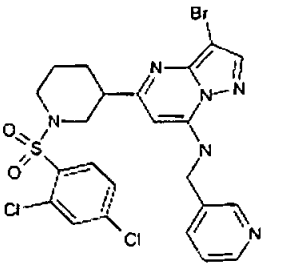
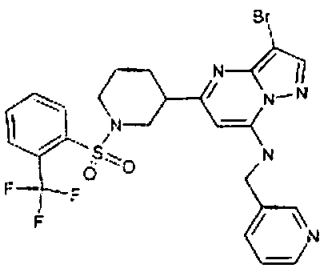
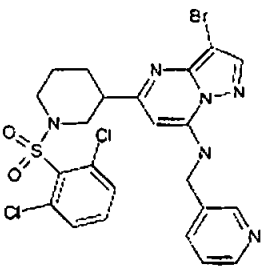
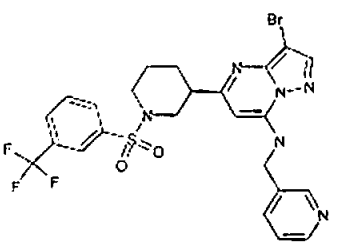
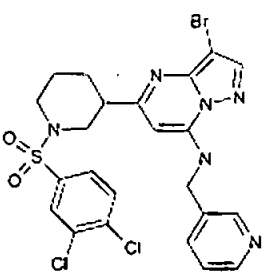
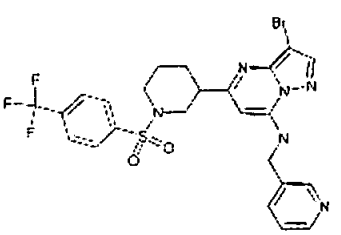
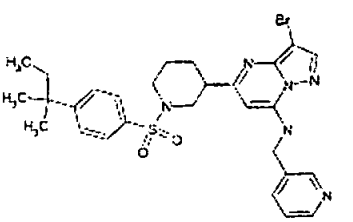
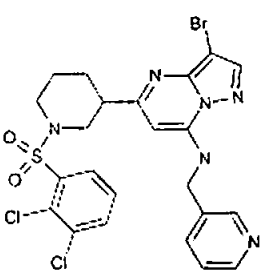
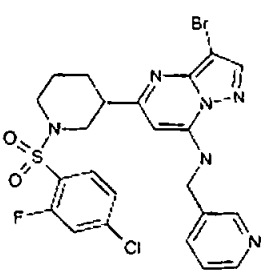
1232

TABLA 57

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5701 2. 535.29		1. 5706 2. 547.3
	1. 5702 2. 540.3		1. 5707 2. 547.3
	1. 5703 2. 543.3		1. 5708 2. 554.3
	1. 5704 2. 543.3		1. 5709 2. 555.31
	1. 5705 2. 547.3		1. 5710 2. 555.31

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5711 2. 559.31		1. 5716 2. 563.31
	1. 5712 2. 559.31		1. 5717 2. 565.31
	1. 5713 2. 561.31		1. 5718 2. 565.31
	1. 5714 2. 562.31		1. 5719 2. 565.31
	1. 5715 2. 563.31		1. 5720 2. 565.31

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5721 2. 569.31		1. 5726 2. 581.32
	1. 5722 2. 571.31		1. 5727 2. 585.32
	1. 5723 2. 579.32		1. 5728 2. 587.32
	1. 5724 2. 579.32		1. 5729 2. 589.32
	1. 5725 2. 581.32		1. 5730 2. 589.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5731 2. 591.33		1. 5736 2. 597.33
	1. 5732 2. 597.33		1. 5737 2. 597.33
	1. 5733 2. 595.33		1. 5738 2. 596.33
	1. 5734 2. 597.33		1. 5739 2. 597.33
	1. 5735 2. 597.33		1. 5740 2. 581.32

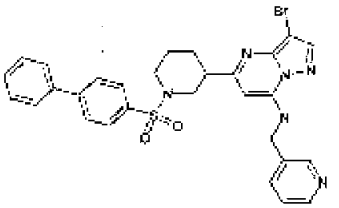
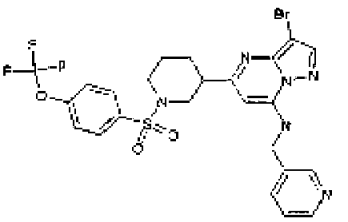
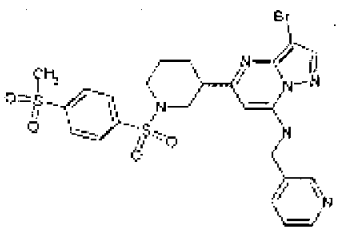
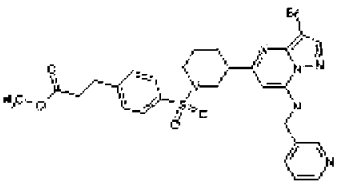
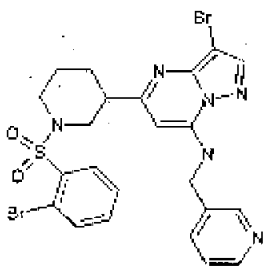
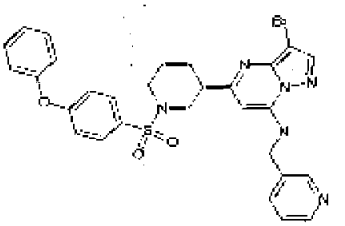
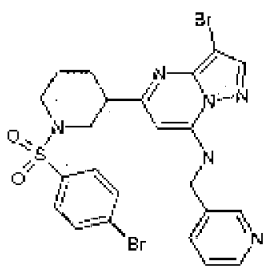
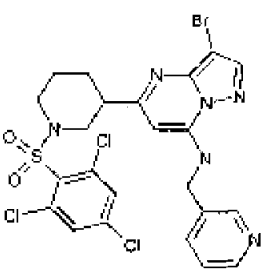
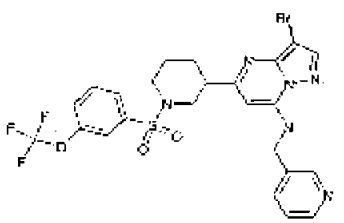
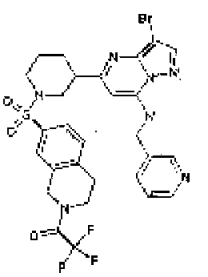
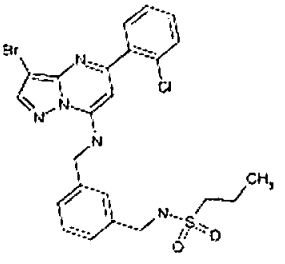
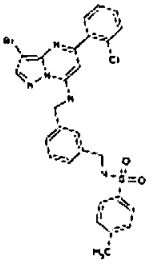
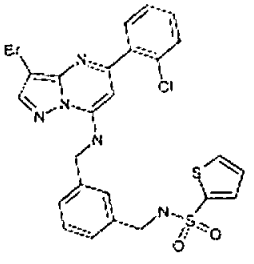
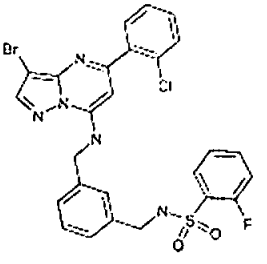
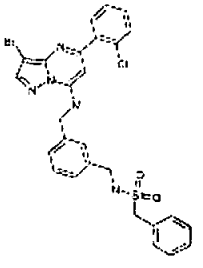
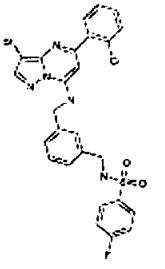
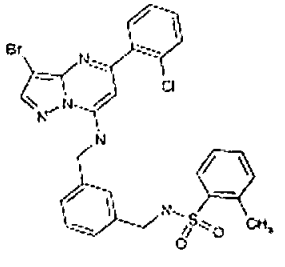
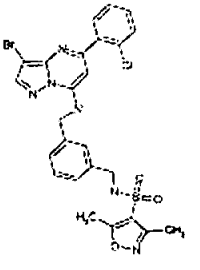
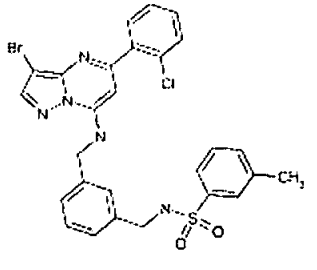
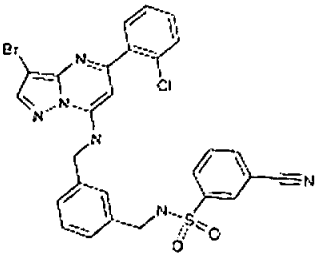
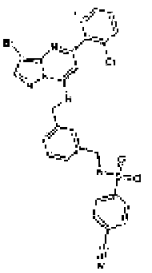
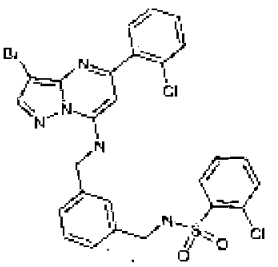
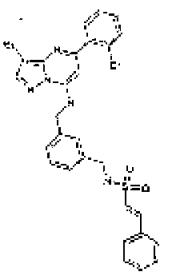
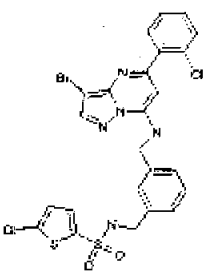
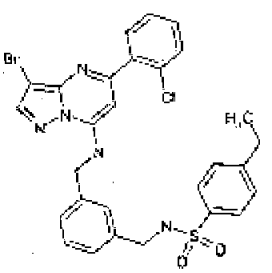
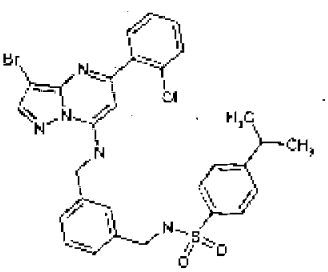
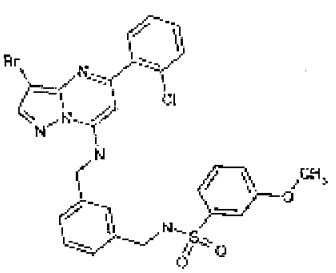
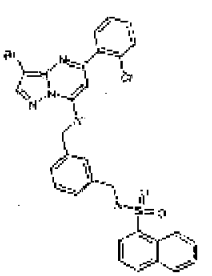
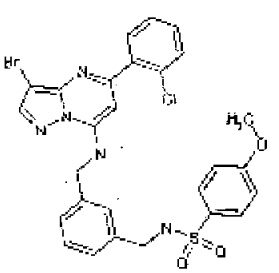
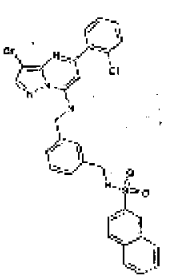
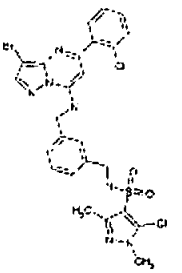
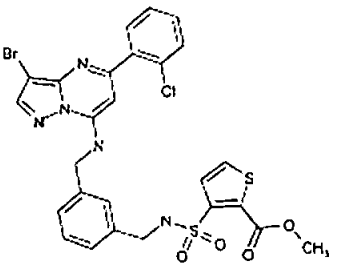
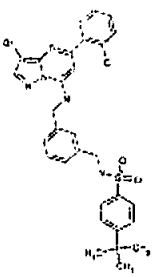
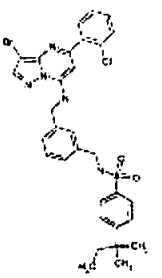
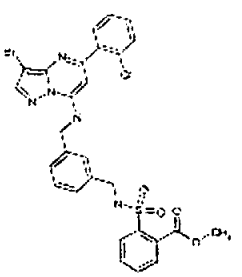
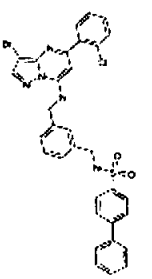
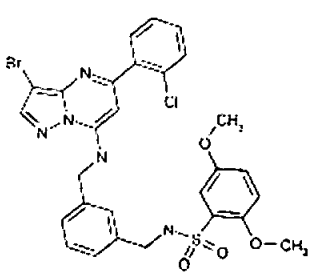
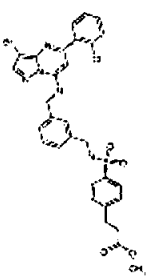
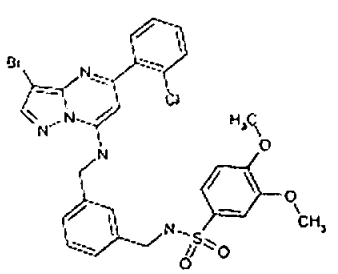
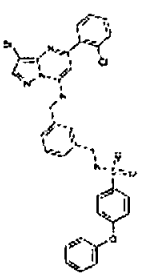
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5741 2. 605.33		1. 5746 2. 613.34
	1. 5742 2. 607.33		1. 5747 2. 615.34
	1. 5743 2. 607.33		1. 5748 2. 621.34
	1. 5744 2. 607.33		1. 5749 2. 631.35
	1. 57454 2. 613.34		1. 5750 2. 680.37

TABLA 58

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5801 2. 550.3		1. 5806 2. 598.33
	1. 5802 2. 590.32		10 5807 2. 602.33
	1. 5803 2. 598.33		1. 5808 2. 602.33
	1. 5804 2. 598.33		1. 5809 2. 603.33
	1. 5805 2. 598.33		1. 5810 2. 609.33

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5811 2. 609.33		1. 5816 2. 618.34
	1. 5812 2. 610.34		1. 5817 2. 624.34
	1. 5813 2. 612.34		1. 5818 2. 626.34
	1. 5814 2. 614.34		1. 5819 2. 634.35
	1. 5815 2. 614.34		1. 5820 2. 632.35

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5821 2. 636.35		1. 5826 2. 648.36
	1. 5822 2. 640.35		1. 5827 2. 654.36
	1. 5823 2. 642.35		1. 5828 2. 660.36
	1. 5824 2. 644.35		1. 5829 2. 670.37
	1. 5825 2. 644.35		1. 5830 2. 676.37

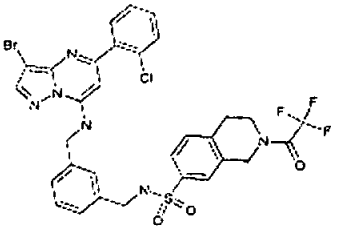
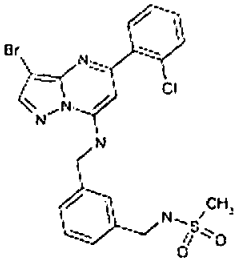
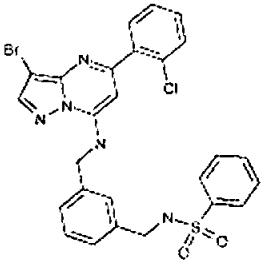
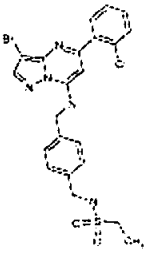
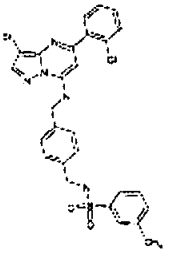
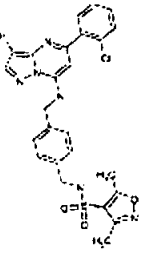
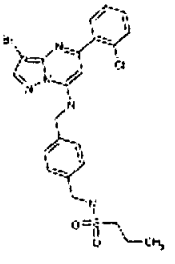
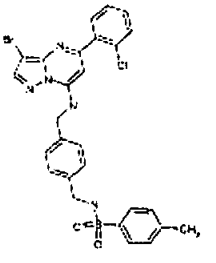
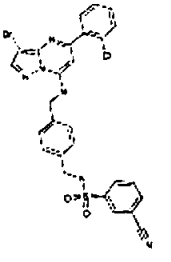
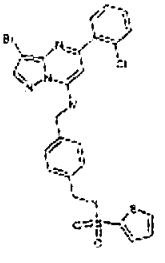
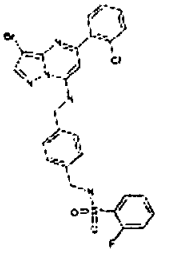
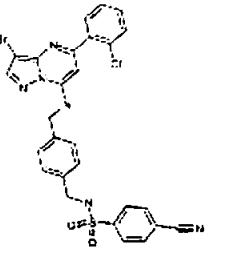
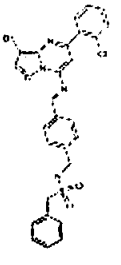
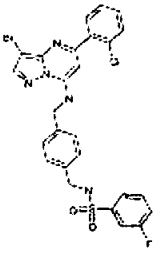
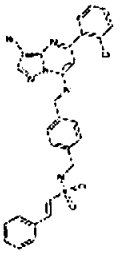
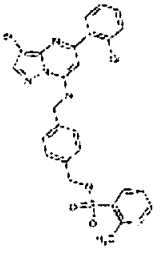
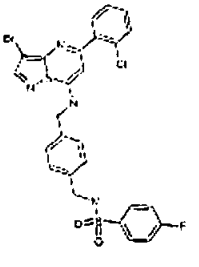
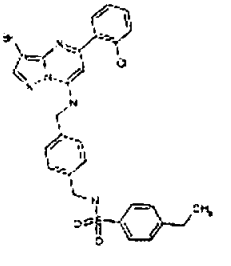
Producto	1. Ej. 2. m/z
	1. 5831 2. 735.4
	1. 5832 2. 522.29
	1. 5833 2. 584.32

TABLA 59

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5901 2. 536.29		1. 5906 2. 598.33		1. 5911 2. 603.33
	1. 5902 2. 550.3		1. 5907 2. 598.33		1. 5912 2. 609.33
	1. 5903 2. 590.32		1. 5908 2. 602.33		1. 5913 2. 609.33
	1. 5904 2. 598.33		1. 5909 2. 602.33		1. 5914 2. 610.34
	1. 5905 2. 598.33		1. 5910 2. 602.33		1. 5915 2. 612.34

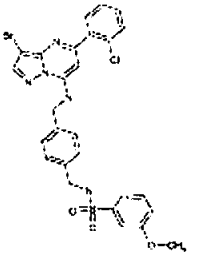
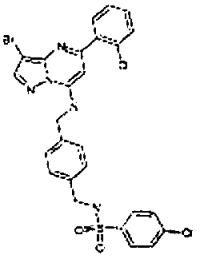
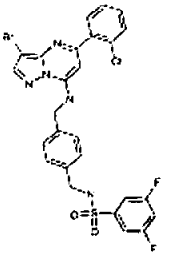
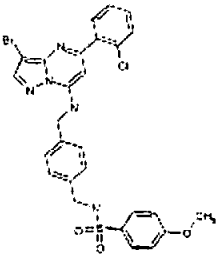
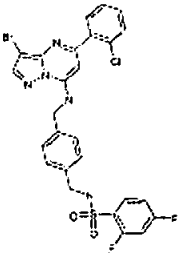
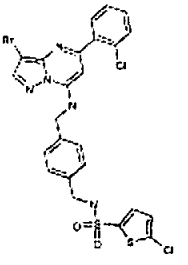
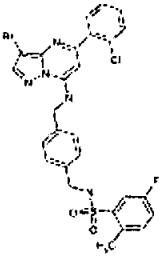
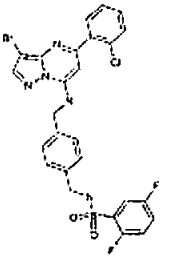
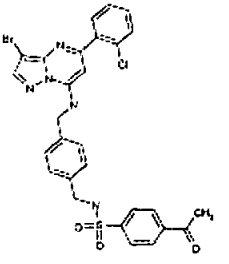
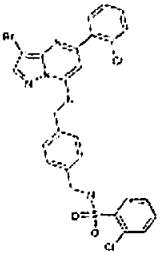
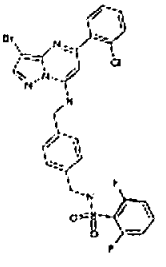
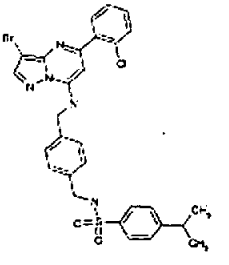
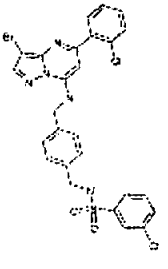
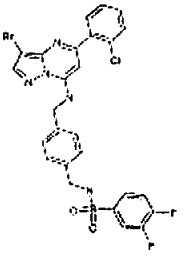
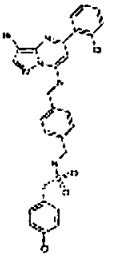
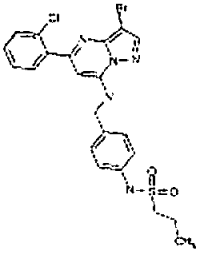
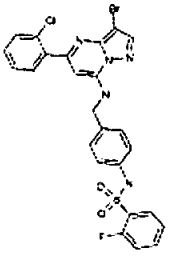
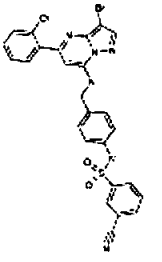
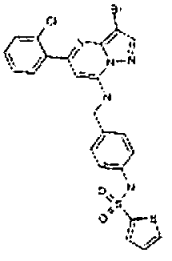
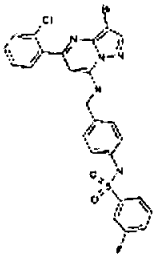
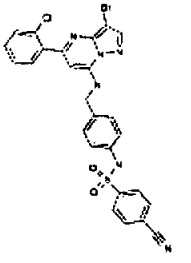
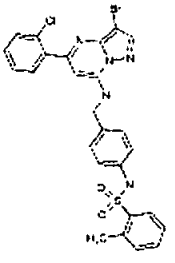
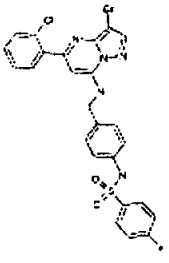
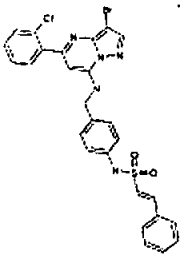
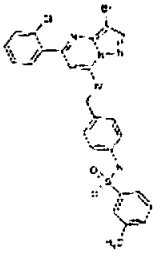
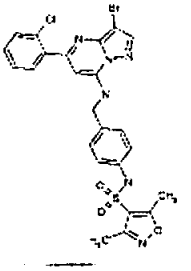
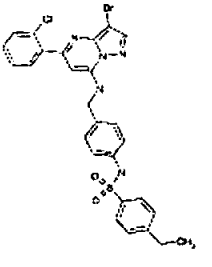
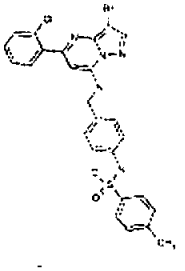
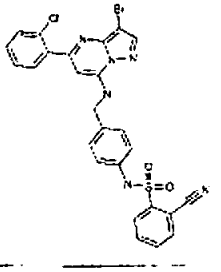
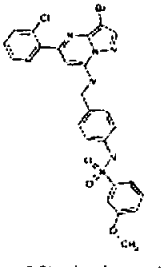
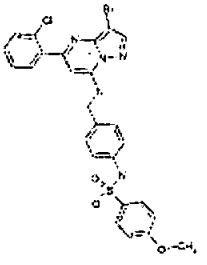
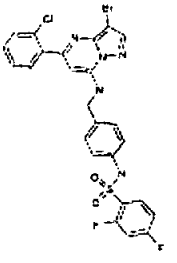
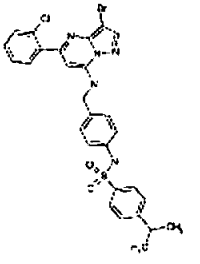
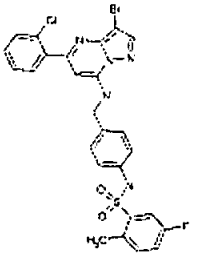
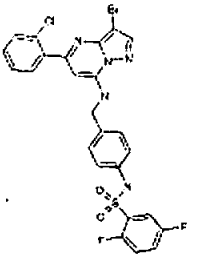
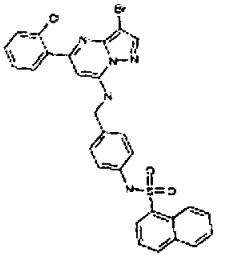
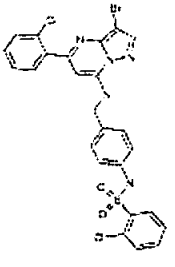
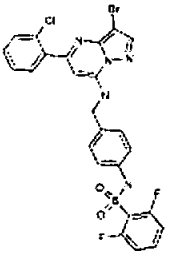
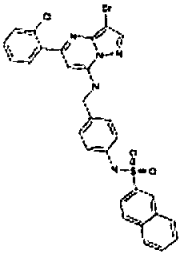
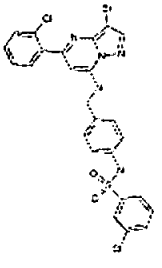
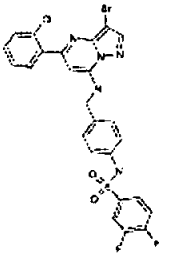
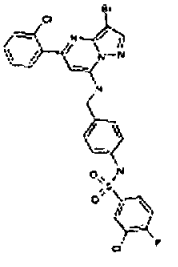
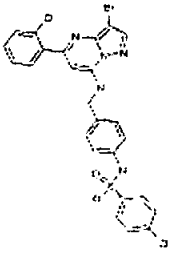
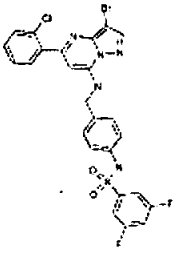
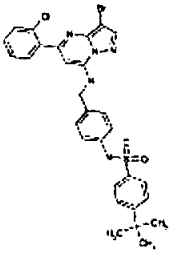
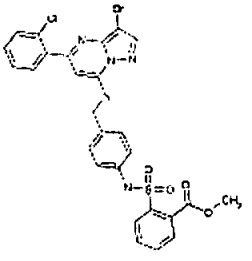
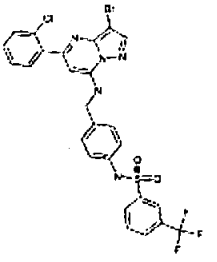
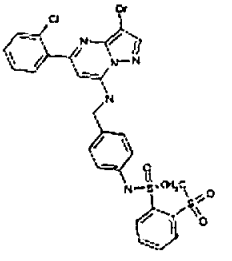
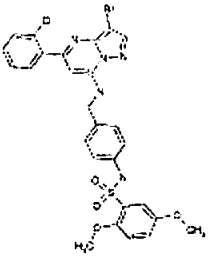
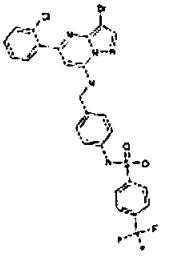
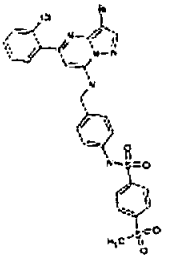
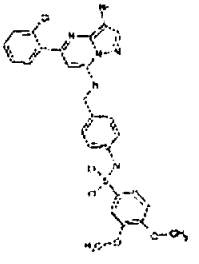
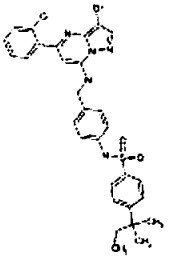
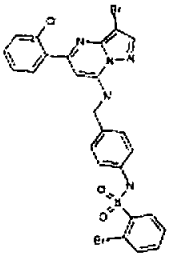
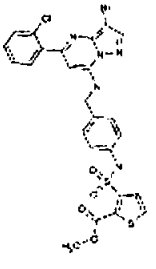
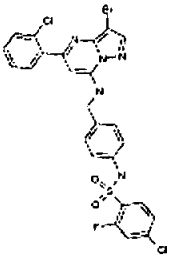
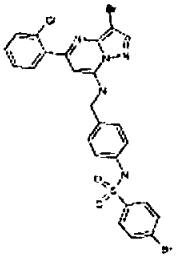
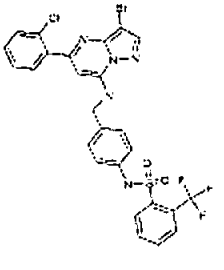
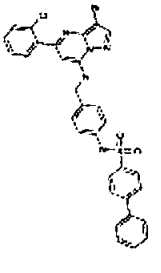
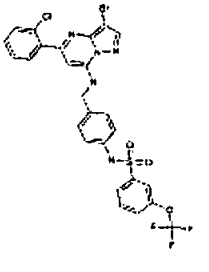
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5916 2. 614.34		1. 5921 2. 618.34		1. 5926 2. 620.34
	1. 5917 2. 614.34		1. 5922 2. 620.34		1. 5927 2. 624.34
	1. 5918 2. 616.34		1. 5923 2. 620.34		1. 5928 2. 626.34
	1. 5919 2. 618.34		1. 5924 2. 620.34		1. 5929 2. 626.34
	1. 5920 2. 618.34		1. 5925 2. 620.34		1. 5930 2. 632.35

TABLA 60

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6001 2. 536.29		1. 6006 2. 588.32		1. 6011 2. 595.33
	1. 6002 2. 576.32		1. 6007 2. 588.32		1. 6012 2. 595.33
	1. 6003 2. 584.32		1. 6008 2. 588.32		1. 6013 2. 596.33
	1. 6004 2. 584.32		1. 6009 2. 589.32		1. 6014 2. 598.33
	1. 6005 2. 584.32		1. 6010 2. 595.33		1. 6015 2. 600.33

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 60 2. m/z
	1. 6016 2. 600.33		1. 6021 2. 606.33		1. 6026 2. 612.34
	1. 6017 2. 602.33		1. 6022 2. 606.33		1. 6027 2. 620.34
	1. 6018 2. 604.33		1. 6023 2. 606.33		1. 6028 2. 620.34
	1. 6019 2. 604.33		1. 6024 2. 606.33		1. 6029 2. 622.34
	1. 6020 2. 604.33		1. 6025 2. 606.33		1. 6030 2. 626.34

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6031 2. 628.35		1. 6036 2. 638.35		1. 6041 2. 648.36
	1. 6032 2. 630.35		1. 6037 2. 638.35		1. 60425 2. 648.36
	1. 6033 2. 630.35		1. 6038 2. 638.35		1. 6043 2. 648.36
	1. 6034 2. 634.35		1. 6039 2. 622.34		1. 6044 2. 648.36
	1. 6035 2. 638.35		1. 6040 2. 646.36		1. 6045 2. 654.36

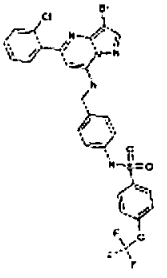
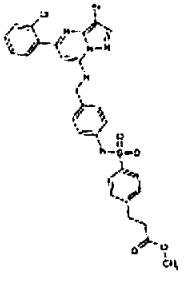
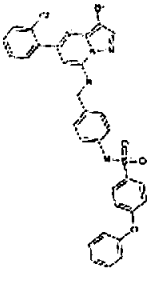
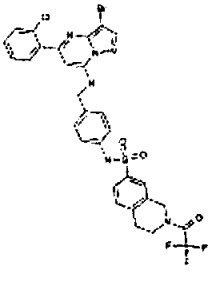
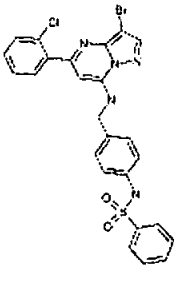
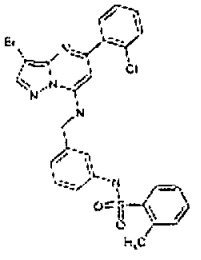
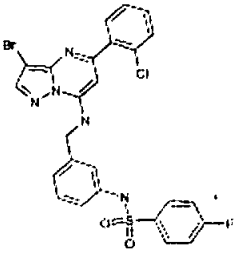
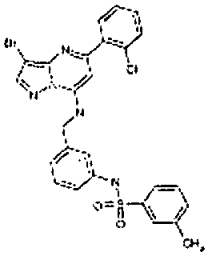
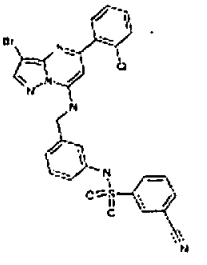
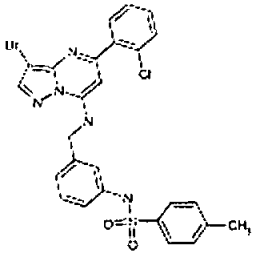
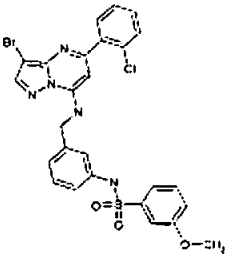
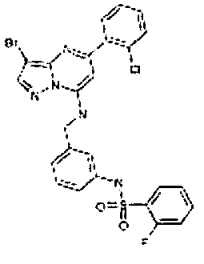
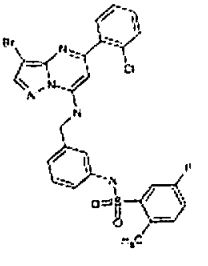
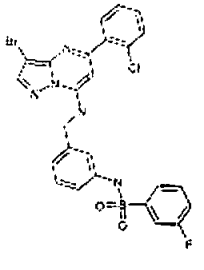
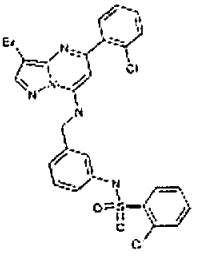
Producto	1. Ej. 2. m/z
	1. 6046 2. 654.36
	1. 6047 2. 656.36
	1. 6048 2. 662.36
	1. 6049 2. 721.4
	1. 6050 2. 570.31

TABLA 61

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6101 2. 584.32		1. 6106 2. 588.32
	1. 6102 2. 584.32		1. 6107 2. 595.33
	1. 6103 2. 584.32		1. 6108 2. 600.33
	1. 6104 2. 588.32		1. 6109 2. 602.33
	1. 6105 2. 588.32		1. 6110 2. 604.33

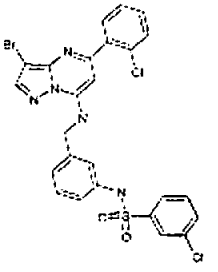
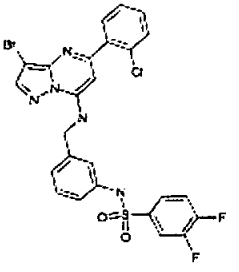
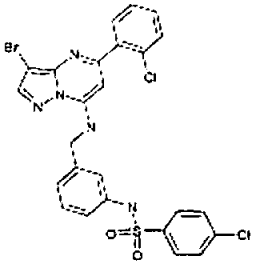
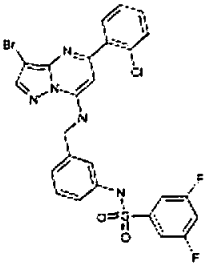
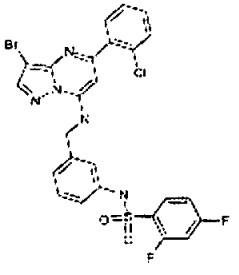
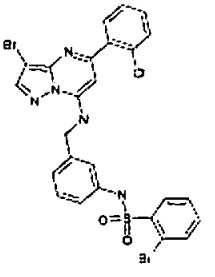
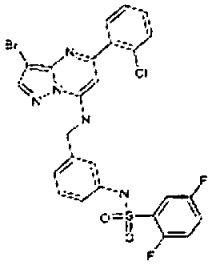
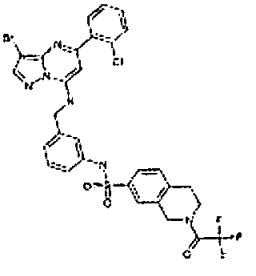
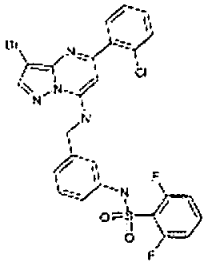
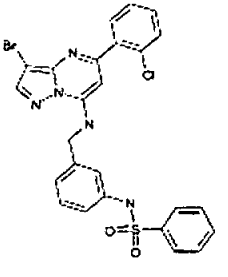
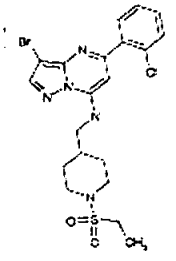
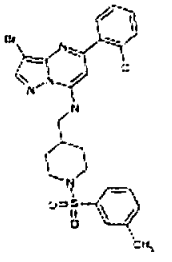
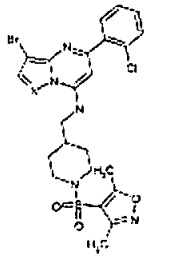
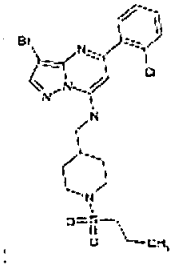
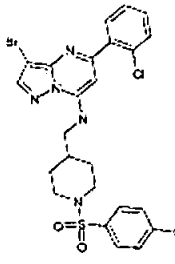
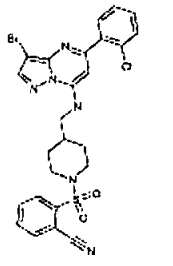
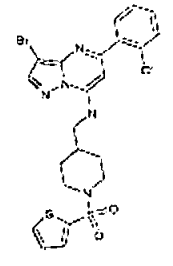
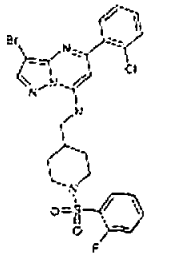
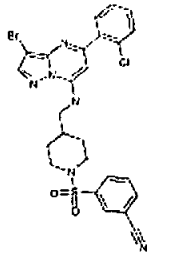
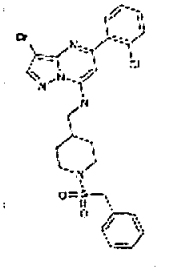
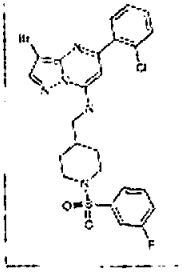
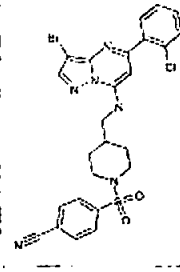
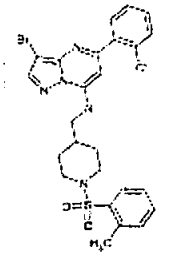
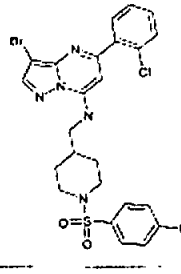
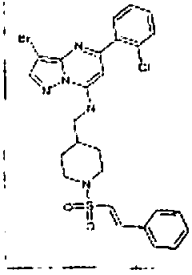
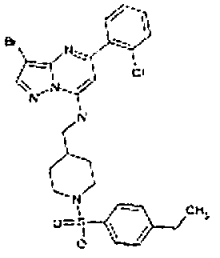
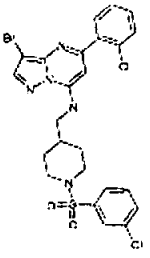
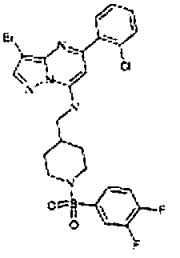
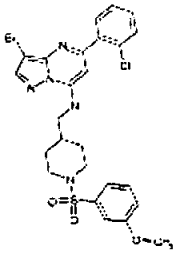
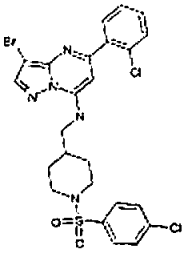
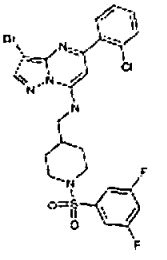
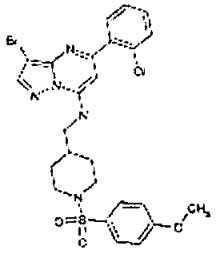
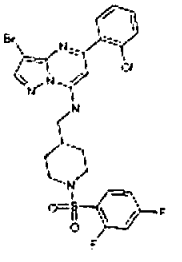
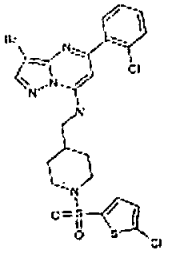
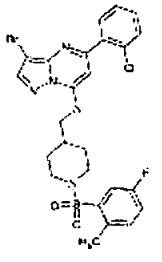
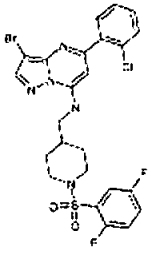
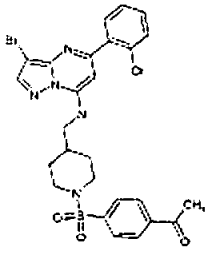
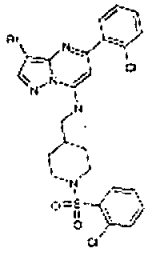
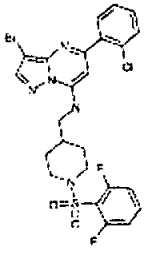
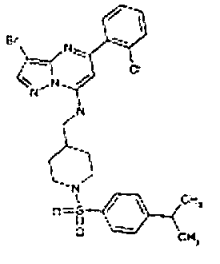
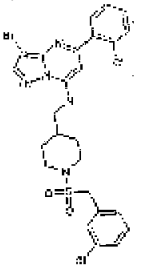
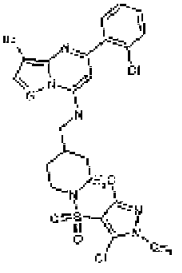
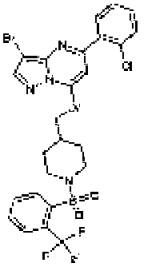
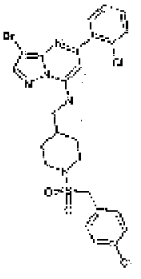
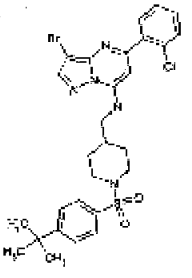
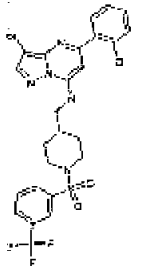
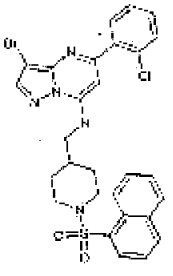
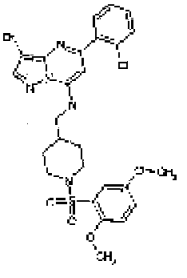
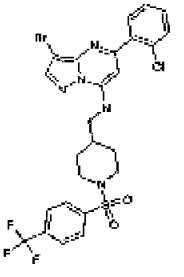
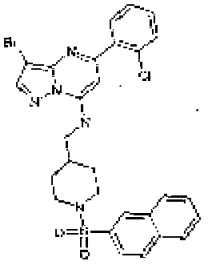
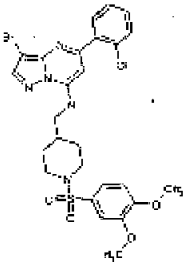
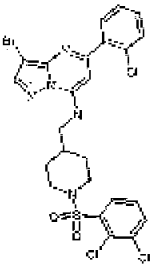
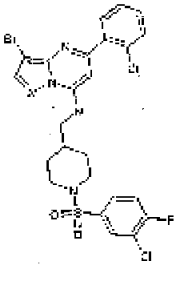
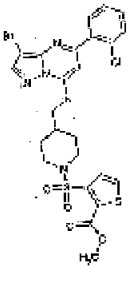
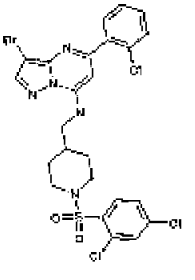
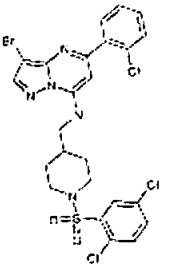
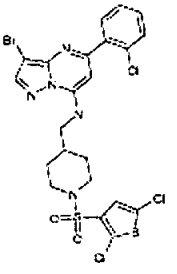
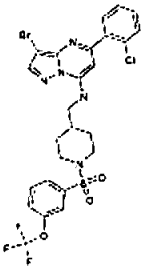
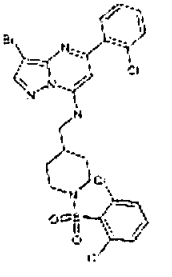
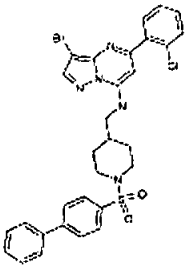
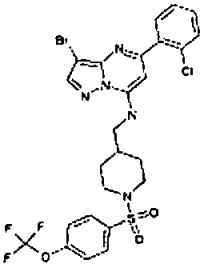
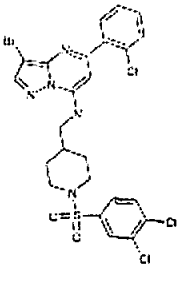
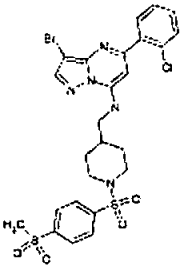
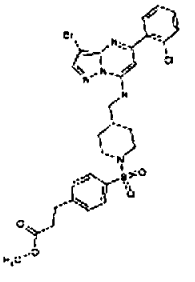
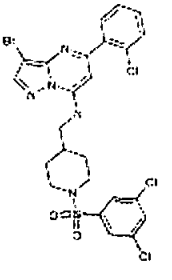
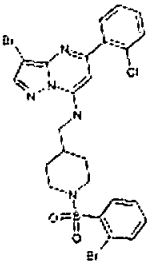
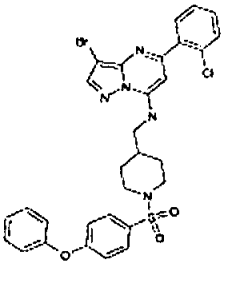
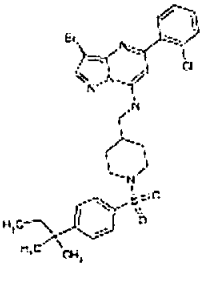
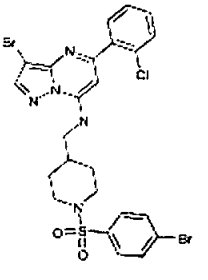
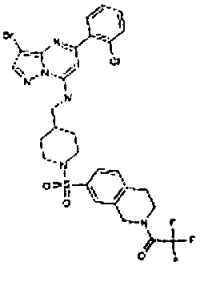
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6111 2. 604.33		1. 6116 2. 606.33
	1. 6112 2. 604.33		1. 6117 2. 606.33
	1. 6113 2. 606.33		1. 6118 2. 648.36
	1. 6114 2. 606.33		1. 6119 2. 721.4
	1. 6115 2. 606.33		1. 6120 2. 570.31

