Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT-

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 06-78330

54. **TÍTULO** Pirazolopirimidinas Novedosas como Inhibidores de Quinasa Cíclina-Dependientes

51. **CLASIFICACIÓN INTERNACIONAL** C07D 487/04 A61K 31/495

71. **SOLICITANTE** Schering Corporation y Pharmacopeia Drug-Discovery Inc.

DOMICILIO 2000 Galloping Hill Road.-Kenilworth NJ. 07033-0530 y 3000 Eastpark Boulevard-Granbury -NJ 08512 E.U.A

74. **APODERADO** J. Ion Reisbeck

22. **BOGOTÁ, D. C.,** Agosto 9- 2006

(FORMA P-10)

OLARTERAISBECK

1

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-078330- -00000-0000
Fec: 2006-08-09 17:38:53 Dep: 2020 NUECREACIONES
Tra: 11 PATENTEYR
Eve: 370 FASENACIONALII
Act 411 PRESENTACION Folios: 1004

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

11/09/06

SOLICITUD DE:

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

[ ] Capítulo I. [X] Capítulo II.

(2) SOLICITANTE (71)

Nombre: SCHERING CORPORATION y PHARMACOPEIA DRUG DISCOVERY, INC.
Dirección: 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530, y 3000 Eastpark Boulevard, Cranbury, NJ 08512 E.U.A.
Nacionalidad o Domicilio: ESTADOUNIDENSE
Lugar de Constitución: Kenilworth y Cranbury E.U.A.
Teléfono: _____ Fax: _____
E-mail: _____

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

(3) REPRESENTANTE APODERADO

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Teléfono: 601-7700 Fax: 601-7799
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C.C. [x] NIT [ ]
C.E. [ ] Otro [ ]
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Número 79.376.996 Btá
TP 135.799

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

(5) PCT (86)

Solicitud Internacional No. PCT/US2005/003859 Fecha Febrero 8, 2005

Publicación Internacional No. WO 2005/077954 Fecha Agosto 25, 2005

(6) Título (54): PIRAZOLOPIRIMIDINAS NOVEDOSAS COMO INHIBIDORES DE QUINASA CICLINA-DEPENDIENTES

(7) Clasificación Internacional (51) C07D 487/04, A61K 31/495, A61P 35/00

(8) Prioridad SI [X] NO [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Febrero 11, 2004	10/776.988

(9) Comprobante de pago No. 06 – 58,177 **Fecha** Agosto 1, 2006

(10) **ANEXOS**

[x]	Comprobante de pago de la tasa de presentación de la solicitud.
[ ]	Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
[x]	Poderes, si fuere el caso. Copia Simple ver expediente No. 06-057.472, Adjunto sustitución
[ ]	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).
[x]	Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).
[x]	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

(12) Solicito la concesión de la patente,

NOMBRE: J. IAN RAISBECK FIRMA:

C.C. 79.376.996 Btá T.P. 135.799

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Nacionalidad: Estadounidense

5

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-078330- -00000-0000
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Act 411 PRESENTACION Folios: 1004

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 58,177
FECHA : AGOSTO 1 DE 2006

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBECK	CONSIGNACION	BANCO POPULAR	050-00110-6	52198857	01/08/2006	2,612,000.00

C O N C E P T O

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	463,000.00
		TOTAL : $	463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. S. D.

Ref.: NUEVA SOLICITUD DE PATENTE DE INVENCION TITULADA: "PIRAZOLOPIRIMIDINAS NOVEDOSAS COMO INHIBIDORES DE QUINASA CICLINA-DEPENDIENTES". SOLICITANTES: SCHERING CORPORATION Y PHARMACOPEIA DRUG DISCOVERY INC.

SUSTITUCIÓN DE PODER

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá D.C., identificado como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad de la referencia, respetuosamente me permito manifestar que **SUSTITUYO** el poder a mi conferido por la mencionada sociedad, en el doctor **J. IAN RAISBECK LLINAS,** mayor de edad, domiciliado en Bogotá D.C., identificado con la Cédula de Ciudadanía No. 79.376.996 de Bogotá y portador de la Tarjeta Profesional No. 135.799 del Consejo Superior de la Judicatura, para que sea él quien en adelante asuma el trámite de la presente acción.

El apoderado sustituto conserva las mismas facultades del principal.

Atentamente,

CARLOS R. OLARTE
C.C. No. 79.782.747 de Bogotá
T.P. 74.295 del C. S. de la J.

DILIGENCIA DE PRESENTACION PERSONAL Y
RECONOCIMIENTO DE CONTENIDO Y FIRMA.
NOTARIA EL ANTERIOR ESCRITO DIRIGIDO A:
27
FUE PRESENTADO PERSONALMENTE
ANTE EL SUSCRITO NOTARIO VEINTISIETE
DE SANTAFE DE BOGOTA D.C.
Con C.C.
Y MANIFESTO QUE EL CONTENIDO ES VERIDICO
Y QUE LA FIRMA QUE APARECE ES LA SUYA
El usuario firmó
HUELLA
21 JUL. 2000
MARIA EUGENIA ROJAS DE URUETA
NOTARIA VEINTISIETE
REPUBLICA DE COLOMBIA

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

SCHERING CORPORATION

APOSTILLA

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

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

CERTIFICADO

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

PODER DE REPRESENTACIÓN

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

CERTIFICADO NOTARIAL

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

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

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

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

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

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

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

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

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

CERTIFIED

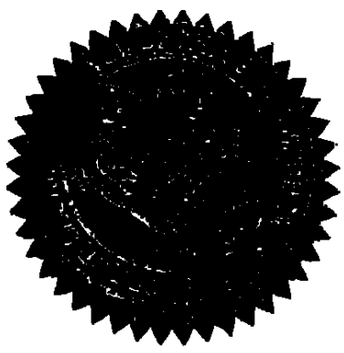
5. AT TRENTON, NEW JERSEY

6. THE 29TH DAY OF AUGUST 2003

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

8. NO. A180345

9. SEAL/STAMP:



10. SIGNATURE

OLARTERAISBECK
OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

WORLD TRADE CENTER – TORRE C
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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. Hazer, 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

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Notarial Certification

On this date, August 7, 2003

The undersigned Notary Public certifies:

1. That Edward H. Mazer

of legal age and domiciled in 189 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.S.A.. is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

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

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

Power of Attorney, dated November 4, 2002.

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

mayor de edad y domiciliado

suscribió el documento que antecede.

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

de

4. Que

con sede principal ubicada en

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

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

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

NOTARY PUBLIC (Signature): Marguerite LaCorte

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

TRADUCCION OFICIAL No. 04-368

Efectuada el día 2 de noviembre de 2004, de un documento escrito en Inglés, al cual para su identificación se le estampa el sello de María del Pilar Iglesias, Traductora e Intérprete Oficial por Resolución No. 819 del 15 de abril de 1971 expedida por el Ministerio de Justicia de Colombia.

Traducción Oficial de las autenticaciones notariales y subsiguientes correspondientes a un Poder otorgado por **Pharmacopeia Drug Discovery, Inc** a **Carlos R. Olarte**, y/o **Ana María Frieri**, documento este que fue firmado en Granbury, New Jersey, Estados Unidos de América el 1 de octubre de 2004, viene en español y se explica por sí solo.

La firma y cargo de Brian M. Posner, como Vicepresidente Financiero de la compañía arriba citada fueron debidamente certificados por el Notario Público Melanie J. Rice el 1 de octubre de 2004, quien estampó su firma y sello en la Certificación Notarial correspondiente.

APOSTILLA

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

1. País: Estados Unidos de América

   El presente documento público

2. Fue firmado por: Melanie J. Rice

María del Pilar Iglesias
TRADUCTORA E
INTERPRETE OFICIAL

3. Que actuó en su calidad de Notario Público de Nueva Jersey

4. Lleva el sello del mencionado Notario Público.

Se certificó:

5. En Trenton, Nueva Jersey

6. El 25 de octubre de 2004

7. Por parte de John E. McCormac, CPA, Tesorero

8. Bajo el Número **A211395**

9. Aparece Sello del Estado de Nueva Jersey

10. Firmado por John E. McCormac

Es traducción fiel y completa efectuada por:

María del Pilar Iglesias
C.C.41.339.183 de Bogotá

María del Pilar Iglesias
C. C. 41.339.183 de Bogotá
Intérprete Oficial según Resolución No. 819 de
Abril de 1971 del Ministerio de Justicia

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 August 2005 (25.08.2005)

PCT

(10) International Publication Number
WO 2005/077954 A2

(51) International Patent Classification[7]: C07D 487/04, A61K 31/495, A61P 35/00

(21) International Application Number: PCT/US2005/003859

(22) International Filing Date: 8 February 2005 (08.02.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/776,988 11 February 2004 (11.02.2004) US

(71) Applicants *(for all designated States except US)*: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, New Jersey 07033 (US). PHARMACOPEIA DRUG DISCOVERY, INC. [US/US]; 3000 Eastpark Boulevard, Cranbury, New Jersey 08512 (US).

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(74) Agent: KALYANARAMAN, Palaiyur S.; SCHERING 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, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, 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, 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)) for all designations*

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 2005/077954 A2

NOVEL PYRAZ LOPYRIMIDINES AS CYCLIN DEPENDENT KINASE INHIBIT RS

Reference to Related Applications

This application is a Continuation-In-Part of U.S. Patent Application, Serial No. 10/654,546 filed September 3, 2003, which claims priority to U.S. provisional patent applications, Serial Nos. 60/408,027 filed September 4, 2002 and 60/421,959 filed October 29, 2002.

Filed of the Invention

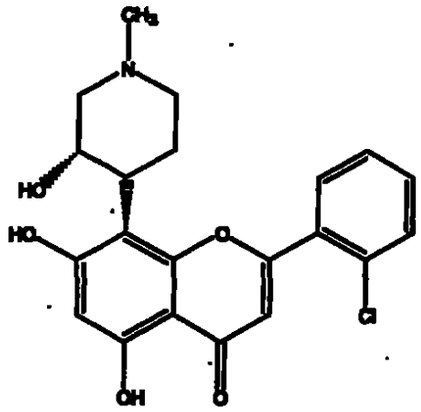
The present invention relates to pyrazolo[1,5-a]pyrimidine compounds useful as protein kinase inhibitors (such as for example, the inhibitors of the cyclin-dependent kinases, mitogen-activated protein kinase (MAPK/ERK), glycogen synthase kinase 3(GSK3beta) and the like), pharmaceutical compositions containing 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 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

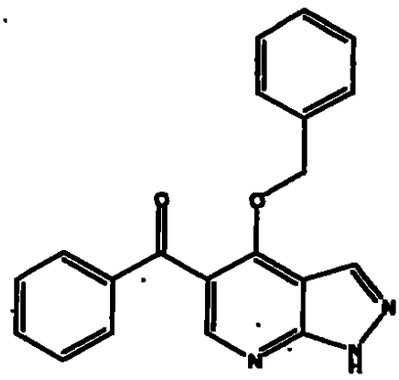
important solid tumors. CDK2 and CDK4 are of particular interest because their activities are frequently misregulated in a wide variety of human cancers. CDK2 activity is required for progression through G1 to the S phase of the cell cycle, and CDK2 is one of the key components of the G1 checkpoint. 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.

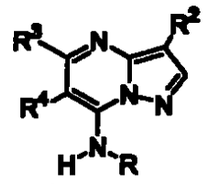
Pyrazolopyrimidines are known. For Example, WO92/18504, WO02/50079, WO95/35298, WO02/40485, EP94304104.6, EP0628559 (equivalent to US Patents 5,602,136, 5,602,137 and 5,571,813), U.S. 6,383,790, *Chem. Pharm. Bull.*, (1999) 47 928, *J. Med. Chem.*, (1977) 20, 296, *J. Med. Chem.*, (1976) 19 517 and *Chem. 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

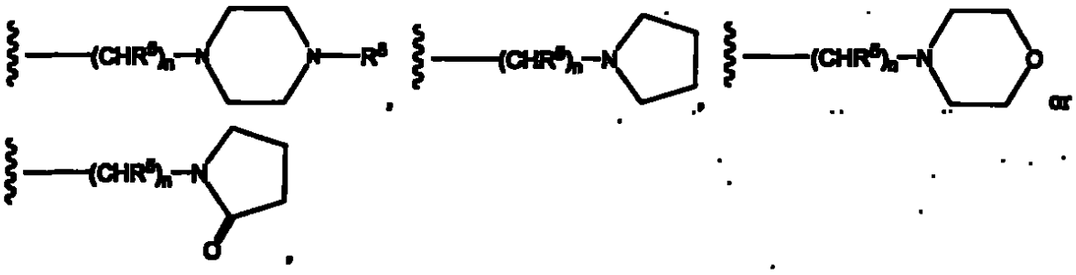
In its many embodiments, the present invention provides a novel class of pyrazolo[1,5-a]pyrimidine compounds as inhibitors of cyclin dependent kinases, methods of preparing such compounds, pharmaceutical compositions comprising one or more such compounds, methods of preparing pharmaceutical formulations 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:



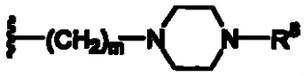
Formula III

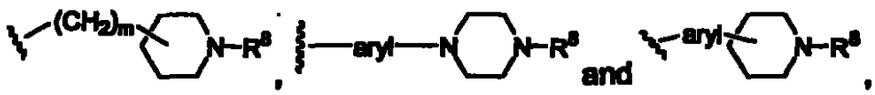
wherein:

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,  ,  ,  , or

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

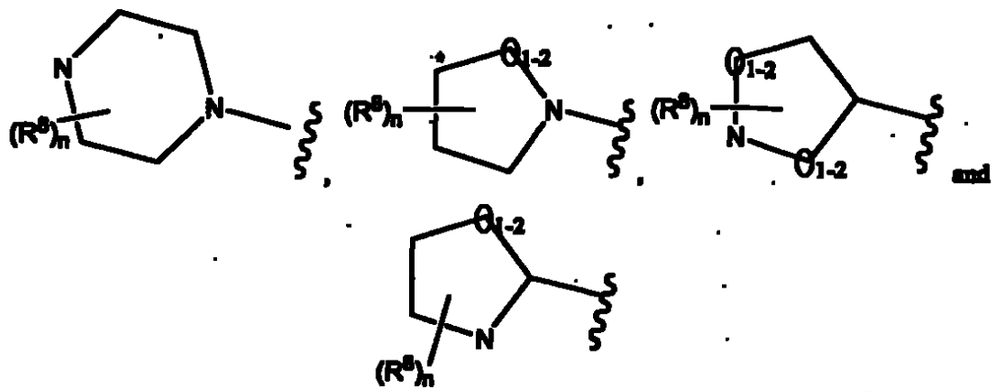
selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, heterocyclylalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^{10}$, $-C(R^4R^5)_p-R^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^{10}$, $-SO_3H$, $-SR^{10}$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$,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

R^2 is selected from the group consisting of 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,



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, $-OCF_3$, $-(CR^4R^5)_pOR^5$, $-OR^5$, $-NR^5R^6$, $-(CR^4R^5)_pNR^5R^6$, $-C(O_2)R^6$, $-C(O)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ 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 or cycloalkyl;

R^6 is selected from the group consisting of H, 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, $-OR^5$, $-NR^5R^{10}$, $-C(R^4R^5)_p-R^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^{10}$, $-SO_3H$, $-SR^{10}$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^{10}$;

R^{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, $-OR^5$, $-NR^4R^5$, $-C(R^4R^5)_p-R^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^8$, $-C(O)NR^4R^5$, $-C(O)R^5$, $-SO_3H$, $-SR^5$, $-S(O_2)R^7$, $-S(O_2)NR^4R^5$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ 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^8 in the moiety $-NR^5R^8$, 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, $-CN$, $-NR^5R^{10}$, $-C(O_2)R^6$, $-C(O)NR^5R^{10}$, $-OR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ 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

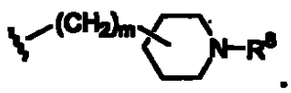
that when R is arylalkyl, then any heteroaryl substituent on the aryl of said arylalkyl contains at least three heteroatoms.

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

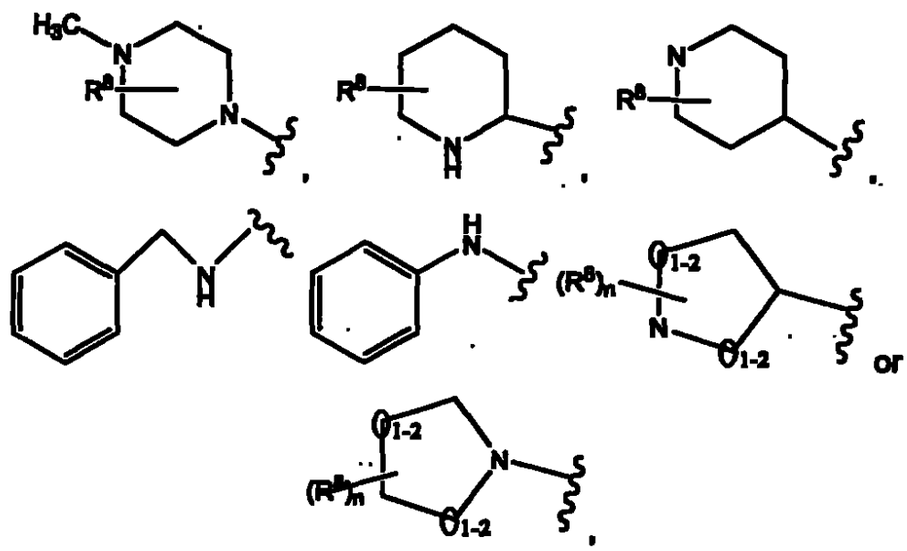
In one embodiment, the present invention discloses pyrazolo[1,5-a]pyrimidine compounds which are represented by structural Formula III, or a pharmaceutically acceptable salt or solvate thereof, wherein the various moieties are as described above.

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 $-OR^5$ moiety.

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

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

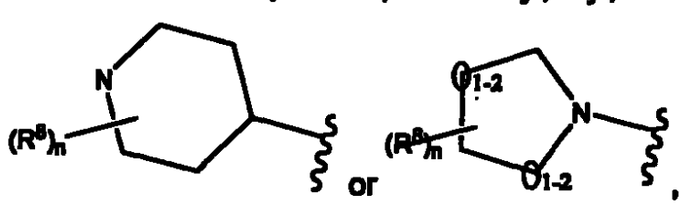
In another embodiment, n is 1 to 2.

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 th 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.

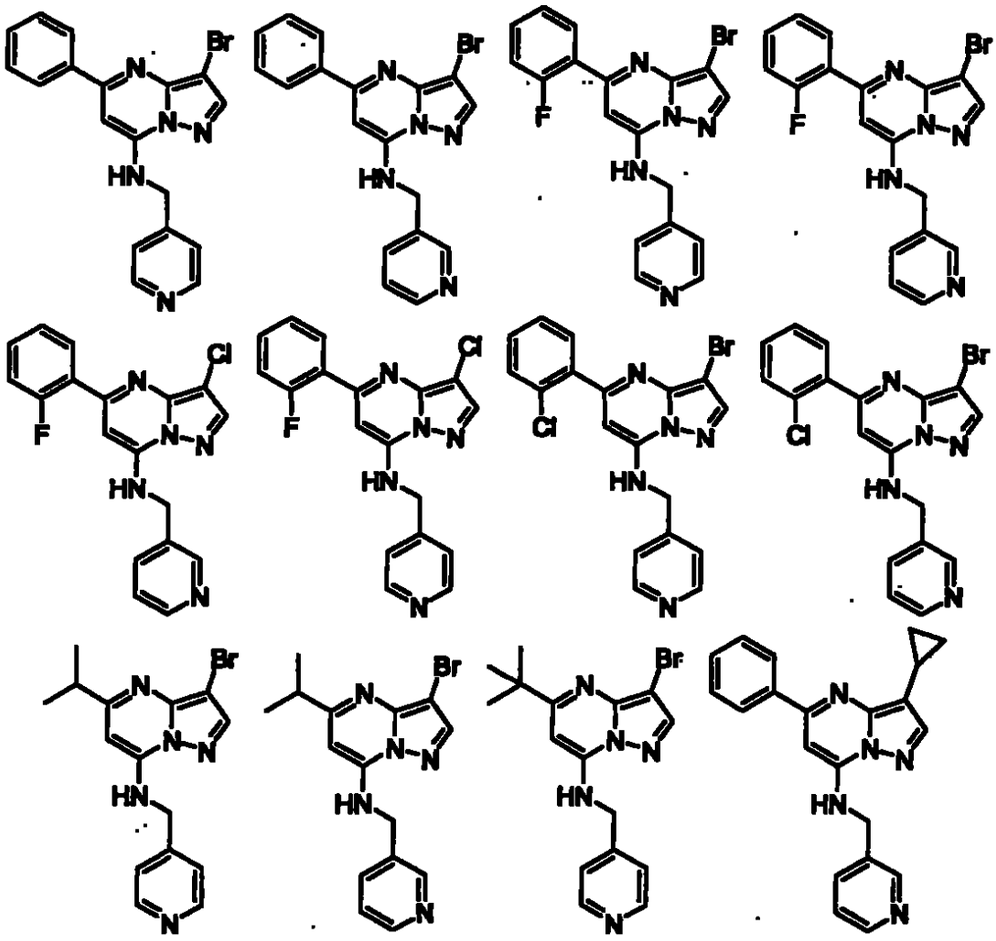
In an additional embodiment, R^6 is alkyl or hydroxyalkyl.

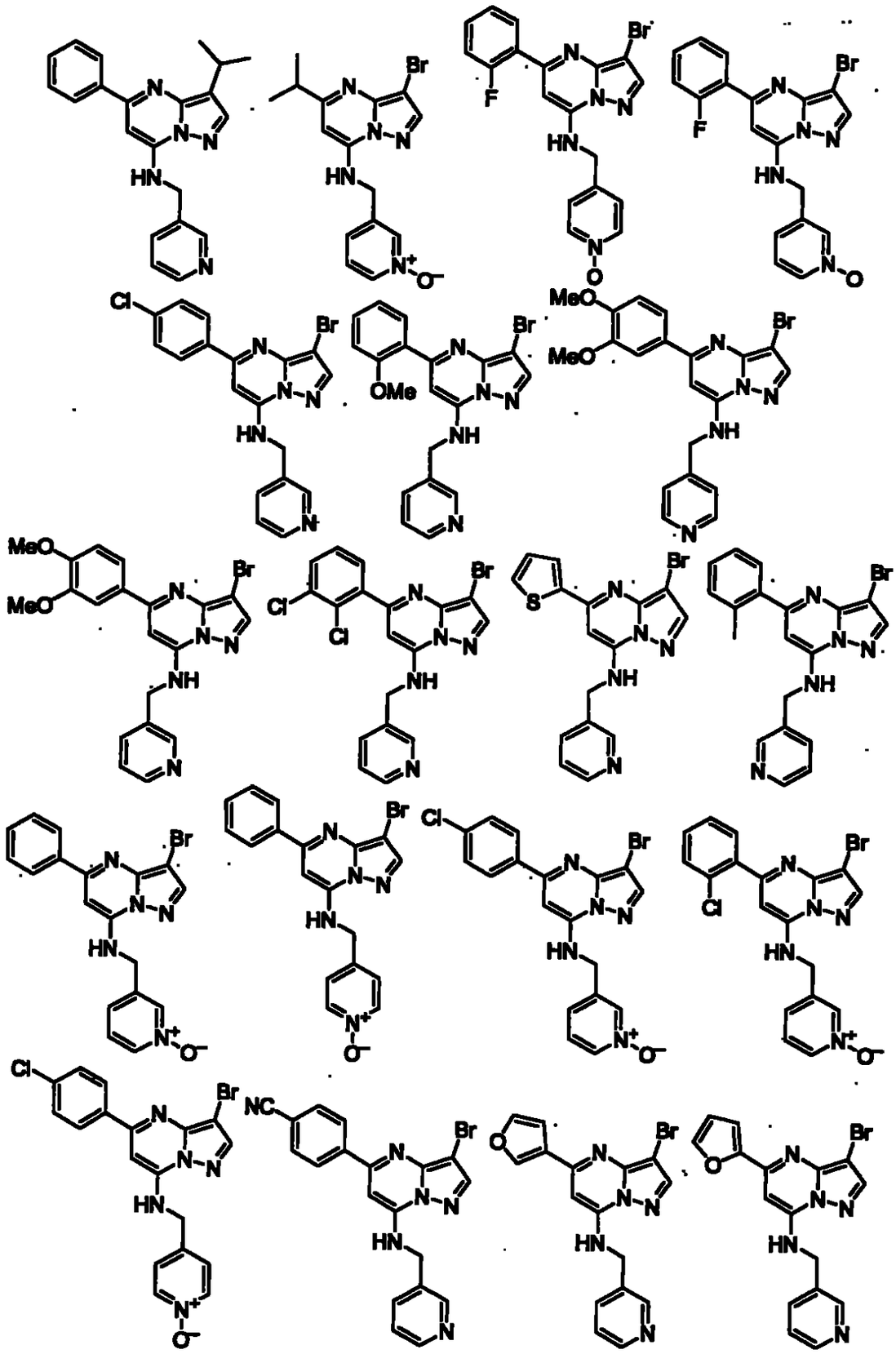
In an additional embodiment, n is 1.

In an additional embodiment, p is 1 or 2.

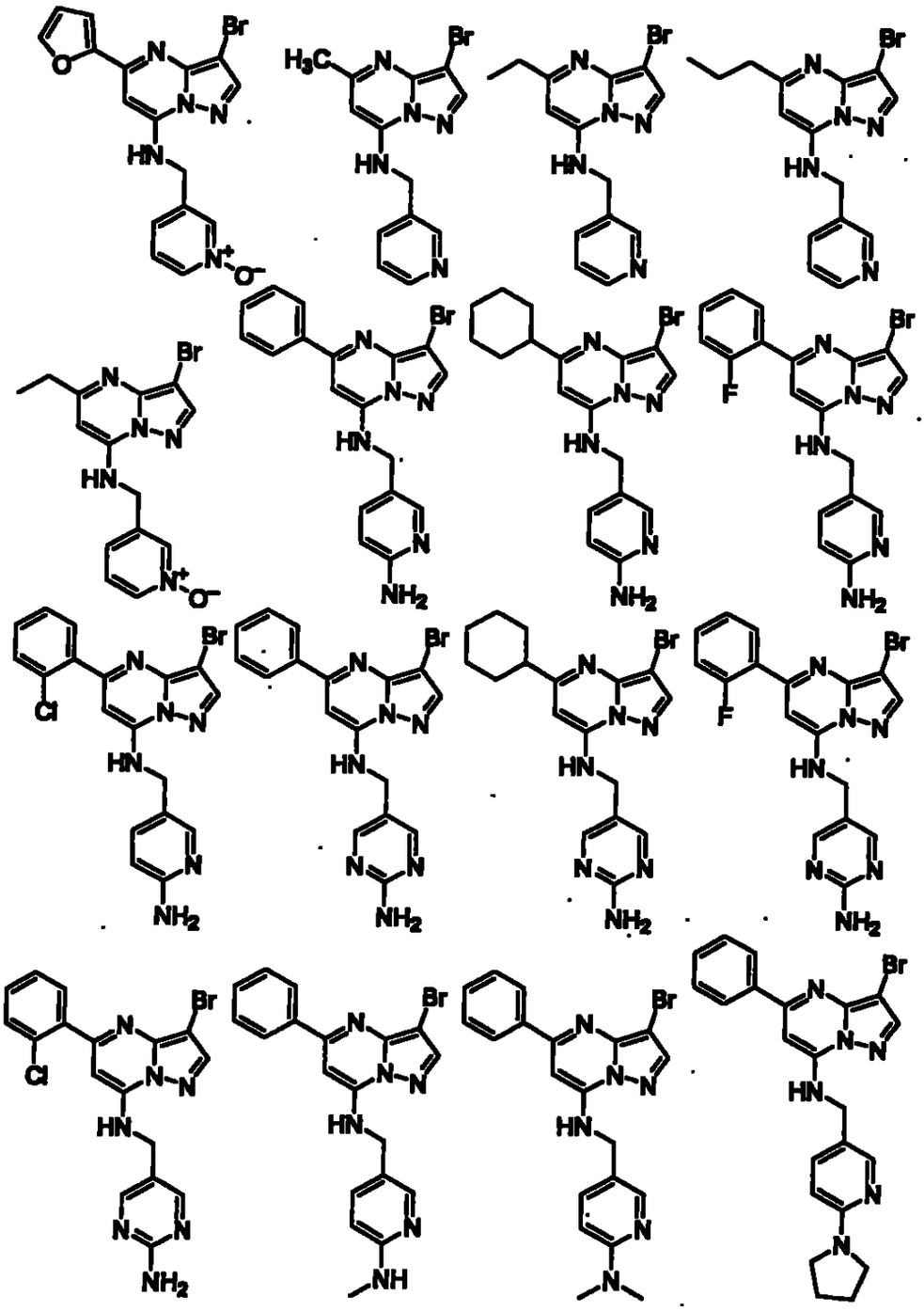
Another embodiment discloses the inventive compounds shown in Table 1, which exhibited CDK2 inhibitory activity of about 0.0001μM to > about 5 μM. The assay methods are described later (from page 333 onwards).

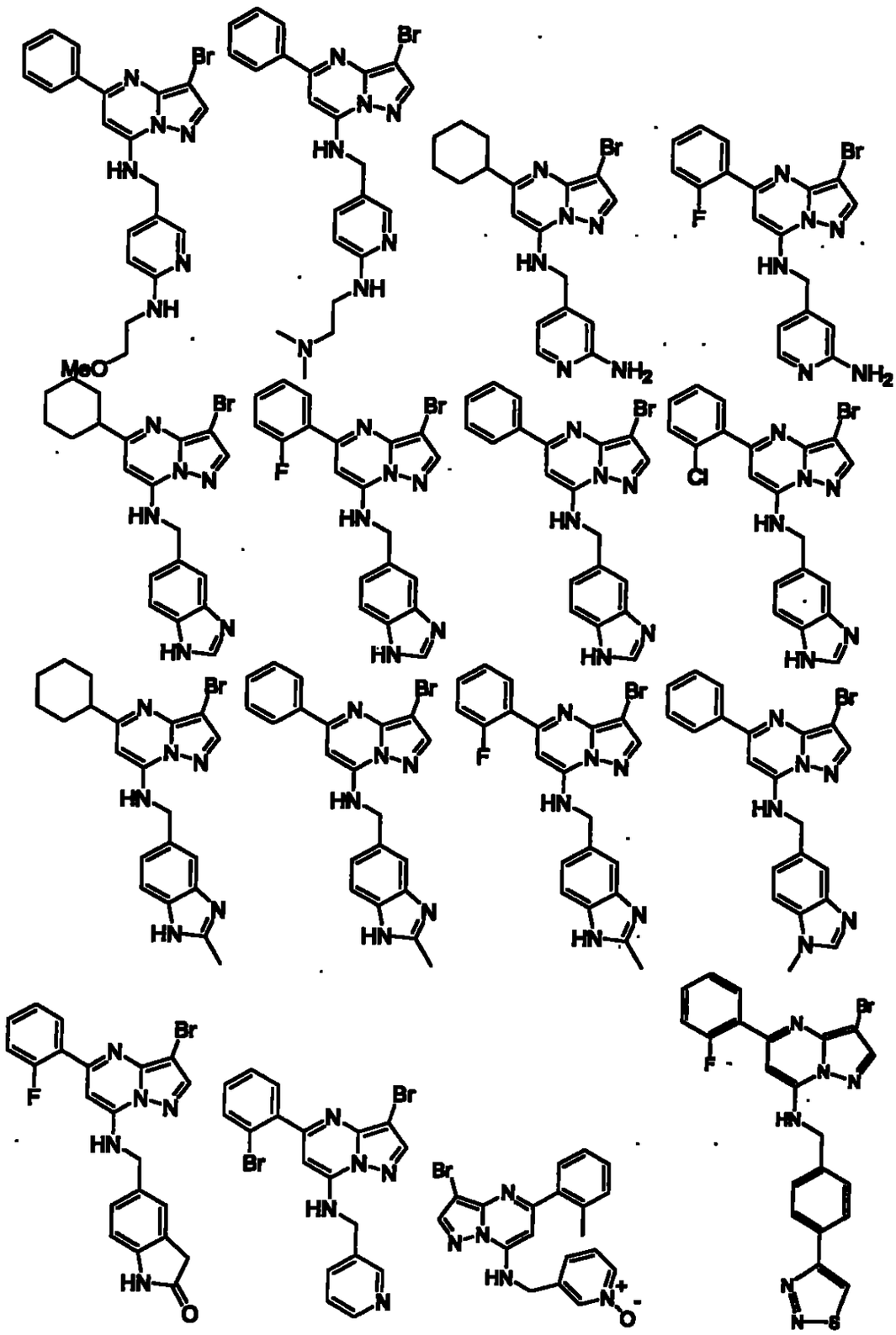
Table 1

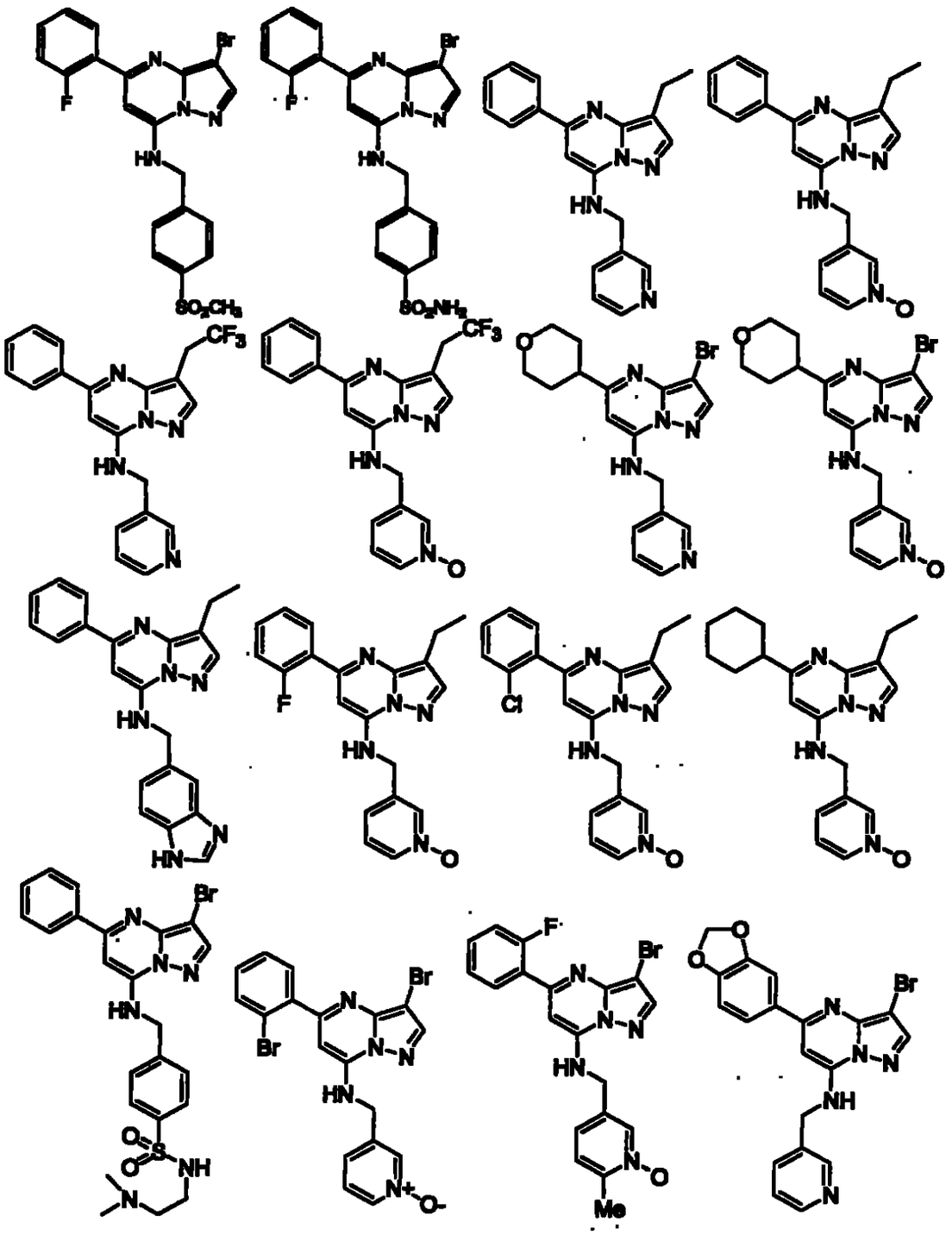


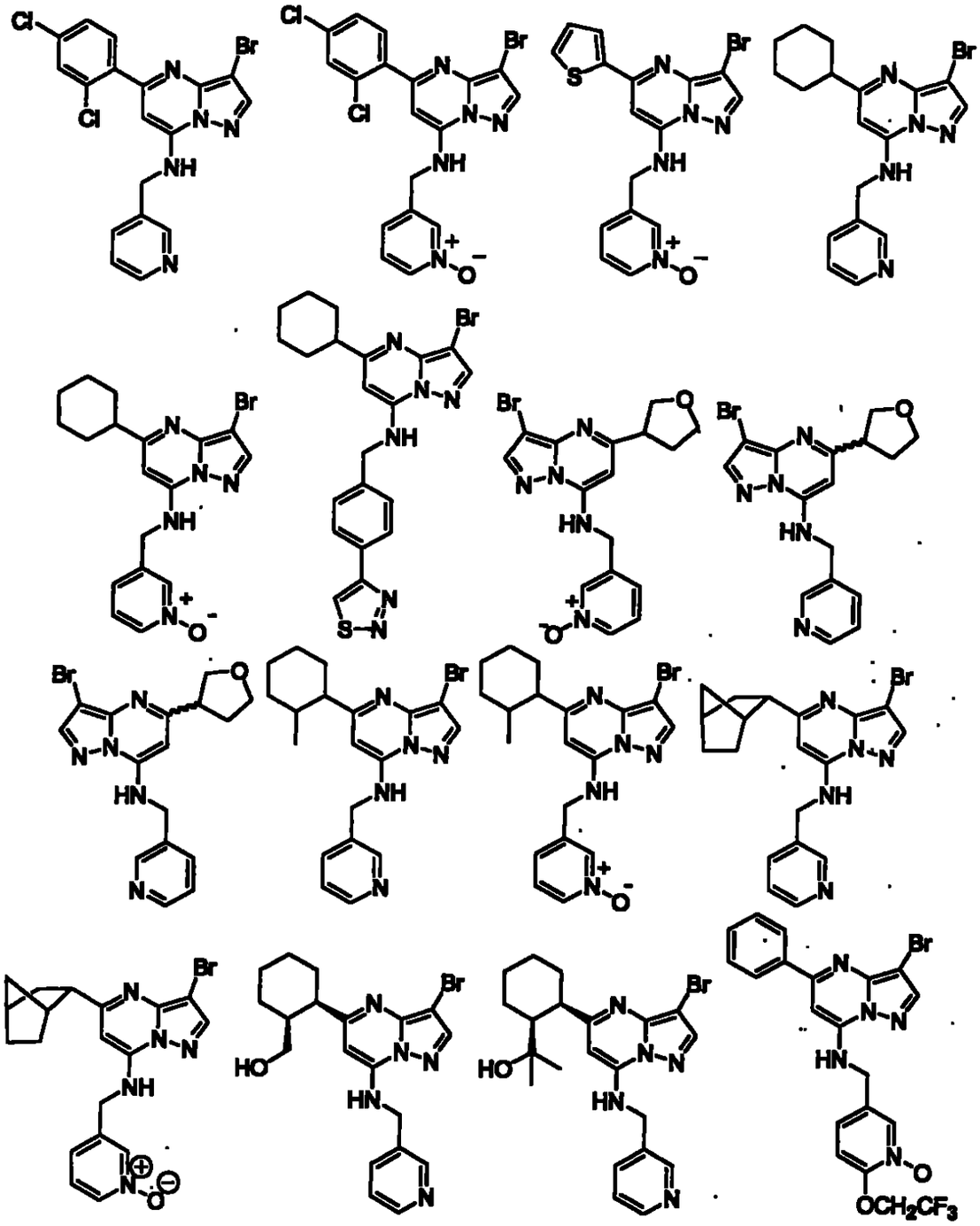


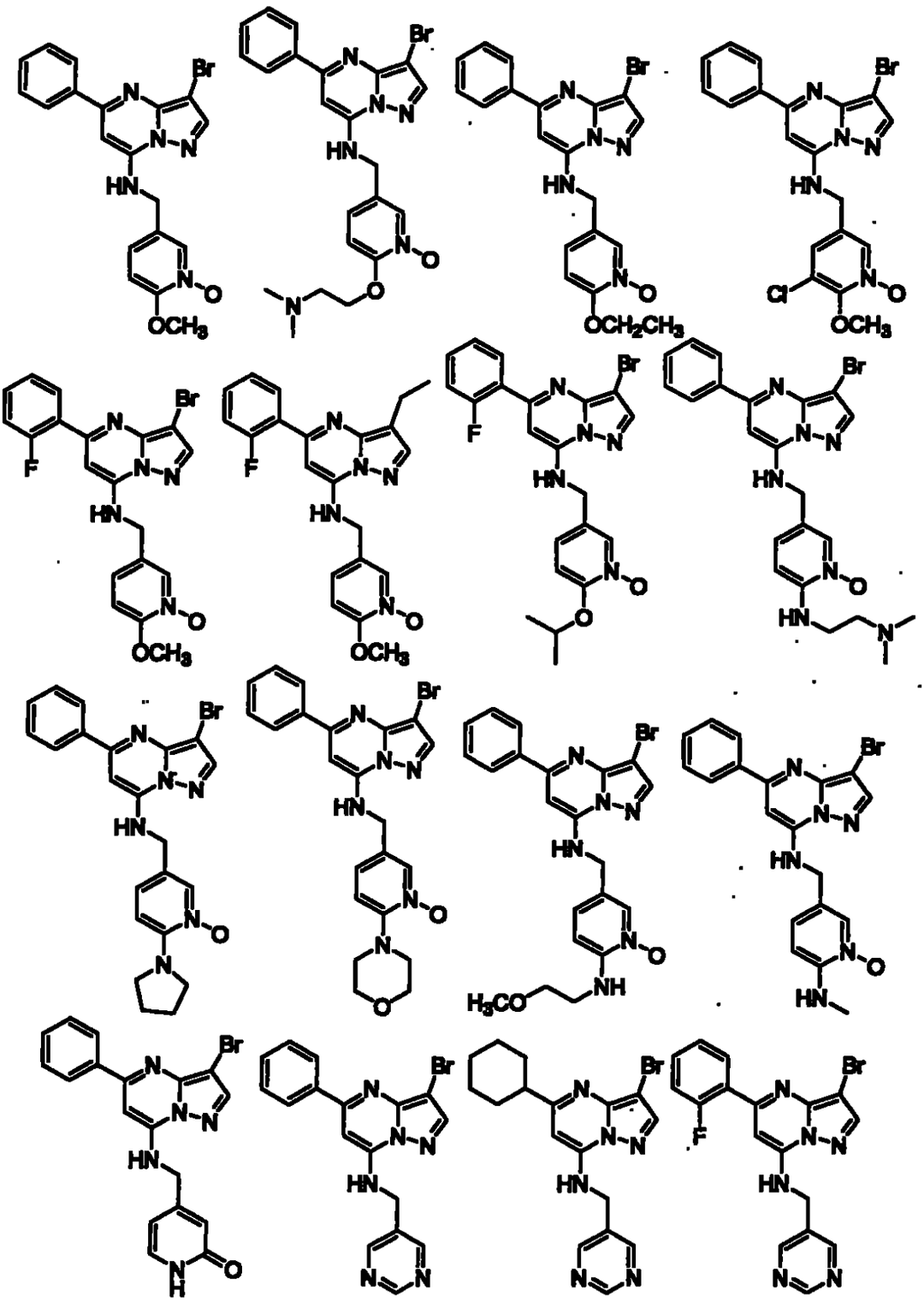
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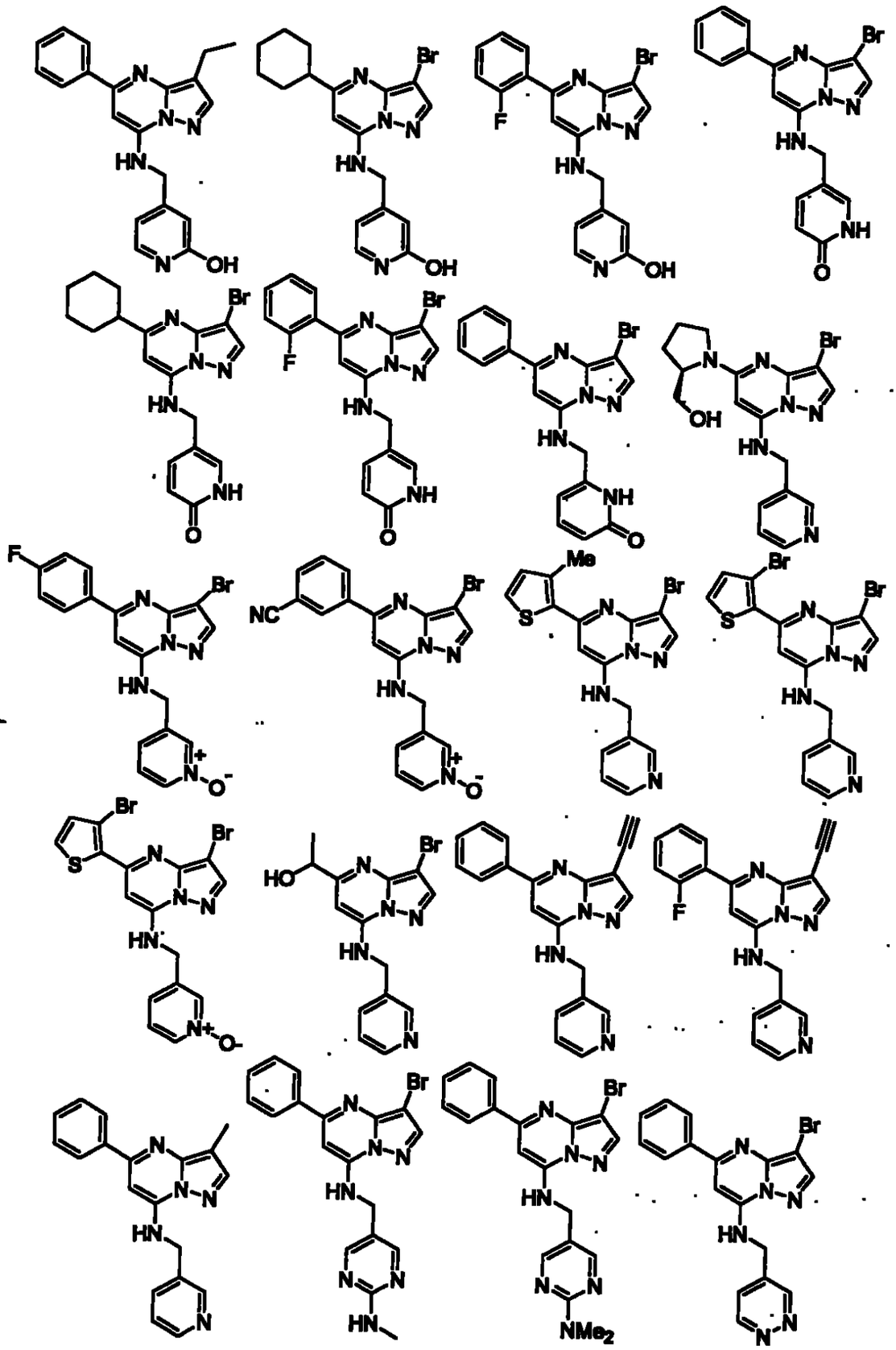


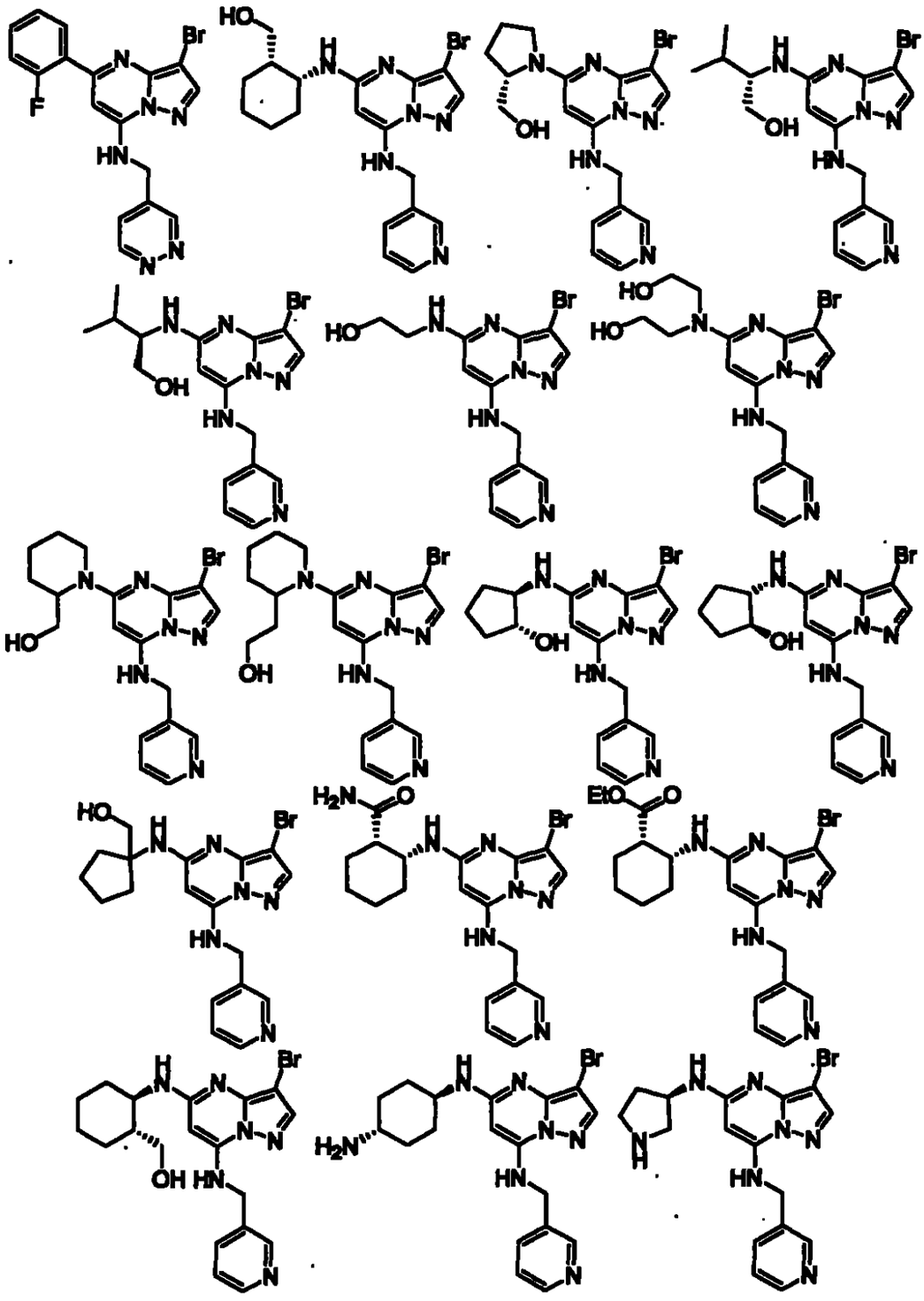




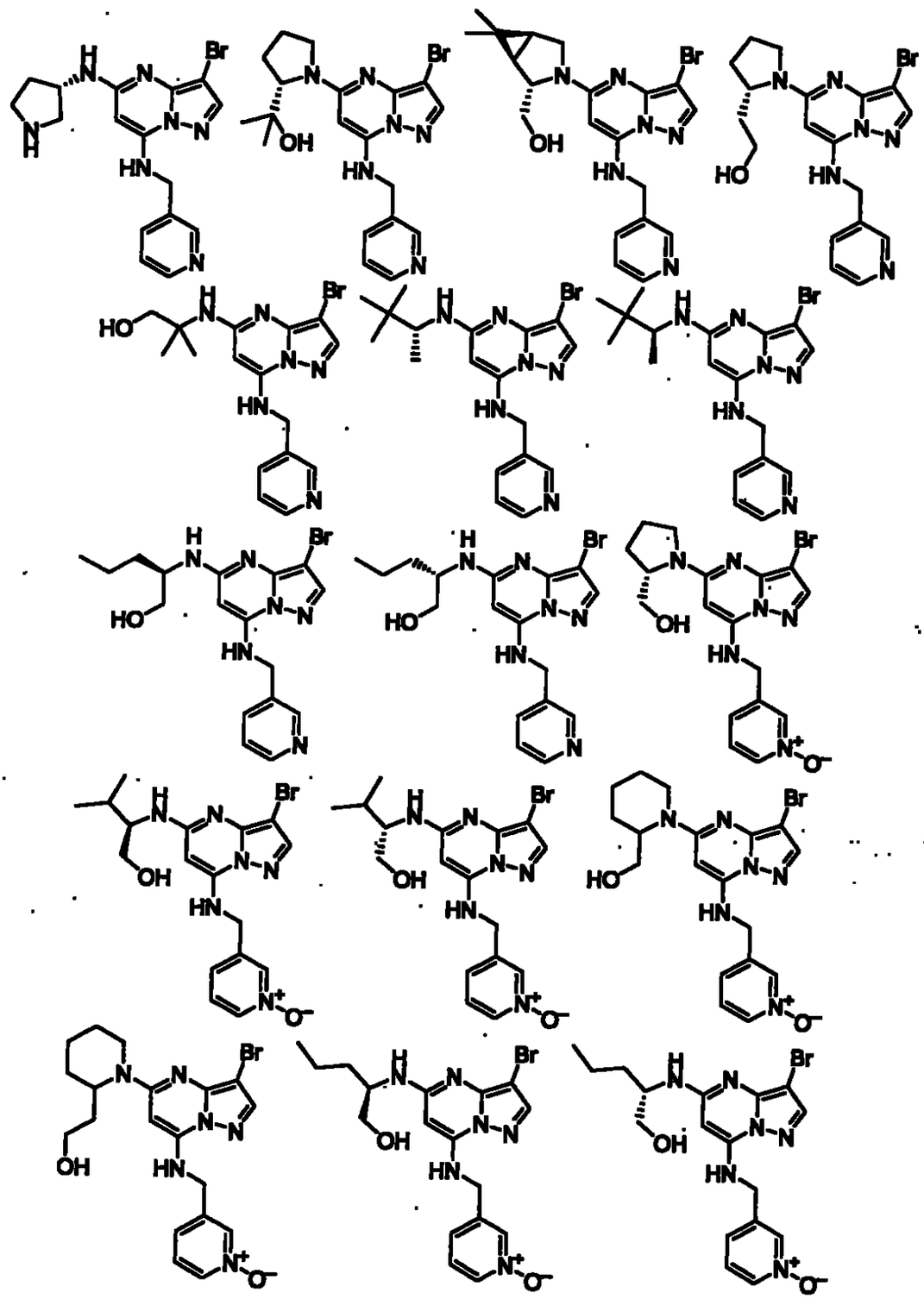




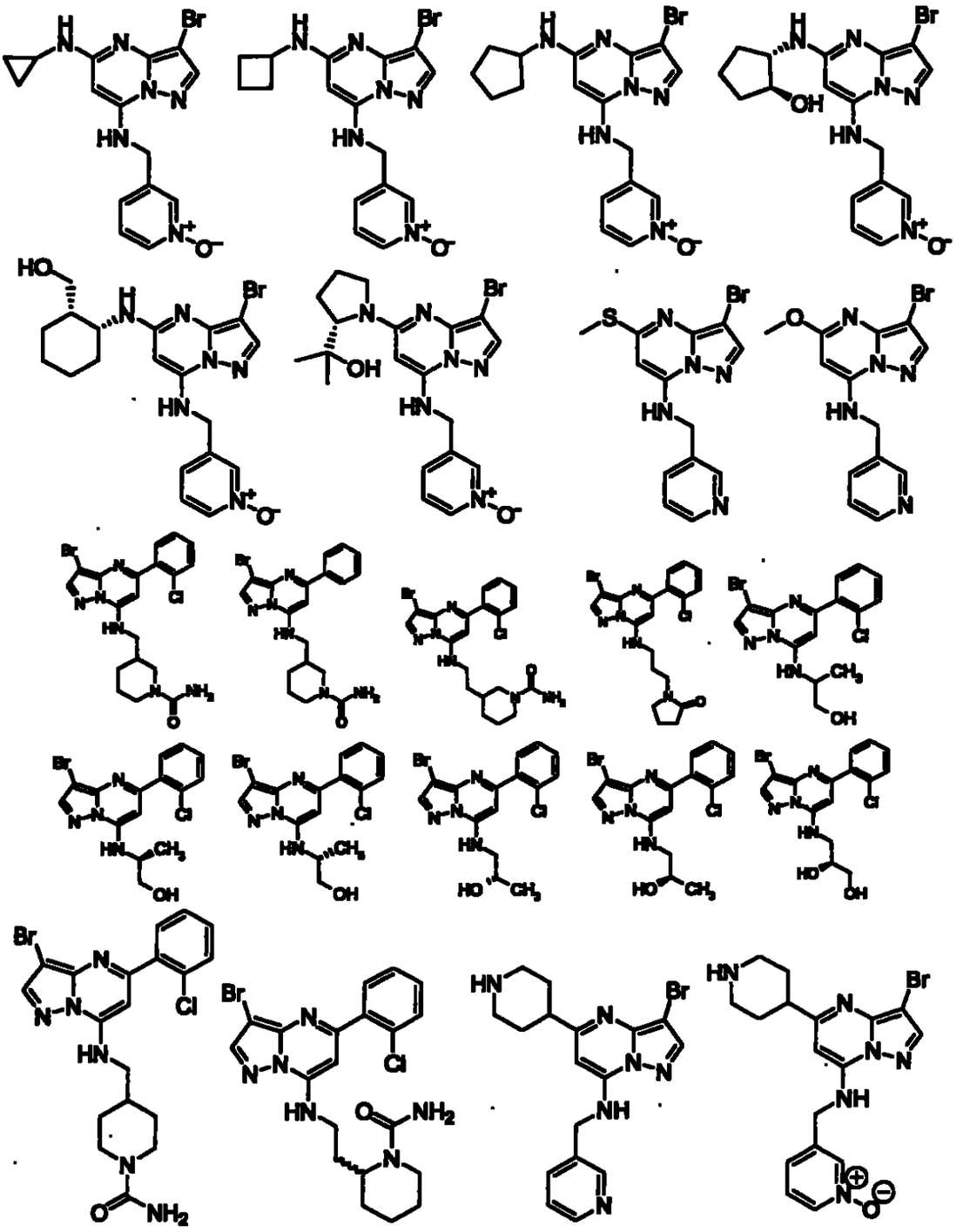


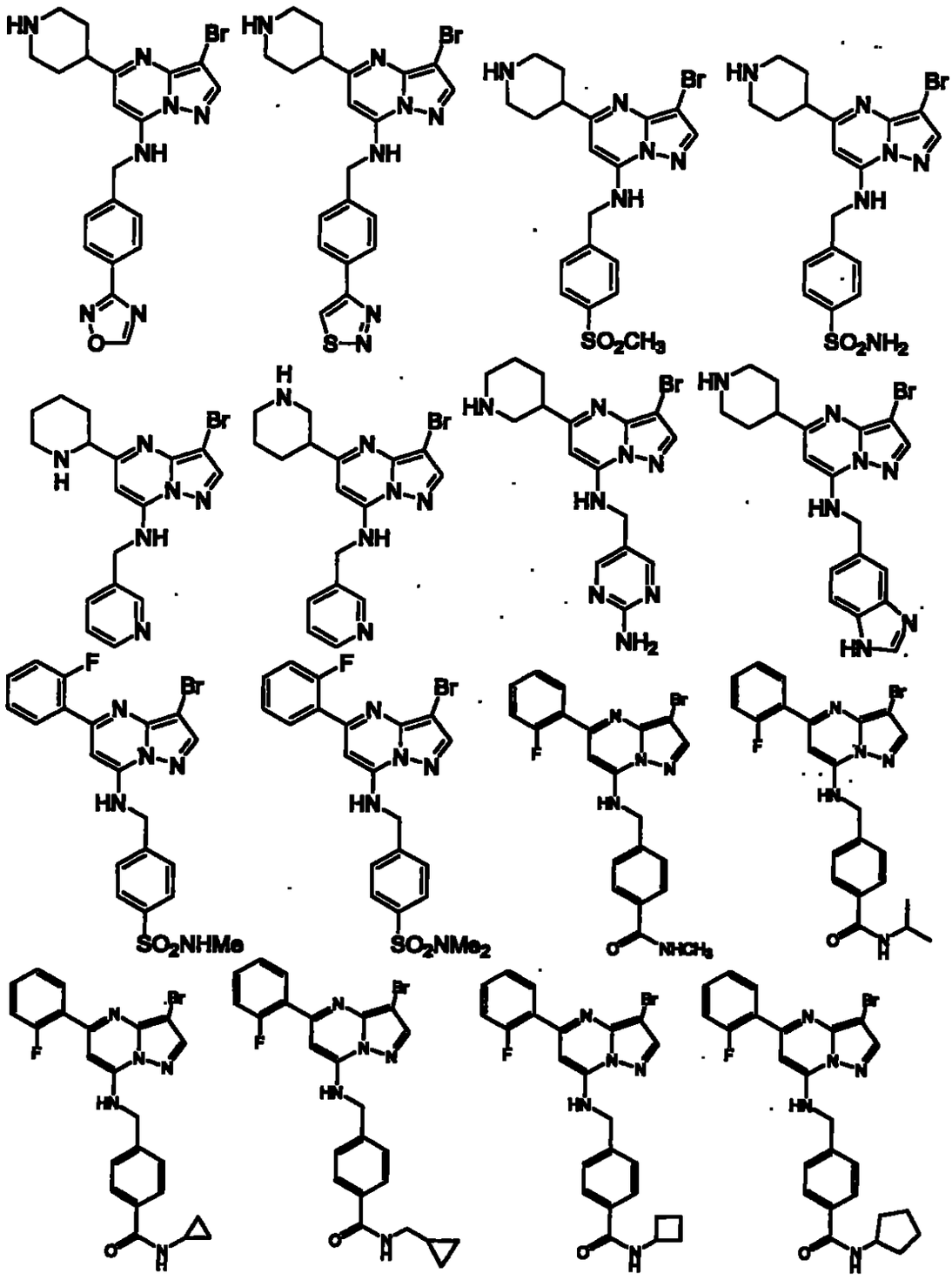


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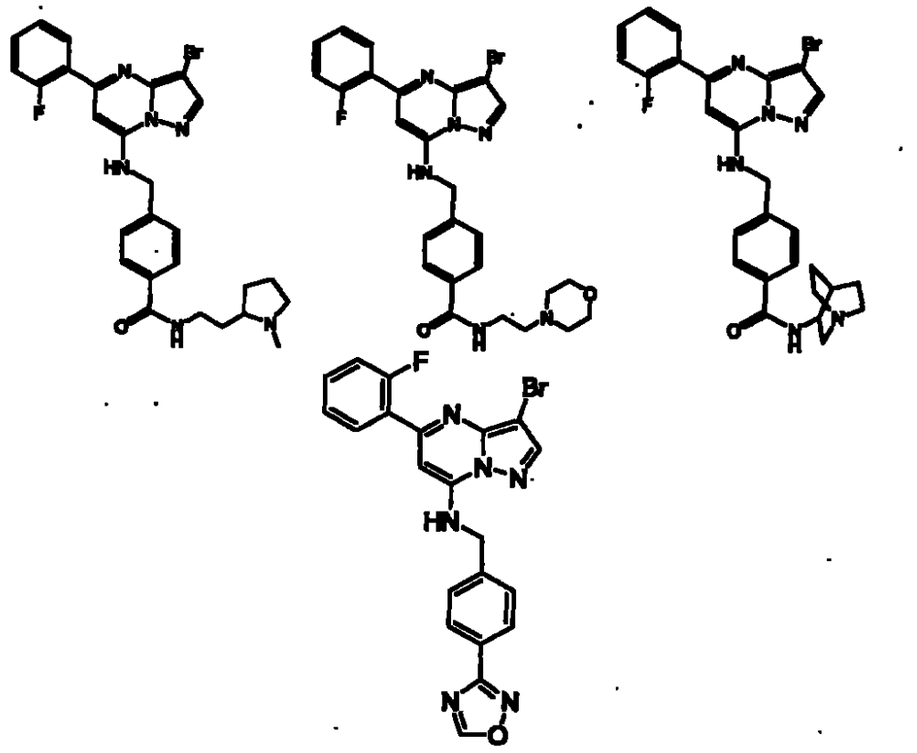