TABLA 62

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6201 2. 514.28		1. 6206 2. 576.32		1. 6211 2. 581.32
	1. 6202 2. 528.29		1. 6207 2. 576.32		1. 6212 2. 587.32
	1. 6203 2. 568.31		1. 6208 2. 580.32		1. 6213 2. 587.32
	1. 6204 2. 576.32		1. 6209 2. 580.32		1. 6214 2. 587.32
	1. 6205 2. 576.32		1. 6210 2. 580.32		1. 6215 2. 588.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6216 2. 590.32		1. 6221 2. 596.33		1. 6226 2. 598.33
	1. 6217 2. 592.33		1. 6222 2. 596.33		1. 6227 2. 596.33
	1. 6218 2. 592.33		1. 6223 2. 598.33		1. 6228 2. 602.33
	1. 6219 2. 592.33		1. 6224 2. 596.33		1. 6229 2. 604.33
	1. 6220 2. 594.33		1. 6225 2. 598.33		1. 6230 2. 604.33

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6231 2. 610.34		1. 6236 2. 614.34		1. 6241 2. 630.35
	1. 6232 2. 610.34		1. 6237 2. 618.34		1. 6242 2.
	1. 6233 2. 612.34		1. 6238 2. 622.34		1. 6243 2. 630.35
	1. 6234 2. 612.34		1. 6239 2. 622.34		1. 6244 2. 630.35
	1. 6235 2. 614.34		1. 6240 2. 626.34		1. 6245 2. 630.35

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1 .6246 2. 630.35		1 .6251 2. 636.35		1. 6256 2. 646.36
	1. 6247 2. 630.35		1.0 6252 2. 638.35		1. 6257 2. 646.36
	1. 6248 2. 630.35		1. 6253 2. 640.35		1. 6258 2. 648.36
	1. 6249 2. 630.35		1. 6254 2. 640.35		1. 6259 2. 654.36
	1 .6250 2. 632.35		1. 6255 2. 638.35		1. 6260 2. 713.39

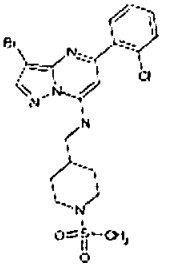
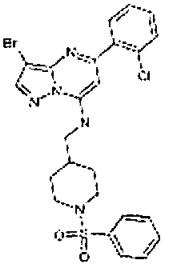
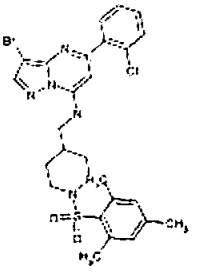
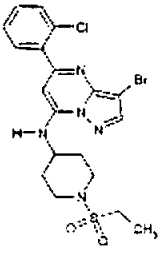
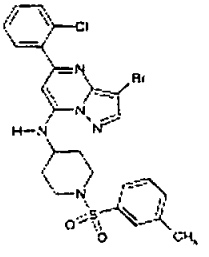
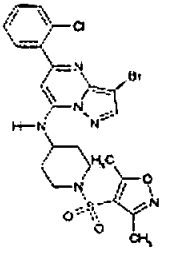
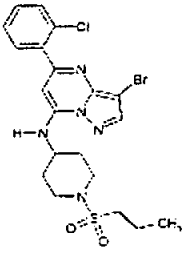
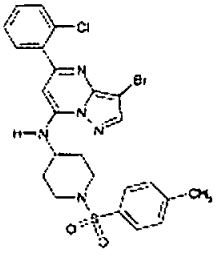
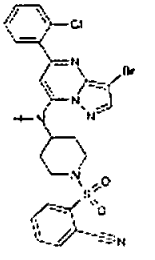
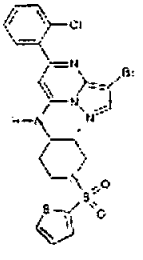
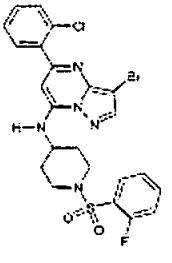
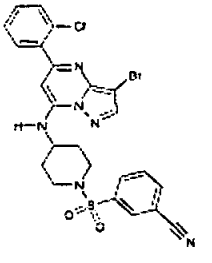
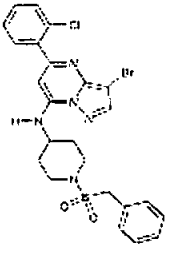
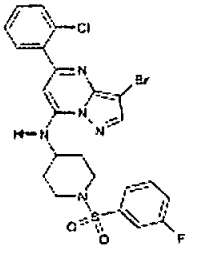
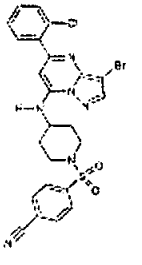
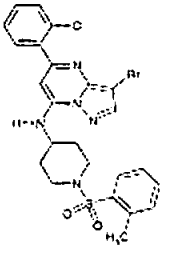
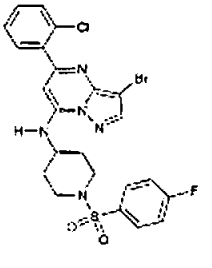
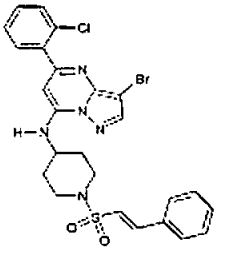
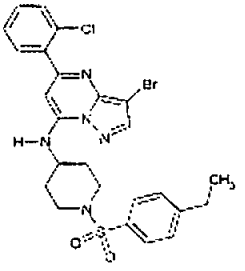
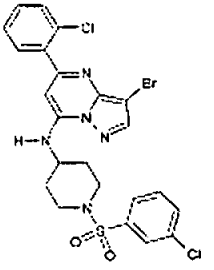
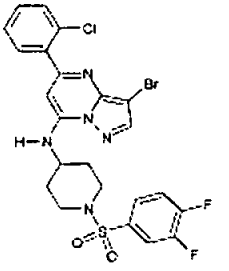
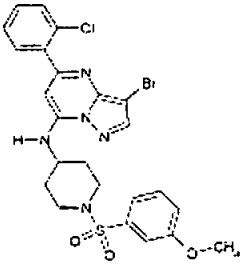
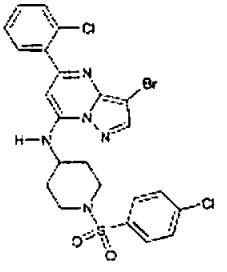
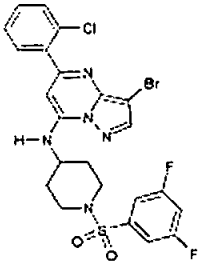
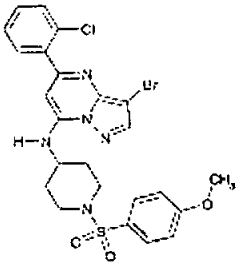
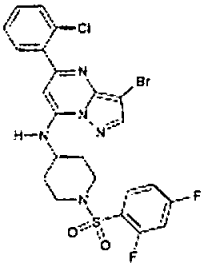
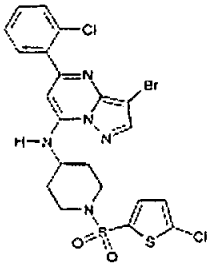
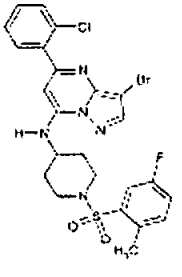
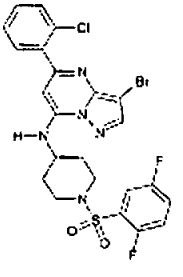
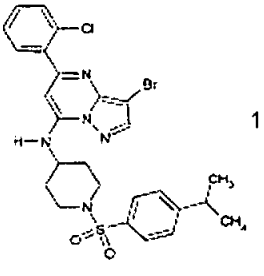
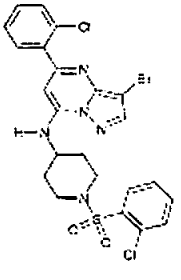
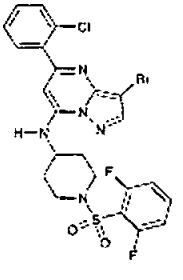
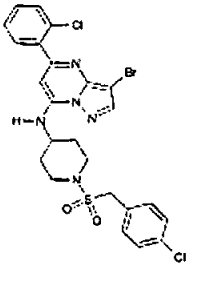
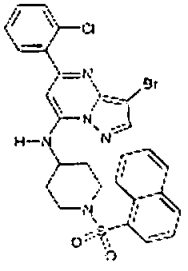
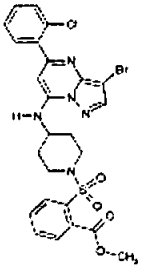
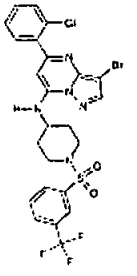
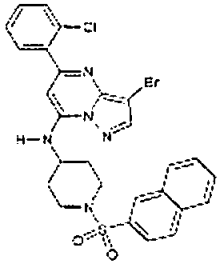
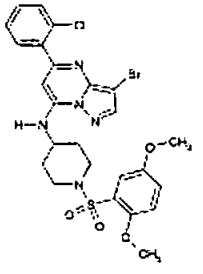
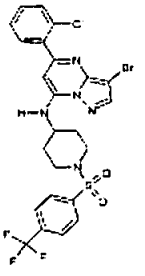
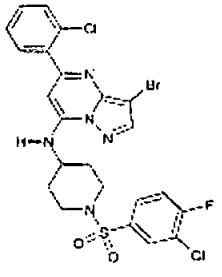
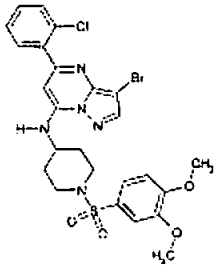
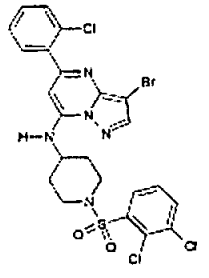
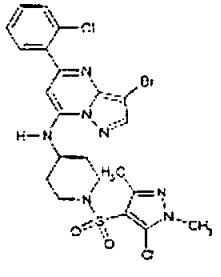
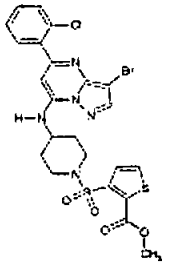
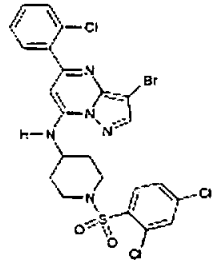
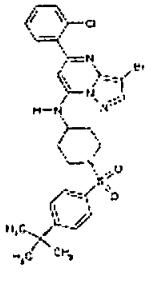
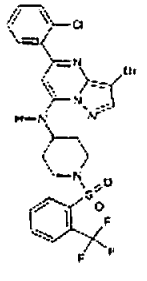
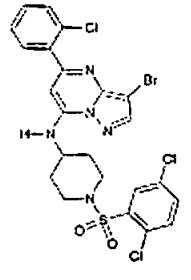
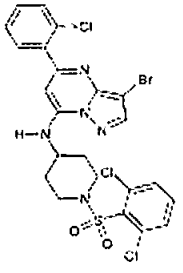
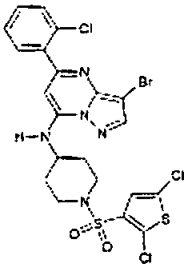
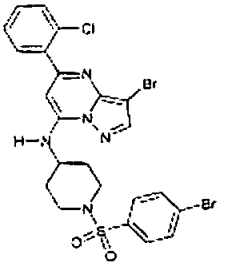
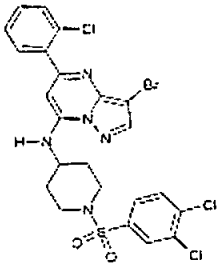
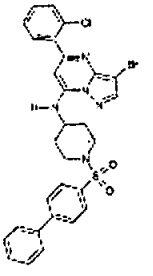
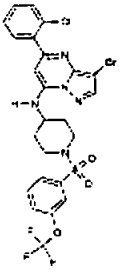
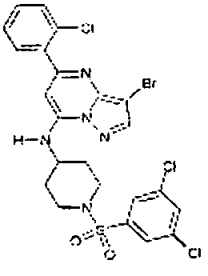
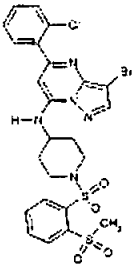
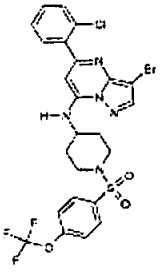
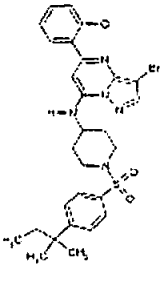
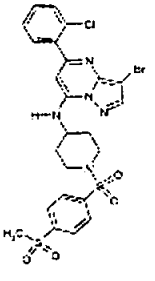
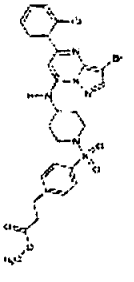
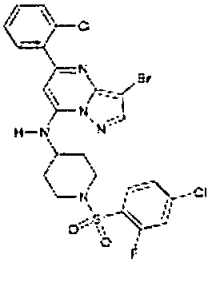
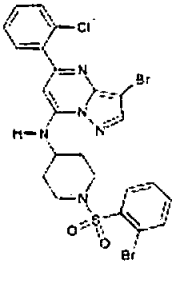
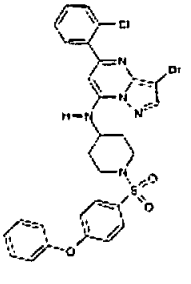
Producto	1. Ej. 2. m/z
	1. 6261 2. 500.27
	1. 6262 2. 562.31
	1. 6263 2. 604.33

TABLA 63

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6301 2. 500.27		1. 6306 2. 562.31		1. 6311 2. 567.31
	1. 6302 2. 514.28		1. 6307 2. 562.31		1. 6312 2. 573.32
	1. 6303 2. 554.3		1. 6308 2. 566.31		1. 6313 2. 573.32
	1. 6304 2. 562.31		1. 6309 2. 566.31		1. 6314 2. 573.32
	1. 6305 2. 562.31		1. 6310 2. 566.31		1. 6315 2. 574.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6316 2. 576.32		1. 6321 2. 582.32		1. 6326 2. 584.32
	1. 6317 2. 578.32		1. 6322 2. 582.32		1. 6327 2. 584.32
	1. 6318 2. 578.32		1. 6323 2. 584.32		1. 6328 2. 588.32
	1. 6319 2. 580.32		1. 6324 2. 582.32		1. 6329 2. 590.32
	1. 6320 2. 582.32		1. 6325 2. 584.32		1. 6330 2. 596.33

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6331 2. 598.33		1. 6336 2. 606.33		1. 6341 2. 616.34
	1. 6332 2. 598.33		1. 6337 2. 608.33		1. 6342 2. 616.34
	1. 6333 2. 600.33		1. 6338 2. 608.33		1. 6343 2. 616.34
	1. 6334 2. 600.33		1. 6339 2. 612.34		1.6344 2. 616.34
	1. 6335 2. 604.33		1. 6340 2. 616.34		1. 6345 2. 616.34

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6346 2. 616.34		1. 6351 2. 622.34		1. 6356 2. 626.34
	1. 6347 2. 616.34		1. 6352 2. 624.34		1. 6357 2. 632.35
	1. 6348 2. 616.34		1. 6353 2. 626.34		1. 6358 2. 632.35
	1. 6349 2. 618.34		1. 6354 2. 626.34		1. 6359 2. 634.35
	1. 6350 2. 600.33		1. 6355 2. 626.34		1. 6360 2. 640.35

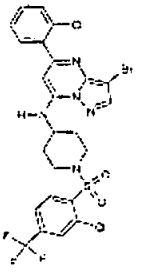
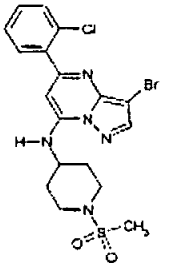
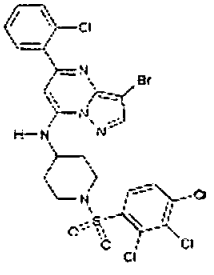
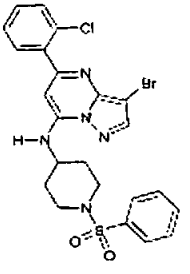
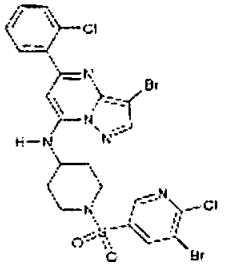
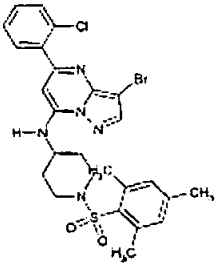
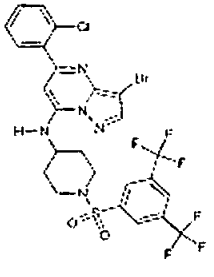
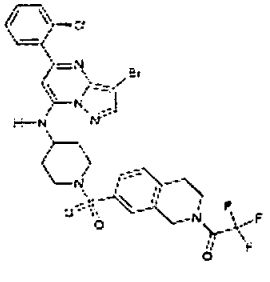
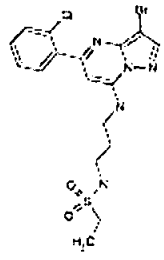
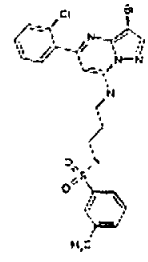
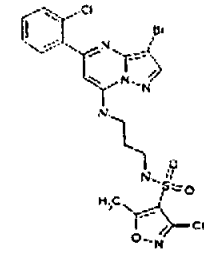
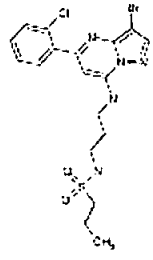
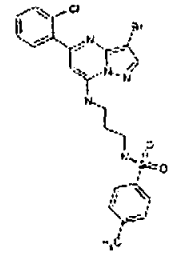
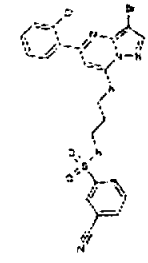
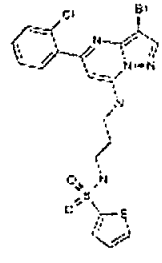
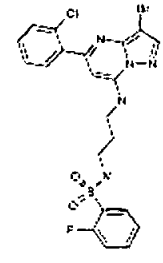
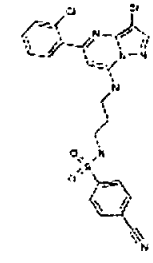
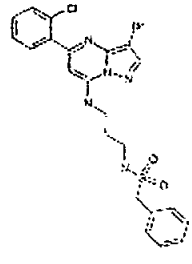
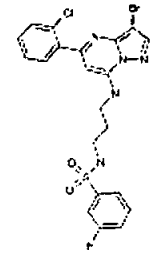
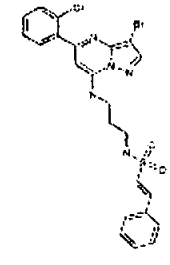
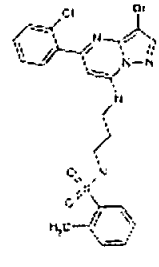
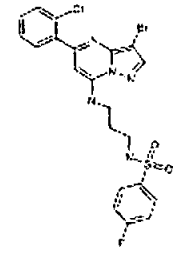
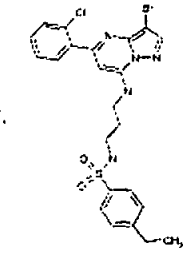
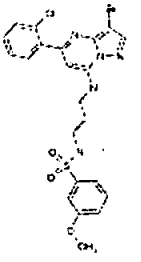
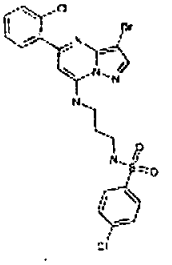
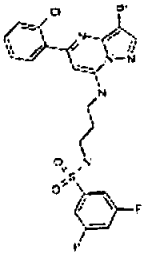
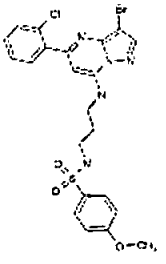
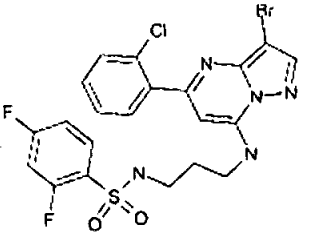
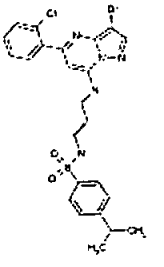
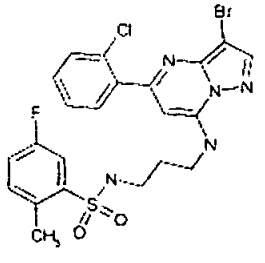
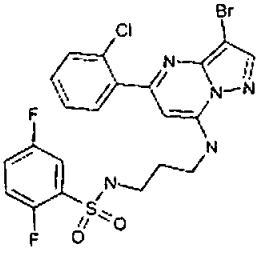
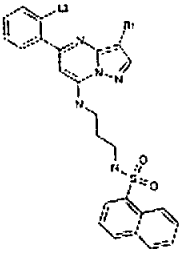
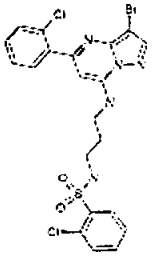
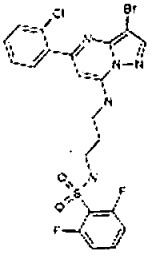
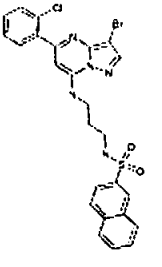
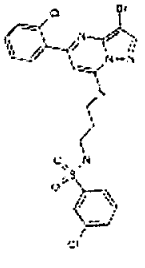
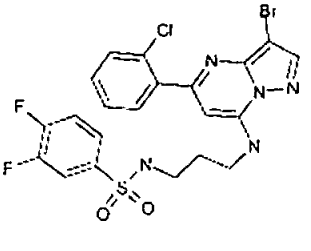
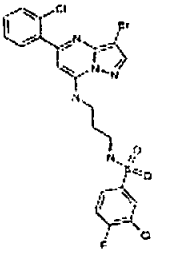
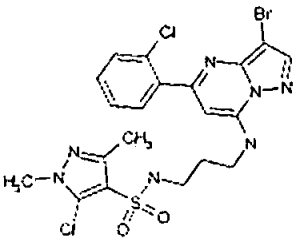
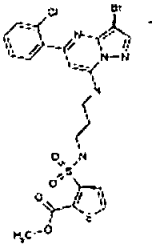
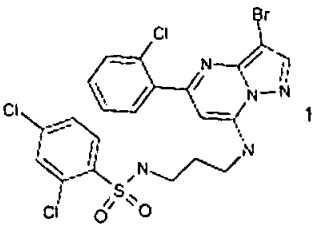
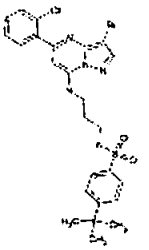
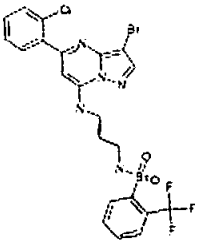
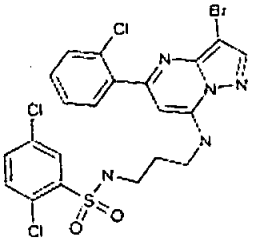
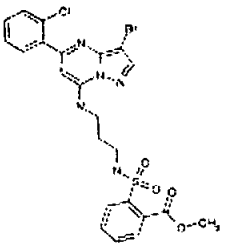
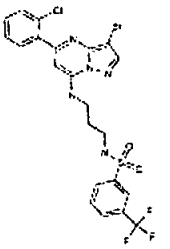
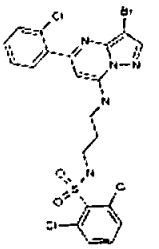
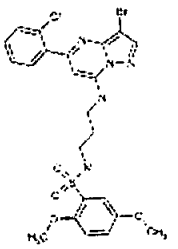
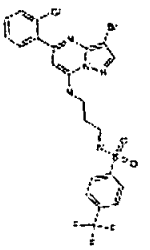
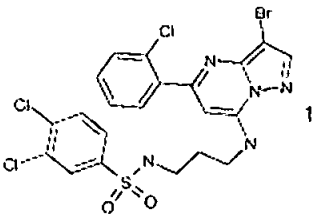
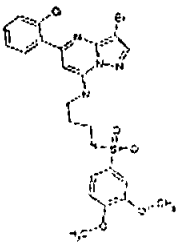
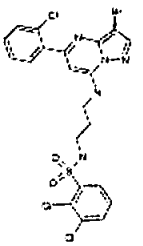
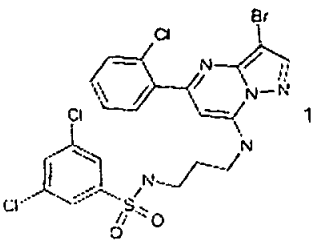
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6361 2. 650.36		1. 6366 2. 486.27
	1. 6362 2. 650.36		1. 6367 2. 548.3
	1. 6363 2. 661.36		1. 6368 2. 590.32
	1. 6364 2. 684.38		
	1. 6365 2. 699.38		

TABLA 64

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6401 2. 474.26		1. 6406 2. 536.29		1. 6411 2. 541.3
	1. 6402 2. 488.27		1. 6407 2. 536.29		1. 6412 2. 547.3
	1. 6403 2. 528.29		1. 6408 2. 540.3		1. 6413 2. 547.3
	1. 6404 2. 536.29		1. 6409 2. 540.3		1. 6414 2. 548.3
	1. 6405 2. 536.29		1. 6410 2. 540.3		1. 6415 2. 550.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6416 2. 552.3		1. 6421 2. 556.31		1. 6426 2. 558.31
	1. 6417 2. 552.3		1. 6122 2. 558.31		1. 6427 2. 564.31
	1. 6418 2. 554.3		1. 6423 2. 558.31		1. 6428 2. 572.31
	1. 6419 2. 556.31		1. 6424 2. 558.31		1. 6429 2. 572.31
	1. 6420 2. 556.31		1. 6425 2. 558.31		1. 6430 2. 574.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6431 2. 574.32		1. 6436 2. 586.32		1. 6441 2. 590.32
	1. 6432 2. 578.32		1. 6437 2. 590.32		1. 6442 2. 590.32
	1. 6433 2. 580.32		1. 6438 2. 590.32		1. 6443 2. 590.32
	1. 6434 2. 582.32		1. 6439 2. 590.32		1. 6444 2. 590.32
	1. 6435 2. 582.32		1. 6440 2. 589.32		1. 6445 2. 590.32

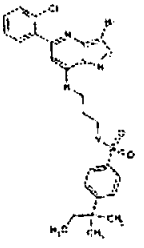
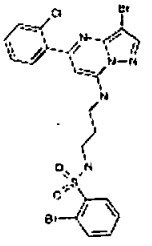
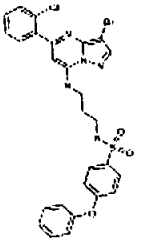
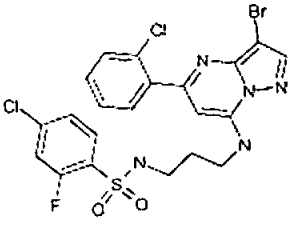
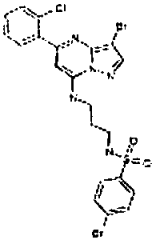
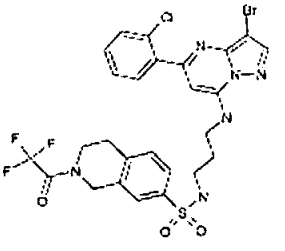
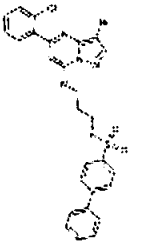
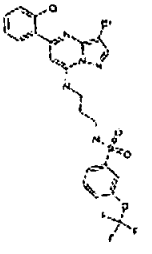
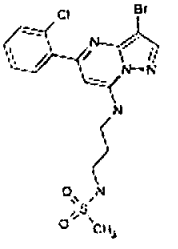
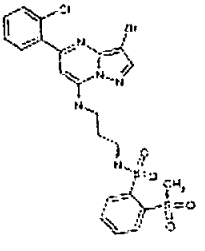
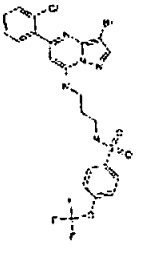
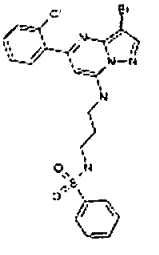
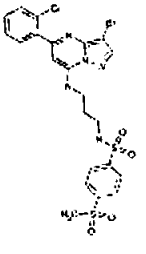
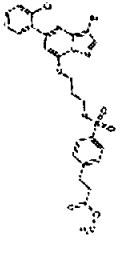
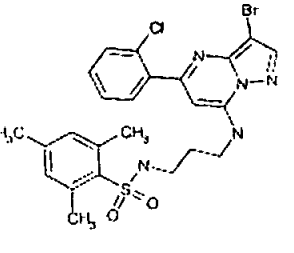
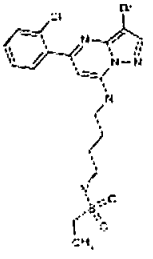
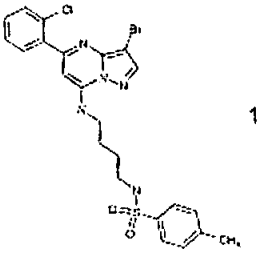
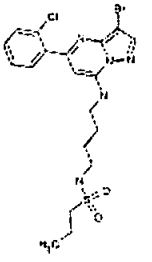
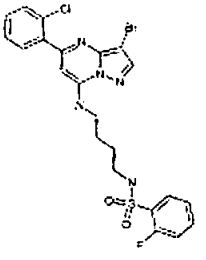
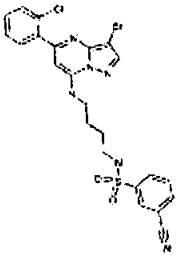
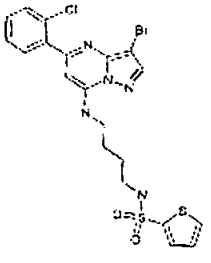
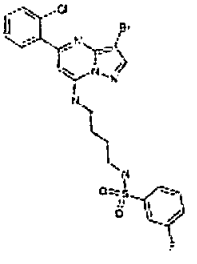
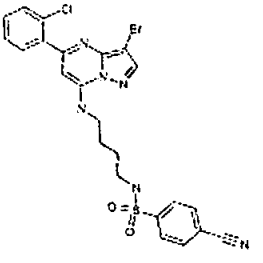
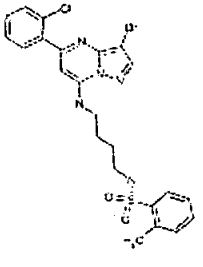
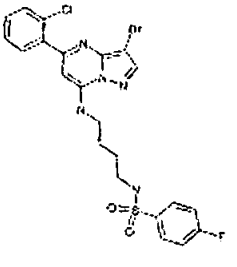
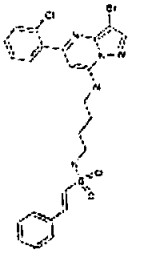
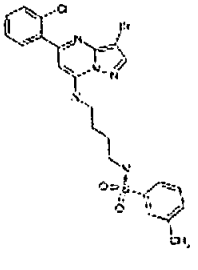
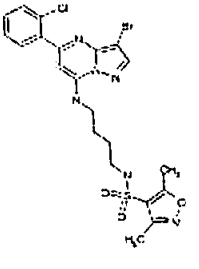
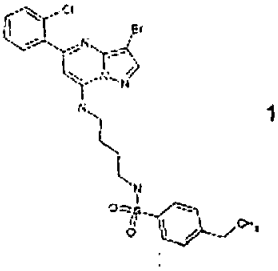
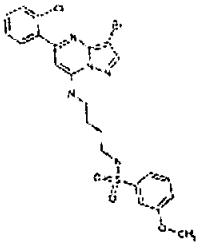
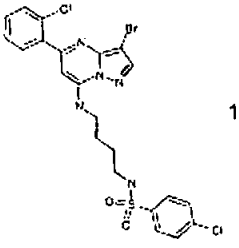
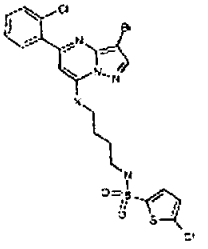
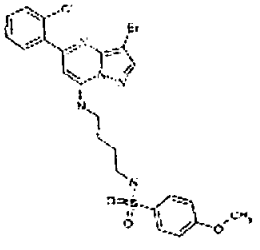
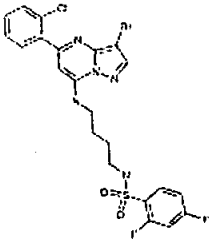
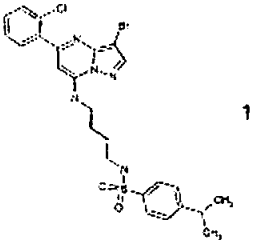
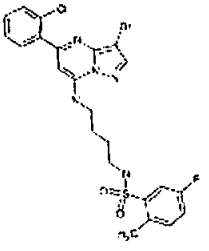
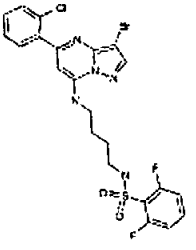
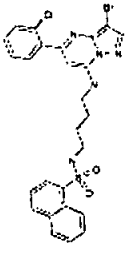
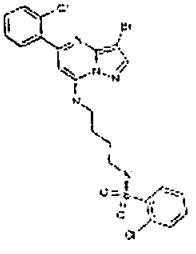
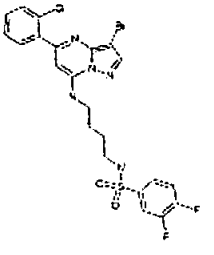
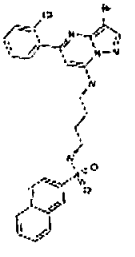
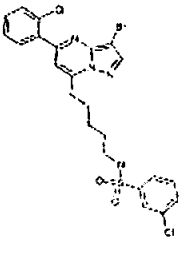
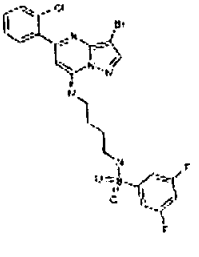
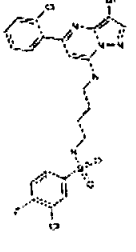
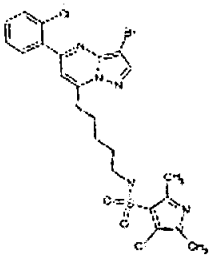
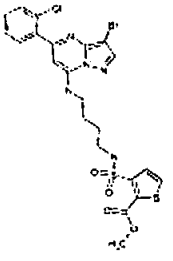
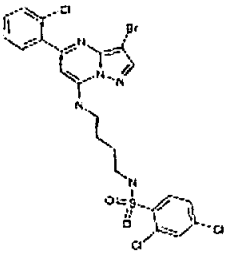
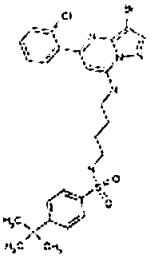
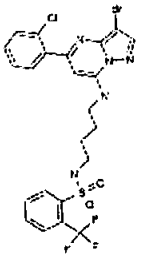
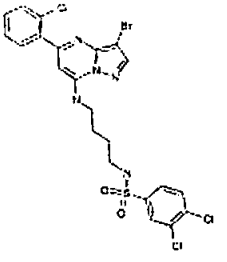
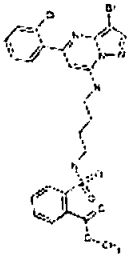
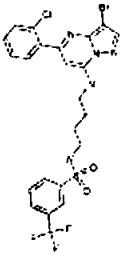
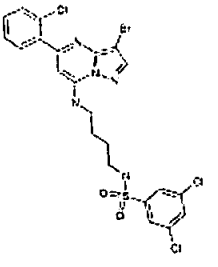
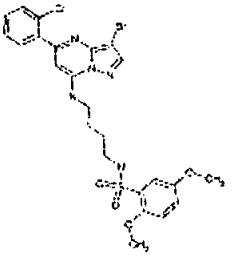
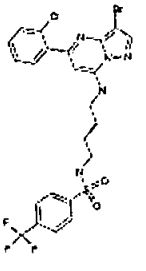
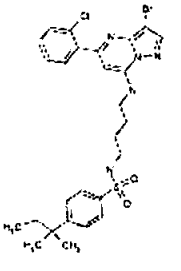
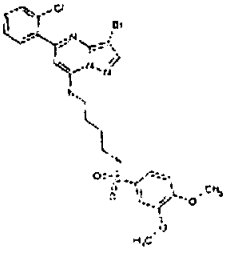
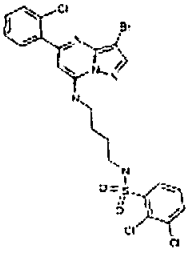
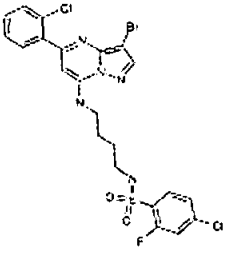
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6446 2. 592.33		1. 6451 2. 600.33		1. 6456 2. 614.34
	1. 6447 2. 574.32		1. 6452 2. 600.33		1. 6447 2. 673.37
	1. 6448 2. 598.33		1. 6453 2. 606.33		1. 6458 2. 460.25
	1. 6449 2. 600.33		1. 6454 2. 606.33		6459 2.
	1. 6450 2. 600.33		1. 6455 2. 608.33		1. 6460 2. 564.31

TABLA 65

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6501 2. 488.27		1. 6506 2. 550.3		1. 6511 2. 561.31
	1. 6502 2. 502.28		1. 6507 2. 554.3		1. 6512 2. 561.31
	1. 6503 2. 542.3		1. 6508 2. 554.3		1. 6213 2. 561.31
	1. 6504 2. 550.3		1. 6509 2. 554.3		1. 6514 2. 562.31
	1. 6505 2. 550.3		1. 6510 2. 555.31		1. 6515 2. 564.31

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6516 2. 566.31		1. 6521 2. 570.31		1. 6526 2. 576.32
	1. 6517 2. 566.31		1. 6522 2. 572.31		1. 6527 2. 578.32
	1. 6518 2. 568.31		1. 6523 2. 572.31		1. 6528 2. 586.32
	1. 6519 2. 570.31		1. 6524 2. 572.31		1. 6529 2. 586.32
	1. 6520 2. 570.31		1. 6525 2. 572.31		1. 6530 2. 588.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6531 2. 588.32		1. 6536 2. 600.33		1. 6541 2. 604.33
	1. 6532 2. 592.33		1. 6537 2. 604.33		1. 6542 2. 604.33
	1. 6533 2. 594.33		1. 6538 2. 604.33		1. 6543 2. 604.33
	1. 6534 2. 596.33		1. 6539 2. 604.33		1. 6544 2. 606.33
	1. 6535 2. 596.33		1. 6540 2. 604.33		1. 6545 2. 588.32

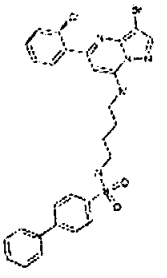
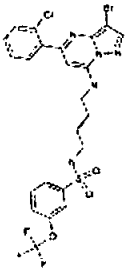
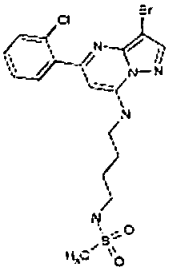
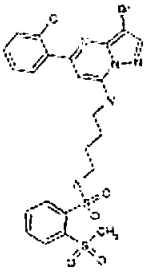
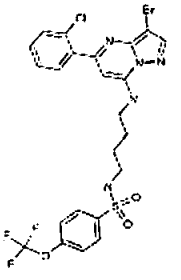
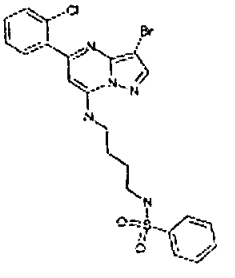
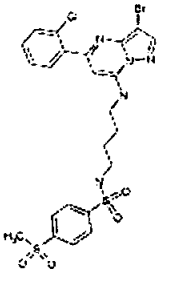
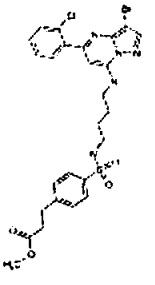
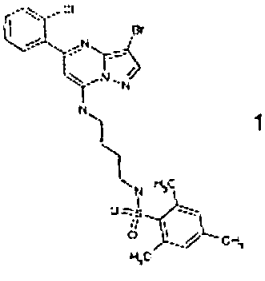
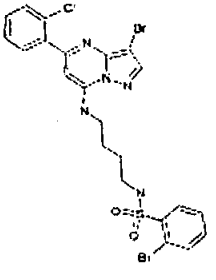
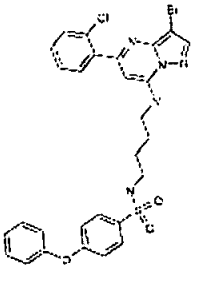
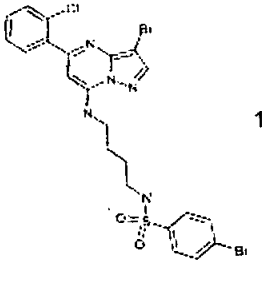
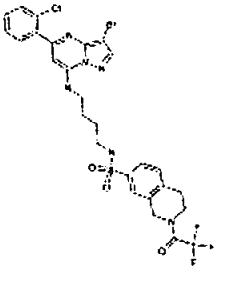
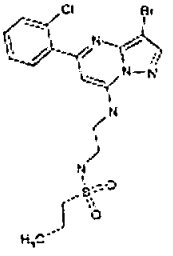
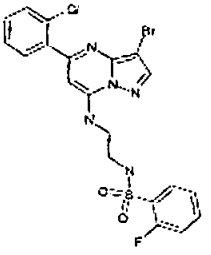
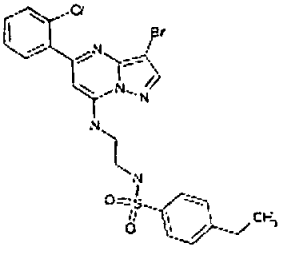
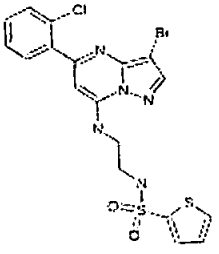
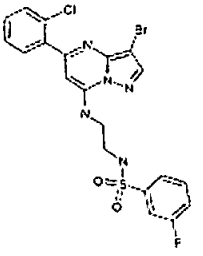
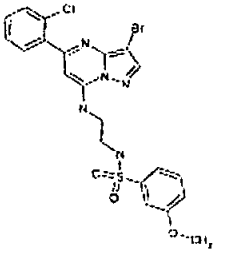
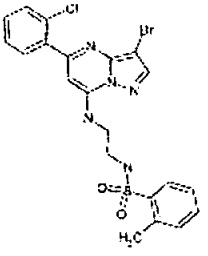
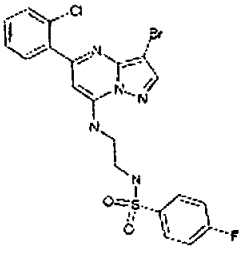
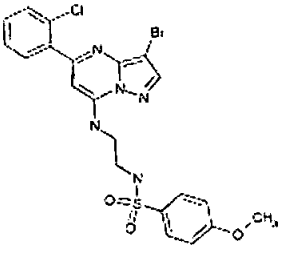
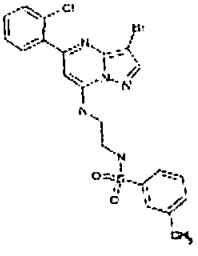
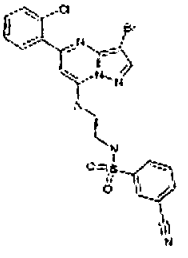
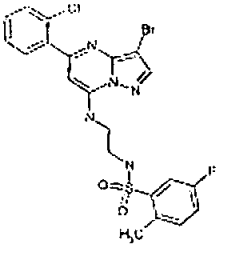
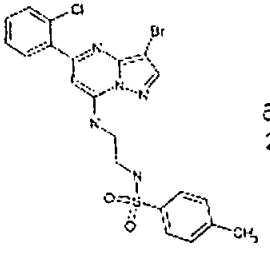
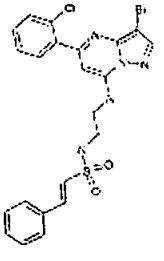
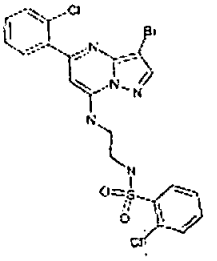
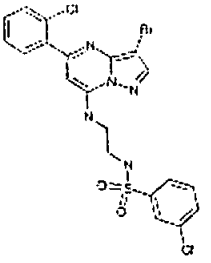
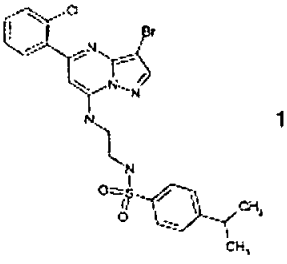
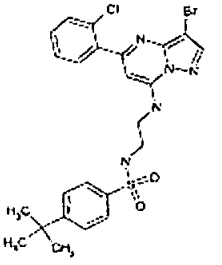
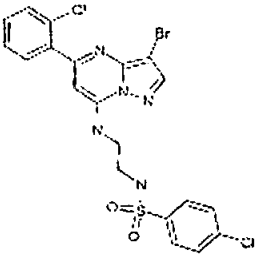
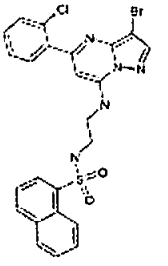
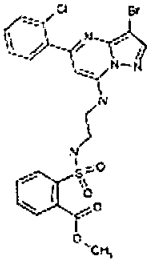
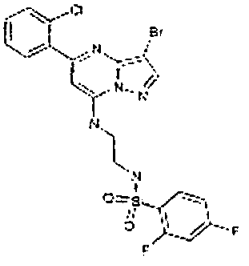
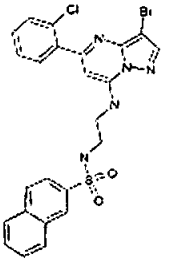
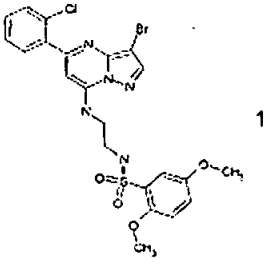
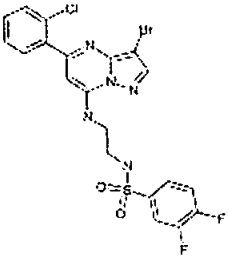
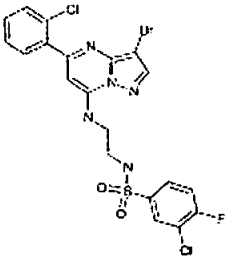
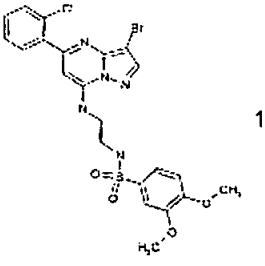
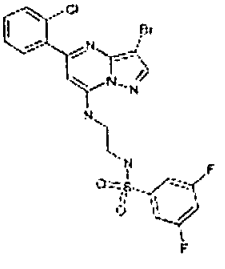
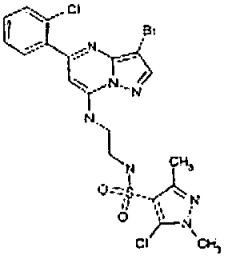
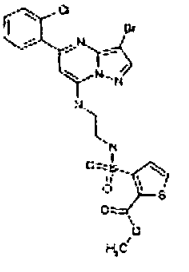
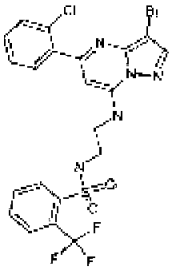
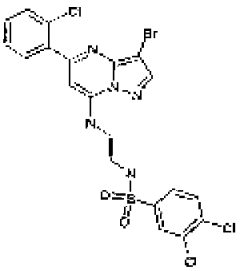
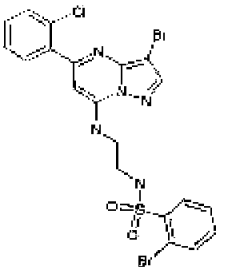
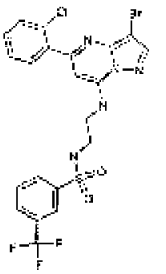
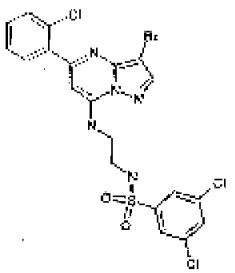
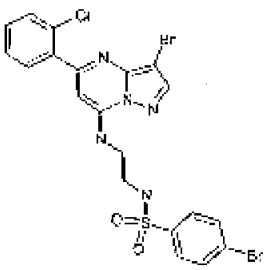
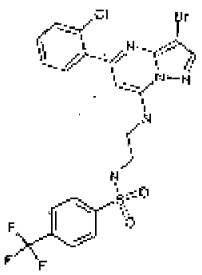
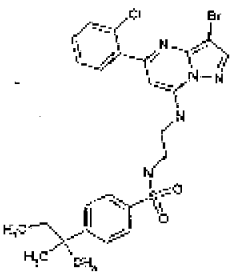
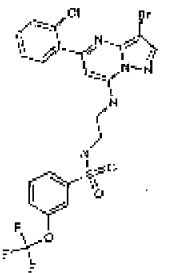
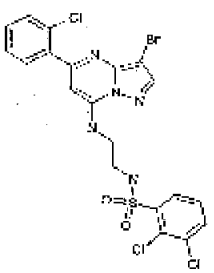
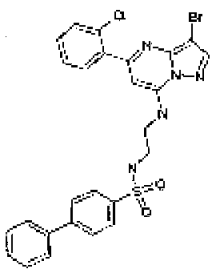
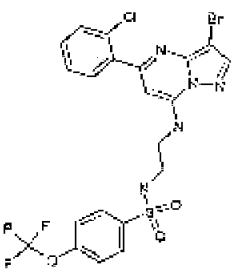
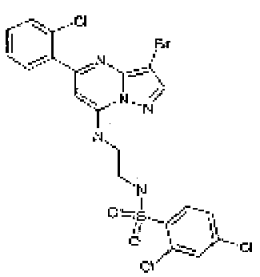
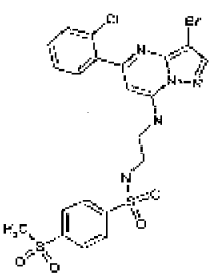
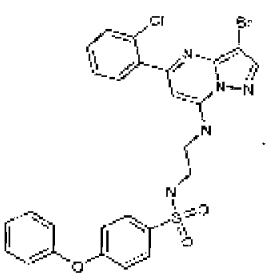
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6546 2. 612.34		1. 6551 2. 620.34		1. 6556 2. 474.26
	1. 6547 2. 614.34		1. 6552 2. 620.34		1. 6557 2. 536.29
	1. 6548 2. 614.34		1. 6553 2. 622.34		1. 6558 2. 578.32
	1. 6549 2. 614.34		1. 6554 2. 628.35		
	1. 6550 2. 614.34		1. 6555 2. 687.38		

TABLA 67

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6701 2. 474.26		1. 6706 2. 526.29		1. 6711 2. 536.29
	1. 6702 2. 514.28		1. 6707 2. 526.29		1. 6712 2. 538.3
	1. 6703 2. 522.29		1. 6708 2. 526.29		1. 6713 2. 538.3
	1. 6704 2. 522.29		1. 6709 2. 533.29		1. 6714 2.
	6705 2. 22.29		1. 6710 2. 534.29		1. 6715 2. 542.3

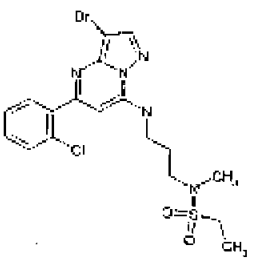
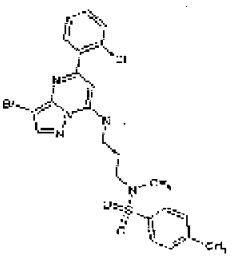
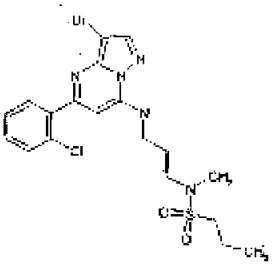
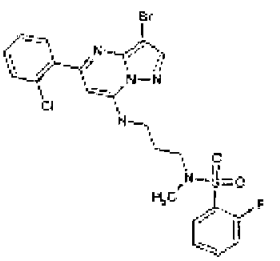
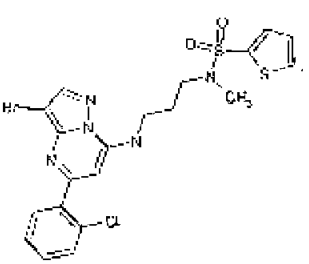
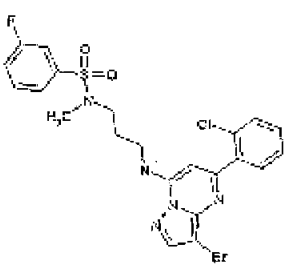
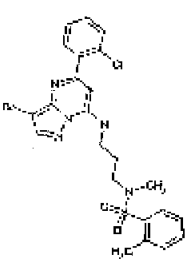
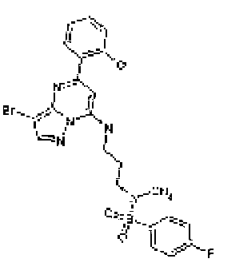
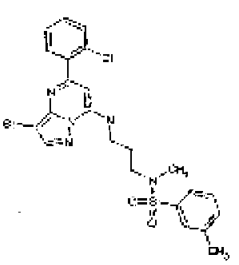
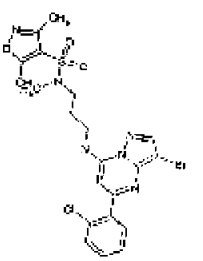
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6716 2. 542.3		1. 6721 2. 550.3		1. 6726 2. 564.31
	1. 6717 2. 542.3		1. 6722 2. 558.31		1. 6727 2. 566.31
	1. 6718 2. 544.3		1. 6723 2. 558.31		1. 6728 2. 568.31
	1. 6719 2. 544.3		1. 6724 2. 560.31		1. 6729 2. 568.31
	1. 6720 2. 544.3		1. 6725 2. 560.31		1. 6730 2. 572.31

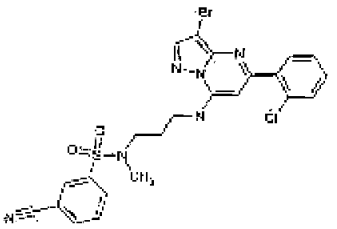
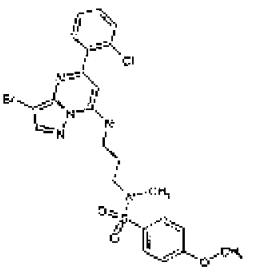
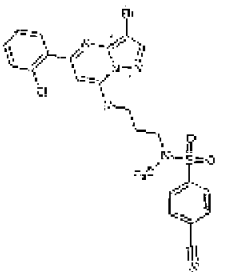
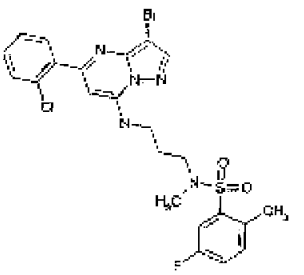
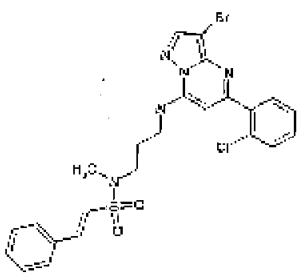
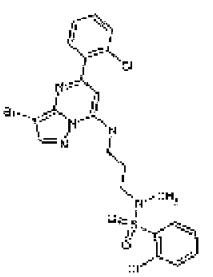
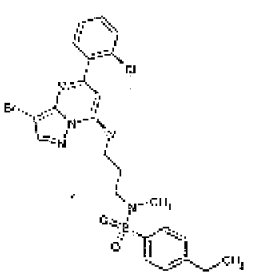
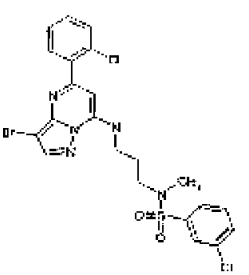
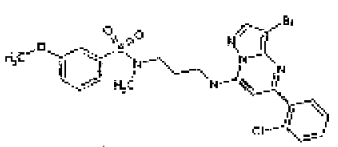
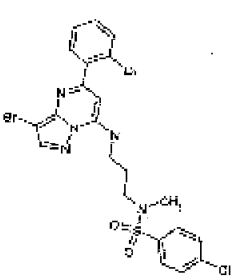
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6731 2. 576.32		1. 6736 2. 576.32		1. 6741 2. 586.32
	1. 6732 2. 576.32		1. 6737 2. 576.32		1. 6742 2. 586.32
	1. 6733 2. 576.32		1. 6738 2. 576.32		1. 6743 2. 592.33
	1. 6734 2. 576.32		1. 6739 2. 584.32		1. 6744 2. 592.33
	1. 6735 2. 576.32		1. 6740 2. 586.32		1. 6745 2. 600.33

1769

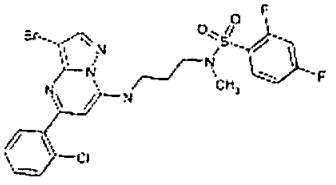
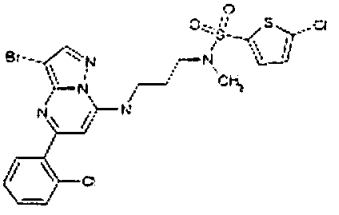
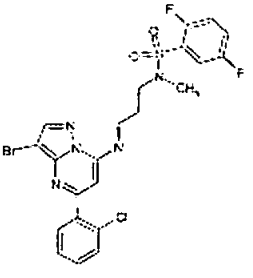
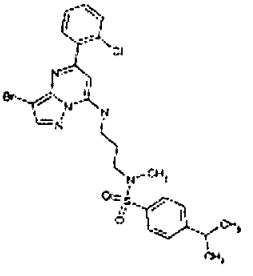
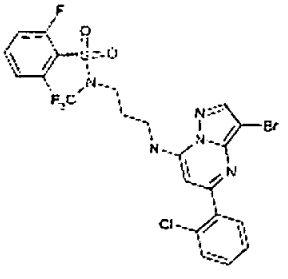
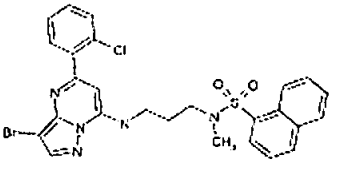
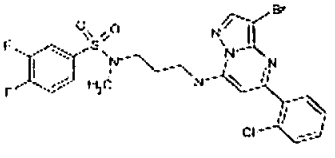
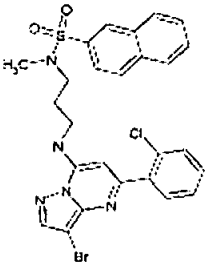
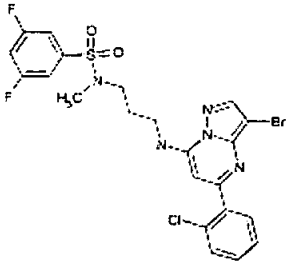
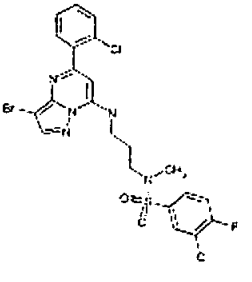
1220

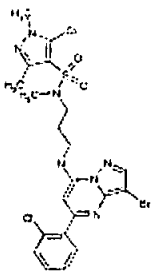
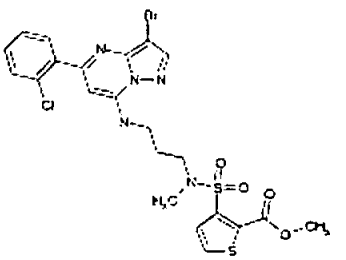
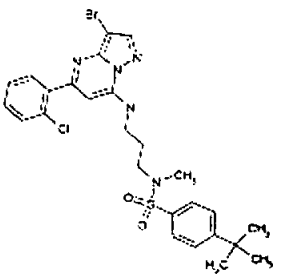
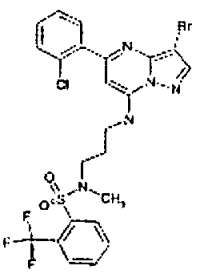
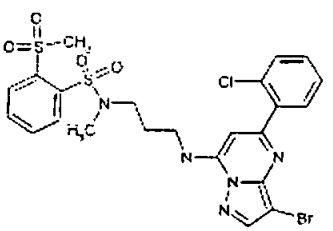
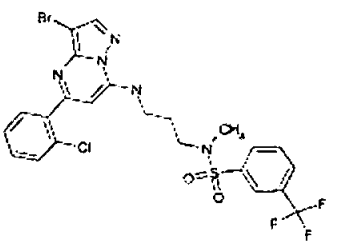
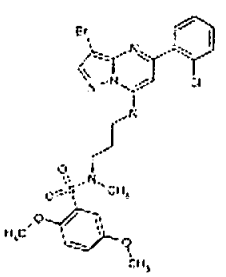
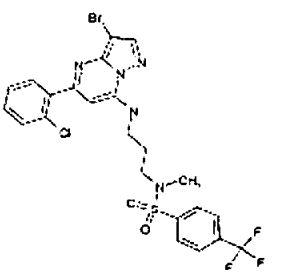
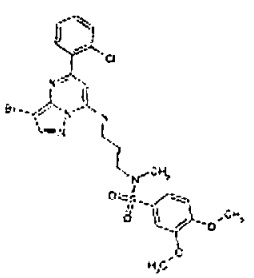
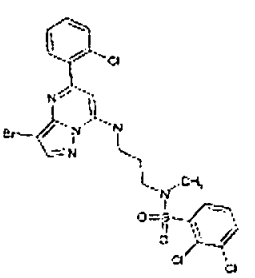
TABLA 68

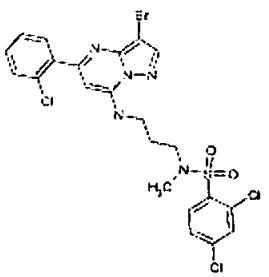
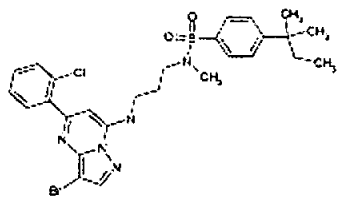
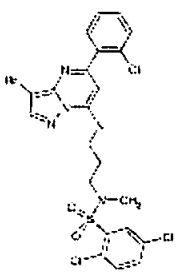
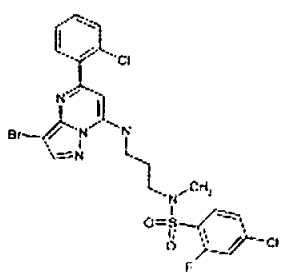
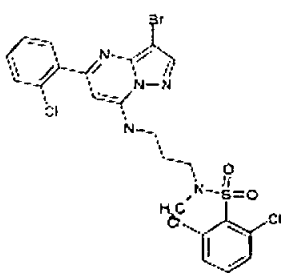
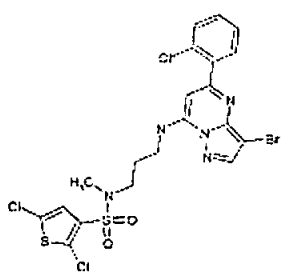
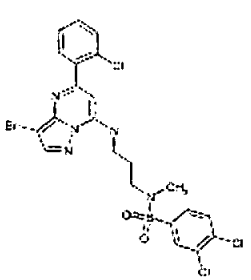
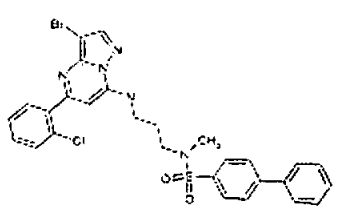
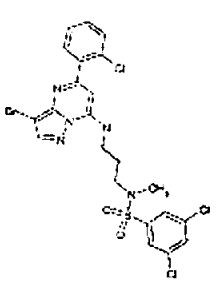
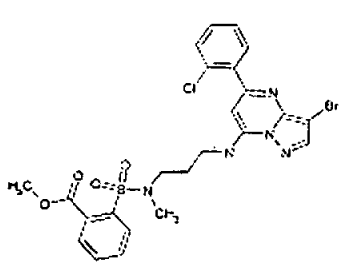
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6801 2. 488.27		1. 6806 2. 550.3
	1. 6802 2. 502.28		1. 6807 2. 554.3
	1. 6803 2. 542.3		1. 6808 2. 554.3
	1. 6804 2. 550.3		1. 6809 2. 554.3
	1. 68058 2. 550.3		1. 6810 2. 555.31

Producto	1. Ej. 2. m/z	Product	1. Ex. 2. m/z
	1. 6811 2. 561.31		1. 6816 2. 566.31
	1. 6812 2. 561.31		1. 6817 2. 568.31
	1. 6813 2. 562.31		1. 6818 2. 570.31
	1. 6814 2. 564.31		1. 6819 2. 570.31
	1. 6815 2. 566.31		1. 6820 2. 570.31

1272

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6821 2. 571.31		1. 6826 2. 576.32
	1. 6822 2. 572.31		1. 6827 2. 578.32
	1. 6823 2. 572.31		1. 6828 2. 586.32
	1. 6824 2. 572.31		1. 6829 2. 586.32
	1. 6825 2. 572.31		1. 6830 2. 588.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6831 2. 588.32		1. 6836 2. 600.33
	1. 6832 2. 592.33		1. 6837 2. 602.33
	1. 6833 2. 614.34		1. 6838 2. 604.33
	1. 6834 2. 596.33		1. 6839 2. 604.33
	1. 6835 2. 596.33		1. 6840 2. 604.33

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6841 2. 604.33		1. 6846 2. 606.33
	1. 6842 2. 604.33		1. 6847 2. 588.32
	1. 6843 2. 605.33		1. 6848 2. 610.34
	1. 6844 2. 604.33		1. 6849 2. 612.34
	1. 6845 2. 604.33		1. 6850 2. 594.33

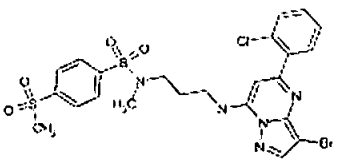
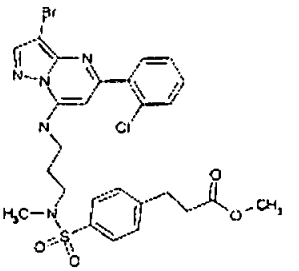
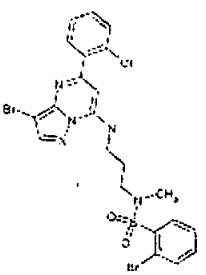
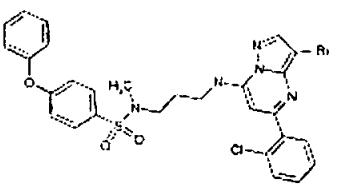
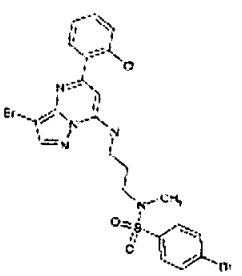
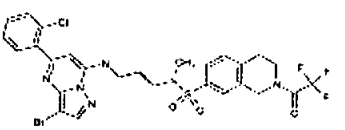
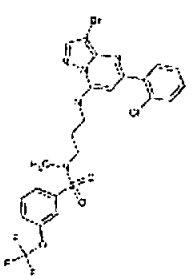
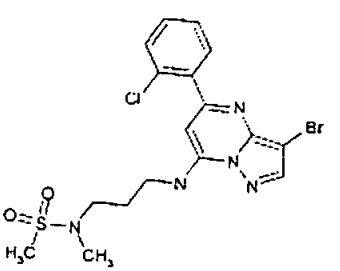
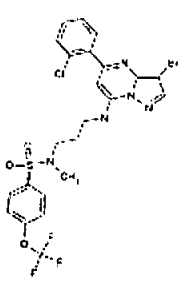
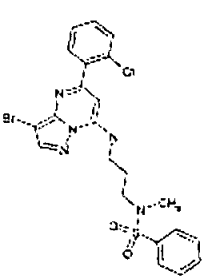
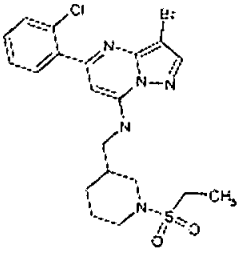
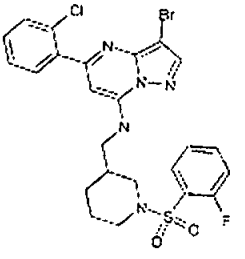
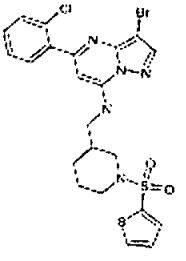
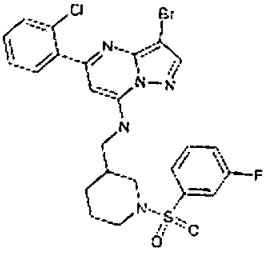
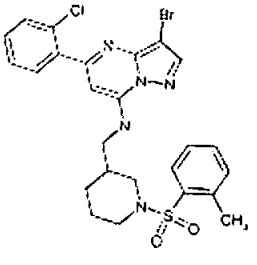
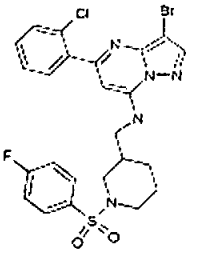
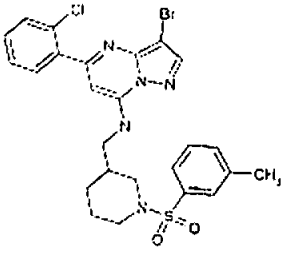
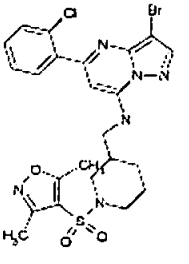
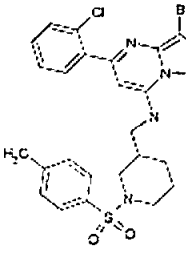
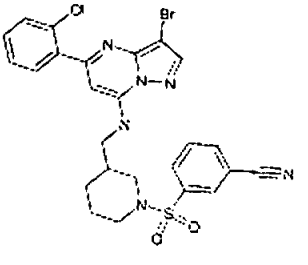
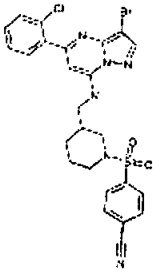
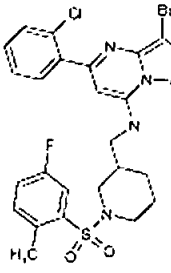
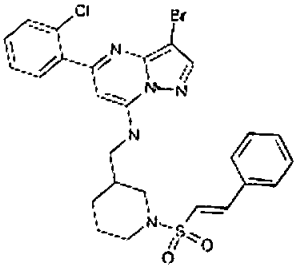
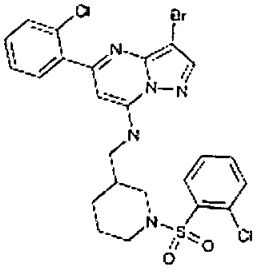
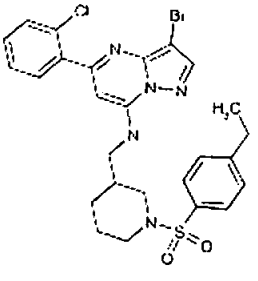
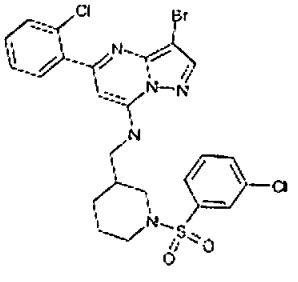
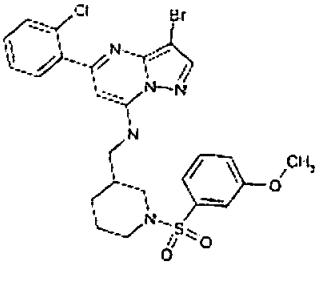
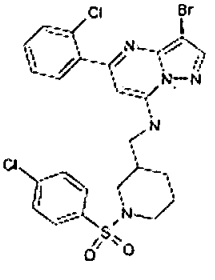
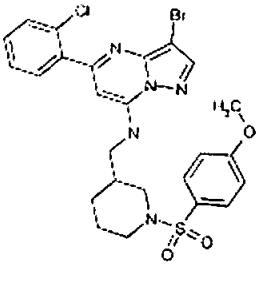
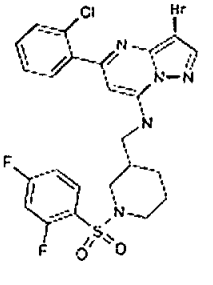
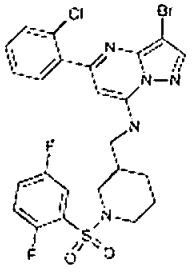
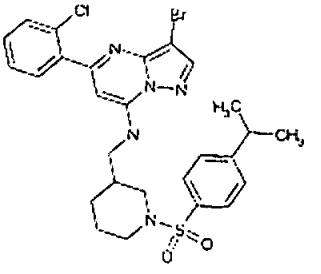
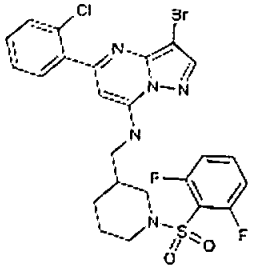
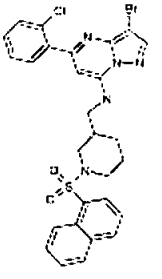
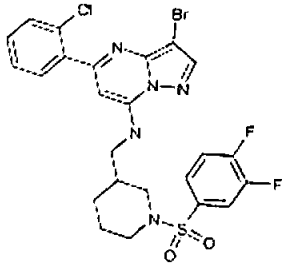
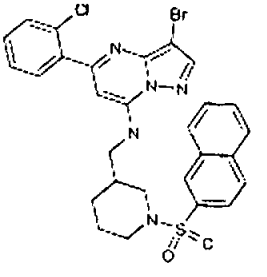
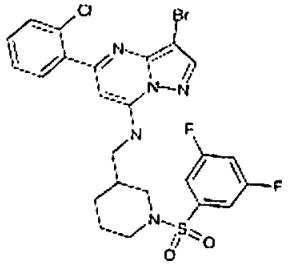
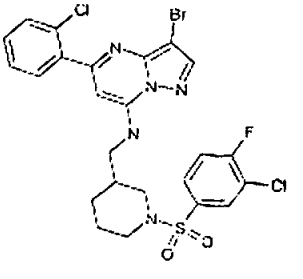
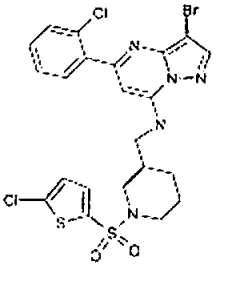
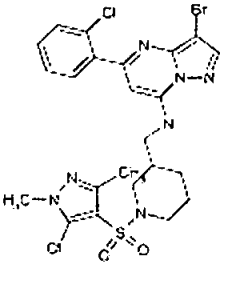
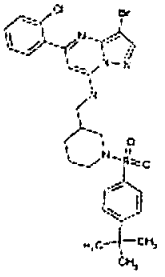
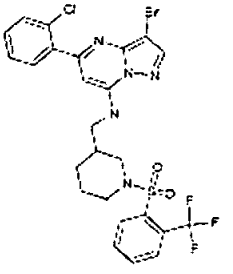
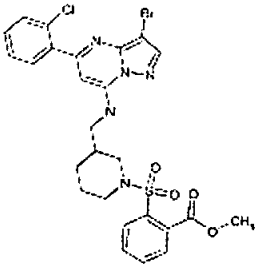
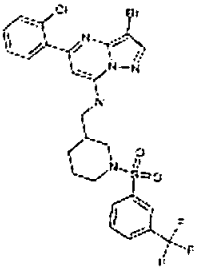
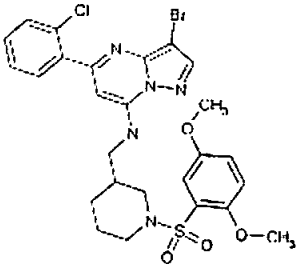
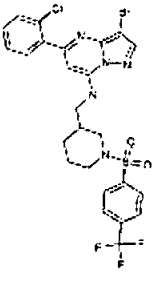
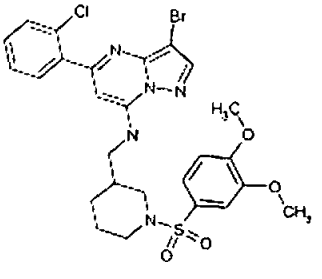
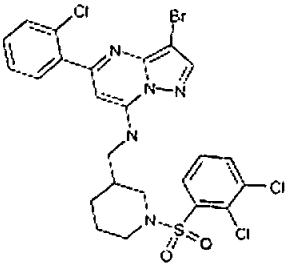
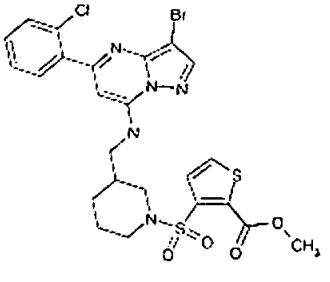
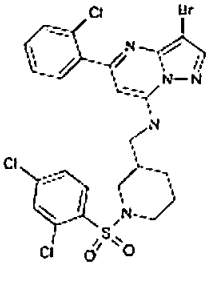
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6851 2. 614.34		1. 6856 2. 620.34
	1. 6852 2. 614.34		1. 6856 2. 628.35
	1. 6853 2. 614.34		1. 6857 2. 687.38
	1. 6854 2. 620.34		1. 6859 2. 474.26
	1. 6855 2. 620.34		1. 6860 2. 536.29

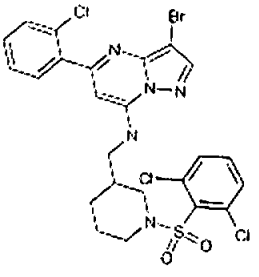
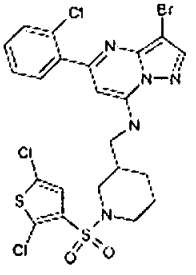
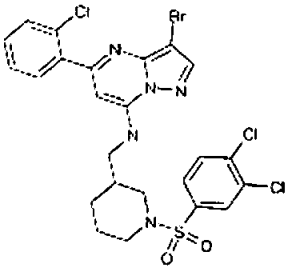
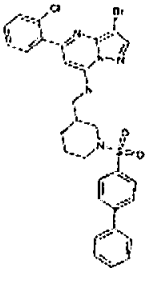
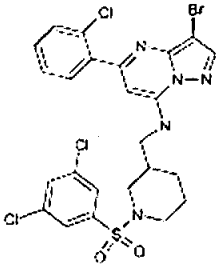
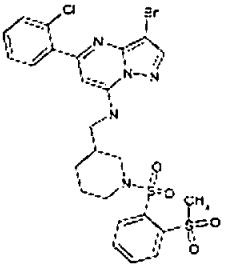
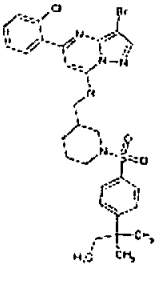
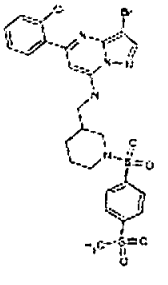
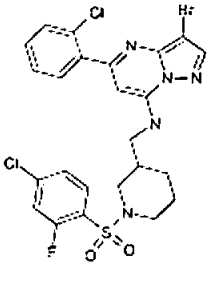
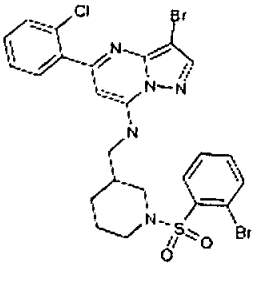
TABLA 69

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1 .6901 2. 514.28		1. 6906 2. 580.32
	1. 6902 2. 568.31		1. 6907 2. 580.32
	1. 6903 2. 576.32		1. 6908 2. 580.32
	1. 6904 2. 576.32		1. 6909 2. 581.32
	1. 6905 2. 576.32		1. 6910 2. 587.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6911 2. 587.32		1. 6916 2. 594.33
	1. 6912 2. 588.32		1. 6917 2. 596.33
	1. 6913 2. 590.32		1. 6918 2. 596.33
	1. 6914 2. 592.33		1. 6919 2. 596.33
	1. 6915 2. 592.33		1. 6920 2. 598.33

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6921 2. 598.33		1. 6926 2. 604.33
	1. 6922 2. 598.33		1. 6927 2. 612.34
	1. 6923 2. 598.33		1. 6928 2. 612.34
	1. 6924 2. 598.33		1. 6929 2. 614.34
	1. 6925 2. 602.33		1. 6930 2. 614.34

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6931 2. 618.34		1. 6936 2. 630.35
	1. 6932 2. 620.34		1. 6937 2. 630.35
	1. 6933 2. 622.34		1. 6938 2. 630.35
	1. 6934 2. 622.34		1. 6939 2. 630.35
	1. 6935 2. 626.34		1. 6940 2. 630.35

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6941 2. 630.35		1. 6946 2. 636.35
	1. 6942 2. 630.35		1. 6947 2. 638.35
	1. 6943 2. 630.35		1. 6948 2. 640.35
	1. 6944 2. 632.35		1. 6949 2. 640.35
	1. 6945 2. 614.34		1. 6950 2. 640.35

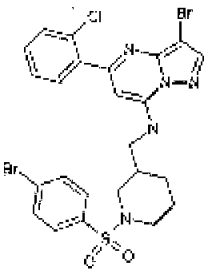
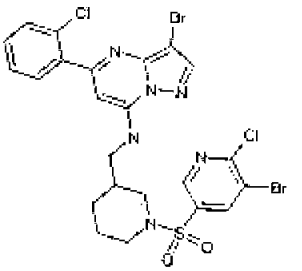
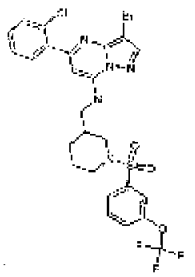
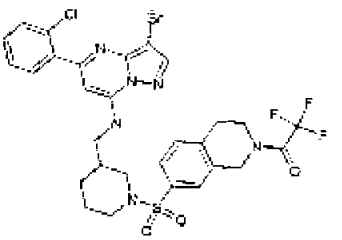
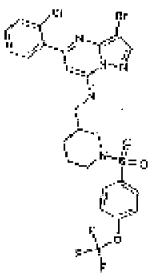
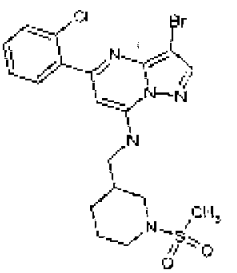
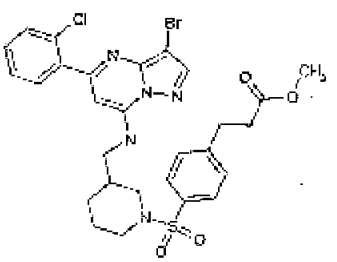
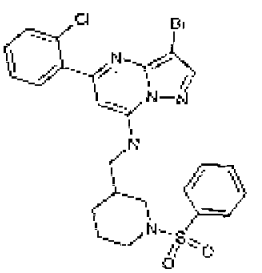
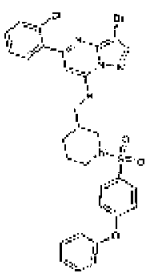
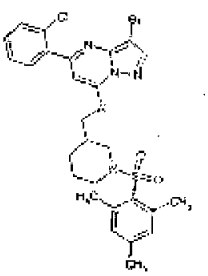
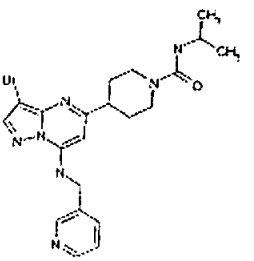
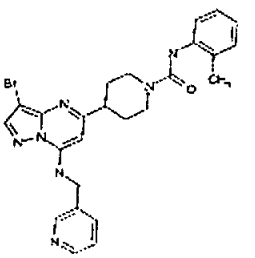
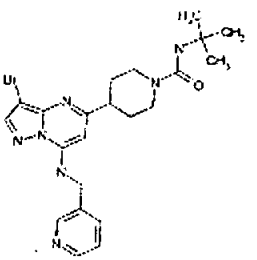
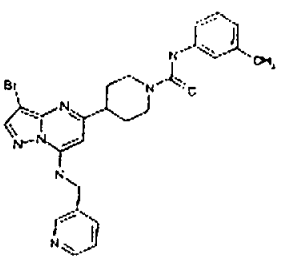
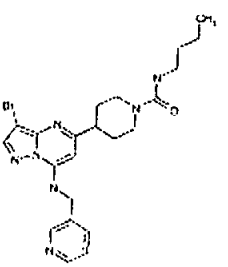
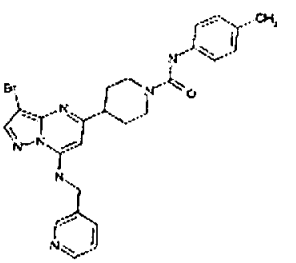
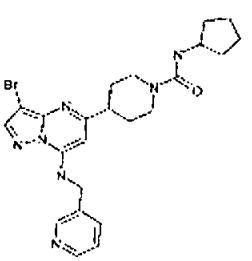
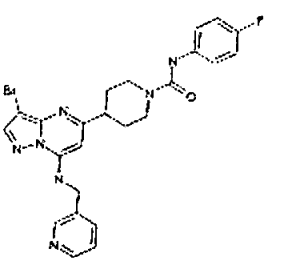
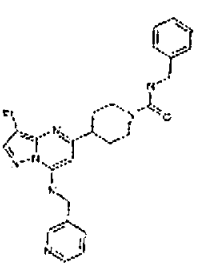
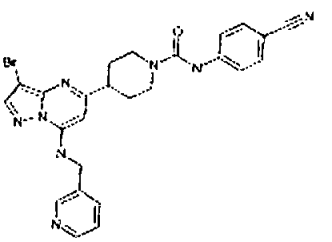
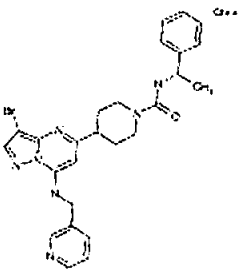
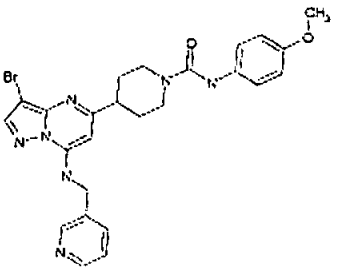
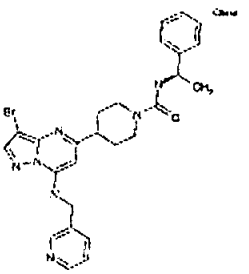
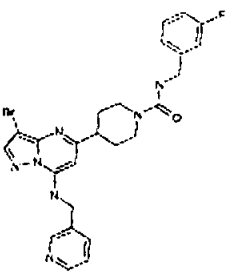
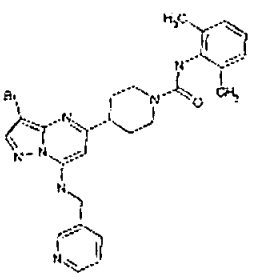
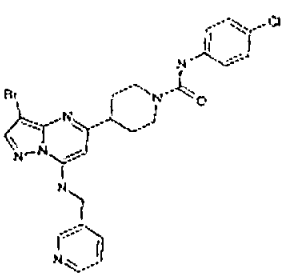
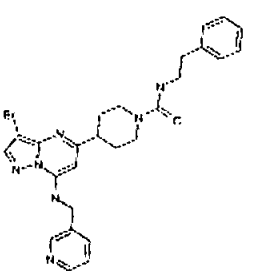
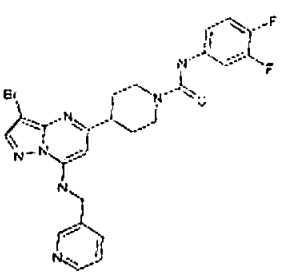
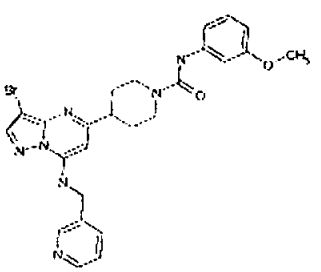
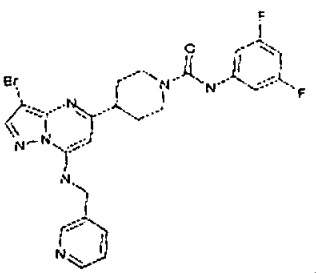
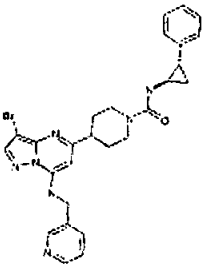
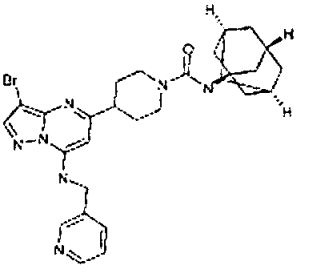
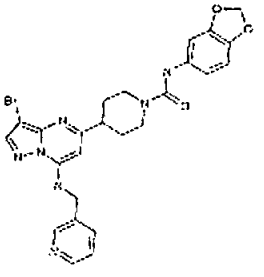
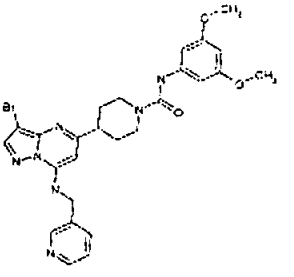
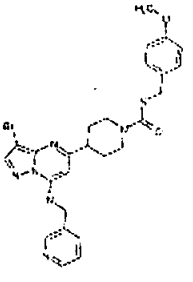
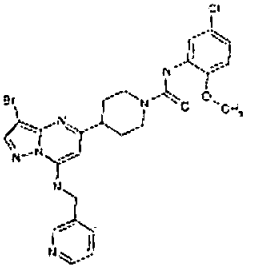
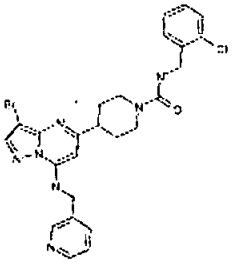
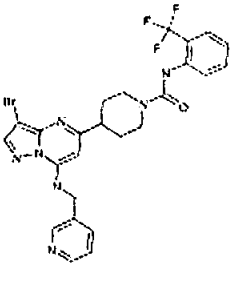
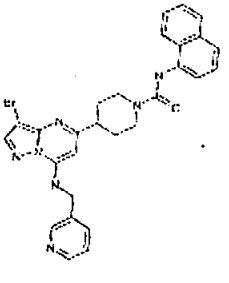
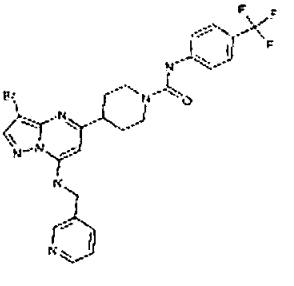
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6951 2. 640.35		1. 6956 2. 675.23
	1. 6952 2. 646.36		1. 6957 2. 713.39
	1. 6953 2. 646.36		1. 6958 2. 500.27
	1. 6954 2. 648.36		1. 6959 2. 562.31
	1. 6955 2. 654.36		1. 6960 2. 604.33