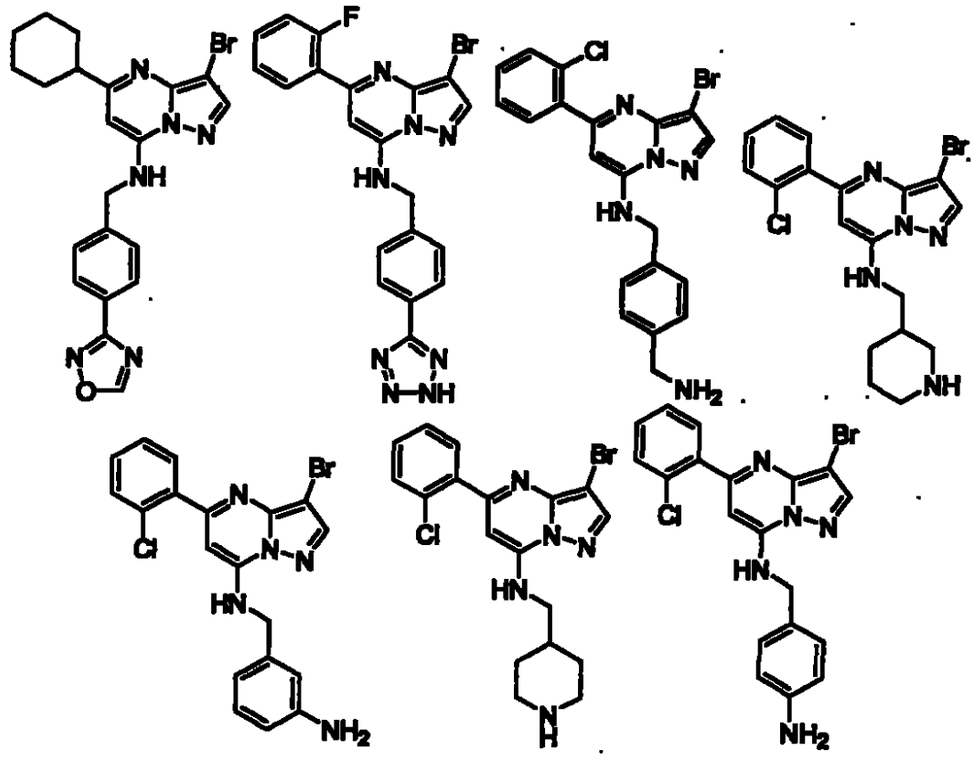
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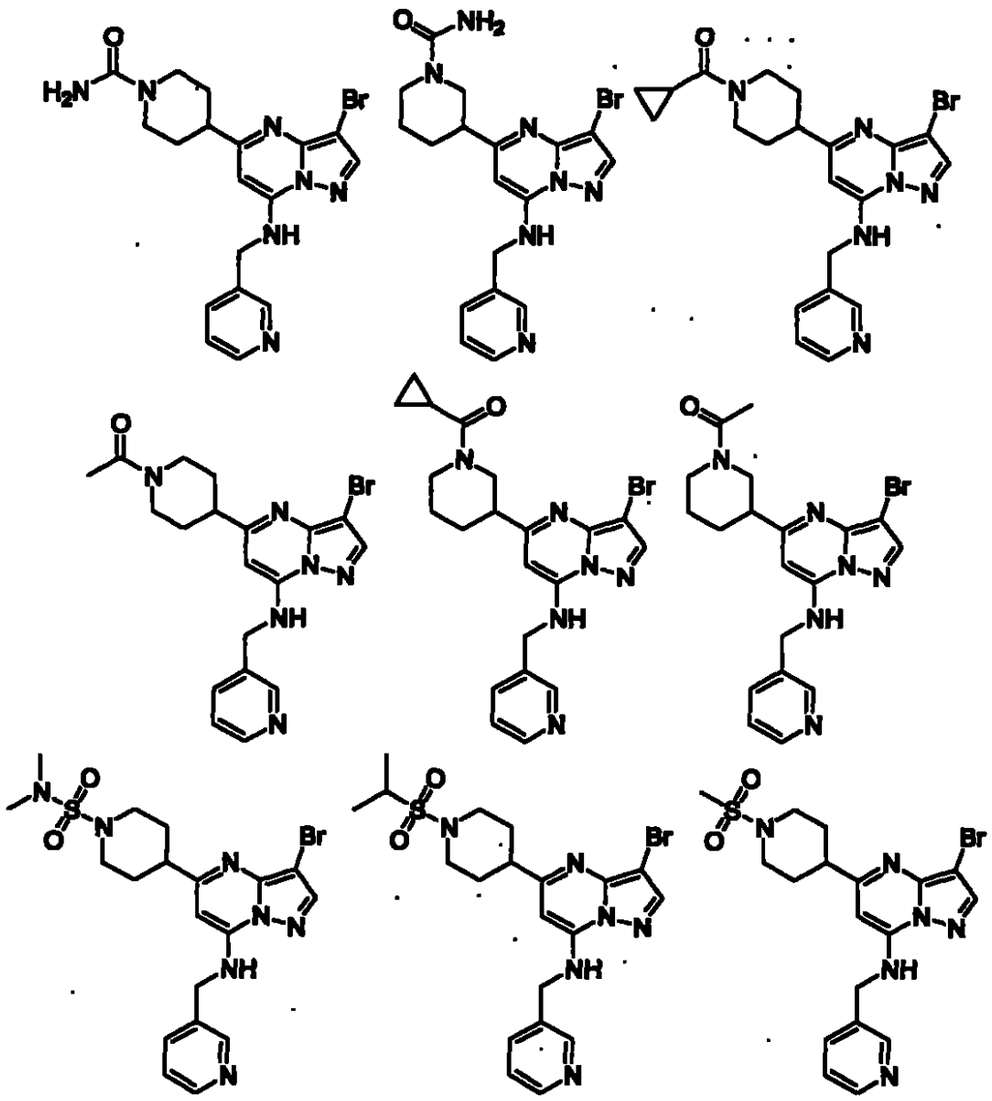


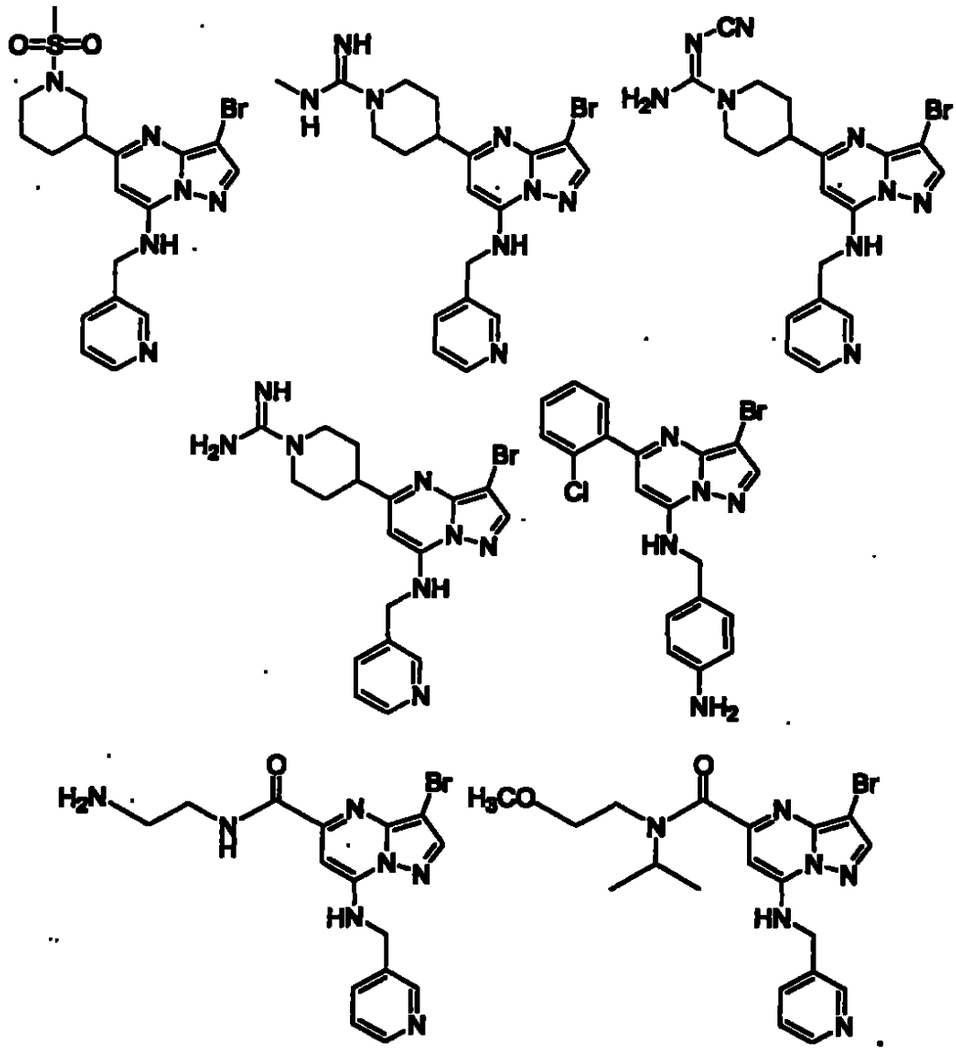
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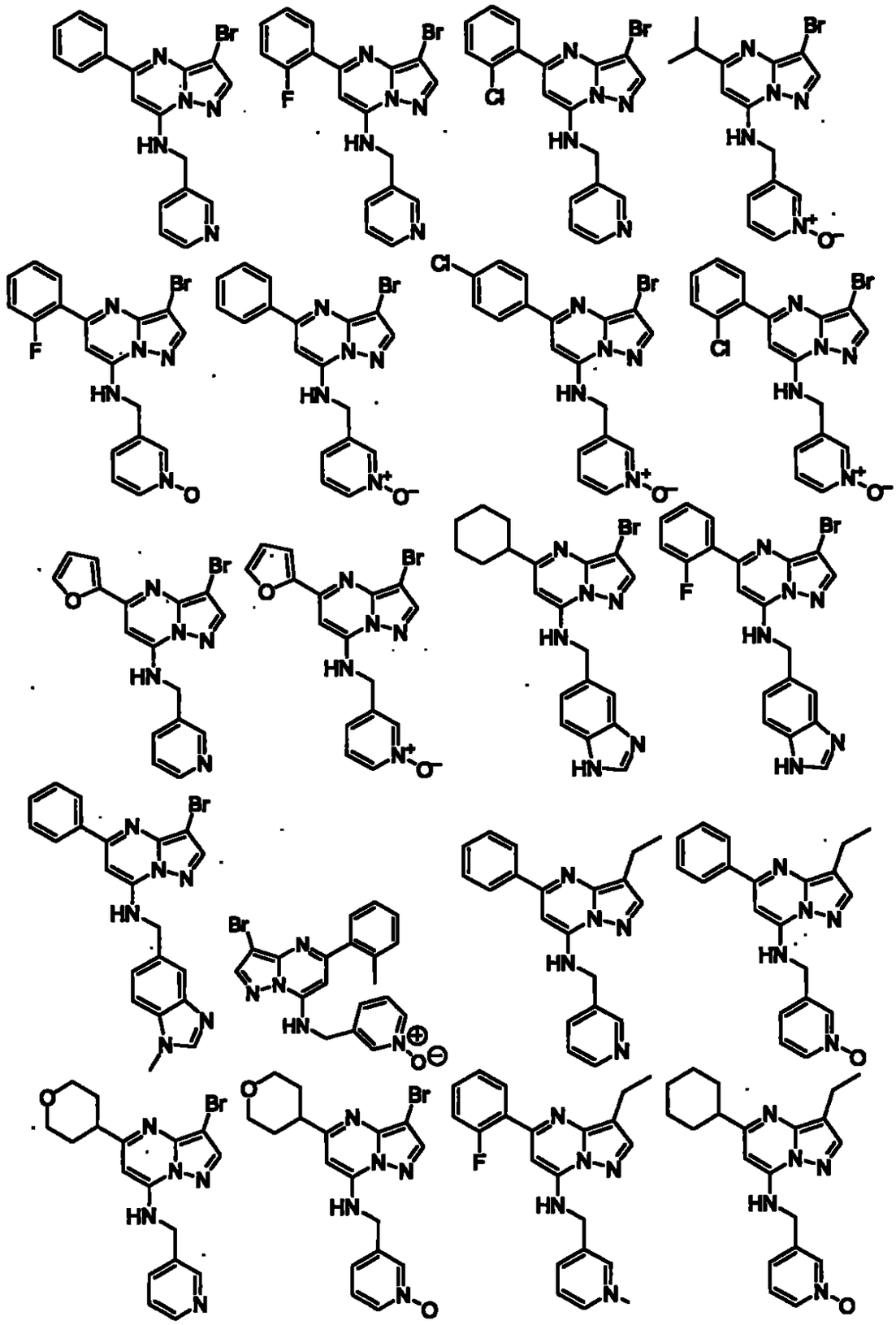


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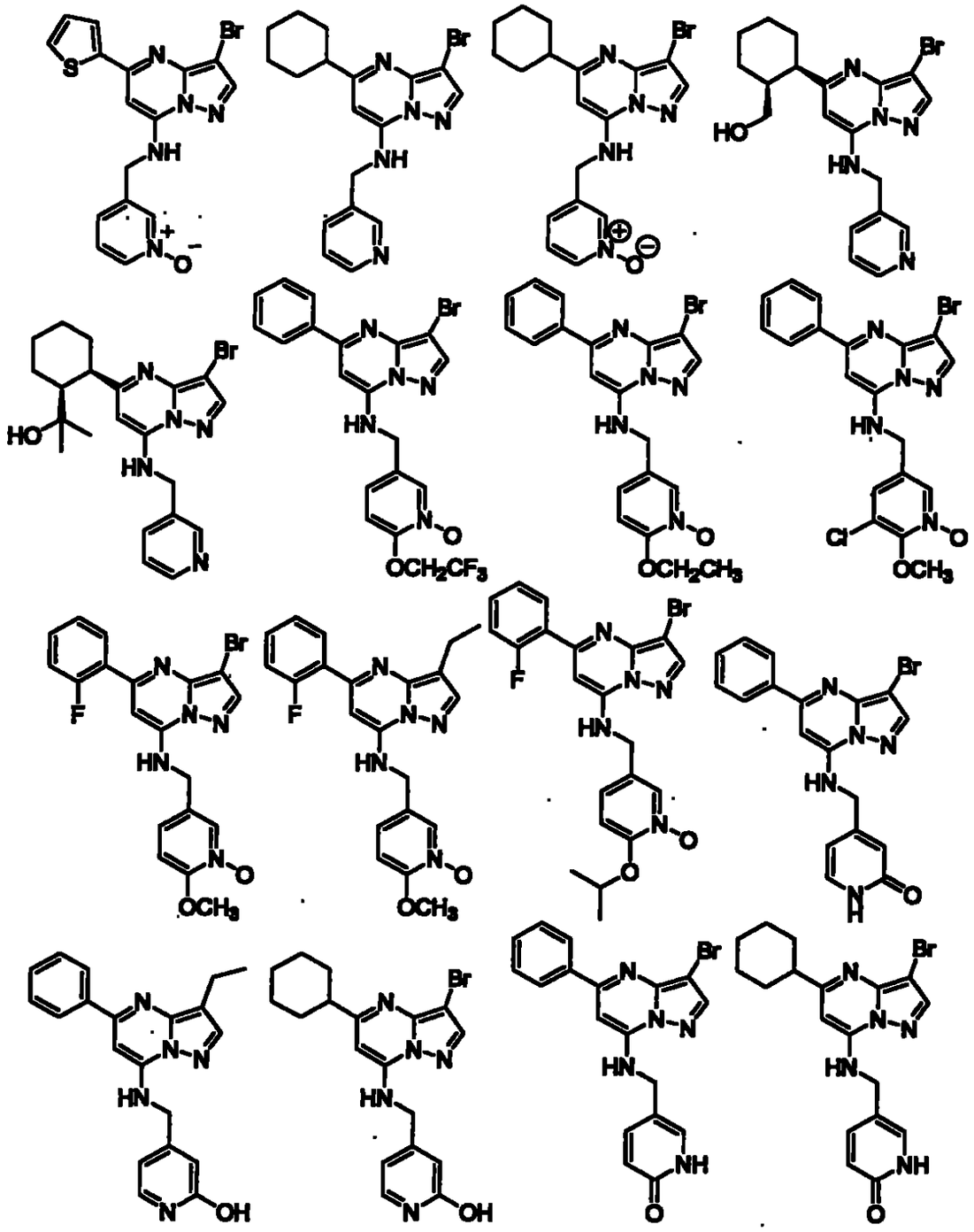


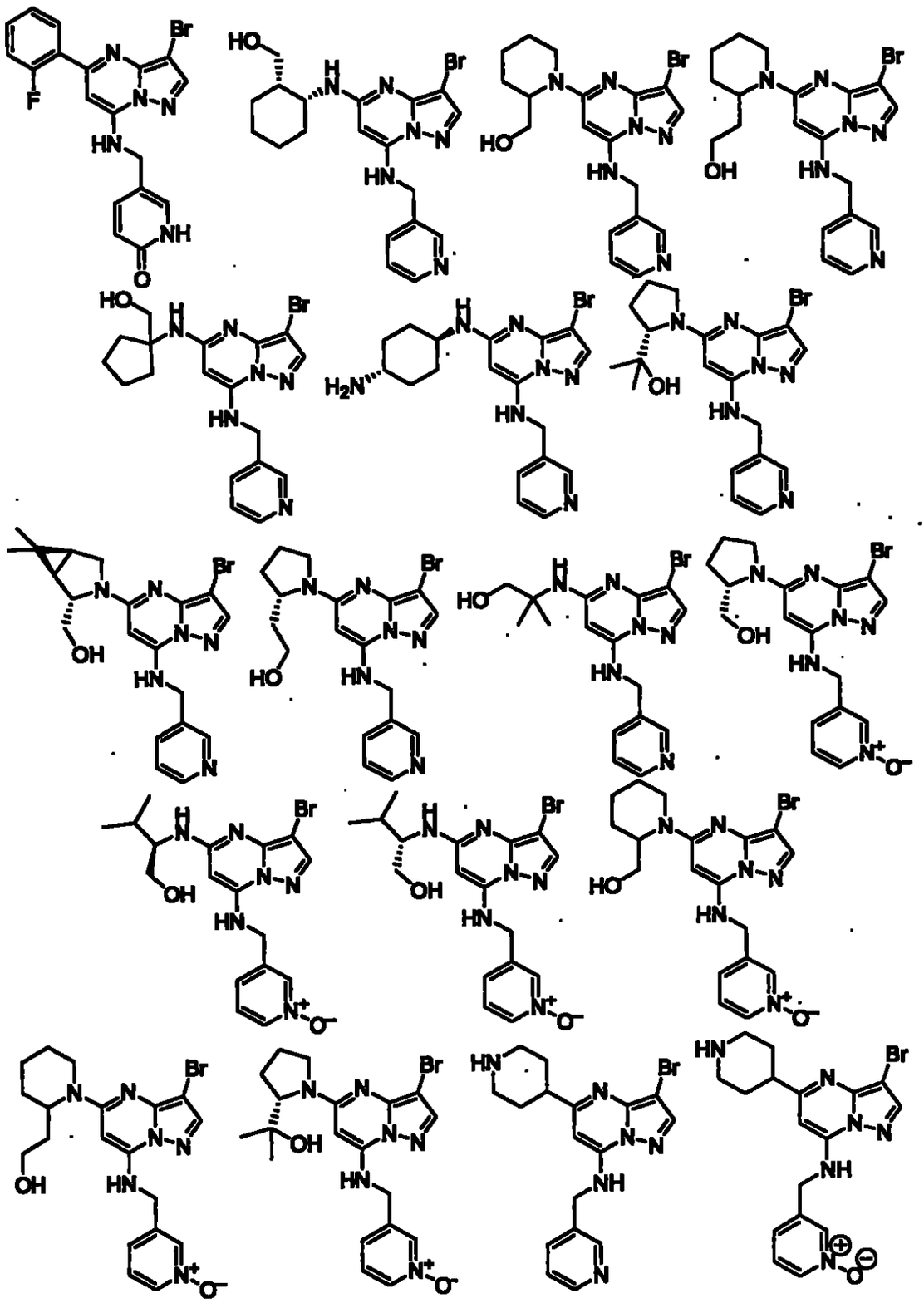


Another embodiment of the invention discloses the following compounds, which exhibited CDK2 inhibitory activity of about 0.0001μM to about 0.5μM:

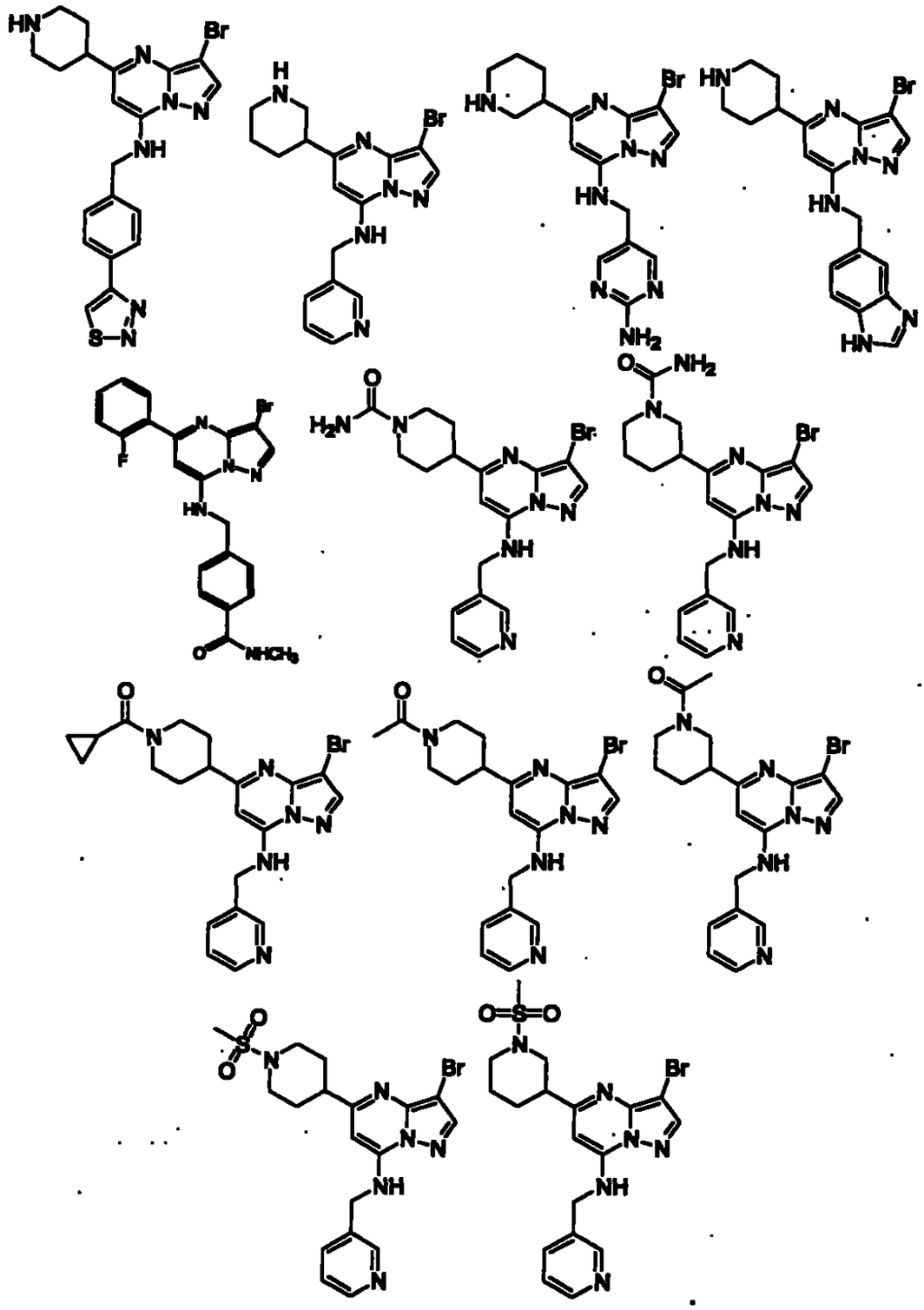


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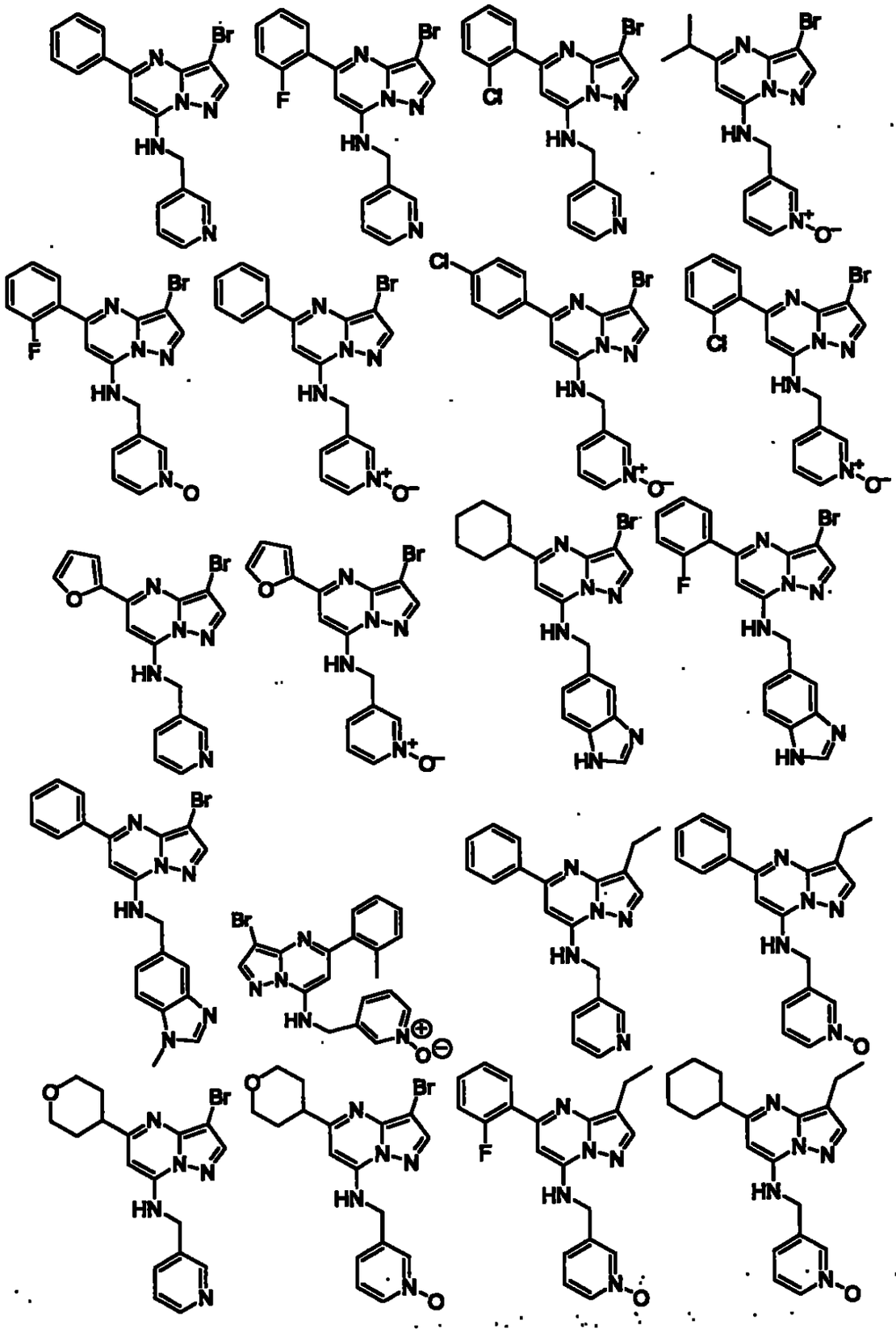




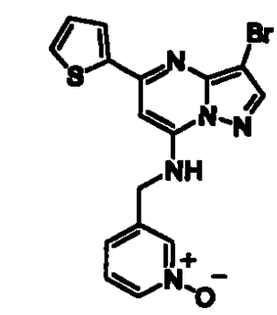
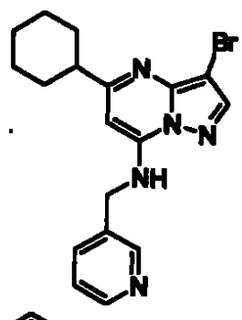
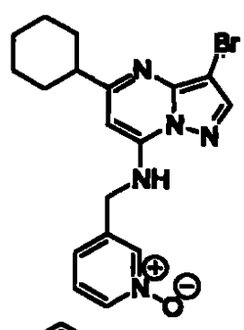
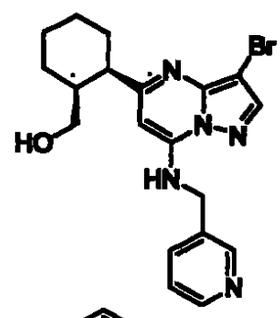
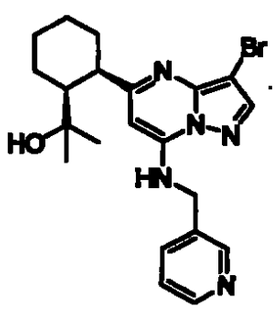
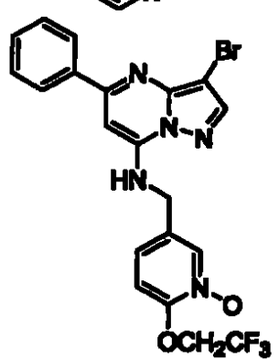
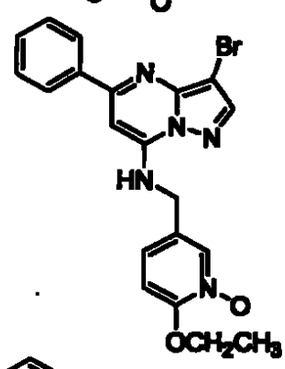
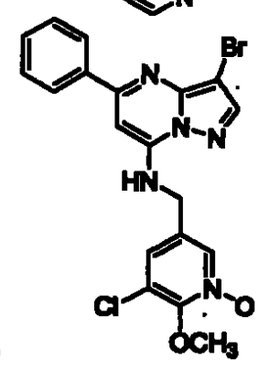
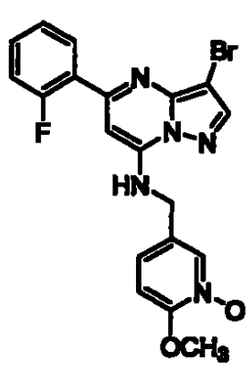
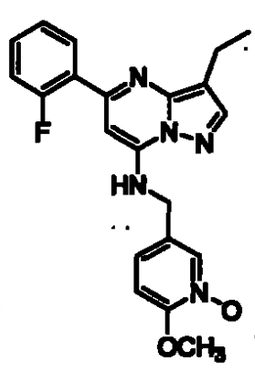
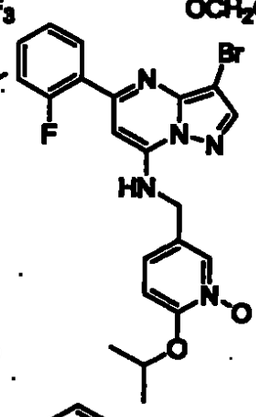
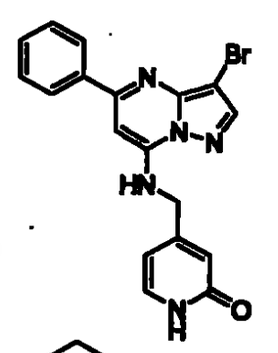
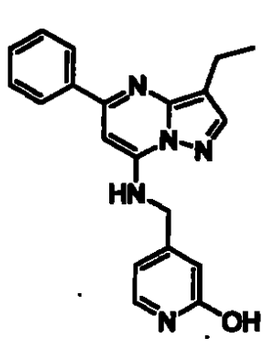
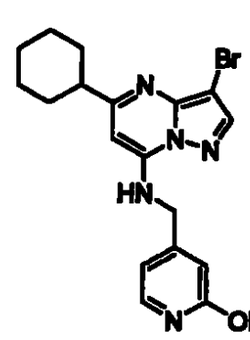
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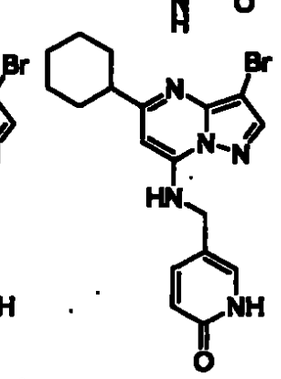


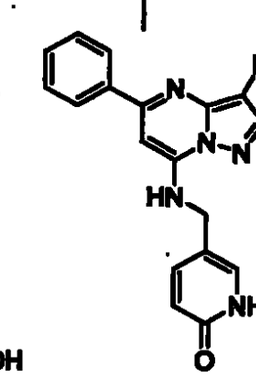
Another embodiment of the invention discloses the following compounds, which exhibited CDK2 inhibitory activity of about 0.0001μM to about 0.1μM:

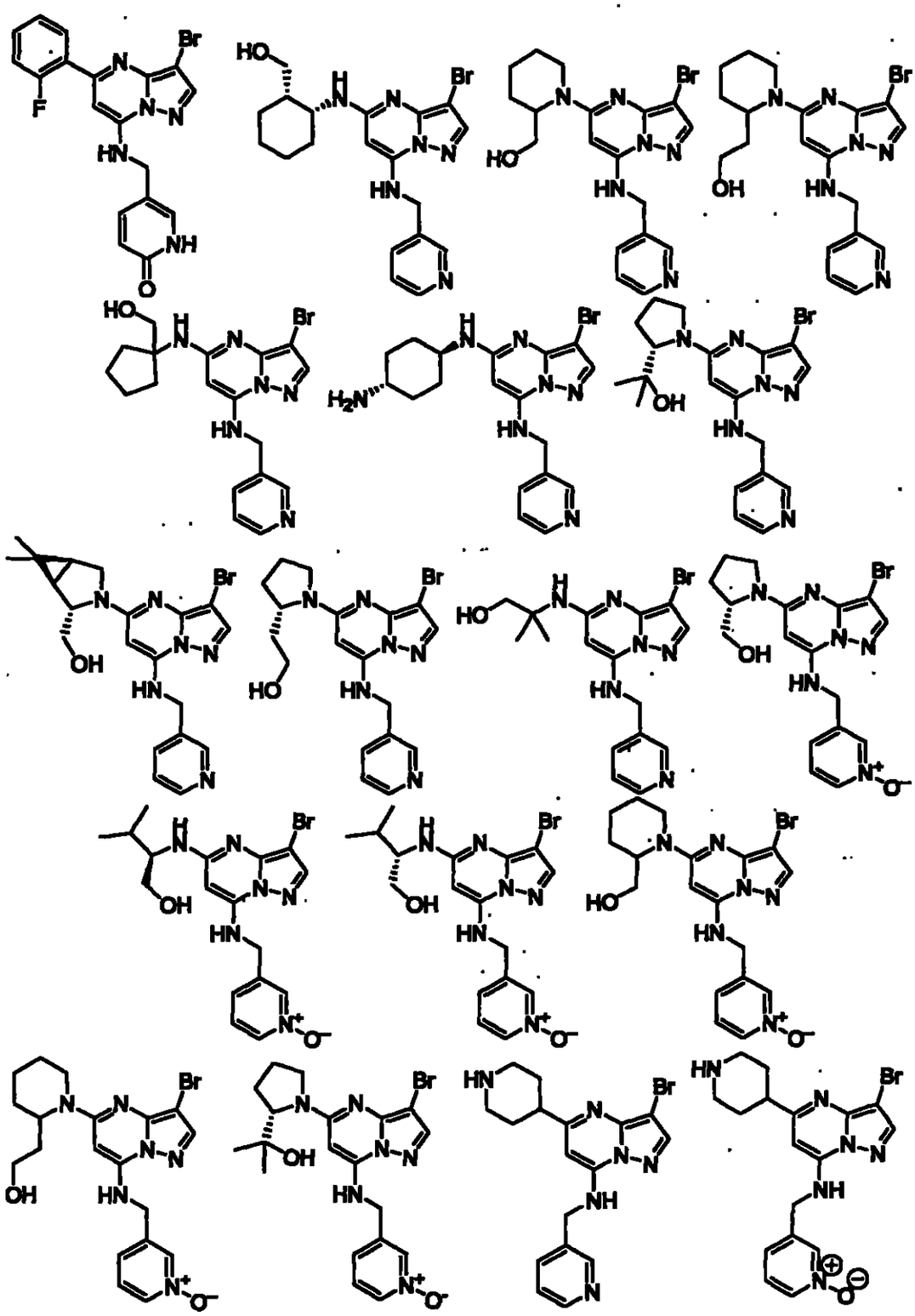


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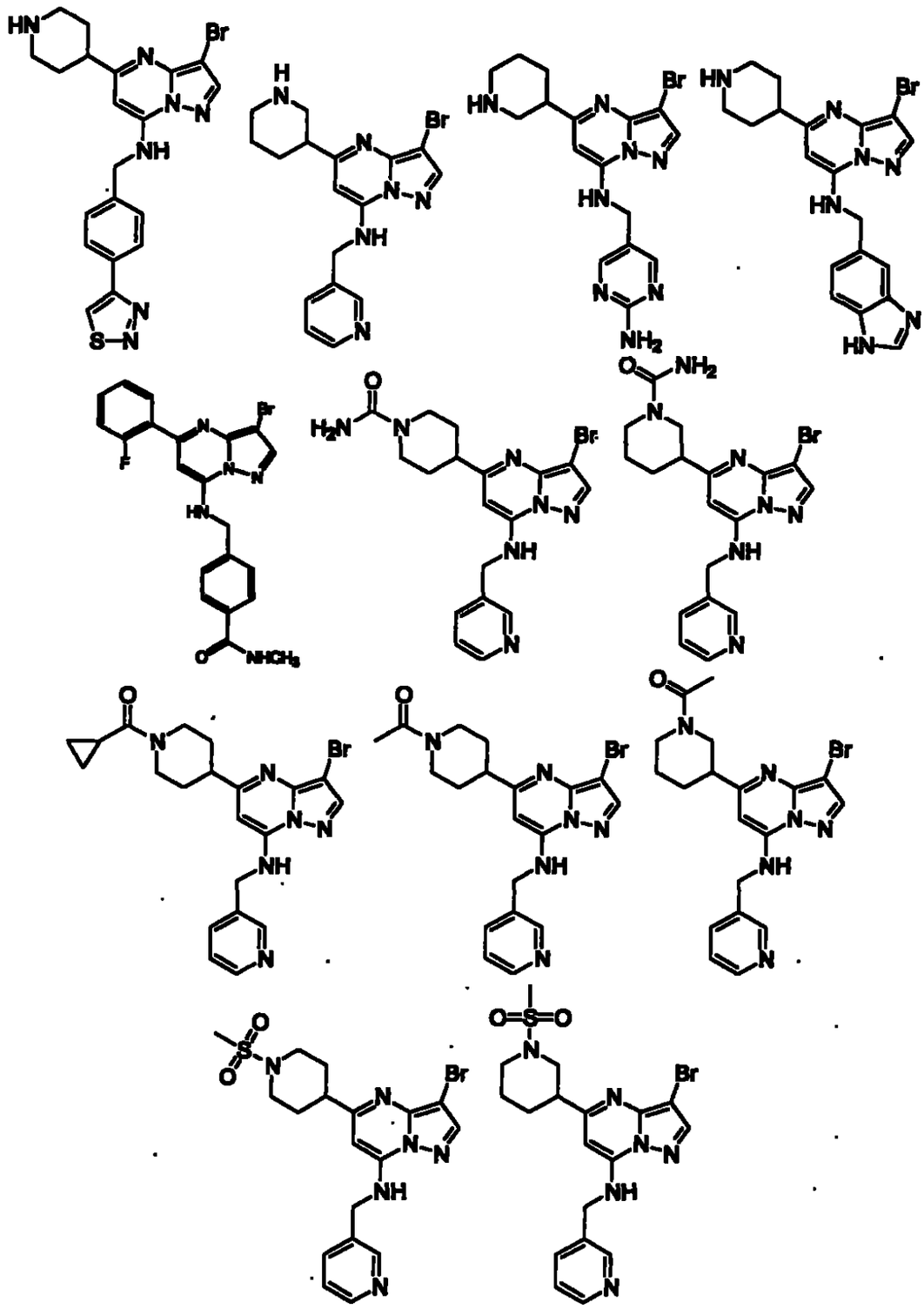





















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As used above, and throughout this disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

"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. The term "substituted alkyl" means that the alkyl group may be 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.

"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. The term "substituted alkynyl" means that the alkynyl group may be 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.

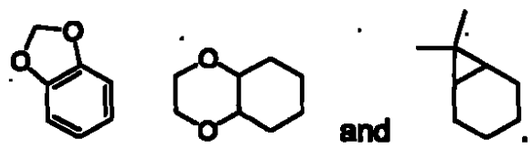
"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the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

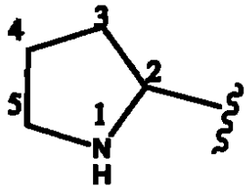
"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

"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

"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.

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 "isolated" or "in isolated 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. The term "purified" or "in 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 heteroatom with unsatisfied valences in the text, schemes, examples and Tables herein is assumed to have the 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. The term "prodrug", as employed herein, denotes a compound that is a drug precursor which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of Formula III or a salt and/or solvate thereof. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 of the A.C.S. Symposium Series, and in *Bioreversible*

Carriers in Drug Design, (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, both of which are incorporated herein by reference thereto.

"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.

"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 CDK(s) 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 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.

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

All stereoisomers (for example, geometric isomers, optical isomers and the like) of the present compounds (including those of the salts, solvates and prodrugs of the compounds as well as the salts and solvates of the prodrugs),

such as those which may exist due to asymmetric carbons on various substituents, including enantiomeric forms (which may exist even in the absence of asymmetric carbons), rotameric forms, atropisomers, and diastereomeric forms, are contemplated within the scope of this invention, as are positional isomers (such as, for example, 4-pyridyl and 3-pyridyl). Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers, or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention can have the S or R configuration as defined by the *IUPAC* 1974 Recommendations. The use of the terms "salt", "solvate" "prodrug" and the like, is intended to equally apply to the salt, solvate and prodrug of enantiomers, stereoisomers, rotamers, tautomers, positional isomers, racemates or prodrugs of the inventive compounds.

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 and CDK8. 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, 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 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, or Hexamethylmelamine.

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 obeserved 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

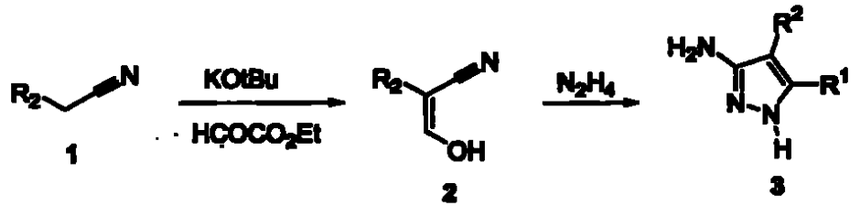
room temperature or rt (ambient): about 25°C.

dimethoxyethane: DME

EXAMPLES

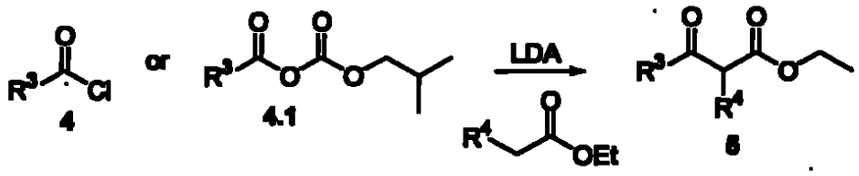
In general, the compounds described in this invention can be prepared through the general routes described below in Scheme 1. Treatment of the

Scheme 1



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.

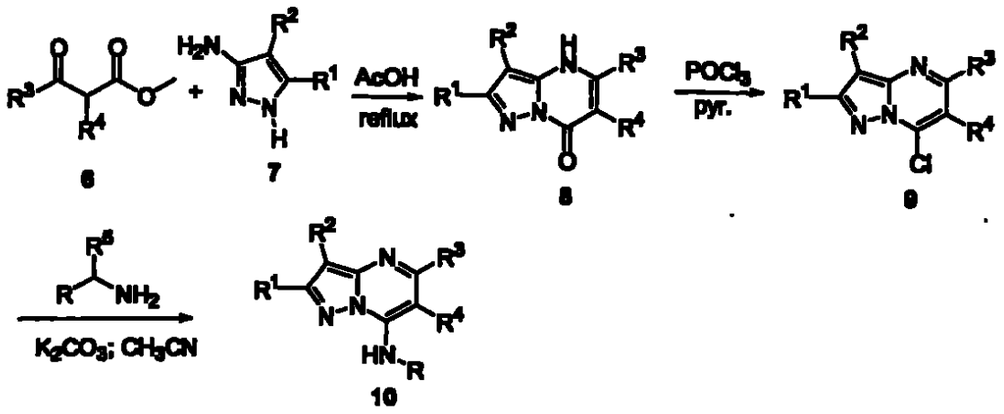
Scheme 2



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

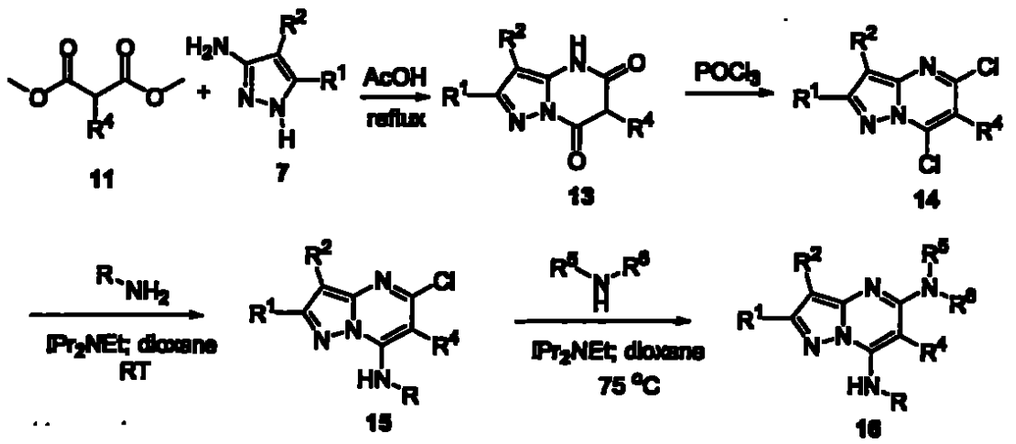


Condensation of compounds of type 7 with the appropriately functionalized malonate ester of type 11 gives rise to the pyridones 13 as shown in Scheme 4.

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.

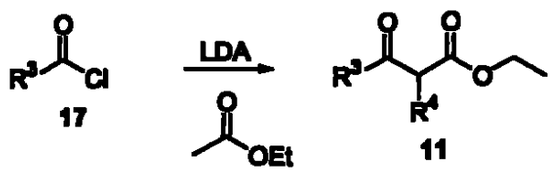
Incorporation of the N7-amino functionality can be accomplished through regioselective displacement of the chloride of compounds of type 14. Incorporation of the N5-amino functionality by addition of an appropriate amine at higher temperature.

Scheme 4



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

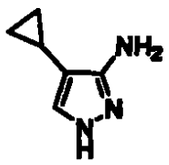


The chlorides of type 14 can be prepared by treatment of the pyridones 13 with $POCl_3$. When R^2 is equal to H, substitution in this position is possible on compounds of type 14 by electrophilic halogenation, acylation, and various other electrophilic aromatic substitutions.

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

Preparative Examples:

PREPARATIVE EXAMPLE 1:



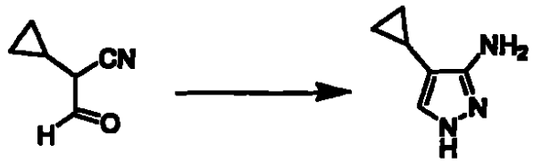
Step A:



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:

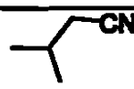
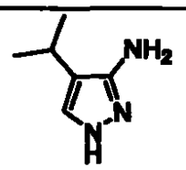
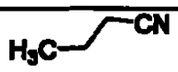
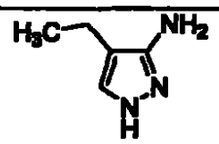
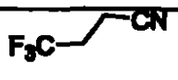
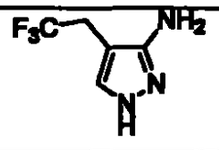


The product from Preparative Example 1, Step A (2.12 g, 0.0195 mol), $NH_2NH_2 \cdot H_2O$ (1.95 g, 0.039 mol) and 1.8 g (0.029 mole) of glacial CH_3CO_2H (1.8 g, 0.029 mol) were dissolved in EtOH (10 mL). It was refluxed for 6 hr and concentrated under vacuum. The residue was slurried in CH_2Cl_2 (150 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.

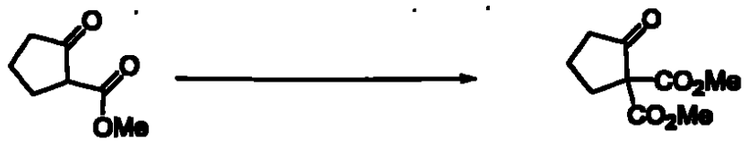
PREPARATIVE EXAMPLES 2-4:

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

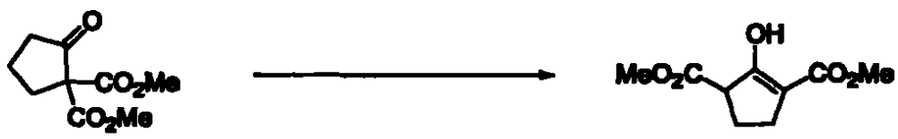
Prep. Ex.	Column 2	Column 3
2		
3		
3.10		

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:

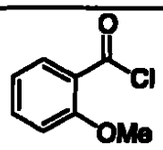
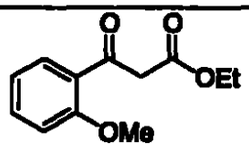


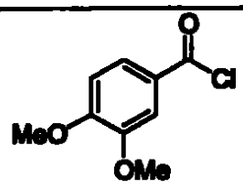
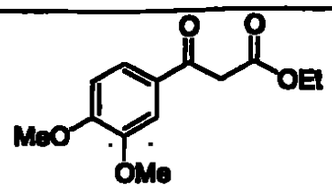
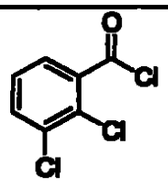
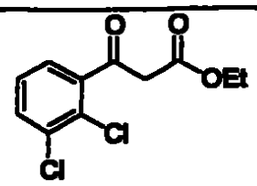
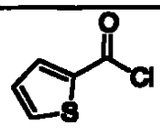
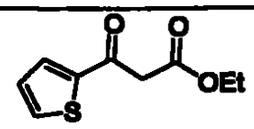
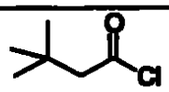
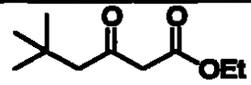
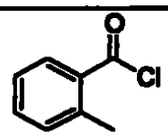
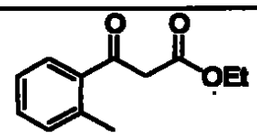
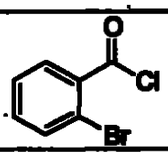
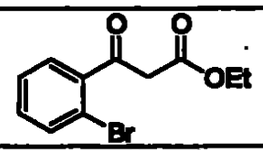
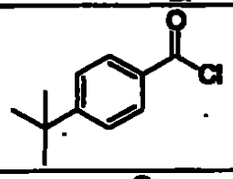
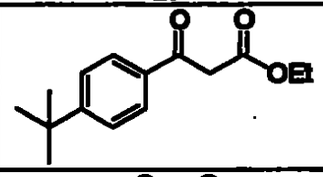
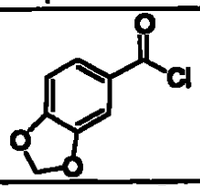
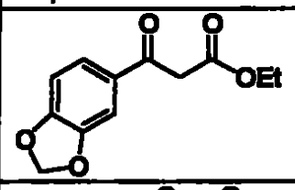
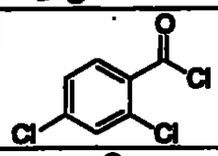
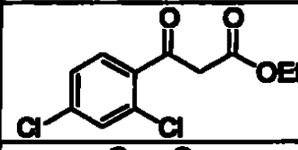
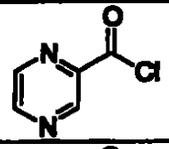
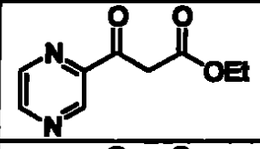
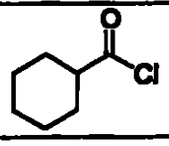
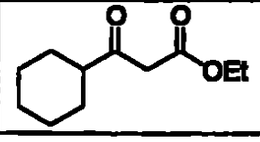
The reactions were done as outlined in (K. O. Olsen, *J. Org. Chem.*, (1987) 52, 4531 – 4536). Thus, to a stirred solution of lithium diisopropylamide in THF at -65 to –70 C was added freshly distilled ethyl acetate, dropwise. The resulting solution was stirred for 30 min and the acid chloride was added 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.

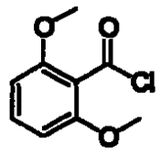
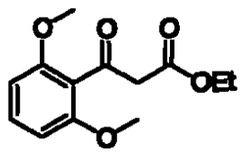
PREPARATIVE EXAMPLES 7-19:

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:

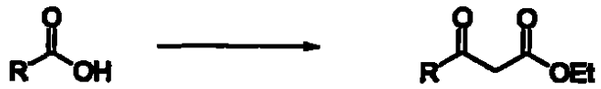
TABLE 3

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^+ = 282
17			Yield = 48 MH^+ = 195
18			Yield = 99 MH^+ =199

19			Yield=77% ^{1}H NMR ($CDCl_3$) δ 7.42(t, 1H), 6.66(d, 2H), 4.29(q, 2H), 3.97(d, 2H), 3.95(s, 3H), 1.38(t, 3H).

PREPARATIVE EXAMPLE 20:

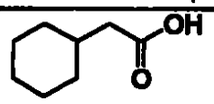
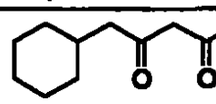
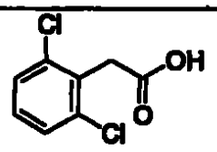
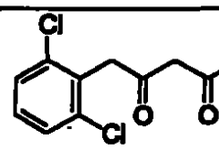
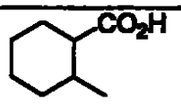
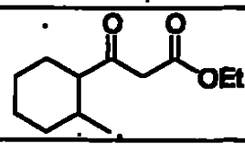


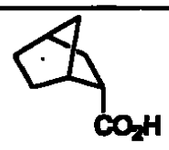
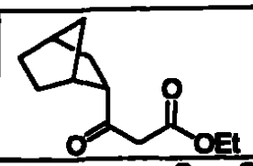
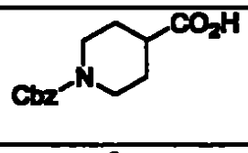
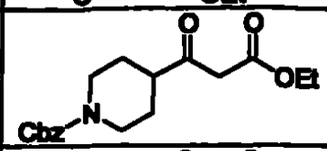
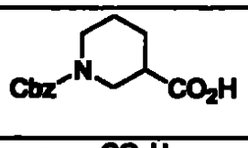
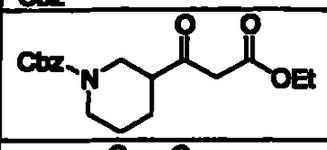
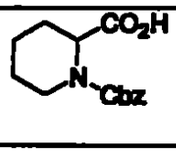
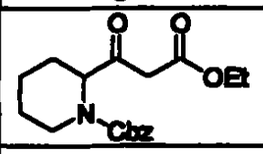
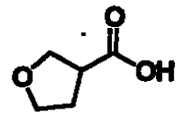
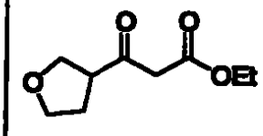
To a solution of the acid in THF was added Et_3N, followed by isobutyl chloroformate at –20 to –30°C. After the mixture was stirred for 30 min at –20 to –30°C, triethylamine hydrochloride was filtered off under argon, and the filtrate was added to the LDA-EtOAc reaction mixture (prepared as outlined 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:

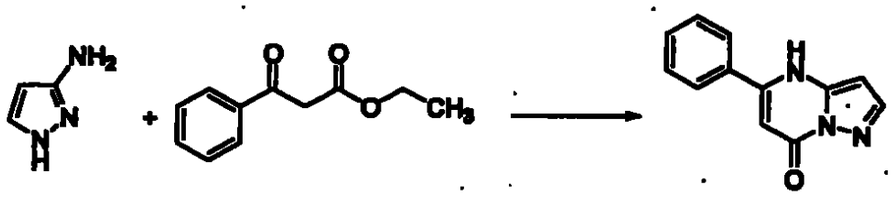
By essentially the same conditions set forth in Preparative Example 20 only substituting the carboxylic acid shown in Column 2 of Table 4, the compounds shown in Column 3 of Table 4 were prepared:

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% ^{1}H NMR ($CDCl_3$) δ 4.21(q, 2H), 3.95(d, 2H), 3.93-3.79(m, 4H), 3.52(s, 2H), 2.85(m, 1H), 1.25(t, 3H), 1.23-1.2(m, 2H).

PREPARATIVE EXAMPLE 29:



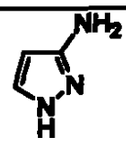
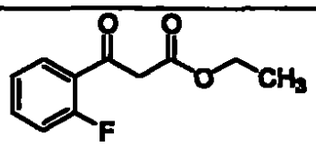
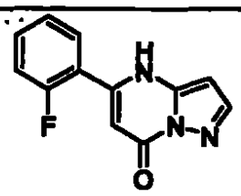
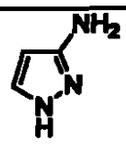
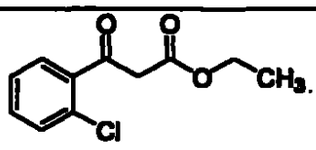
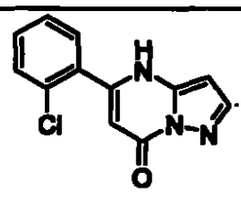
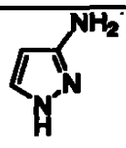
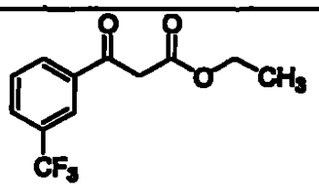
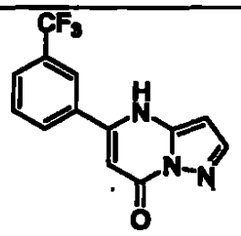
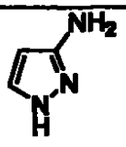
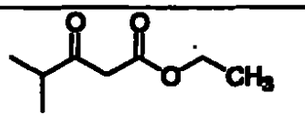
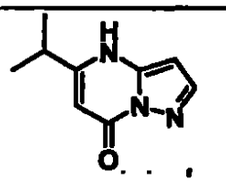
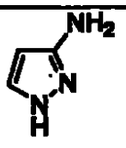
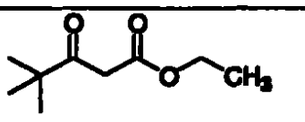
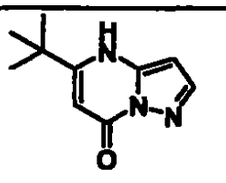
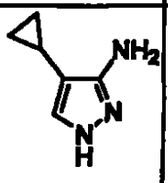
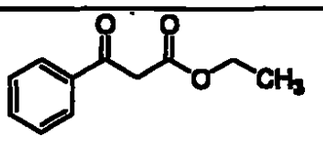
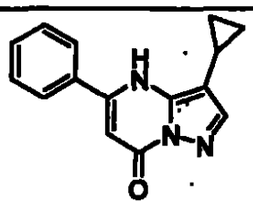
A solution of 3-aminopyrazole (2.0g, 24.07 mmol) and ethyl benzoylacetate (4.58 mL, 1.1 eq.) in AcOH (15 mL) was heated at reflux for 3 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The resulting solid was diluted with EtOAc and filtered to give a white solid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

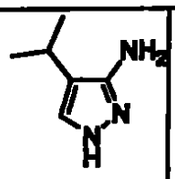
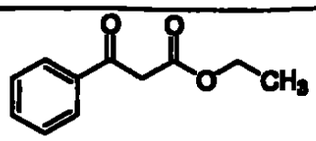
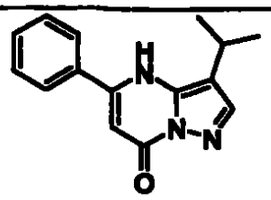
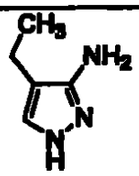
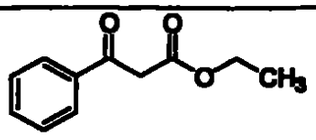
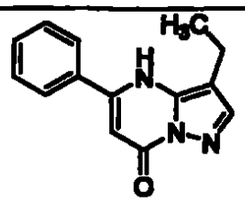
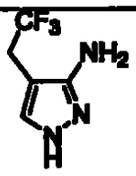
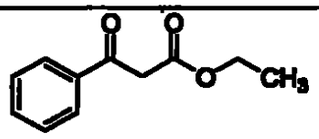
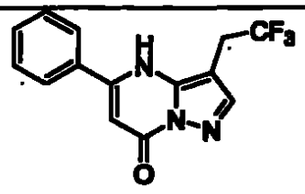
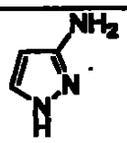
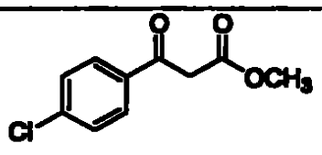
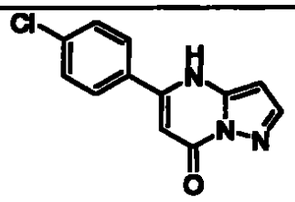
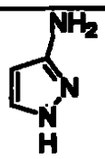
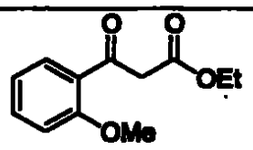
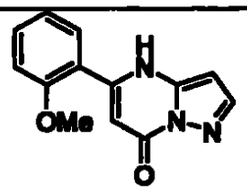
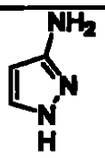
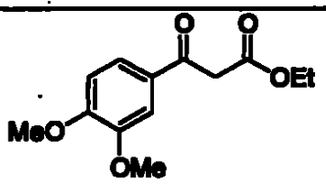
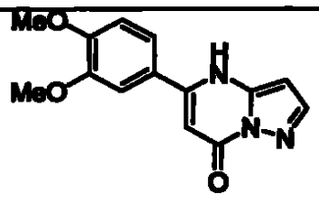
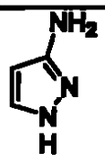
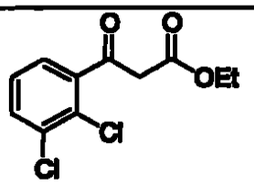
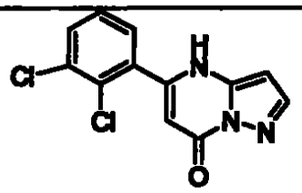
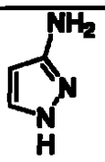
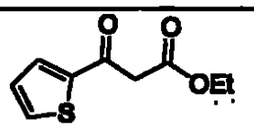
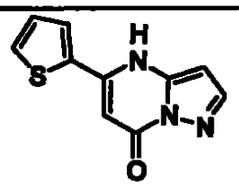
PREPARATIVE EXAMPLES 30-73:

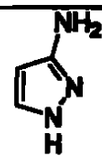
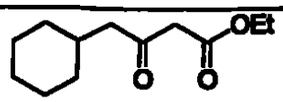
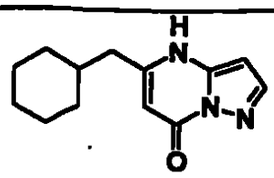
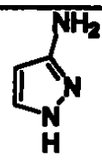
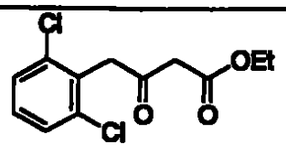
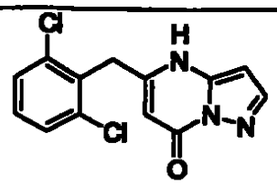
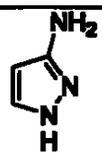
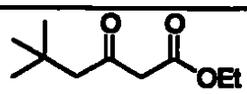
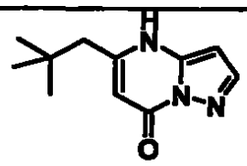
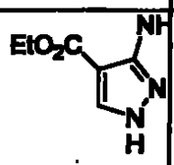
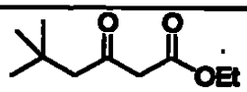
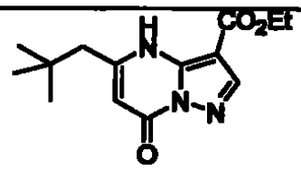
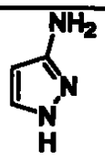
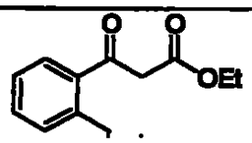
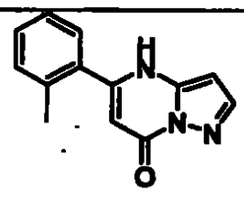
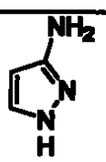
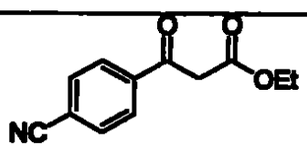
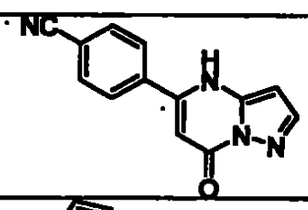
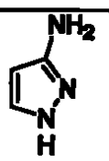
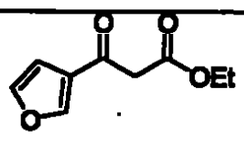
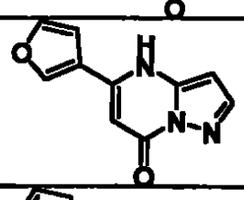
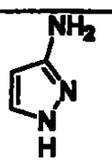
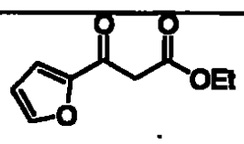
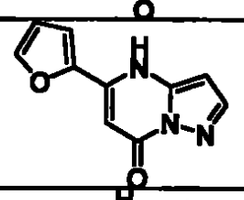
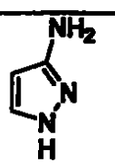
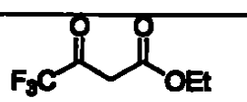
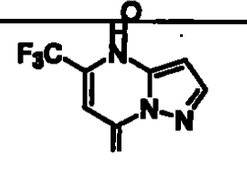
By essentially the same procedure set forth in Preparative Example 29 only substituting the aminopyrazole shown in Column 2 of Table 5 and the ester

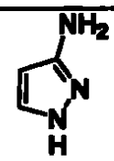
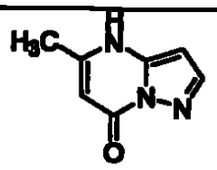
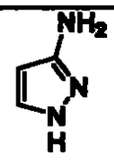
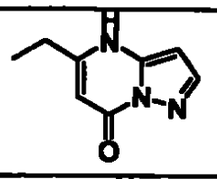
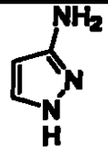
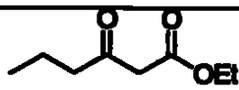
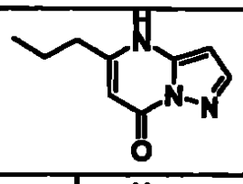
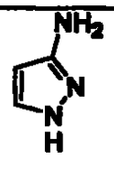
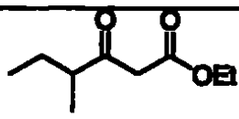
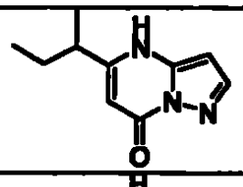
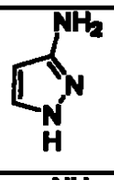
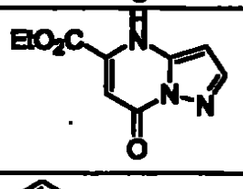
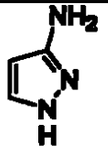
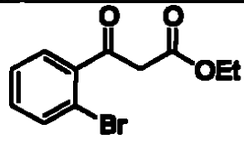
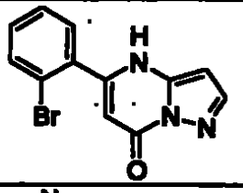
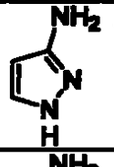
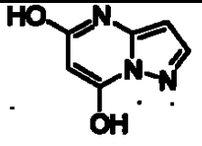
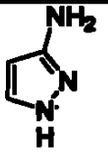
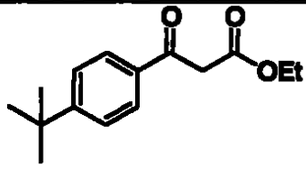
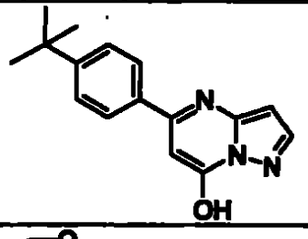
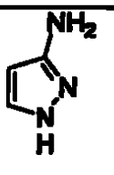
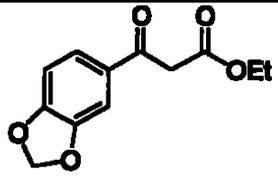
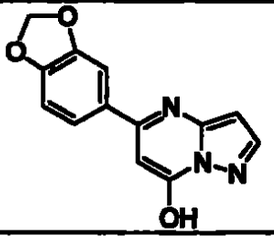
shown in Column 3 of Table 5, the compounds shown in Column 4 of Table 5 were prepared:

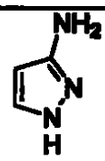
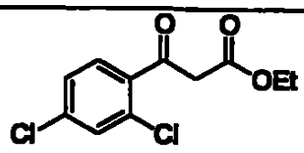
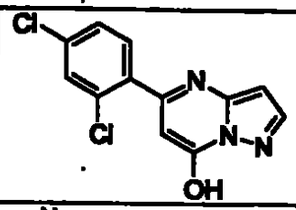
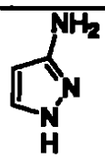
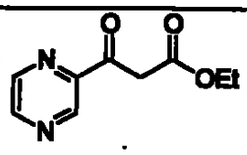
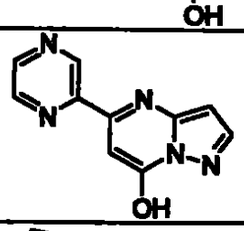
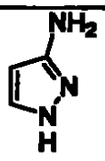
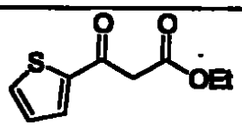
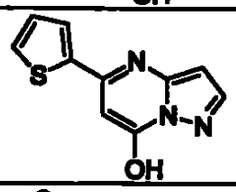
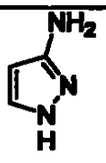
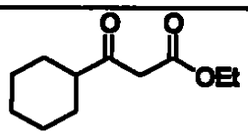
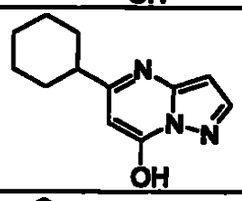
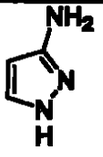
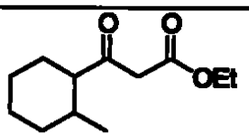
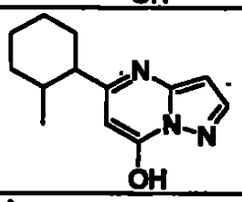
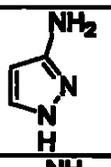
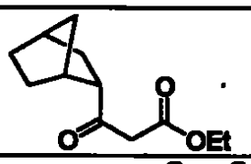
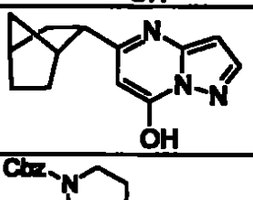
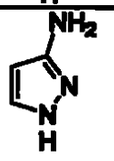
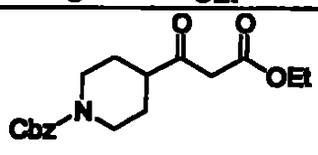
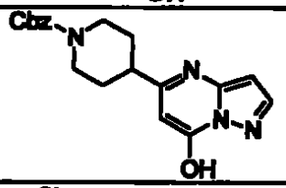
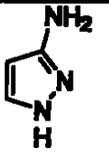
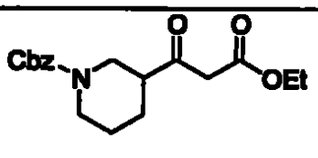
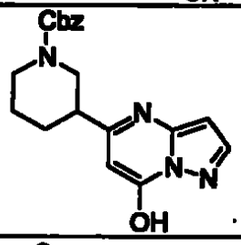
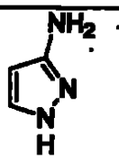
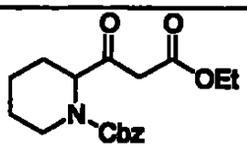
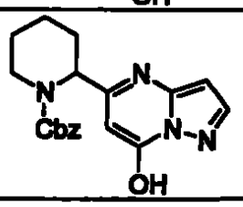
TABLE 5

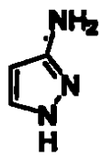
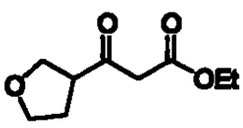
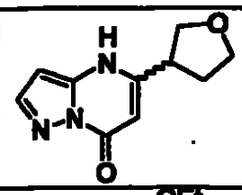
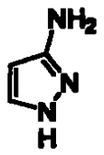
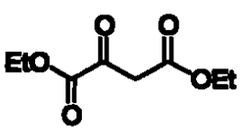
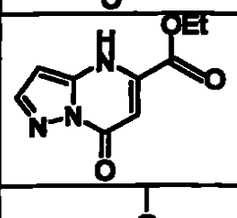
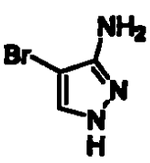
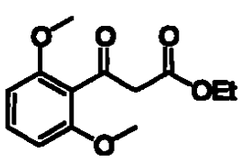
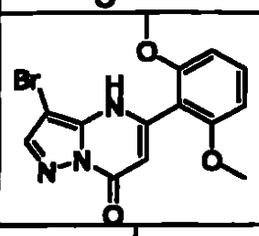
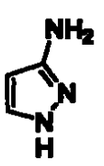
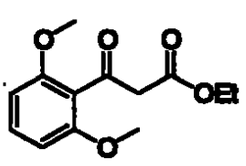
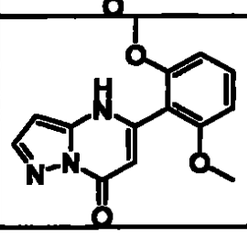
Prep. Ex.	Column 2	Column 3	Column 4	Column 5
30				
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32				
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35				

36				
37				
37.10				
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42				

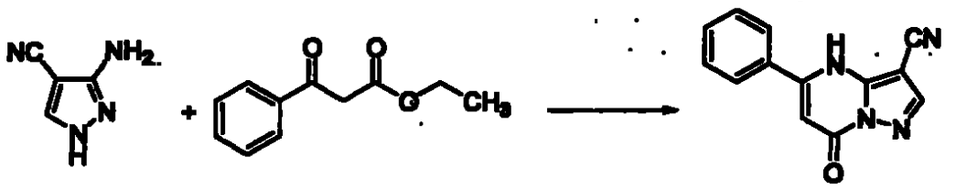
43				
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49				
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52				
53				
54				
55				
56				
57				
58				Yield = 68 MH^+ = 152
59				Yield = 46 MH^+ = 268
60				Yield = 63 MH^+ = 255

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

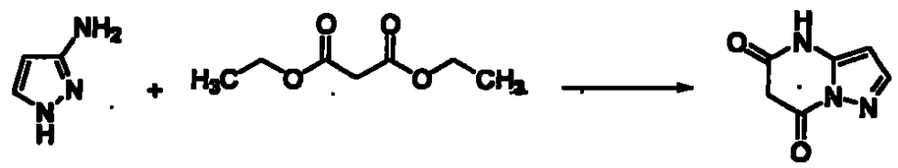
70				
71				
72				
73				

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



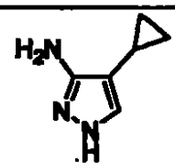
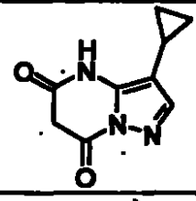
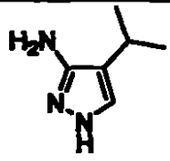
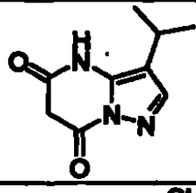
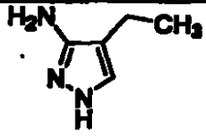
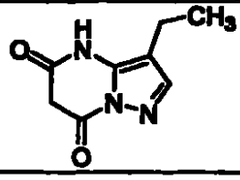
A procedure in US patent 3,907,799 was followed. Sodium (2.3 g, 2 eq.) was added to EtOH (150 mL) portionwise. When the sodium was completely

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).

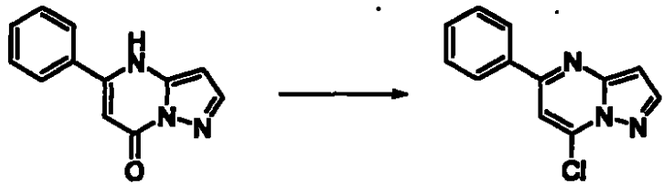
PREPARATIVE EXAMPLES 76-78:

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
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77		
78		

PREPARATIVE EXAMPLE 79:



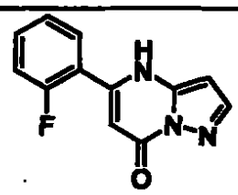
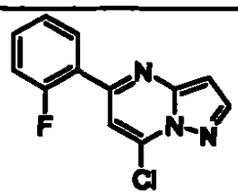
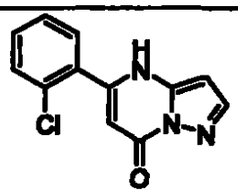
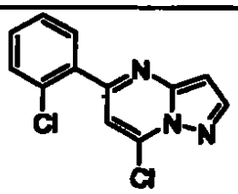
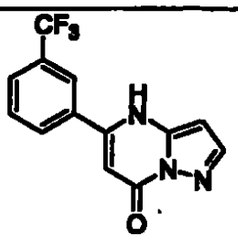
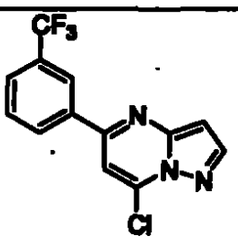
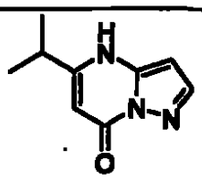
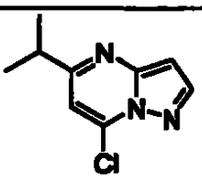
A solution of the compound prepared in Preparative Example 29 (1.0 g, 4.73 mmol) in $POCl_3$ (5 mL) and pyridine (0.25 mL) was stirred at room

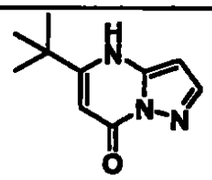
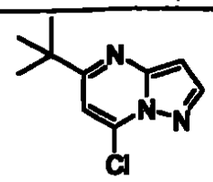
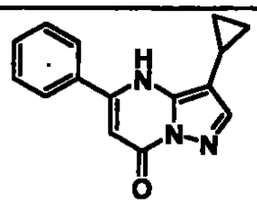
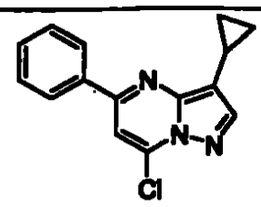
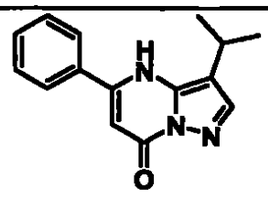
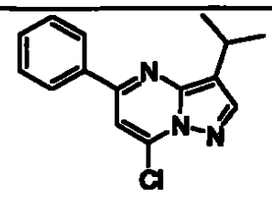
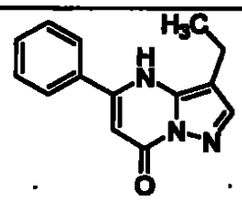
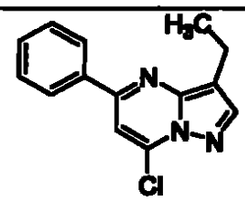
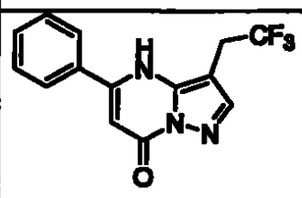
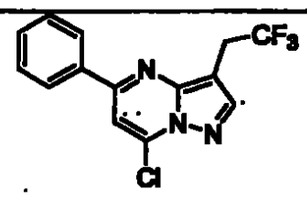
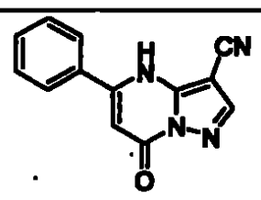
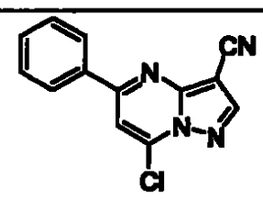
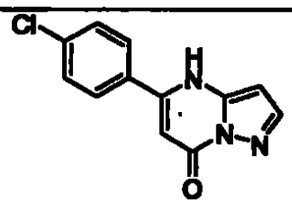
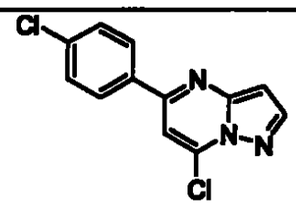
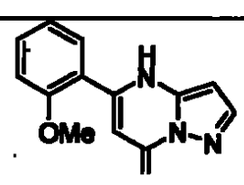
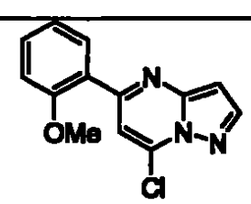
temperature 3 days. The resulting slurry was diluted with Et_2O, filtered, and the solid residue washed with Et_2O. The combined Et_2O washings were cooled to 0°C and treated with ice. When the vigorous reaction ceased, the resulting mixture was diluted with H_2O, separated, and the aqueous layer extracted 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.

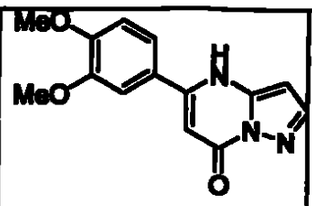
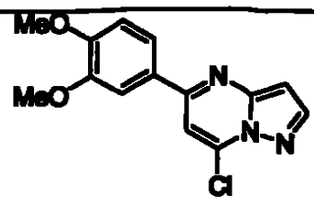
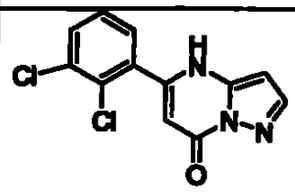
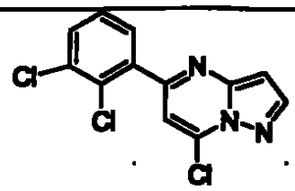
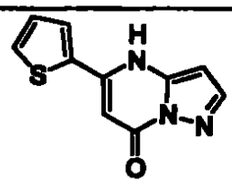
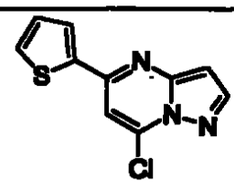
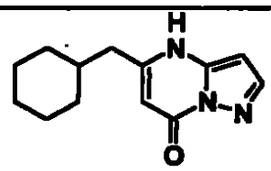
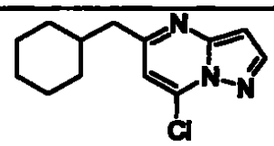
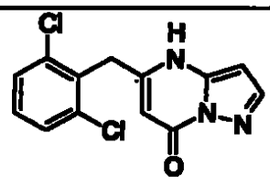
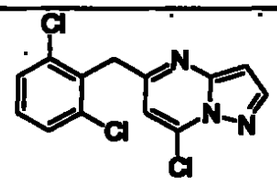
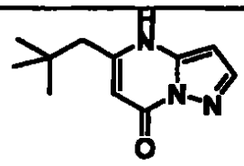
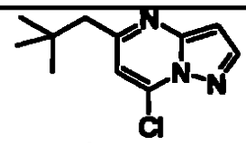
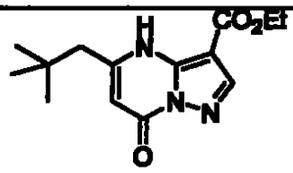
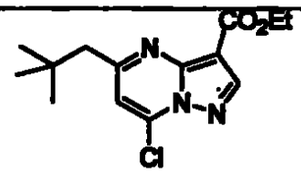
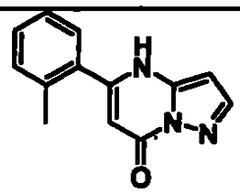
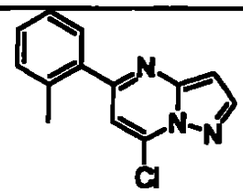
PREPARATIVE EXAMPLE 80-122:

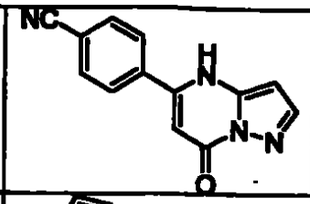
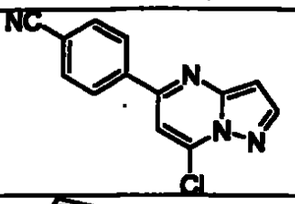
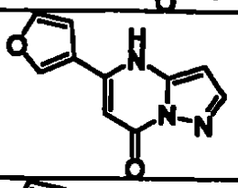
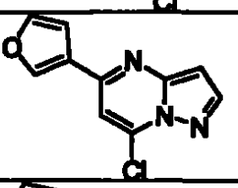
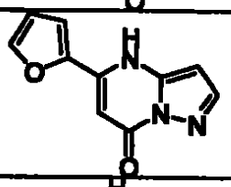
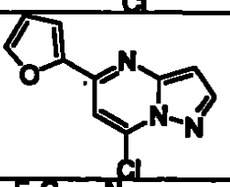
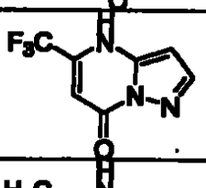
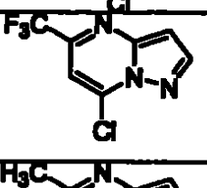
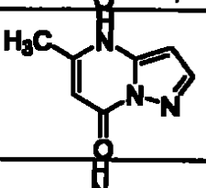
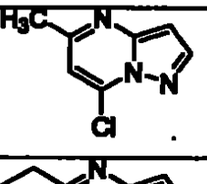
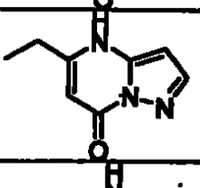
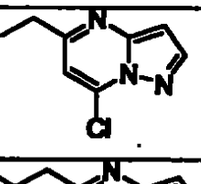
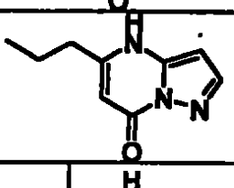
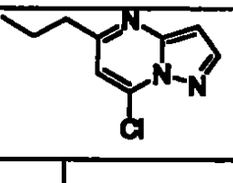
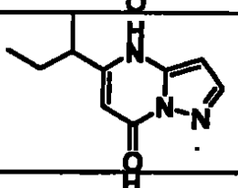
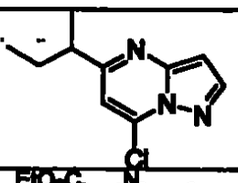
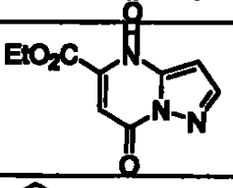
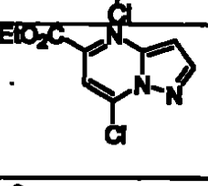
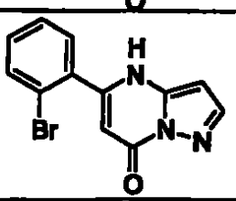
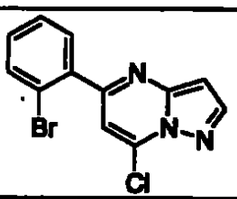
By essentially the same procedure set forth in Preparative Example 79, only substituting the compound shown in Column 2 of Table 7, the compounds shown in Column 3 of Table 7 were prepared:

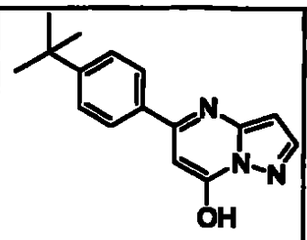
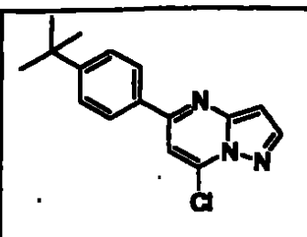
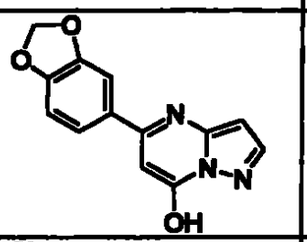
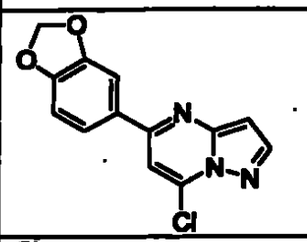
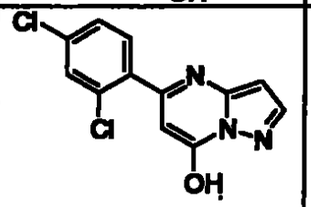
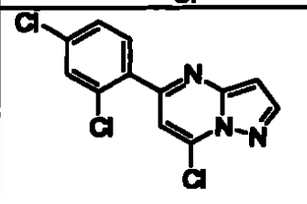
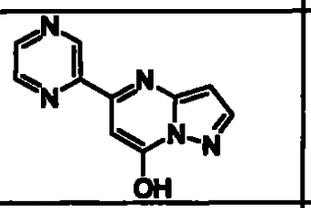
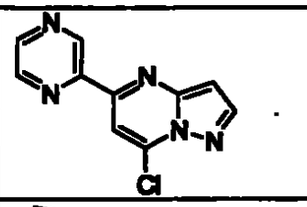
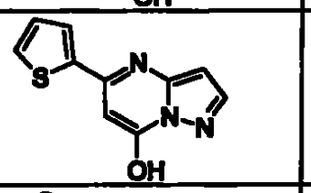
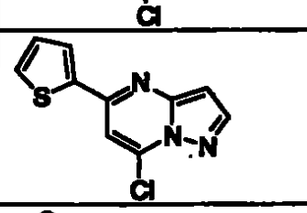
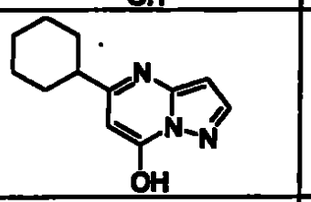
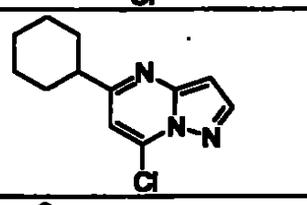
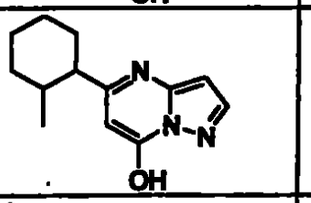
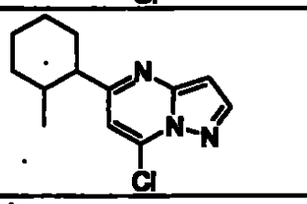
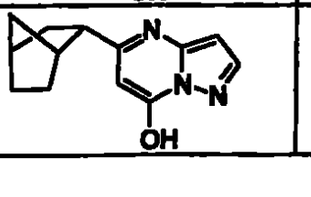
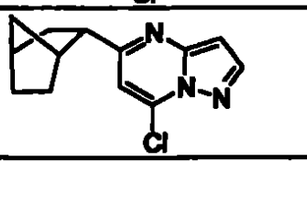
TABLE 7

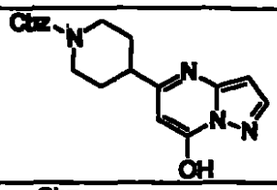
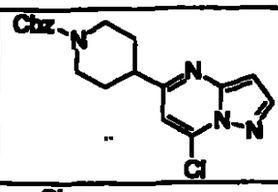
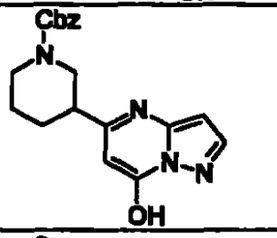
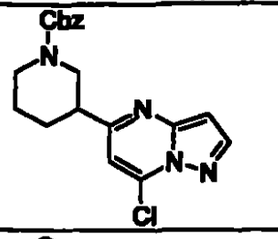
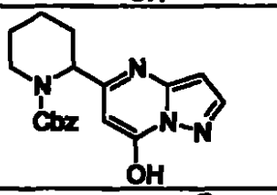
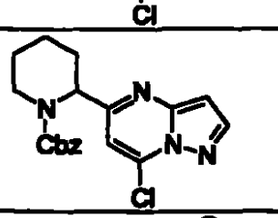
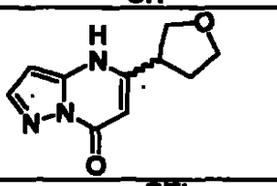
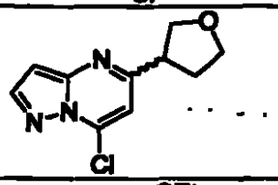
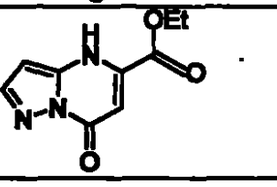
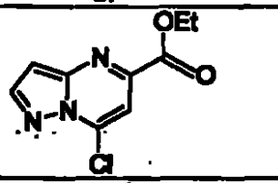
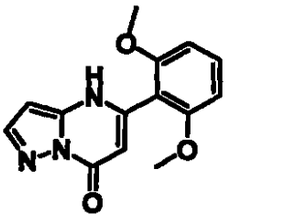
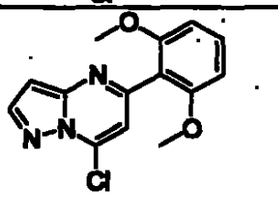
Prep. Ex.	Column 2	Column 3	CMPD
80			MS: MH^+=248
81			
82			MS: MH^+=298
83			MS: MH^+=198

84			MS: MH^+=210
85			
86			MS: MH^+=272
87			
87.10			
88			MS: MH^+=255
89			
90			Yield = 65% MS: MH^+ = 280

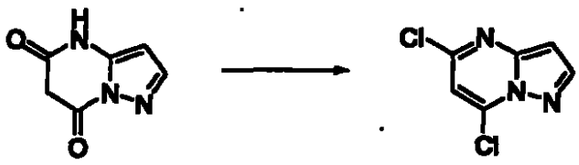
91			Yield = 35% MS: MH^+ = 290
92			Yield = 32% MS: MH^+ = 298
93			Yield = 45% MS: MH^+ = 236
94			Yield = 100% LCMS: MH^+ = 250
95			Yield = 88% MS: MH^+ = 314
96			Yield=43% MS: MH^+=223
97			Yield=30% MS: MH^+=295
98			Yield=98% MS: MH^+=244

99			
100			
101			
102			
103			
104			
105			
106			
107			45% yield; MS: MH^+=228
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



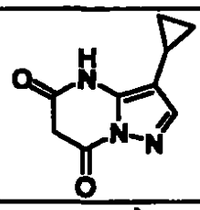
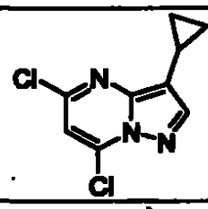
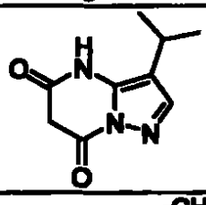
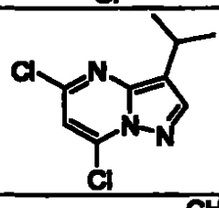
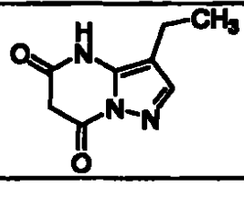
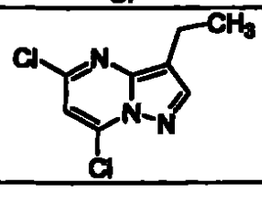
$POCl_3$ (62 mL) was cooled to 5 °C under nitrogen and dimethylaniline (11.4 g, 2.8 eq.) and the compound prepared in Preparative Example 75 (4.75 g,

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.

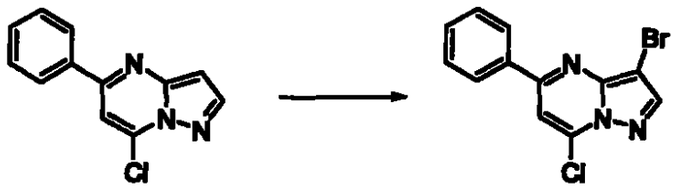
PREPARATIVE EXAMPLES 124-126

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:

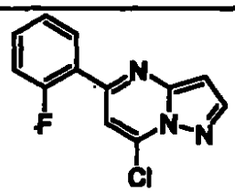
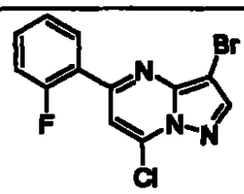
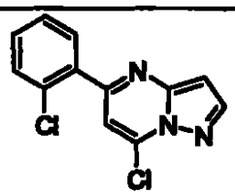
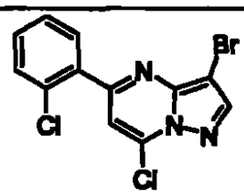
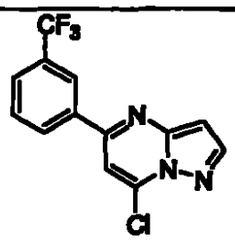
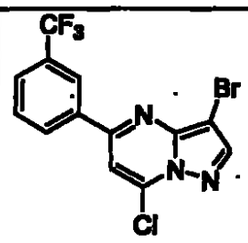


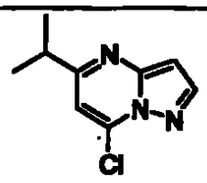
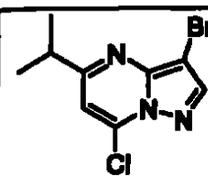
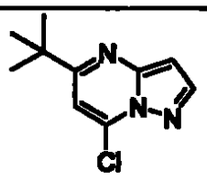
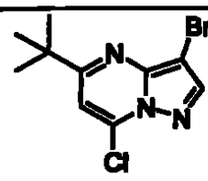
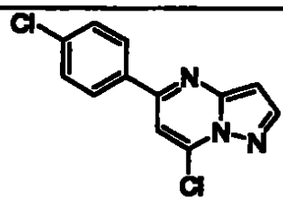
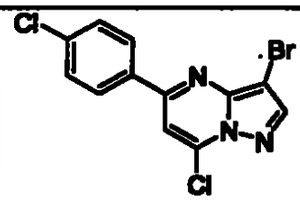
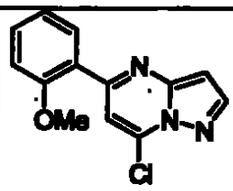
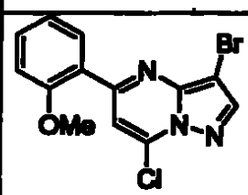
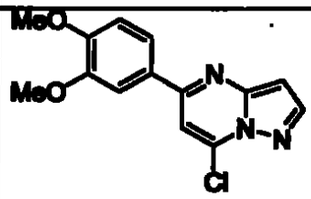
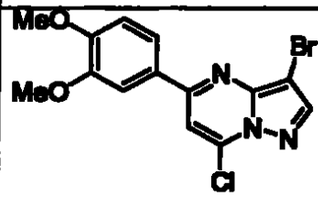
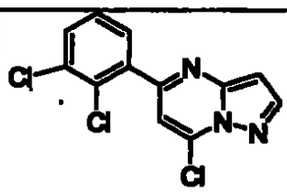
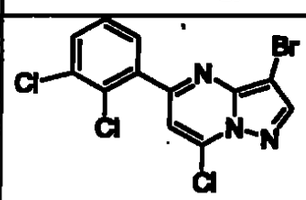
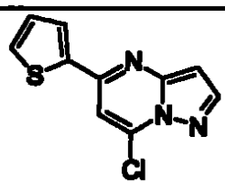
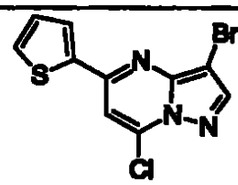
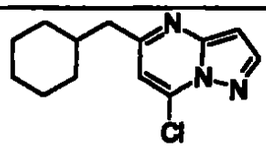
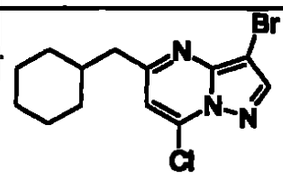
A solution of the compound prepared in Preparative Example 79 (0.10 g, 0.435 mmol) in CH_3CN (3 mL) was treated with NBS (0.085 g, 1.1 eq.). The reaction mixture was stirred at room temperature 1 hour and concentrated under reduced pressure. The crude product was purified by flash chromatography using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

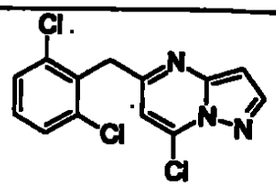
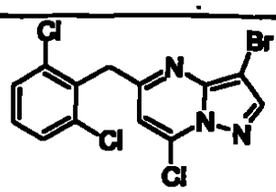
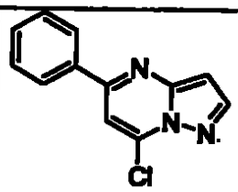
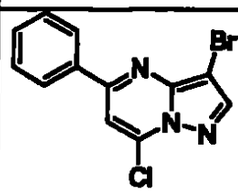
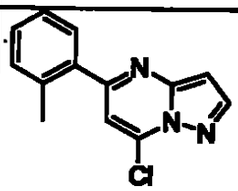
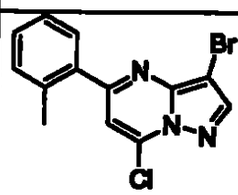
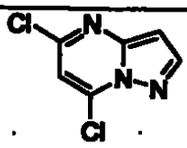
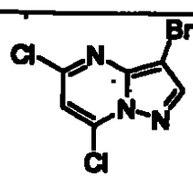
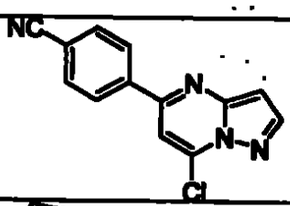
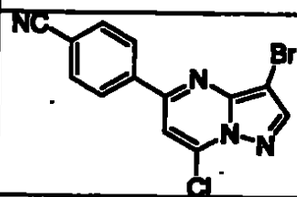
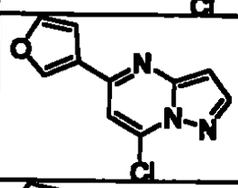
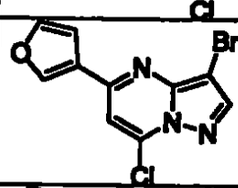
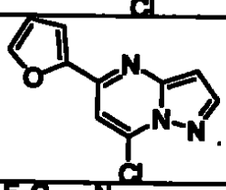
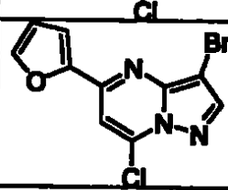
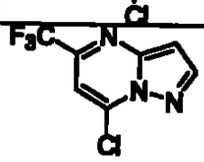
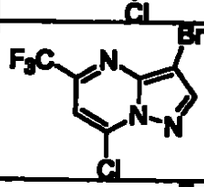
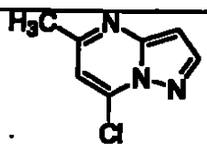
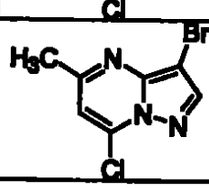
PREPARATIVE EXAMPLES 128-164:

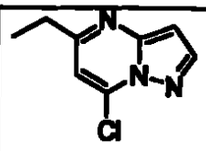
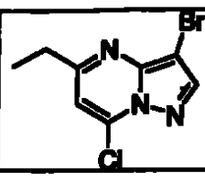
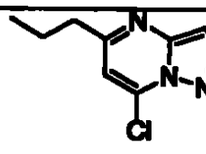
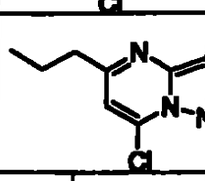
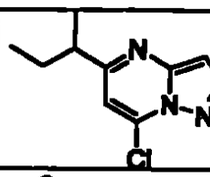
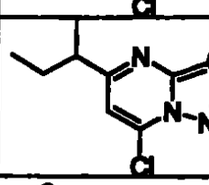
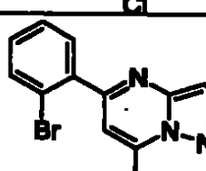
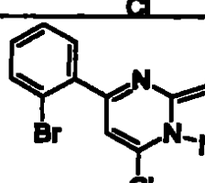
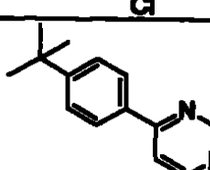
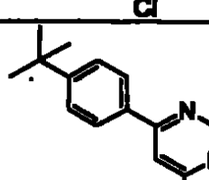
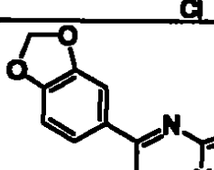
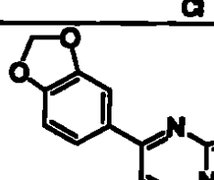
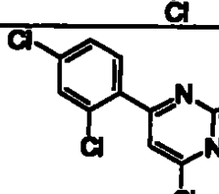
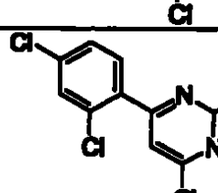
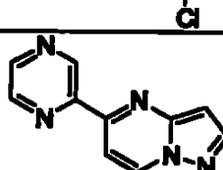
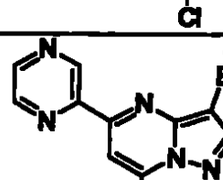
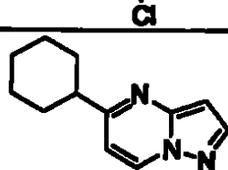
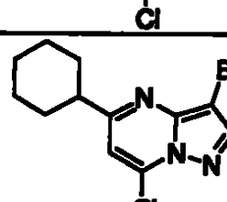
By essentially the same procedure set forth in Preparative Example 127 only substituting the compounds shown in Column 2 of Table 9, the compounds shown in Column 3 of Table 9 were prepared:

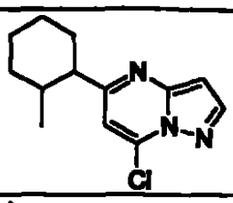
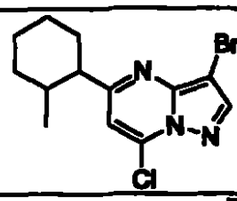
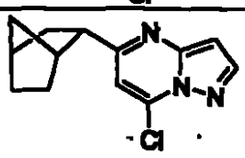
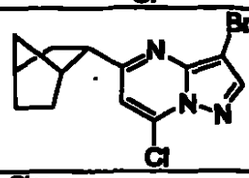
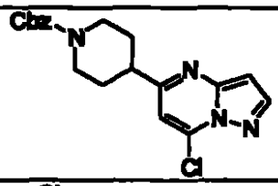
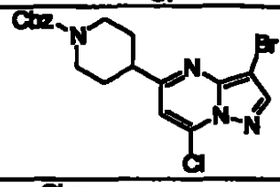
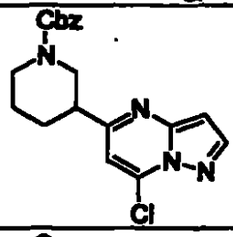
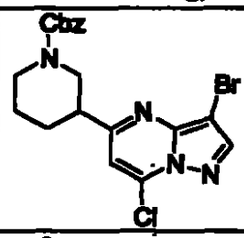
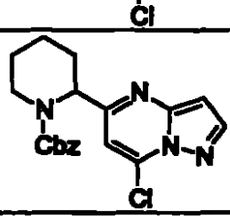
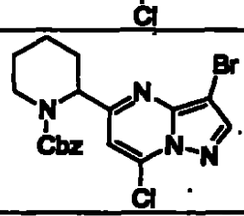
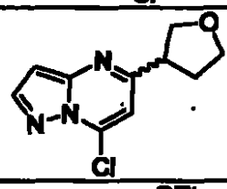
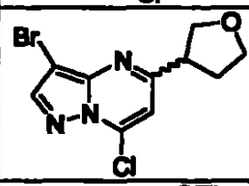
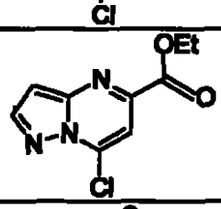
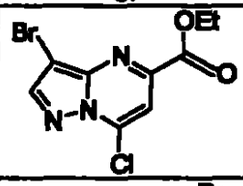
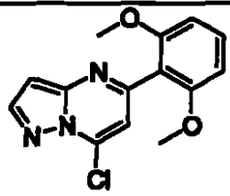
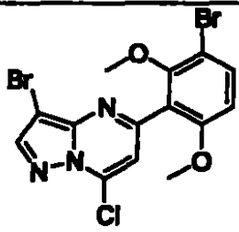
TABLE 9

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 = 57% MS: MH^+ = 376
137			Yield = 100% MS: MH^+ = 316
138			Yield = 92% MS: MH^+ = 330

139			Yield = 82% MS: MH^+ = 395
140			Yield=68% MS: MH^+=308
141			Yield=100% MS: MH^+=322
142			MH^+=286
143			
144			
145			
146			
147			

148			
149			
150			
151			LCMS: MH^+ = 386
152			Yield = quant MH^+ = 384
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:

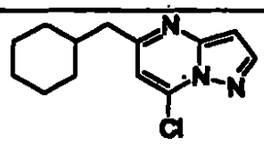
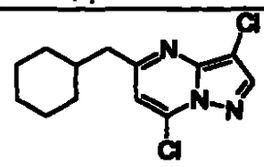
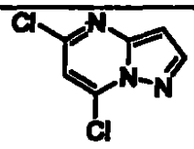
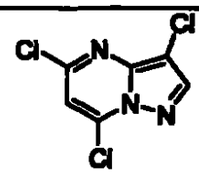


A solution of the compound prepared in Preparative Example 80 (0.3 g, 1.2 mmol) in CH_3CN (15 mL) was treated with NCS (0.18 g, 1.1 eq.) and the resulting solution heated to reflux 4 hours. Additional NCS (0.032 g, 0.2 eq.) added and the resulting solution was stirred at reflux overnight. The reaction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

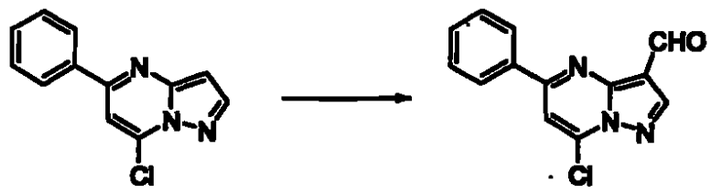
Prep. Ex.	Column 2	Column 3	CMPD
166			Yield = 82% LCMS: MH^+ = 286
167			

PREPARATIVE EXAMPLE 167.10:



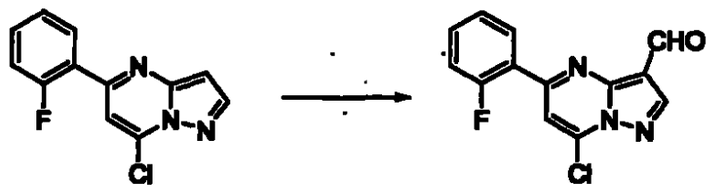
By essentially the same procedure set forth in Preparative Example 165 only substituting N-Iodosuccinimide, the above compound was prepared.

PREPARATIVE EXAMPLE 168:



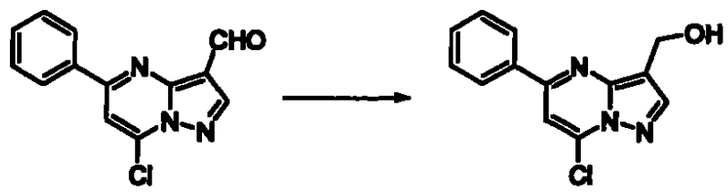
To a solution of the compound from Preparative Example 79 (1.0 g, 4.35 mmol) in DMF (6 mL) was added $POCl_3$ (1.24 mL, 3.05 eq.) and the resulting mixture was stirred at room temperature overnight. The reaction mixture was cooled to 0°C and the excess $POCl_3$ was quenched by the addition of ice. The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

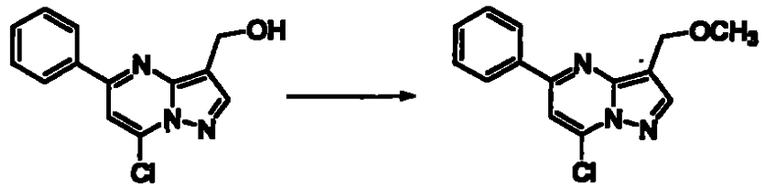
PREPARATIVE EXAMPLE 170:



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

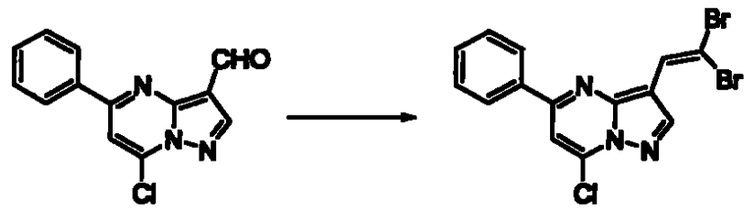
crude product was purified by flash chromatography using a 60: 40 hexanes : EtOAc mix as eluent (0.17 g, 69% yield). MS: MH^+=260.

PREPARATIVE EXAMPLE 171:



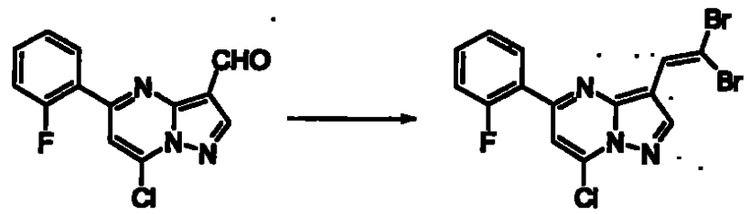
A solution of the compound prepared in Preparative Example 170 (0.12 g, 0.462 mmol), dimethyl sulfate (0.088 mL, 2.0 eq), 50% NaOH (0.26 mL) and catalytic Bu_4NBr in CH_2Cl_2 (4 mL) was stirred at room temperature overnight. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The 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:

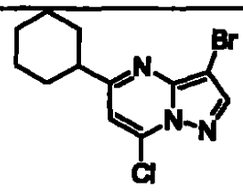
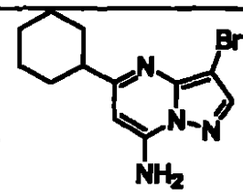
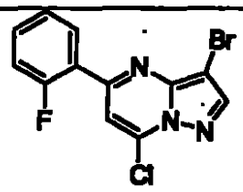
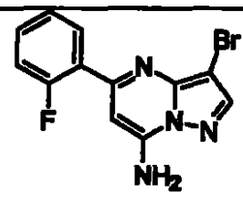


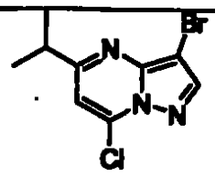
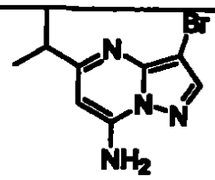
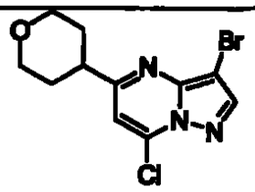
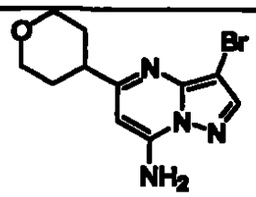
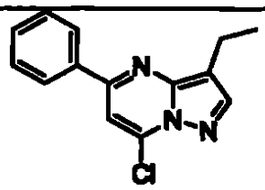
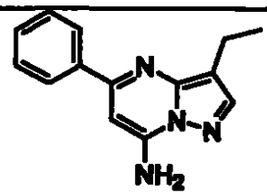
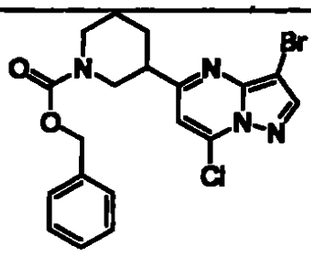
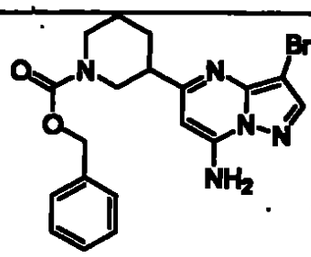
The compound prepared in Preparative Example 127 (3.08 g, 10.0 mmol), 2.0 M NH_3 in 2-propanol (50 mL, 100.0 mmol), and 37 % aqueous NH_3 (10.0 mL) were stirred in a closed pressure vessel at 50°C for 1 day. The solvent was evaporated and the crude product was purified by flash chromatography using 3:1 CH_2Cl_2:EtOAc as eluent. Pale yellow solid (2.30 g, 80%) was obtained. LCMS: M^+=289.