TABLA 70

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7001 2. 472.26		1. 7006 2. 522.29
	1. 7002 2. 488.27		1. 7007 2. 520.29
	1. 7003 2. 488.27		1. 7008 2. 520.29
	1. 7004 2. 500.27		1. 7009 2. 526.29
	1. 7005 2. 520.29		1. 7010 2. 533.29

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7011 2. 536.29		1. 7016 2. 538.3
	1. 7012 2. 536.29		1. 7017 2. 540.3
	1. 7013 2. 536.29		1. 7018 2. 542.3
	1. 7014 2. 536.29		1. 7019 2. 544.3
	1. 7015 2. 536.29		1. 7020 2. 544.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7021 2. 548.3		1. 7026 2. 566.31
	1. 7022 2. 552.3		1. 7027 2. 568.31
	1. 7023 2. 552.3		1. 7028 2. 572.31
	1. 7024 2. 556.31		1. 7029 2. 576.32
	1. 7025 2. 558.31		1. 7030 2. 576.32

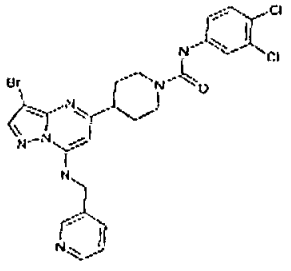
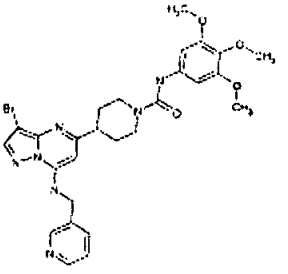
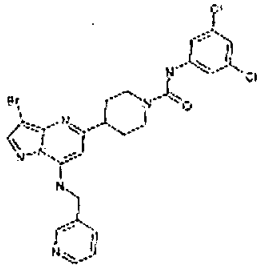
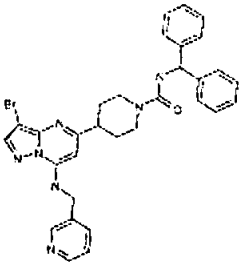
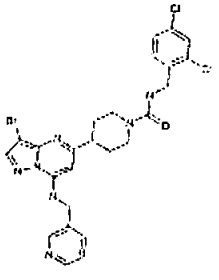
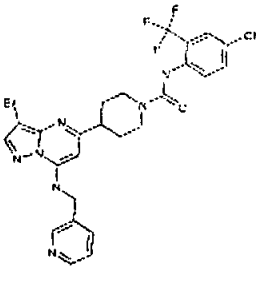
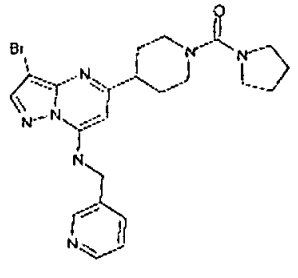
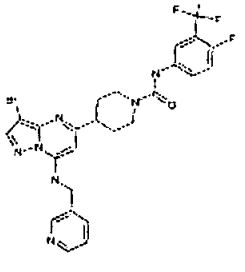
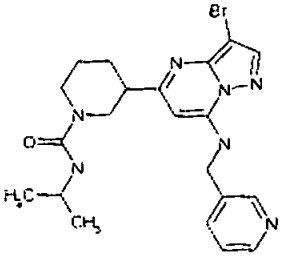
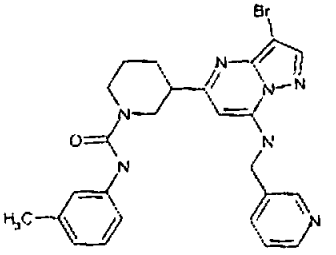
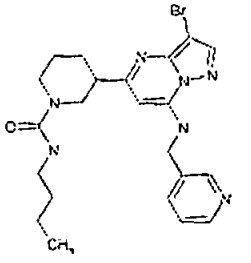
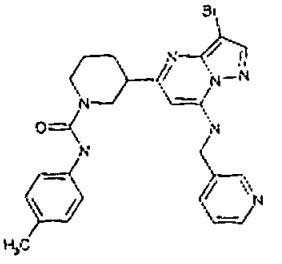
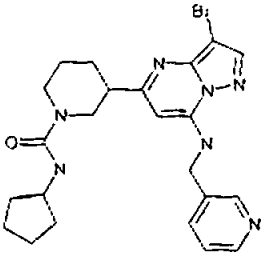
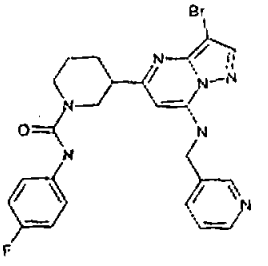
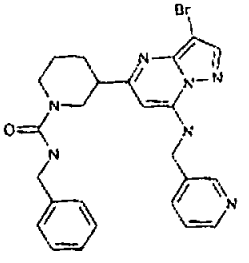
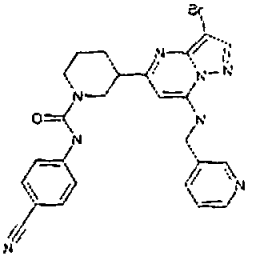
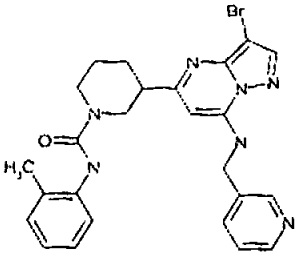
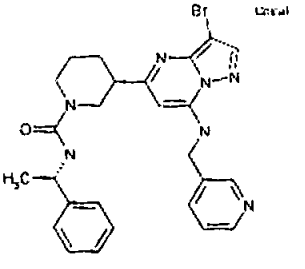
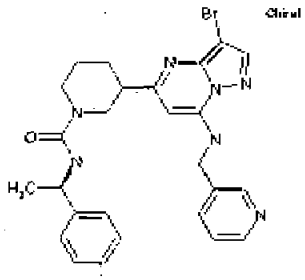
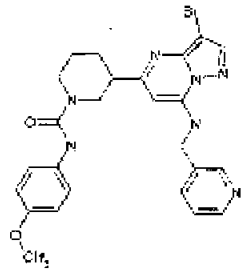
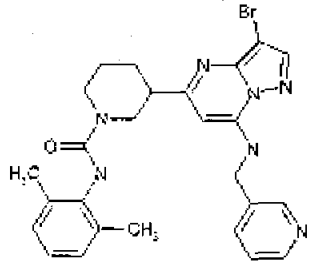
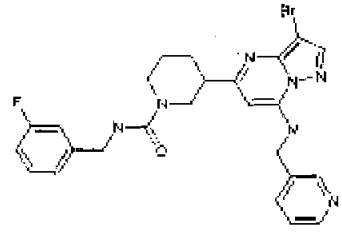
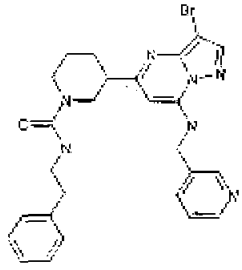
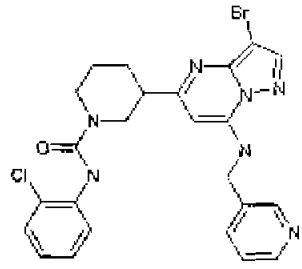
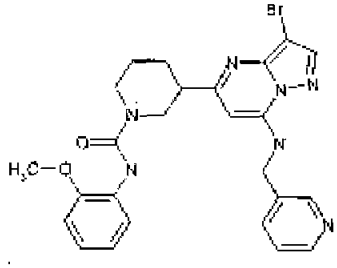
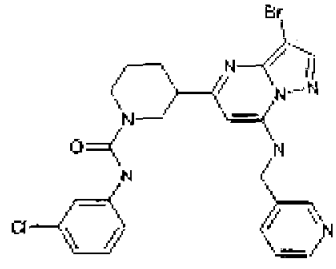
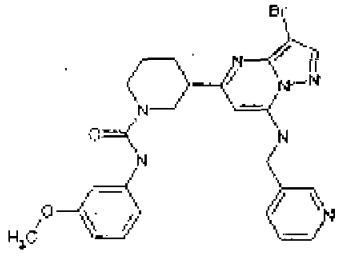
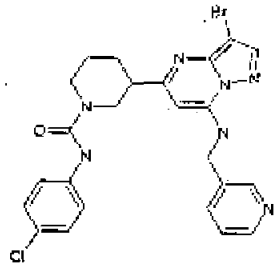
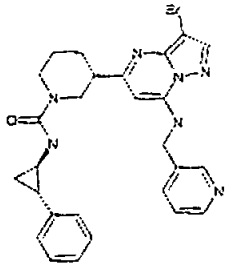
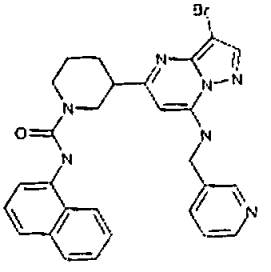
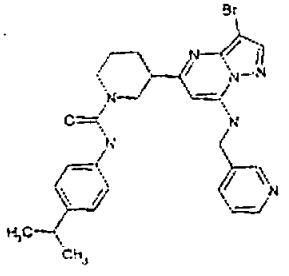
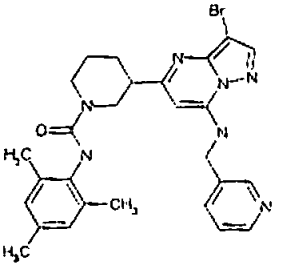
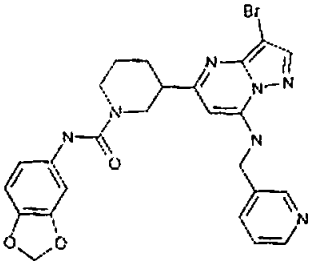
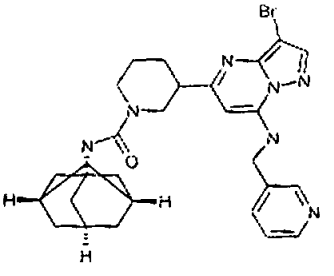
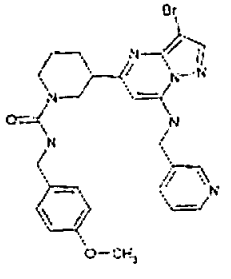
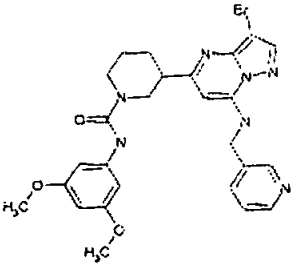
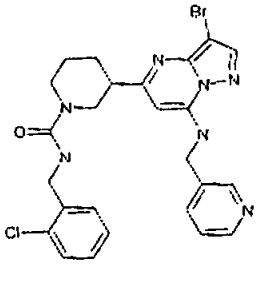
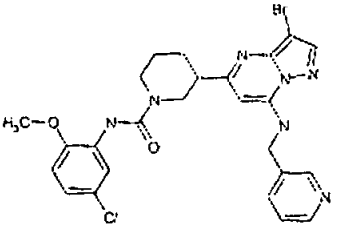
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7031 2. 576.32		1. 7036 2. 598.33
	1. 7032 2. 576.32		1. 7037 2. 598.33
	1. 7033 2. 590.32		1. 7038 2. 610.34
	1. 7034 2. 486.27		
	1. 7035 2. 594.33		

TABLA 71

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1 . 7101 2. 474.26		1. 7106 2. 522.29
	1. 7102 2. 488.27		1. 7107 2. 522.29
	1. 7103 2. 500.27		1. 7108 2. 526.3
	1. 7104 2. 522.29		1. 7109 2. 533.29
	1. 7105 2. 522.29		1. 7110 2. 536.29

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7111 2. 536.29		1. 7116 2. 538.3
	1. 7112 2. 536.29		1. 7117 2. 540.3
	1. 7113 2. 536.29		1. 7118 2. 542.3
	1. 7114 2. 536.29		1. 7119 2. 542.3
	1. 7115 2. 536.3		1. 7120 2. 542.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7121 2. 546.3		1. 7126 2. 558.31
	1. 7122 2. 550.3		1. 7127 2. 550.3
	1. 7123 2. 552.3		1. 7128 2. 566.31
	1. 7124 2. 552.3		1. 7129 2. 565.31
	1. 7125 2. 556.31		1. 7130 2. 572.31

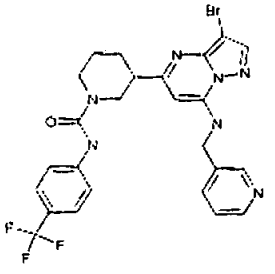
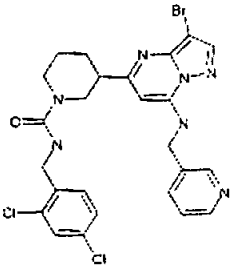
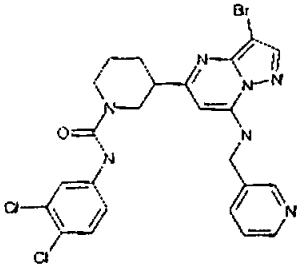
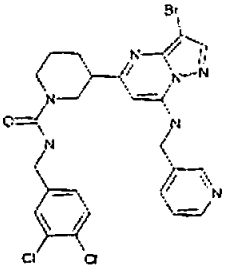
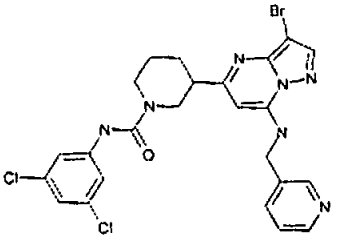
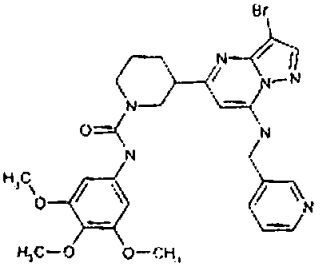
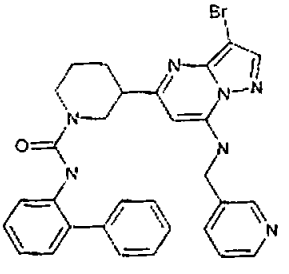
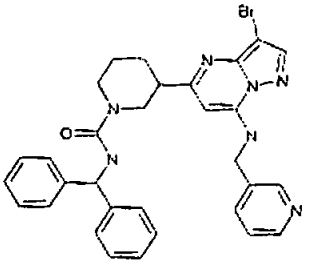
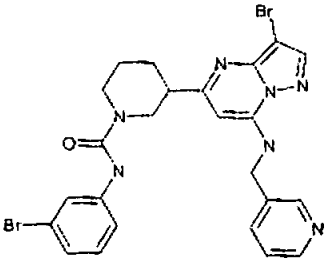
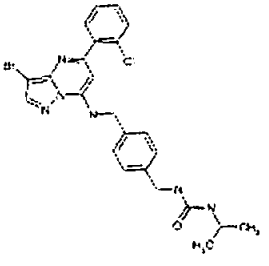
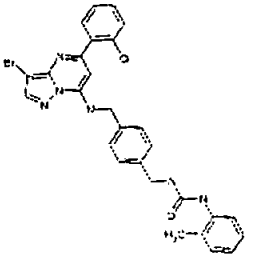
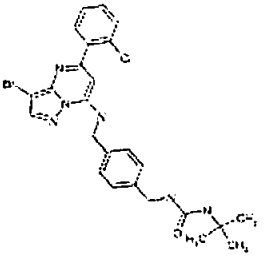
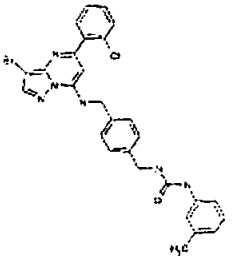
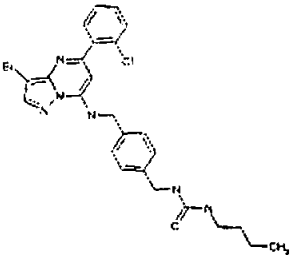
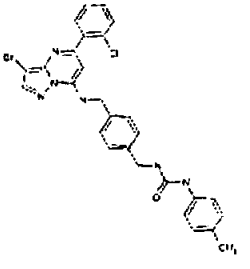
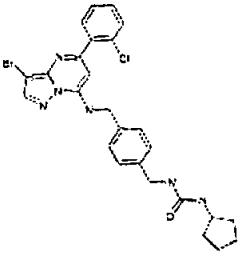
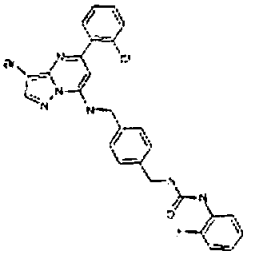
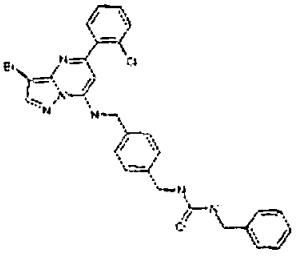
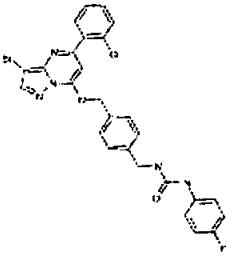
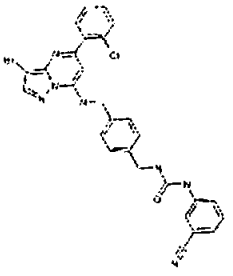
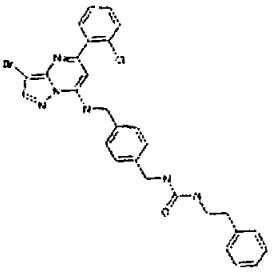
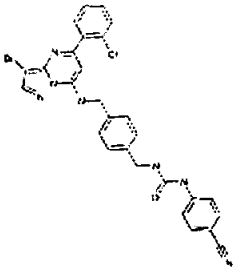
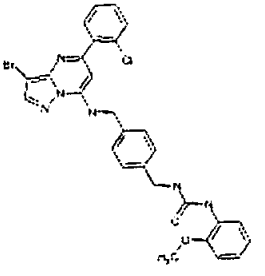
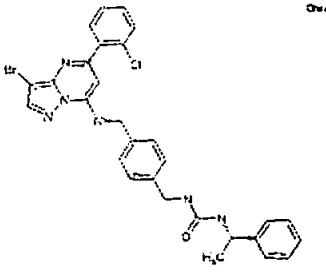
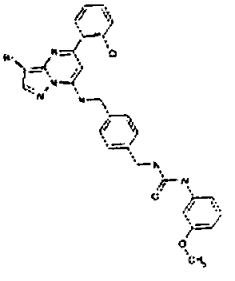
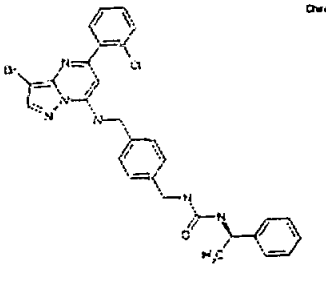
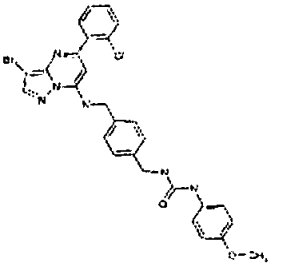
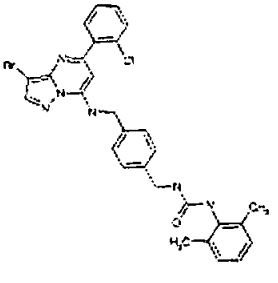
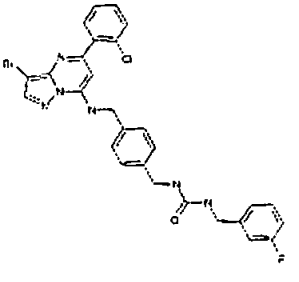
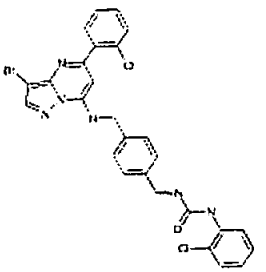
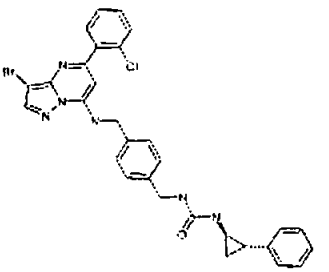
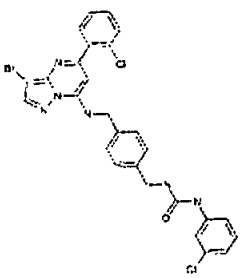
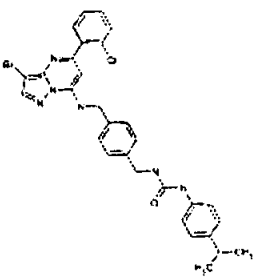
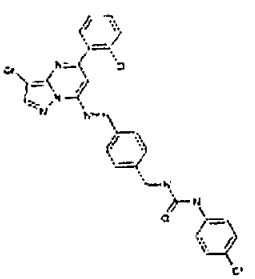
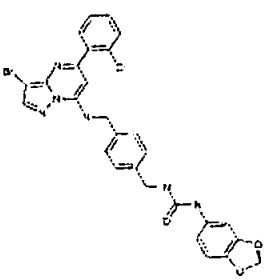
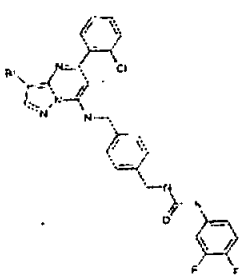
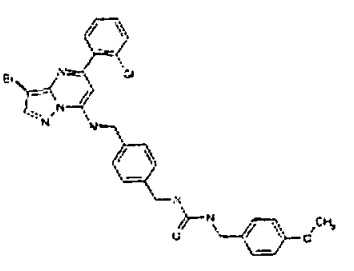
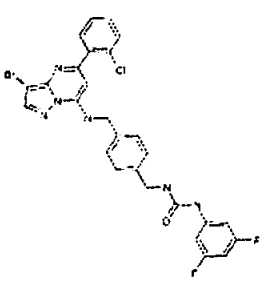
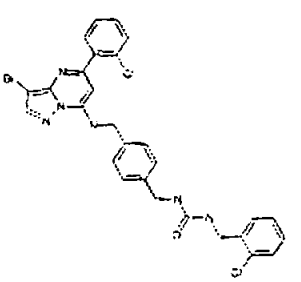
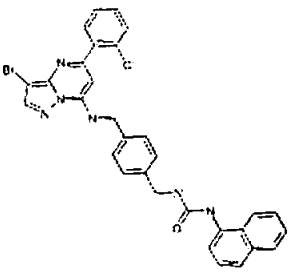
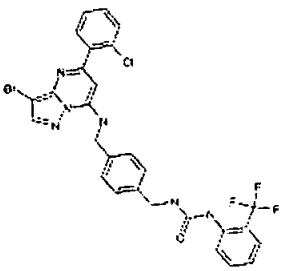
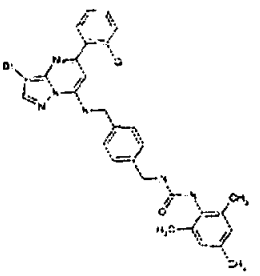
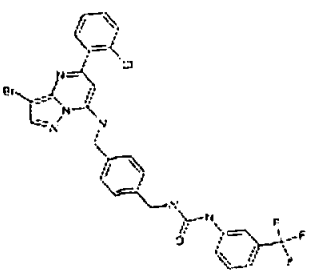
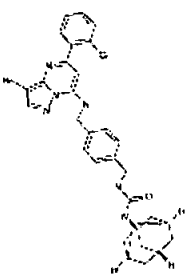
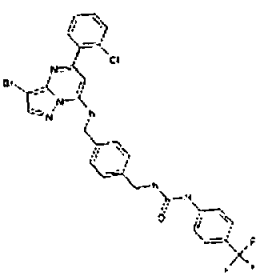
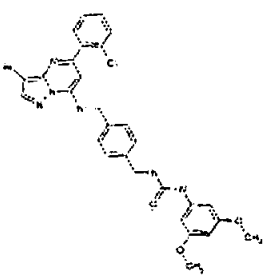
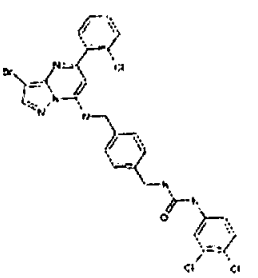
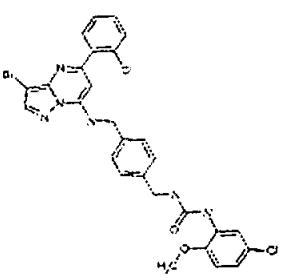
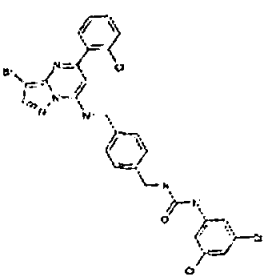
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7131 2. 576.32		1. 7136 2. 590.32
	1. 7132 2. 576.32		1. 7137 2. 590.32
	1. 7133 2. 576.32		1. 7138 2. 598.33
	1. 7134 2. 584.32		1. 7139 2. 598.33
	1. 7135 2. 585.3		

TABLA 72

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7201 2. 529.29		1. 7206 2. 577.32
	1. 7202 2. 543.3		1. 7207 2. 577.32
	1. 7203 2. 543.3		1. 7208 2. 577.32
	1. 7204 2. 555.31		1. 7209 2. 581.32
	1. 7205 2. 577.32		1. 7210 2. 581.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7211 2. 588.32		1. 7216 2. 591.33
	1. 7212 2. 588.32		1. 7217 2. 593.33
	1. 7213 2. 591.33		1. 7218 2. 593.33
	1. 7214 2. 591.33		1. 7219 2. 593.33
	1. 7215 2. 591.33		1. 7220 2. 595.33

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7221 2. 597.33		1. 7226 2. 603.33
	1. 7222 2. 597.33		1. 7227 2. 603.33
	1. 7223 2. 597.33		1. 7228 2. 607.33
	1. 7224 2. 599.33		1. 7229 2. 607.14
	1. 7225 2. 599.33		1. 7230 2. 611.34

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7231 2. 613.34		1. 7236 2. 631.35
	1. 7232 2. 605.33		1. 7237 2. 631.35
	1. 7233 2. 621.34		1. 7238 2. 631.35
	1. 7234 2. 623.34		1. 7239 2. 631.35
	1. 7235 2. 627.34		1. 7240 2. 631.35

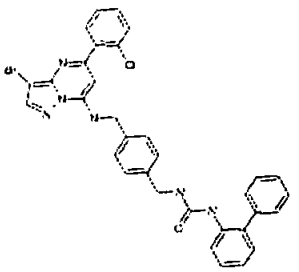
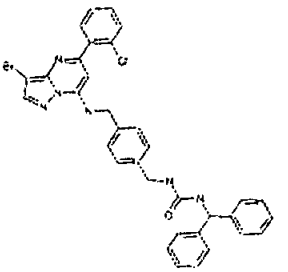
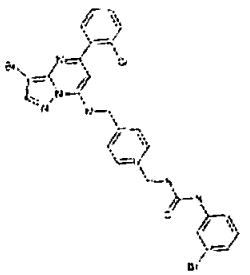
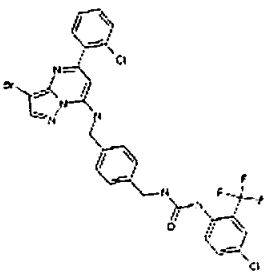
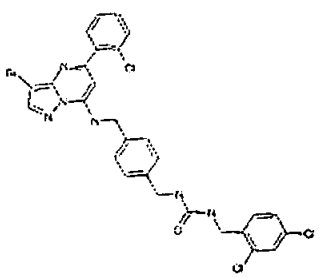
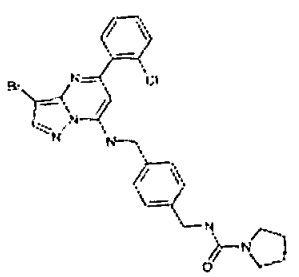
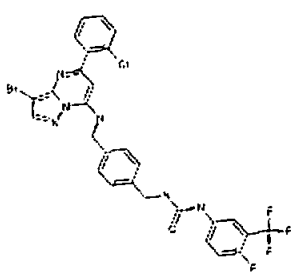
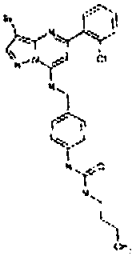
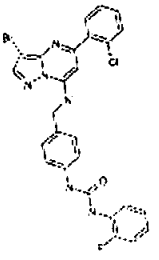
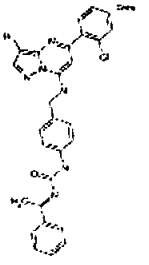
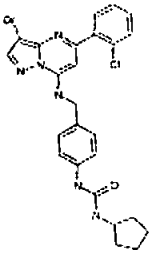
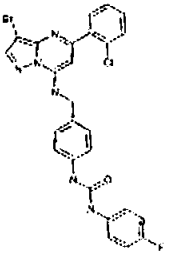
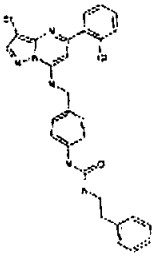
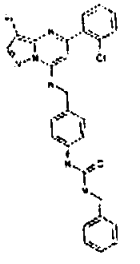
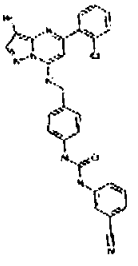
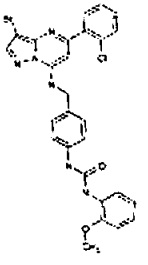
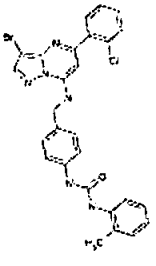
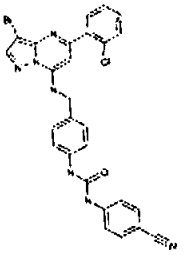
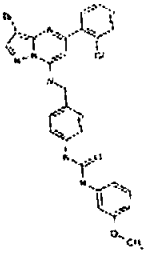
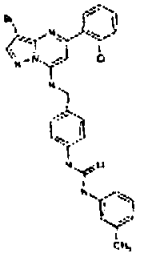
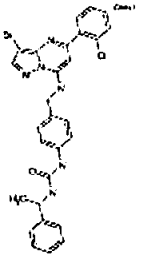
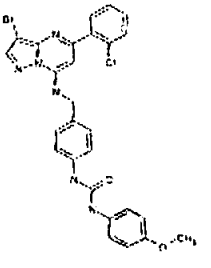
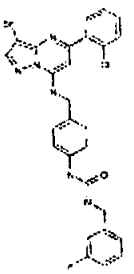
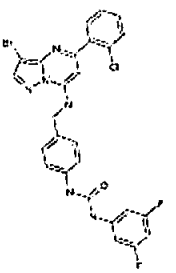
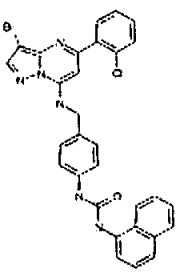
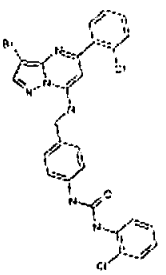
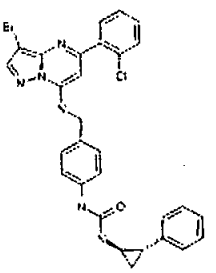
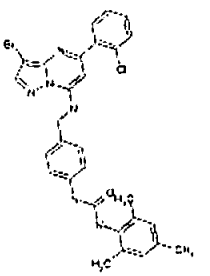
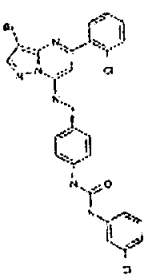
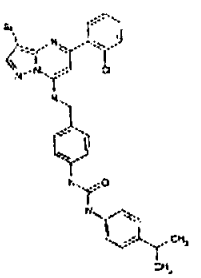
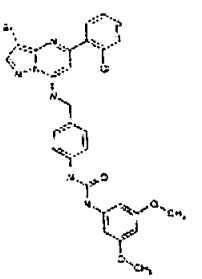
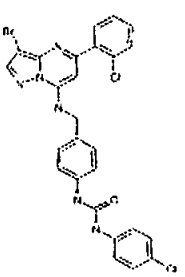
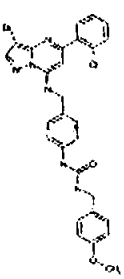
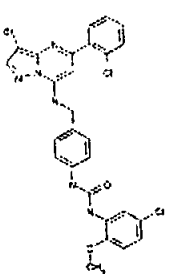
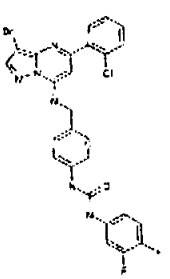
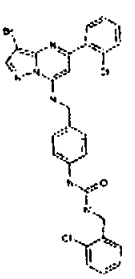
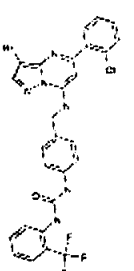
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7241 2. 639.35		1. 7246 2. 653.36
	1. 7242 2. 641.35		1. 7247 2. 665.37
	1. 7243 2. 645.35		
	1. 7244 2. 541.3		
	1. 7245 2. 649.36		

TABLA 73

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7301 2. 529.29		1. 7306 2. 567.31		1. 7311 2. 577.32
	1. 7302 2. 541.3		1. 7307 2. 567.31		1. 7312 2. 577.32
	1. 7303 2. 563.13		1. 7308 2. 574.32		1. 7313 2. 579.32
	1. 7304 2. 563.31		1. 7309 2. 574.32		1. 7314 2. 579.32
	1. 7305 2. 563.31		1. 7310 2. 577.32		1. 7315 2. 579.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7316 2. 581.32		1. 7321 2. 585.32		1. 7326 2. 599.33
	1. 7317 2. 583.32		1. 7322 2. 589.32		1. 7327 2. 591.33
	1. 7318 2. 583.32		1. 7323 2. 591.33		1. 7328
	1. 7319 2. 583.32		1. 7324 2. 593.33		1.7329 2. 613.34
	1. 7320 2. 585.32		1. 7325 2. 597.33		1. 7330 2. 617.34

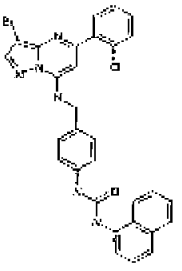
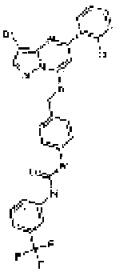
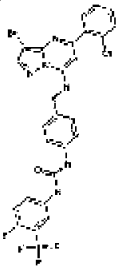
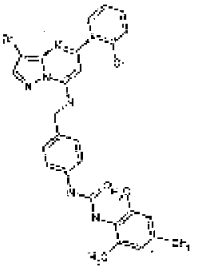
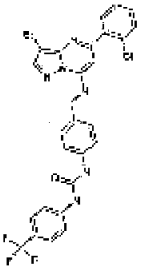
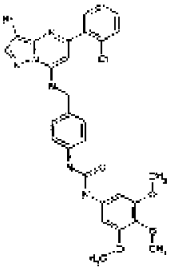
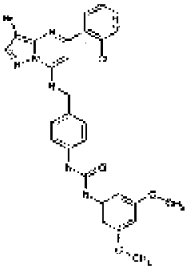
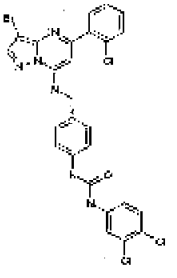
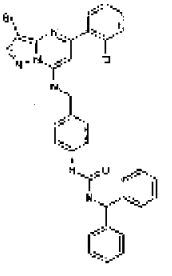
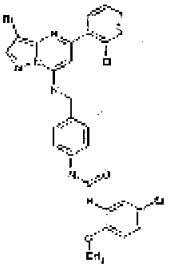
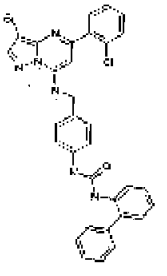
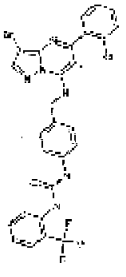
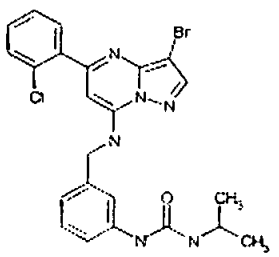
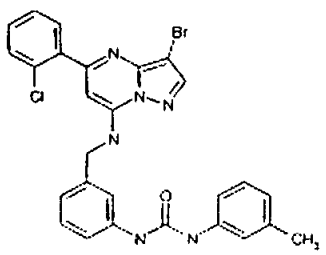
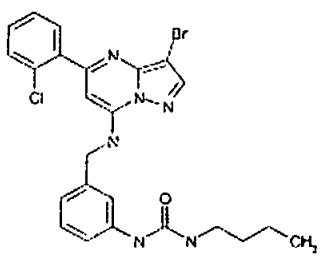
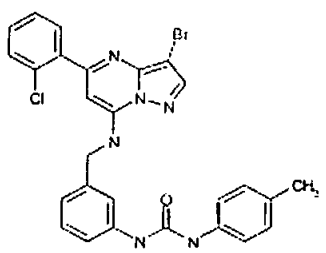
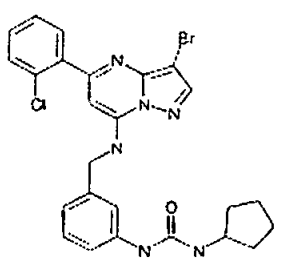
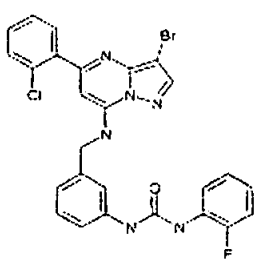
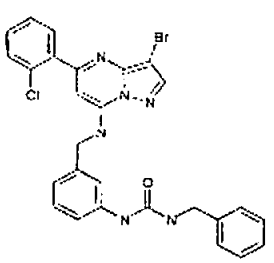
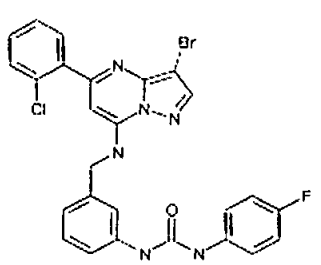
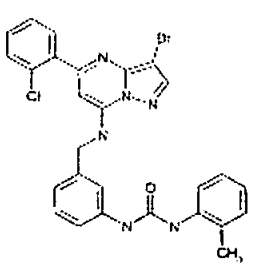
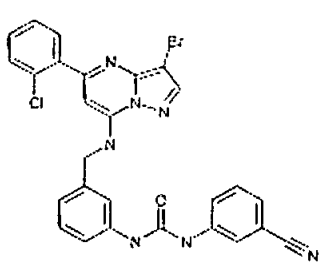
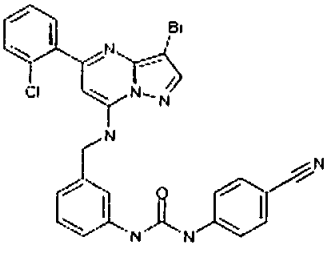
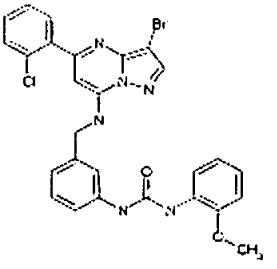
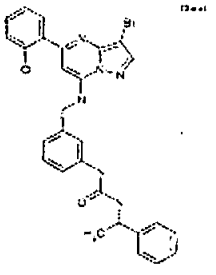
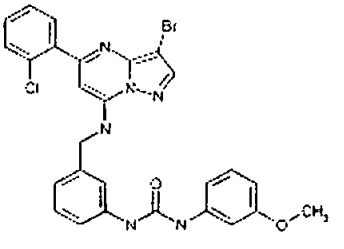
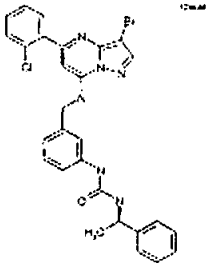
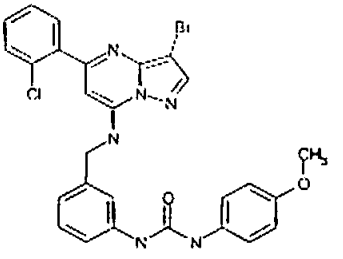
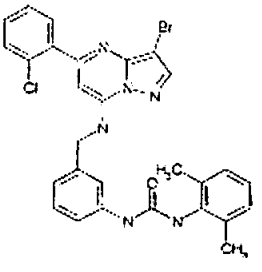
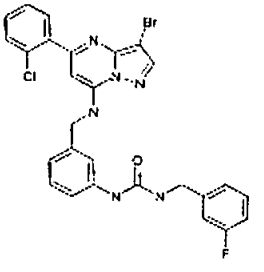
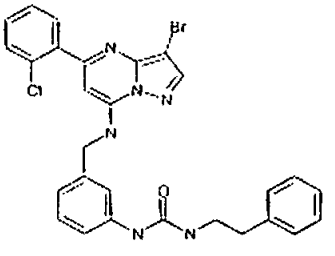
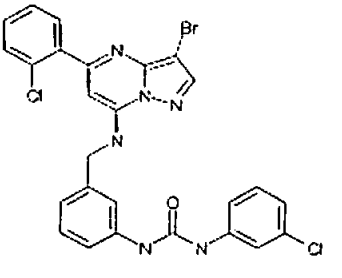
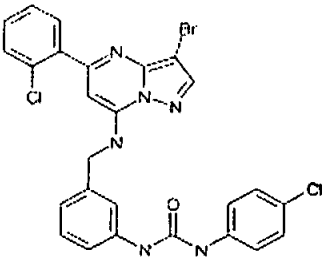
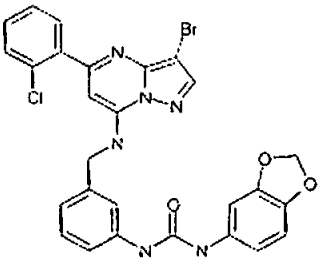
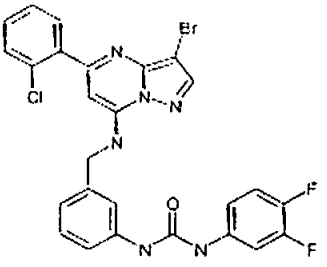
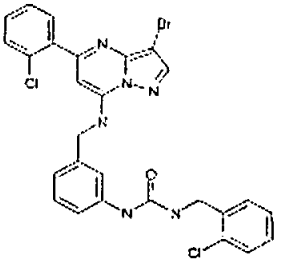
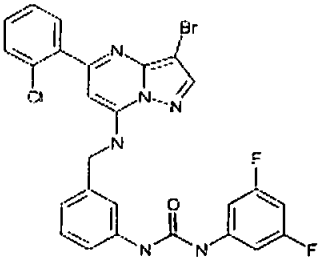
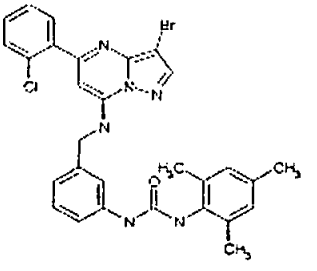
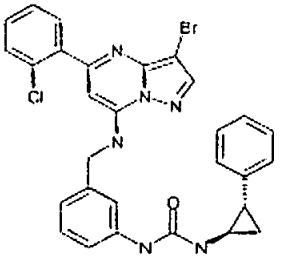
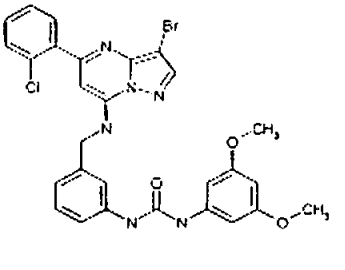
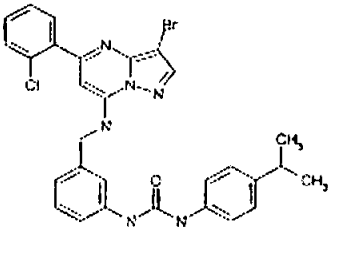
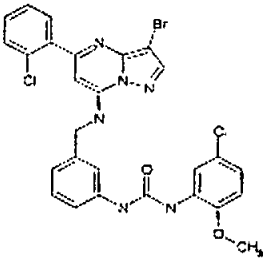
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7331 2. 599.33		1. 7336 2. 617.34		1. 73412. 635.36
	1. 7332 2. 591.33		1. 7337 2. 617.34		1. 7342 2. 639.35
	1. 7333 2. 609.33		1. 7338 2. 617.34		1. 7343 2. 639.35
	1. 7334 2. 613.34		1. 7339 2. 625.34		
	1. 7335 2. 617.34		1. 7340 2. 631.35		

TABLA 74

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7401 2. 515.28		1. 7406 2. 563.31
	1. 7402 2. 529.29		1. 7407 2. 563.31
	1. 7403 2. 541.3		1. 7408 2. 567.31
	1. 7404 2. 563.13		1. 7409 2. 567.31
	1. 7405 2. 563.31		1. 7410 2. 574.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7411 2. 574.32		1. 7416 2. 579.32
	1. 7412 2. 577.14		1. 741 7 2. 579.32
	1. 7413 2. 577.32		1. 7418 2. 579.32
	1. 7414 2. 577.32		1. 7419 2. 581.32
	1. 7415 2. 577.32		1. 7420 2. 583.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7421 2. 583.32		1. 7426 2. 593.33
	1. 7422 2. 585.32		1. 7427 2. 597.33
	1. 7423 2. 585.32		1. 7428 2. 591.33
	1. 7424 2. 589.32		1. 7429 2. 609.33
	1. 7425 2. 591.33		1. 7430 2. 613.34