PREPARATIVE EXAMPLES 175-180:

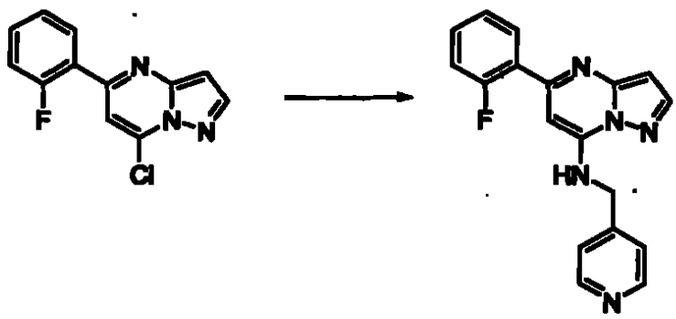
By essentially the same procedure set forth in Preparative Example 174 only substituting the compound shown in Column 2 of Table 11, the compounds shown in Column 3 of Table 11 were prepared.

TABLE 11

Prep. Ex.	Column 2	Column 3
175		
176		

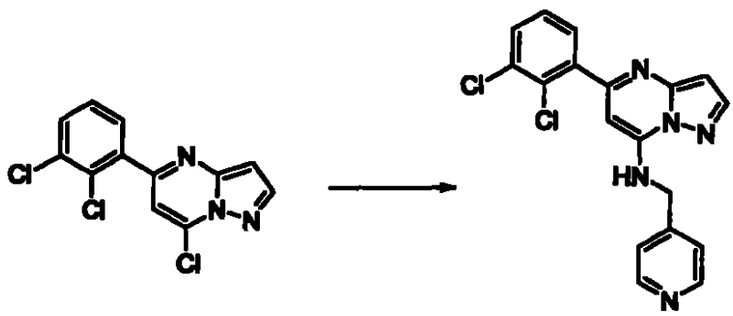
177		
178		
179		
180		

PREPARATIVE EXAMPLE 181:



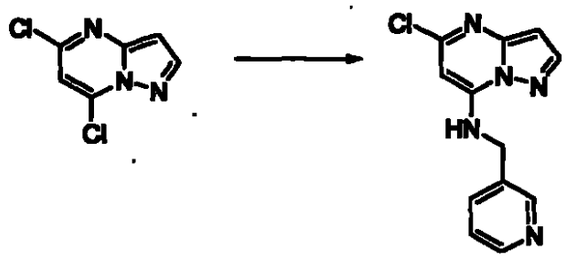
The compound prepared in Preparative Example 80 (0.3 g, 1.2 mmol), K_2CO_3 (0.33 g, 2 eq.), and 4-aminomethylpyridine (0.13 mL, 1.1 eq.) was heated to reflux overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with H_2O and extracted 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:



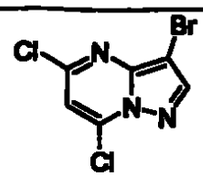
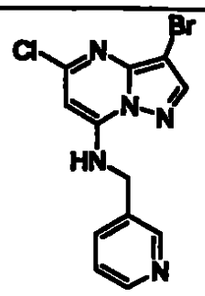
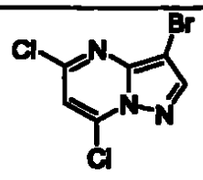
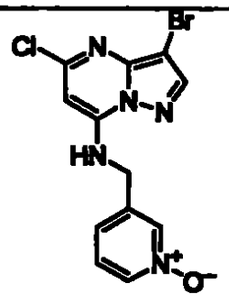
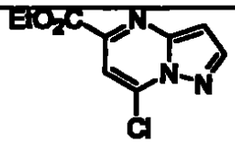
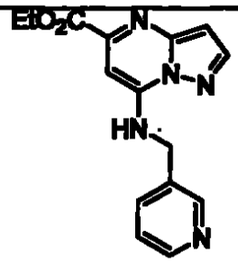
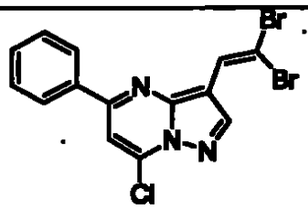
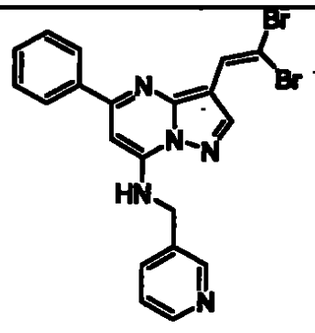
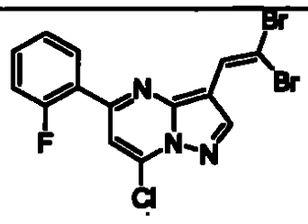
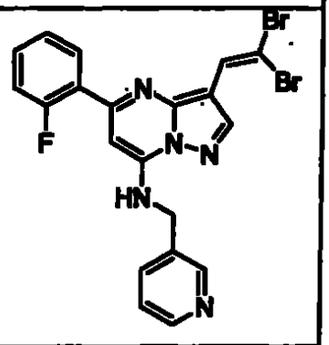
To a solution of the compound prepared in Preparative Example 123 (0.25 g, 1.3 mmol) in dioxane (5 mL) was added iPr_2NEt (0.47 mL, 2.0 eq.) and 3-aminomethylpyridine (0.15 ml, 1.1 eq.). The resulting solution was stirred at room temperature 72 hours. The reaction mixture was diluted with H_2O and extracted 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.

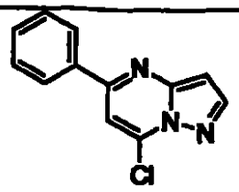
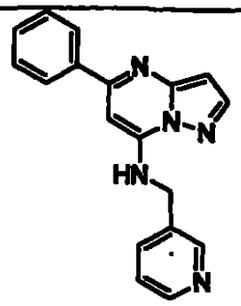
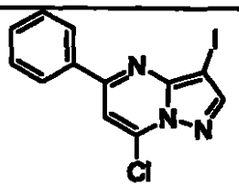
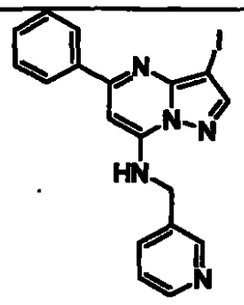
PREPARATIVE EXAMPLES 184-187:

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.

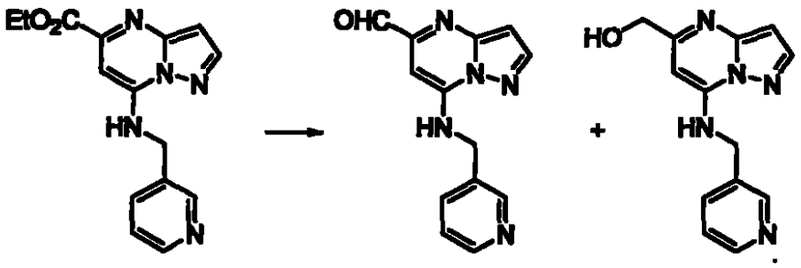
TABLE 12

Prep. Ex.	Column 2	Column 3

184		
184.1		
185		
186		
187		

187.1		
187.11		

PREPARATIVE EXAMPLE 188 and PREPARATIVE EXAMPLE 189:

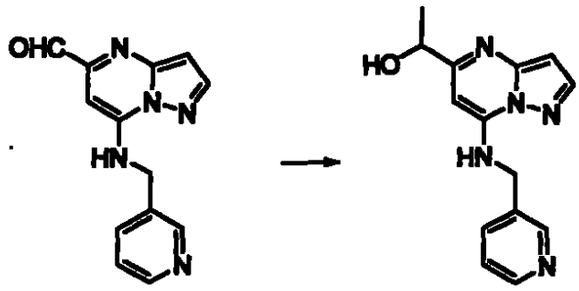


To a solution of the compound prepared in Preparative Example 185 (1.18 g, 3.98 mmol) in THF (35 mL) at -78 °C was added LAH (4.78 mL, 1M in Et_2O, 1.0 eq.) dropwise. The reaction mixture was stirred at -78 °C for 3 hours at which time additional LAH (2.0 mL, 1M in Et_2O, 0.42 eq.) was added dropwise. 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.

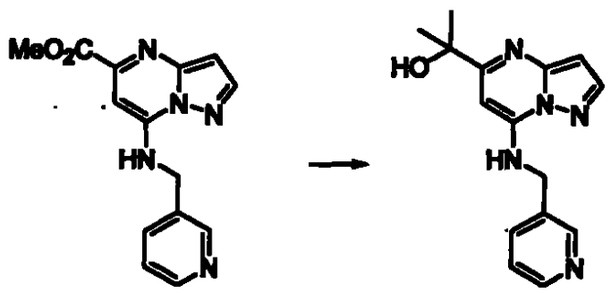
Preparative Example 189: (alcohol): 0.25 g, 24% yield. MS: MH^+ = 256.

PREPARATIVE EXAMPLE 190:



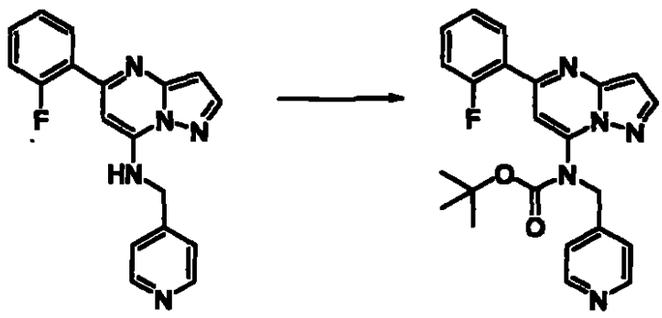
To a solution of the compound prepared in Preparative Example 188 (0.075 g, 0.30 mmol) in THF (2.0 mL) at 0 °C was added CH_3MgBr (0.3 mL, 3.0M solution in Et_2O, 3.0 eq.) dropwise. The resulting solution was stirred at 0 °C an additional 1.5 hours, warmed to room temperature, and stirred overnight. 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:



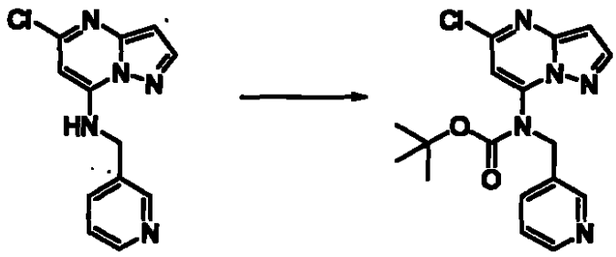
By essentially the same procedure set forth in Preparative Example 190 only substituting the compound prepared in Preparative Example 185 and using excess MeMgBr (5 eq.), the above compound was prepared.

PREPARATIVE EXAMPLE 192:



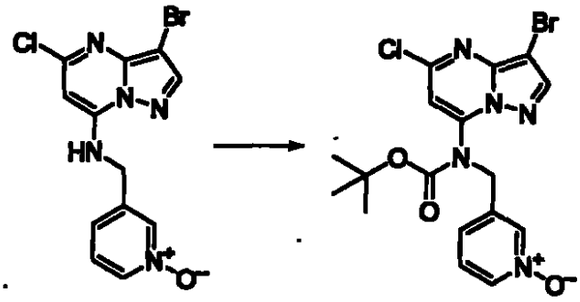
The compound prepared in Preparative Example 181 (0.29 g, 0.91 mmol), BOC_2O (0.22 g, 1.1 eq), and DMAP (0.13 g, 1.1 eq.) in dioxane (10 mL) was stirred at room temperature 3 days. Additional BOC_2O (0.10g, 0.5 eq.) was added and the reaction mixture was stirred 4 hours. The reaction mixture was concentrated *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:



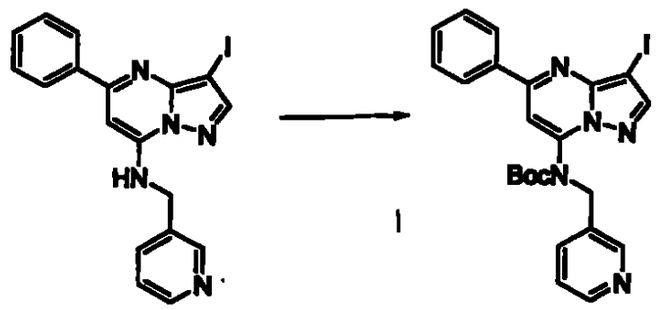
By essentially the same procedure set forth in Preparative Example 192 only substituting the compound prepared in Preparative Example 183, the above compound was prepared. MS: MH^+ = 360.

PREPARATIVE EXAMPLE 193.10:



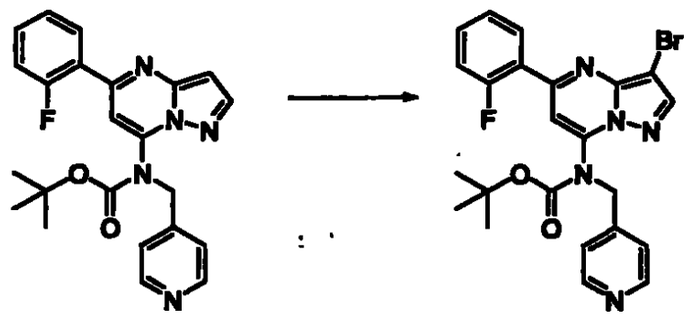
By essentially the same procedure set forth in Preparative Example 192 only substituting the compound prepared in Preparative Example 184.1, the above compound was prepared. MS: MH^+ = 454.

PREPARATIVE EXAMPLE 194:



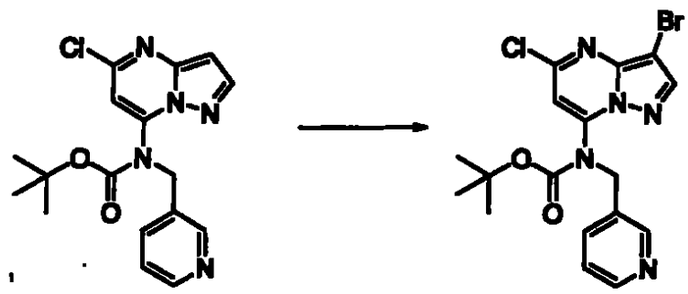
By essentially the same procedure set forth in Preparative Example 192 only substituting the above compound prepared in Preparative Example 187.11, the above compound was prepared (0.223 g, 88% yield). MS: MH^+ = 528.

PREPARATIVE EXAMPLE 195:



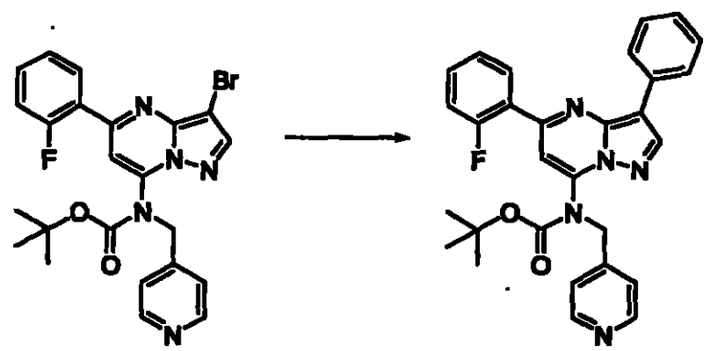
By essentially the same procedure set forth in Preparative Example 127 only substituting the compound prepared in Preparative Example 192, the above compound was prepared (0.38 g, 95% yield). LCMS: MH^+= 498.

PREPARATIVE EXAMPLE 196:



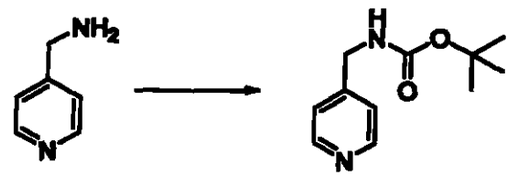
By essentially the same procedure set forth in Preparative Example 195, only substituting the compound prepared in Preparative Example 193, the above compound was prepared (0.3 g, 83% yield). MS: MH^+ = 438.

PREPARATIVE EXAMPLE 197:



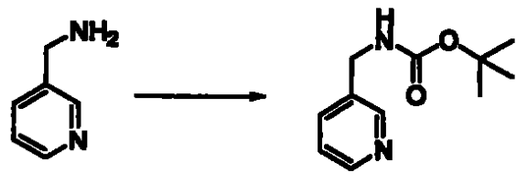
A solution of the compound prepared in Preparative Example 195 (0.15 g, 0.3 mmol), phenylboronic acid (0.073 g, 2.0 eq.), K_3PO_4 (0.19 g, 3.0 eq.), and $Pd(PPh_3)_4$ (0.017 g, 5 mol %) was heated at reflux in DME (16 mL) and H_2O (4 mL) 7 hours. The resulting solution was cooled to room temperature, 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:



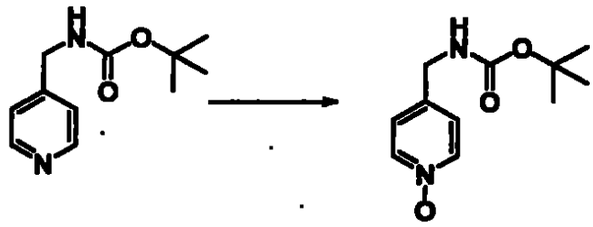
To a solution of 4-aminomethylpyridine (1.41 mL, 13.87 mmol) in CH_2Cl_2 (50 mL) was added BOC_2O (3.3 g, 1.1 eq.) and TEA and the resulting solution was stirred a room temperature 2 hours. The reaction mixture was diluted with H_2O (50 mL) and extracted with CH_2Cl_2. The combined organics were dried 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:



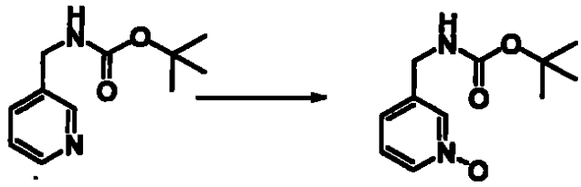
By essentially the same procedure set forth in Preparative Example 198 only substituting 3-aminomethylpyridine, the above compound was prepared as a yellow oil (2.66 g, 92% yield). LCMS: MH^+= 209.

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.

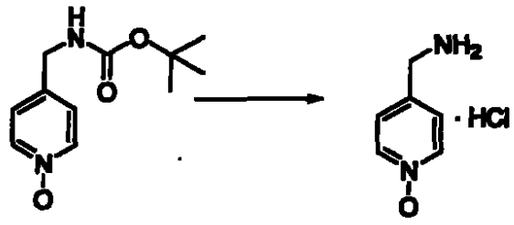
PREPARATIVE EXAMPLE 201:



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,

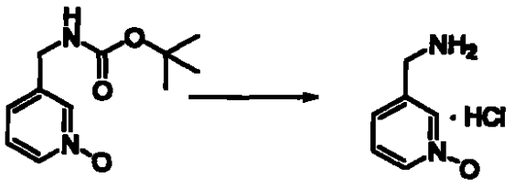
filtered, and concentrated under reduced pressure to give a white solid (21.0 g, 72% yield). MS: MH^+= 255.

PREPARATIVE EXAMPLE 202:



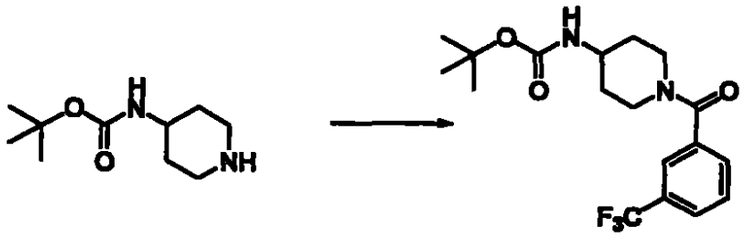
The compound prepared in Preparative Example 200 (0.29 g, 1.29 mmol) was stirred at room temperature in 4M HCl in dioxane (0.97 mL) 2 hours. The reaction mixture was concentrated *in vacuo* and used without further purification. LCMS: MH^+= 125.

PREPARATIVE EXAMPLE 203:



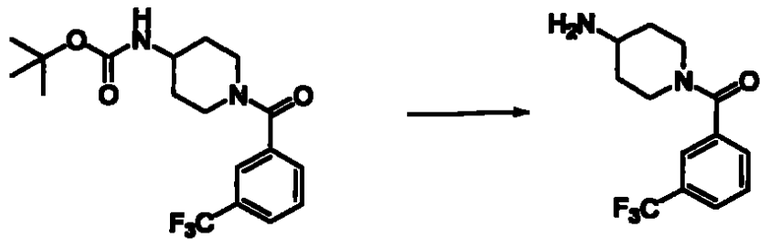
By essentially the same procedure set forth in Preparative Example 202 only substituting the compound prepared in Preparative Example 201, the compound shown above was prepared. LCMS: MH^+= 125.

PREPARATIVE EXAMPLE 204:



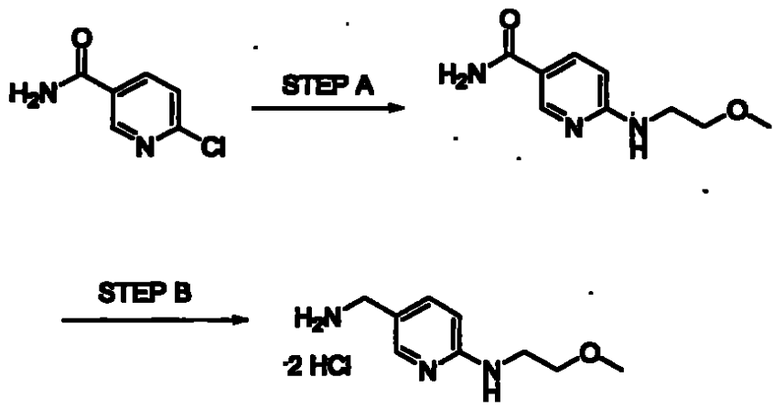
To 4-N-t-Butoxycarbonylaminopiperidine (0.8 g, 4.0 mmol) in CH_2Cl_2 (10 mL) at 0°C was added TEA (1.40 mL, 2.5 eq.) and 3-trifluoromethyl benzoyl chloride (1.05 g, 1.25 eq.). The resulting solution was stirred 15 minutes and warmed to room temperature and stirred 3 hours. The reaction mixture was diluted 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.

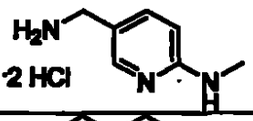
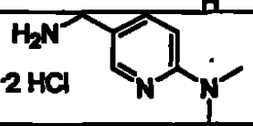
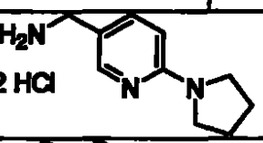
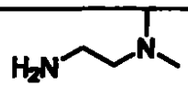
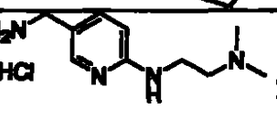
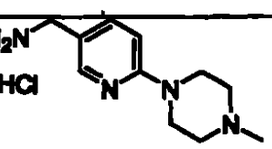
STEP B:

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.

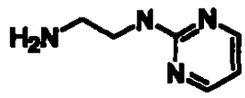
PREPARATIVE EXAMPLES 207-211:

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

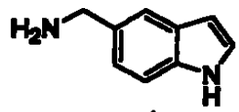
Prep.Ex.	Column 2 (Amine)	Column 3 (Amine)	CMPD M+H (free base)
207			M+H = 138
208			M+H = 152
209			M+H = 178
210			M+H = 195
211			M+H = 207

PREPARATIVE EXAMPLE 212:



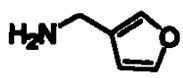
The above compound was prepared accordingly to the methods described in WO 91/18904.

PREPARATIVE EXAMPLE 213:



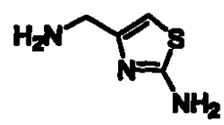
The above compound was prepared accordingly to the methods described in US 6,180,627 B1.

PREPARATIVE EXAMPLE 214:



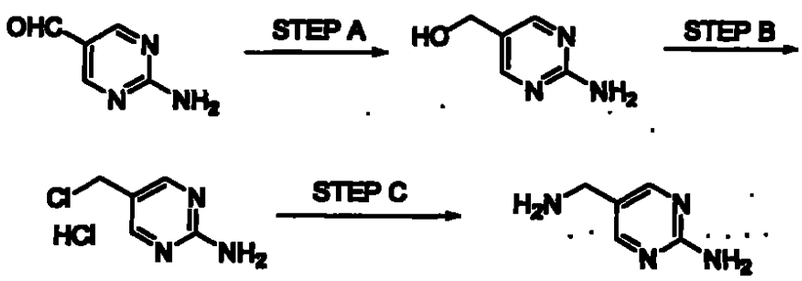
The known amine was prepared as described in *J. Med. Chem.* (2001), *44*, 4505-4508.

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.

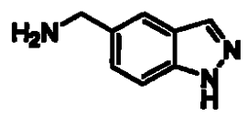
STEP B:

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:

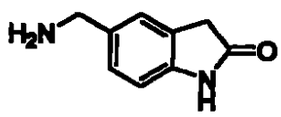
To a 15 mL pressure tube charged with a stir bar was added chloride (150 mg, 0.83 mmol) from Preparative Example 216, Step B followed by 7 M NH_3/MeOH (10 mL). The resulting solution was stirred for 48 h at rt where upon the mixture was concentrated under reduced pressure to afford a light yellow solid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

PREPARATIVE EXAMPLE 217:



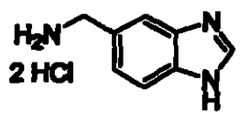
The above compound was prepared accordingly to methods described in WO 00/26210.

PREPARATIVE EXAMPLE 218:



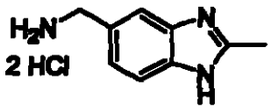
The above compound was prepared accordingly to methods described in WO 99/10325.

PREPARATIVE EXAMPLE 219:



The known amine dihydrochloride was prepared according to methods described in WO 02/64211.

PREPARATIVE EXAMPLE 220:



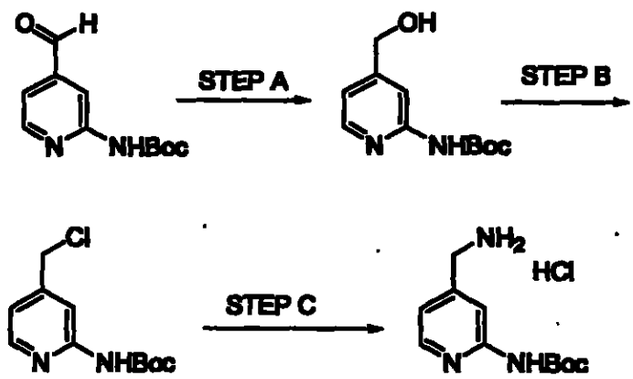
The above compound was prepared according to methods described in WO 02/64211.

PREPARATIVE EXAMPLE 221:



The known primary alcohol was prepared according to WO 00/37473 and was converted to the desired amine dihydrochloride in analogous fashion as Preparative Example 220 according to WO 02/064211.

PREPARATIVE EXAMPLE 222:



STEP A:

To a solution of aldehyde (WO 02/32893) (0.46 g, 2.07 mmol) in MeOH/THF (2 mL/2 mL) at 0 °C was added $NaBH_4$ (94 mg, 2.48 mmol) in one portion. The resulting mixture was stirred for 12 h at rt and was diluted with sat.

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.

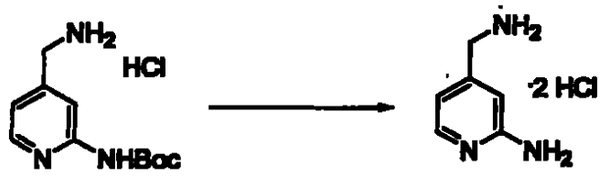
STEP B:

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:

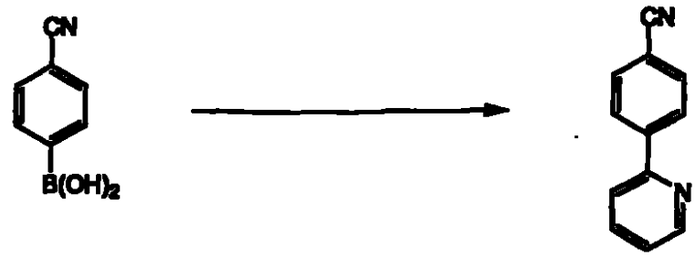
To a solution of crude chloride from Preparative Example 222, Step B (0.33 g, 1.36 mmol) in a pressure tube charged with 7M NH_3/MeOH (35 mL) and the mixture was stirred for 72 h. The mixture was concentrated under reduced pressure to afford 257 mg (85%) of a yellow semisolid. M+H (free base) = 224.

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:

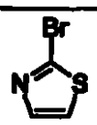
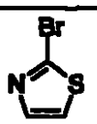
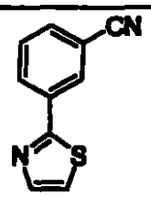


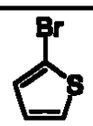
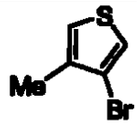
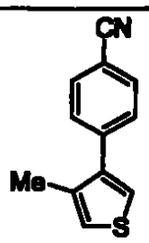
$Pd(PPh_3)_4$ (0.404 gm, 0.35 mmol) was added to a degassed solution of 4-cyanobenzene boronic acid (1.029 g, 7 mmol) and 2-bromopyridine (1.11 g, 7 mmol) in 75 mL acetonitrile. 0.4 M sodium carbonate solution (35 mL) was added to the reaction mixture and the resulting solution was refluxed at 90°C under 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:

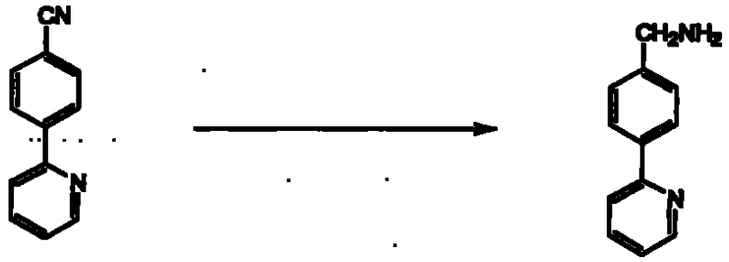
By following essentially same procedure described in Preparative Example 224, only substituting the bromides in column 2 of Table 14, compounds in column 3 of Table 14 were prepared.

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:

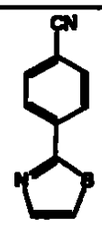
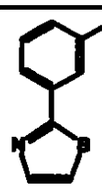
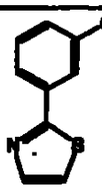
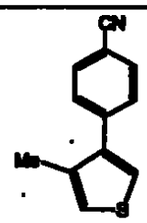
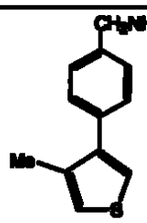


BH_3-THF solution (1 M, 24 mL, 5 eq) was added slowly to a stirring solution of 4-(2-pyridyl)-benzonitrile (0.85 g, 4.72 mmol) in anhydrous THF (25 mL) under Ar, and the resulting solution was refluxed for about 12 hr. The solution was cooled to 0°C using ice-water. Methanol (15 mL) was added drop-wise 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).

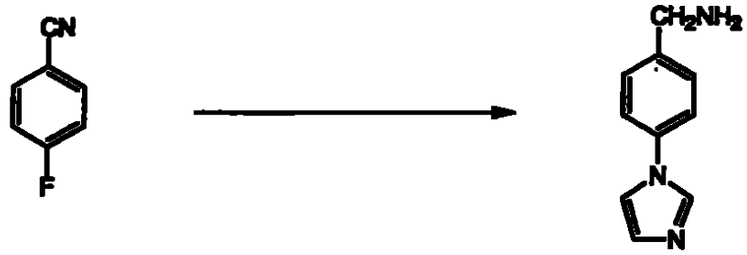
PREPARATIVE EXAMPLES 230-233:

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:

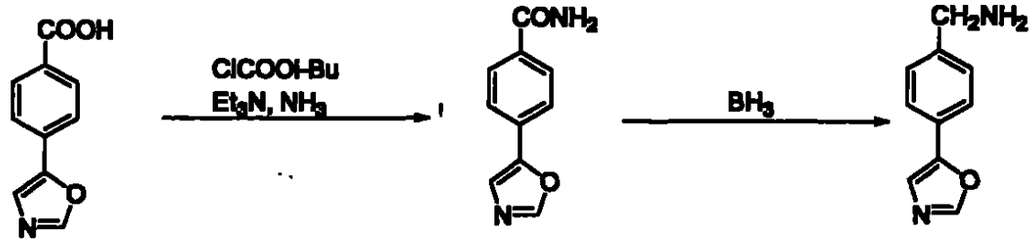
A mixture 4-fluorobenzonitrile (3 g, 25 mmol) and imidazolyl sodium (2.48 g, 27.5 mmol) in DMF (50 mL) was stirred at 80°C under Ar for 12 h. Progress of reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo* and the residue was diluted with 50 mL water and stirred. The aqueous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

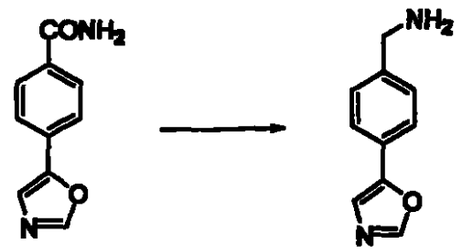
4-(1-imidazolyl)-benzonitrile (1g, 5.92 mmol) was dissolved in anhydrous THF (10 mL) and added drop-wise to a stirring solution of LAH –THF (1 M in THF, 18 mL) at room temperature. The reaction mixture was refluxed under Ar for 2 h and the progress was monitored by TLC. The mixture was cooled to 0°C 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:

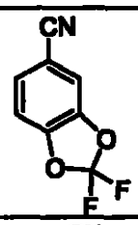
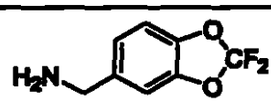
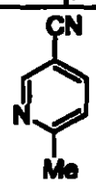
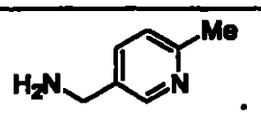


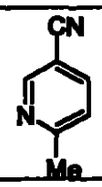
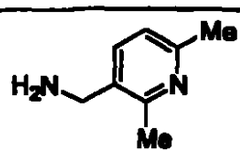
A suspension of 4-(5-oxazolyl)benzamide (500 mg, 2.657 mmol) in 10 mL of dry THF was cooled to 0 °C and 10 mL of 1 M BH_3.THF (10.00 mmol) was added. The contents were refluxed overnight and the excess borane was destroyed by dropwise addition of methanol. The solvent was evaporated and the residue was 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:

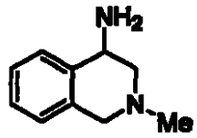
By essentially the same procedures set forth above, the compounds in Column 2 of Table 16 were reduced using the method indicated in Column 3 of Table 16 to give the amine indicated in Column 4 of Table 16.

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		

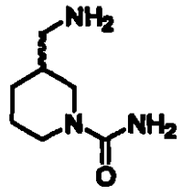
PREPARATIVE EXAMPLE 240



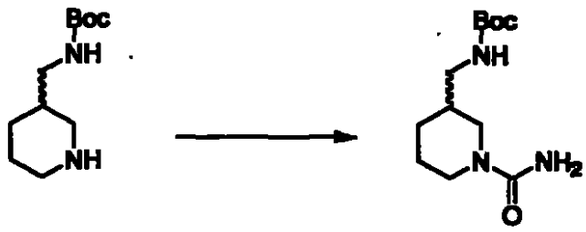
Prepared by the literature procedure (PCT Int. Appl, WO 0105783): ^{1}H NMR ($CDCl_3$) δ 7.35 (d, 1H), 7.24-7.10 (m, 2 H), 7.02 (d, 1H), 3.95 (t, 1H), 3.70 (d, 1H), 3.37 (d, 1H), 2.65 (m, 2H), 2.45 (s, 3H), 1.90 (bs, 2H)

PREPARATIVE EXAMPLE 241:

3-(AMINOMETHYL)PIPERIDINE-1-CARBOXAMIDE



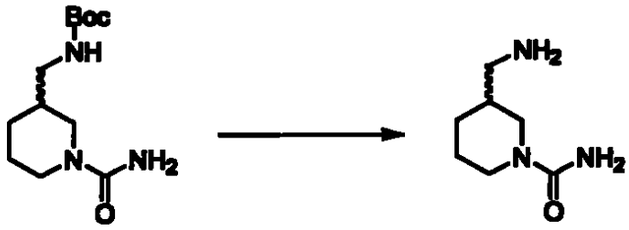
A. 3-(*tert*-BUTOXYCARBONYLAMINOMETHYL)PIPERIDINE-1-CARBOXAMIDE



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($C\underline{H}_3$)$_3$), 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_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.

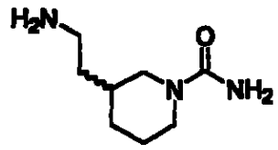
B. 3-(AMINOMETHYL)PIPERIDINE-1-CARBOXAMIDE



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, -$CH_2N\underline{H}_2$), 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, -$C\underline{H}_2NH_2$) 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 $C_{13}H_{25}O_3$: 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

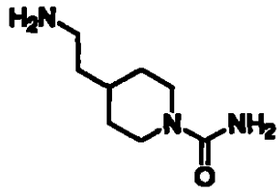


3-(2-*tert*-Butoxycarbonylaminoethyl)piperidine-1-carboxamide (392.7mg, 1.45mmoles) (prepared as described in Preparative Example 242, Step A above) was dissolved in methanol (7.5mL) and 10% conc. sulfuric acid in 1,4-dioxane (19.5mL) was added. The mixture was stirred at 25°C for 1.25h. The mixture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

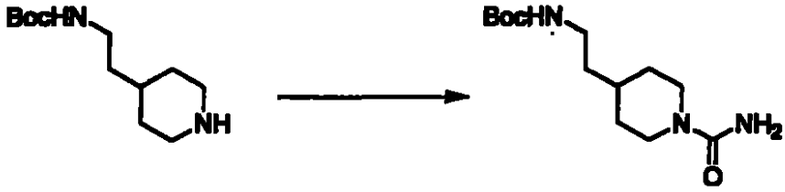
diluted with methanol and BioRad AG1-X8 resin (OH^- form) was added until the pH was basic. The resin was filtered off, washed with methanol, evaporated to dryness and chromatographed on a silica gel column (30x2.5cm) using 15% (10% conc, ammonium hydroxide in methanol)-dichloromethane as the eluant 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



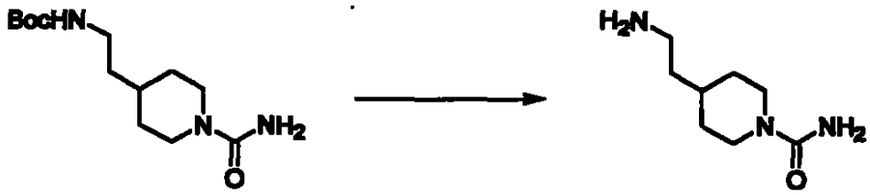
A. 4-(2-tert-BUTOXYCARBONYLAMINOETHYL)PIPERIDINE-1-CARBOXAMIDE



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 $C_{13}H_{25}O_3N_3$: 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.

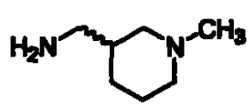
A. 3-(2-AMINOETHYL)PIPERIDINE-1-CARBOXAMIDE



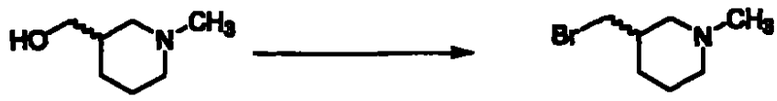
4-(2-*tert*-Butoxycarbonylaminoethyl)piperidine-1-carboxamide (283.3mg, 1.04mmoles) (prepared as described in Preparative Example 243, Step A above) was dissolved in methanol (5.4mL) and 10% conc. sulfuric acid in 1,4-dioxane (14.2mL) was added and the mixture was stirred at 25°C for 1.25h. The mixture 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

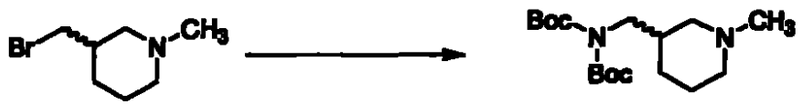


A. 3-(BROMOMETHYL)-1-METHYLPIPERIDINE



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, -CH_2Br) 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.

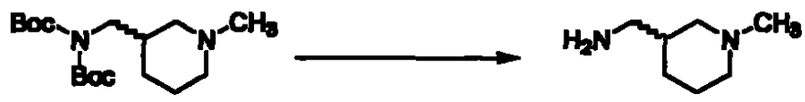
A. 3-(Di-tert-BUTOXYCARBONYLAMINOMETHYL)-1-METHYLPIPERIDINE



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.

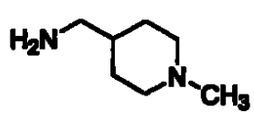
A. 3-(AMINOMETHYL)-1-METHYLPIPERIDINE



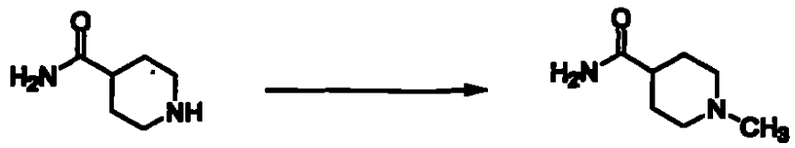
3-(Di-*tert*-butoxycarbonylamino)-1-methylpiperidine (500mg, 1.52mmoles) (from Preparative Example 244, Step B above) was dissolved in methanol (7.5mL) and 10% (v/v) conc. sulfuric acid in 1,4-dioxane (19.75mL) was added. The solution was stirred at 25°C for 0.5h. Methanol (300mL) was added, followed 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

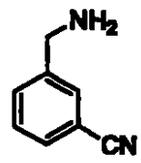


1-Methylisonipecotamide (6.75g, 47.5mmoles) (prepared as described in Preparative Example 245, Step A above) was dissolved in anhydrous THF (350mL) and the resulting mixture was added in portions to a stirred slurry of lithium aluminum hydride (1.8g, 47.5mmoles) in anhydrous THF (100mL) at 0°C under 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

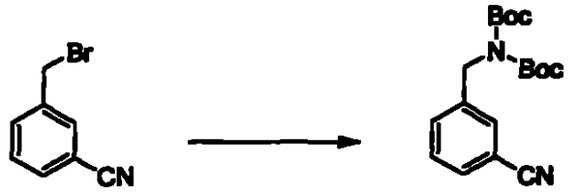
stirred mixture at 0°C, followed by 20% aqueous sodium hydroxide (1.42mL) and then distilled water (6.75mL) and the mixture was stirred for 15min. The mixture was filtered and the solids were washed with THF and dichloromethane. The combined filtrates were evaporated to dryness and chromatographed on 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



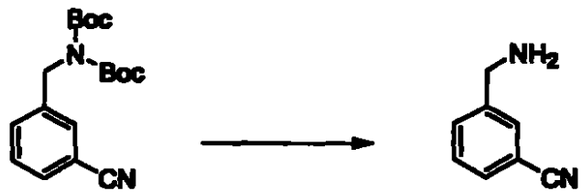
A. 3-(Di-*tert*-BUTOXYCARBONYLAMINO)BENZONITRILE



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 $C_{16}H_{25}N_2O_4$: 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.

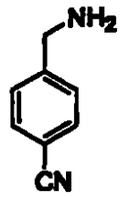
B. 3-(AMINOMETHYL)BENZONITRILE



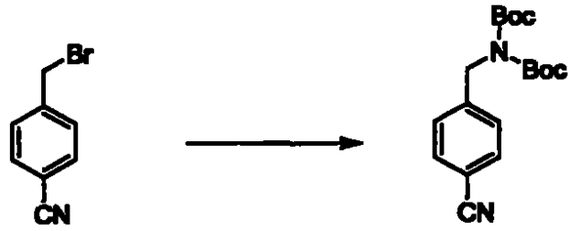
3-(Di-*tert*-butoxycarbonylamino)benzonitrile (2g, 6.0mmoles) (prepared as described in Preparative Example 246, Step A above) was dissolved in methanol (30mL) and 10%(v/v) (10% conc. sulfuric acid in 1,4-dioxane) (79mL) was added. The solution was stirred at 25°C for 0.25h and worked up as described 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, -$CH_2\underline{NH_2}$), 3.92 (2H, s, -$C\underline{H_2}NH_2$), 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

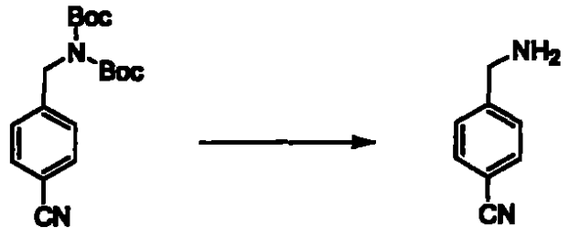


A. 3-(Di-*tert*-BUTOXYCARBONYLAMINOMETHYL)BENZONITRILE



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.

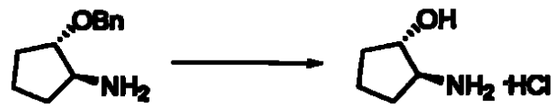
B. 4-(AMINOMETHYL)BENZONITRILE



4-(Di-*tert*-butoxycarbonylaminomethyl)benzonitrile (2g, 6.0mmoles) (prepared as described in Preparative Exampl 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, $-CH_2N\underline{H}_2$), 3.89 (2H, s, $-C\underline{H}_2NH_2$), 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



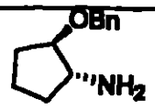
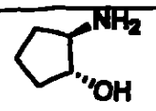
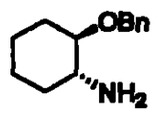
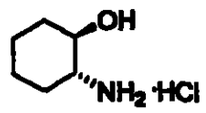
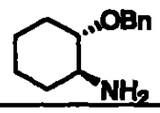
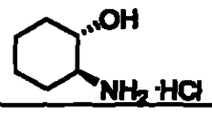
To a solution of (1*S*,2*S*)-2-benzyloxycyclopentyl amine (1.5 g, 7.84 mmol) in MeOH (50 mL) at rt was added 10 % Pd/C (50% wet, 1.0 g) followed by dropwise addition of conc. HCl (0.7 mL). The mixture was stirred under a balloon of H_2 for 14 h and the catalyst was filtered off thru a pad of Celite. 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

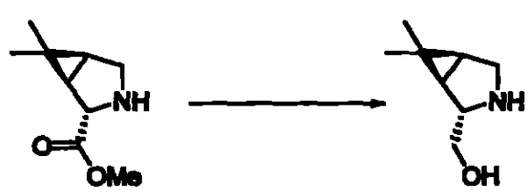
In an analogous fashion to Preparative Example 248, the benzyl protected cycloalkyl amines (Column 2) were converted to the desired aminocycloalkanol hydrochloride derivatives (Column 3) as listed in Table 17.

TABLE 17

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

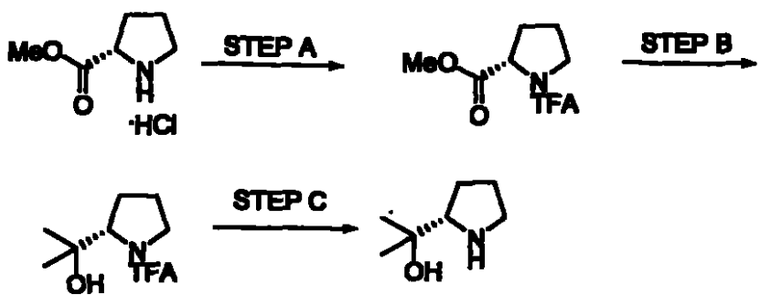
249			M+H = 102 (free base)
250			M+H = 116 (free base)
251			M+H = 116 (free base)

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 (65%) 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:

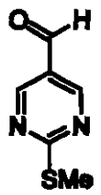
To a solution of the compound prepared in Preparative Example 253, Step A (0.68 g, 3.0 mmol) in THF (20 mL) at 0 °C was added MeMgI (5.1 mL, 3.0M in Et_2O) dropwise over 10 min. The resulting solution was stirred for 16 h at rt whereupon the mixture was quenched by addition of sat. aq. NH_4Cl. The mixture 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

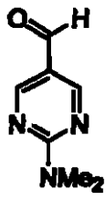
concentrated under reduced pressure to afford 128 mg (33%) of a maroon/orange oil. M+H = 130. This material was used without purification in the subsequent coupling step.

PREPARATIVE EXAMPLE 254:



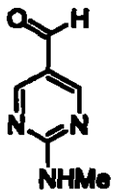
The aldehyde was prepared according to the procedure of Gupton (*J. Heterocyclic Chem.* (1991), *28*, 1281).

PREPARATIVE EXAMPLE 255



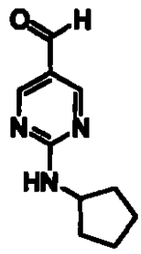
Using the aldehyde from Preparative Example 254, the procedure of Gupton (*J. Heterocyclic Chem.* (1991), *28*, 1281) was employed to prepare the title aldehyde.

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.

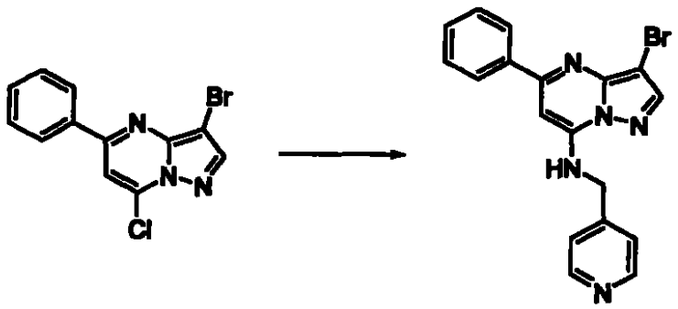
PREPARATIVE EXAMPLE 258



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

EXAMPLES

EXAMPLE 1:

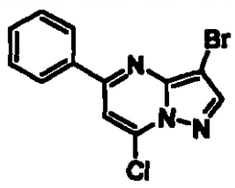
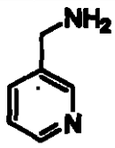
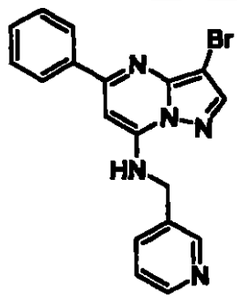
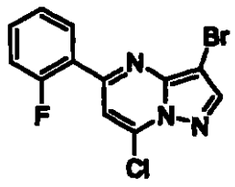
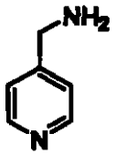
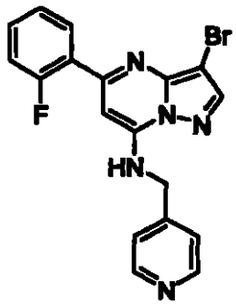
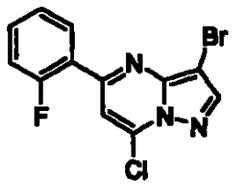
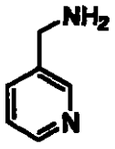
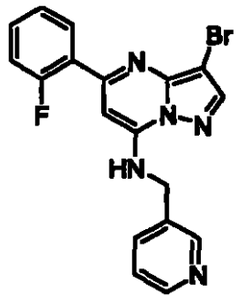


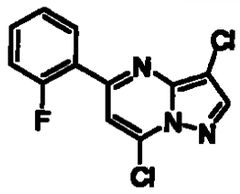
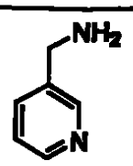
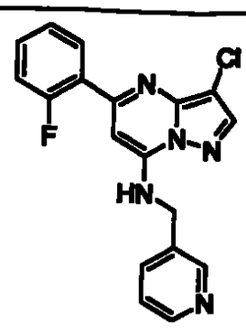
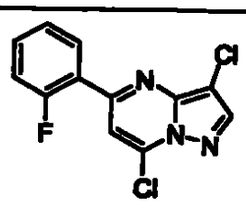
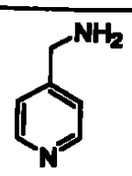
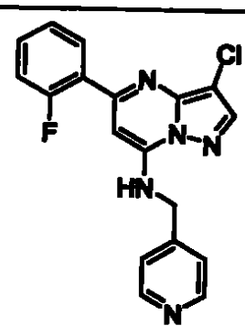
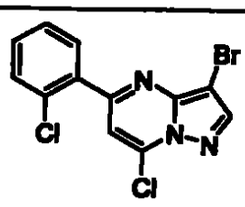
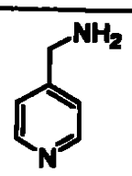
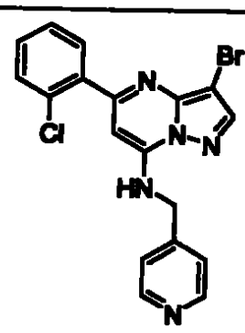
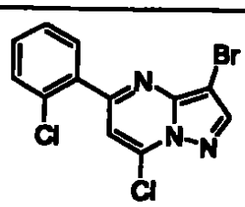
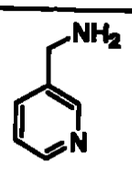
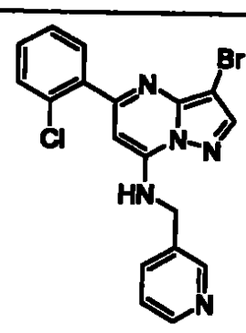
A solution of the product from Preparative Example 127 (0.27 g, 0.875 mmol), 4-aminomethylpyridine (0.12 g, 1.3 eq.), and K_2CO_3 (0.24 g, 2 eq.) in CH_3CN (5 mL) was stirred at room temperature 48 hours. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organics were 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).

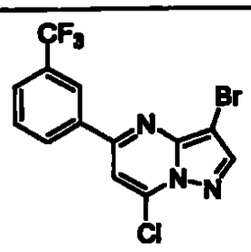
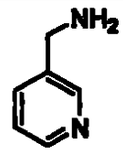
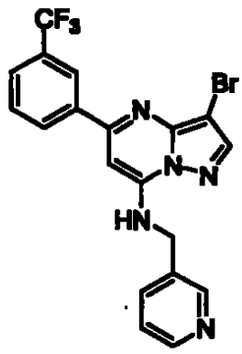
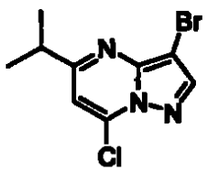
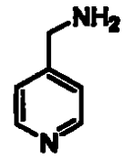
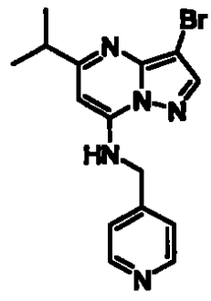
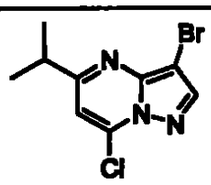
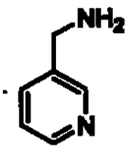
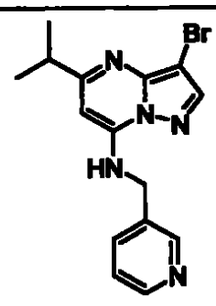
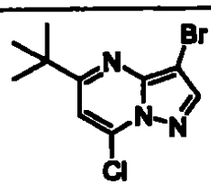
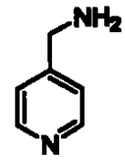
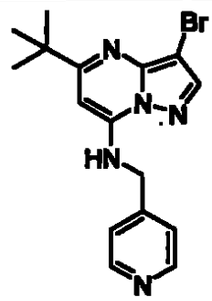
EXAMPLES 2-210:

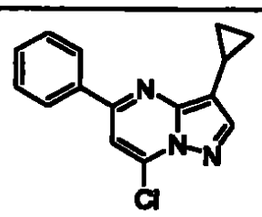
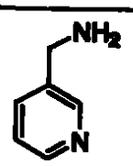
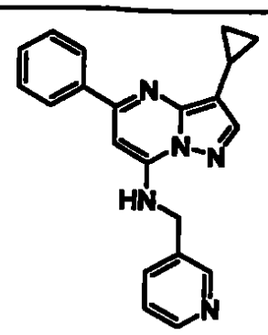
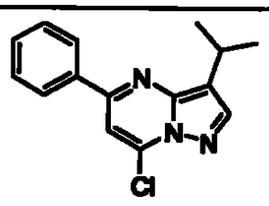
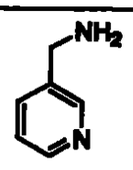
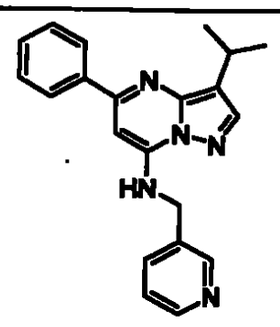
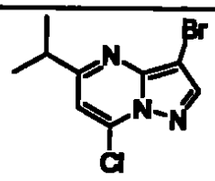
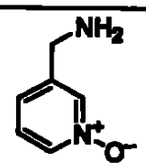
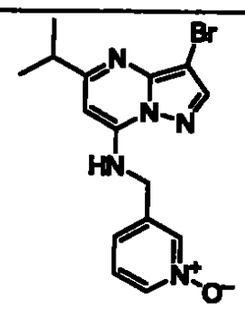
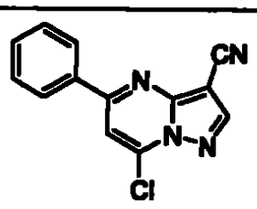
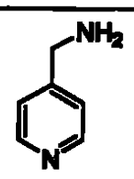
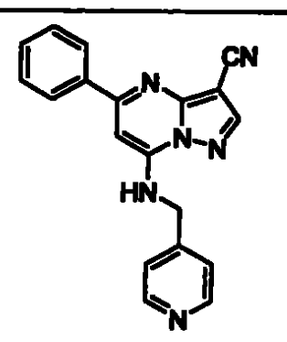
By following essentially the same procedure set forth in Example 1 only substituting the chlorides shown in Column 2 of Table 18 and the amines shown in Column 3 of Table 18, the compounds in Column 4 of Table 18 were prepared:

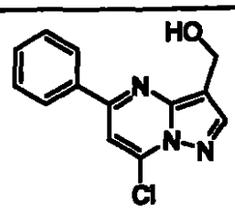
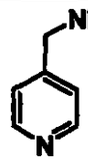
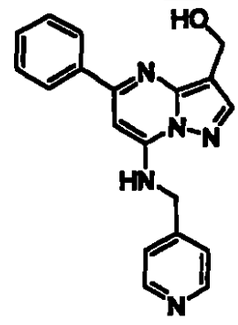
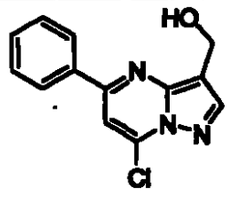
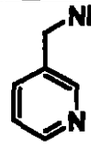
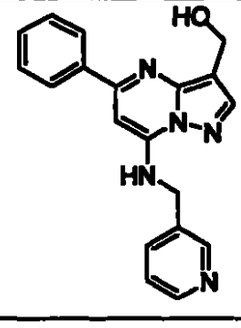
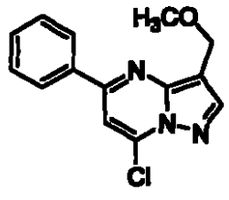
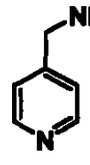
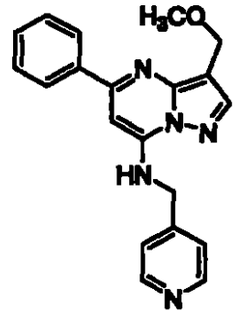
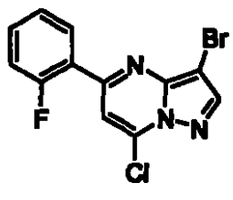
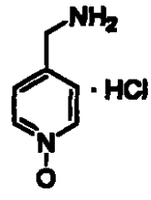
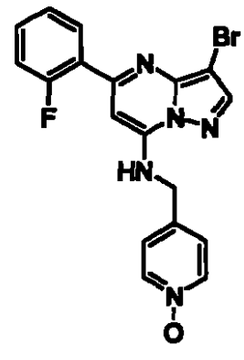
TABLE 18

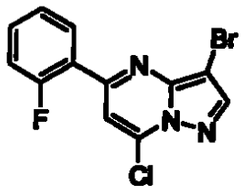
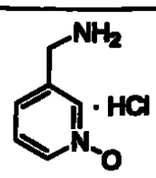
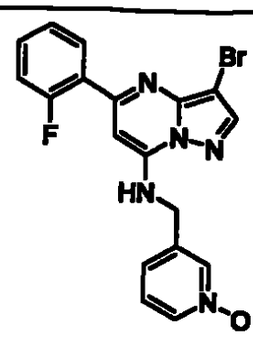
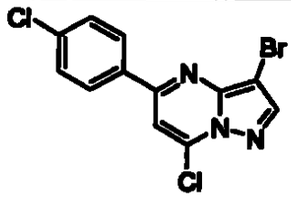
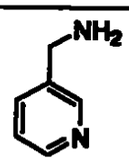
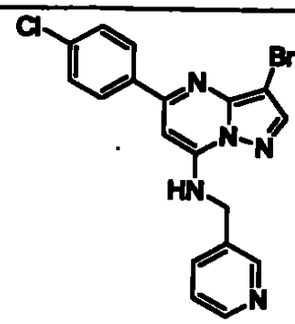
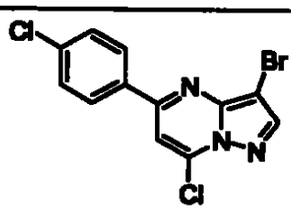
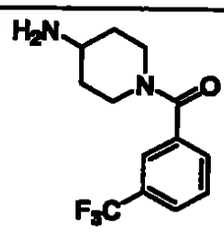
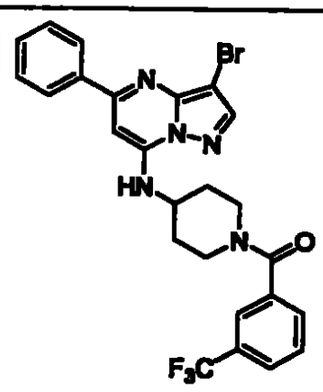
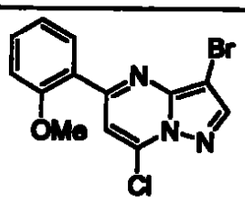
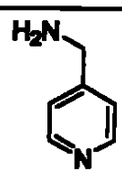
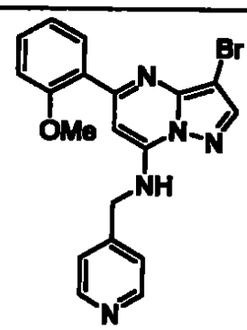
Ex.	Column 2	Column 3	Column 4	Data
2				LCMS: MH^+= 380; mp=175-176°C
3				LCMS: MH^+= 398; mp= 156-157°C
4				LCMS: MH^+= 398; mp= 45-49°C

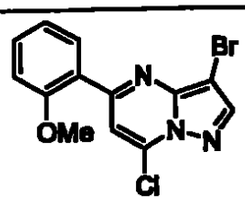
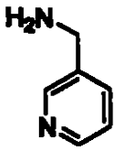
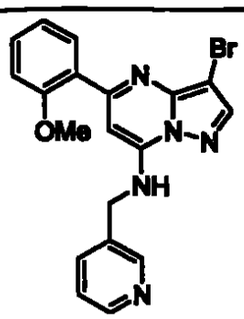
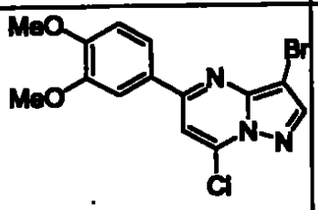
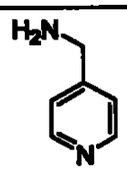
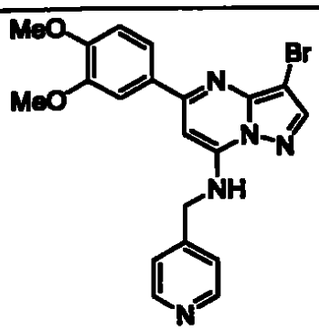
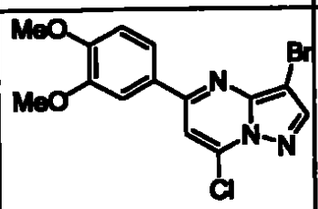
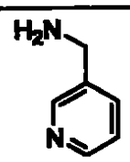
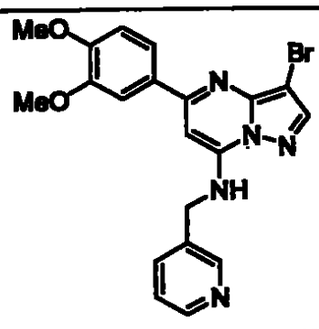
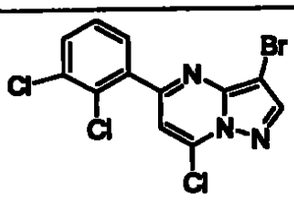
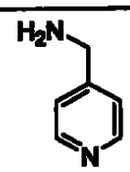
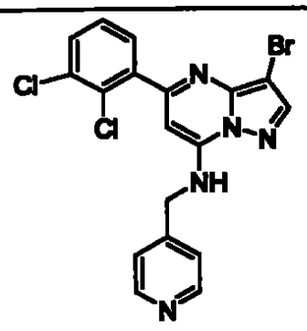
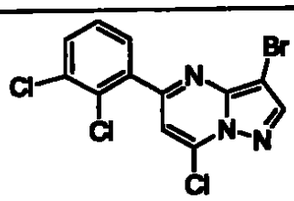
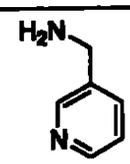
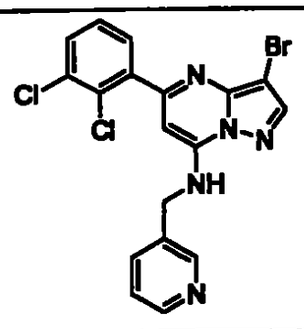
5				LCMS: MH^+= 354; mp= 43-46°C
6				LCMS: MH^+= 354; mp= 149-150°C
7				LCMS: MH^+= 414; mp= 86-92°C
8				LCMS: MH^+= 414; mp= 185-186°C

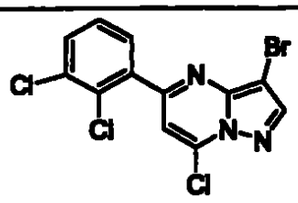
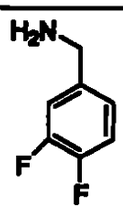
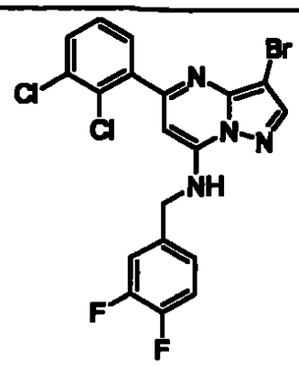
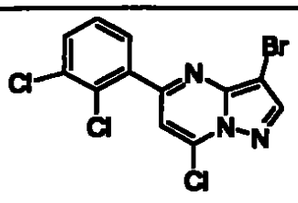
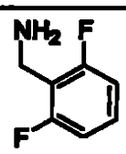
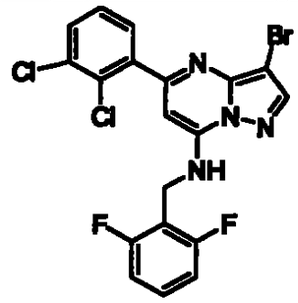
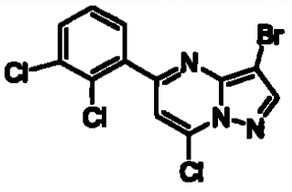
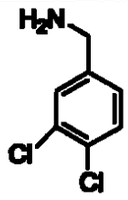
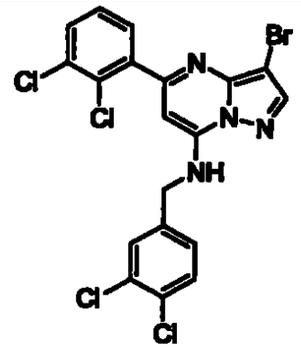
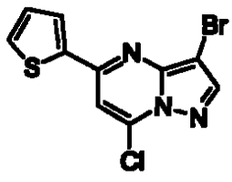
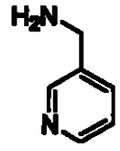
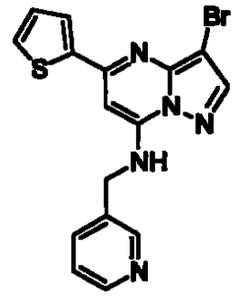
9				LCMS: MH^+= 446; mp= 167-168°C
10				LCMS: MH^+= 346; mp= 57-58°C
11				LCMS: MH^+= 347; mp=122.9-125.3 °C
12				LCMS: MH^+= 360; mp= 127-128°C

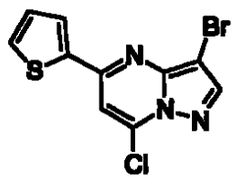
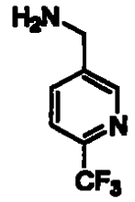
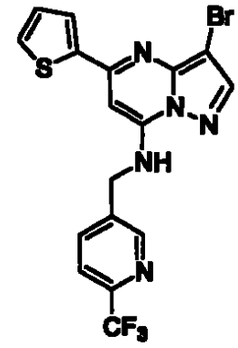
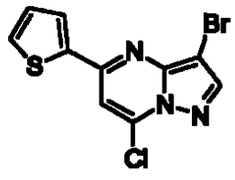
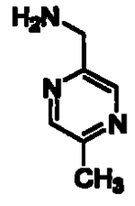
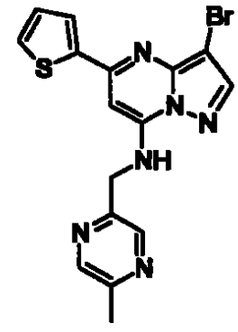
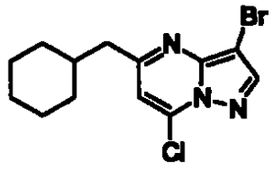
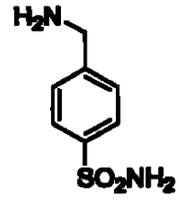
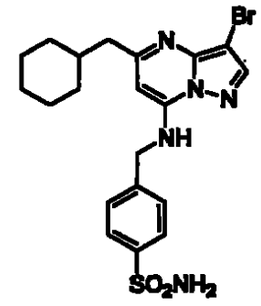
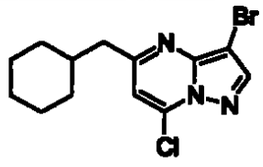
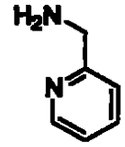
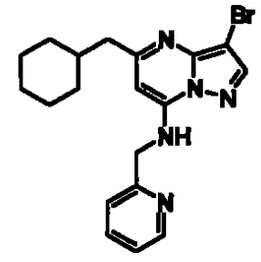
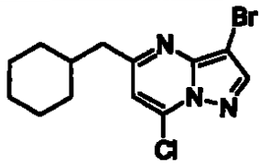
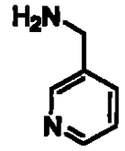
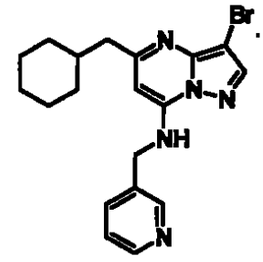
13				LCMS: MH^+= 342; mp= 133-135°C
14				LCMS: MH^+= 344; mp= 152-155°C
15				LCMS: MH^+= 362; mp= 164-167°C
16				LCMS: MH^+= 327; mp= 146-155°C

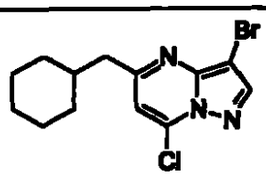
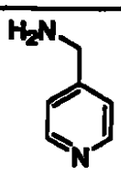
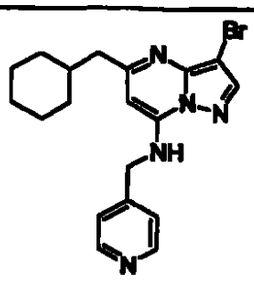
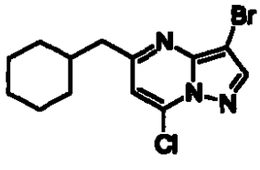
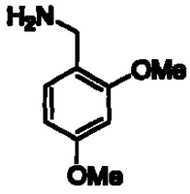
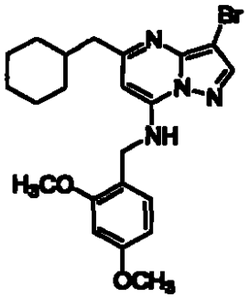
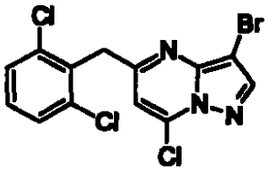
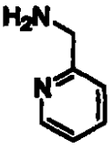
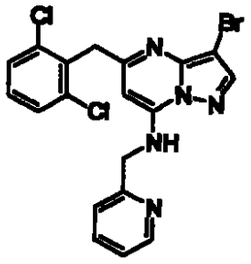
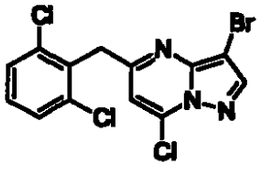
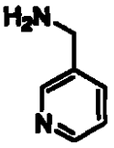
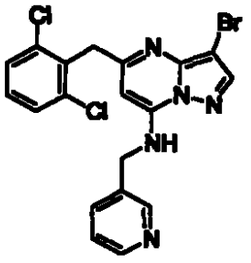
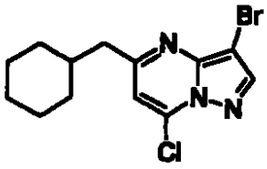
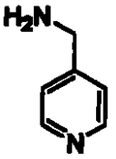
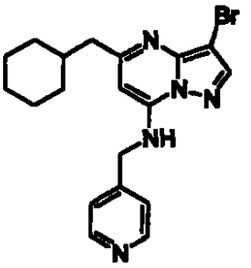
17				LCMS: MH^+= 332; mp= 71-82°C
17.1				MS: MH^+ = 332.
18				LCMS: MH^+= 346; mp= 58-65°C
19				LCMS: MH^+= 414; mp= 211-213°C

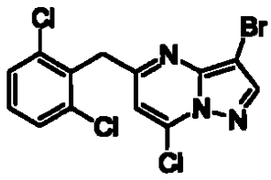
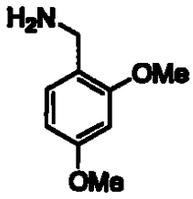
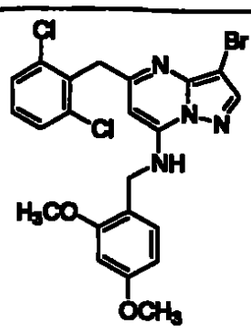
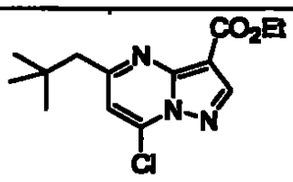
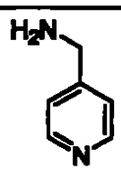
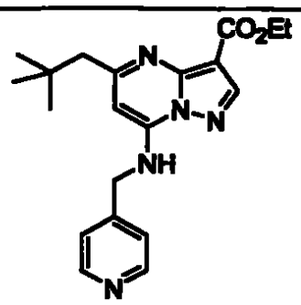
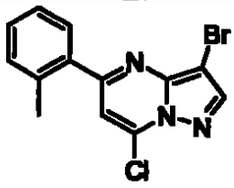
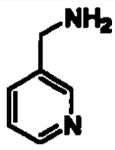
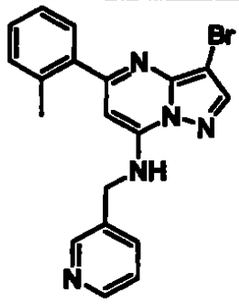
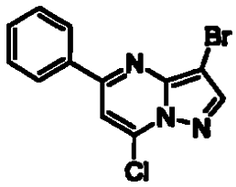
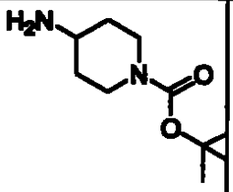
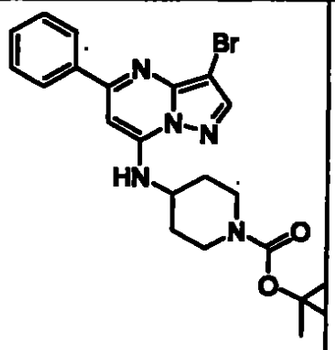
20				LCMS: MH^+= 414; mp= 194-197°C
21				MS: MH^+ = 414 m.p. 211 – 216°C
22				LCMS: MH^+= 544; mp= 104-107°C
23				Yield = 83% LCMS: MH^+ = 410.

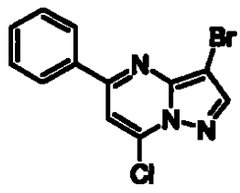
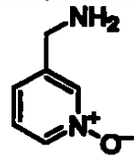
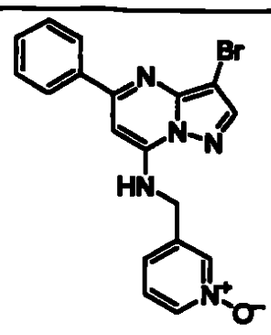
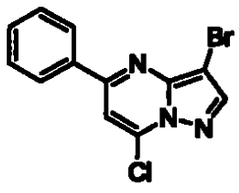
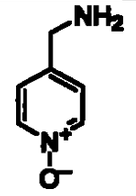
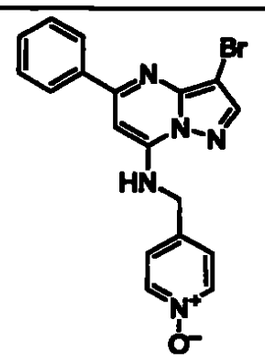
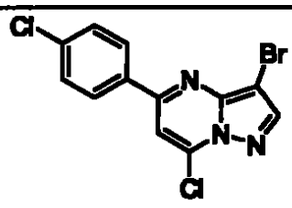
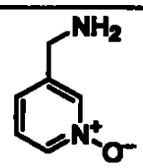
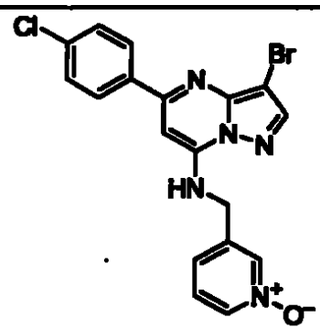
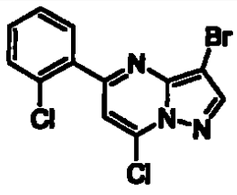
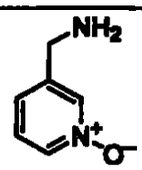
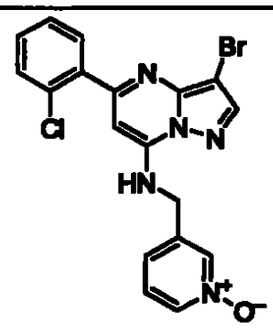
24				Yield = 84% LCMS: MH^+ = 410.
25				Yield = 96% LCMS: MH^+ = 440.
26				Yield = 99% LCMS: MH^+ = 440.
27				Yield = 89% LCMS: MH^+ = 448.
28				Yield = 78% LCMS: MH^+ = 448.

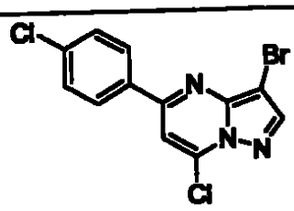
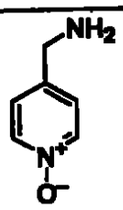
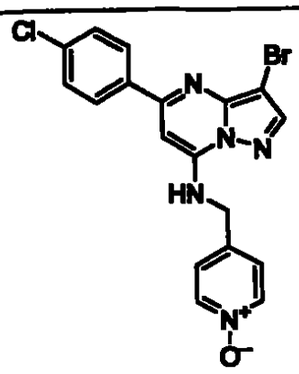
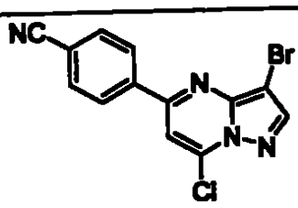
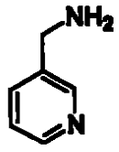
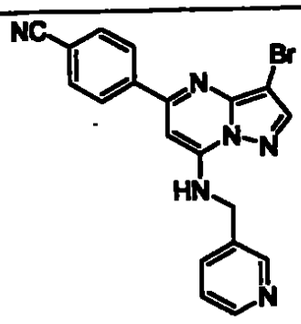
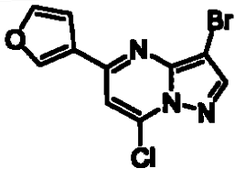
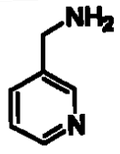
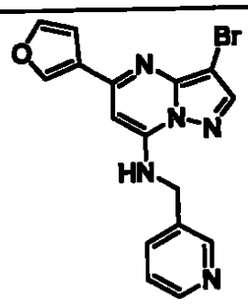
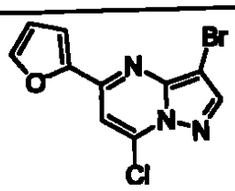
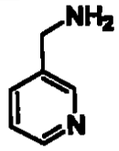
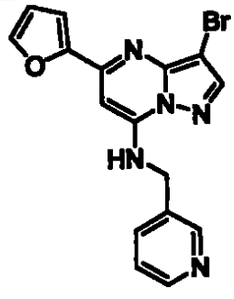
30				Yield = 98% LCMS: MH^+ = 483.
31				Yield = 35% LCMS: MH^+ = 483.
32				Yield = 77% LCMS: MH^+ = 515.
33				Yield = 100% m.p. 179°C LCMS: MH^+ = 388

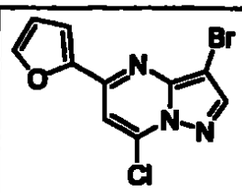
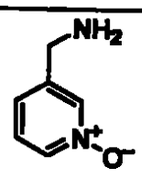
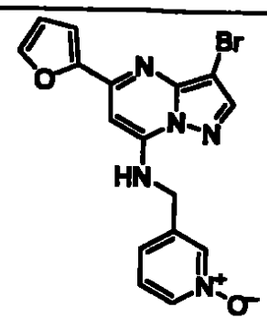
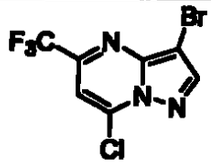
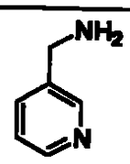
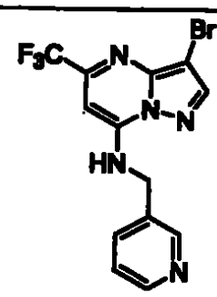
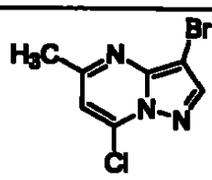
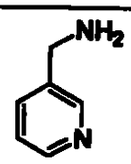
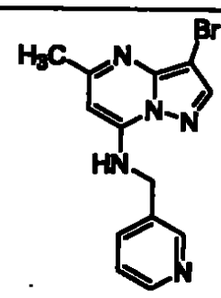
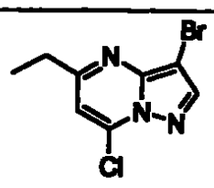
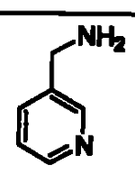
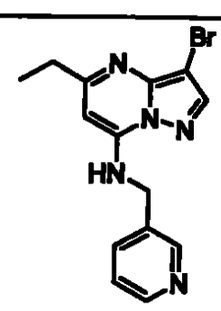
34				Yield = 99% m.p. 186°C LCMS: MH^+ = 456
35				Yield = 98% m.p. 181°C LCMS: MH^+ = 401
36				Yield = 63% m.p. 192°C LCMS: MH^+ = 480
37				Yield = 75% m.p. 126 – 127°C LCMS: MH^+ = 400
38				Yield = 94% m.p. 132 -133°C LCMS: MH^+ = 400

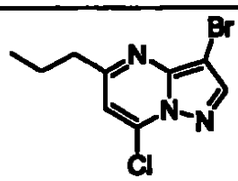
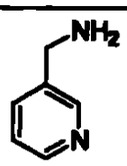
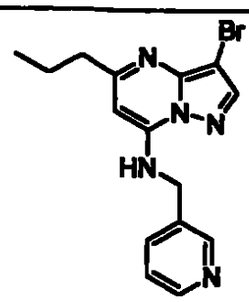
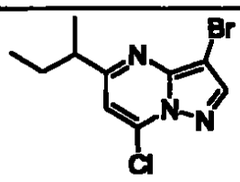
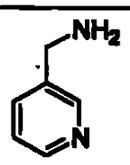
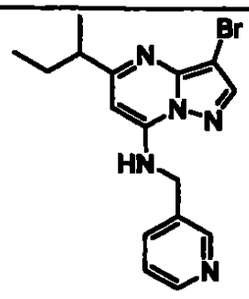
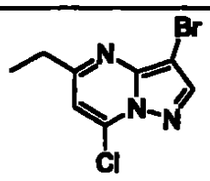
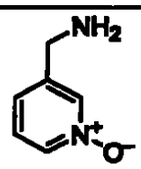
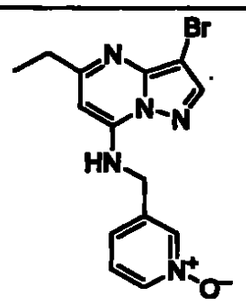
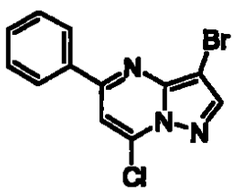
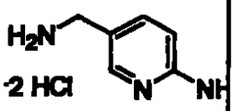
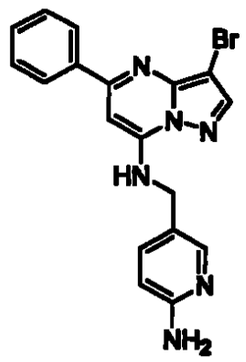
39				Yield = 95% m.p. 121 – 122°C LCMS: MH^+ = 400
40				Yield = 98% LCMS: MH^+ = 460
41				Yield = 87% m.p. 170 - 171°C LCMS: MH^+ = 464
42				Yield = 84% m.p. 216 -217°C LCMS: MH^+ = 464
43				Yield = 96% m.p. 214°C LCMS: MH^+ = 464

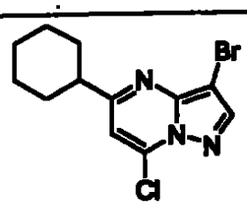
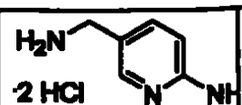
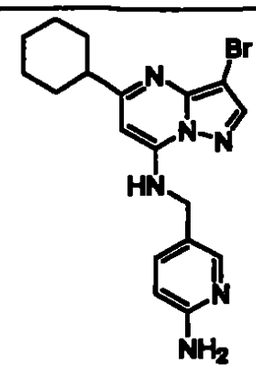
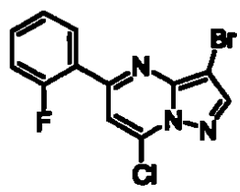
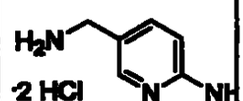
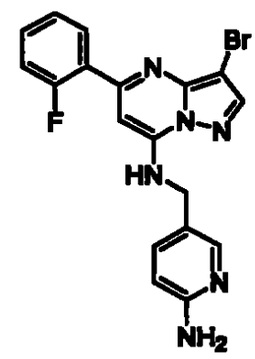
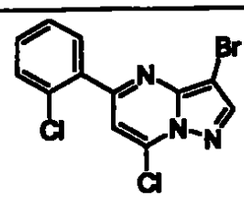
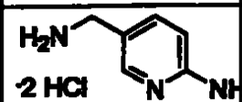
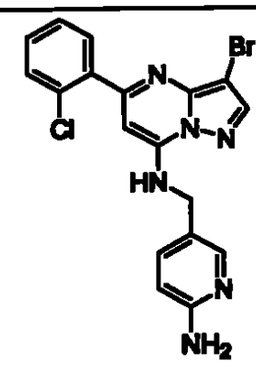
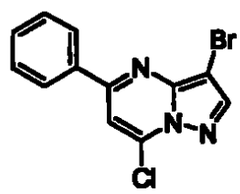
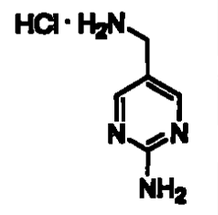
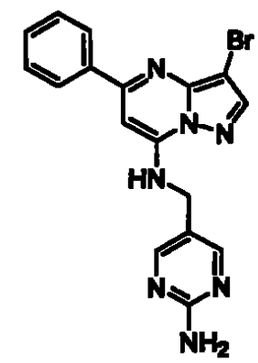
44				Yield = 95% m.p. 158°C LCMS: MH^+ = 522
45				Yield=90 % LCMS: MH^+= 278
46				Yield=10 0% ; LCMS: MH^+=394
47				LCMS: MH+ = 473 m.p. 84 - 87°C

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

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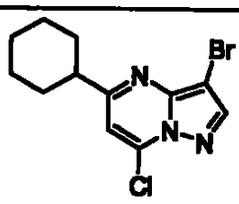
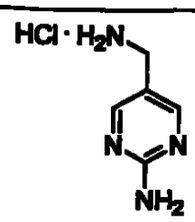
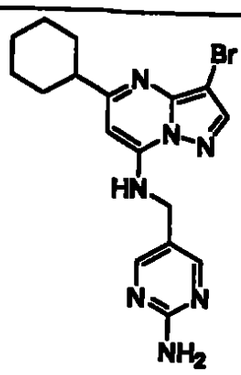
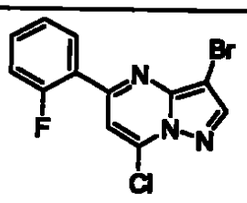
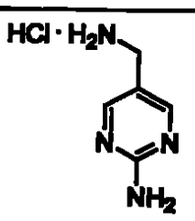
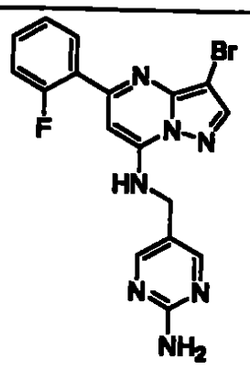
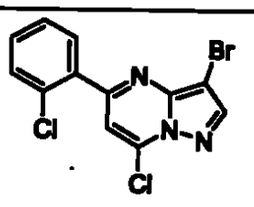
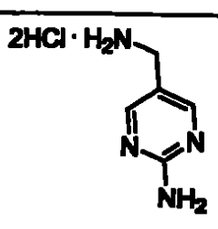
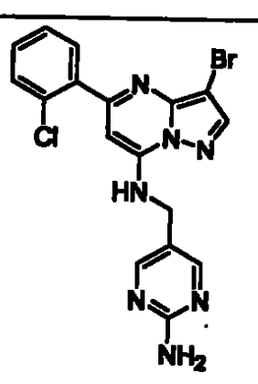
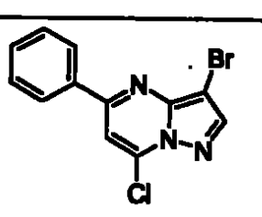
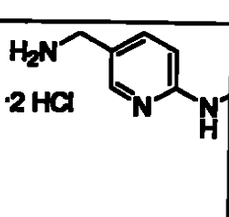
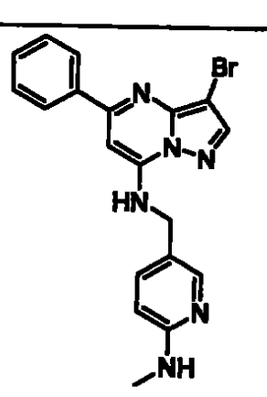
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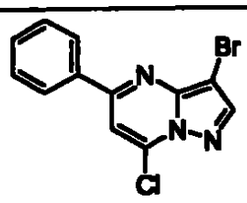
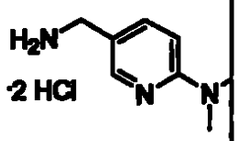
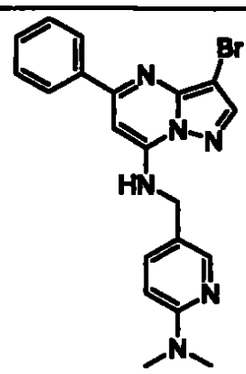
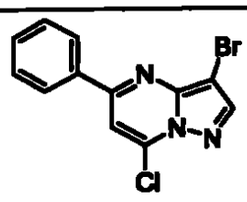
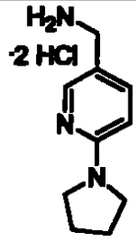
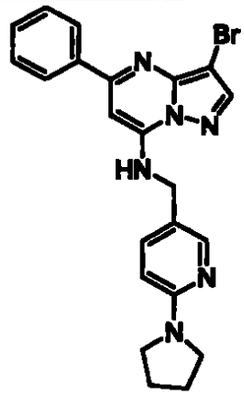
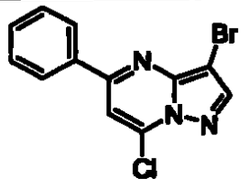
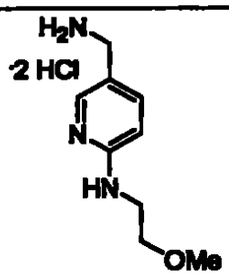
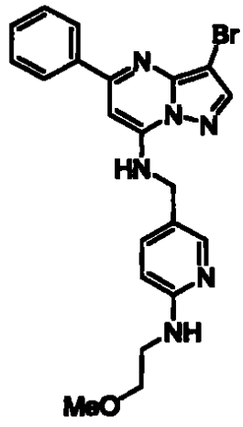
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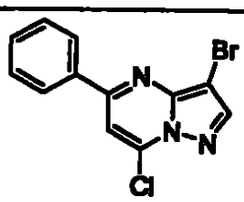
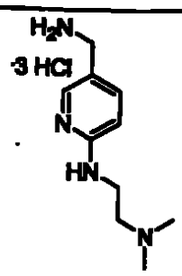
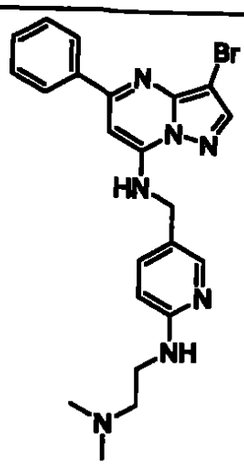
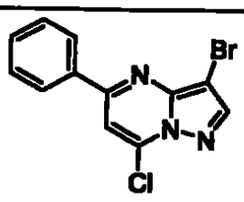
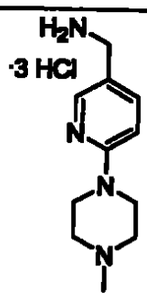
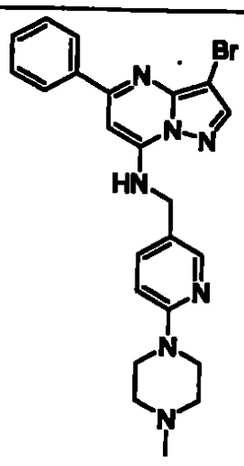
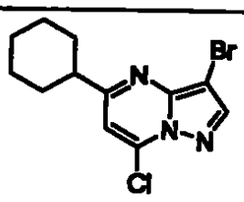
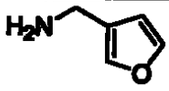
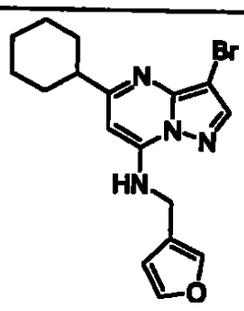
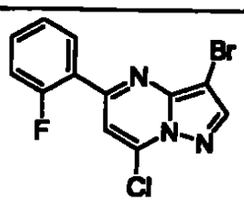
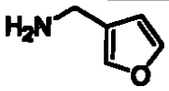
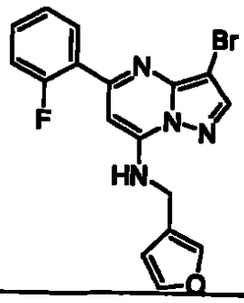
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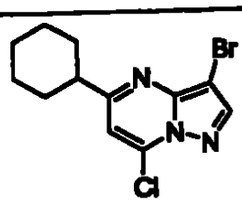
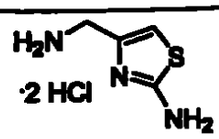
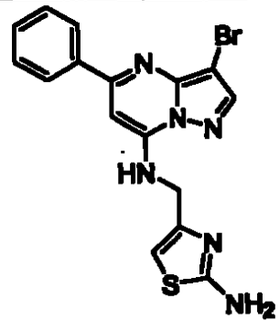
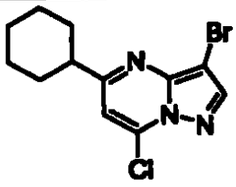
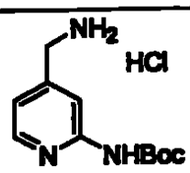
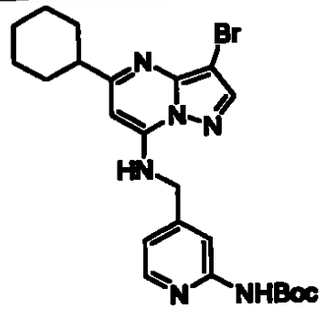
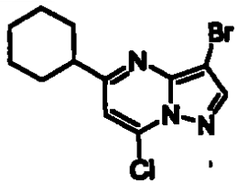
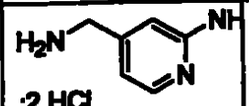
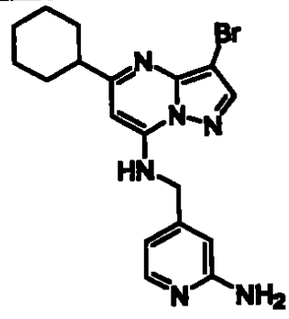
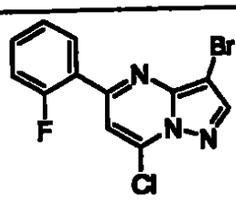
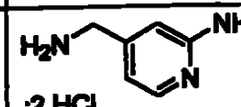
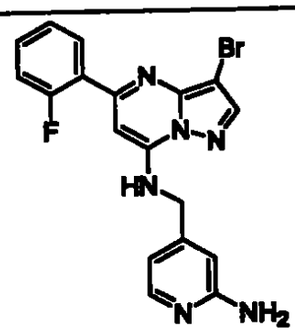
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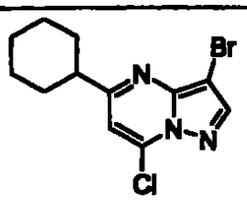
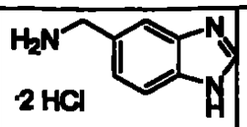
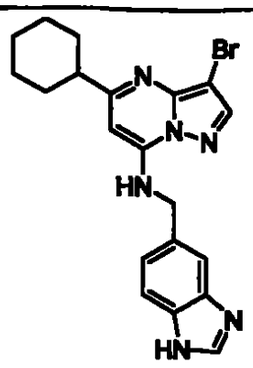
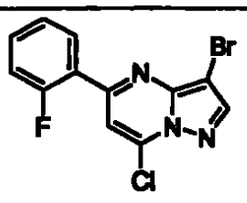
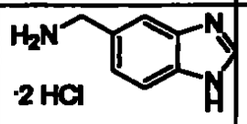
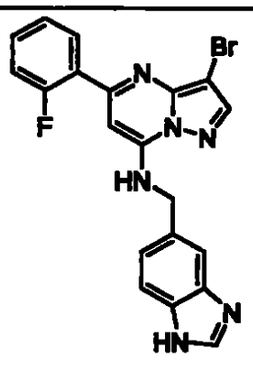
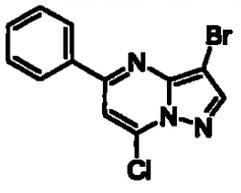
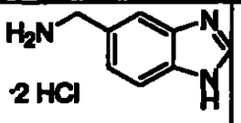
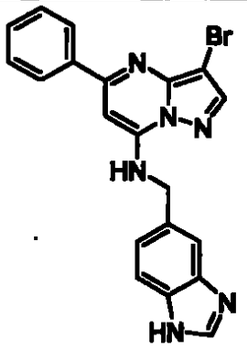
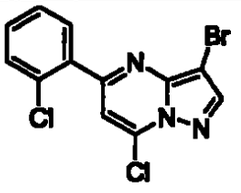
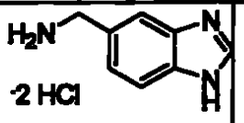
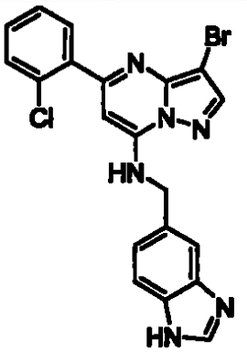
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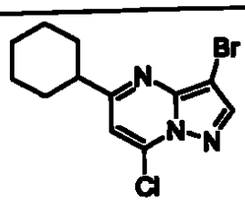
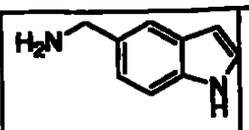
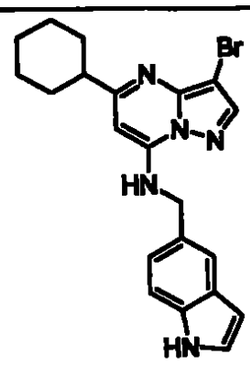
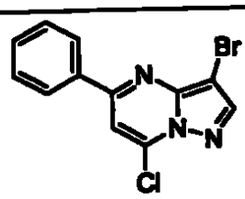
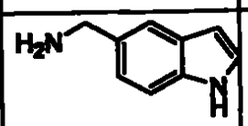
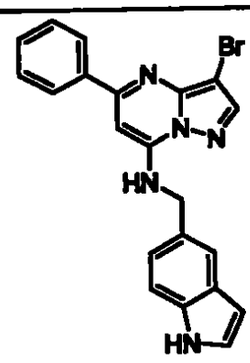
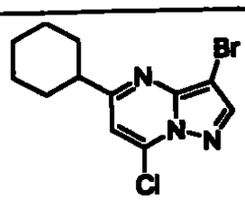
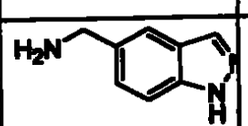
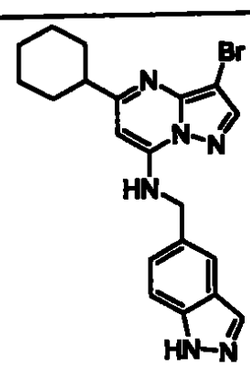
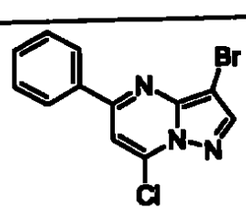
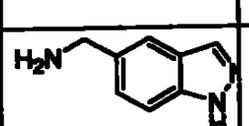
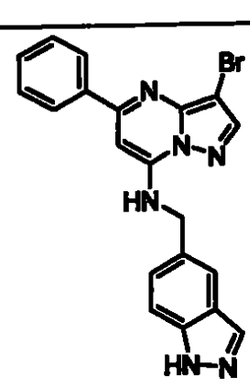
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70				1. mp = 230-232 2. M+H = 415
71				1. mp = 235-238 2. M+H = 431
72				1. mp = 186-188 2. M+H = 410

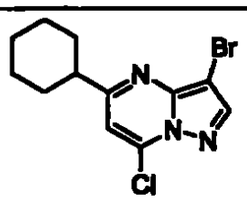
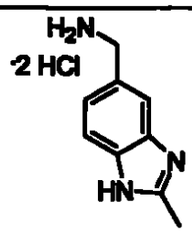
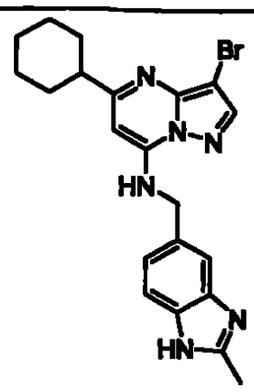
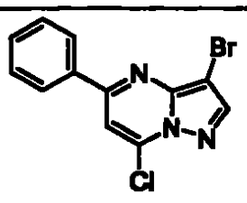
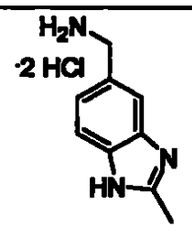
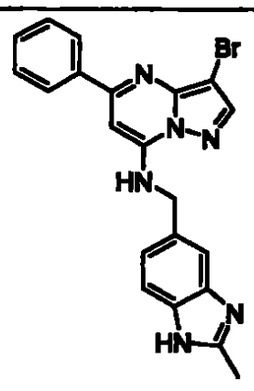
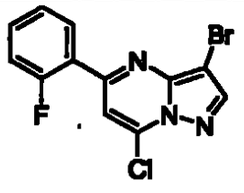
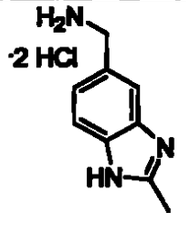
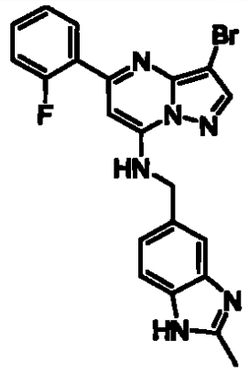
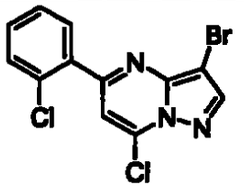
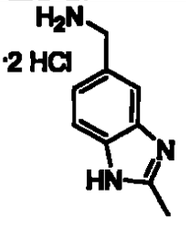
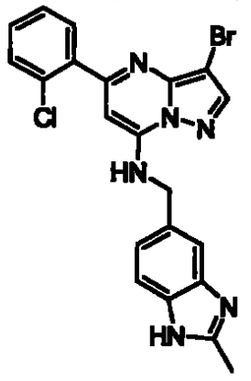
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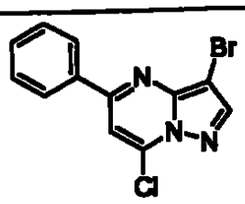
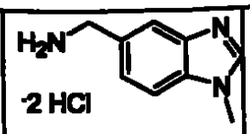
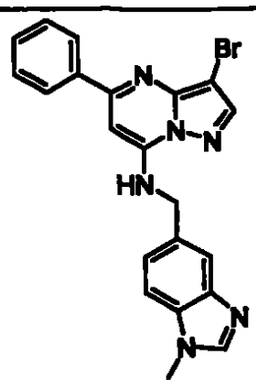
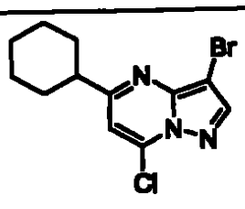
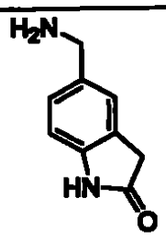
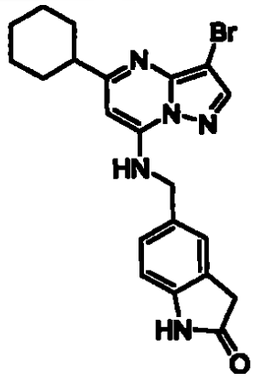
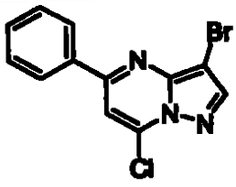
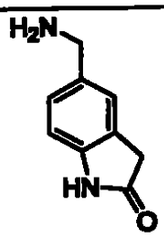
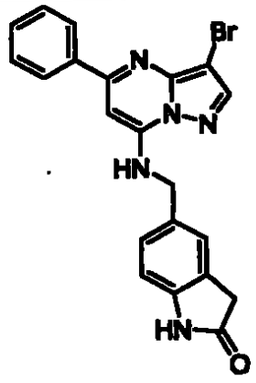
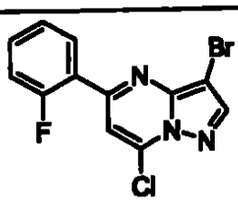
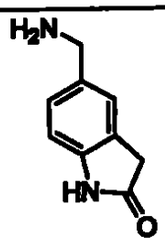
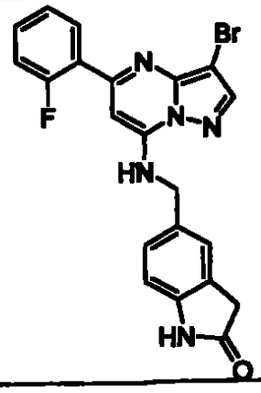
76				1. mp = 230-232 2. M+H = 467
77				1. mp = 131-133 2. M+H = 479
78				1. mp = 85-88 2. M+H = 376
79				1. mp = 131-133 2. M+H = 388

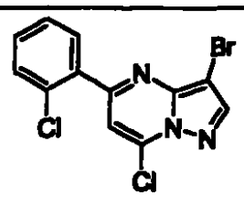
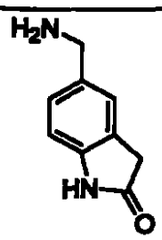
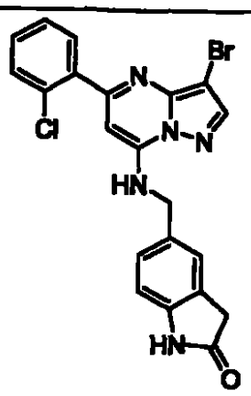
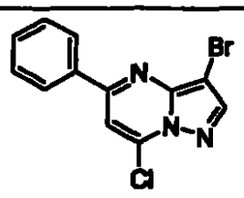
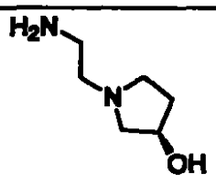
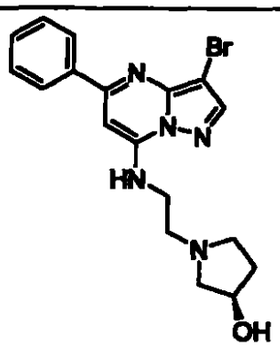
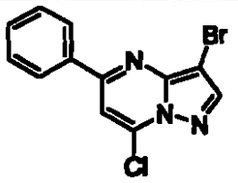
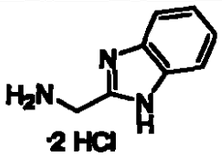
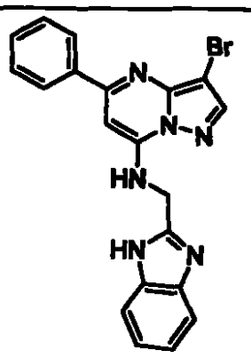
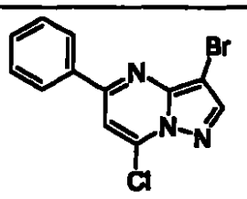
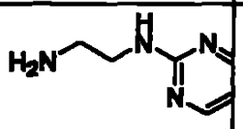
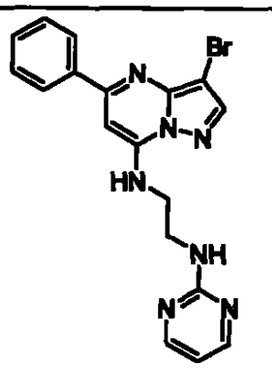
80				1. mp = 206-208 2. M+H = 408
81				1. mp = 108-110 2. M+H = 502
82				1. mp = 83-85 2. M+H = 402
83				1. mp = 220 2. M+H = 414

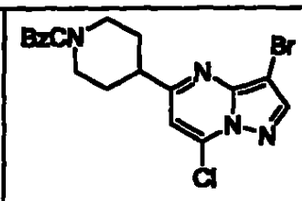
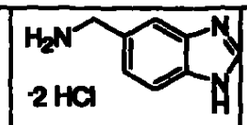
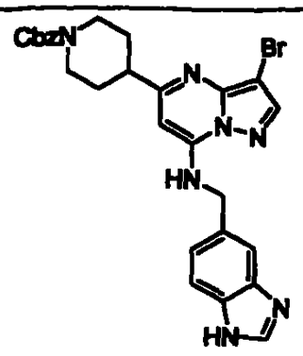
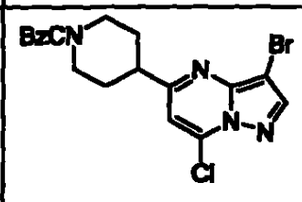
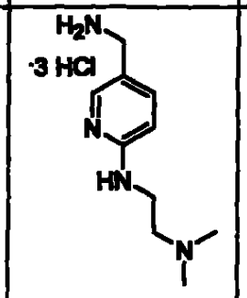
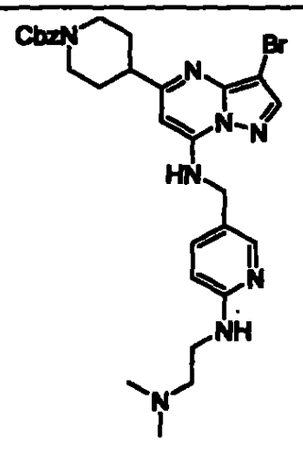
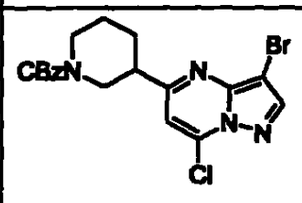
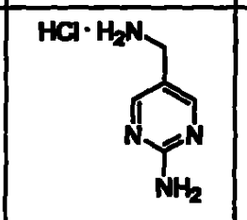
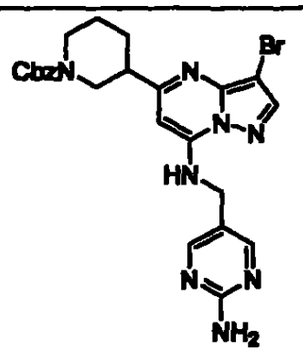
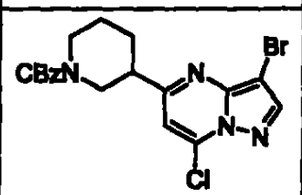
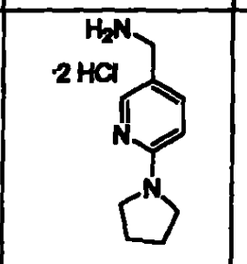
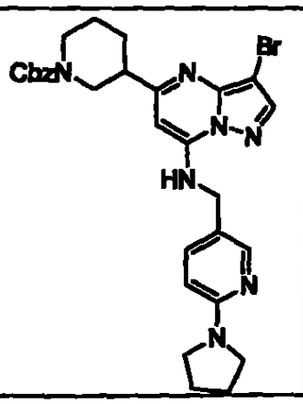
84				1. mp = 154-156 2. M+H = 426
85				1. mp = 152-153 2. M+H = 438
86				1. mp = 159-161 2. M+H = 420
87				1. mp = >220 2. M+H = 455

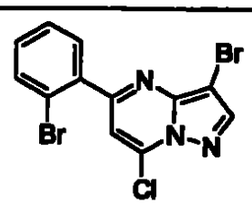
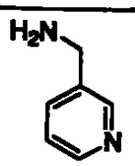
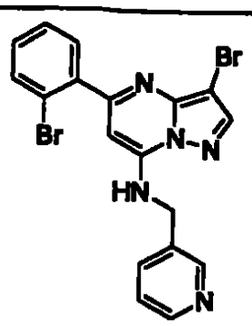
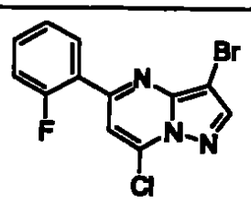
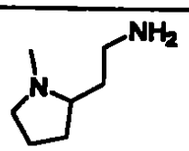
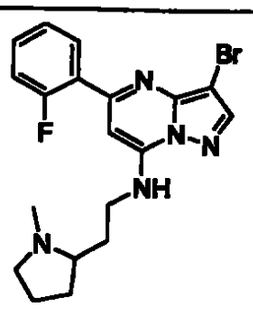
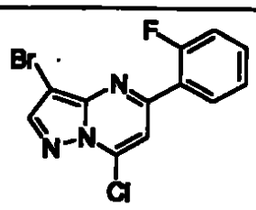
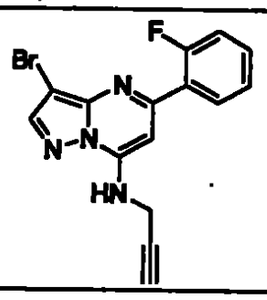
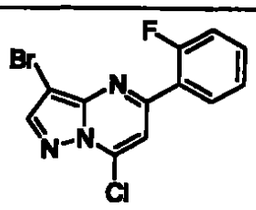
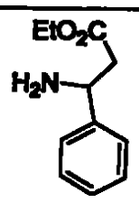
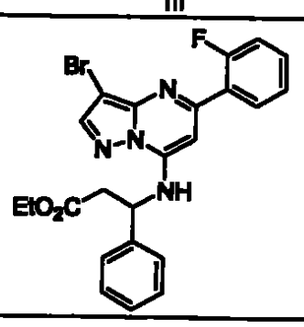
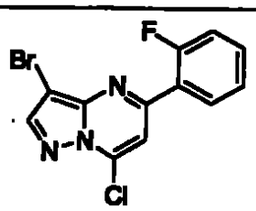
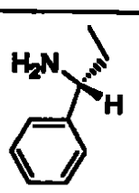
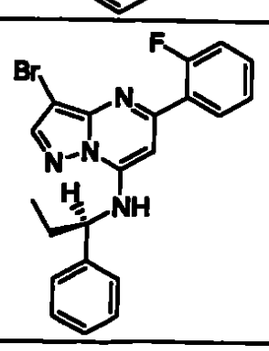
88				1. mp = 223-225 2. M+H = 425
89				1. mp = 199-201 2. M+H = 419
90				1. mp = 184-186 2. M+H = 426
91				1. mp = 196-198 2. M+H = 420

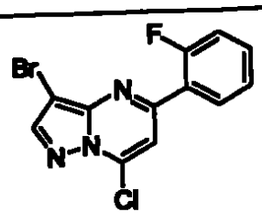
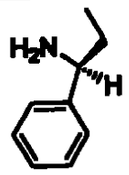
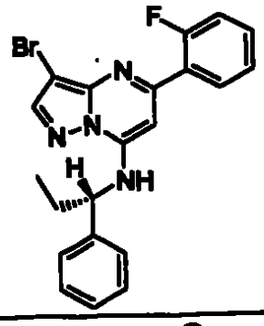
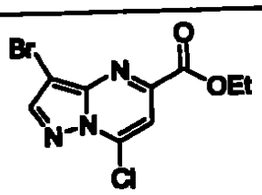
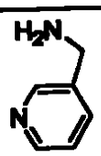
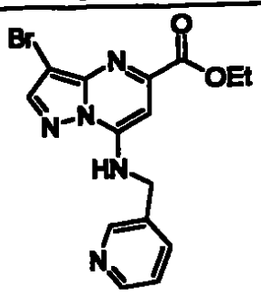
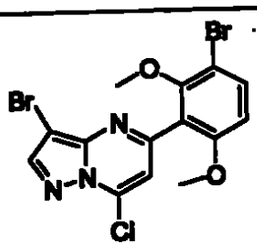
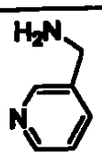
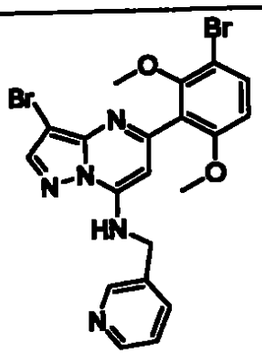
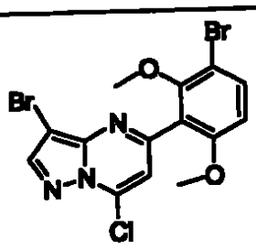
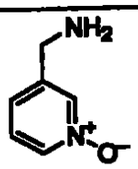
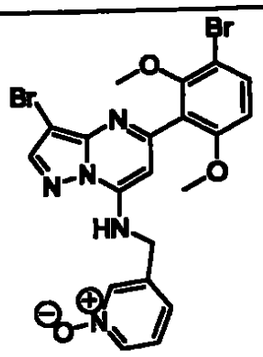
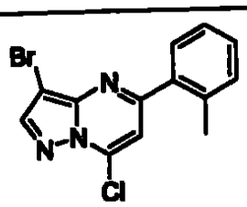
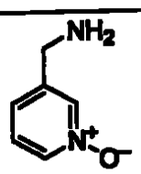
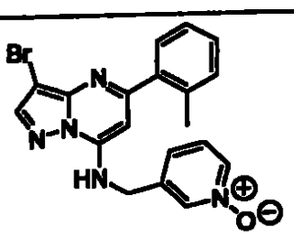
92				1. mp = 156-159 2. M+H = 440
93				1. mp = 173-176 2. M+H = 434
94				1. mp = 173-175 2. M+H = 452
95				1. mp = 174-176 2. M+H = 469