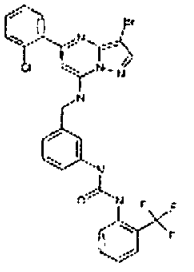
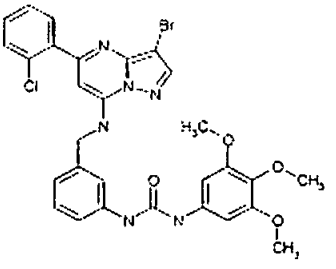
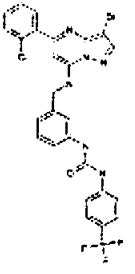
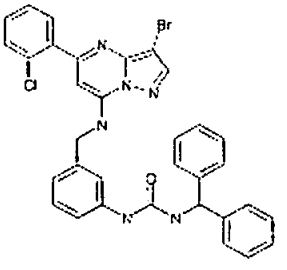
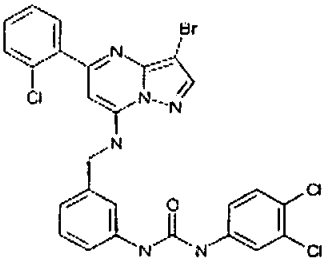
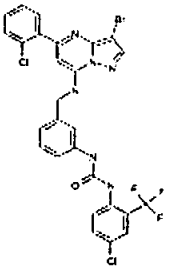
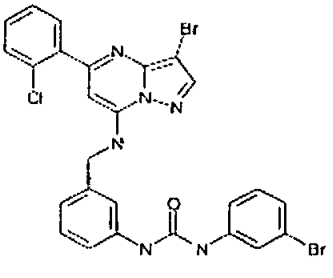
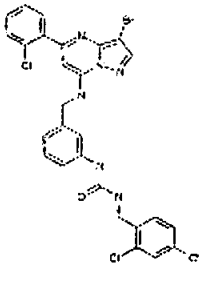
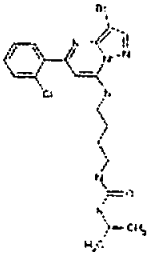
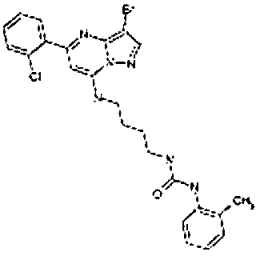
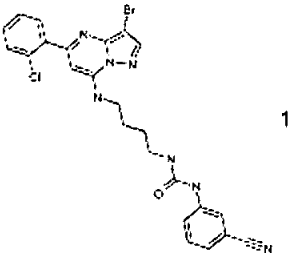
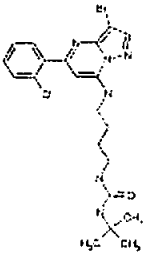
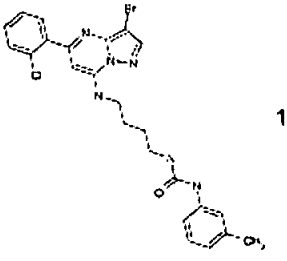
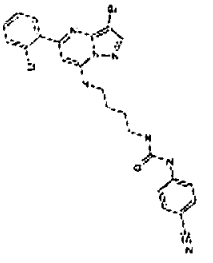
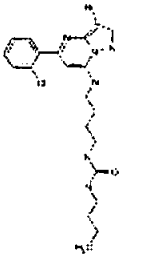
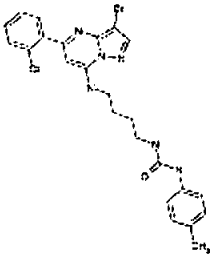
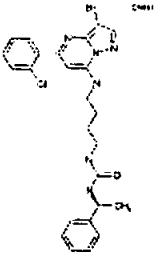
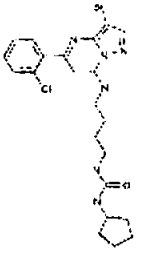
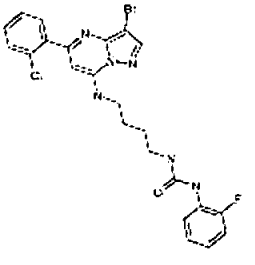
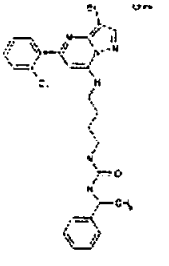
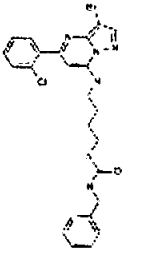
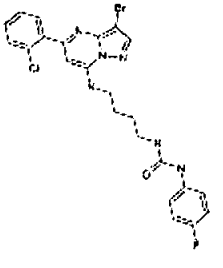
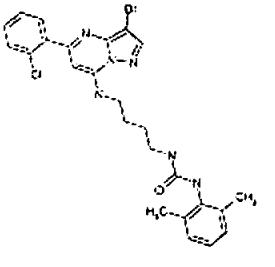
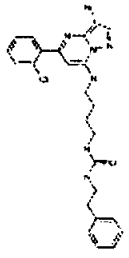
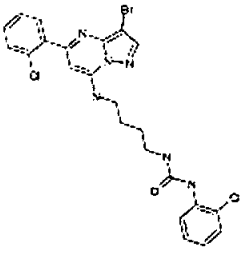
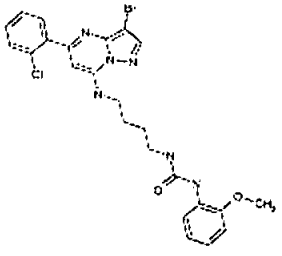
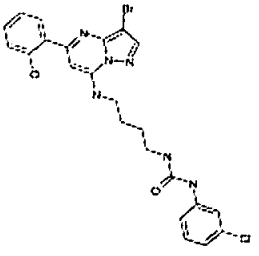
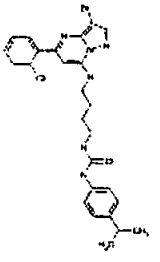
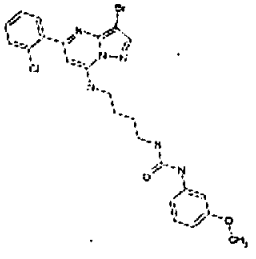
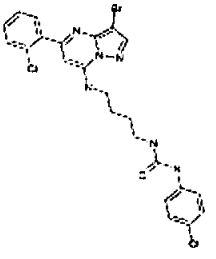
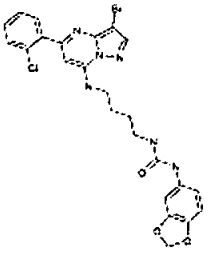
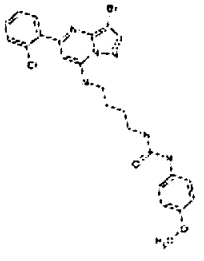
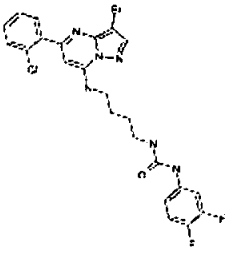
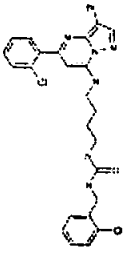
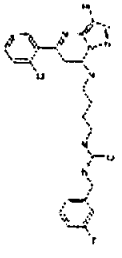
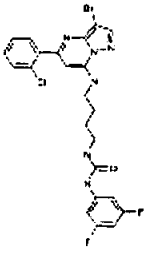
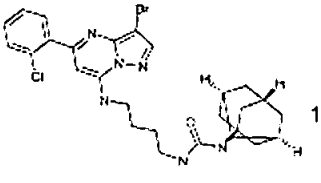
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7431 2. 617.34		1. 7436 2. 639.35
	1. 7432 2. 617.34		1. 7437 2. 639.35
	1. 7433 2. 617.34		1. 7438 2. 651.36
	1. 7434 2. 627.34		
	1. 7435 2. 631.35		

TABLA 75

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7501 2. 481.26		1. 7506 2. 529.29		1. 7511 2. 540.3
	1. 7502 2. 495.27		1. 7507 2. 529.29		1. 7512 2. 540.3
	1. 7503 2. 495.27		1. 7508 2. 529.29		1. 7513 2. 543.3
	1. 7504 2. 507.28		1. 7509 2. 533.29		1. 7514 2. 543.3
	1. 7505 2. 529.29		1. 7510 2. 533.29		1. 7515 2. 543.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7516 2. 543.3		1. 7521 2. 549.3		1. 7526 2. 555.31
	1. 7517 2. 545.3		1. 7522 2. 549.3		1. 7527 2. 557.31
	1. 7518 2. 545.3		1. 7523 2. 549.3		1. 7528 2. 559.31
	1. 7519 2. 545.3		1. 7524 2. 551.3		1. 7529 2. 560.31
	1. 7520 2. 547.3		1. 7525 2. 551.3		1. 7530 2. 573.32

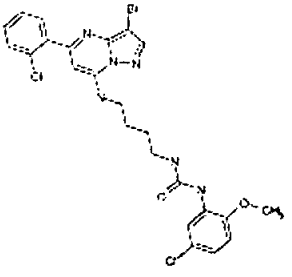
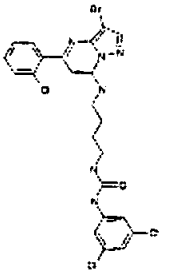
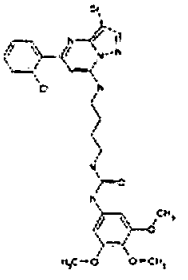
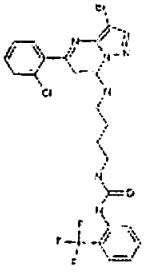
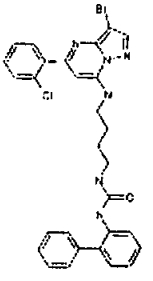
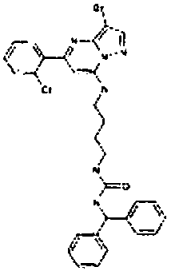
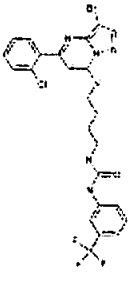
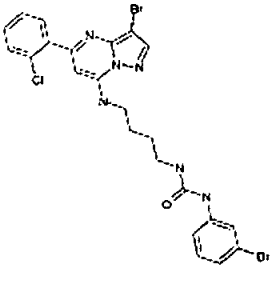
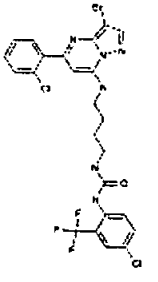
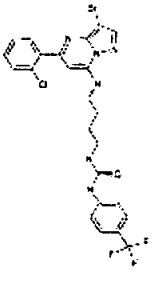
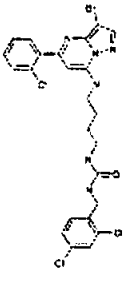
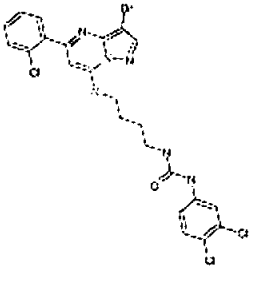
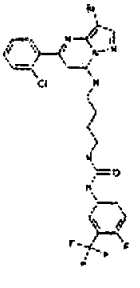
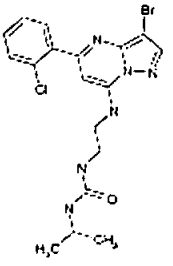
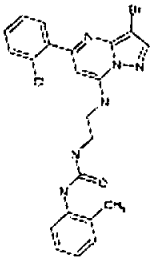
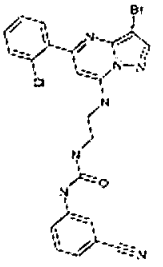
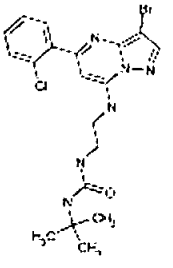
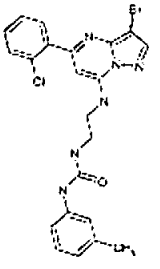
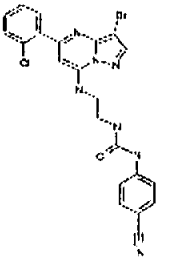
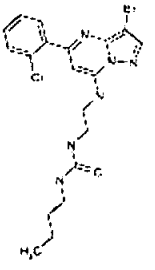
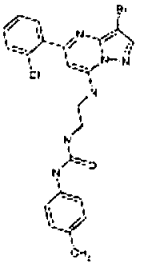
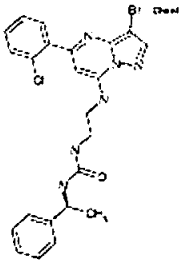
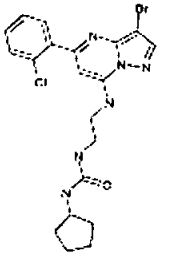
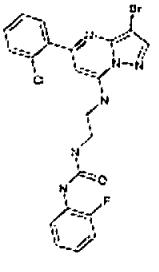
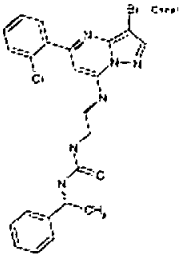
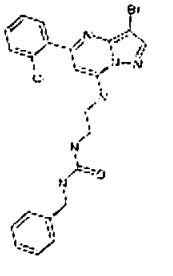
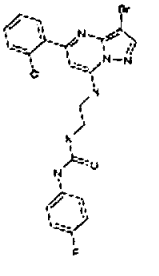
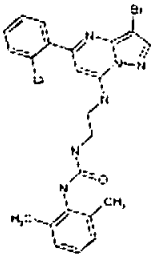
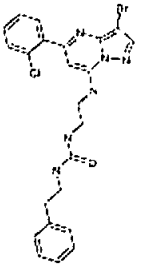
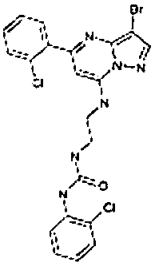
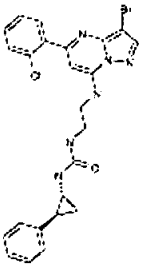
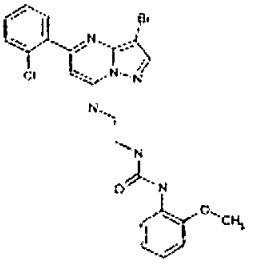
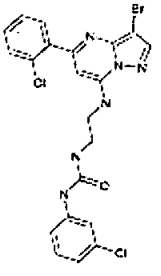
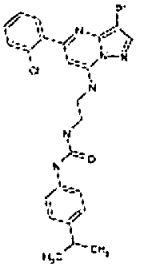
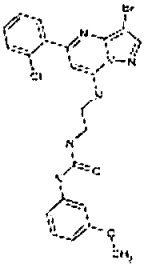
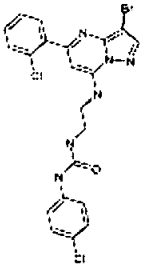
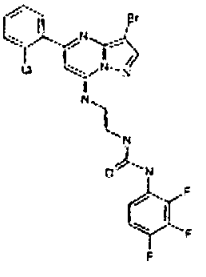
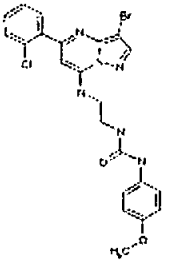
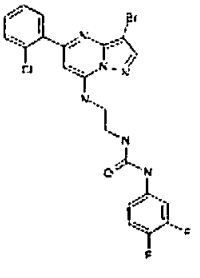
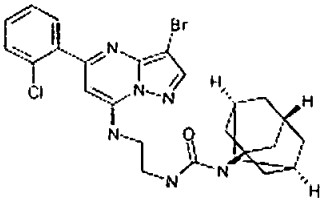
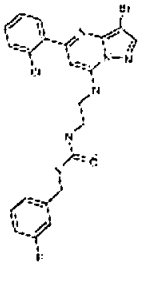
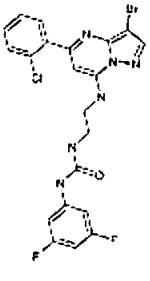
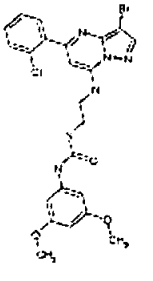
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7531 2. 579.32		1. 7536 2. 583.32		1. 7541 2. 605.33
	1. 7532 2. 583.32		1. 7537 2. 591.33		1. 7542 2. 605.33
	1. 7533 2. 583.32		1. 7538 2. 593.33		1. 7543 2. 614.34
	1. 7534 2. 583.32		1. 7539 2. 597.33		
	1. 7535 2. 583.32		1. 7540 2. 601.33		

TABLA 76

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7601 2. 453.25		1. 7606 2. 501.28		1. 7611 2. 512.28
	1. 7602 2. 467.26		1. 7607 2. 501.28		1. 7612 2. 512.28
	1. 7603 2. 467.26		1. 7608 2.501.28		1. 7613 2. 515.28
	1. 7604 2. 479.26		1. 7609 2. 505.28		1. 7614 2. 515.28
	1. 7605 2. 501.28		1. 7610 2. 505.28		1. 7615 2. 515.28

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 761 6 2. 515.28		1. 7621 2. 521.29		1. 7626 2. 527.29
	1. 7617 2. 517.28		1. 7622 2. 521.29		1. 7627 2. 529.29
	1. 7618 2. 517.28		1. 7623 2. 521.29		1. 7628 2. 541.3
	1. 7619 2. 517.28		1. 7624 2. 523.29		1. 7629 2. 545.3
	1. 7620 2. 519.29		1. 7625 2. 523.29		1. 7630 2. 547.3

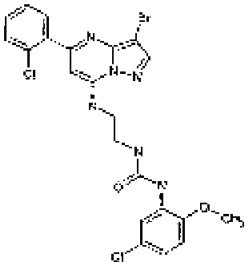
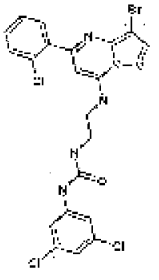
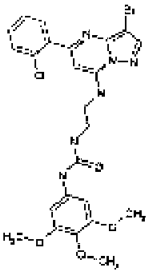
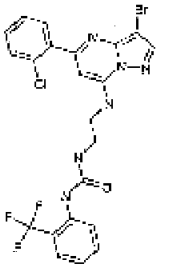
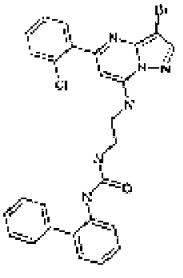
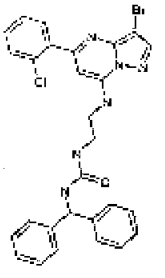
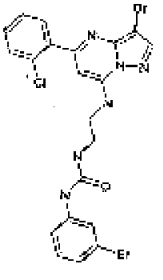
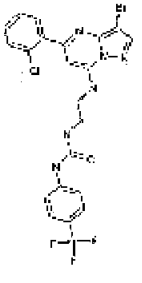
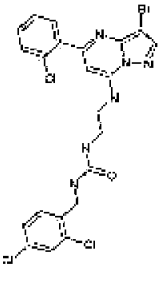
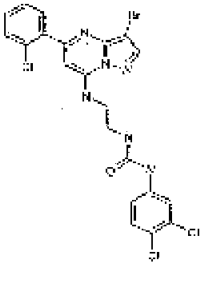
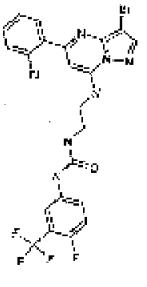
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7631 2. 551.3		1. 7636 2. 555.31		1. 7641 2. 577.32
	1. 7632 2. 555.31		1. 7637 2. 563.31		1. 7642 2. 577.32
	1. 7633 2. 555.31		1. 7638 2. 565.31		
	1. 7634 2. 555.31		1. 7639 2. 569.31		
	1. 7635 2. 555.31		1. 7640 2. 573.32		

TABLA 77

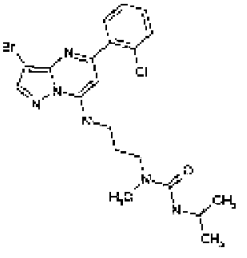
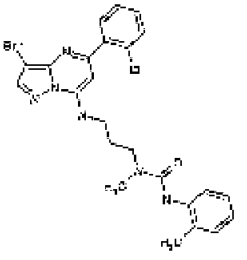
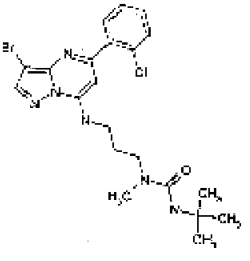
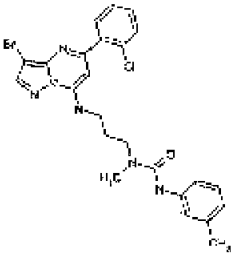
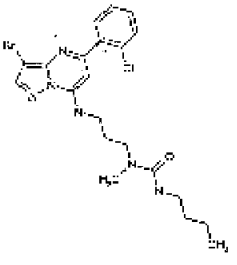
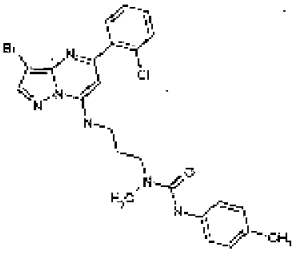
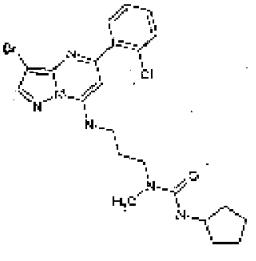
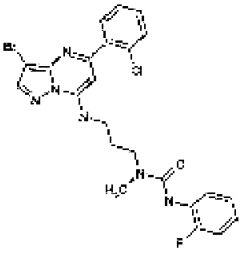
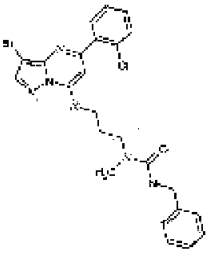
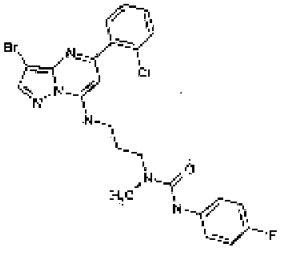
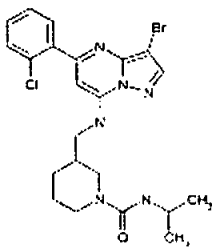
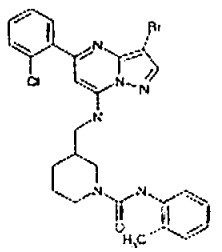
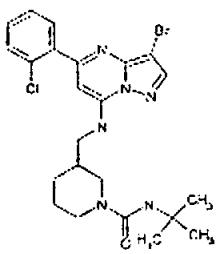
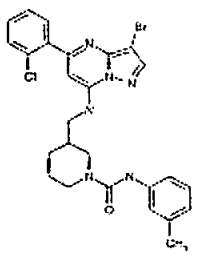
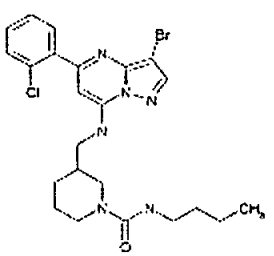
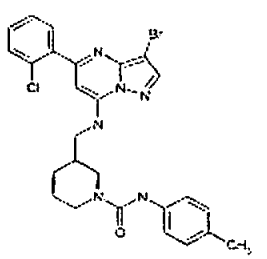
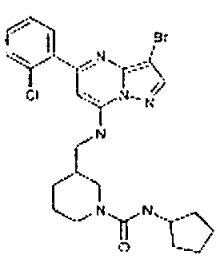
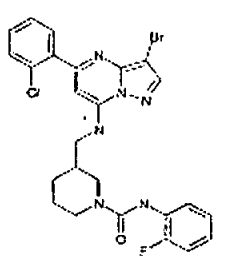
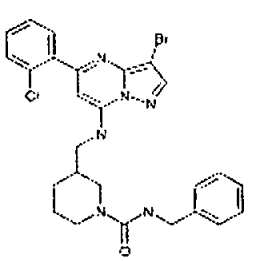
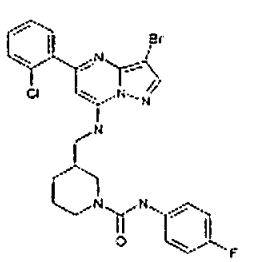
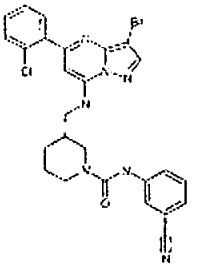
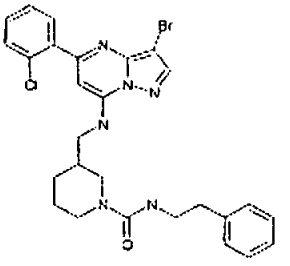
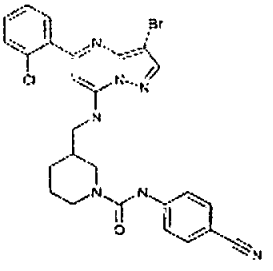
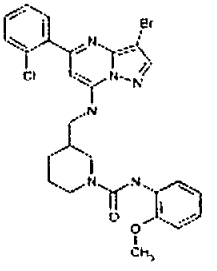
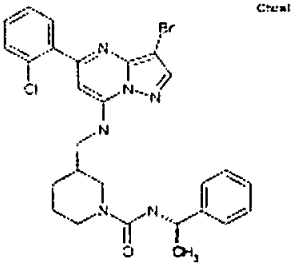
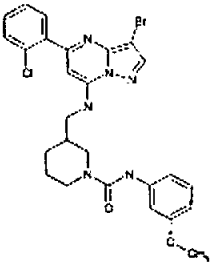
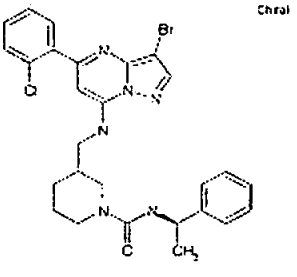
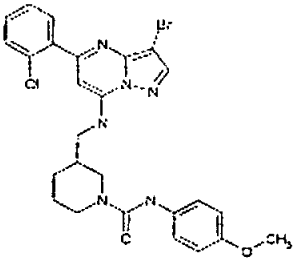
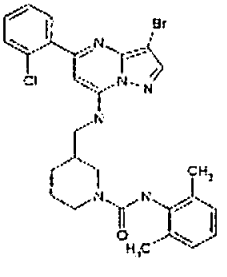
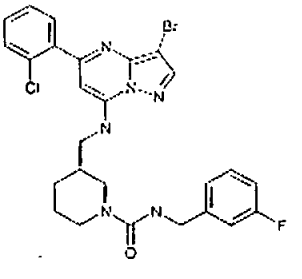
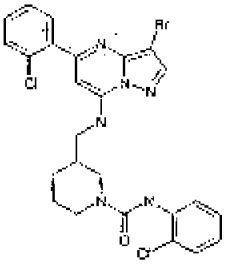
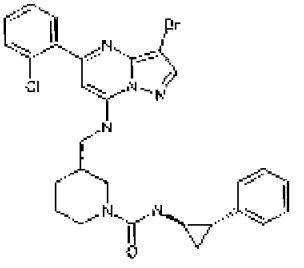
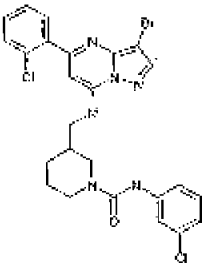
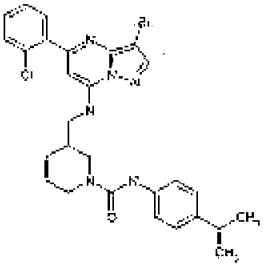
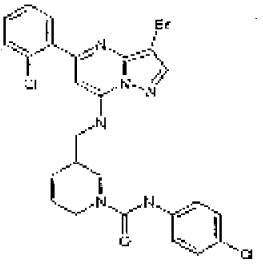
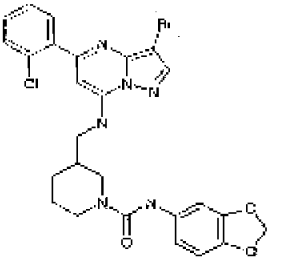
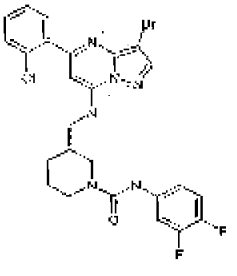
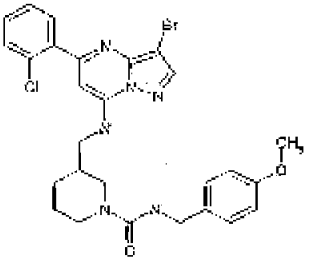
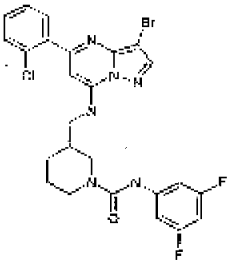
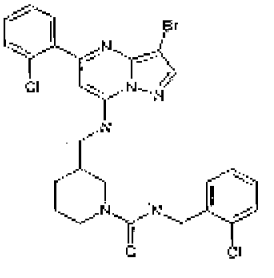
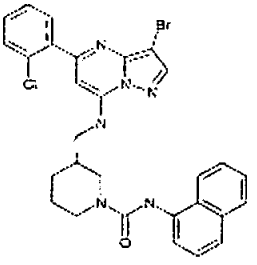
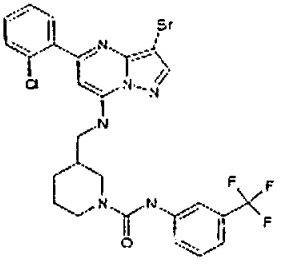
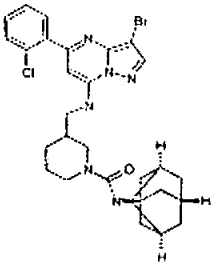
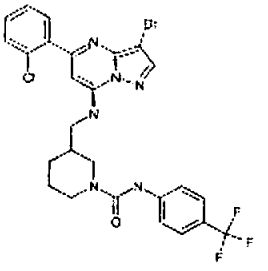
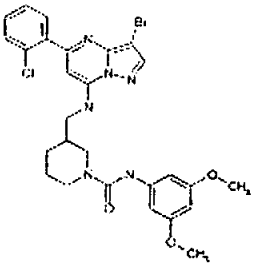
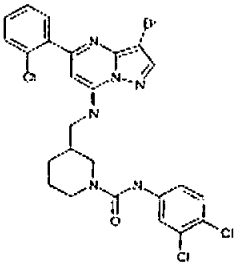
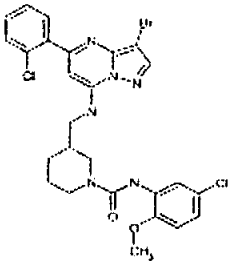
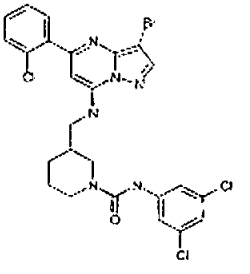
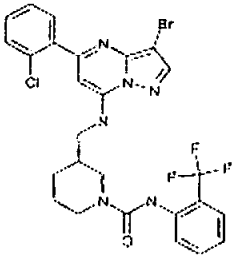
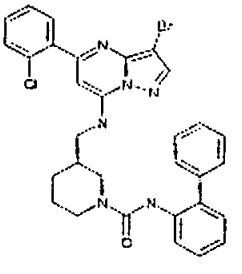
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7701 2. 481.26		1. 7706 2. 529.29
	1. 7702 2. 495.27		1. 7707 2. 529.29
	1. 7703 2. 495.27		1. 7708 2. 529.29
	1. 7704 2. 507.28		1. 7709 2. 533.29
	1. 7705 2. 529.29		1. 7710 2. 533.29

TABLA 78

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7801 2. 507.28		1. 7806 2. 555.31
	1. 7802 2. 521.29		1. 7807 2. 555.31
	1. 7803 2. 521.29		1. 7808 2. 555.31
	1. 7804 2. 533.29		1. 7809 2. 559.31
	1. 7805 2. 555.31		1. 7810 2. 559.31

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7811 2. 566.31		1. 7816 2. 569.31
	1. 7812 2. 566.31		1. 7817 2. 571.31
	1. 7813 2. 569.31		1. 7818 2. 571.31
	1. 7814 2. 569.31		1. 7819 2. 571.31
	1. 7815 2. 569.31		1. 7820 2. 573.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7821 2. 575.32		1. 7826 2. 581.32
	1. 7822 2. 575.32		1. 7827 2. 583.32
	1. 7823 2. 575.32		1. 7828 2. 585.32
	1. 7824 2. 577.32		1. 7829 2. 585.32
	1. 7825 2. 577.32		1. 7830 2. 589.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7831 2. 591.33		1. 7836 2. 609.33
	1. 7832 2. 599.33		1. 7837 2. 609.33
	1. 7833 2. 601.33		1. 7838 2. 609.33
	1. 7834 2. 605.33		1. 7839 2. 609.33
	1. 7835 2. 609.33		1. 7840 2. 617.34

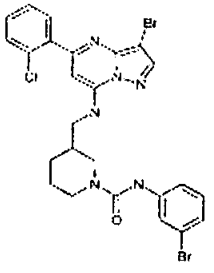
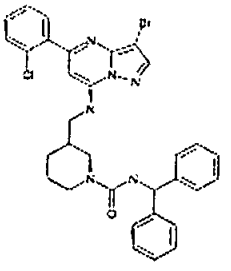
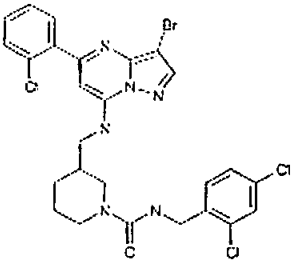
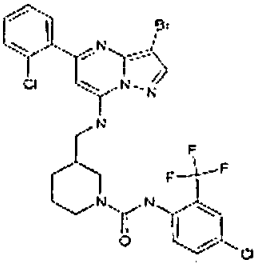
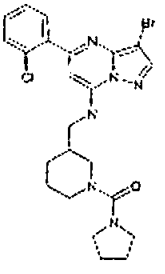
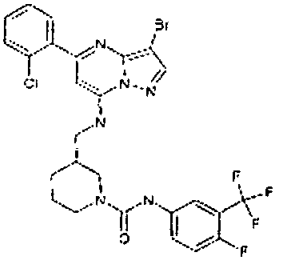
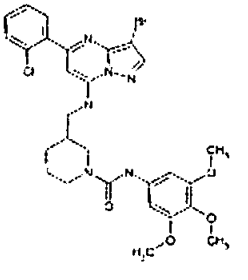
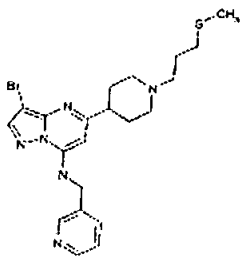
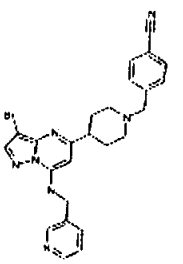
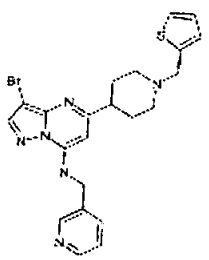
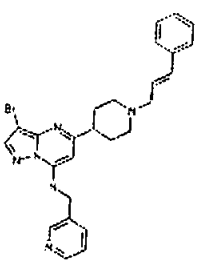
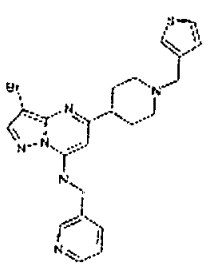
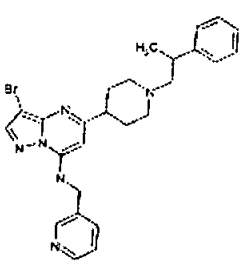
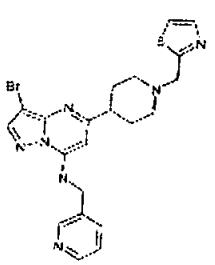
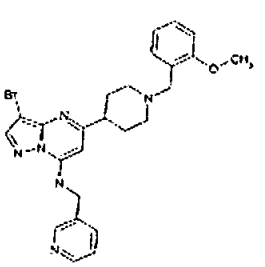
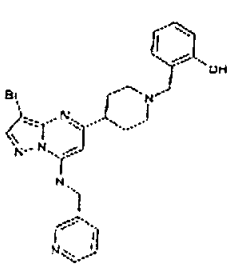
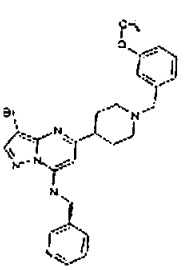
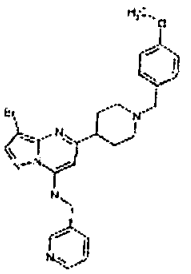
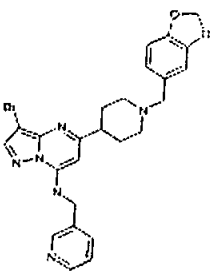
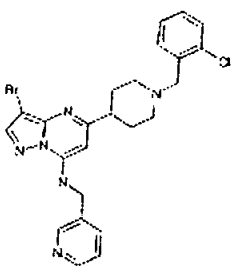
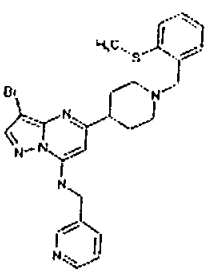
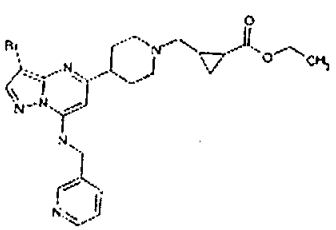
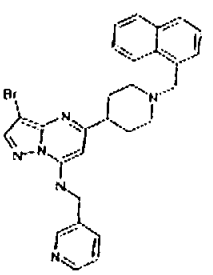
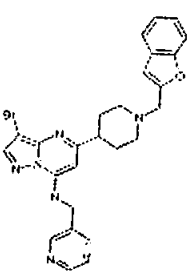
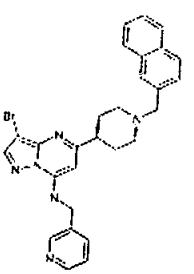
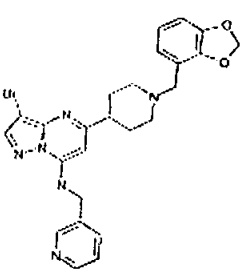
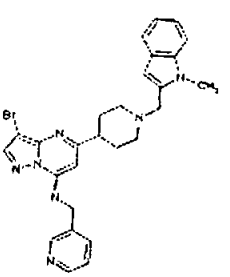
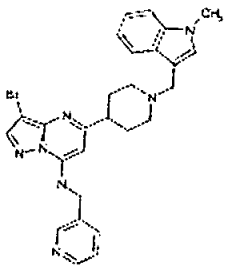
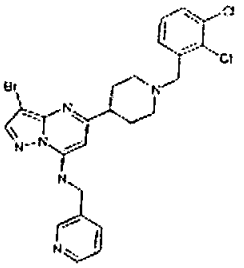
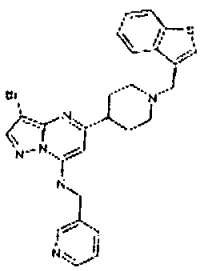
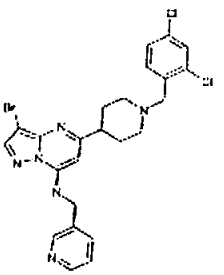
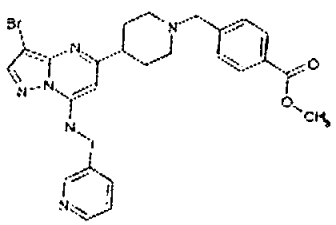
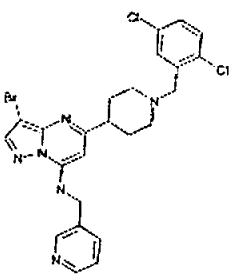
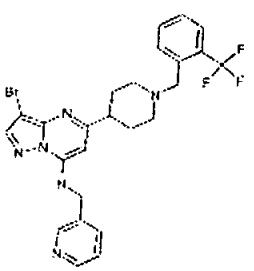
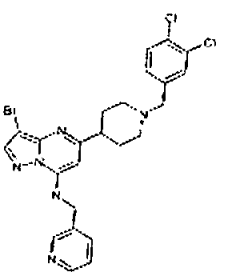
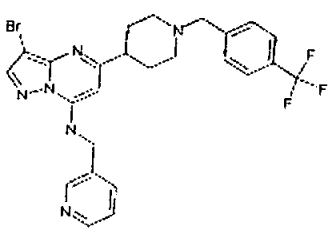
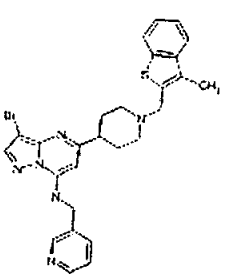
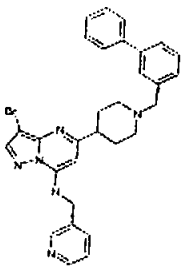
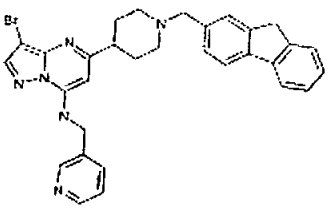
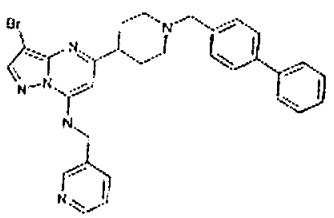
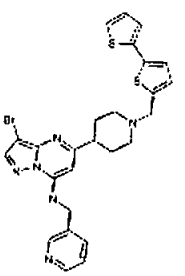
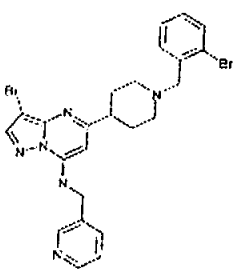
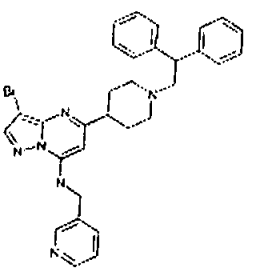
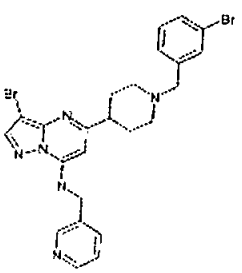
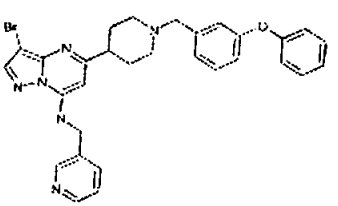
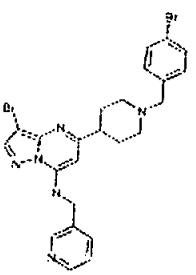
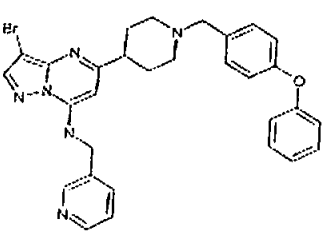
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7841 2. 619.34		1. 7846 2. 631.35
	1. 7842 2. 623.34		1. 7847 2. 643.35
	1. 7843 2. 519.29		
	1. 7844 2. 627.34		
	1. 7845 2. 631.35		

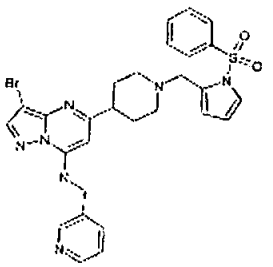
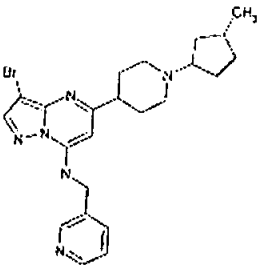
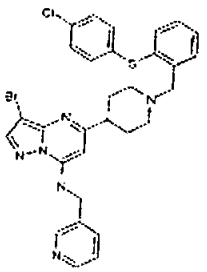
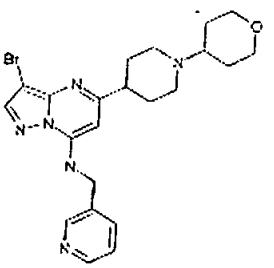
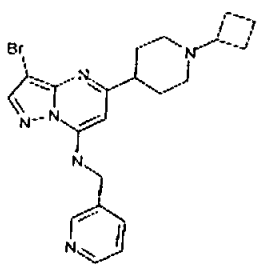
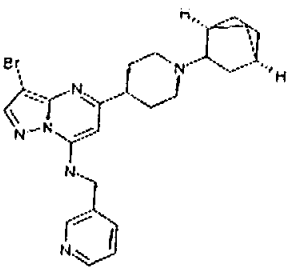
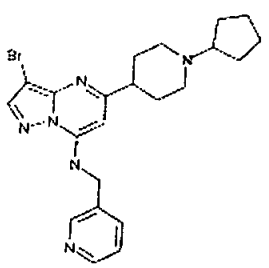
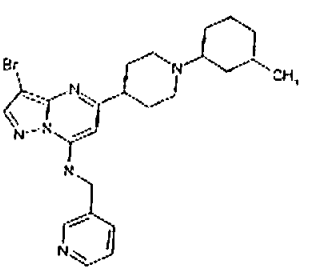
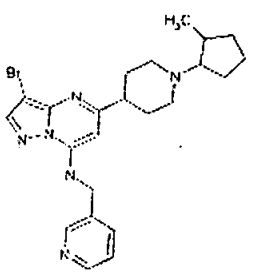
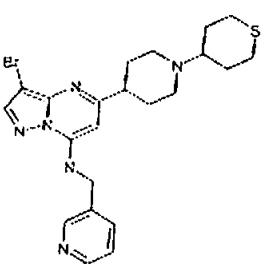
TABLA 79

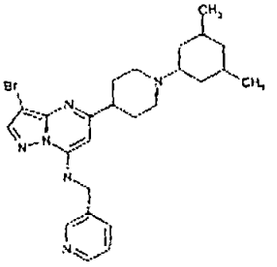
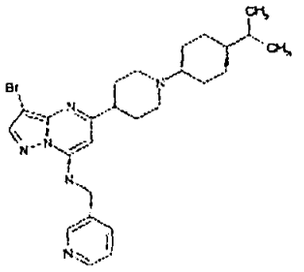
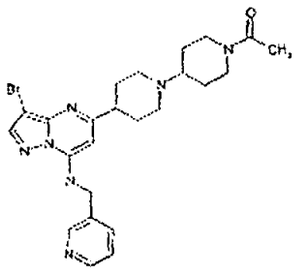
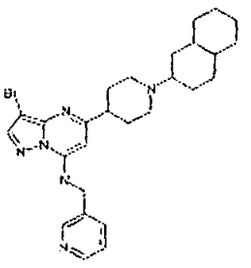
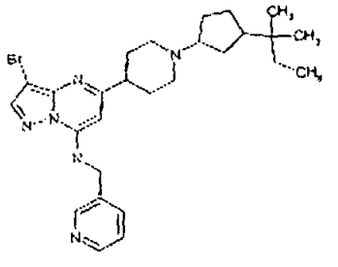
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7901 2. 477.26		1. 7906 2. 504.28
	1. 7902 2. 485.27		1. 7907 2. 505.28
	1. 7903 2. 485.27		1. 7908 2. 507.28
	1. 7904 2. 486.27		1. 7909 2. 509.28
	1. 7905 2. 495.27		1. 7910 2. 509.28