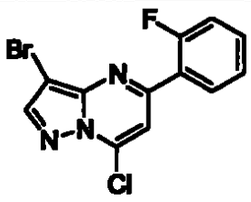
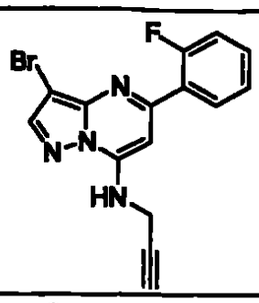
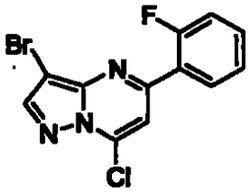
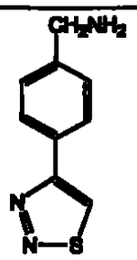
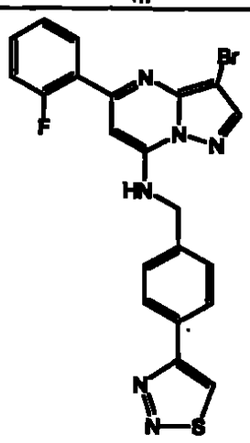
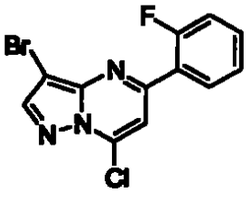
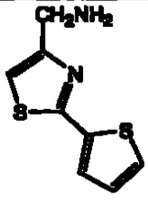
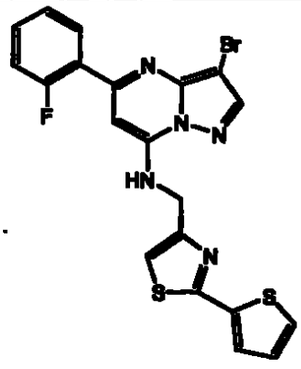
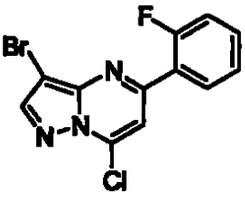
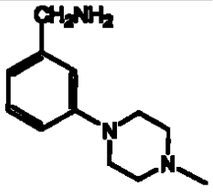
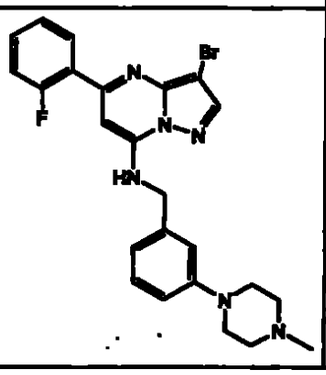
96		 ·2 HCl		1. mp = 230-234 2. M+H = 434
97				1. mp = 191-193 2. M+H = 441
98				1. mp = 202-205 2. M+H = 434
99				1. mp = 209-212 2. M+H = 453

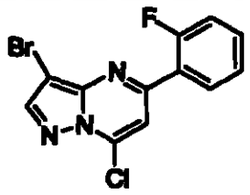
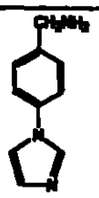
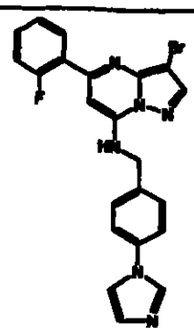
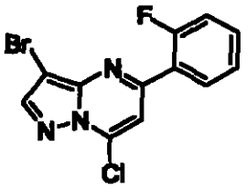
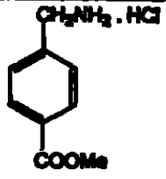
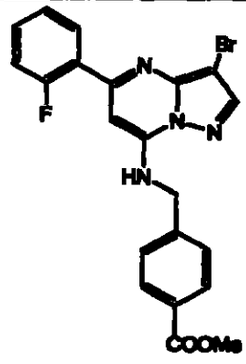
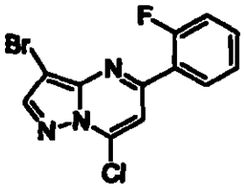
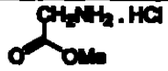
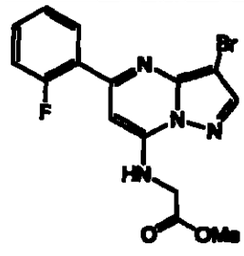
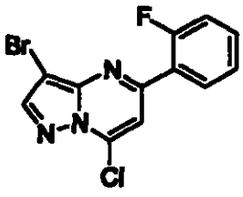
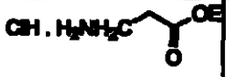
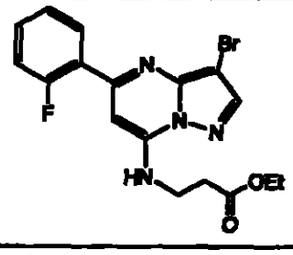
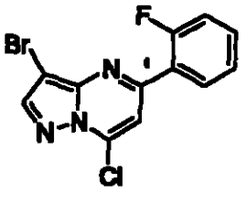
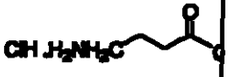
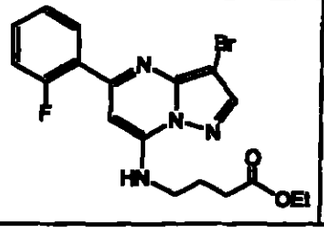
100				1. mp = 219-221 2. M+H = 469
101				1. mp = 64-66 2. M+H = 403
102				1. mp = 168-170 2. M+H = 420
103				1. mp = 213-216 2. M+H = 411

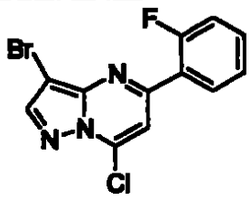
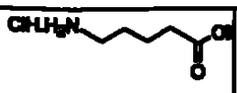
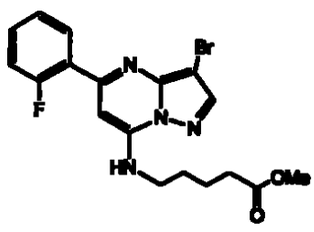
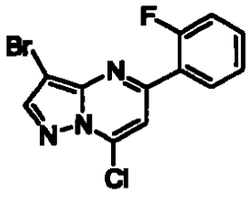
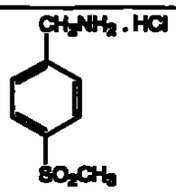
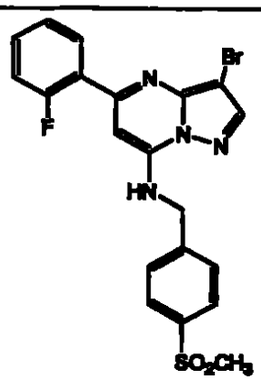
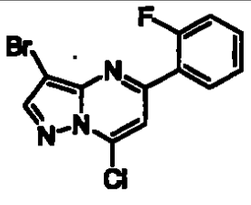
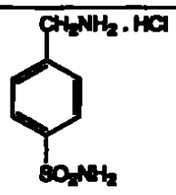
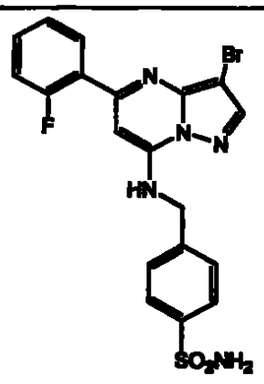
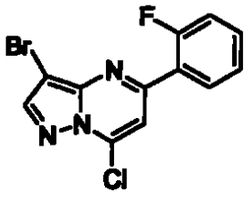
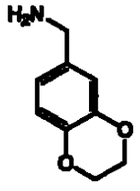
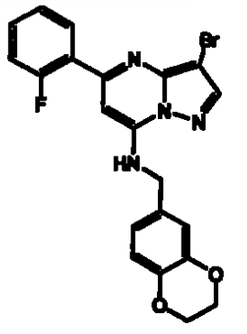
104				1. mp = 98-100 2. M+H = 561
105				1. mp 70-72 2. M+H = 608
106				1. mp 168-170 2. M+H = 538
107				1. mp 169-191 2. M+H = 592

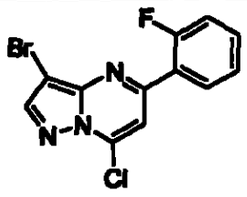
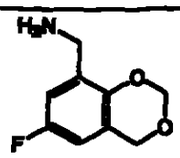
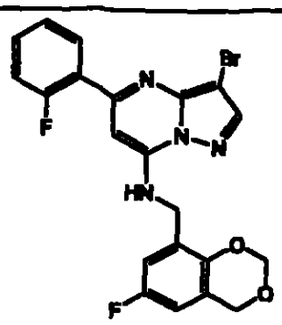
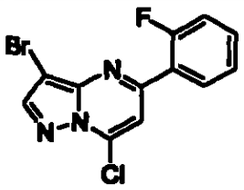
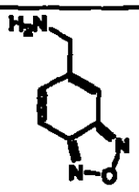
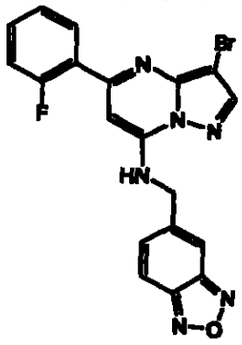
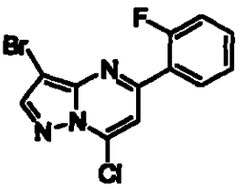
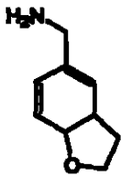
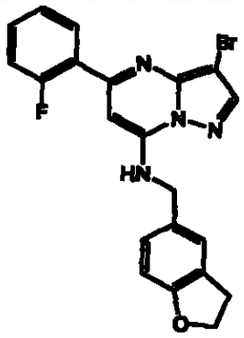
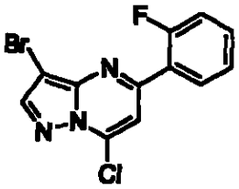
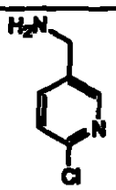
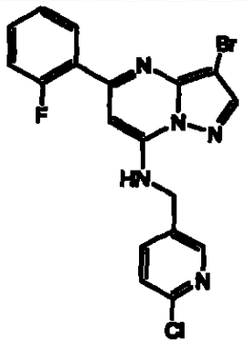
108				LCMS: MH^+ = 458;
109				Yield = 89 LCMS: MH^+ = 418 m. p. = 131-132 °C
110				Yield=95% LCMS: MH^+= 347
111				Yield=91% 3H); LCMS: MH^+= 484
112				Yield=87% LCMS: MH^+= 427

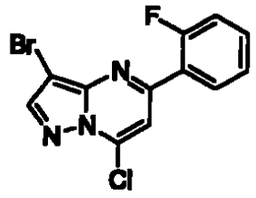
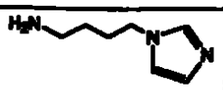
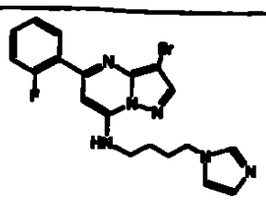
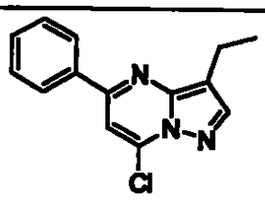
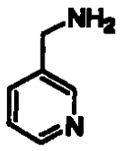
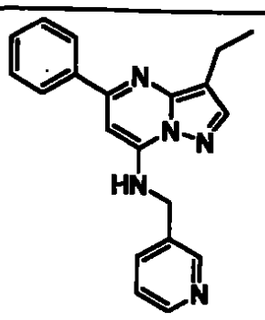
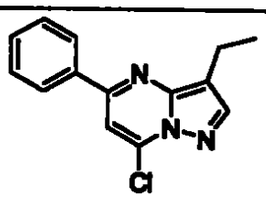
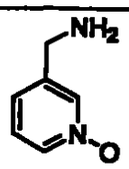
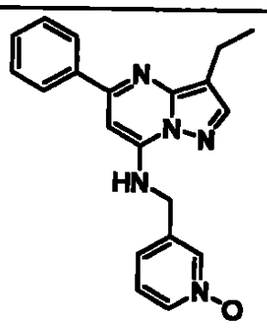
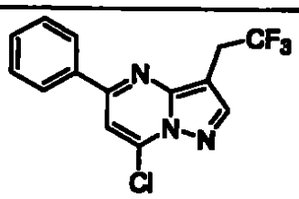
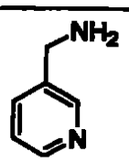
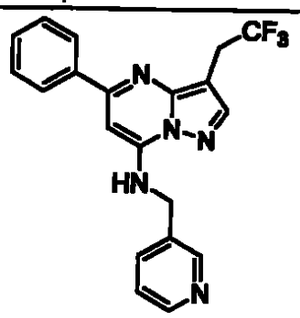
113				Yield=80% LCMS: MH$^+$= 427
114				Yield=91% LCMS: MH$^+$= 376
115				Yield=92% , 3H); LCMS: MH$^+$=520
116				Yield=98% LCMS: MH$^+$=536
117				Yield=82% LCMS: MH$^+$=410

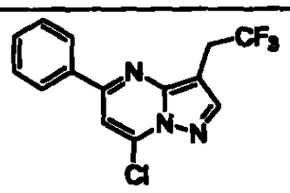
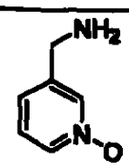
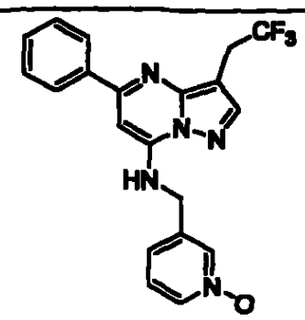
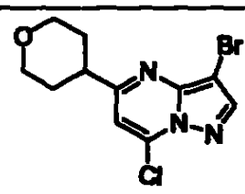
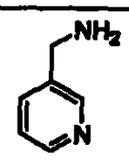
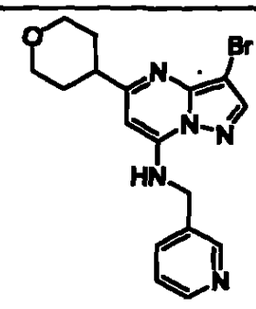
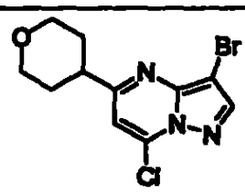
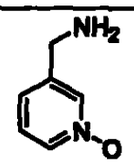
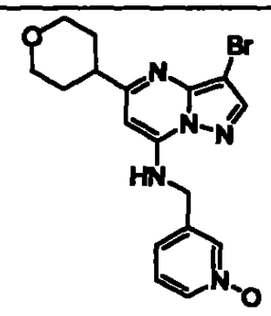
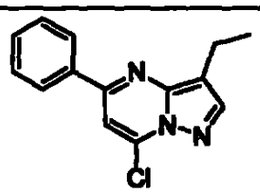
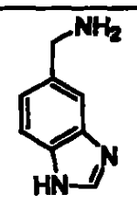
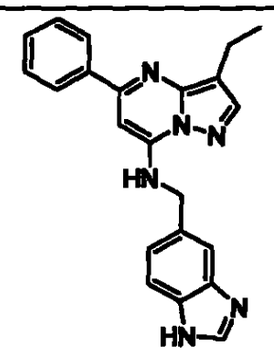
118				Yield=85% LCMS: MH^+= 347
121				Yield = 65% LCMS: MH^+ = 481.02
126				Yield=71% MH^+ = 486
127				Yield=71% MH^+ = 495.1

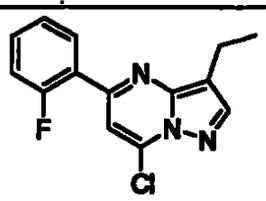
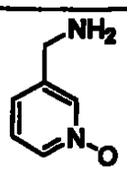
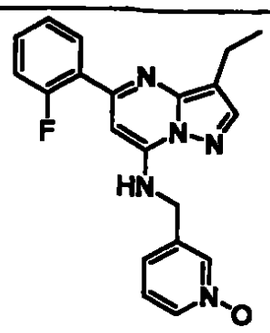
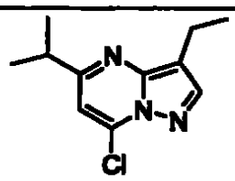
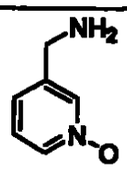
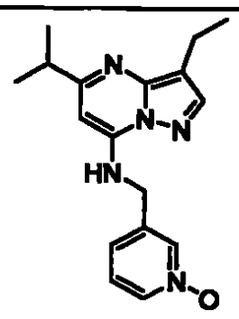
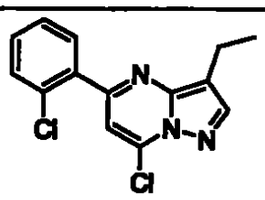
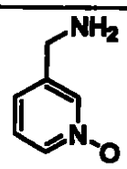
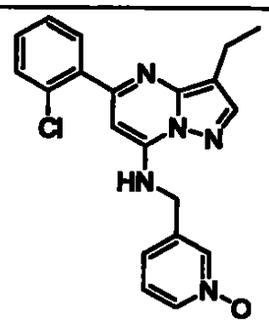
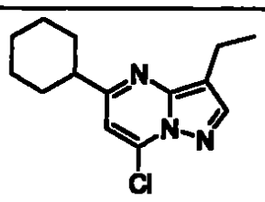
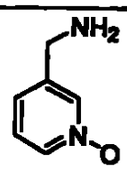
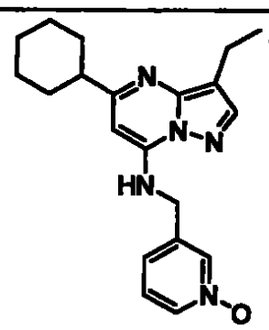
128				Yield=55% MH^+ = 463
129				Yield = 77% LCMS: MH^+ = 455
130				^1H NMR (Yield = 75% LCMS: MH^+ = 379
131				Yield = 75% LCMS: MH^+ = 407
132				Yield = 75% LCMS: MH^+ = 421

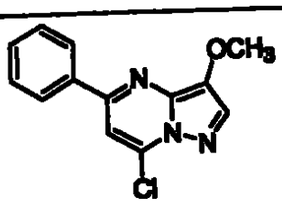
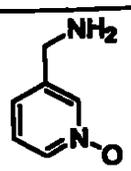
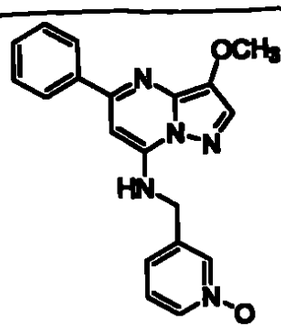
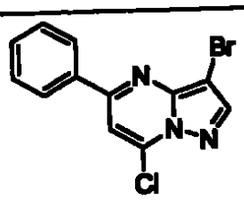
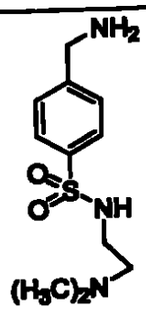
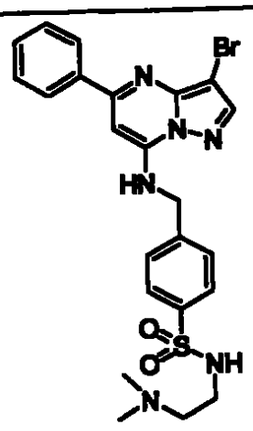
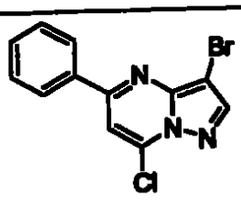
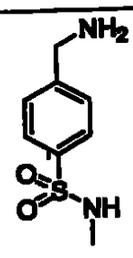
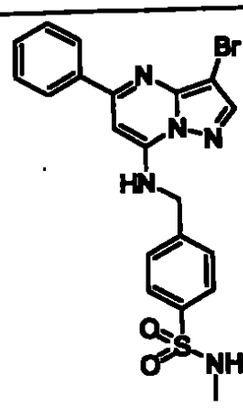
133				Yield = 70% LCMS: MH^+ = 421
134				Yield = 78% LCMS: MH^+ = 475
135				Yield = 75% LCMS: MH^+ = 476
136				Yield = 65% LCMS: MH^+ = 455

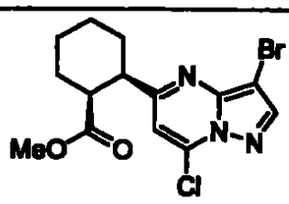
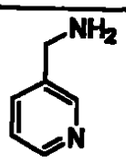
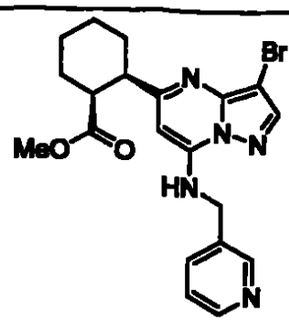
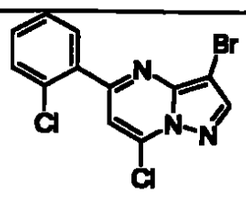
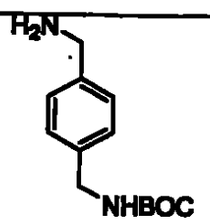
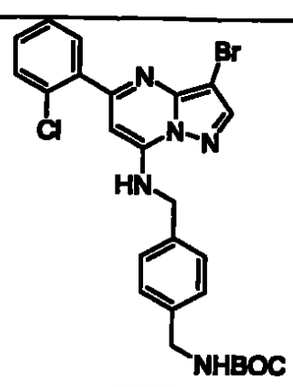
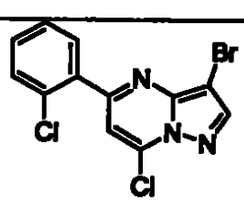
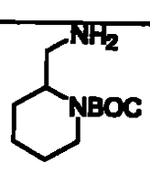
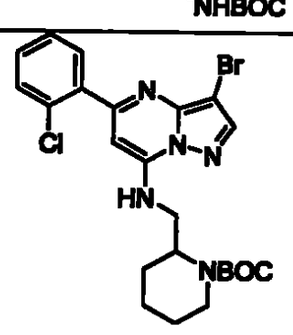
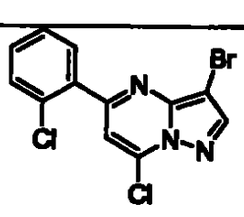
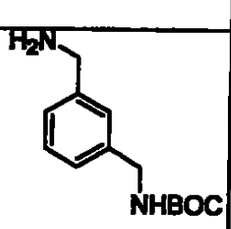
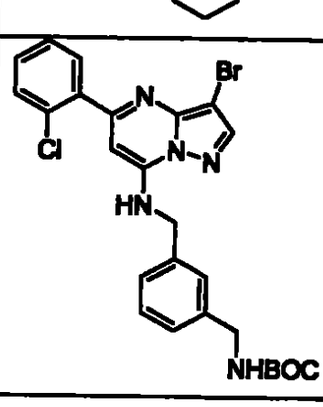
137				Yield = 55% LCMS: MH^+ = 473)
138				Yield = 60% LCMS: MH^+ = 439
139				Yield = 65% LCMS: MH^+ = 441
140				Yield = 80% LCMS: MH^+ = 432

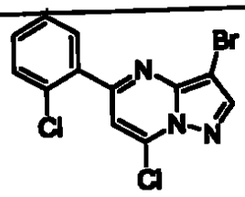
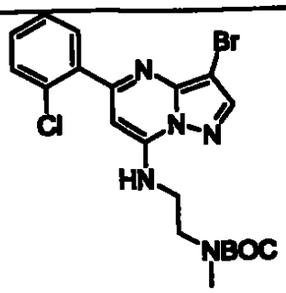
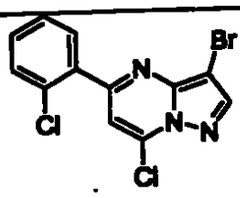
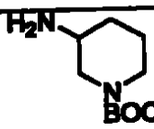
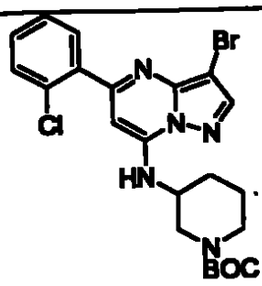
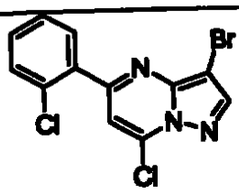
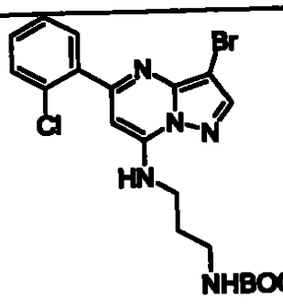
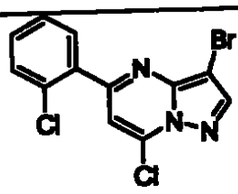
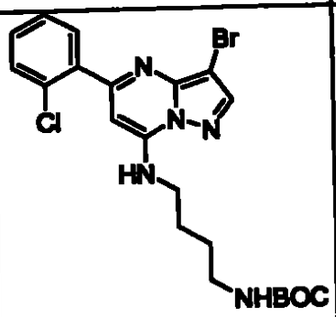
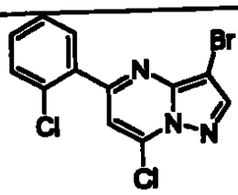
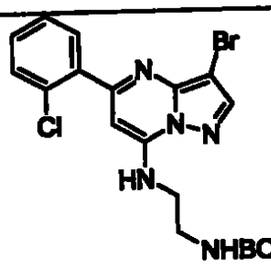
141				Yield = 60% LCMS: MH^+ = 429
142				LCMS: MH^+=330 ; mp=109-111°C
143				LCMS: MH^+=346 ; mp=186-188°C
144				LCMS: MH^+=384 ; mp=148-150°C

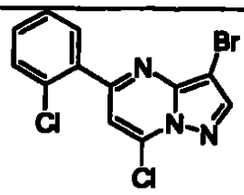
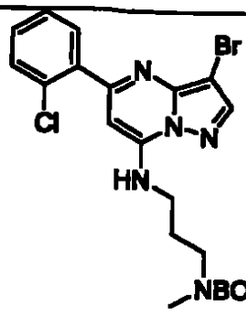
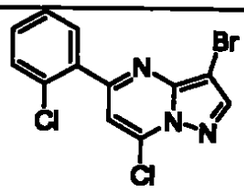
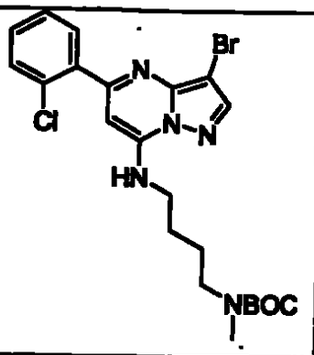
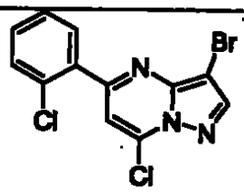
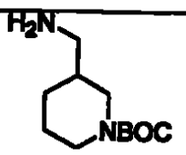
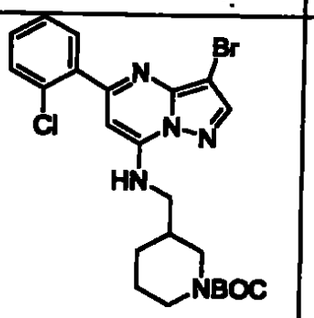
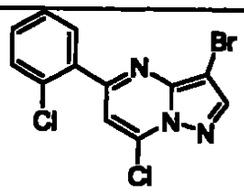
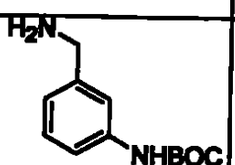
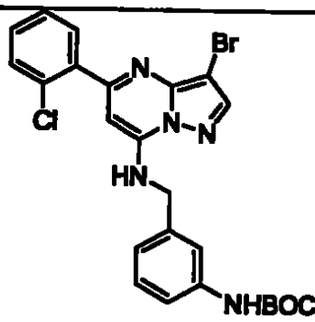
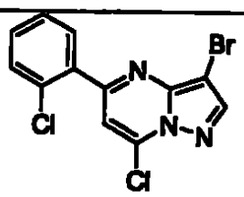
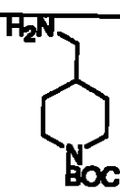
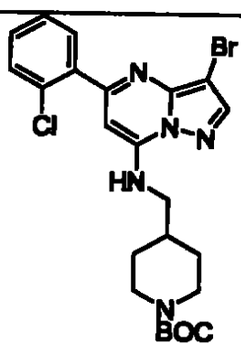
145				LCMS: MH^+=400; mp=186-188°C
146				LCMS: $M2H^+$=390; mp=192-194°C
147				LCMS: M^+=404; mp=220-222°C
148				LCMS: MH^+=369; mp>230° C

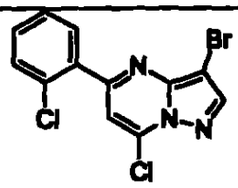
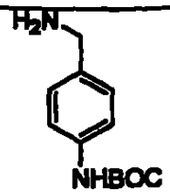
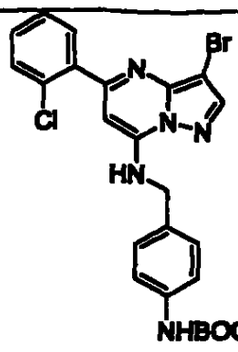
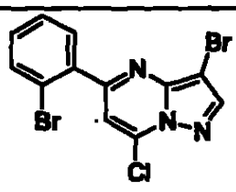
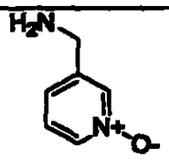
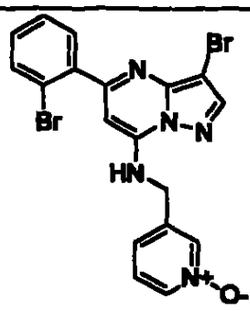
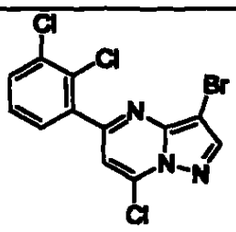
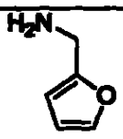
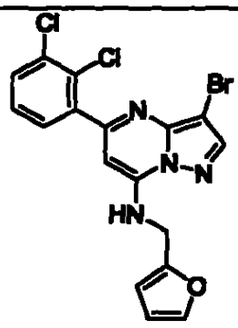
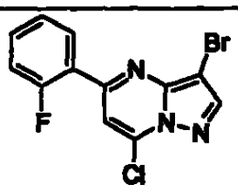
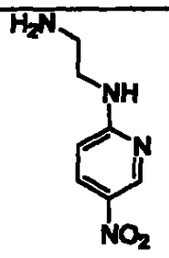
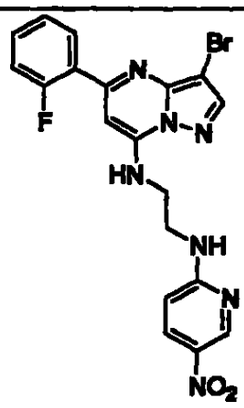
149				LCMS: MH^+=364 ; mp=186-188°C
150				LCMS: MH^+=312 ; mp=138-140°C
151				LCMS: M^+=380; mp=172-174°C
152				LCMS: MH^+=352 ; mp=201-203°C

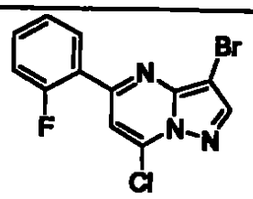
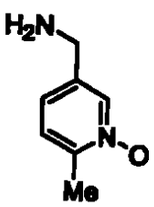
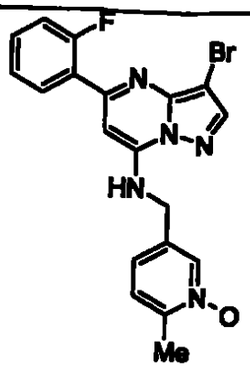
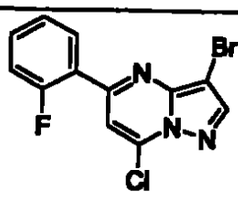
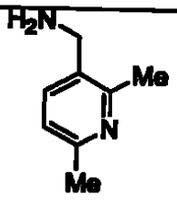
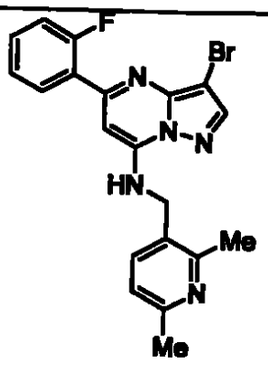
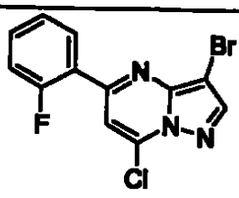
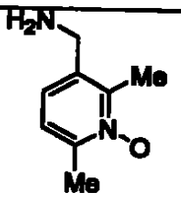
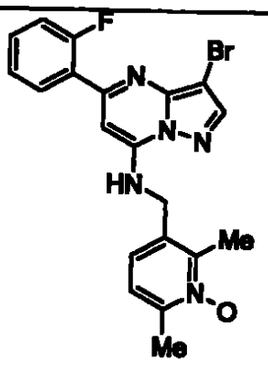
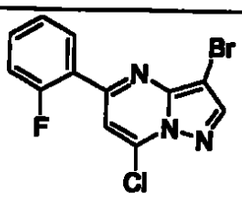
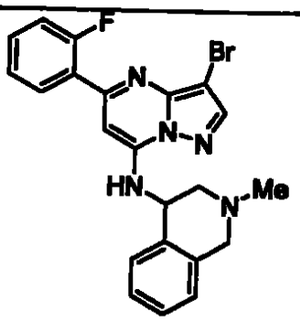
153				LCMS: MH^+=348 ; mp=166-168°C
154				LCMS: $M2H^+$=531; mp=78-80°C
155				LCMS: $M2H^+$=474; mp=161-163°C

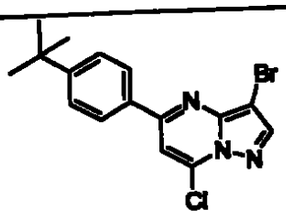
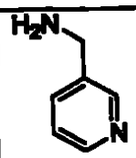
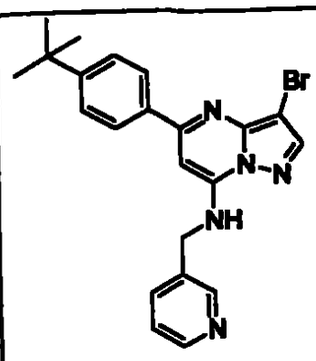
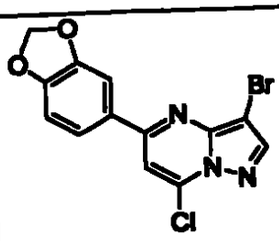
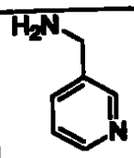
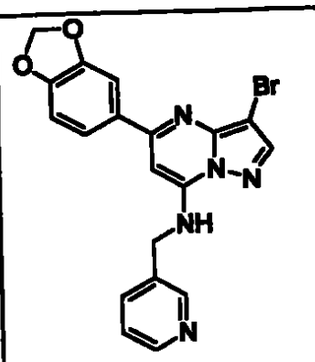
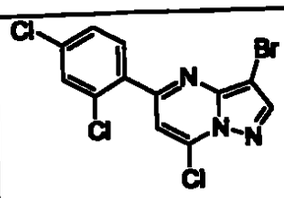
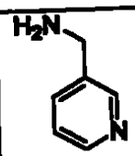
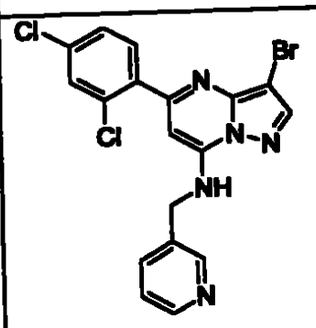
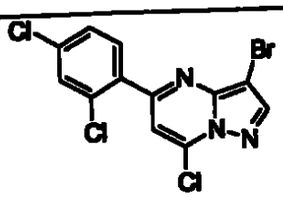
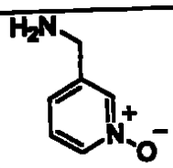
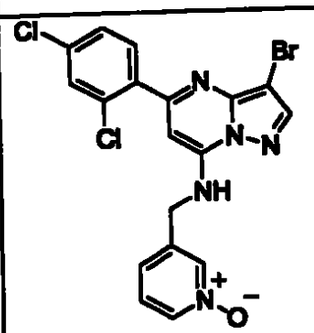
156				LCMS: M^+=444; mp=48-51°C
157				MH^+ = 542.1
158				MH^+ = 520.1
159				MH^+ = 542.1

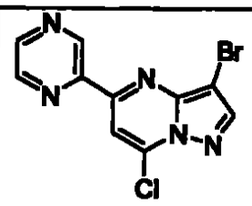
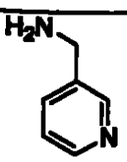
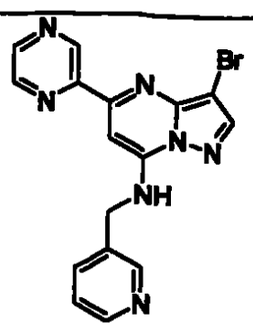
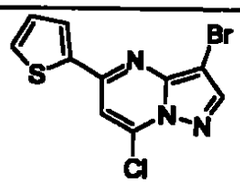
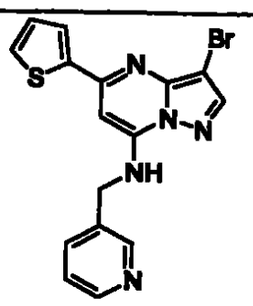
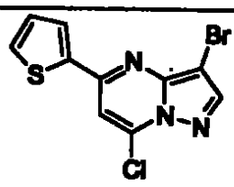
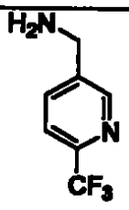
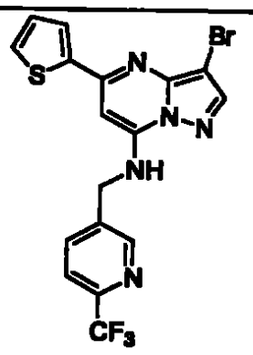
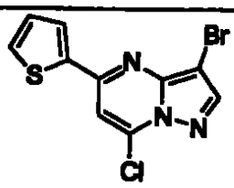
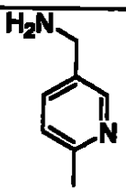
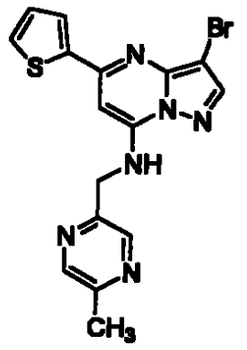
160				MH^+ = 480.1
161				MH^+ = 506.1
162				MH^+ = 480.1
163				MH^+ = 494.1
164				MH^+ = 466.1

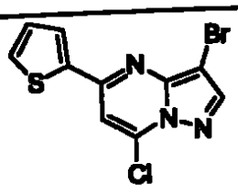
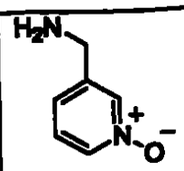
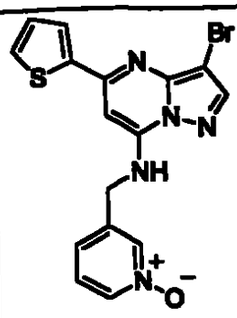
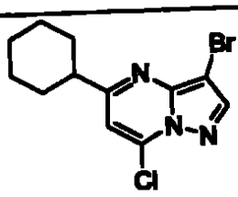
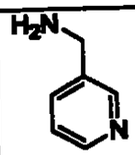
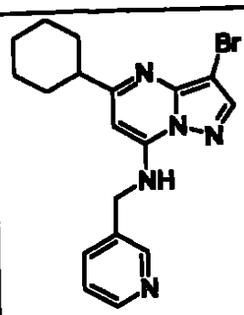
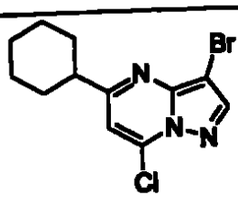
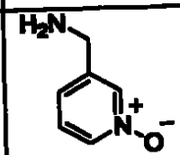
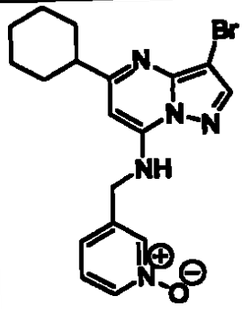
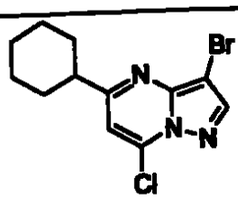
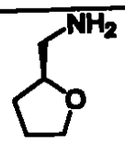
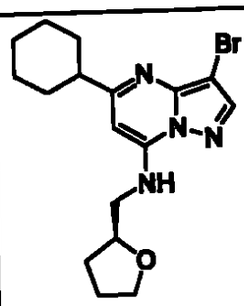
165				MH^+ = 494.1
166				MH^+ = 508.1
167				MH^+ = 520.1
168				MH^+ = 528.1
169				MH^+ = 520.1

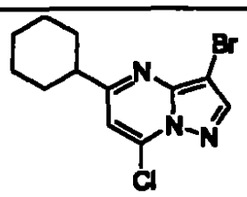
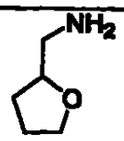
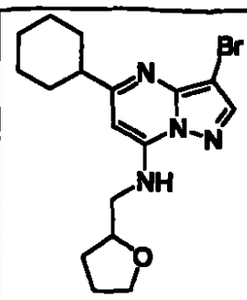
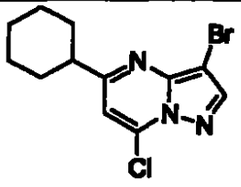
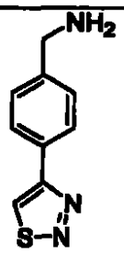
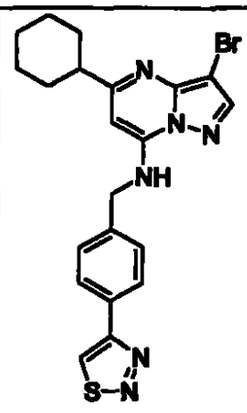
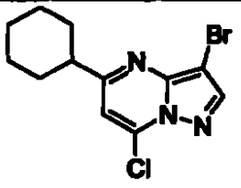
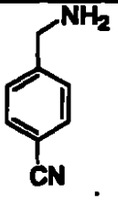
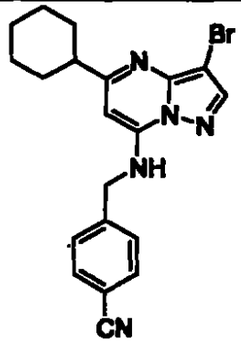
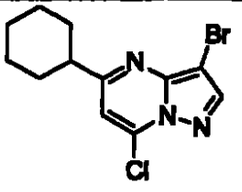
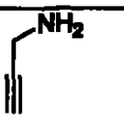
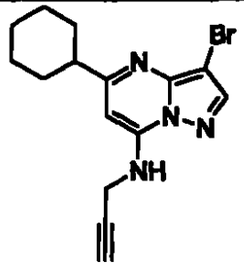
170				MH^+ = 528.1
171				LCMS: MH^+ = 474;
172				LCMS: MH^+ = 437;
173				LCMS: MH^+ = 472;

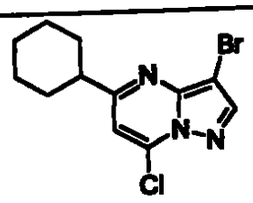
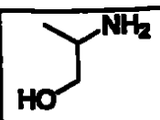
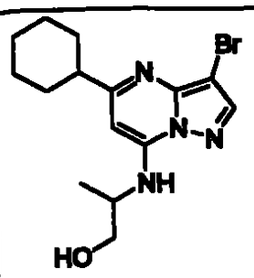
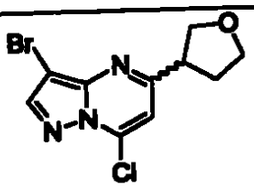
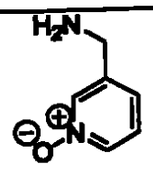
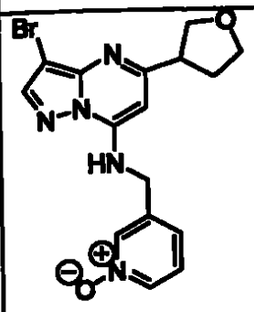
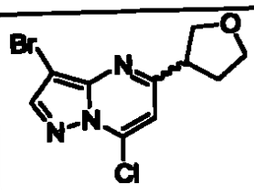
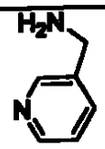
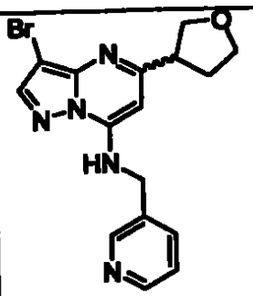
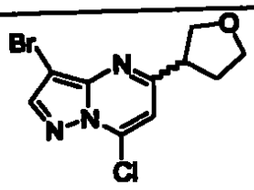
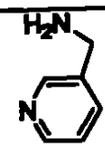
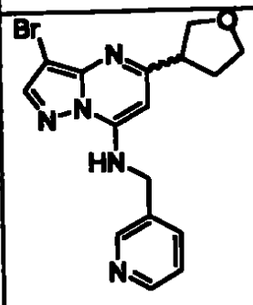
174				LCMS: MH$^+$ = 428.1
175				LCMS: MH$^+$ = 428.2
176				LCMS: MH$^+$ = 442.0
177				LCMS: MH$^+$ = 452.0

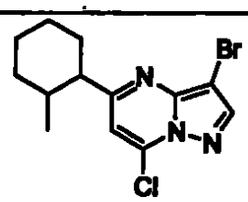
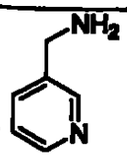
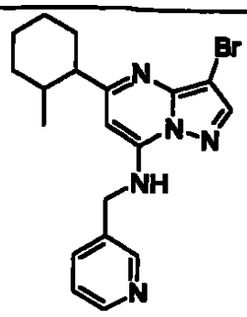
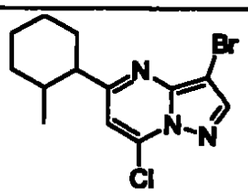
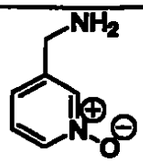
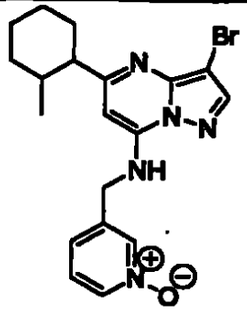
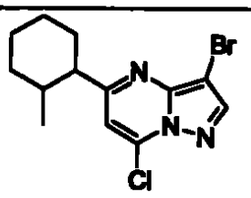
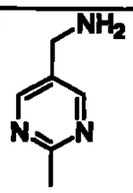
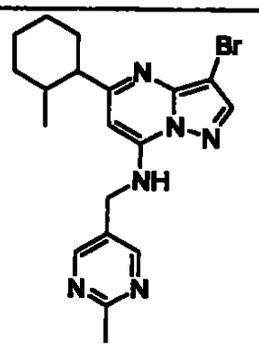
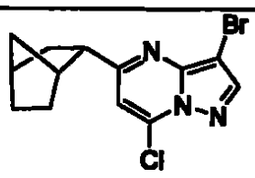
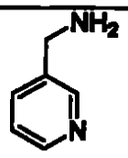
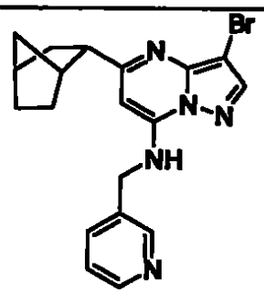
178				Yield = 90 MH^+ =436 m. pt. = 89.1 °C
179				MH^+ =424 m. pt. = 188.2 °C
180				MH^+ =448 m. pt. = 211.3 °C
181				Yield = quant. MH^+ = 464

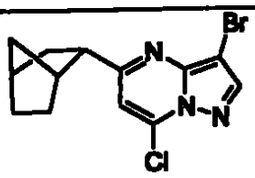
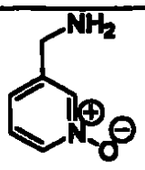
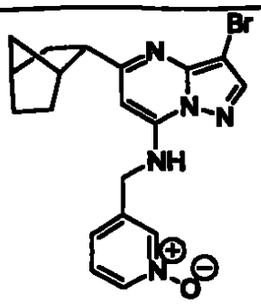
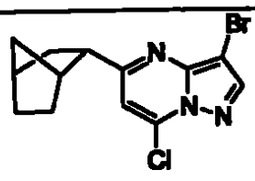
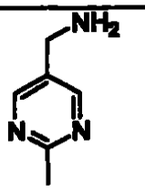
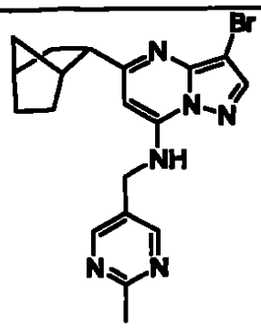
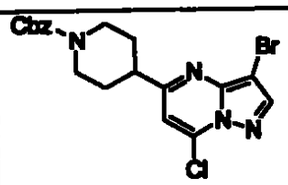
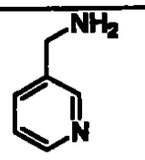
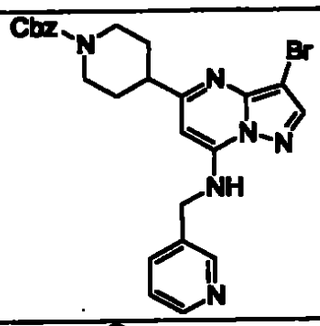
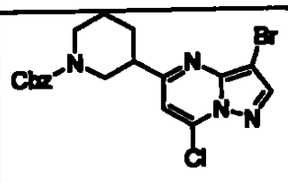
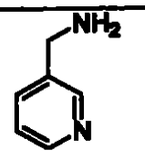
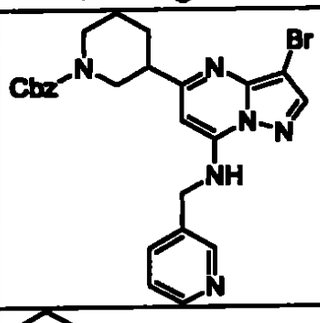
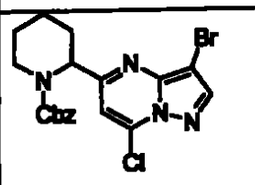
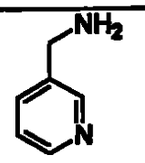
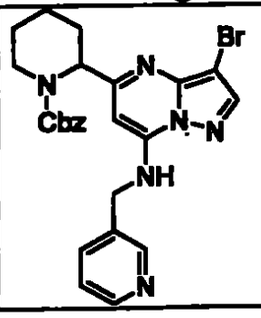
182				MH^+ = 382 m. pt. = 185.8 °C
183				MH^+ = 387 m. pt. = 181 – 182 °C
184				MH^+ = 453
185				MH^+ = 401 m. pt. = 178.3 °C

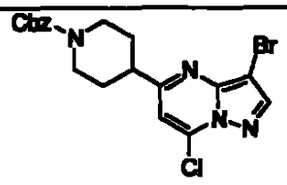
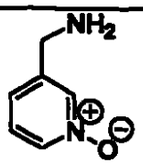
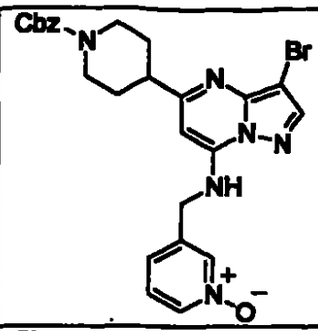
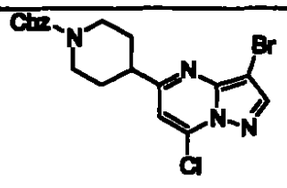
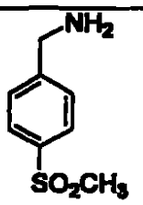
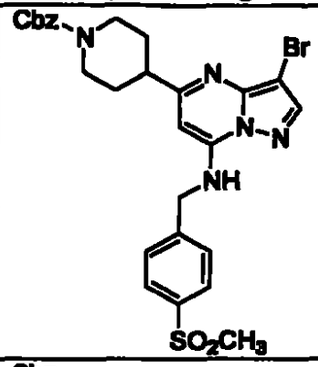
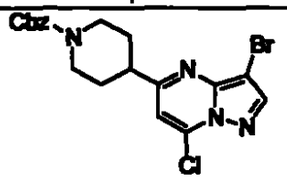
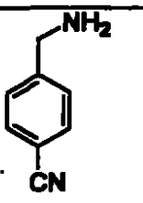
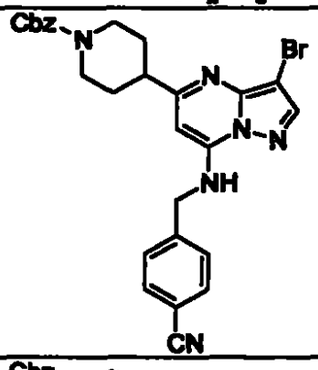
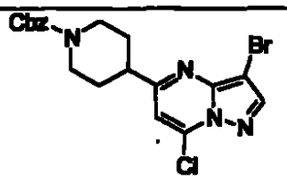
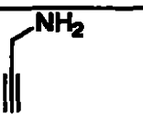
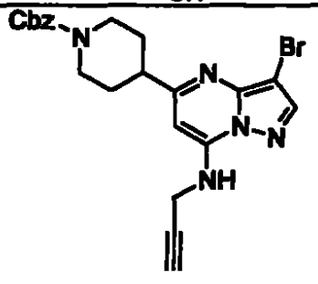
186				MH^+ = 402
187				Yield = 91 MH^+ = 386 m. pt. = 148.3 °C
188				Yield = 65 MH^+ = 402 m. pt. = 174.5 °C
189				MH^+ = 379 m. pt. = 82 – 83 °C

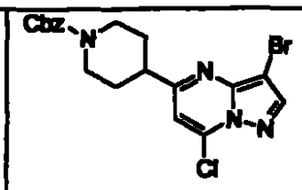
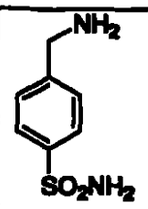
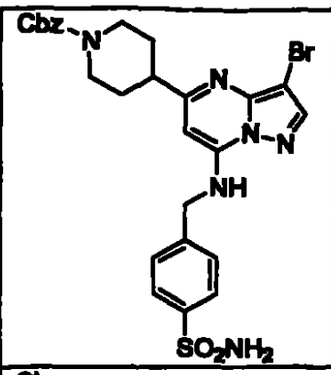
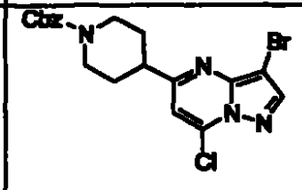
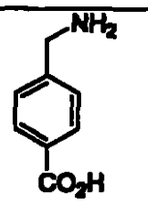
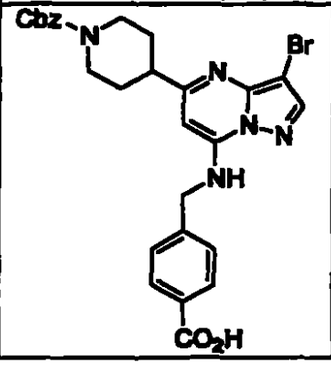
190				MH^+ = 379 m. pt. = 50.7 °C
191				Yield = 89 MH^+ = 469 m. pt. = 186.7°C
192				Yield = 93 MH^+ = 410 m. pt. = 86.7°C
193				Yield = 76 MH^+ = 333 m. pt. = 120.3°C

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+ = 416
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), 4.83 (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), 6.96 (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), 7.69 –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).

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).

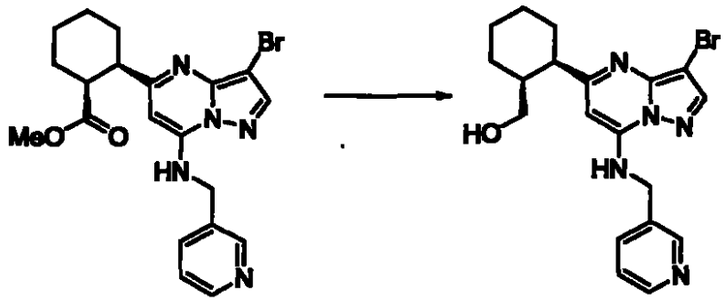
Example 197: ^{1}H NMR (CD_3OD) δ 8.73(d, 1H), 8.58(q, 1H), 8.12(s, 1H), 8.00(d, 1H), 7.54(q, 1H), 6.19(s, 1H), 4.86(s, 2H), 4.22-4.08(m, 2H), 4.03-3.93(m, 2H), 3.63(m, 1H), 2.50-2.39(m, 1H), 2.32-2.21(m, 1H).

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).

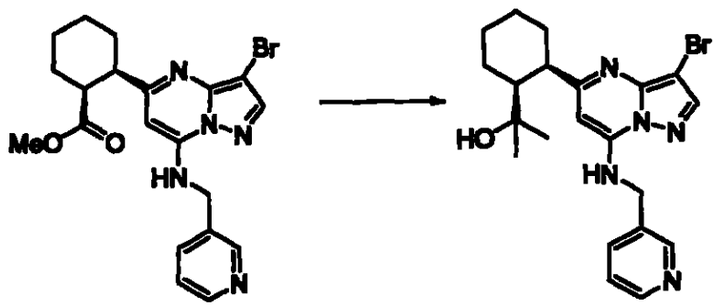
Example 203: ^{1}H NMR (300MHz, $CDCl_3$) □□8.10 (s, 1H), 8.08 (s, 1H), 6.27 (s, 2H), 4.95 (s, 2H), 3.00 – 2.90 (dd, 2H), 2.60 (m, 2H), 2.48 (br s, 1H), 2.39 (s, 3h), 2.25 m, 1H), 1.95 – 1.70 (m, 3H).