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7911 2. 509.28		1. 7916 2. 523.29
	1. 7912 2. 513.28		1. 7917 2. 525.29
	1. 7913 2. 515.28		1. 7918 2. 529.29
	1. 7914 2. 519.29		1. 7919 2. 529.29
	1. 7915 2. 523.29		1. 7920 2. 530.29

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7921 2. 530.29		1. 7926 2. 547.3
	1. 7922 2. 535.29		1. 7927 2. 547.3
	1. 7923 2. 537.3		1. 7928 2. 547.3
	1. 7924 2. 547.3		1. 7929 2. 547.3
	1. 7925 2. 547.3		1. 7930 2. 549.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7931 2. 555.31		1. 7936 2. 567.31
	1. 7932 2. 555.31		1. 7937 2. 567.31
	1. 7933 2. 557.31		1. 7938 2. 569.31
	1. 7934 2. 557.31		1. 7939 2. 571.31
	1. 7935 2. 557.31		1. 7940 2. 571.31

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7941 2. 608.33		1. 7946 2. 471.26
	1. 7942 2. 621.34		1. 7947 2. 473.26
	1. 7943 2. 443.24		1. 7948 2. 483.27
	1. 7944 2. 457.25		1. 7949 2. 485.27
	1. 7945 2. 471.26		1. 7950 2. 489.27

Producto	1. Ej. 2. m/z
	1. 7951 2. 499.27
	1. 7952 2. 513.28
	1. 7953 2. 514.28
	1. 7954 2. 525.29
	1. 7955 2. 525.29

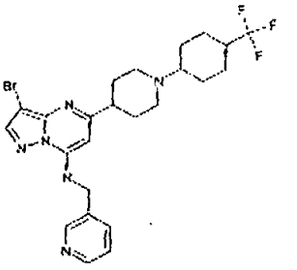
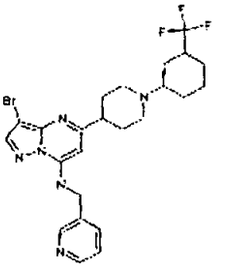
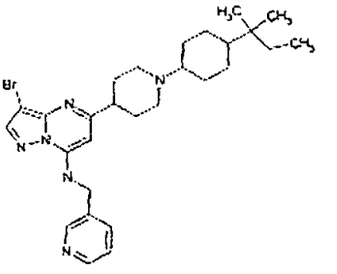
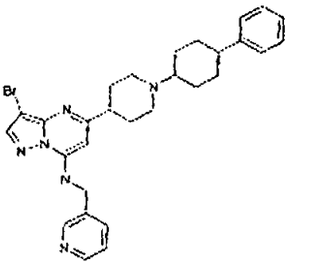
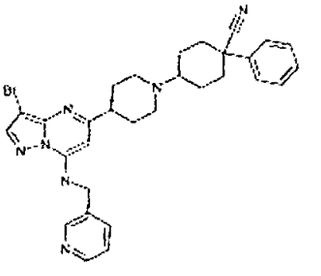
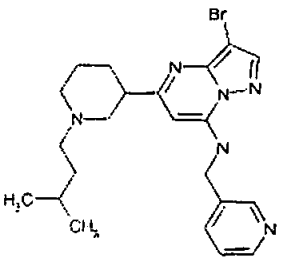
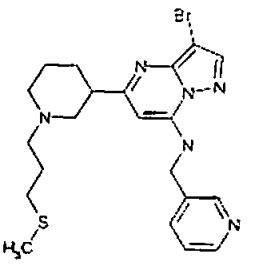
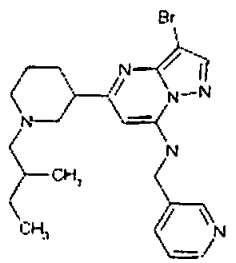
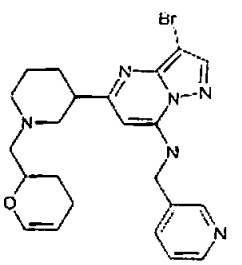
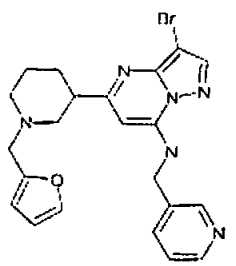
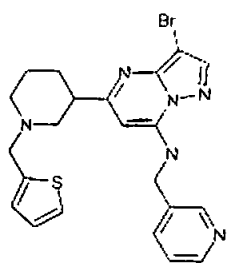
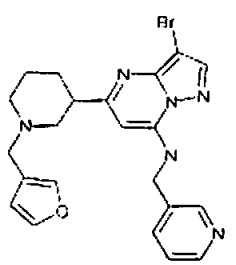
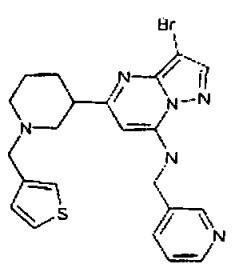
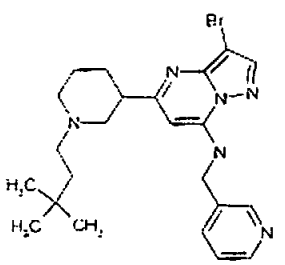
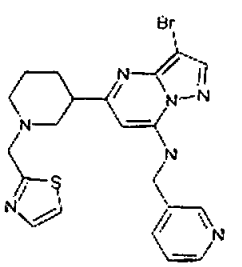
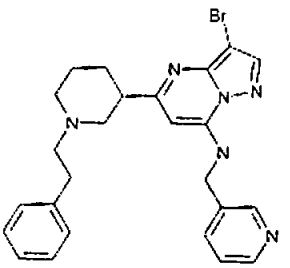
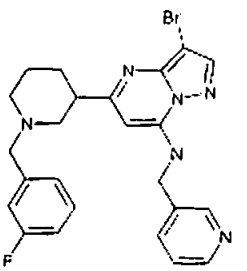
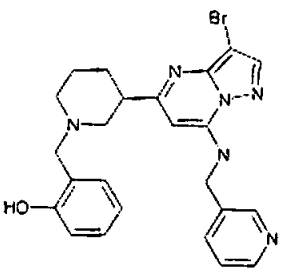
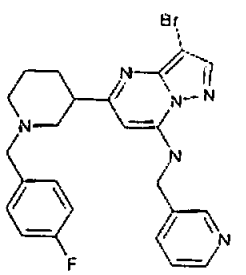
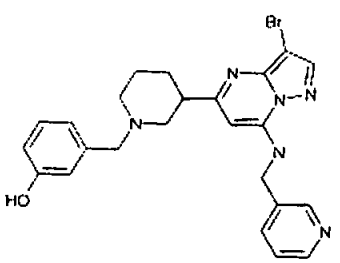
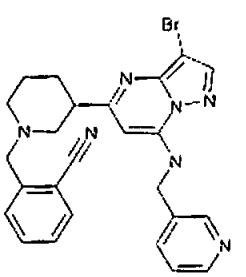
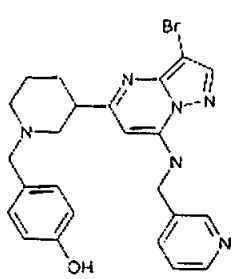
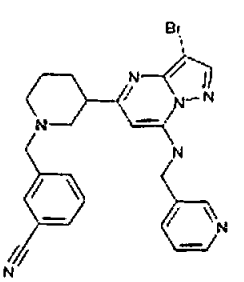
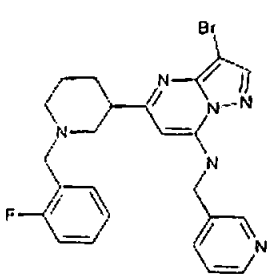
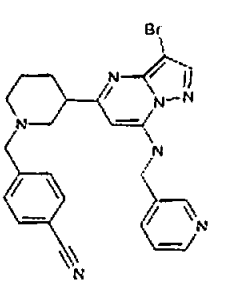
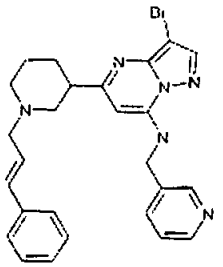
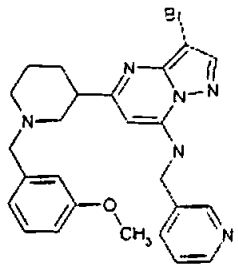
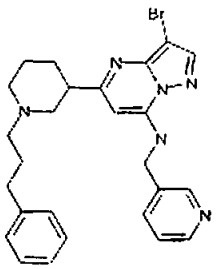
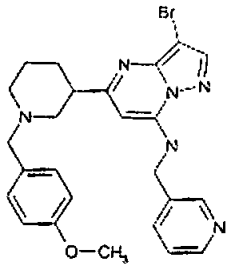
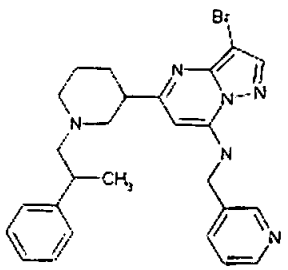
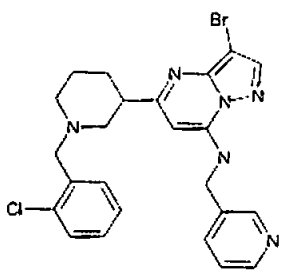
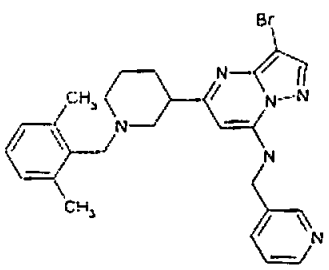
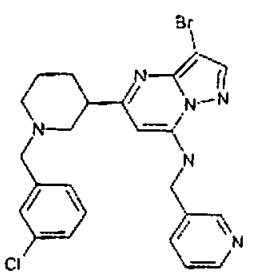
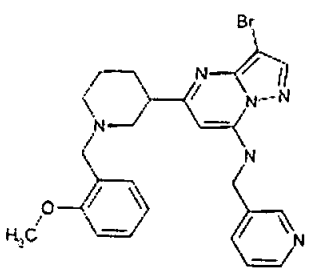
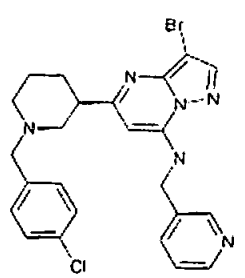
Producto	1. Ej. 2. m/z
	1. 7956 2. 536.29
	1. 7957 2. 539.3
	1. 7958 2. 541.3
	1. 7959 2. 547.3
	1. 7960 2. 572.31

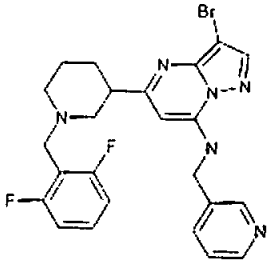
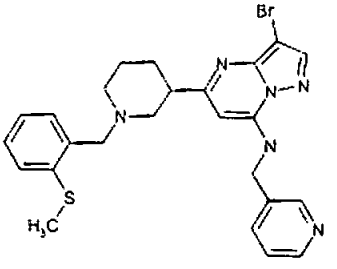
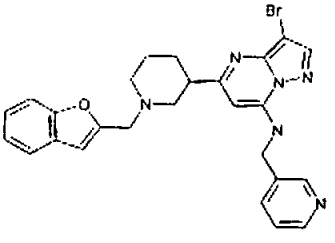
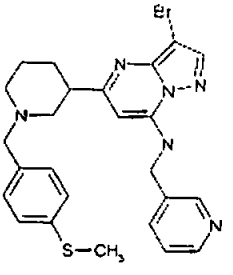
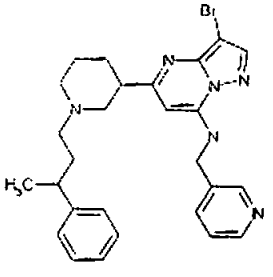
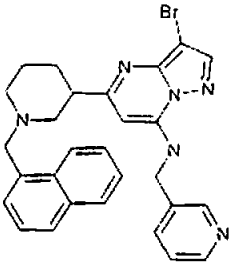
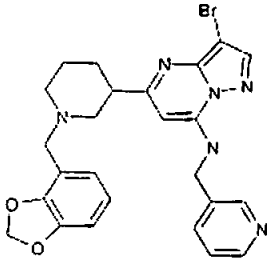
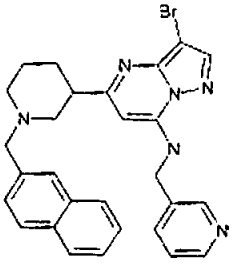
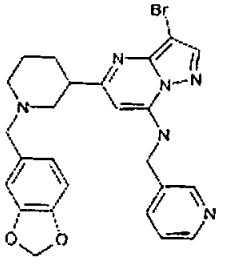
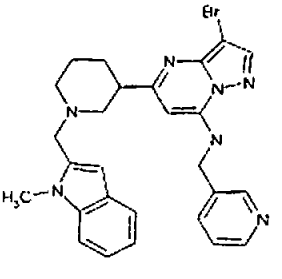
TABLA 80

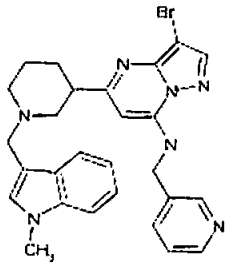
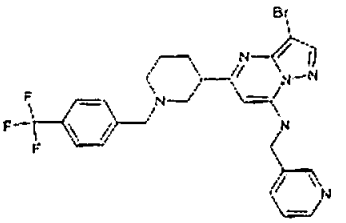
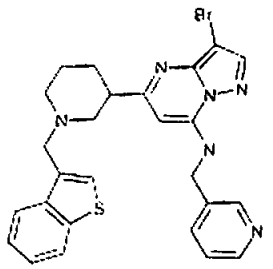
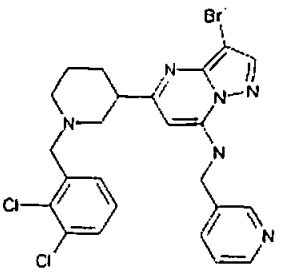
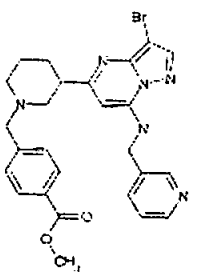
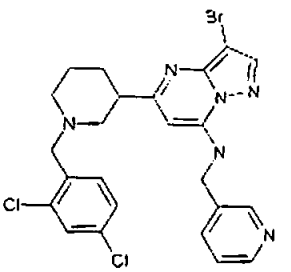
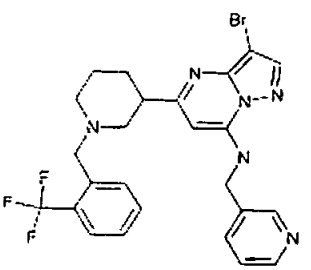
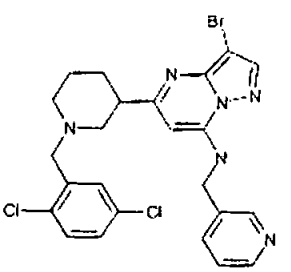
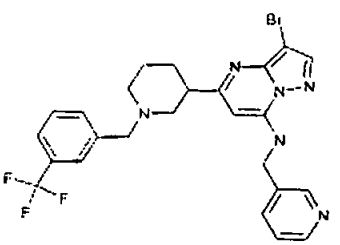
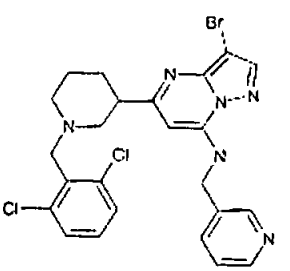
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8001 2. 459.25		1. 8006 2. 477.26
	1.8002 2. 459.25		1. 8007 2 485.27
	1. 8003 2. 469.26		1. 8008 2. 485.27
	1. 8004 2. 469.26		1. 8009 2. 485.27
	1. 8005 2. 473.26		1. 8010 2. 486.27

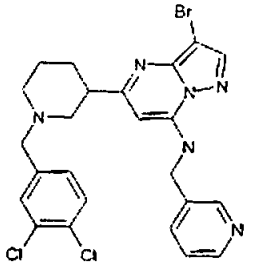
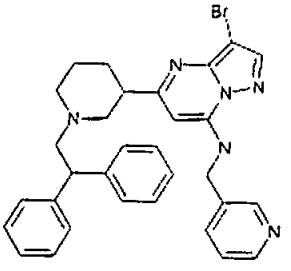
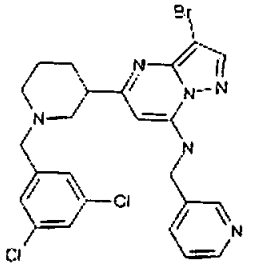
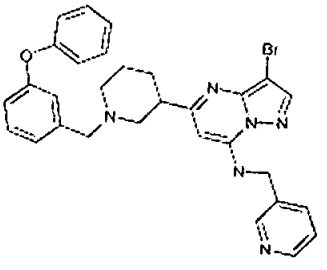
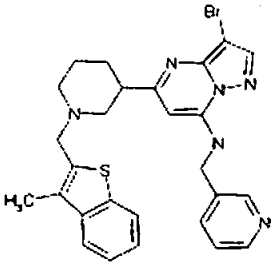
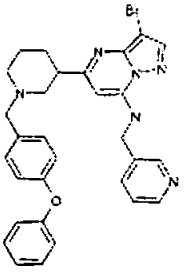
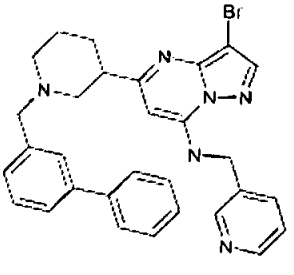
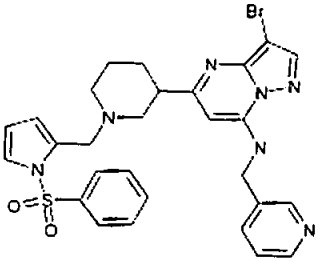
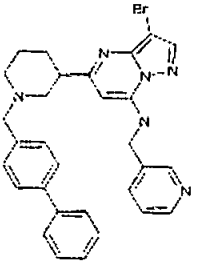
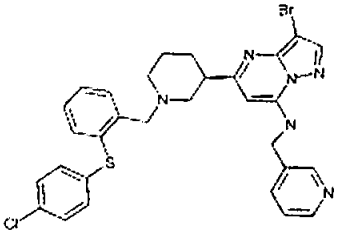
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8011 2. 493.27		1. 8016 2. 495.27
	1. 8012 2. 495.27		1. 8017 2. 495.27
	1. 8013 2. 495.27		1. 8018 2. 502.28
	1. 8014 2. 495.27		1. 8019 2. 502.28
	1. 8015 2. 495.27		1. 8020 2. 502.28

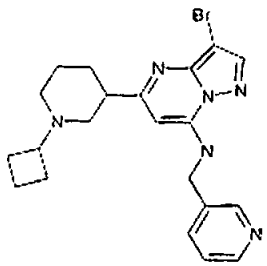
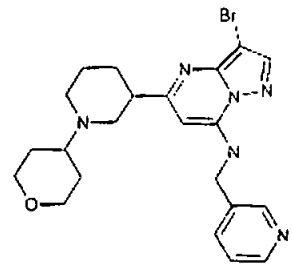
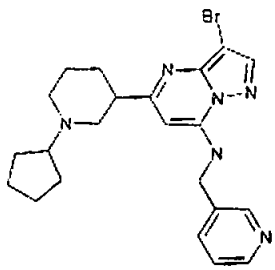
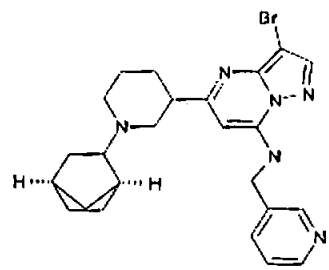
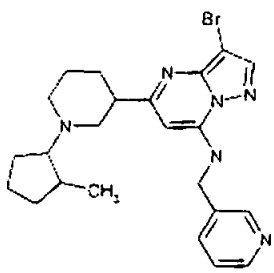
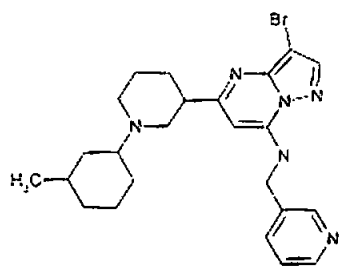
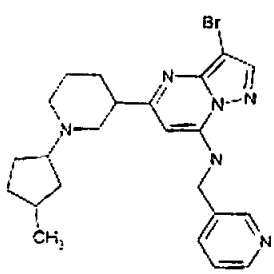
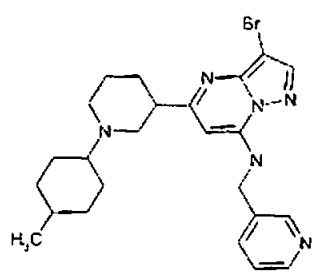
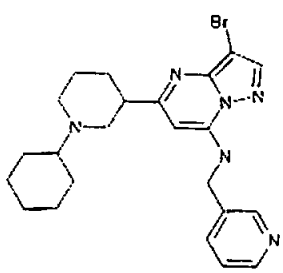
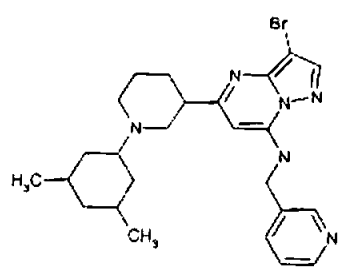
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8021 2. 505.28		1. 8026 2. 509.28
	1. 8022 2. 505.28		1. 8027 2. 509.28
	1. 8023 2. 507.28		1. 8028 2. 513.28
	1. 8024 2. 507.28		1. 8029 2. 513.28
	1. 8025 2. 507.28		1. 8030 2. 513.28

13723

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8031 2. 515.28		1. 8036 2. 523.29
	1. 8032 2. 519.29		1. 8037 2. 525.29
	1. 8033 2. 521.29		1. 8038 2. 529.29
	1. 8034 2. 523.29		1. 8039 2. 529.29
	1. 8035 2. 523.29		1. 8040 2. 530.29

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8041 2. 530.29		1. 8046 2. 547.3
	1. 8042 2. 535.29		1. 8047 2. 544.3
	1. 8043 2. 537.3		1. 8048 2. 547.3
	1. 8044 2. 547.3		1. 8049 2. 547.3
	1. 8045 2. 547.3		1. 8050 2. 547.3

Producto	1. Ej. 2. m/z	Producto	1. E. 2. m/z
	1. 8051 2. 548.3		1. 8056 2. 569.31
	1. 8052 2. 548.3		1. 8057 2. 569.31
	1. 8053 2. 547.3		1. 8058 2. 571.31
	1. 8054 2. 555.31		1. 8059 2. 608.33
	1. 8055 2. 553.3		1. 8060 2. 621.34

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8061 2. 443.24		1. 8066 2. 473.26
	1. 8062 2. 457.25		1. 8067 2. 483.27
	1. 8063 2. 471.26		1. 8068 2. 485.27
	1. 8064 2. 471.26		1. 8069 2. 483.27
	1. 8065 2. 469.26		1. 8070 2. 499.27

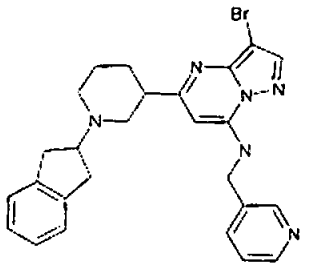
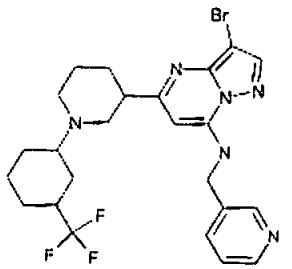
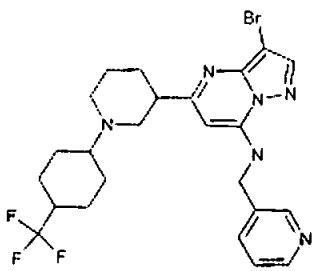
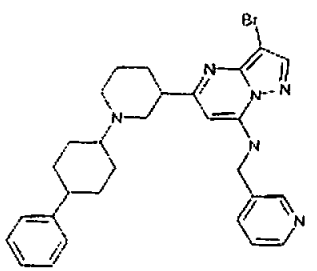
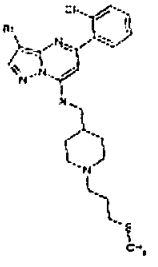
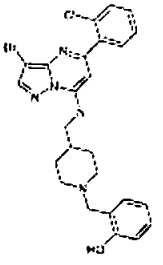
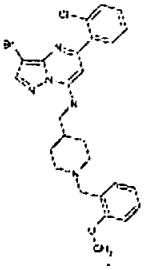
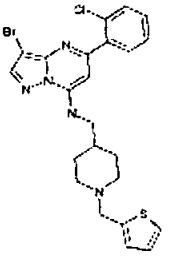
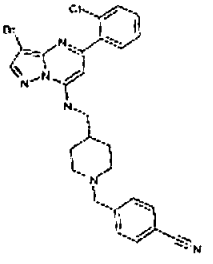
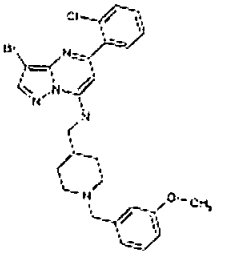
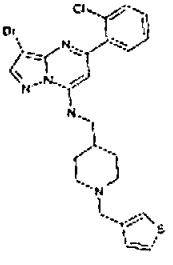
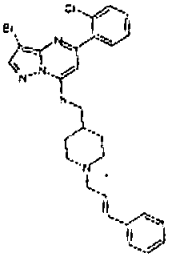
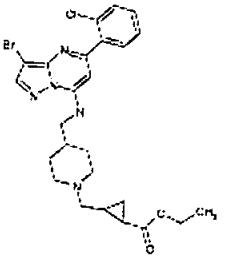
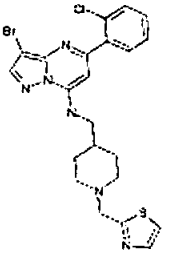
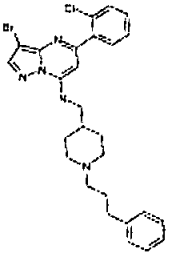
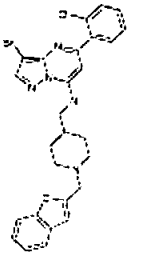
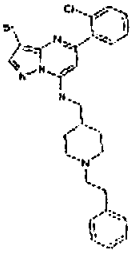
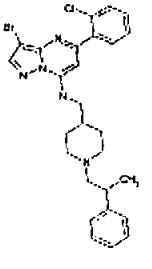
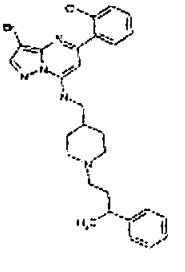
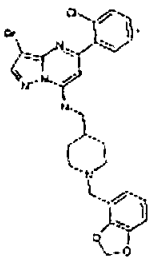
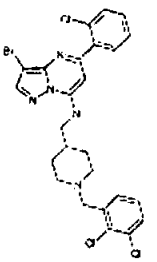
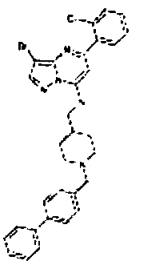
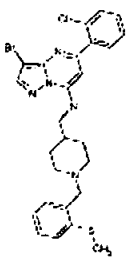
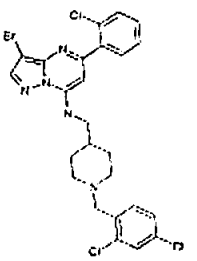
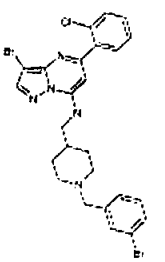
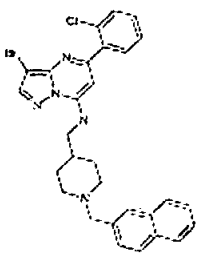
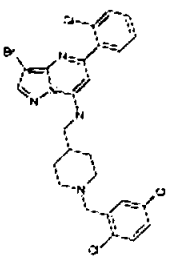
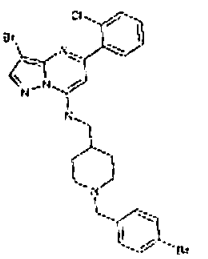
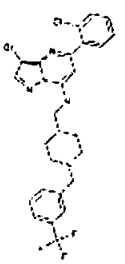
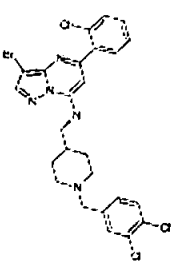
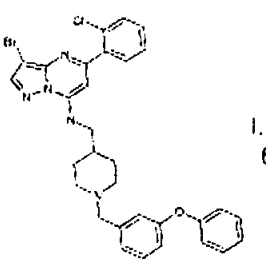
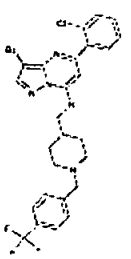
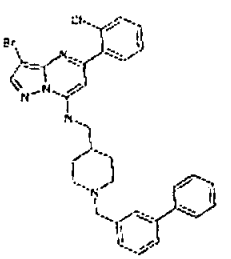
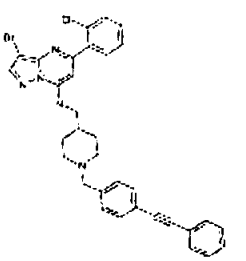
Producto	1. Ej 2. m/z
	1. 8071 2. 505.28
	1. 8072 2. 537.3
	1. 8073 2. 537.3
	1. 8074 2. 547.3

TABLA 81

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8101 2. 510.28		1. 8106 2. 528.29		1. 8111 2. 542.3
	1. 8102 2. 518.28		1. 8107 2. 537.3		1. 8112 2. 542.3
	1. 8103 2. 518.28		1. 8108 2. 538.3		1. 8113 2. 548.3
	1. 8104 2. 519.29		1. 8109 2. 540.3		1. 8114 2. 552.3
	1. 8105 2. 526.29		1. 8110 2. 540.3		1. 8115 2. 554.3

Producto	1. Ej. 2. m/zz	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8116 2. 556.31		1. 8121 2. 580.32		1. 8126 2. 588.32
	1. 8117 2. 558.31		1. 8122 2. 580.32		1. 8127 2. 590.32
	1. 8118 2. 562.31		1. 8123 2. 580.32		1. 8128 2. 590.32
	1. 8119 2. 580.32		1. 8125 2. 580.32		I. 8129 2. 604.33
	1. 8120 2. 580.32		1. 8126 2. 588.32		1. 8130 2. 612.34

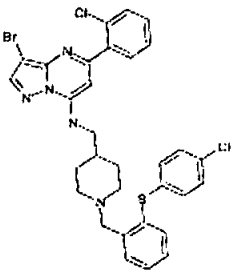
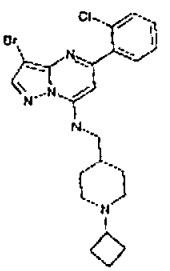
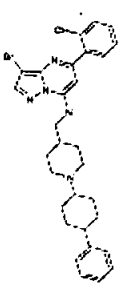
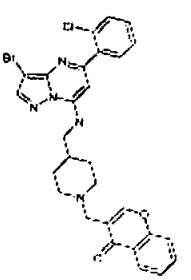
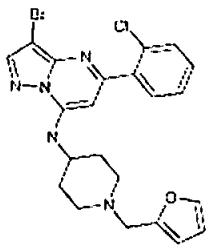
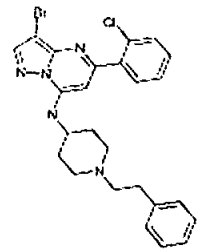
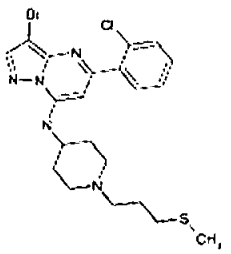
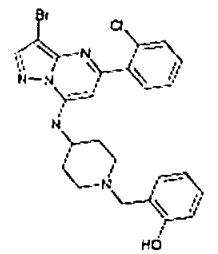
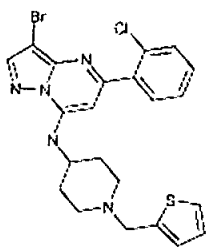
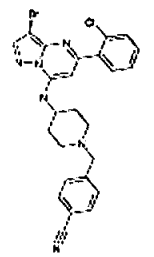
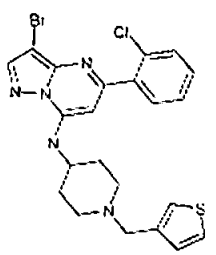
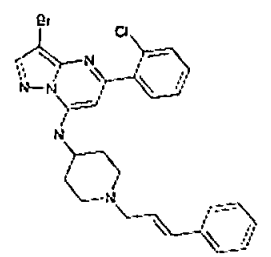
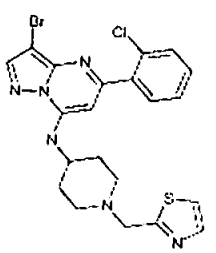
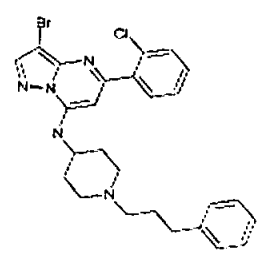
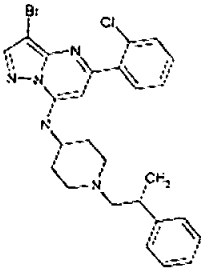
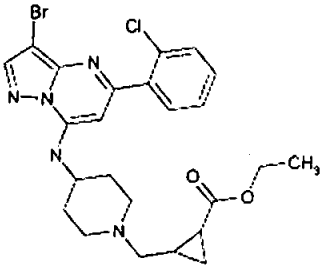
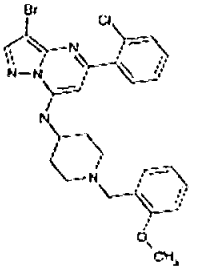
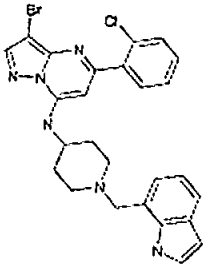
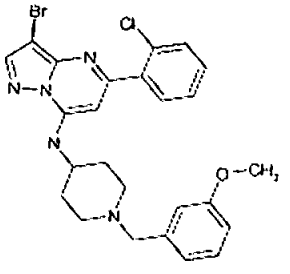
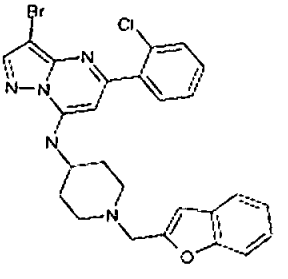
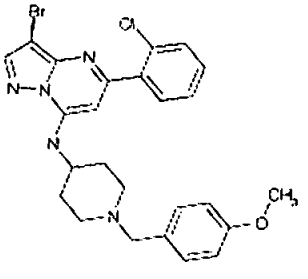
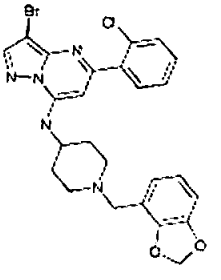
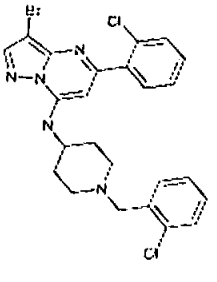
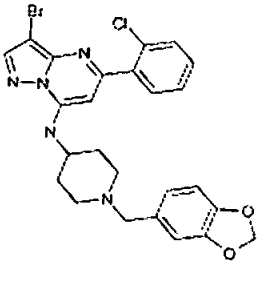
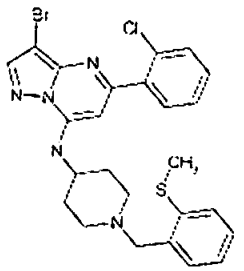
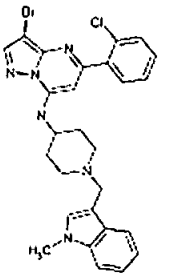
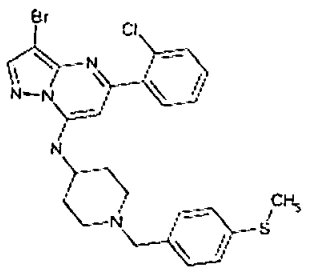
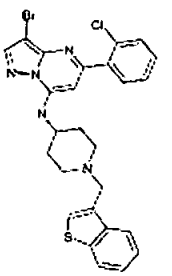
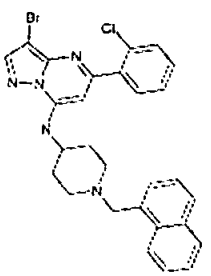
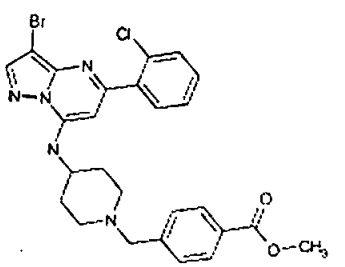
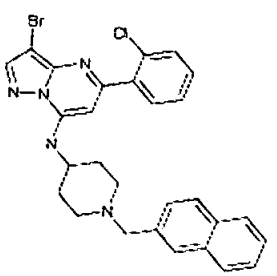
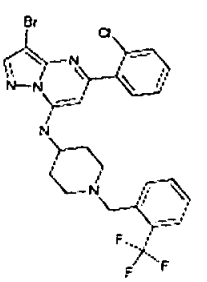
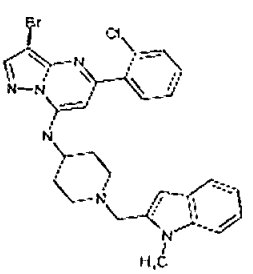
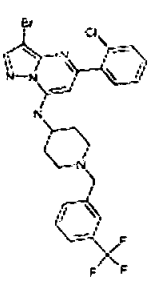
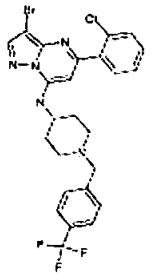
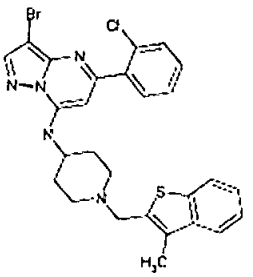
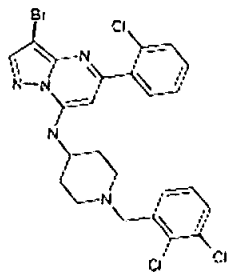
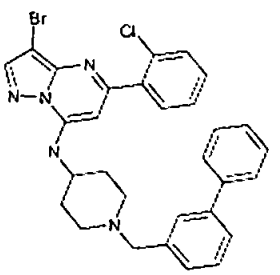
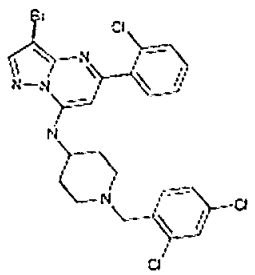
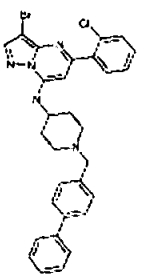
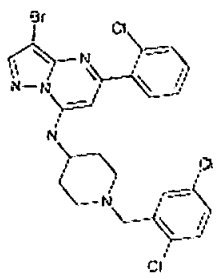
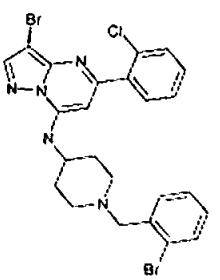
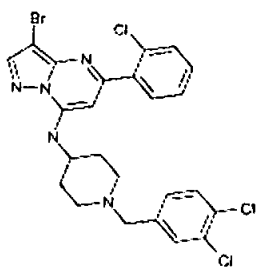
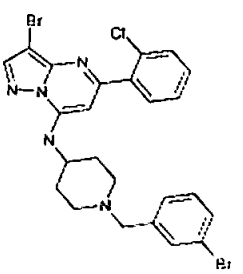
Producto	1. Ej. 2. m/z
	1. 8131 2. 654.36
	1. 8132 2. 476.26
	1. 8133 2. 580.32
	1. 8134 2. 580.32

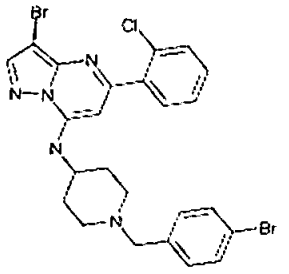
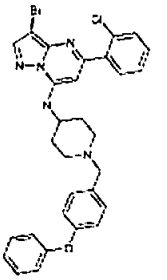
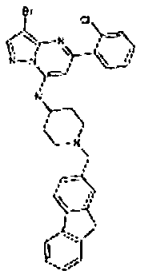
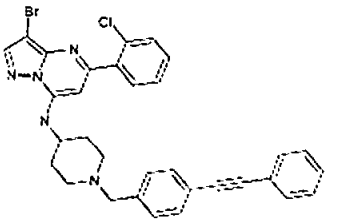
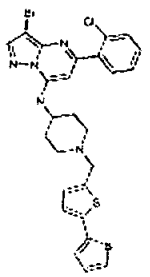
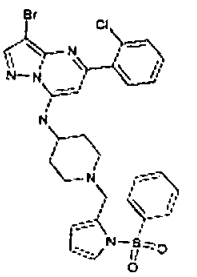
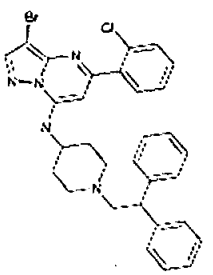
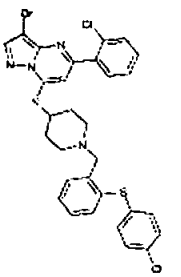
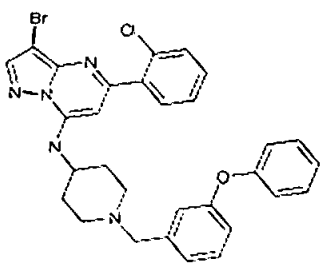
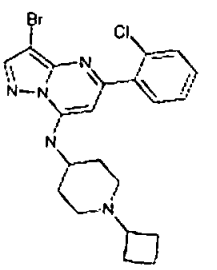
TABLA 82

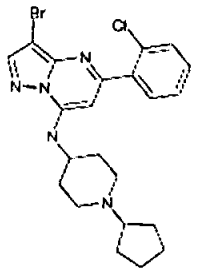
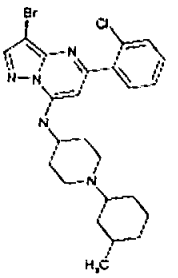
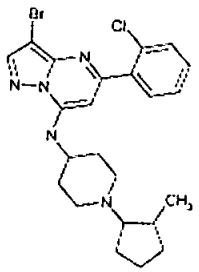
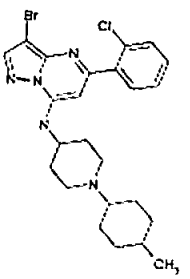
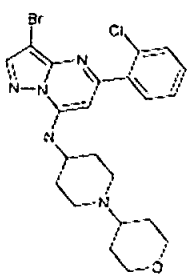
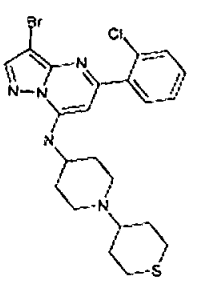
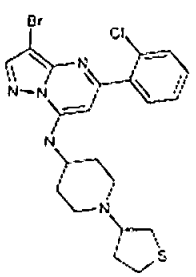
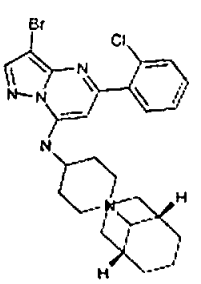
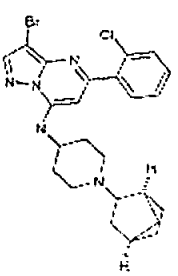
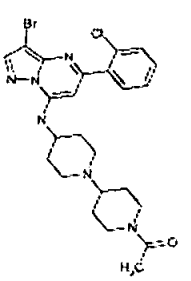
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8201 2. 488.27		1. 8206 2. 512.28
	1. 8202 2. 496.27		1. 8207 2. 514.28
	1. 8203 2. 504.28		1. 8208 2. 523.29
	1. 8204 2. 504.28		1. 8209 2. 524.29
	1. 8205 2. 505.28		1. 8210 2. 526.29

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8211 2. 526.29		1. 8216 2. 534.29
	1. 8212 2. 528.29		1. 8217 2. 537.3
	1. 8213 2. 528.29		1. 8218 2. 538.3
	1. 8214 2. 528.29		1. 8219 2. 542.3
	1. 8215 2. 532.29		1. 8220 2. 542.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8221 2. 544.3		1. 8226 2. 551.3
	1. 8222 2. 544.3		1. 8227 2. 554.3
	1. 8223 2. 548.3		1. 8228 2. 556.31
	1. 8224 2. 548.3		1. 8229 2. 566.31
	1. 8225 2. 551.3		1. 8230 2. 566.31

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8231 2. 566.31		1. 8236 2. 568.31
	1. 8232 2. 566.31		1. 8237 2. 574.32
	1. 8233 2. 566.31		1. 8238 2. 574.32
	1. 8243 2. 566.31		1. 8239 2. 576.32
	1. 8235 2. 566.31		1. 8240 2. 576.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8241 2. 576.32		1. 8246 2. 590.32
	1. 8242 2. 586.32		1. 8247 2. 598.33
	1. 8243 2. 586.32		1. 8248 2. 627.34
	1. 8244 2. 588.32		1. 8249 2. 640.35
	1. 8245 2. 590.32		1. 8250 2. 462.25

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8251 2. 476.26		1. 8256 2. 504.28
	1. 8252 2. 490.27		1. 8257 2. 504.28
	1. 8253 2. 492.27		1. 8258 2. 508.28
	1. 8254 2. 492.27		1. 8259 2. 530.29
	1. 8255 2. 502.28		1. 8260 2. 533.29