EXAMPLE 211:



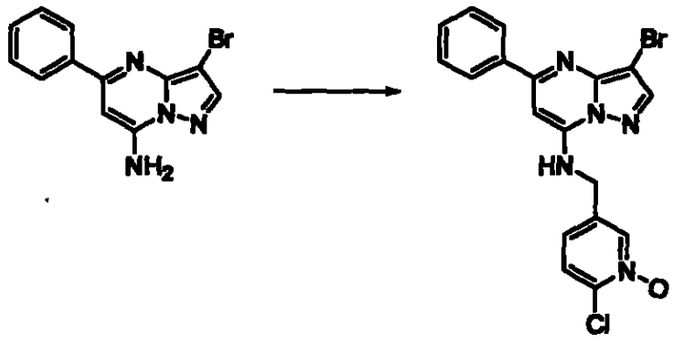
To a solution of the compound prepared in Example 156 (100 mg, 0.23 mmol) in dry THF (4 mL) was added $LiAlH_4$ (1.0 M in THF, 0.110 mL, 0.110 mmol) at 0°C under N_2. The mixture was stirred at 0°C for 1hr, warmed to 25°C, then additional $LiAlH_4$ (1.0 M in THF, 0.400 mL) was added, the mixture was 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, 49%) 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:



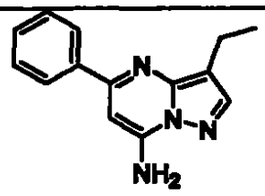
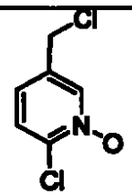
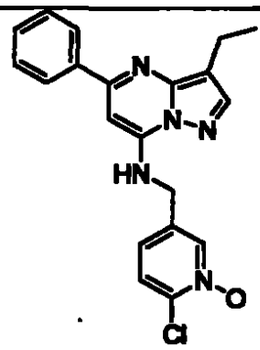
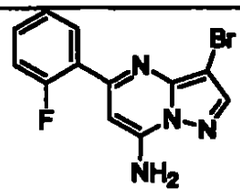
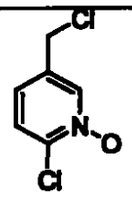
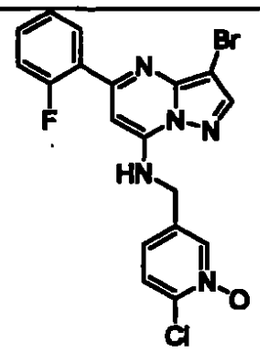
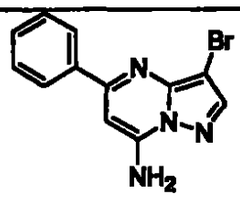
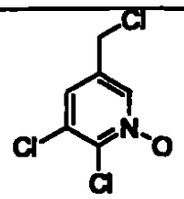
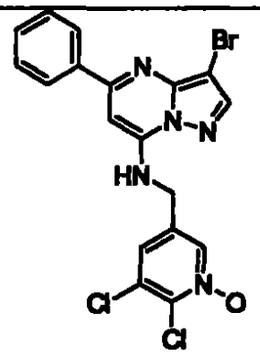
Anhydrous DMF (40 mL) was added under N_2 to the compound prepared in Preparative Example 174 (2.50 g, 8.65 mmol) and 60 % NaH in mineral oil (346 mg, 8.65 mmol). The mixture was stirred at 25°C for 1 hr, then 2-chloro-5-chloromethylpyridine N-oxide (1.54 g, 8.65 mmol) in anhydrous DMF (20 mL) was added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

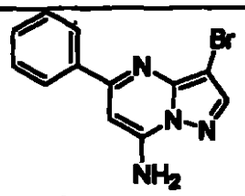
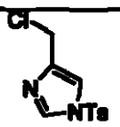
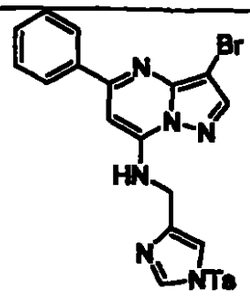
30:1 CH_2Cl_2:MeOH as eluent. So obtained solid was triturated by 50 mL of 1:1 EtOAc: hexane. Pale yellow solid (1.25 g, 34%) was obtained. LCMS: MH^+=432. Mp=224-226 °C.

EXAMPLES 214-217:

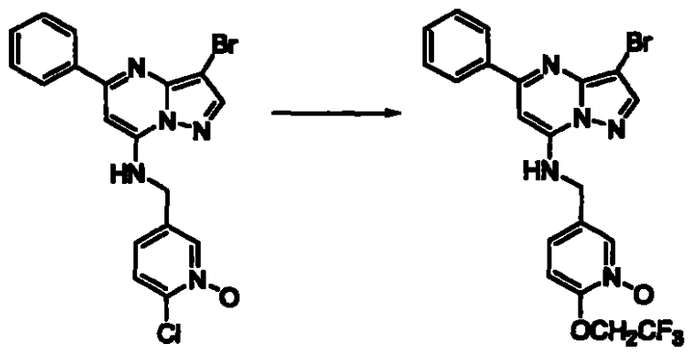
By essentially the same procedure set forth in Example 213 combining the compounds shown in Column 2 of Table 19 with compounds in Column 3 of Table 19, the compounds shown in Column 3 of Table 19 were prepared.

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^+=486; mp=126-128°C

217				LCMS: M^+=523

EXAMPLE 218:



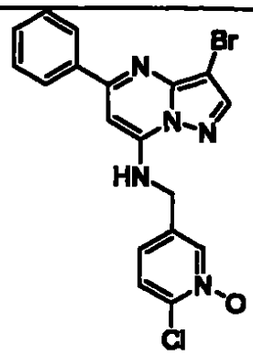
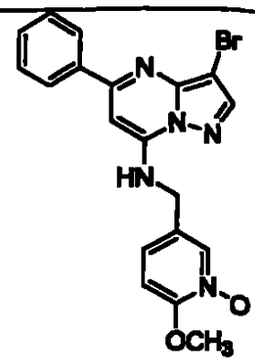
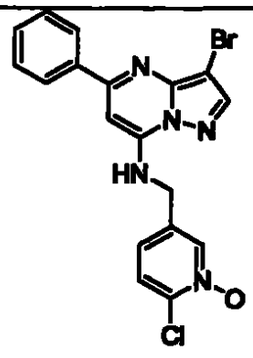
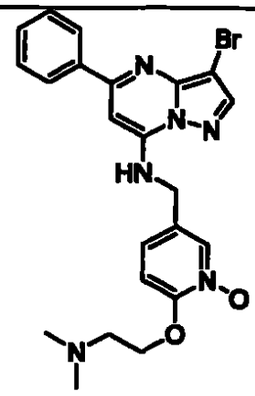
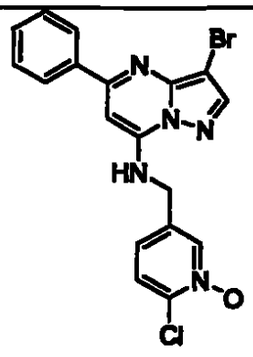
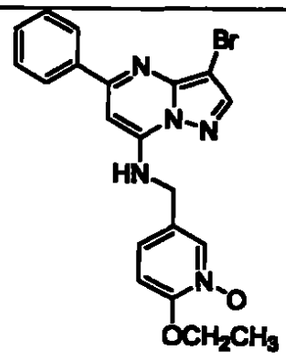
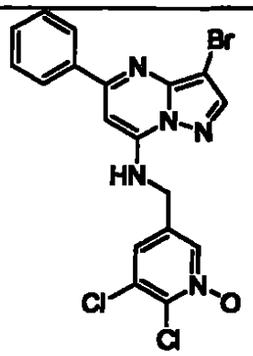
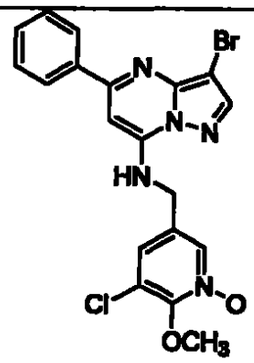
CF_3CH_2OH (3.0 mL) was added under N_2 to 60% NaH in mineral oil (40 mg, 1.0 mmol), the mixture was stirred for 20 min, then the product prepared in Example 213 (50 mg, 0.12 mmol) was added. The mixture was refluxed for 20 hr, the solvent was evaporated, and the residue was purified by flash chromatography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

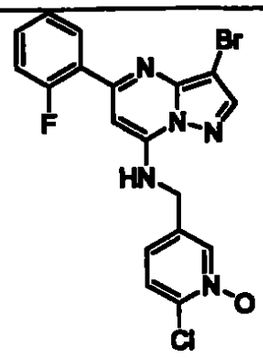
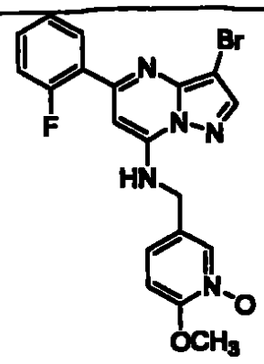
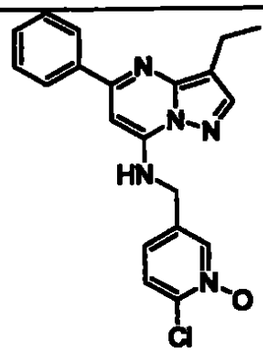
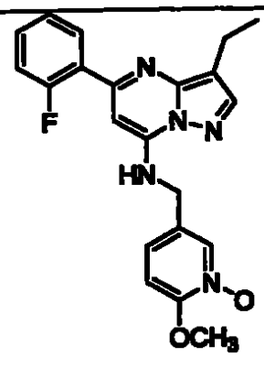
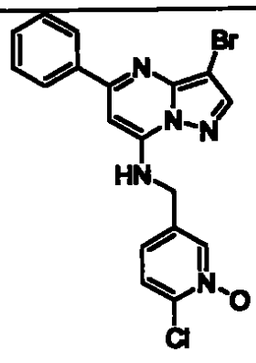
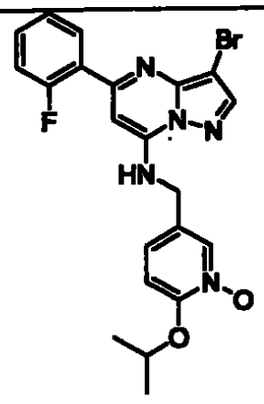
EXAMPLES 219-225:

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.

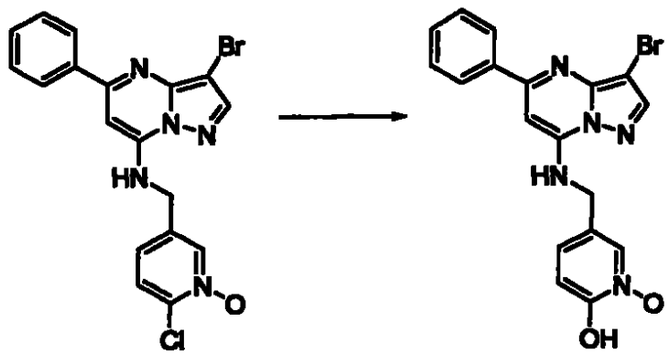
TABLE 20

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

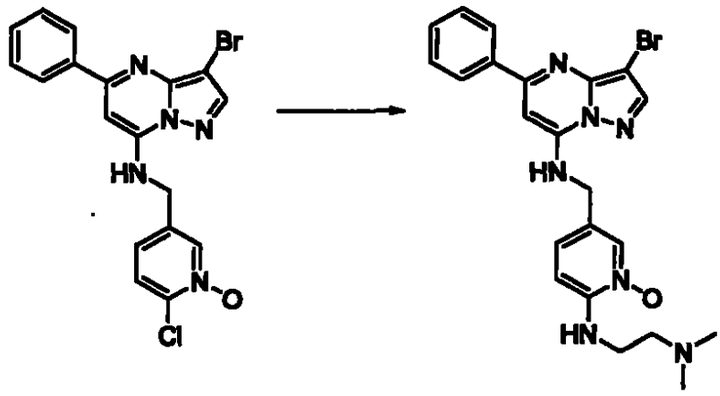
223			LCMS: MH^+=444; mp=112-114°C
224			LCMS: M^+=376; mp=°C
225			LCMS: MH^+=; mp=°C

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:



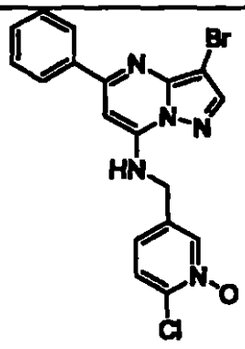
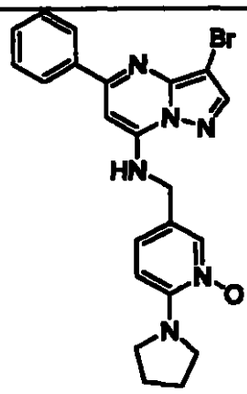
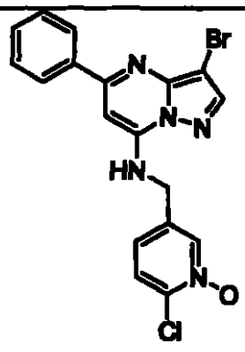
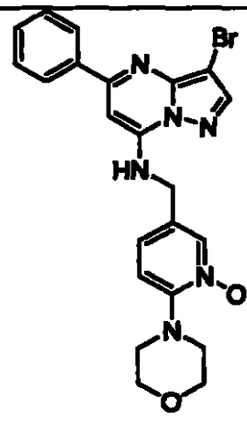
A mixture of the product prepared in Example 213 (129 mg, 0.30 mmol), N,N-dimethylethylenediamine (0.165 mL, 1.50 mmol), and diisopropylethylamine (0.10 mL) in anhydrous N-methylpyrrolidinone (1.0 mL) was stirred at 100°C for

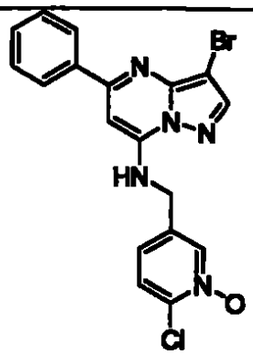
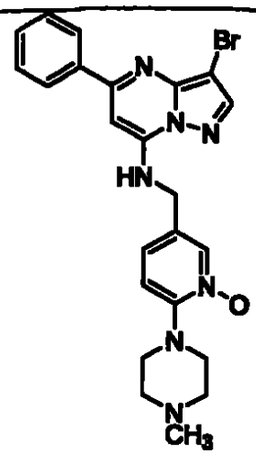
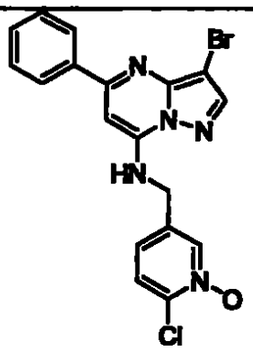
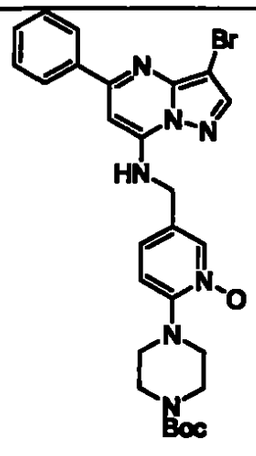
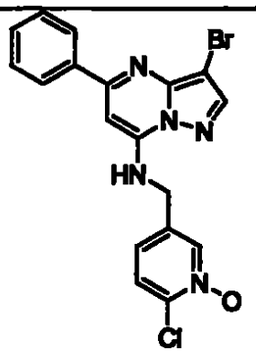
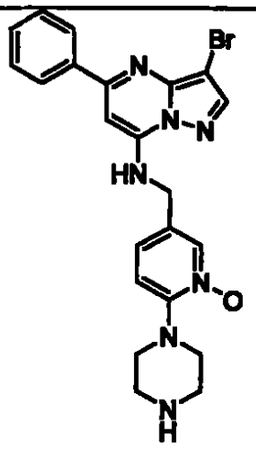
24 hr. The solvent was evaporated, and the residue was purified by flash chromatography using 20:1 CH_2Cl_2: 7N NH_3 in MeOH as eluent to yield pale yellow solid (110 mg, 78%). LCMS: M^+=482. Mp=76-78 °C.

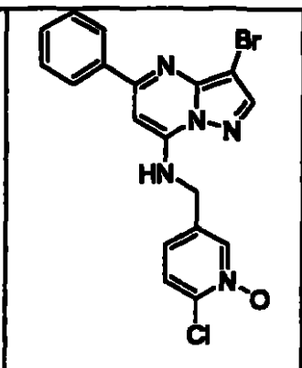
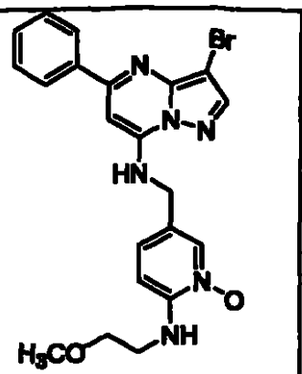
EXAMPLES 228-233:

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.

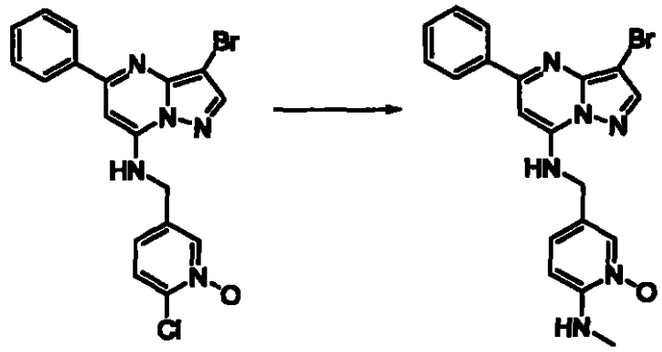
TABLE 21

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

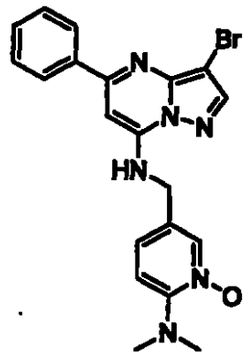
233			LCMS: $M2H^+$=471 ; mp=88-90°C

EXAMPLE 234:



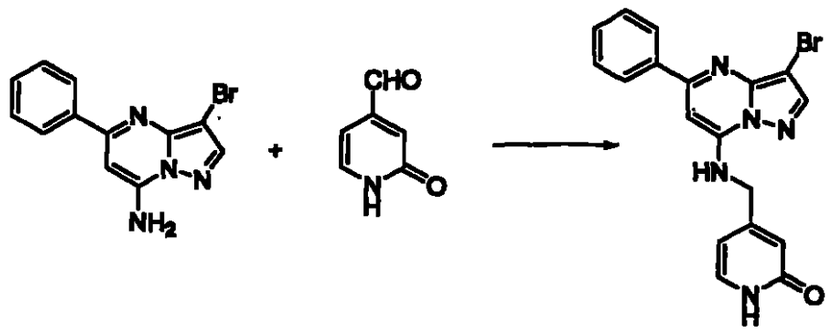
A mixture of the product prepared in Example 213 (80 mg, 0.19 mmol) and 2.0 M methylamine in THF was stirred in a closed pressure vessel at 50°C for 72 hr. The solvent was evaporated, and the residue was purified by flash chromatography using 10:1 CH_2Cl_2: MeOH as eluent to yield pale yellow solid (40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



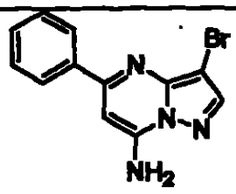
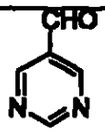
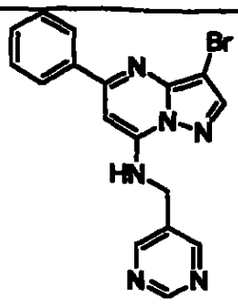
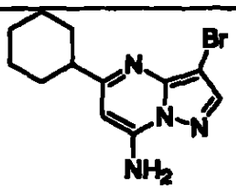
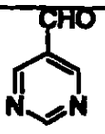
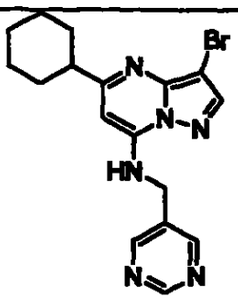
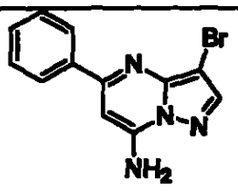
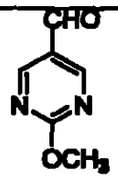
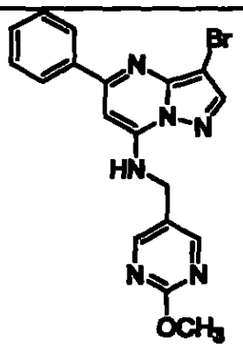
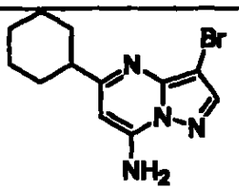
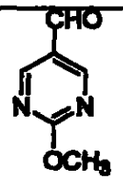
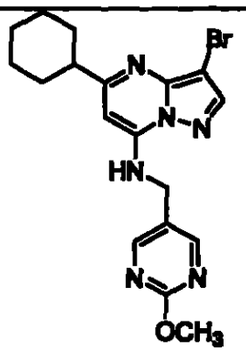
The compound prepared in Preparative Example 174 (140 mg, 0.48 mmol) and the aldehyde (71 mg, 0.58 mmol) were stirred in anhydrous THF (4 mL) at 50°C under N_2. $Ti(OiPr)_4$ (0.574 mL, 1.92 mmol) was added, the mixture was stirred at 50°C 3 hr, and cooled to 25°C. $NaBH_3CN$ (181 mg, 2.88 mmol) was added, 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.

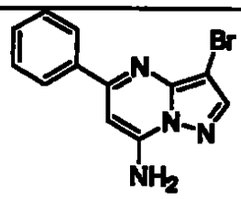
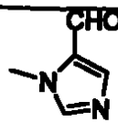
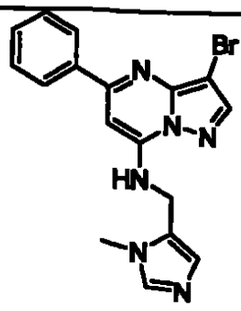
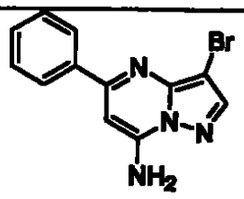
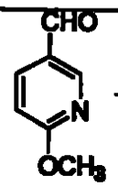
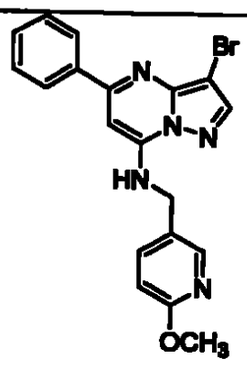
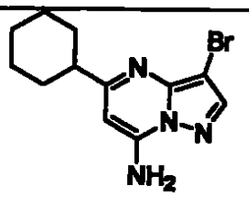
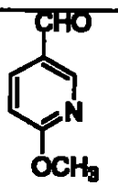
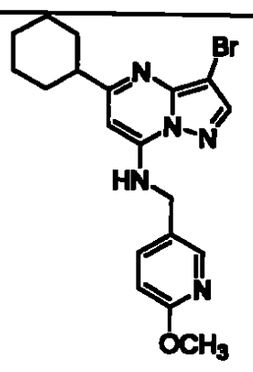
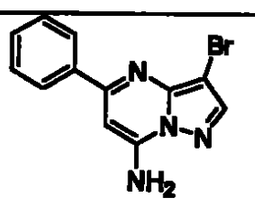
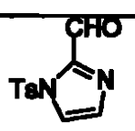
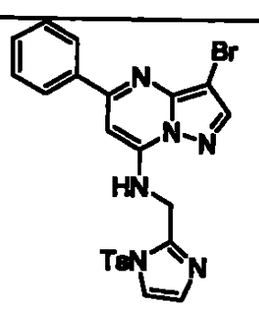
EXAMPLES 237-256:

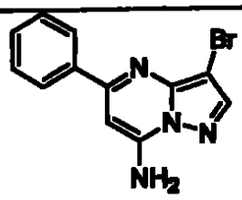
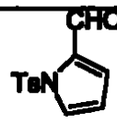
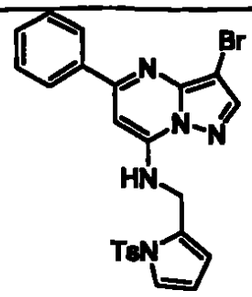
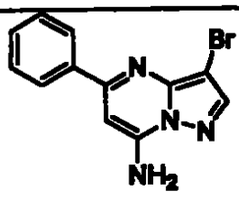
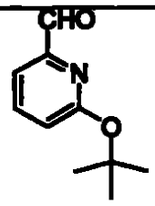
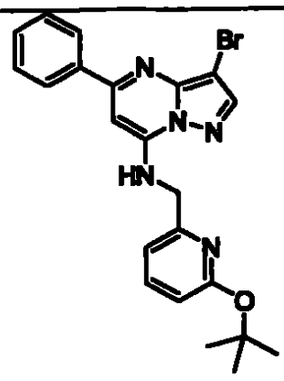
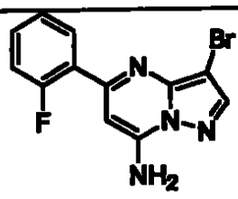
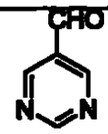
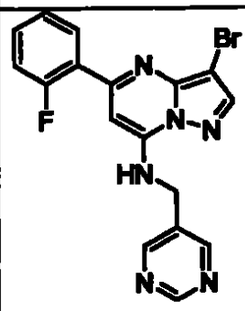
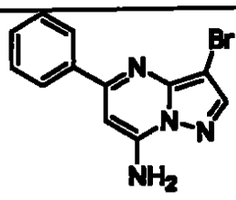
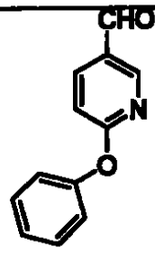
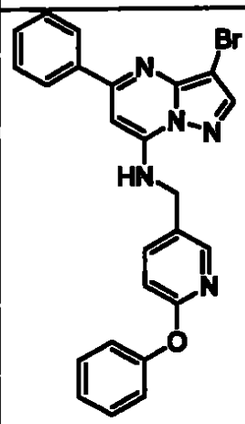
By essentially the same procedure set forth in Example 236 combining the compounds shown in Column 2 and 3 of Table 22, the compounds shown in Column 4 of Table 22 were prepared.

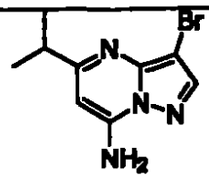
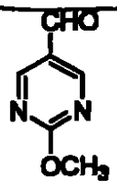
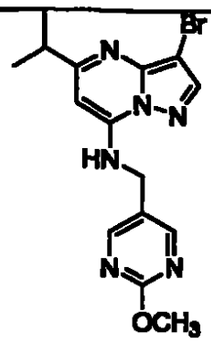
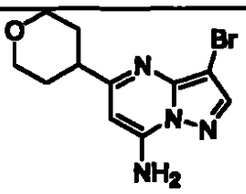
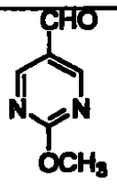
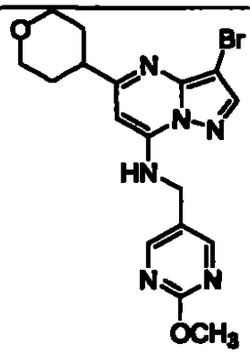
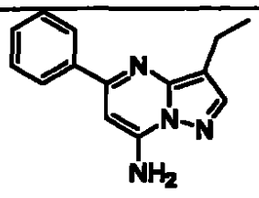
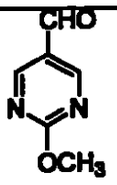
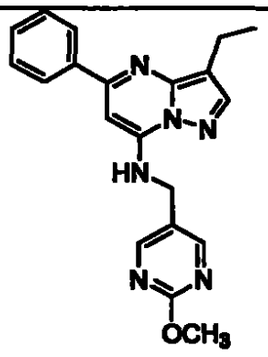
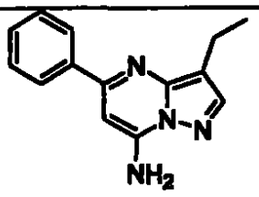
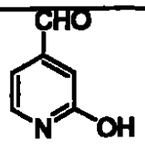
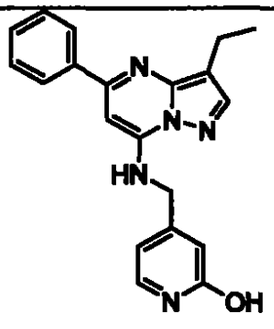
TABLE 22

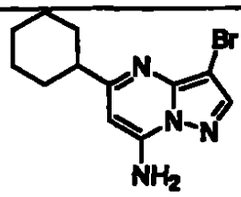
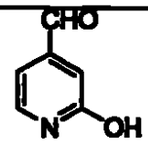
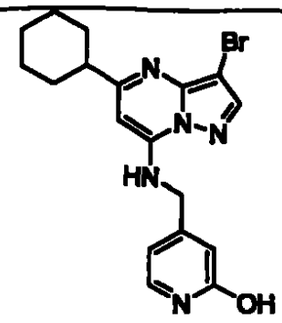
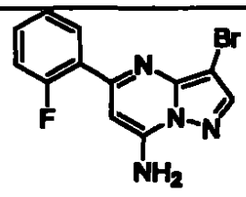
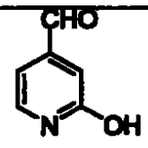
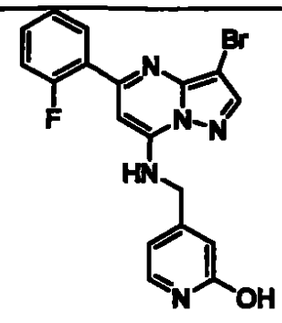
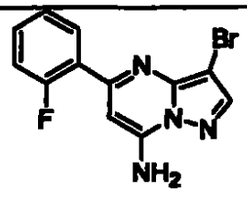
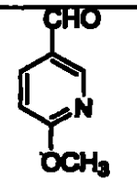
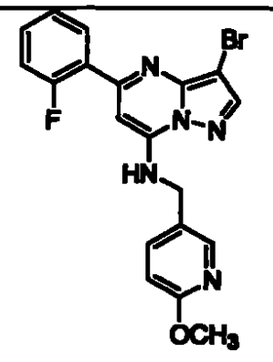
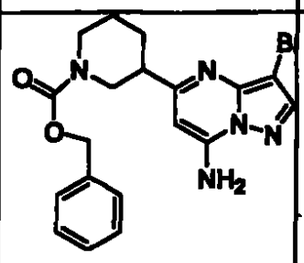
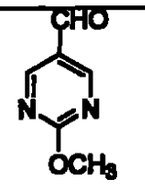
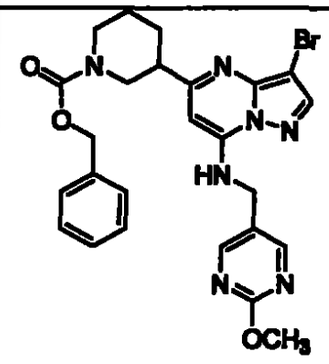
Ex.	Column 2	Column 3	Column 4	Data

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

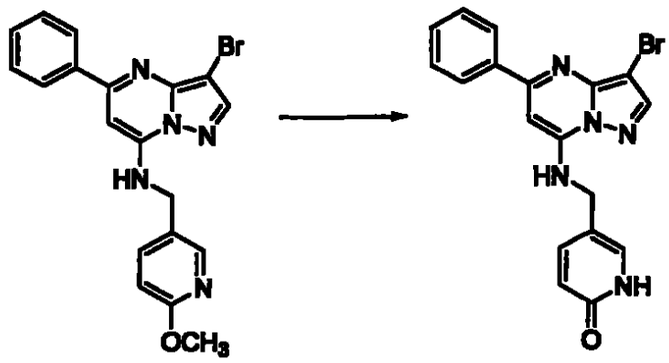
241				LCMS: $M2H^+$=385 ; mp=214-216°C
242				LCMS: MH^+=; mp=°C
243				LCMS: M^+=416; mp=80-82°C
244				

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:

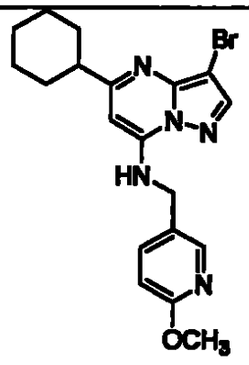
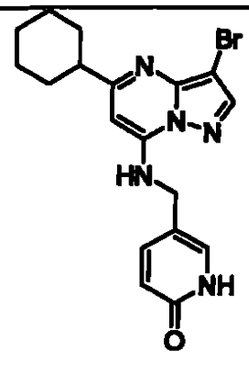


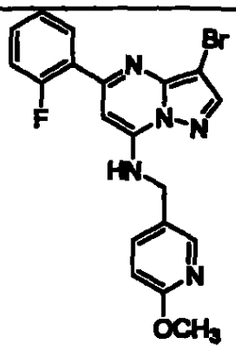
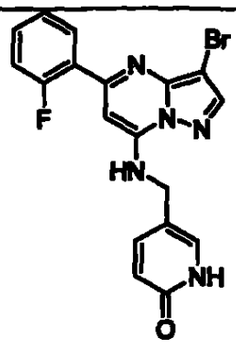
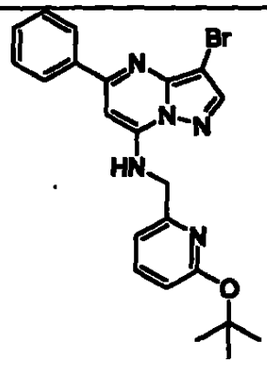
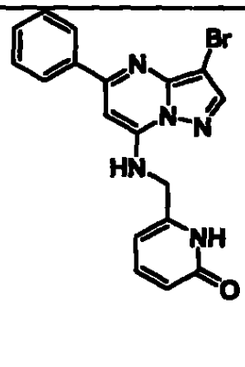
A mixture of the compound prepared in Example 242 (100 mg, 0.24 mmol), conc. aqueous HCl (1.0 mL) and acetic acid (2.0 mL) were stirred at 100°C under N_2 for 2 hr, then poured onto Na_2CO_3 (15 g), and extracted with 1:1 acetone:CH_2Cl_2 (3 x 30 mL). Combined extracts were filtered, and the solvent 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:

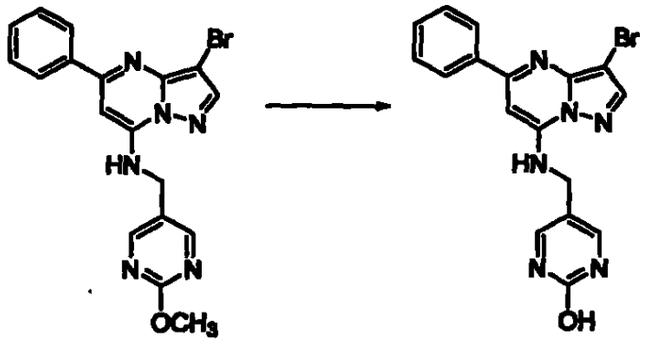
By essentially the same procedure set forth in Example 257 starting from the compounds shown in Column 1 of Table 23, the compounds shown in Column 2 of Table 23 were prepared.

TABLE 23

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

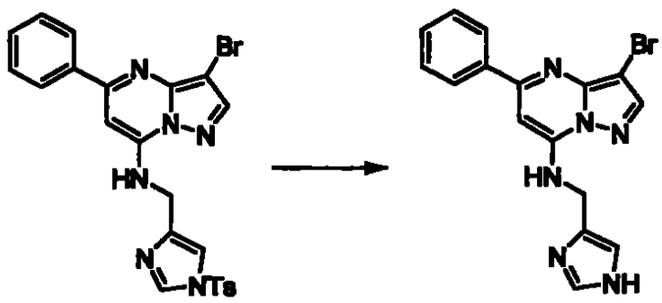
259			LCMS: MH^+=416; mp=215-218°C
260			LCMS: $M2H^+$=398 ; mp>230°C

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:

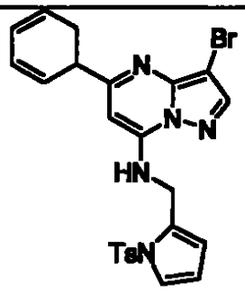
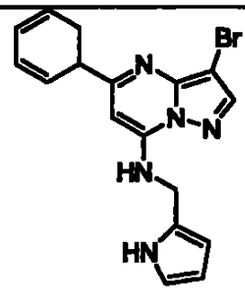


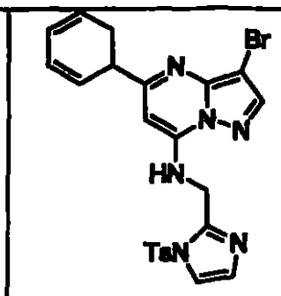
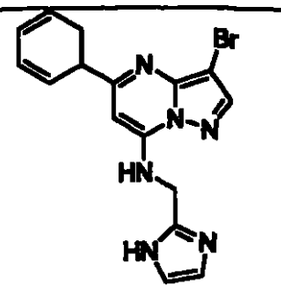
A mixture of the product prepared in Example 217 (40 mg, 0.077 mmol) and 5.0 M aqueous NaOH (0.8 mL) in MeOH (3.0 mL) was refluxed under N_2 for 1 hr. $NaHCO_3$ (700 mg) was added, the solvent evaporated, and the residue was purified by flash chromatography using 10:1:0.1 CH_2Cl_2: MeOH: conc. NH_4OH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

EXAMPLES 263-264:

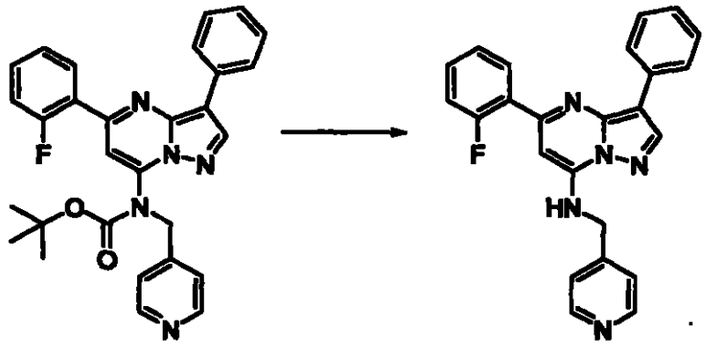
By essentially the same procedure set forth in Example 262 starting from the compounds shown in Column 1 of Table 24, the compounds shown in Column 2 of Table 24 were prepared.

TABLE 24

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

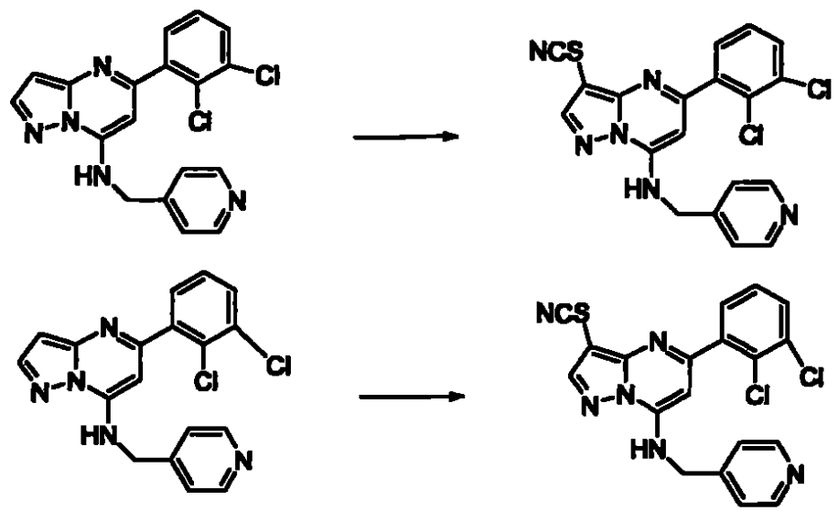
264			LCMS: M2H$^+$=371 ; mp=180-182°C

EXAMPLE 265:



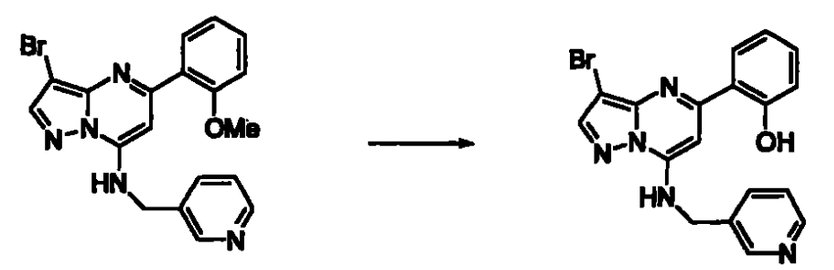
TFA (0.5 mL) was added to a solution of the compound prepared in Preparative Example 197 (0.08 g, 0.16 mmol) in CH_2Cl_2 (2.0 mL) at 0°C and the resulting solution stirred 2.5 hours and stored at 4°C overnight at which time additional TFA (0.5 mL) was added. The resulting solution was stirred 4 hours 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). ^1H 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.

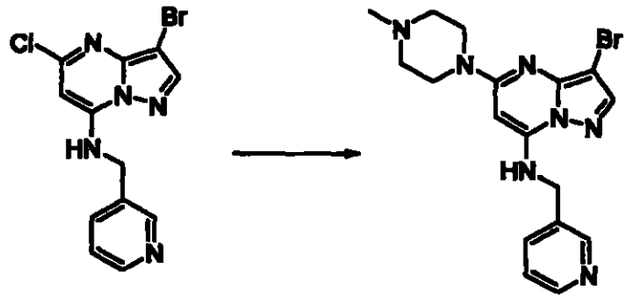
EXAMPLE 267:



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:



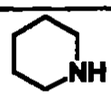
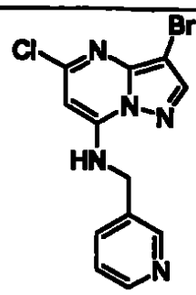
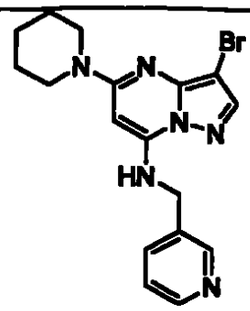
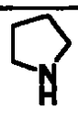
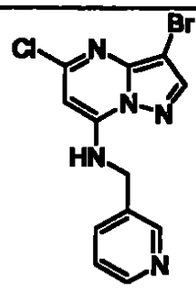
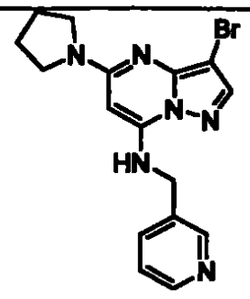
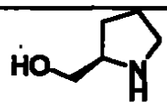
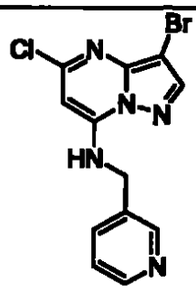
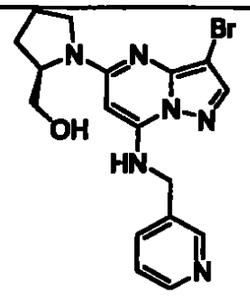
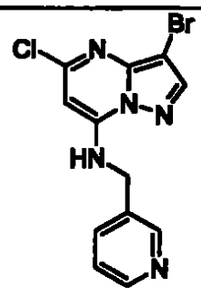
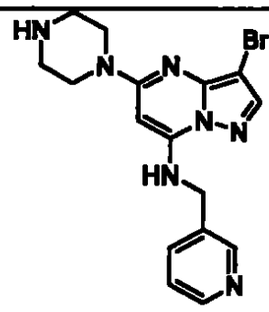
A solution of the compound from Preparative Example 184 (0.05 g, 0.15 mmol), N-methylpiperazine (20 µL, 1.2 eq.) and IPr_2Et (52 µL, 2.0 eq.) in dioxane (1 mL) was heated to 70 °C overnight. The reaction mixture was cooled to room temperature and diluted with H_2O and saturated $NaHCO_3$. The resulting 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.)

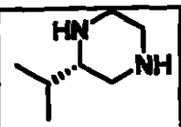
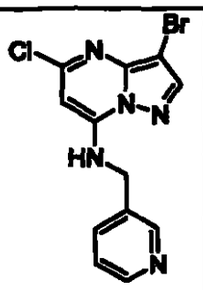
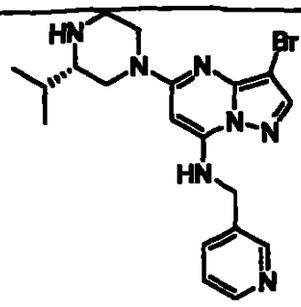
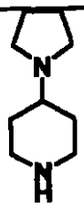
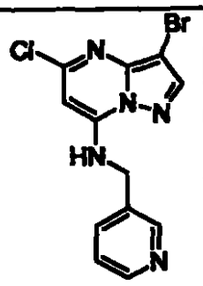
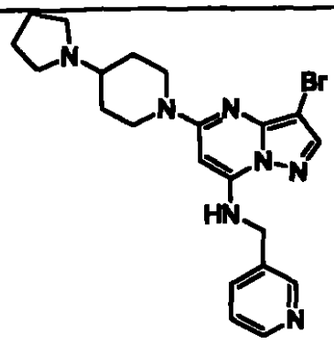
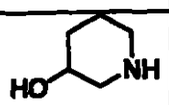
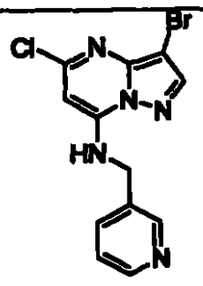
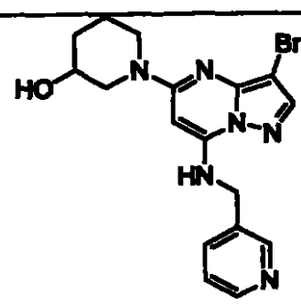
EXAMPLES 269-275:

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

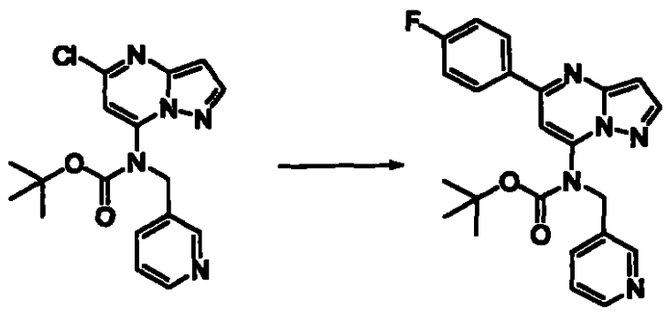
Ex.	Column 2	Column 3	Column 4	CMPD

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

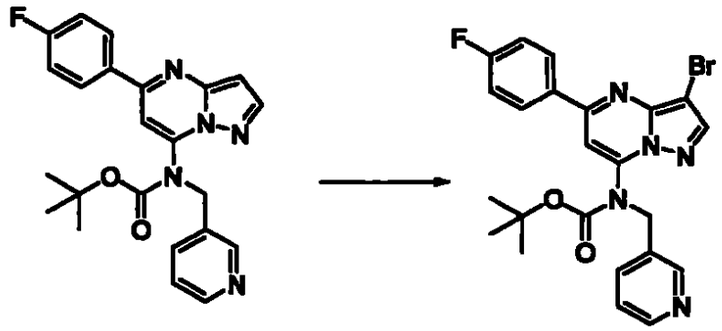
EXAMPLE 276:

Step A:



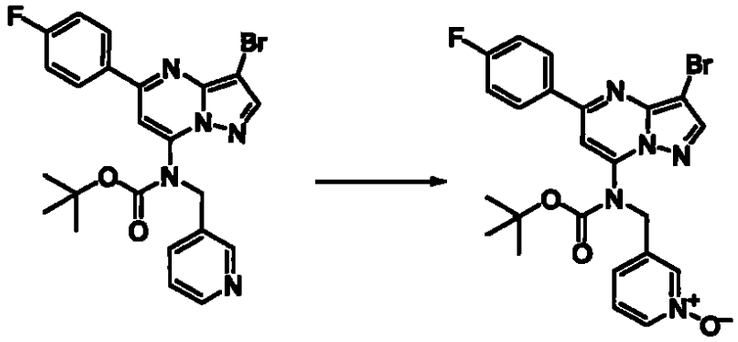
4-Fluorophenyl magnesium bromide (0.68 mL, 1.2 eq.) was added to the compound prepared in Preparative Example 193 (0.20 g, 0.55 mmol) and $PdCl_2(dppf)_2$ (0.037 g, 10 mol%) in THF and the resulting solution was stirred at room temperature 72 hours. The reaction mixture was dilute with saturated NH_4Cl 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:



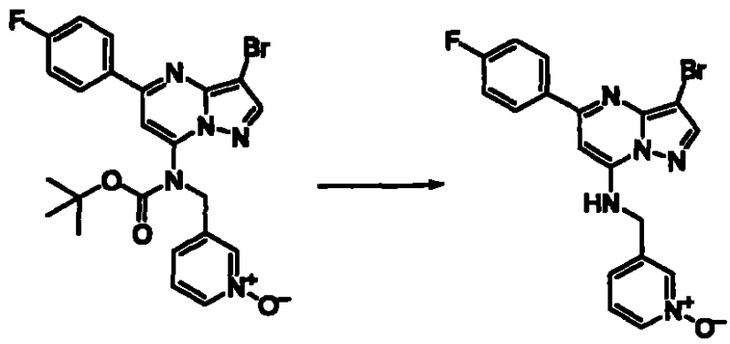
By essentially the same procedure set forth in Preparative Example 127 only substituting the compound prepared in Example 276, Step A, the above compound was prepared (0.17 g, 94% yield).

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).

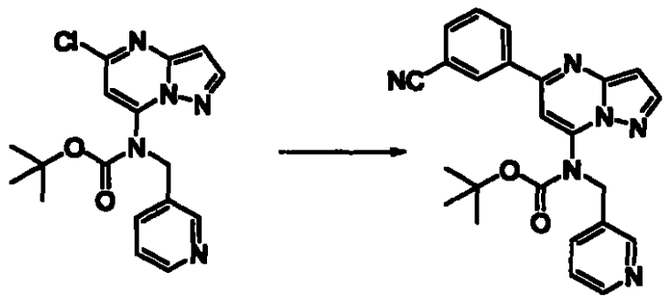
Step D:



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, 82% yield). MS: MH^+ = 414; mp = 110-115 °C.

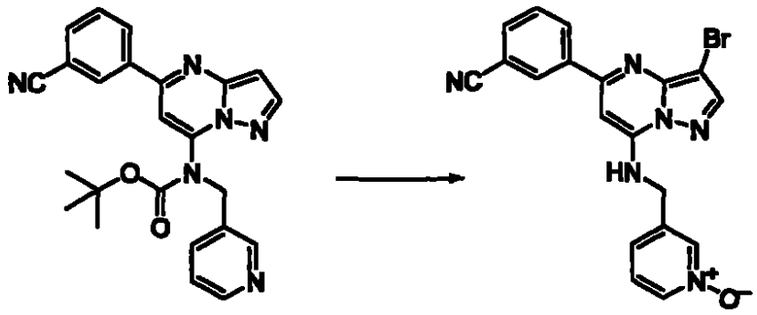
EXAMPLE 277:

Step A:



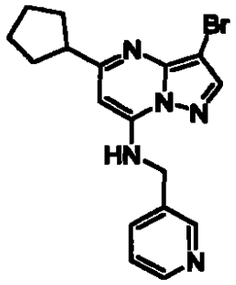
$Pd(PPh_3)_4$ (0.065 g, 10 mol%) was added to 3-cyanophenyl zinc iodide (2.2 mL, 0.5 M solution in THF, 2 eq.) and the compound prepared in Preparative Example 193 (0.2 g, 0.56 mmol) in DMF (2.0 mL) and the resulting solution heated to 80 °C g for 144 hours. The reaction mixture was cooled to room temperature, 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:



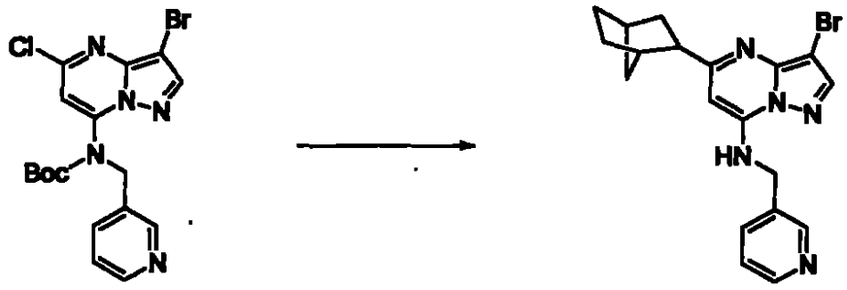
By essentially the same procedures set forth in Example 276, Step B through Step D, the above compound was prepared (0.023 g, 53% yield). MS: MH^+ = 421; mp = 230 °C (dec.)

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:



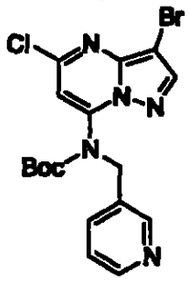
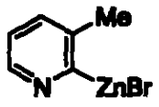
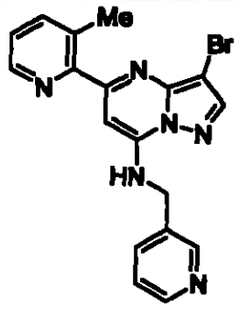
The palladium-catalyzed zinc cross-coupling reaction was carried out in a manner similar to the procedure described in *J. Org. Chem.* (1999), 453. A solution of the chloropyrazol pyrimidine (200 mg, 0.458 mmol), $Pd(PPh_3)_4$ (53

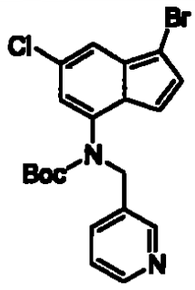
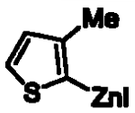
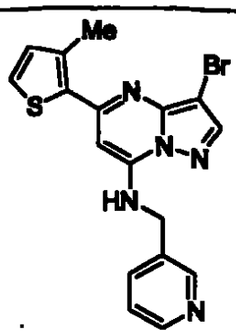
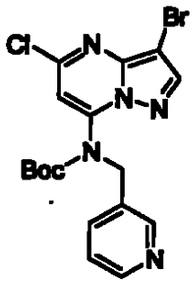
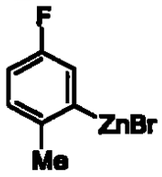
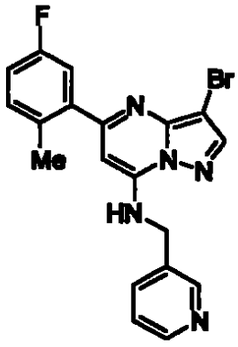
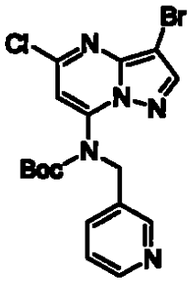
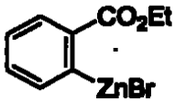
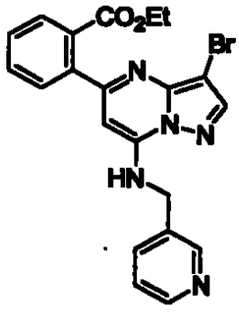
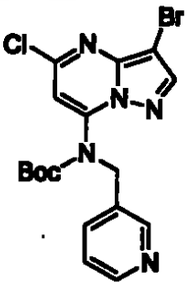
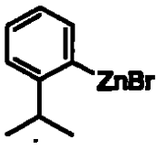
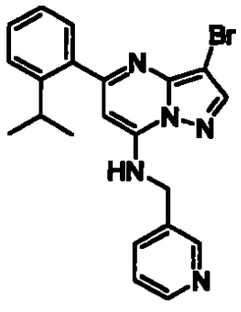
mg, 0.046 mmol), and *exo*-2-norbonylzinc bromide (0.5 M in THF, 0.95 mL, 0.47 mmol) in DMF (2 mL) was refluxed at 100°C (oil bath temp.) overnight. The reaction mixture was quenched with half-saturated NH_4Cl and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under 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).

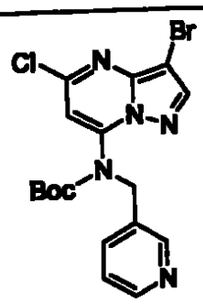
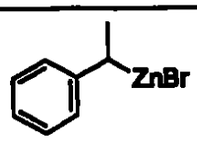
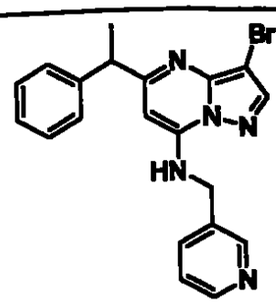
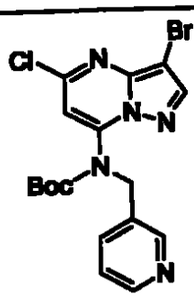
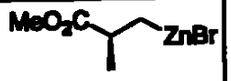
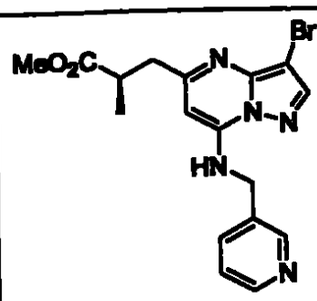
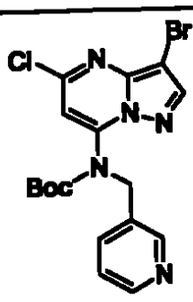
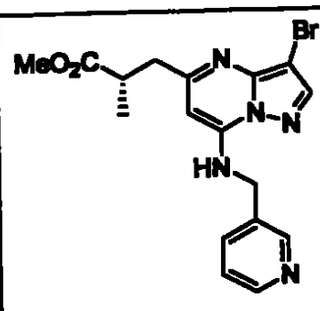
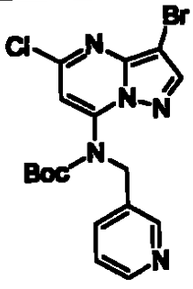
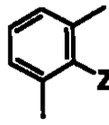
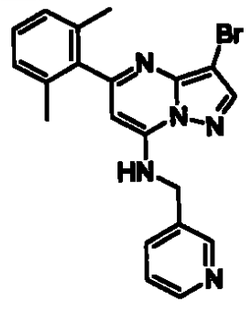
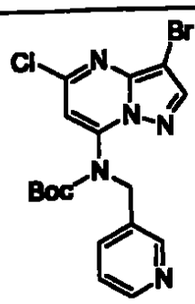
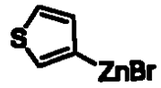
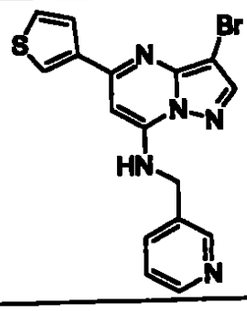
EXAMPLES 280-294:

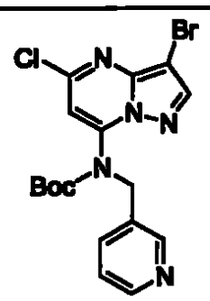
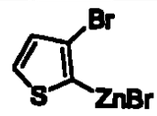
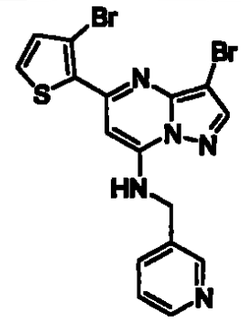
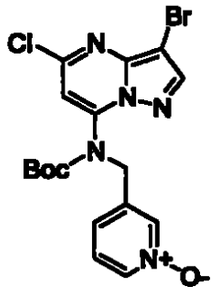
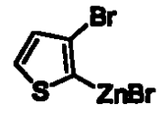
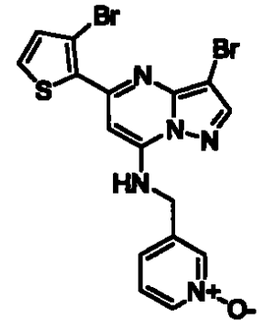
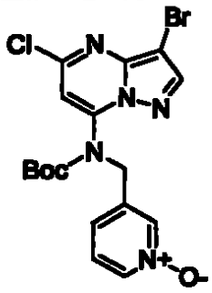
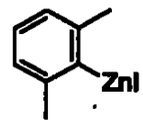
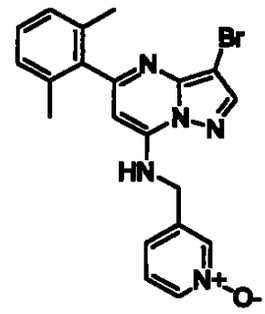
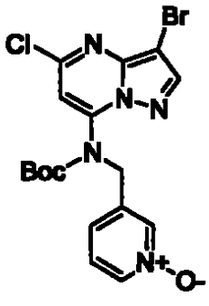
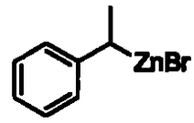
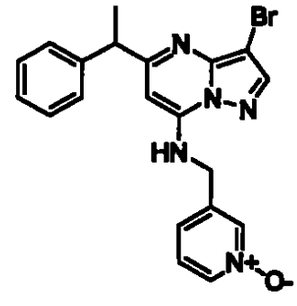
By following essentially the same procedure set forth in Example 279 only substituting the chlorides shown in Column 2 of Table 26 and the organozinc reagents shown in Column 3 of Table 26, the compounds in Column 4 of Table 26 were prepared:

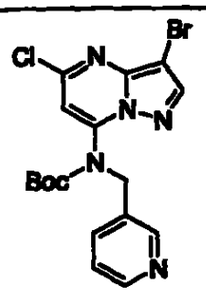
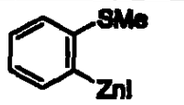
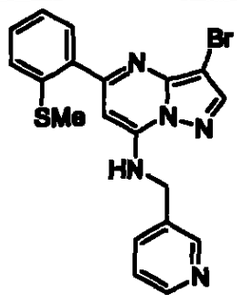
Table 26

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^+ = 484
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), 5.67 (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).