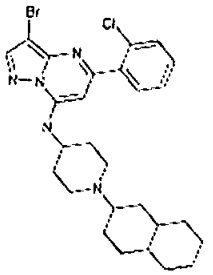
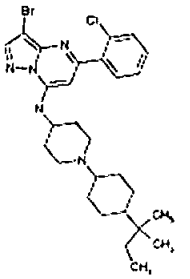
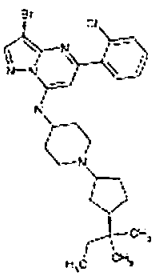
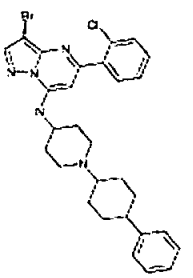
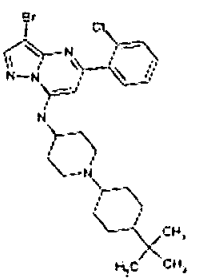
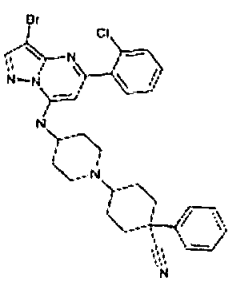
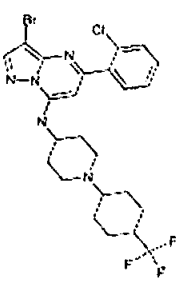
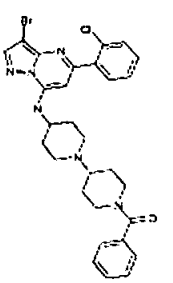
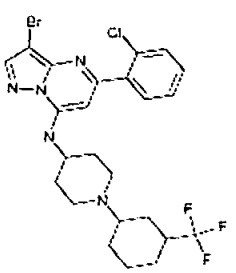
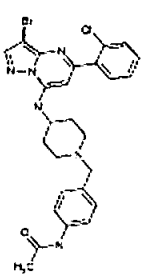
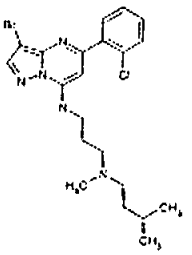
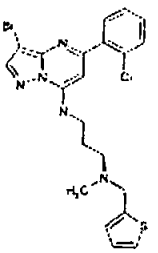
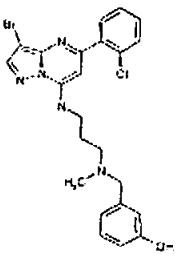
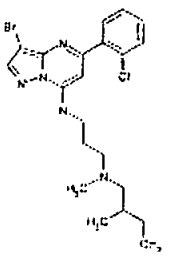
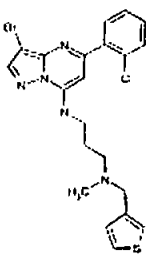
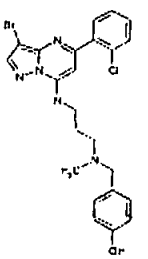
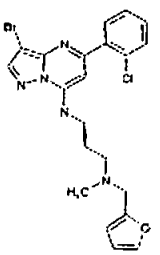
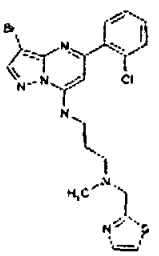
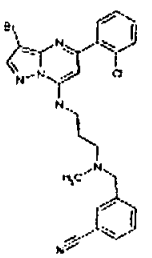
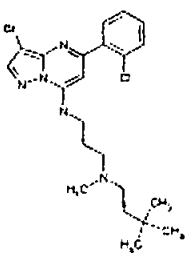
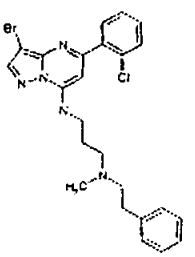
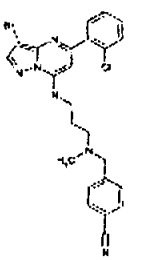
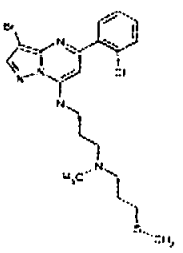
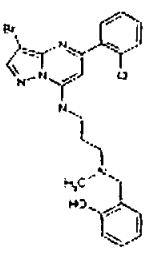
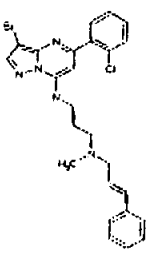
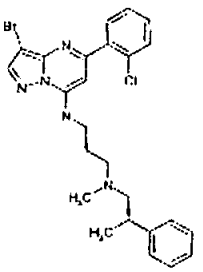
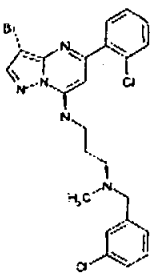
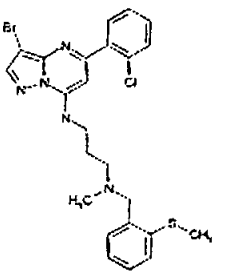
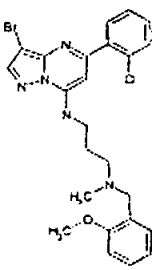
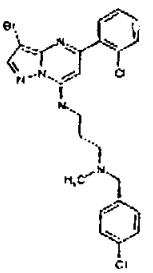
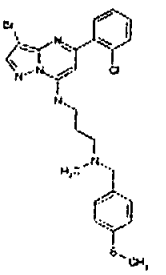
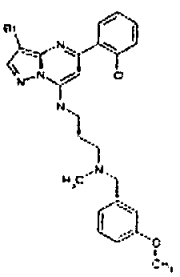
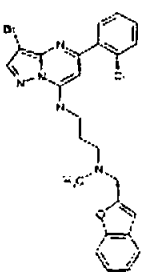
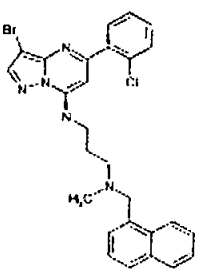
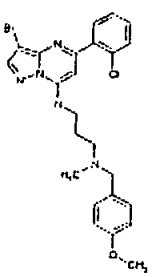
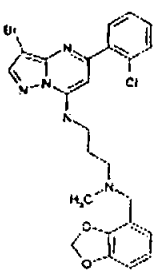
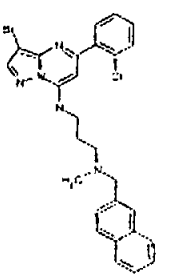
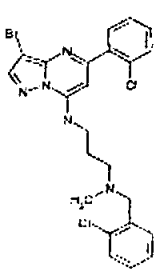
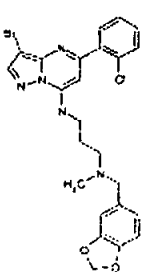
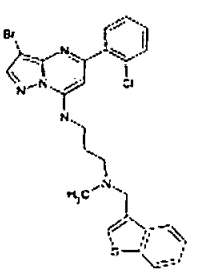
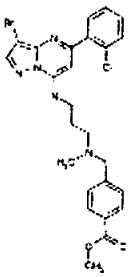
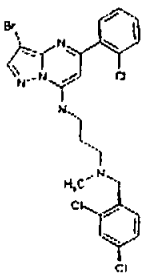
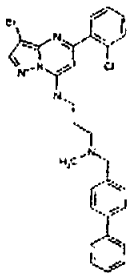
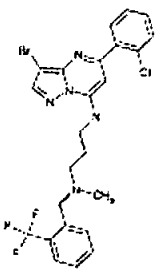
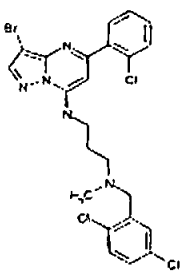
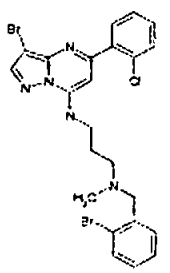
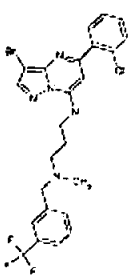
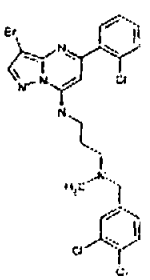
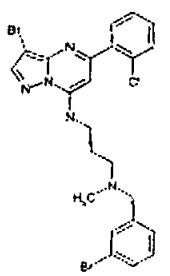
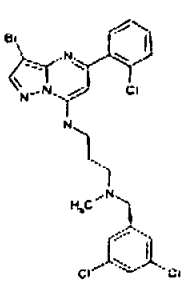
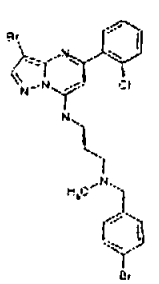
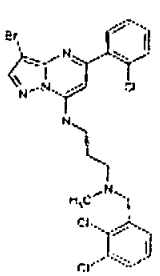
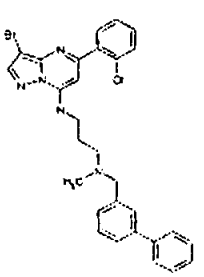
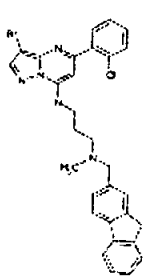
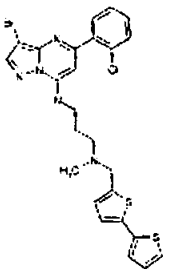
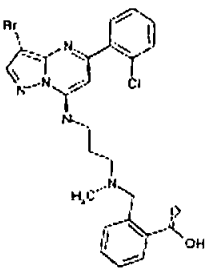
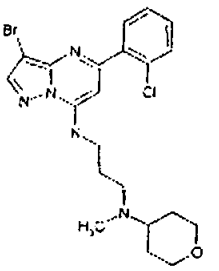
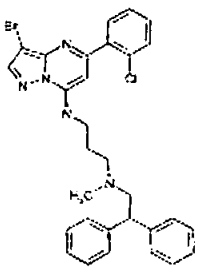
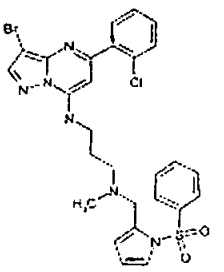
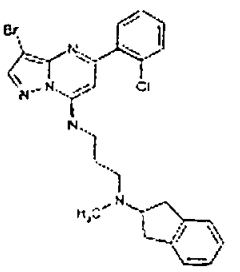
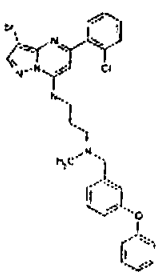
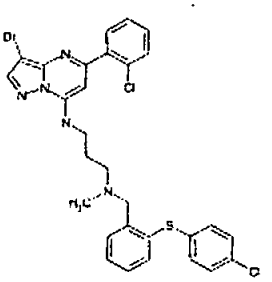
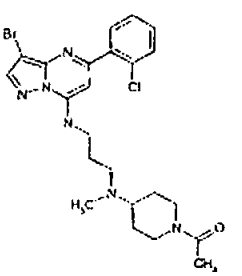
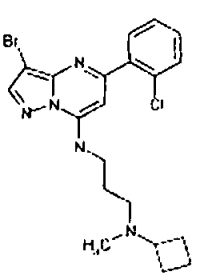
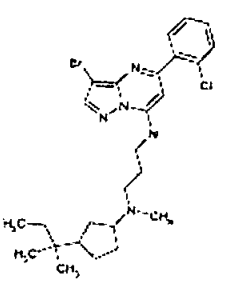
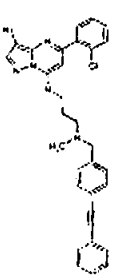
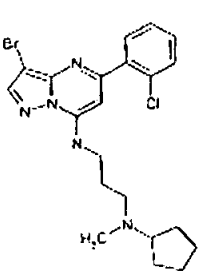
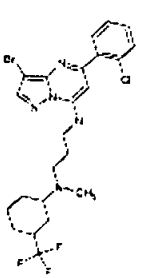
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8261 2. 544.3		1. 8266 2. 560.31
	1. 8262 2. 546.3		1. 8267 2. 566.31
	1. 8263 2. 546.3		1. 8268 2. 591.33
	1. 8264 2. 558.31		1. 8269 2. 595.33
	1. 8265 2. 558.31		1. 8270 2. 555.31

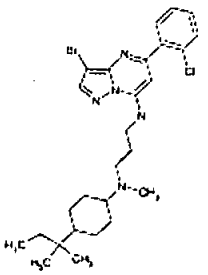
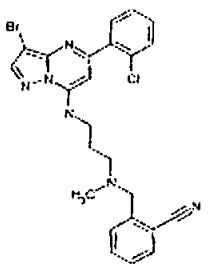
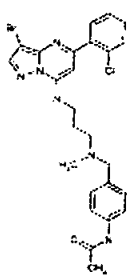
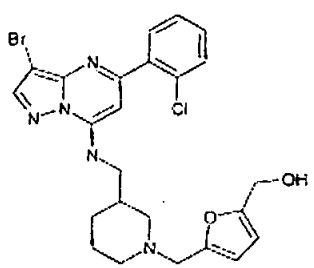
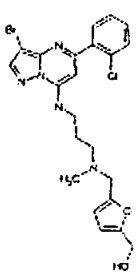
TABLA 83

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8301 2. 465.882		1. 8306 2. 491.79		1. 8311 2. 501.825
	1. 8302 2. 465.885		1. 8307 2. 491.792		1. 8312 2. 501.833
	1. 8303 2. 475.827		1. 8308 2. 492.787		1. 8313 2. 510.822
	1. 8304 2. 479.89		1. 8309 2. 499.846		1. 8314 2. 510.821
	1. 8305 2. 483.829		1. 8310 2. 501.826		1. 8315 2. 511.841

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8316 2. 513.855		1. 8321 2. 519.783		1. 8326 2. 531.804
	1. 8317 2. 515.832		1. 8322 2. 519.781		1. 8327 2. 531.812
	1. 8318 2. 515.832		1. 8323 2. 525.813		1. 8328 2. 535.83
	1. 8319 2. 515.837		1. 8324 2. 529.806		1. 8329 2. 535.831
	1. 8320 2. 519.782		1. 8325 2. 529.81		1. 8330 2. 541.788

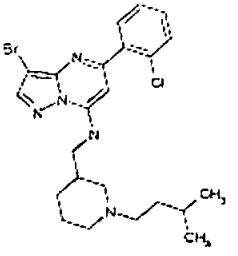
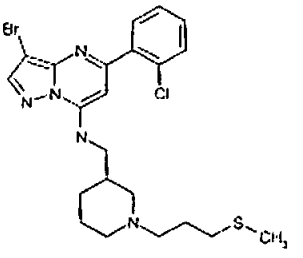
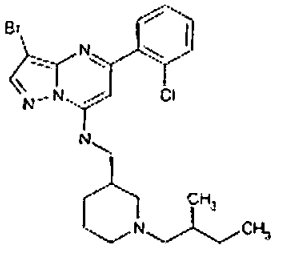
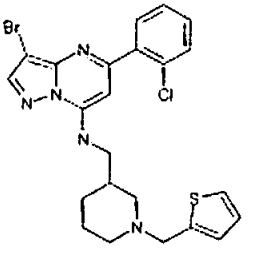
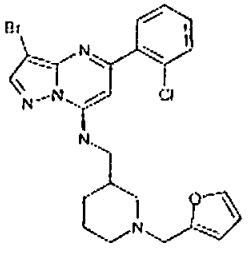
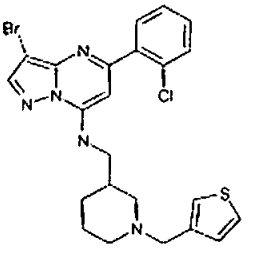
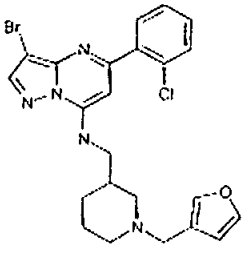
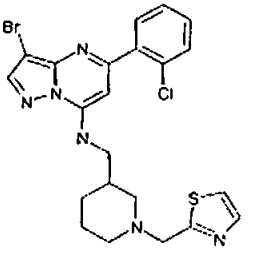
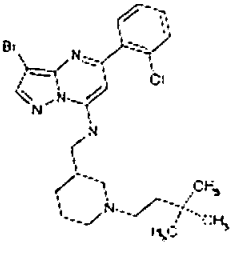
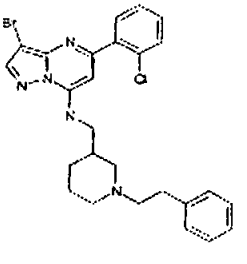
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8331 2. 543.821		1. 8336 2. 554.727		1. 8341 2. 561.838
	1. 8332 2. 553.797		1. 8337 2. 554.738		1. 8342 2. 564.714
	1. 8333 2. 553.796		1. 8338 2. 554.738		1. 8343 2. 564.704
	1. 8334 2. 553.795		1. 8339 2. 554.727		1. 8344 2. 564.72
	1. 8335 2. 554.73		1. 8340 2. 561.836		1. 8345 2. 573.823

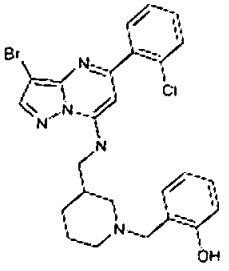
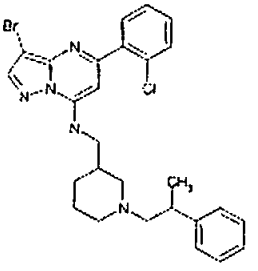
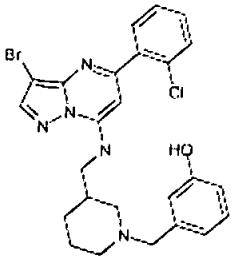
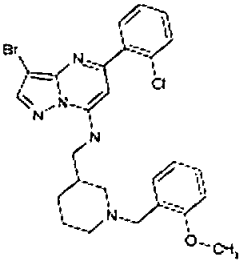
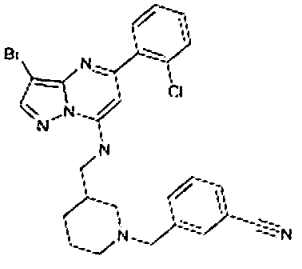
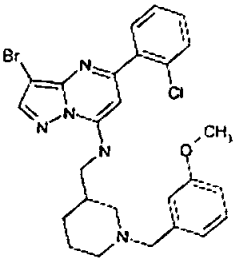
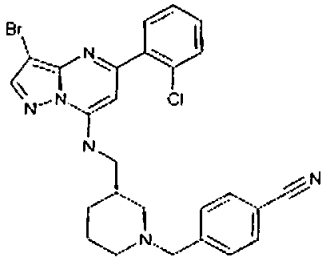
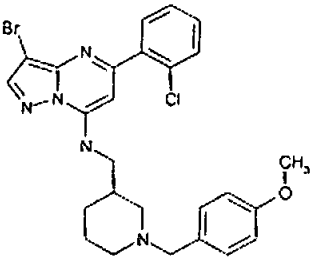
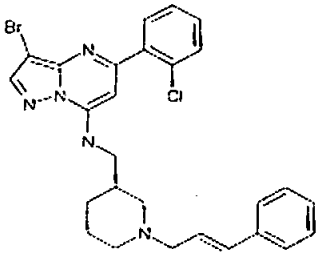
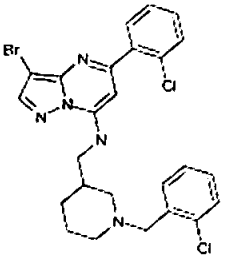
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8346 2. 573.735		1. 8351 2. 529.808		1. 8356 2. 479.856
	1. 8347 2. 575.839		1. 8352 2. 614.763		1. 8357 2. 511.842
	1. 8348 2. 577.818		1. 8353 2. 628.727		1. 8358 2. 520.859
	1. 8349 2. 577.814		1. 8354 2. 449.857		1. 8359 2. 533.903
	1. 9350 2. 585.818		1. 8355 2. 463.867		1. 8360 2. 545.823

Producto	1. Ej. 2. m/z
	1. 8361 2. 547.909
	1. 8362 2. 510.817
	1. 8363 2. 542.833
	1. 8364 2. 573.815
	1. 8365 2. 547.798

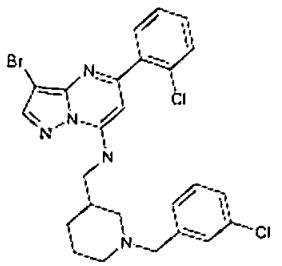
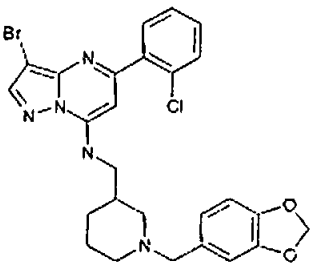
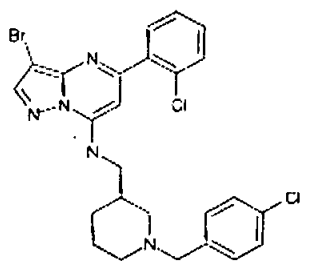
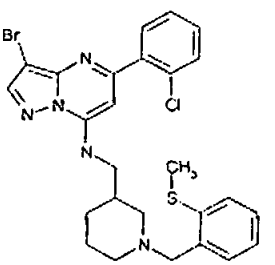
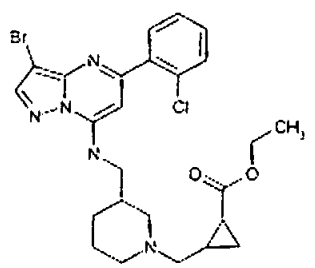
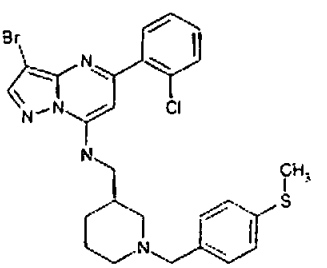
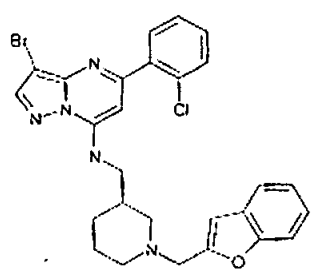
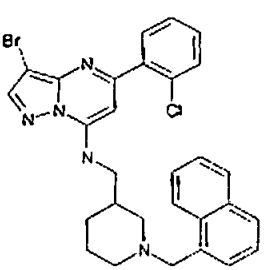
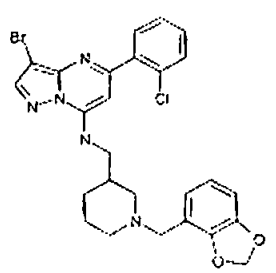
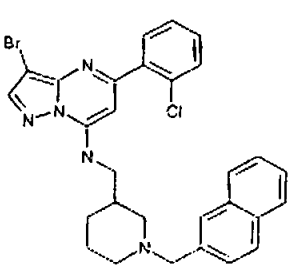
1343

TABLA 84

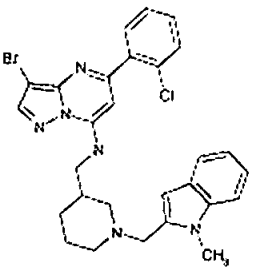
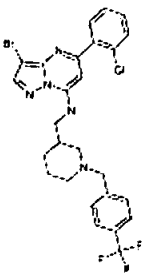
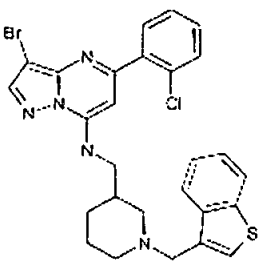
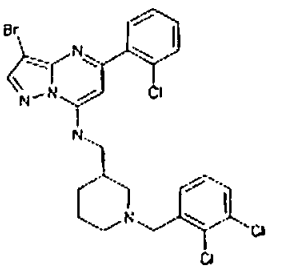
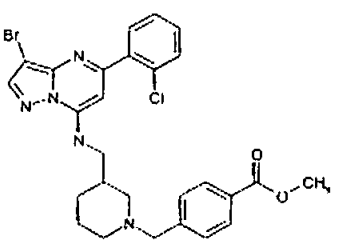
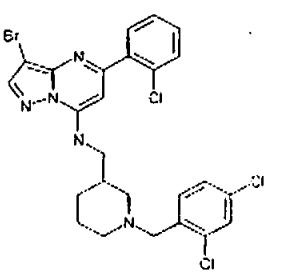
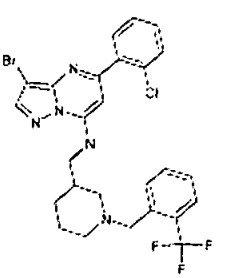
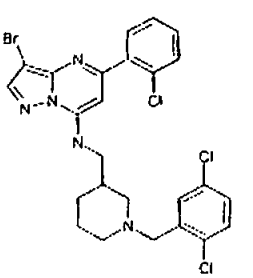
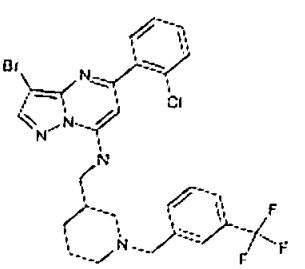
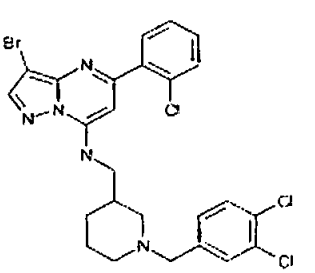
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8401 2. 491.883		1. 8406 2. 509.829
	1. 8402 2. 491.883		1. 8407 2. 517.795
	1. 8403 2. 501.823		1. 8408 2. 517.799
	1. 8404 2. 501.827		1. 8409 2. 518.796
	1. 8405 2. 505.89		1. 8410 2. 525.851

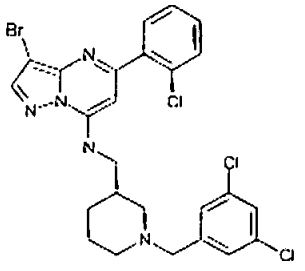
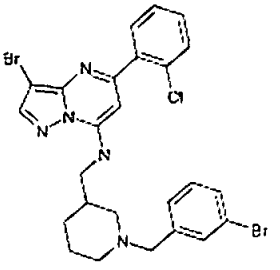
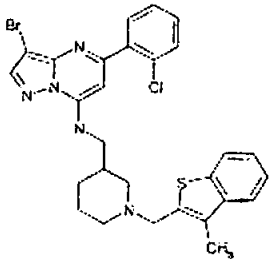
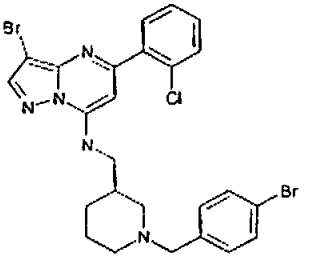
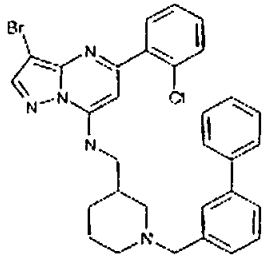
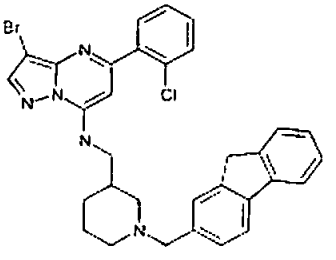
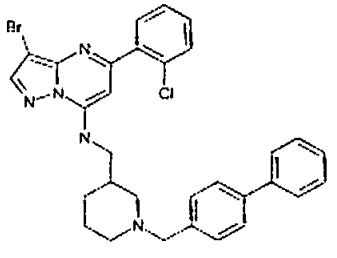
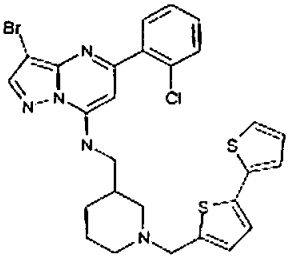
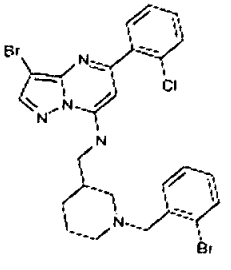
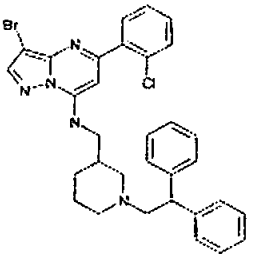
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8411 2. 527.831		1. 8416 2. 539.859
	1. 8412 2. 527.833		1. 8417 2. 541.84
	1. 8413 2. 536.833		1. 8418 2. 541.843
	1. 8414 2. 536.829		1. 8419 2. 541.843
	1. 8415 2. 537.845		1. 8420 2. 546.786

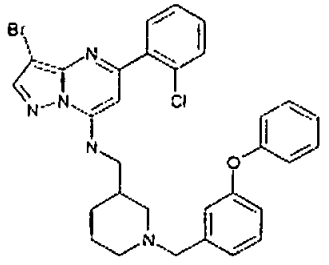
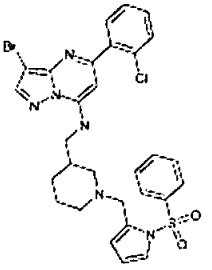
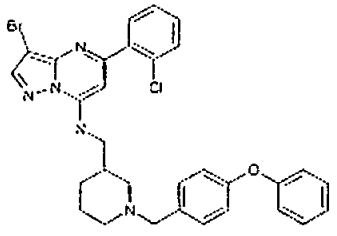
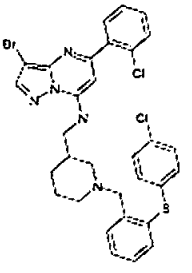
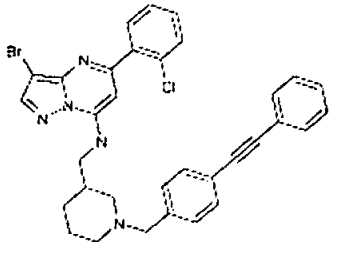
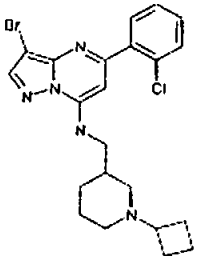
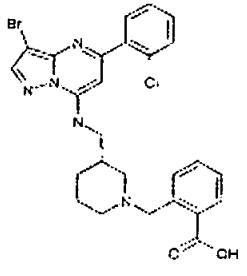
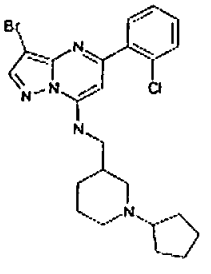
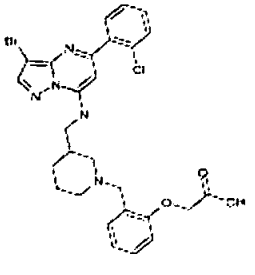
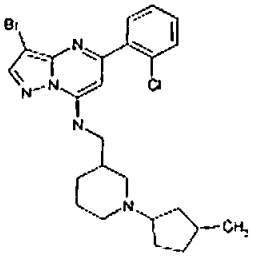
1345

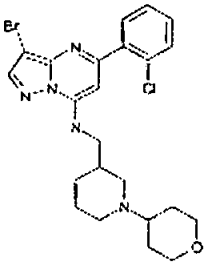
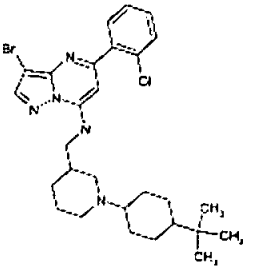
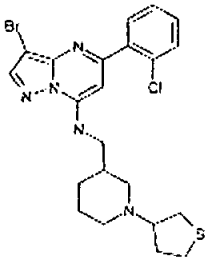
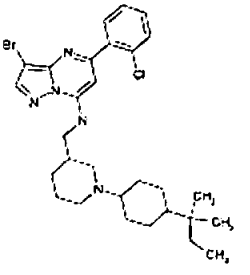
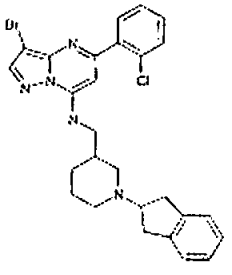
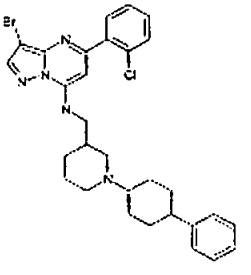
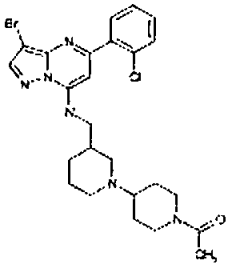
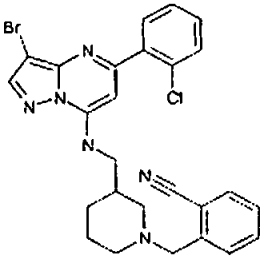
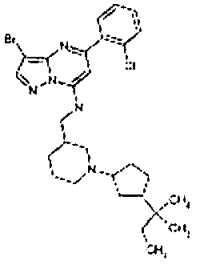
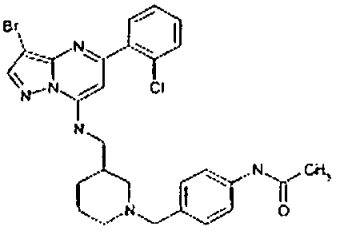
Producto	1. Ej. 2. m/z	Producto	1. E. 2. m/z
	1. 8421 2. 546.792		1. 8426 2. 555.817
	1. 8422 2. 546.79		1. 8427 2. 557.81
	1. 8423 2. 547.854		1. 8428 2. 557.813
	1. 8424 2. 551.826		1. 8429 2. 561.839
	1. 8425 2. 555.819		1. 8430 2. 561.833

1346

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8431 2. 564.841		1. 8436 2. 579.794
	1. 8432 2. 567.795		1. 8437 2. 580.738
	1. 8433 2. 569.823		1. 8438 2. 580.732
	1. 8434 2. 579.797		1. 8439 2. 580.733
	1. 8435 2. 579.796		1. 8440 2. 580.734

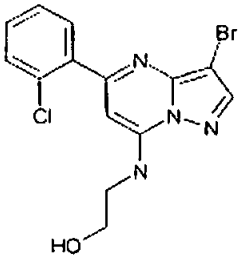
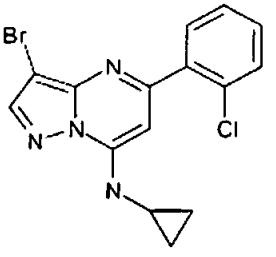
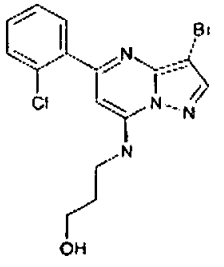
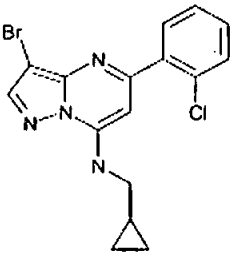
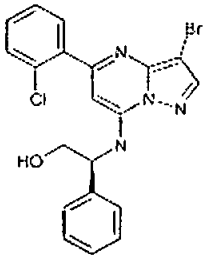
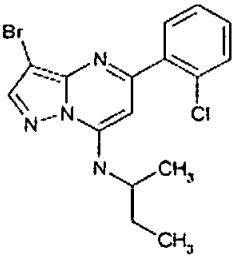
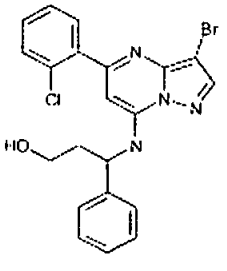
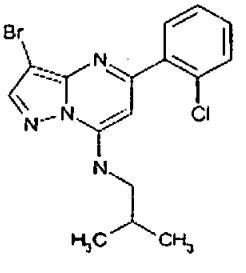
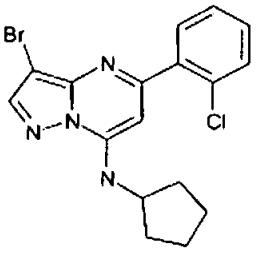
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8441 2. 580.726		1. 8446 2. 590.726
	1. 8442 2. 581.805		1. 8447 2. 590.724
	1. 8443 2. 587.844		1. 8448 2. 599.834
	1. 8444 2. 587.835		1. 8449 2. 599.749
	1. 8445 2. 590.723		1. 8450 2. 601.854

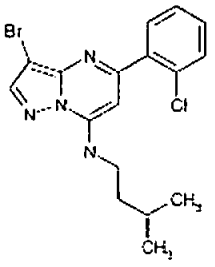
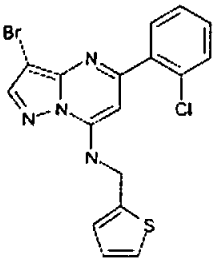
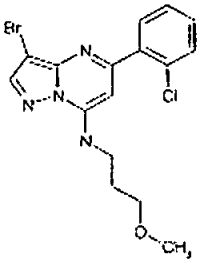
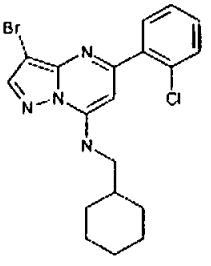
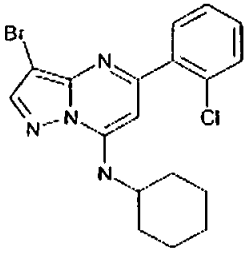
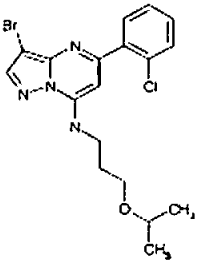
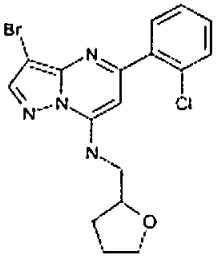
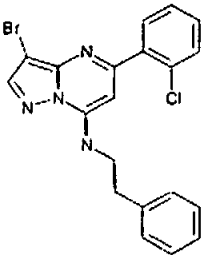
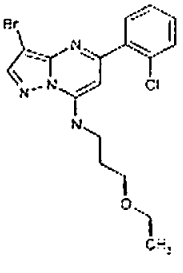
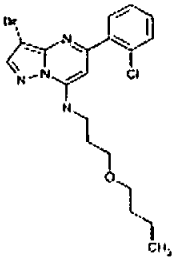
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8451 2. 603.831		1. 8456 2. 640.779
	1. 8452 2. 603.83		1. 8457 2. 654.746
	1. 8453 2. 611.83		1. 8458 2. 475.871
	1. 8454 2. 555.824		1. 8459 2. 489.879
	1. 8455 2. 585.817		1. 8460 2. 503.885

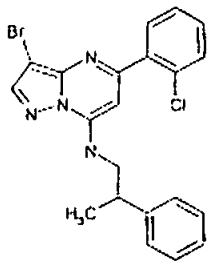
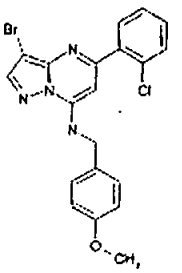
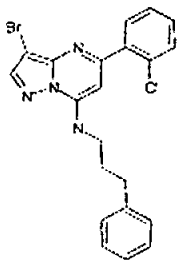
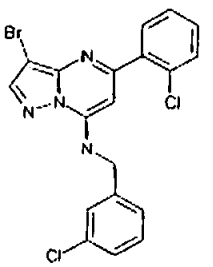
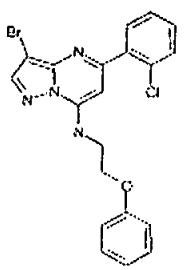
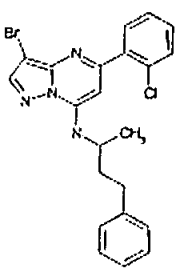
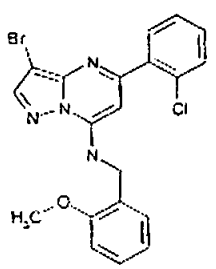
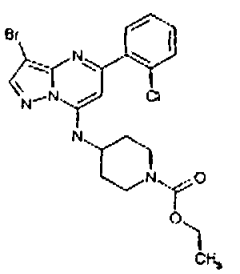
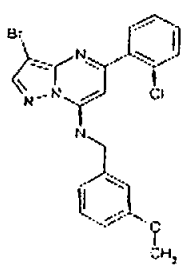
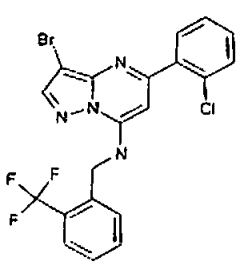
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8461 2. 505.866		1. 8466 2. 559.919
	1. 8462 2. 507.828		1. 8467 2. 573.925
	1. 8463 2. 537.859		1. 8468 2. 579.876
	1. 8464 2. 546.877		1. 8469 2. 536.831
	1. 8465 2. 559.921		1. 8470 2. 568.843

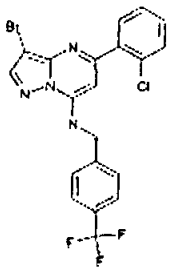
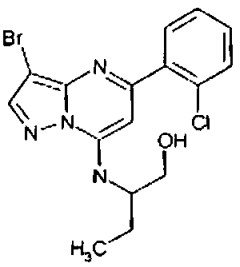
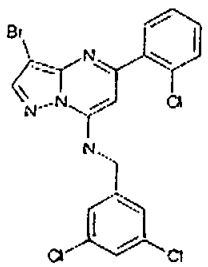
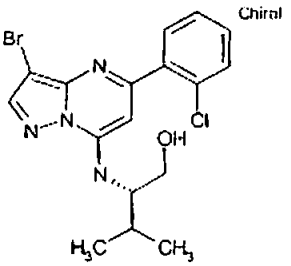
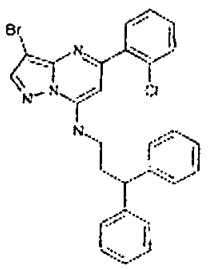
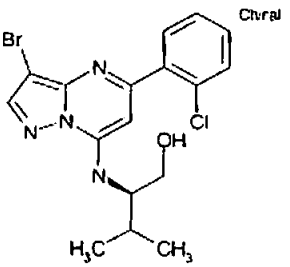
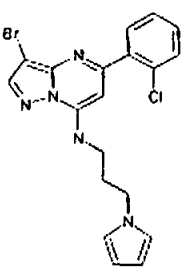
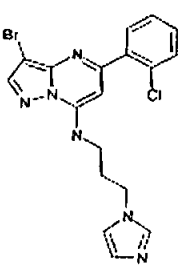
1350

TABLA 85

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1.8501 2. 367.2		1. 8506 2. 443.1
	1. 8502 2. 381.2		1. 8507 2. 323.1
	1. 8503 2. 443.2		1. 8508 2. 365.2
	1. 8504 2. 457.3		1. 8509 2. 379.21
			1. 8510 2. 381.21

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8511 2. 381.21		1. 8516 2. 409.22
	1. 8512 2. 393.22		1. 8517 2. 411.23
	1. 8513 2. 395.22		1. 8518 2. 421.23
	1. 8514 2. 397.22		1. 8519 2. 421.23
	1. 8515 2. 407.22		1. 8520 2. 425.23

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8521 2. 429.24		1. 8526 2. 445.24
	1. 8522 2. 439.24		1. 8527 2 .444.24
	1. 8523 2. 443.24		1. 8528 2. 444.24
	1. 8524 2. 443.24		1. 8529 2. 446.25
	1. 8525 2. 445.24		1. 8530 2. 457.25

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8531 2. 480.26		1. 8536 2. 431.24
	1. 8532 2. 483.27		1. 8537 2. 429.24
	1. 8533 2. 483.27		1. 8538 2. 397.22
			1. 8539 2. 411.23
			1. 8540 2. 411.23

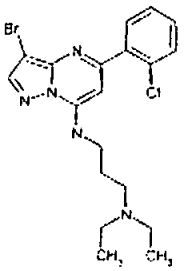
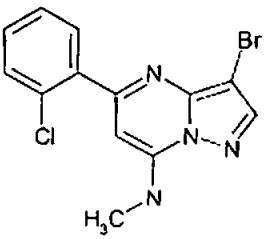
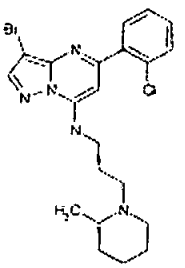
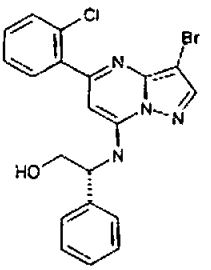
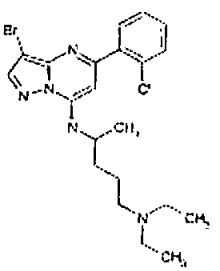
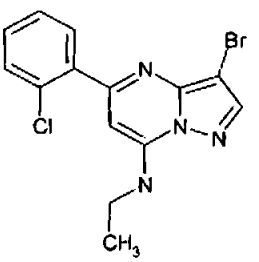
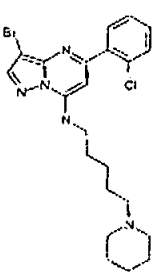
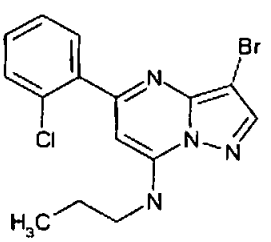
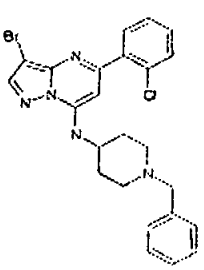
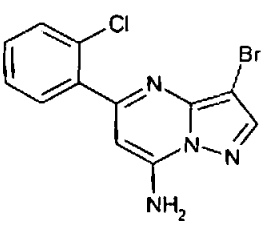
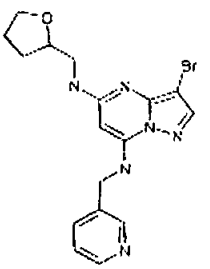
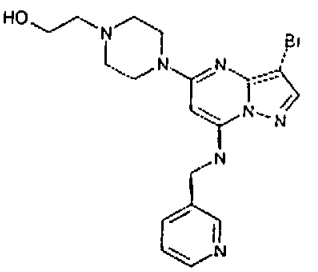
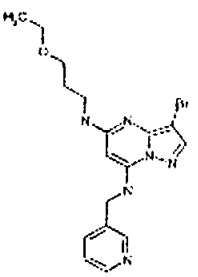
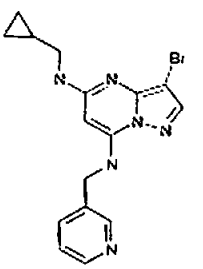
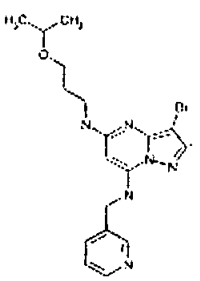
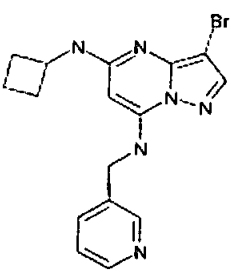
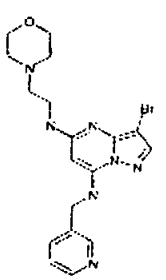
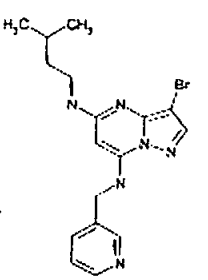
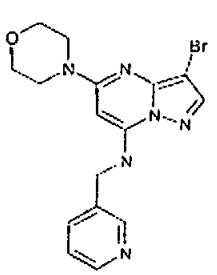
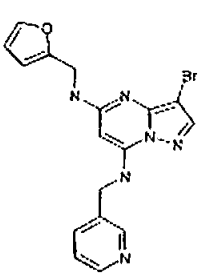
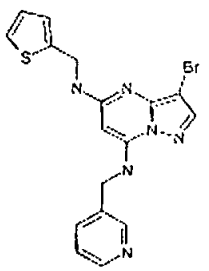
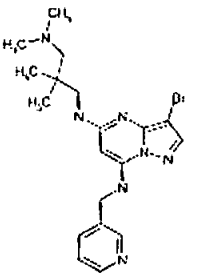
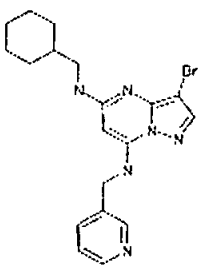
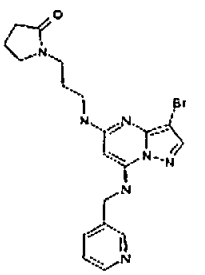
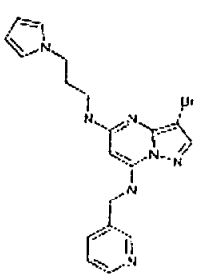
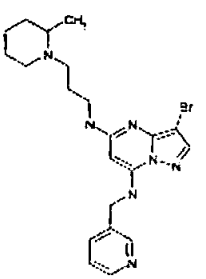
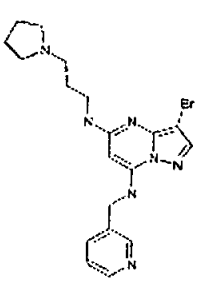
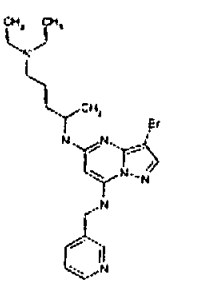
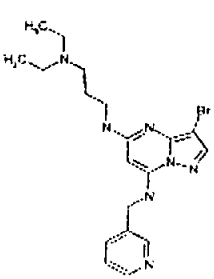
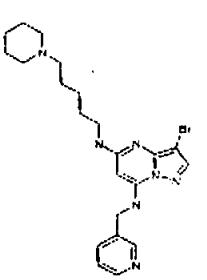
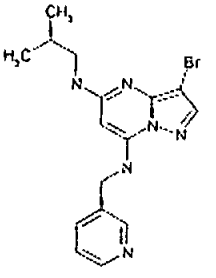
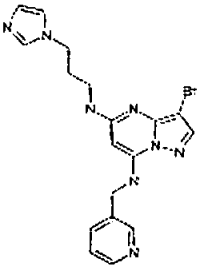
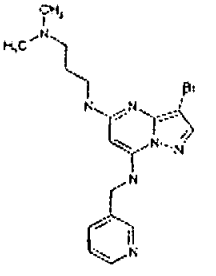
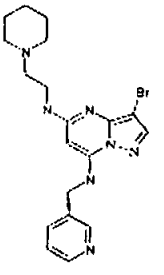
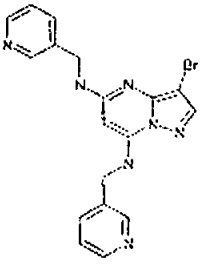
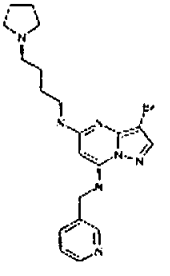
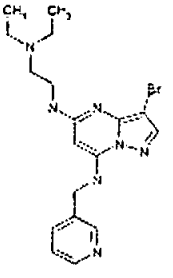
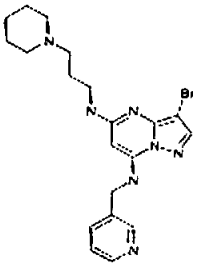
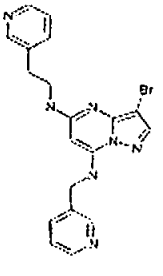
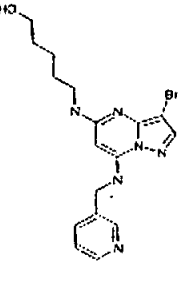
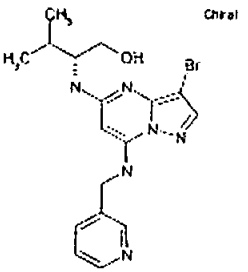
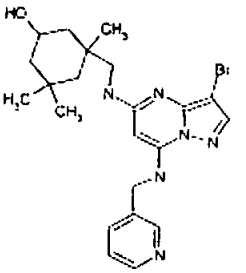
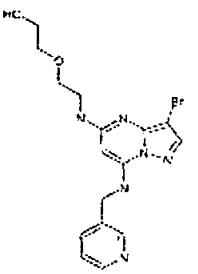
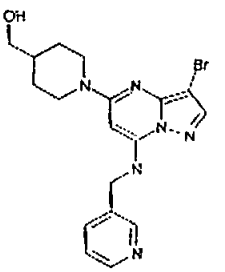
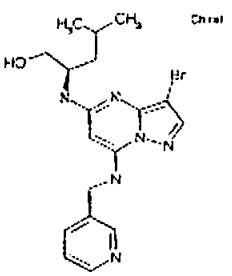
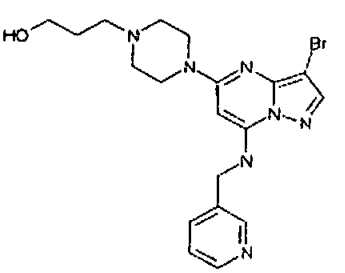
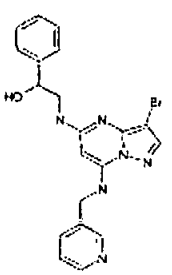
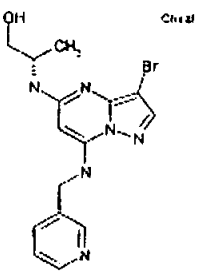
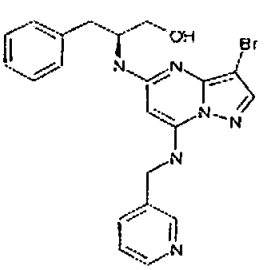
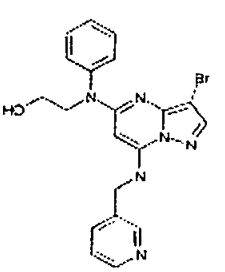
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8541 2. 432.24		1. 8547 2. 478.26
	1. 8542 2. 433.24		1. 8548 2. 498.27
	1. 8543 2. 438.24		1. 8549 2. 365.1
	1. 8545 2. 464.26		1. 8549 2. 337.1
	1. 8546 2. 466.26		1. 8550 2. 351.1

TABLA 86

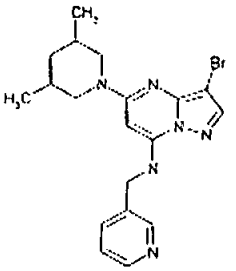
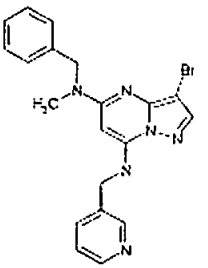
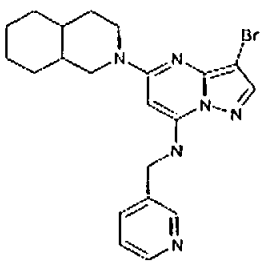
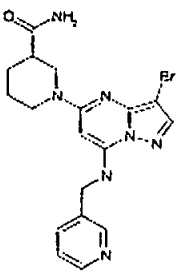
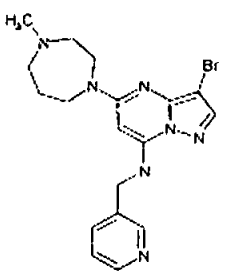
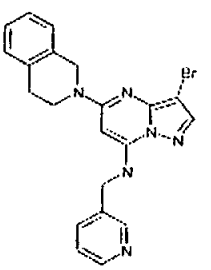
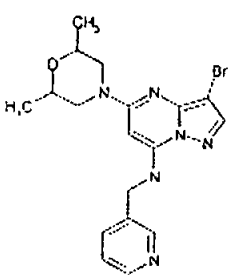
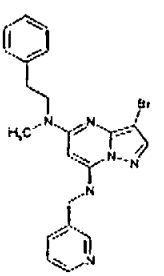
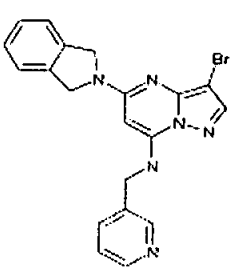
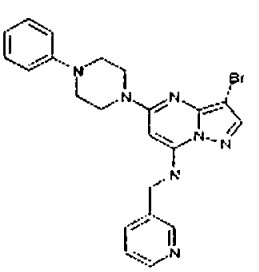
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8601 2. 403.22		1. 8606 2. 434.24
	1. 8602 2. 407.22		1. 8607 2. 375.21
	1. 8603 2. 421.23		1. 8608 2. 375.21
	1. 8604 2. 434.24		1. 8609 2. 391.22
	1. 8605 2. 391.22		1. 8610 2. 399.22

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8611 2. 417.23		1. 8616 2. 434.24
	1. 8612 2. 415.23		1. 8617 2. 446.25
	1. 8613 2. 428.24		1. 8618 2. 460.25
	1. 8614 2. 430.24		1. 8619 2. 459.25
	1. 8615 2. 434.24		1. 8620 2. 474.26

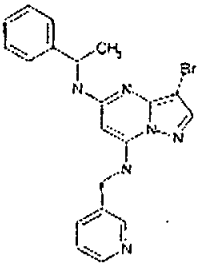
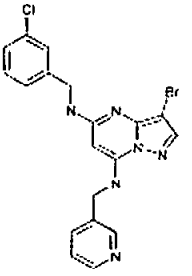
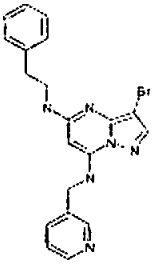
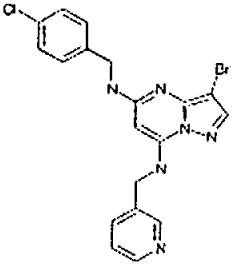
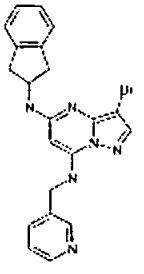
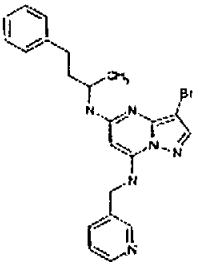
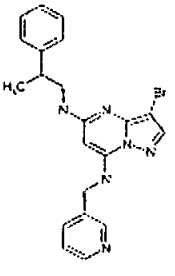
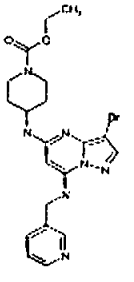
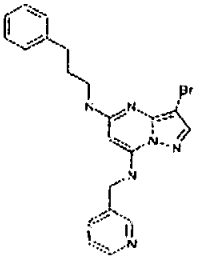
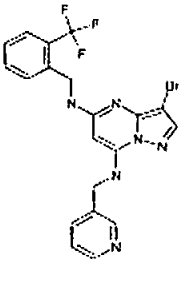
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8621 2. 377.21		1. 8626 2. 427.23
	1. 8622 2. 406.22		1. 8627 2. 431.24
	1. 8623 2. 412.23		1. 8628 2. 446.25
	1. 8624 2. 420.23		1. 8629 2. 446.25
	1. 8625 2. 426.23		1. 8630 2. 407.2

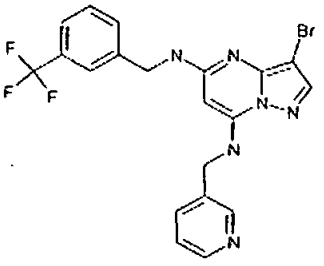
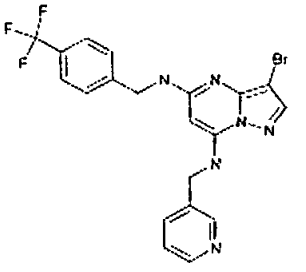
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8631 2. 407.2		1. 8636 2. 475.3
	1. 8632 2. 409.2		1. 8637 2. 419.2
	1. 8633 2. 421.2		1. 8638 2. 448.2
	1. 8634 2. 439.2		1. 8639 2. 379.2
	1. 8635 2. 455.3		1. 8640 2. 437.2

1359

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8641 2. 415.23		1. 8646 2. 423.23
	1. 8642 2. 443.24		1. 8647 2. 430.24
	1. 8643 2. 416.23		1. 8648 2. 437.24
	1. 8644 2. 417.23		1. 8649 2. 439.24
	1. 8645 2. 423.23		1. 8650 2. 466.26

1360

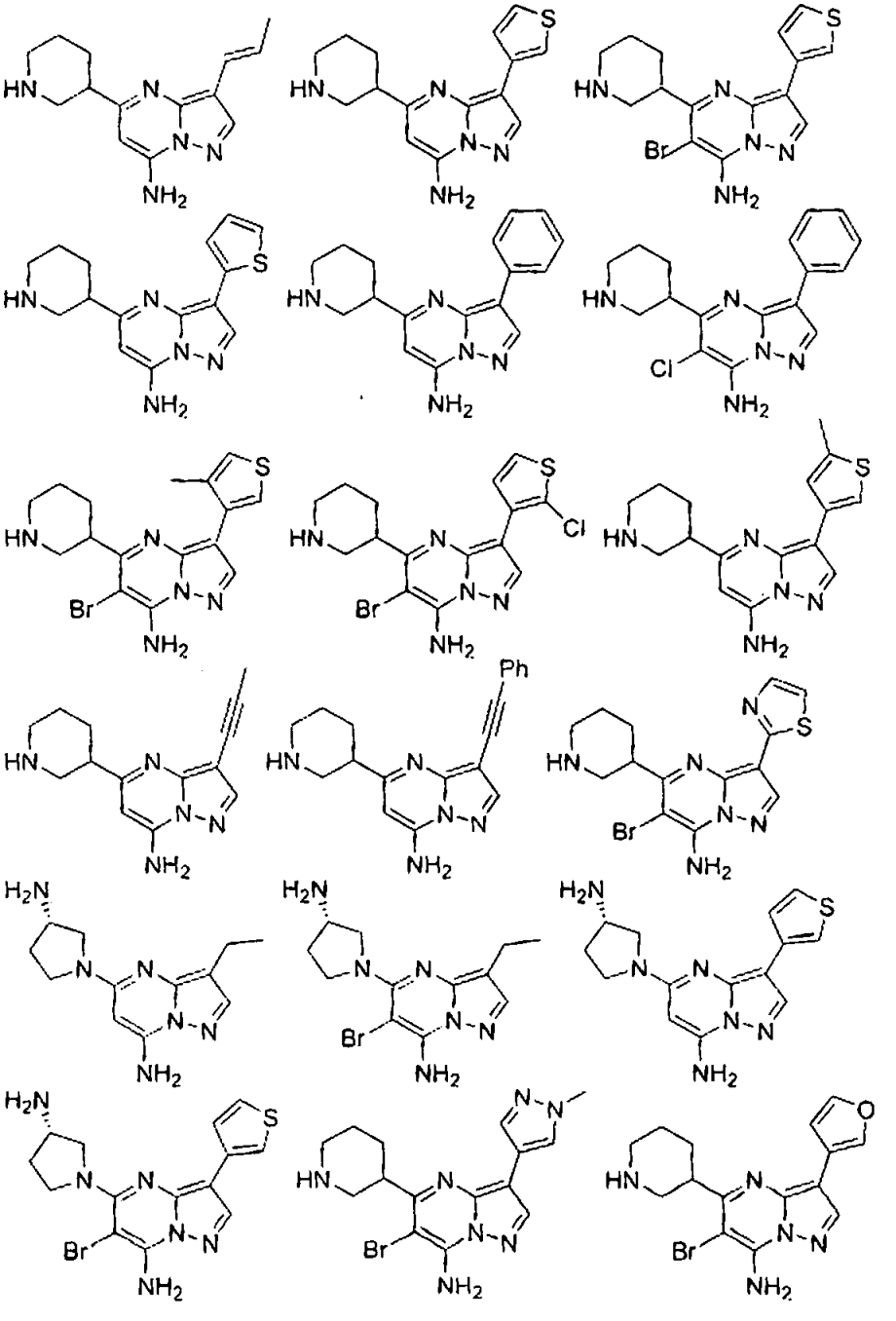
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8651 2. 423.23		1. 8656 2. 445.24
	1. 8652 2. 425.23		1. 8657 2. 445.24
	1. 8653 2. 437.24		1. 8658 2. 451.25
	1. 8654 2. 437.24		1. 8659 2. 476.26
	1. 8655 2. 437.24		1. 8660 2. 479.26

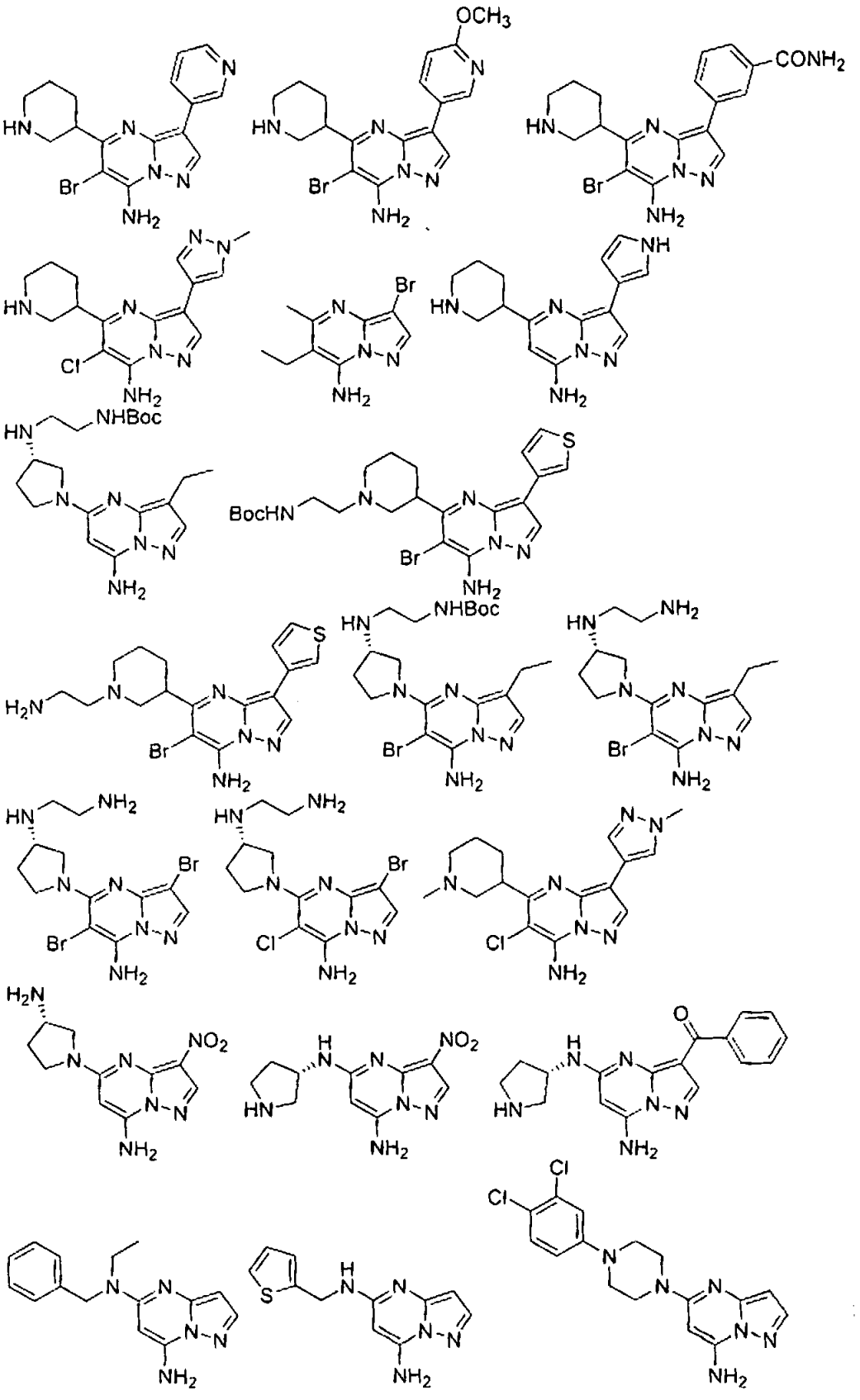
Producto	1. Ej. 2. m/z
	1. 8661 2. 477.26
	1. 8662 2. 479.26

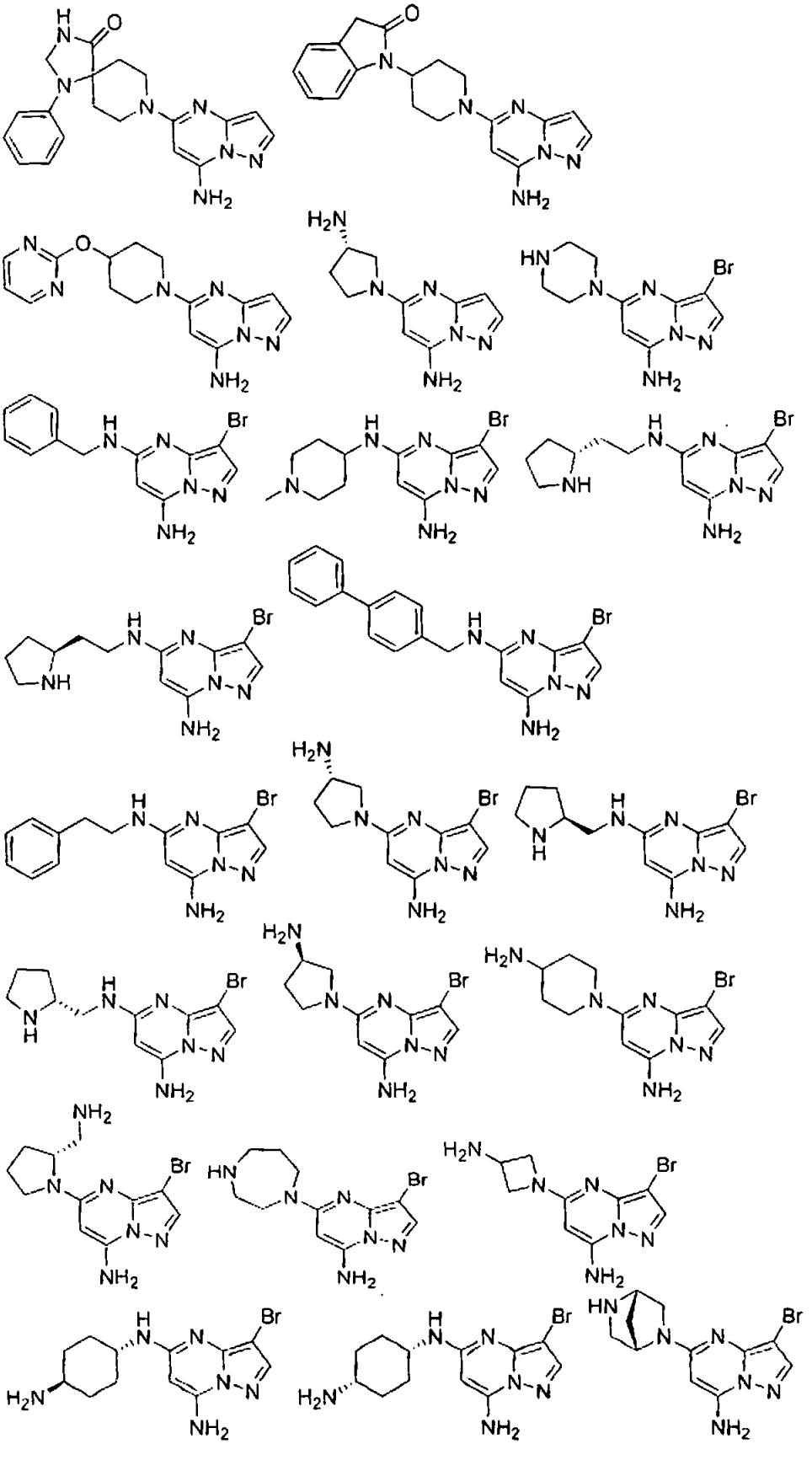
REIVINDICACIONES

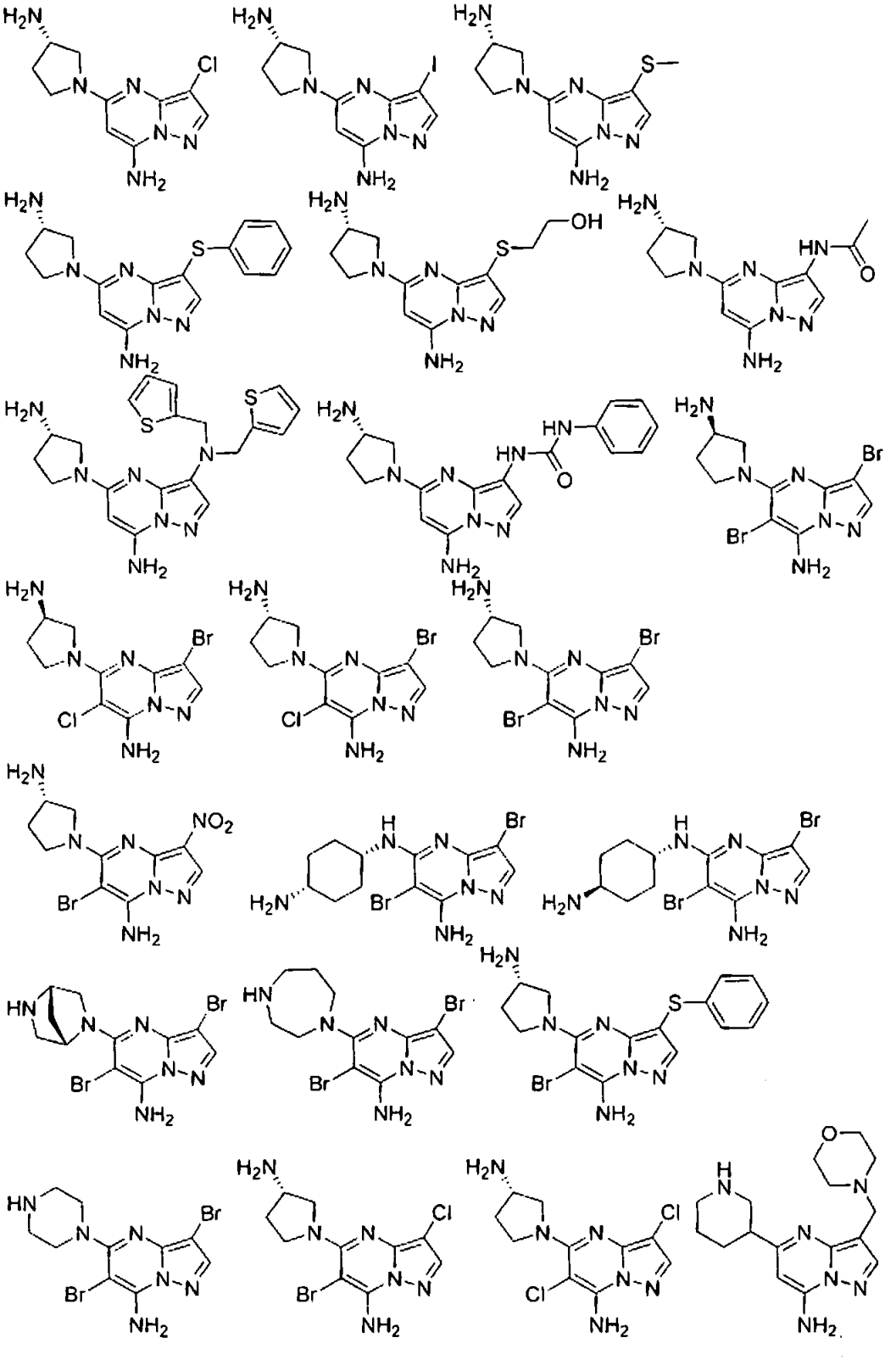
Habiendo así especialmente descripto y determinado la naturaleza de la presente invención y la forma como la misma ha de ser llevada a la práctica, se declara reivindicar como de propiedad y derecho exclusivo:

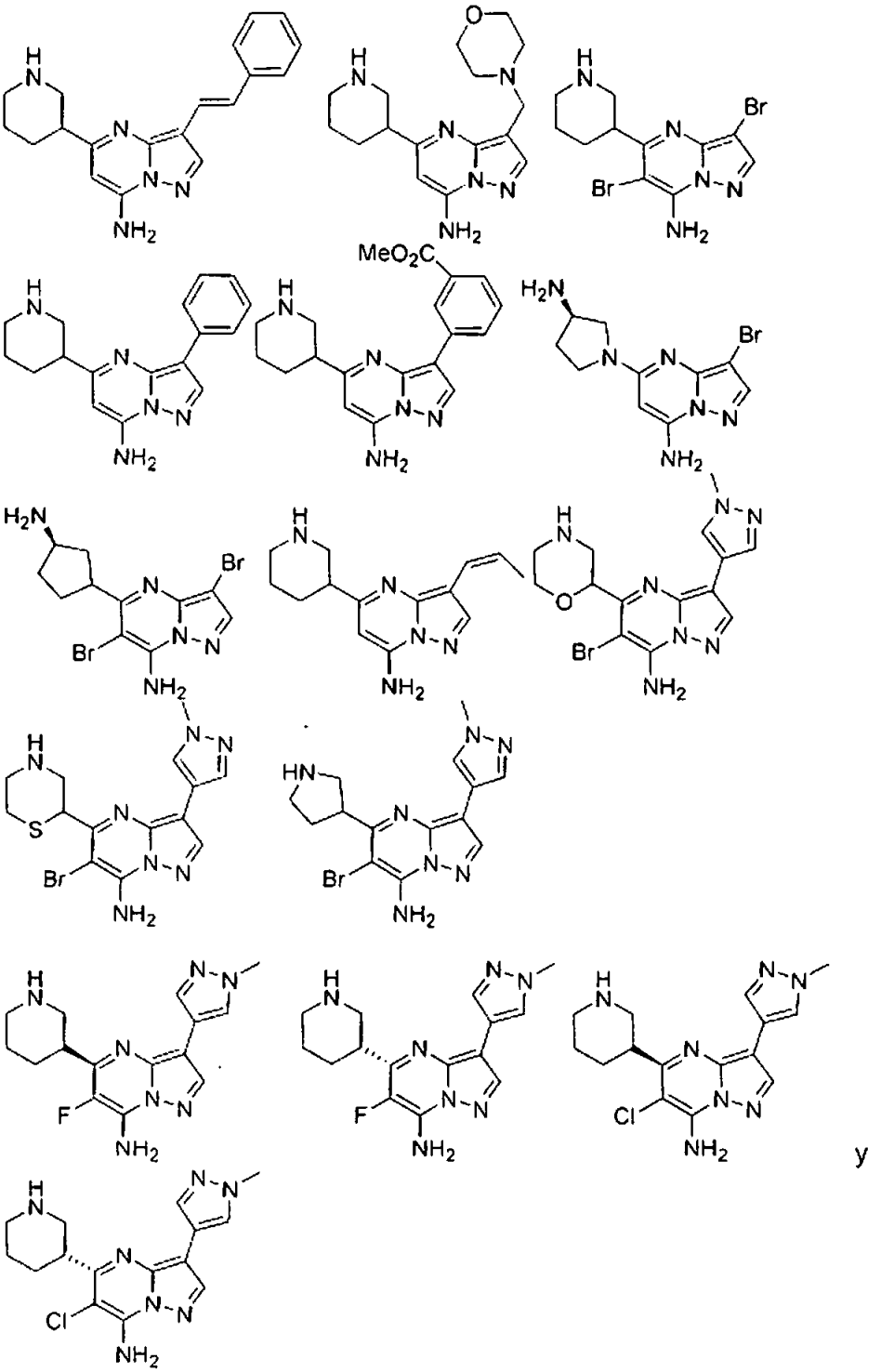
1. Un compuesto seleccionado del grupo que consiste en los compuestos de la fórmula:











y

o una sal, solvato, éster o profármaco de éste farmacéuticamente aceptable.

2. Uso de por lo menos un compuesto de la reivindicación 1, o una sal, solvato, éster o profármaco de éste farmacéuticamente aceptable, para la manufactura de un medicamento para inhibir una o más quinasas dependientes de ciclina en un paciente.

3. Uso de por lo menos un compuesto de la reivindicación 1, o una sal, solvato, éster o profármaco de éste farmacéuticamente aceptable, para la manufactura de un medicamento para el tratamiento de una o más enfermedades asociadas con una quinasa en un paciente.

4. El uso de la reivindicación 3, donde dicha quinasa es una quinasa dependiente de ciclina.

5. El uso de la reivindicación 4, en el cual dicha quinasa dependiente de ciclina es CDK1, CDK2 o CDK9.

6. El uso de la reivindicación 5, en el cual dicha quinasa es CDK2.

7. El uso de la reivindicación 3, en el cual dicha quinasa es una proteinquinasa activada por mitógeno (MAPK/ERK).

8. El uso de la reivindicación 3, en el cual dicha quinasa es glicógeno sintasa quinasa 3 (GSK3beta).

9. El uso de la reivindicación 3, en el cual dicha enfermedad está seleccionada del grupo que consiste en:

cáncer de la vejiga, mama, colon, riñón, hígado, pulmón, cáncer pulmonar de células pequeñas, cáncer pulmonar de células no pequeñas, cabeza y cuello, esófago, vesícula biliar, ovario, páncreas, estómago, cuello uterino, tiroides, próstata y piel, incluyendo carcinoma de células escamosas;

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 del manto celular, mieloma y linfoma de Burkett;

leucemia mielógena aguda y crónica, síndrome mielodisplásico y leucemia promielocítica;

fibrosarcoma, rabdomiosarcoma;

cabeza y cuello, linfoma del manto celular, mieloma;

astrocitoma, neuroblastoma, glioma y schwannomas;

melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentoso, queratoctantoma, cáncer folicular de tiroides y sarcoma de Kaposi.

10. Uso de una combinación que comprende (i) al menos un compuesto de la reivindicación 1, o una sal, solvato, éster o profármaco de éste farmacéuticamente aceptable;

y

(ii) un agente anti-canceroso para la manufactura de un medicamento para el tratamiento de una o más enfermedades asociadas con quinasa dependiente de ciclina.

11. El uso de la reivindicación 10, que además comprende el uso de terapia de radiación.

12. El uso de la reivindicación 10, en el cual dicho agente anti-cáncer está seleccionado del grupo que consiste en un agente citostático, cisplatina, doxorrubicina, taxotero, taxol, etoposida, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epotilonas, tamoxifeno, 5-fluoruracilo, metoxtrexato, temozolomida, ciclofosfamida, SCH 66336, R115777, L778,123, BMS 214662, Iressa, Tarceva, anticuerpos para EGFR, Gleevec, intron, ara-C, adriamicina, citoxan, gemcitabina, Uracilo mostaza, Clormetina, Ifosfamida, Melfalan, Clorambucilo, Pipobroman, Trietilenmelamina, Trietilentiofosforamina, Busulfan, Carmustina, Lomustina, Estreptozocina, Dacarbazina, Floxuridina, Citarabina, 6-Mercaptopurina, 6-Tioguanina, fosfato de Fludarabina, oxaliplatina, leucovirina, ELOXATIN™, Pentostatina, Vinblastina, Vincristina, Vindesina, Bleomicina, Dactinomicina, Daunorrubicina, Doxorrubicina, Epirrubicina, Idarrubicina, Mitramicina, Deoxicoformicina, Mitomicina-C, L-Asparaginasa, Teniposida 17α-Etinilestradiol, Dietilestilbestrol, Testosterona, Prednisona, Fluoximesterona, propionato de Dromostanolona, Testolactona, Megestrolacetato, Metilprednisolona, Metiltestosterona, Prednisolona, Triamcinolona, Clorotrianiseno, Hidroxiprogesterona, Aminoglutetimida, Estramustina, Medroxiprogesteronacetato, Leuprolida, Flutamida, Toremifeno, goserelina, Cisplatina, Carboplatina, Hidroxiurea, Amsacrina, Procarbazina, Mitotana, Mitoxantrona, Levamisol, Navelbeno, Anastrazol, Letrazol, Capecitabina, Reloxafina, Droloxafina, Hexametilmelamina, Avastina, herceptina, Bexxar, Velcade, Zevalin, Trisenox, Xeloda, Vinorelbina, Porfimer, Erbitux, Liposomal,

Tiotepa, Altretamina, Melfalan, Trastuzumab, Lerozol, Fulvestrant, Exemestano, Fulvestrant, Ifosfomida, Rituximab, C225 y Campat.

13. Una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de por lo menos un compuesto de la reivindicación 1, o una sal, solvato, éster o profármaco de éste farmacéuticamente aceptable, en combinación con por lo menos un portador farmacéuticamente aceptable.

14. La composición farmacéutica de la reivindicación 13, que comprende adicionalmente uno o más agentes anti-cancerosos seleccionados del grupo que consiste en un agente citostático, cisplatina, doxorrubicina, taxotero, taxol, etoposida, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epotilonas, tamoxifeno, 5-fluoruracilo, metoxtrexato, temozolomida, ciclofosfamida, SCH 66336, R115777, L778,123, BMS 214662, Iressa, Tarceva, anticuerpos para EGFR, Gleevec, intron, ara-C, adriamicina, citoxano, gemcitabina, Uracilo mostaza, Clormetina, Ifosfamida, Melfalan, Clorambucilo, Pipobroman, Trietilenmelamina, Trietilentiofosforamina, Busulfan, Carmustina, Lomustina, Estreptozocina, Dacarbazina, Floxuridina, Citarabina, 6-Mercaptopurina, 6-Tioguanina, fosfato de Fludarabina, oxaliplatina, leucovirina, ELOXATIN™, Pentostatina, Vinblastina, Vincristina, Vindesina, Bleomicina, Dactinomicina, Daunorrubicina, Doxorrubicina, Epirrubicina, Idarrubicina, Mitramicina, Deoxicoformicina, Mitomicina-C, L-Asparaginasa, Teniposida 17α-Etinilestradiol, Dietilestilbestrol, Testosterona, Prednisona, Fluoximesterona, propionato de Dromostanolona, Testolactona, Megestrolacetato, Metilprednisolona, Metiltestosterona, Prednisolona, Triamcinolona, Clorotrianiseno, Hidroxiprogesterona, Aminoglutetimida, Estramustina, Medroxiprogesteronacetato, Leuprolida, Flutamida, Toremifeno, goserelina, Cisplatina, Carboplatina, Hidroxiurea, Amsacrina, Procarbazina, Mitotano, Mitoxantrona, Levamisol, Navelbeno, Anastrazol, Letrazol, Capecitabina, Reloxafina, Droloxafina, Hexametilmelamina, Avastina, herceptina, Bexxar, Velcade, Zevalin, Trisenox, Xeloda, Vinorelbina, Porfimer, Erbitux, Liposomal, Tiotepa, Altretamina, Melfalan, Trastuzumab, Lerozol, Fulvestrant, Exemestano, Fulvestrant, Ifosfomida, Rituximab, C225 y Campat.

137c

15. Uso de la composición farmacéutica de la reivindicación 13 para la manufactura de un medicamento para inhibir una o más de las quinasas dependientes de ciclina en un paciente.

16. Uso de una combinación que comprende (i) al menos un compuesto de la reivindicación 1, o una sal, solvato, éster o profármaco de éste farmacéuticamente aceptable;

y

(ii) temozolomida;

para el tratamiento de una o más enfermedades asociadas con quinasa dependiente de ciclina.

17. El uso de la reivindicación 16, que comprende además terapia de radiación.

18. Una composición farmacéutica que comprende (i) una cantidad terapéuticamente eficaz de un compuesto de la reivindicación 1 o una sal, solvato, éster o profármaco de éste farmacéuticamente aceptable y (ii) temozolomida.

19. Uso de la composición farmacéutica de la reivindicación 18, para inhibir una o más quinasas.

20. El uso de la reivindicación 19, donde dicha quinasa es una quinasa dependiente de ciclina.

21. Uso de la composición farmacéutica de la reivindicación 18, para el tratamiento de una o más enfermedades asociadas con una quinasa.

22. Uso de la composición farmacéutica de la reivindicación 18, para el tratamiento de cáncer.

23. Uso de por lo menos un compuesto de la reivindicación 1, o una sal, solvato, éster o profármaco de éste farmacéuticamente aceptable para el tratamiento de cáncer.

24. El uso de la reivindicación 23, en el cual dicho cáncer está seleccionado del grupo que consiste en:

cáncer de la vejiga, mama, colon, riñón, hígado, pulmón, cáncer pulmonar de células pequeñas, cáncer pulmonar de células no pequeñas, de cabeza y cuello, de esófago, de vesícula biliar, ovario, páncreas, estómago, cuello uterino, tiroides, próstata y piel, incluyendo carcinoma de células escamosas;

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 del manto celular, mieloma y linfoma de Burkett;

leucemia mielógena aguda y crónica, síndrome mielodisplásico y leucemia promielocítica;

fibrosarcoma, rabdomiosarcoma;

de cabeza y cuello, linfoma del manto celular, mieloma;

astrocitoma, neuroblastoma, glioma y schwannomas;

melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentoso, queratoctantoma, cáncer folicular de tiroides y sarcoma de Kaposi.

25. Uso de una combinación que comprende (i) al menos un compuesto de la reivindicación 1, o una sal, solvato, éster o profármaco de éste farmacéuticamente aceptable;

y

(ii) un agente anti-cáncer;

para el tratamiento de cáncer.

26. El uso de la reivindicación 25, que comprende además terapia de radiación.

27. El uso de la reivindicación 25, donde dicho agente anti-cáncer está seleccionado del grupo que consiste en un agente citostático, cisplatina, doxorrubicina, taxotero, taxol, etoposida, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epotilonas, tamoxifeno, 5-fluoruracilo, metoxtrexato, temozolomida, ciclofosfamida, SCH 66336, R115777, L778,123, BMS 214662, Iressa, Tarceva, anticuerpos para EGFR, Gleevec, intron, ara-C, adriamicina, citoxan, gemcitabina, Uracilo mostaza, Clormetina, Ifosfamida, Melfalan, Clorambucilo, Pipobroman, Trietilenmelamina, Trietilentiofosforamina, Busulfan, Carmustina, Lomustina, Estreptozocina, Dacarbazina, Floxuridina, Citarabina, 6-Mercaptopurina, 6-Tioguanina, fosfato de Fludarabina, oxaliplatina, leucovirina, ELOXATIN™, Pentostatina, Vinblastina, Vincristina, Vindesina, Bleomicina, Dactinomicina, Daunorrubicina, Doxorrubicina, Epirrubicina, Idarrubicina, Mitramicina, Deoxicoformicina, Mitomicina-C, L-Asparaginasa, Teniposida 17α-Etinilestradiol, Dietilestilbestrol, Testosterona, Prednisona, Fluoximesterona, propionato de Dromostanolona, Testolactona, Megestrolacetato, Metilprednisolona, Metiltestosterona, Prednisolona, Triamcinolona, Clorotrianiseno, Hidroxiprogesterona, Aminoglutetimida, Estramustina,

1372

Medroxiprogesteronacetato, Leuprolida, Flutamida, Toremifeno, goserelina, Cisplatina, Carboplatina, Hidroxiurea, Amsacrina, Procarbazina, Mitotano, Mitoxantrona, Levamisol, Navelbeno, Anastrazol, Letrazol, Capecitabina, Reloxafina, Droloxafina, Hexametilmelamina, Avastina, herceptina, Bexxar, Velcade, Zevalin, Trisenox, Xeloda, Vinorelbina, Porfimer, Erbitux, Liposomal, Tiotepa, Altretamina, Melfalan, Trastuzumab, Lerozol, Fulvestrant, Exemestano, Fulvestrant, Ifosfomida, Rituximab, C225 y Campat.

28. Uso de una combinación que comprende (i) por lo menos un compuesto de la reivindicación 1 o una sal, solvato, éster o profármaco de éste farmacéuticamente aceptable, y (ii) temozolomida, para el tratamiento de cáncer.

p. p. de: SCHERING CORPORATION

1373

RESUMEN

En sus muchas realizaciones, la presente invención provee una nueva clase de compuestos pirazolo[1.5-a]pirimidina como inhibidores de quinasas dependientes de ciclina, métodos para la preparación de dichos compuestos, composiciones farmacéuticas que contienen uno o más de dichos compuestos, métodos para la preparación de formulaciones farmacéuticas que comprenden uno o más de dichos compuestos, y métodos para el tratamiento, prevención, inhibición o mejoramiento de una o más enfermedades asociadas con CDKs usando dichos compuestos o composiciones farmacéuticas.

1379

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Firma Responsable

Fecl

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 08-034063- -00000-0000
Fecha: 2008-04-04 16:28:48 Dep: 2020 NUECREACIONI
Tra: 11 PATENTEIYII Eve: 378 PASENACIONALI
Act: 411 PRESENTACION Folios: 1378

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 62 20
E-mail: info@sic.gov.co

1380

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
SCHERING CORPORATION

REFERENCIA	Radicación No.	8 34063
	Solicitud internacional	PCT/US2006/038939
	Fecha inicio fase nacional	06/05/2008
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	3961

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

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.

ALEX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 09 MAYO 2008
adpall