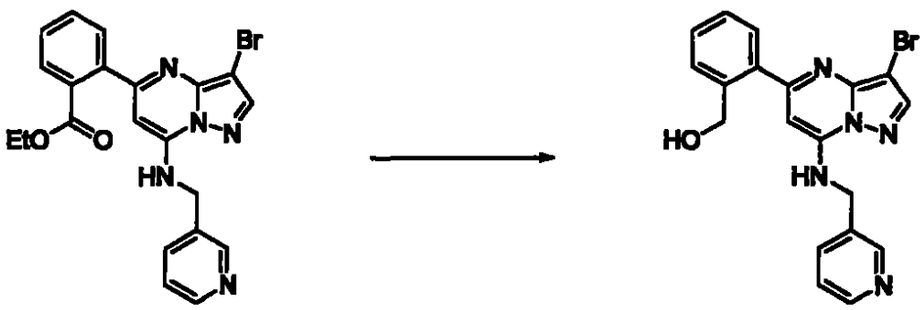
EXAMPLE 291: ^{1}H NMR (DMSO-d_6) δ 9.12 (s, 1H), 8.40 (s, 1H), 8.33 (s, 1H), 8.13 (m, 1H), 7.82 (d, J = 5.1 Hz, 1H), 7.40-7.39 (m, 2H), 7.22 (d, J = 5.1 Hz, 1H), 6.86 (s, 1H), 4.86 (s, 2H).

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).

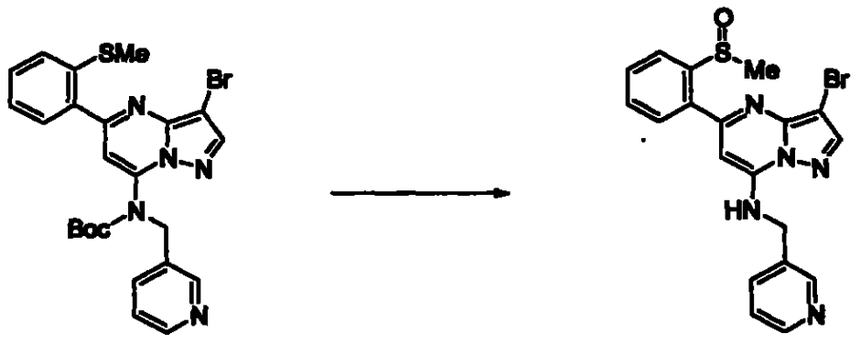
EXAMPLE 294: ^{1}H NMR ($CDCl_3$) δ 8.67 (s, 1H), 8.59 (d, J = 4.8 Hz, 1H), 8.01 (s, 1H), 7.71 (m, 1H), 7.52 (dd, J = 7.8, 1.8 Hz, 1H), 7.40-7.19 (m, 4H), 6.78 (t, J = 6.0 Hz, 1H), 6.32 (s, 1H), 4.67 (d, J = 6.0 Hz, 2H), 2.38 (s, 3H).

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).

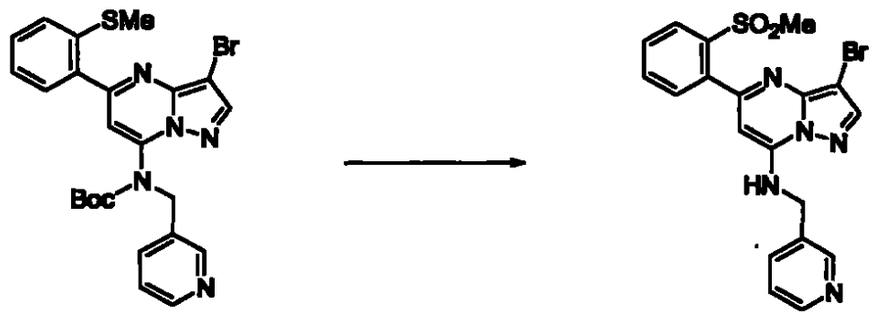
EXAMPLE 296:



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 I 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

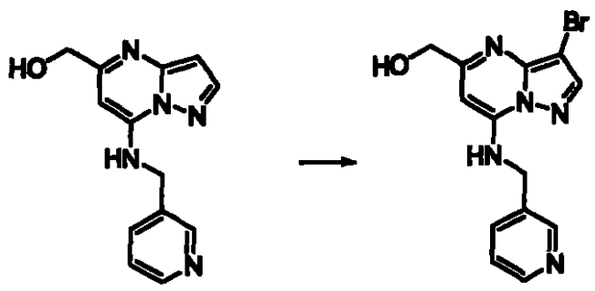
extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by preparative thin-layer chromatography using a 5% MeOH in EtOAc solution as eluent (26 mg, 89% yield). LCMS: MH^+ = 442; ^1H NMR ($CDCl_3$) δ 8.71 (s, 1H), 8.64 (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

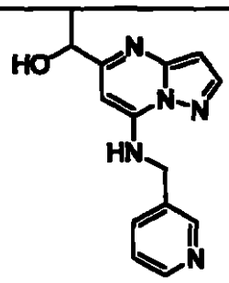
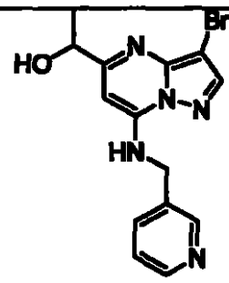
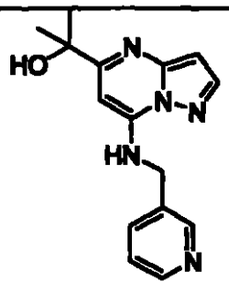
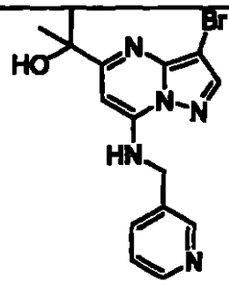


By essentially the same procedure set forth in Preparative Example 127 only substituting the compound prepared in Preparative Example 189, the above compound was prepared. MS: MH^+ = 334; mp = 170-173 °C.

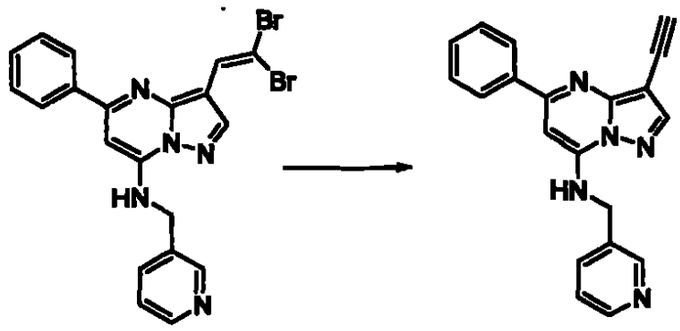
Examples 299-300:

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

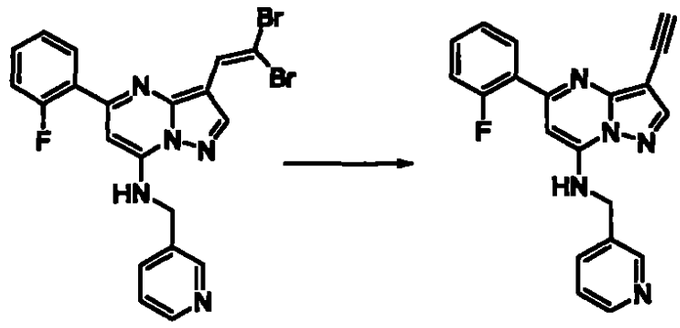
Ex.	Column 2	Column 3	CMPD
299			MS: MH^+ = 348 m.p. = 73 – 83 °C
300			MS: MH^+ = 362 m.p. = 165 – 175 °C

EXAMPLE 301:



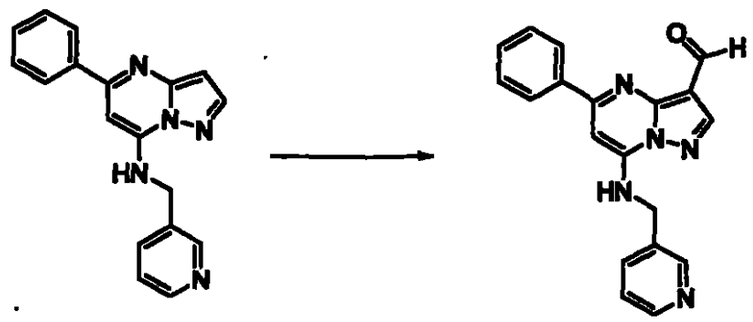
To a solution of the compound prepared in Preparative Example 186 (0.1 g, 0.21 mmol) in THF (4.0 mL) at -78 °C was added nBuLi (0.57 mL, 2.16M in hexanes, 5.0 eq.) at -78 °C. The reaction mixture was stirred 2 hours at -78 °C, quenched with H_2O, warmed to room temperature, and extracted with EtOAc. 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:



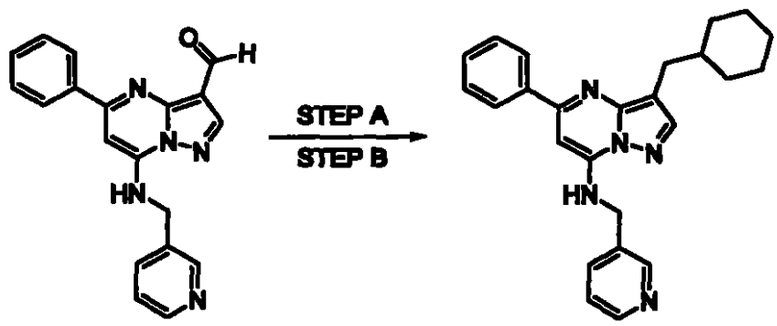
By essentially the same procedure set forth in Example 301 only substituting the compound from Preparative Example 187, the above compound was prepared (0.049 g, 68% yield).MS: MH^+ = 344; mp = 69-71 °C.

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.

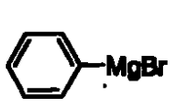
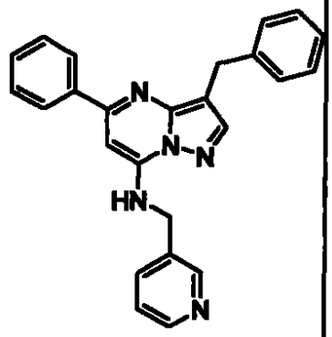
STEP B:

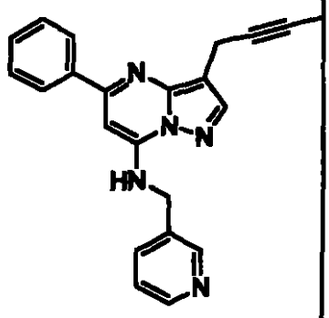
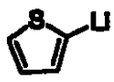
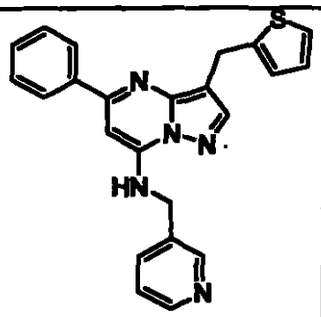
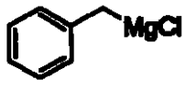
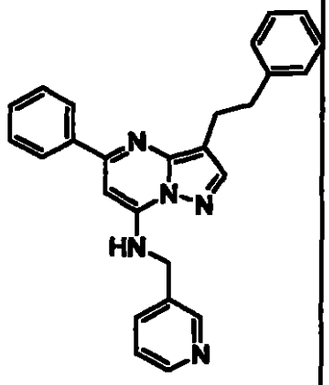
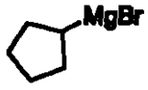
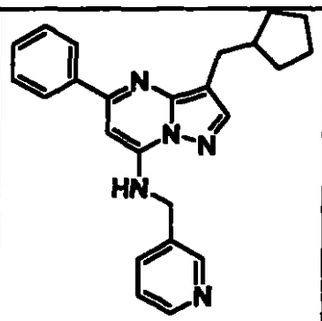
To a solution of alcohol (53 mg, 0.13 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added Et_3SiH (24 μL, 0.15 mmol) followed by TFA (24 μL, 0.30 mmol). The mixture was stirred for 2 h at 0 °C and rt for 2 h whereupon additional portions of Et_3SiH (24 μL, 0.15 mmol) and TFA (24 μL, 0.30 mmol) were added and 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.

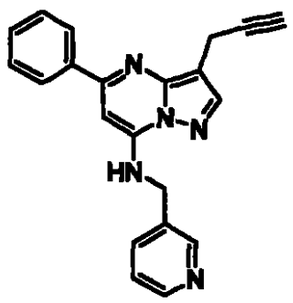
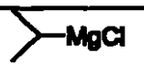
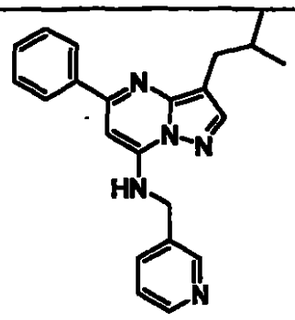
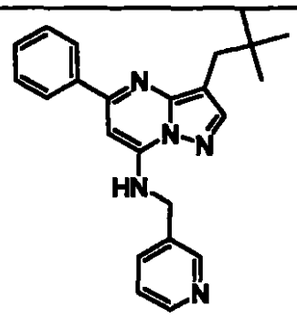
EXAMPLES 305-312:

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:

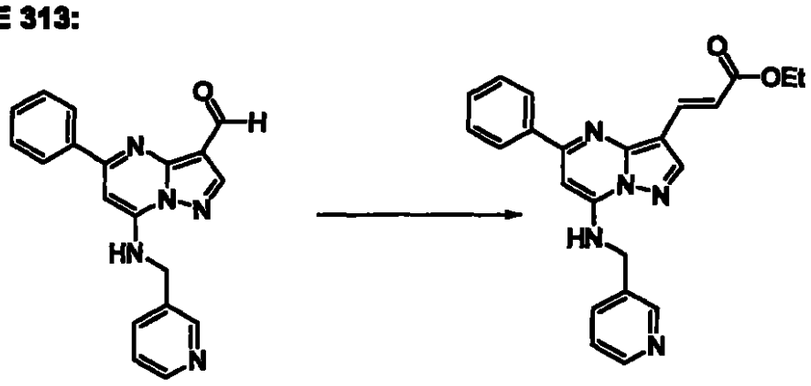
TABLE 28

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

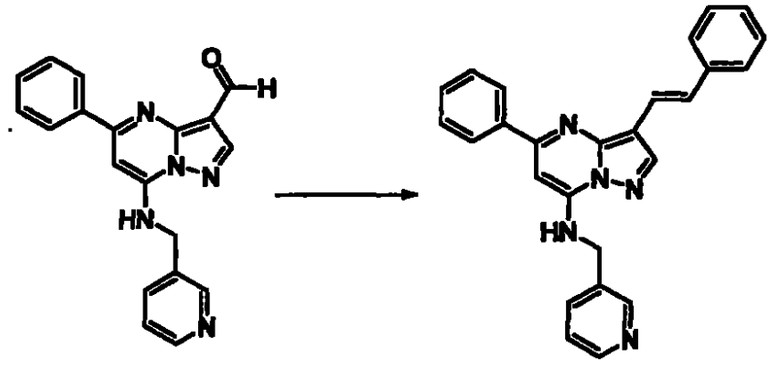
EXAMPLE 313:



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

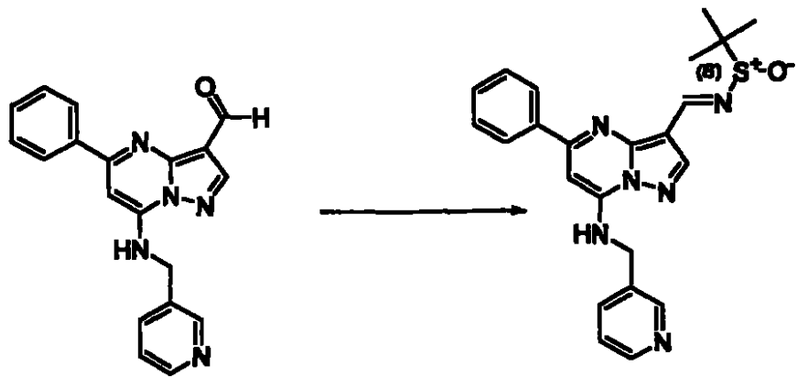
(0.12 g, 0.33 mmol) in one portion. The mixture was heated at reflux for 24h, cooled to rt, and concentrated under reduced pressure. The mixture was diluted CH_2Cl_2 (5 mL), brine (2 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 4 mL). The organic layers 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:



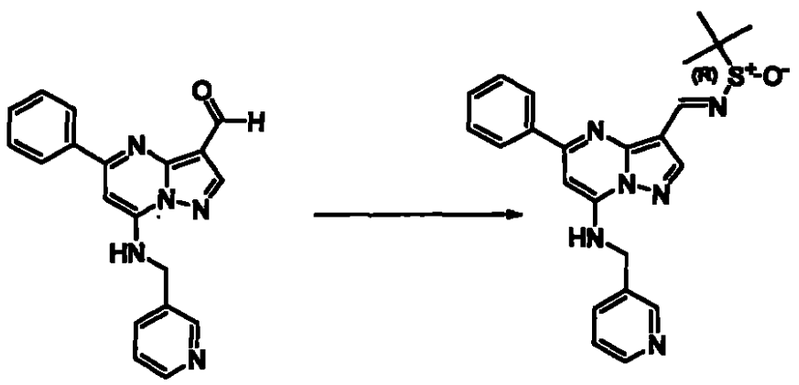
To a mixture of benzyltriphenylphosphonium bromide (0.59 g, 1.37 mmol) in THF (3 mL) was added NaH (55 mg, 1.37 mmol) and the mixture was stirred for 30 min. The aldehyde (0.15 g, 0.46 mmol) from Example 303 was added in a single portion and the mixture was heated at reflux for 36h. The mixture was cooled 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:



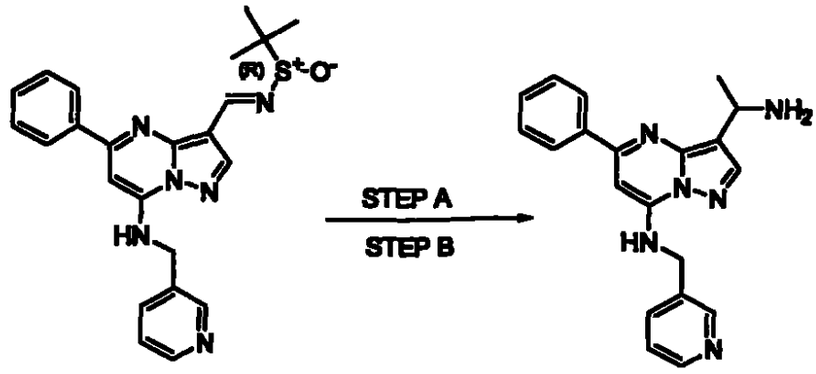
To a solution of aldehyde (0.20 g, 0.60 mmol) from Example 303 in THF (3 mL) was added Ti (i-OPr)$_4$ (0.36 mL, 1.21 mmol) dropwise followed by addition of (*S*)-(-)-2-methyl-2-propanesulfinamide (74 mg, 0.61 mmol). The resulting mixture was stirred for 18h at reflux, cooled to rt, and quenched with 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:



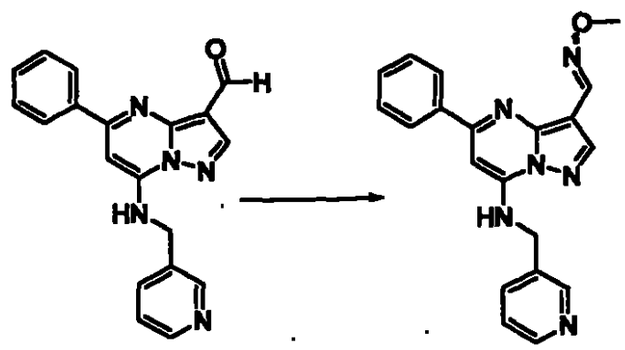
STEP A:

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:

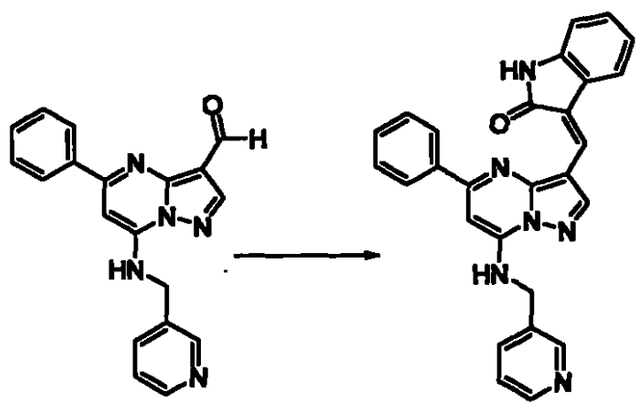
The crude material from Step A (30 mg, 0.067 mmol) in MeOH (2 mL) was added conc. HCl (2 mL). The mixture was stirred at rt for 12h and the mixture was concentrated to dryness. The crude material was partitioned between CH_2Cl_2 (3 mL) and sat. aq. $NaHCO_3$ (2 mL) and the layers were separated. The 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.

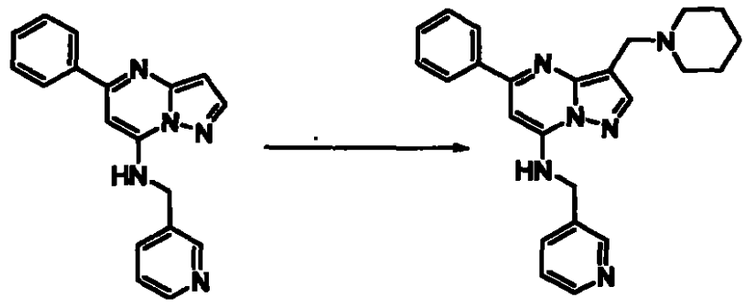
EXAMPLE 319:



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:

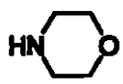


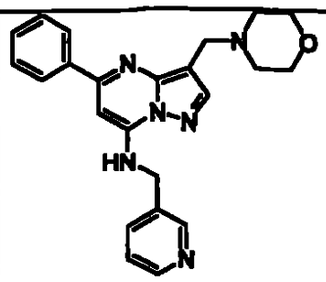
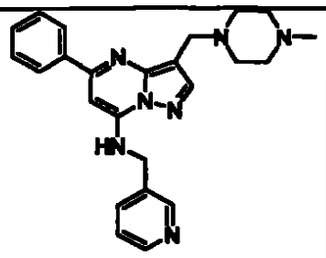
To a solution of 3-H analog (106 mg, 0.35 mmol) from Preparative Example 187.10 in AcOH (2 mL) was added 37% aqueous formaldehyde (1.5 ml; 1.40 mmol) followed by piperidine (100 µL; 0.37 mmol). The resulting mixture was stirred at rt for 24h and the AcOH was removed under reduced pressure. The mixture 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:

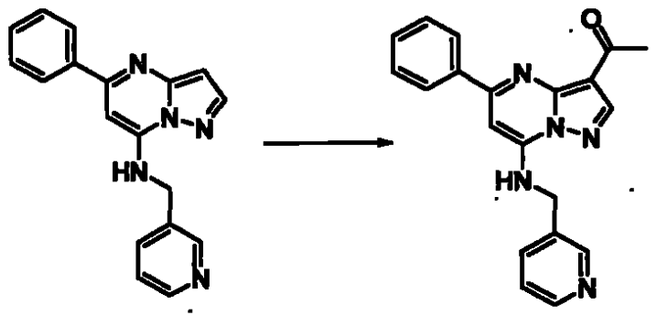
By essentially the same procedure set forth in Example 320 only substituting the amines in Column 2 of Table 29 and employing the 3-H adduct from Preparative Example 187.10, the compounds in Column 3 of Table 29 were prepared:

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

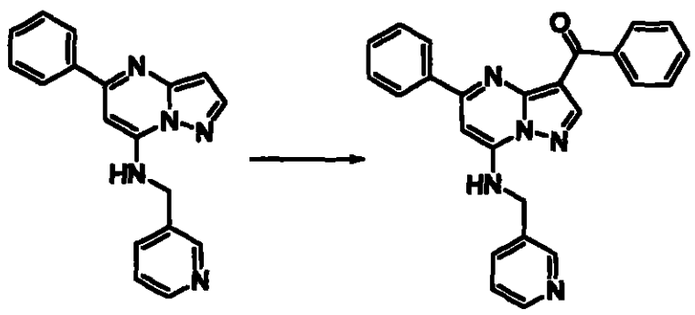
			
322			1. mp = 102-104 2. M+H = 414

EXAMPLE 323:



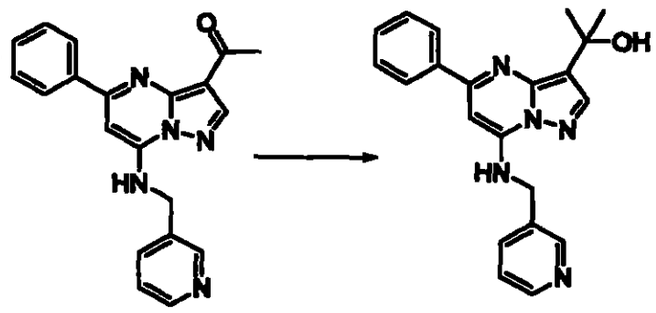
To a solution of 3-H analog (113 mg, 0.38 mmol) from Preparative Example 187.10 in CH_2Cl_2 (5 mL) at rt was added $AlCl_3$ (215 mg, 1.61 mmol) followed by AcCl (100 mL, 1.40 mmol). The mixture was heated at reflux for 12h and was cooled to rt. The mixture was treated sequentially with 3M HCl (3 mL) 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:



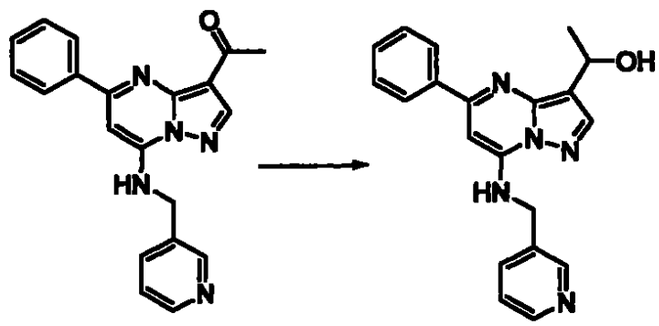
Utilizing the method described in Example 323, except employing benzoyl chloride, the title compound was prepared in 61% yield as a white solid. mp 172-175 °C; M+H = 406.

EXAMPLE 325:



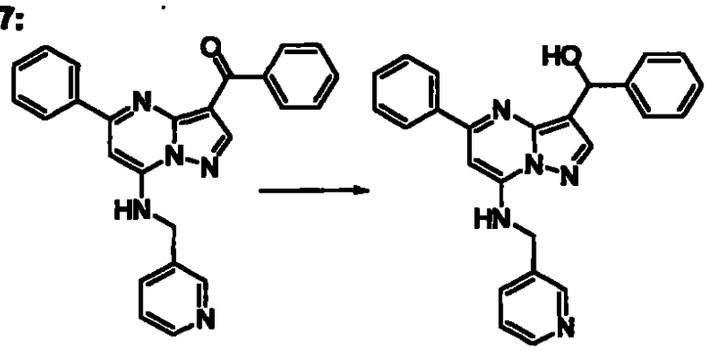
To a solution of ketone (100 mg, 0.29 mmol) from Example 323 in CH_2Cl_2 (2.5 mL) at 0 °C was added MeMgBr (0.35 mL, 3.0M in Et_2O) dropwise. The resulting mixture was stirred for 18h at rt and was carefully quenched by addition of sat. aq. NH_4Cl (2 mL) and CH_2Cl_2 (2 mL) were added. The layers were 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:



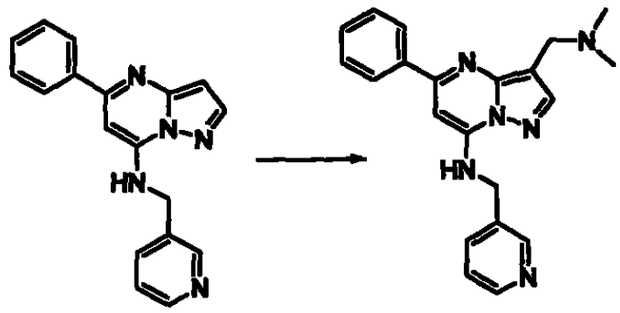
To a solution of ketone (84 mg, 0.24 mmol) from Example 323 in MeOH/THF (1:1; 2 mL total) at 0 °C was added $NaBH_4$ (12 mg, 0.30 mmol) in one portion. The resulting mixture was stirred for 18h at rt whereupon and additional portion of $NaBH_4$ (12 mg, 0.30 mmol) was added. The mixture was stirred for 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:



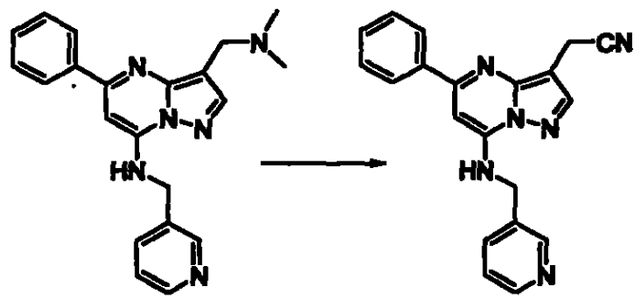
Using the same procedure as outlined in Example 326, the ketone (84 mg, 0.21 mmol) was converted to 53 mg (62%) as a light yellow solid. mp 78-80 °C; M+H = 408.

EXAMPLE 328:



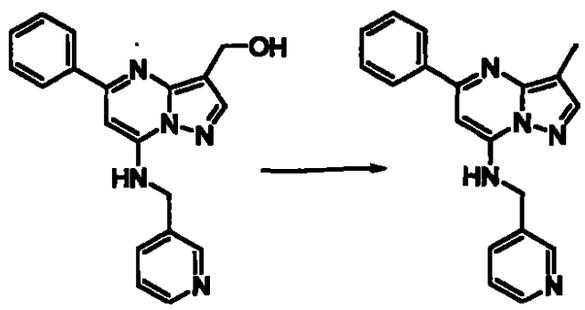
To a solution of 3-H adduct (1.3 g, 4.31 mmol) from Preparative Example 187.10 in CH_2Cl_2 (50 mL) was added Eschenmoser's salt (0.79 g, 4.31 mmol) followed by dropwise addition of TFA (0.56 mL, 7.33 mmol). The mixture was stirred at rt for 48 h and was diluted with CH_2Cl_2 (250 mL). The organic layer 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:



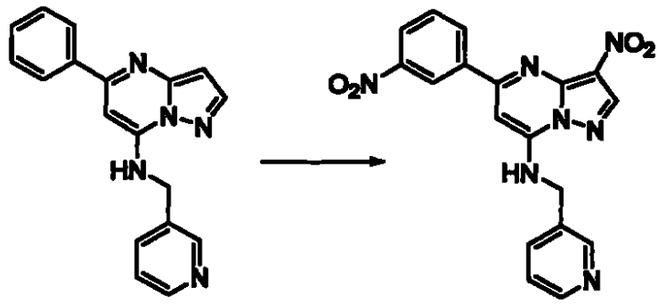
To a solution of tertiary amine adduct (100 mg, 0.28 mmol) from Example 328 in 50% aq. DMF (5 mL) in a pressure tube was added KCN (0.15 g, 2.32 mmol). The tube was capped and heated at 100 °C for 96h. The mixture was cooled to rt and was diluted with EtOAc (25 mL). The organic layer was washed with 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:

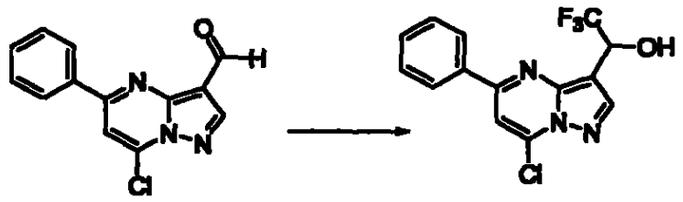


To a solution of 3-H adduct (90 mg, 0.30 mmol) from Preparative Example 187.10 in conc. H_2SO_4 (2 mL) at 0 °C was added fuming HNO_3 (30 µL, 0.72 mmol) dropwise. Th resulting mixture was stirred for 1 h at 0 °C whereupon ice

(~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.

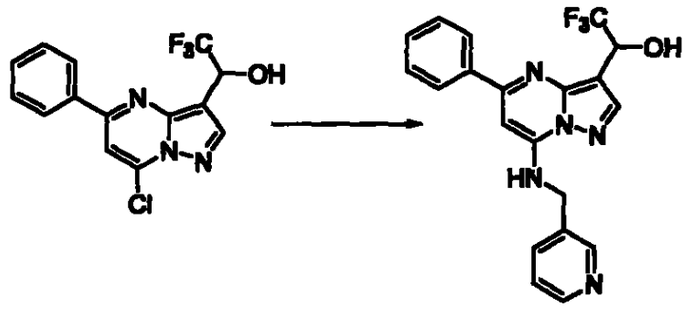
EXAMPLE 332:

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.

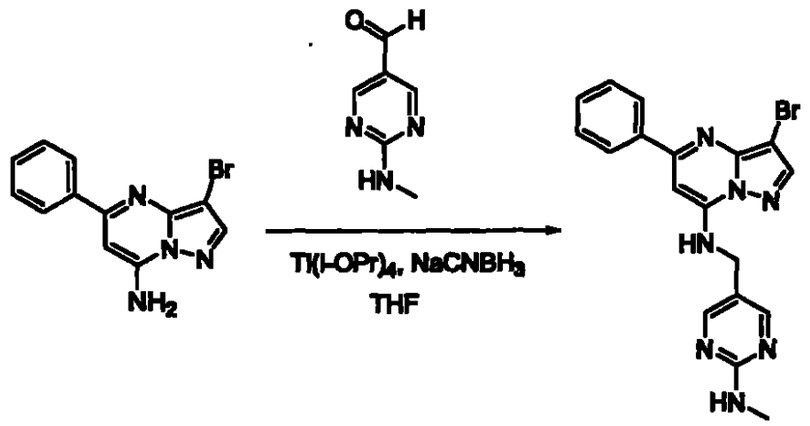
Step B:



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:



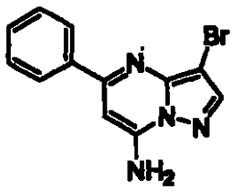
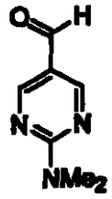
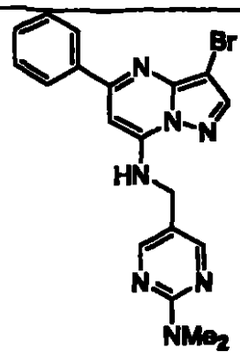
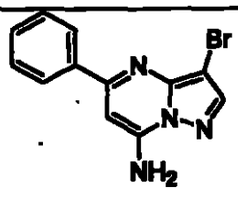
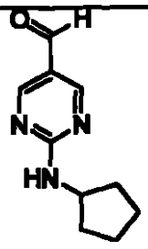
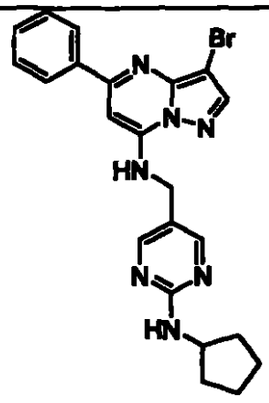
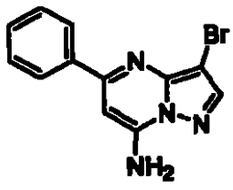
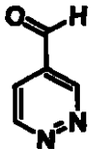
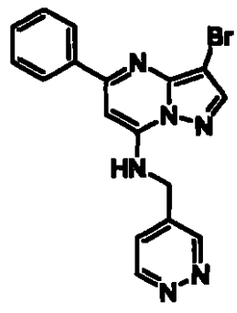
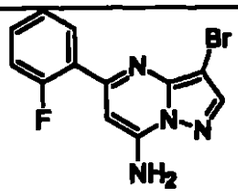
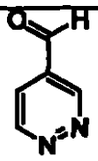
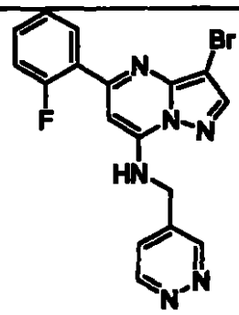
To a solution of aniline (200 mg, 0.69 mmol) from Preparative Example 174 in THF (6 mL) at rt was added aldehyde (114 mg, 0.83 mmol) from Preparative Example 256 followed by dropwise addition of $Ti(i\text{-}OPr)_4$ (0.82 mL, 2.77 mmol). The mixture was stirred at reflux for 4 h and was cooled to rt. $NaCNBH_3$ (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 µM 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:

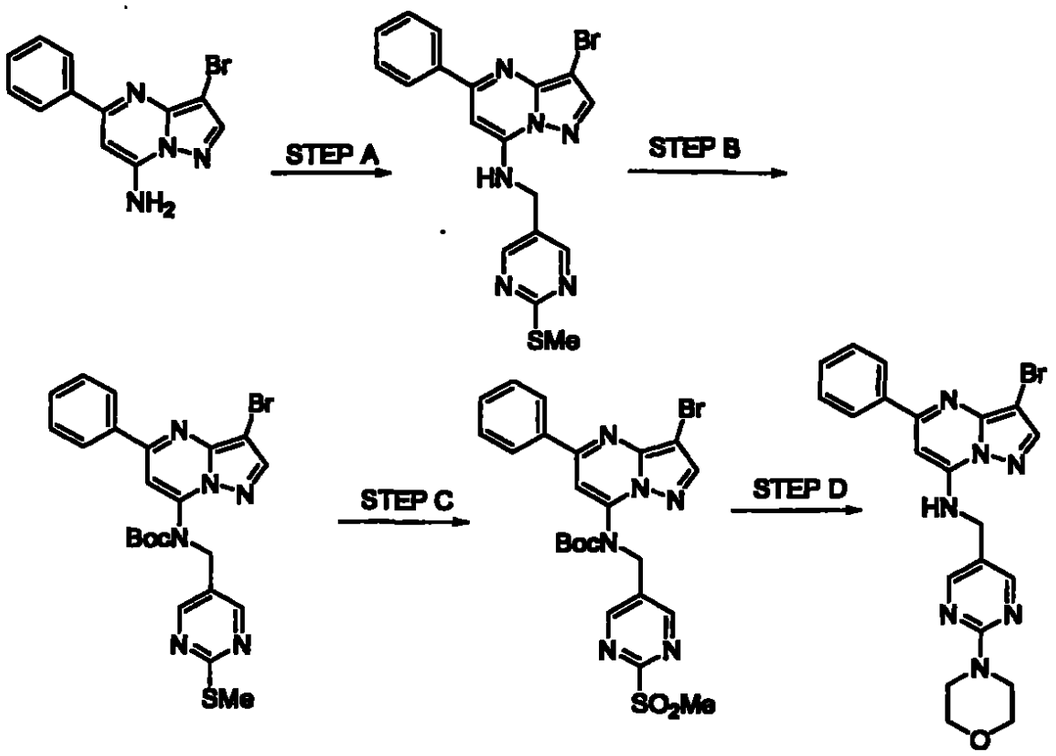
By essentially the same procedure set forth in Example 333 only by utilizing the anilines shown in Column 2 of Table 30 and the aldehydes shown in Column 3 of Table 30, the compounds in Column 4 of Table 30 were prepared:

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:

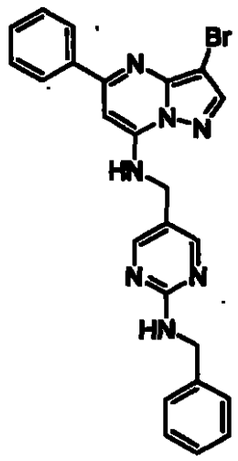
To a solution of thiomethyl derivative from Example 338, Step B (41 mg, 0.078 mmol) in CH_2Cl_2 (2 mL) was added MCPBA (33 mg, 0.19 mmol) in one portion. The resulting mixture was stirred for 3h at rt and the mixture was diluted

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:

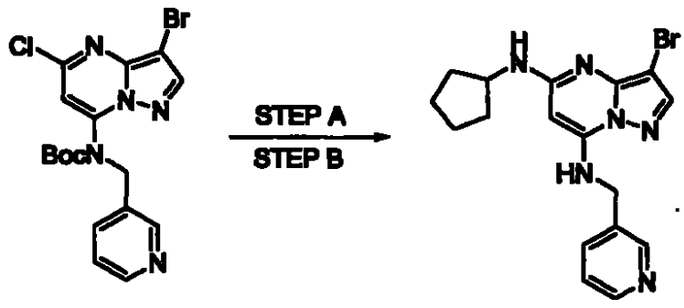
To a flask charged with sulfone from Example 338, Step C (75 mg, 0.13 mmol) and a stir bar was added morpholine (2 ml; 22 mmol). The mixture was heated at reflux for 12h, cooled to rt, and concentrated to dryness under high vacuum. The crude product was purified by preparative thin-layer chromatography (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:



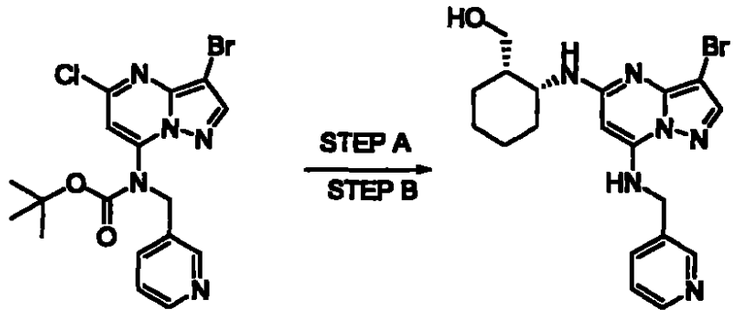
STEP A:

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.

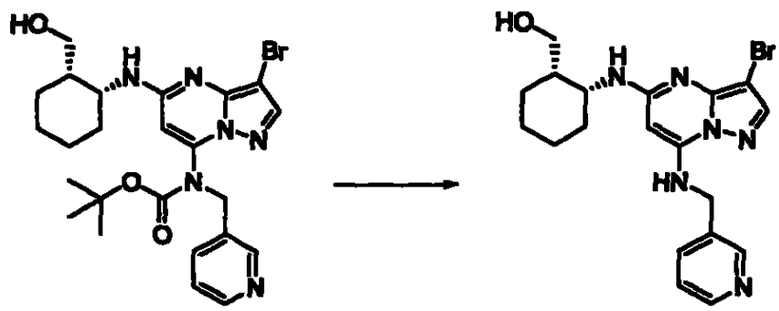
EXAMPLE 341:



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.

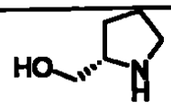
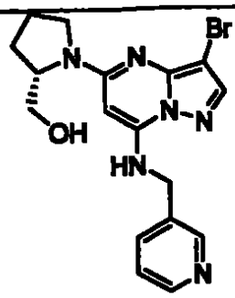
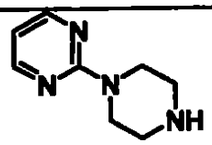
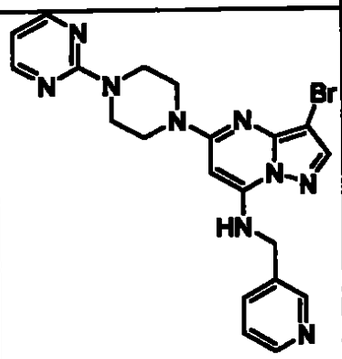
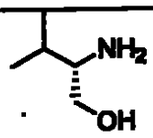
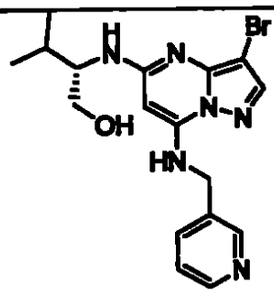
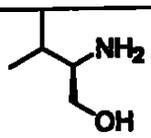
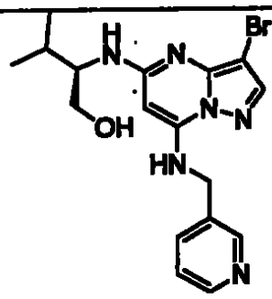


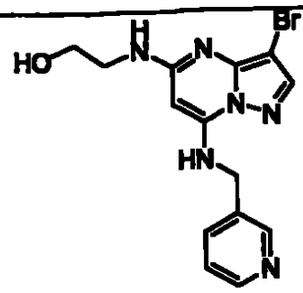
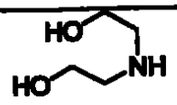
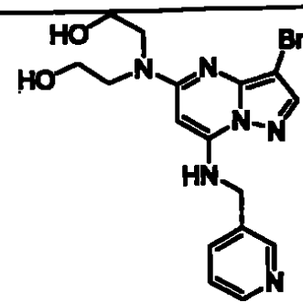
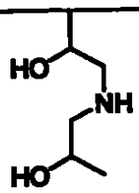
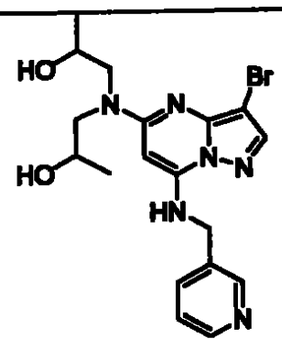
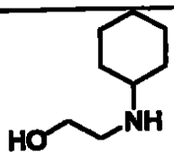
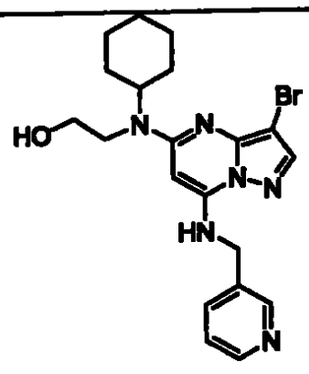
To a mixture of the compound prepared in Example 341, Step A (0.14 g, 0.26 mmol) in EtOH : H_2O (3 mL, 2 : 1) was added KOH (0.29 g, 20 eq.) in one portion. The resulting solution was stirred at reflux 14 hours, cooled to room temperature, and concentrated under reduced pressure. The residue was taken 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.

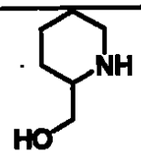
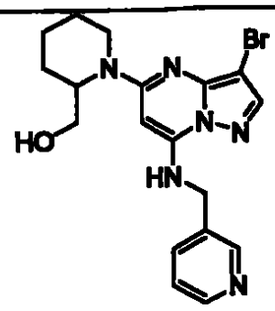
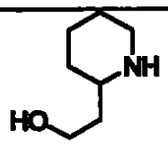
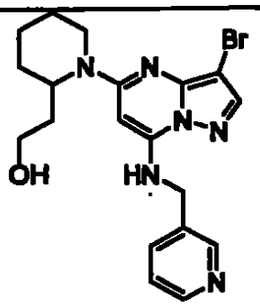
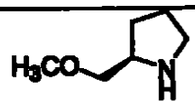
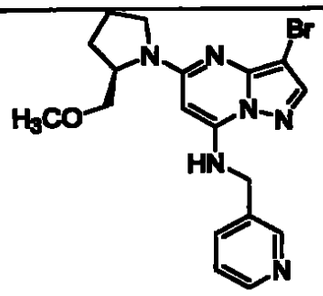
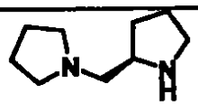
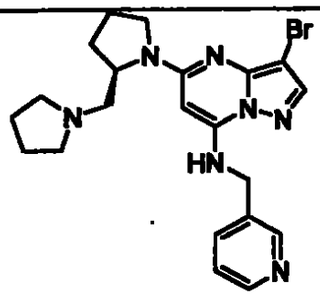
EXAMPLES 342-397:

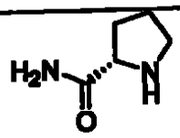
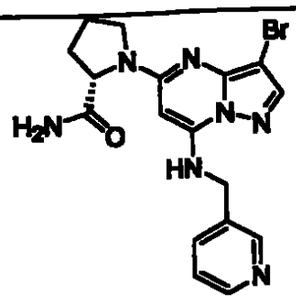
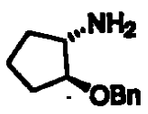
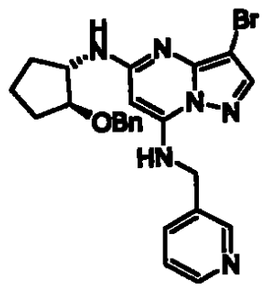
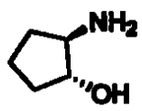
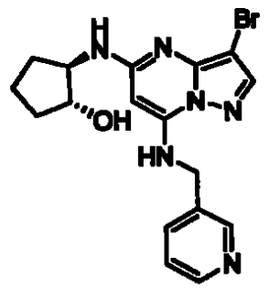
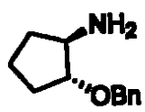
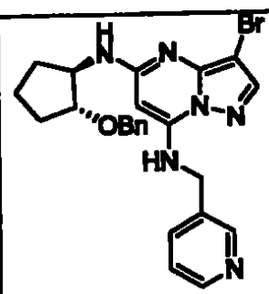
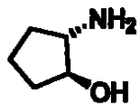
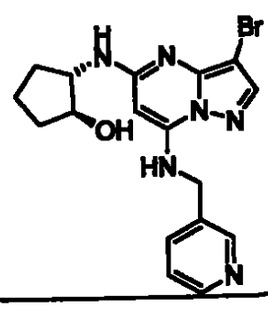
By essentially the same procedure set forth in Example 340 only substituting the chlorides in Column 2 of Table 31 and removing the t-butoxycarbonyl protecting group by the method shown in Column 3 of Table 31, the compounds shown in Column 4 of Table 31 were prepared.

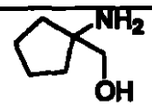
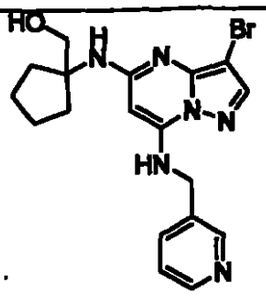
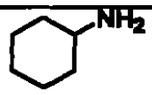
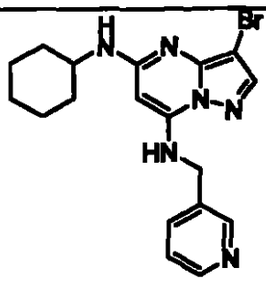
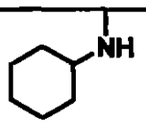
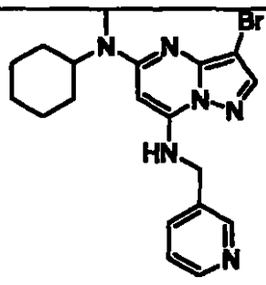
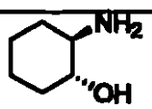
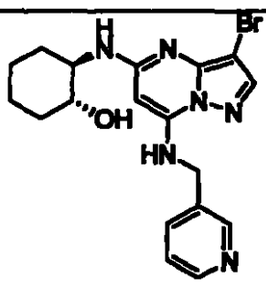
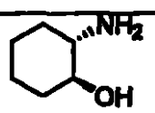
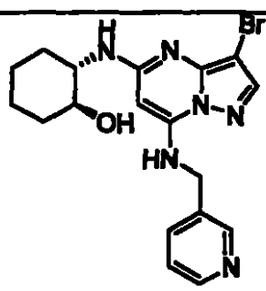
Table 31

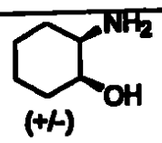
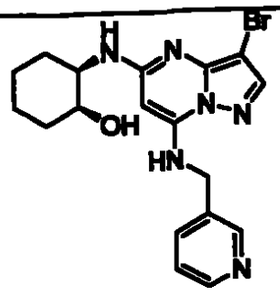
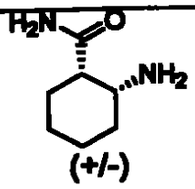
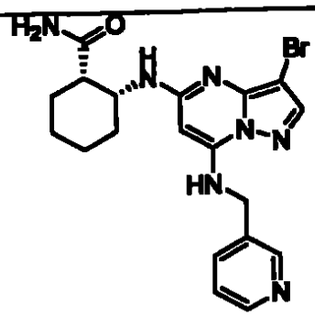
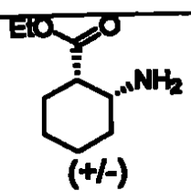
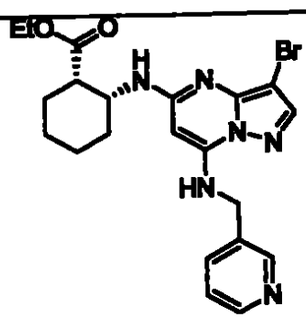
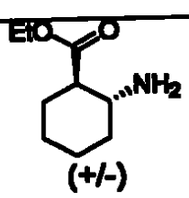
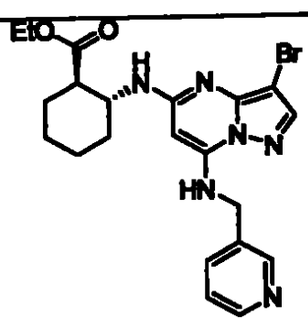
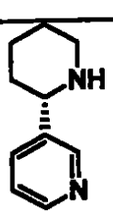
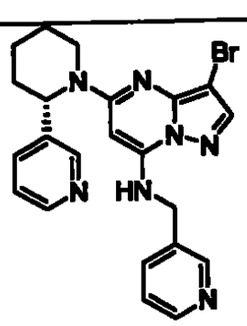
Ex.	Column 2	Column 3	Column 4	CMPD
342		HCl		MS: MH$^+$ = 403 m.p. 151 – 157 °C
343		HCl		MS: MH$^+$ = 466 m.p. 212 – 217 °C
344		HCl		MS: MH$^+$ = 405 m.p. 53 – 58 °C
345		HCl		MS: MH$^+$ = 405 m.p. 63 – 69 °C

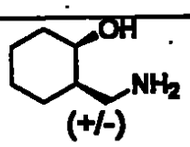
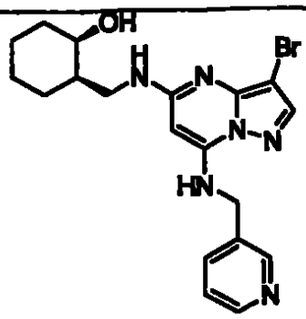
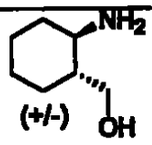
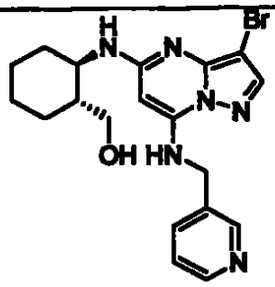
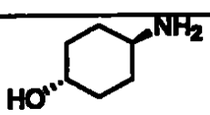
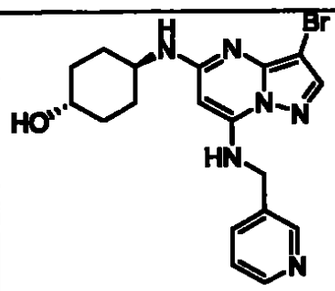
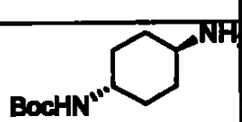
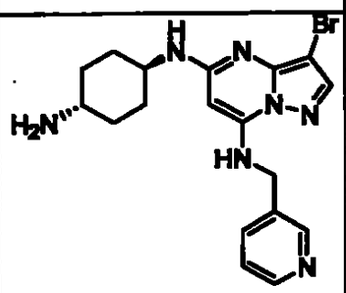
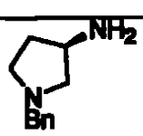
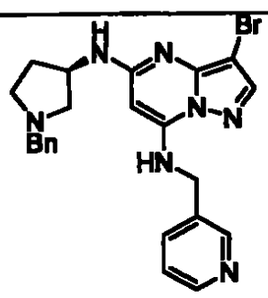
346		HCl		MS: MH^+ = 363 m.p. 170 – 171 °C
347		HCl		MS: MH^+ = 407 m.p. 148 – 151 °C
348		HCl		MS: MH^+ = 435 m.p. 58 – 59 °C
349		HCl		MS: MH^+ = 445 m.p. 66 – 68 °C

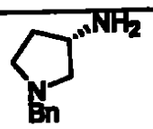
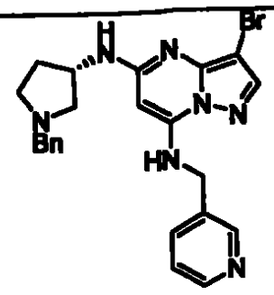
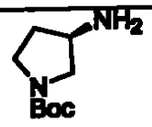
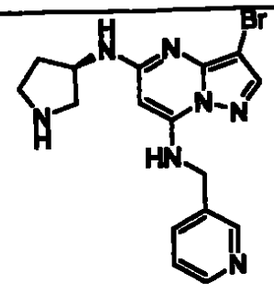
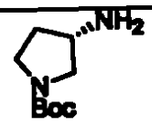
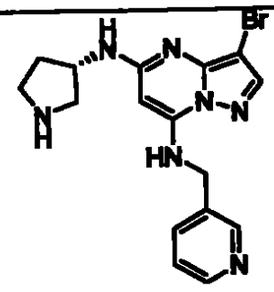
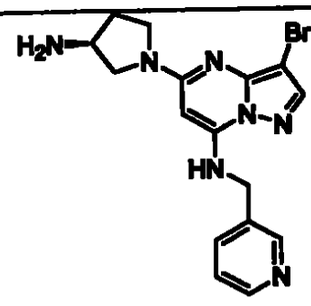
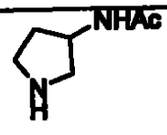
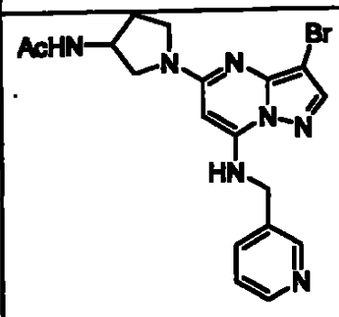
350		KOH		MS: MH$^+$ = 417 m.p. 149 – 151 °C
351		KOH		MS: MH$^+$ = 431 m.p. 111 – 114 °C
352		KOH		MS: MH$^+$ = 417 m.p. 53 – 58 °C
353		KOH		MS: MH$^+$ = 456 m.p. 186 – 189 °C

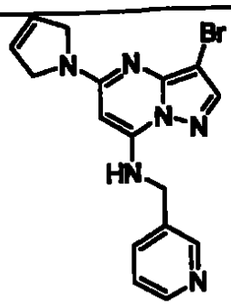
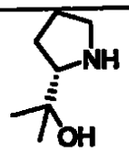
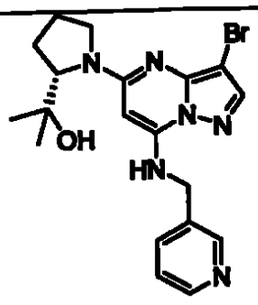
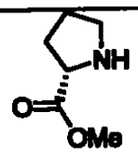
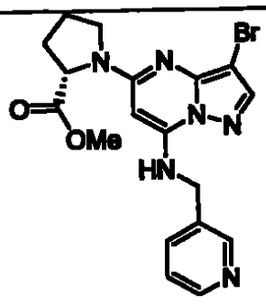
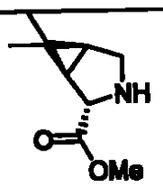
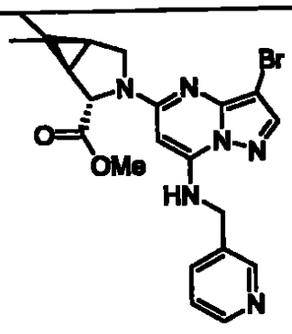
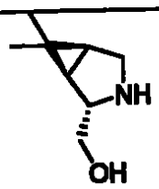
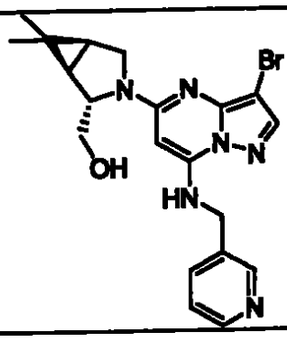
354		KOH		MS: MH$^+$ = 416 m.p. 210 – 213 °C
355		TFA		1. mp = 68-70 2. M+H = 494
356		KOH		1. mp = 181-183 2. M+H = 404
357		TFA		1. mp = 69-71 2. M+H = 494
358		KOH		1. mp = 182-184 2. M+H = 404

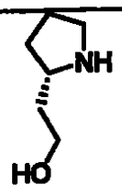
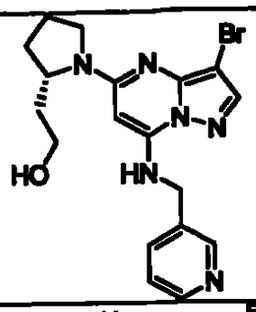
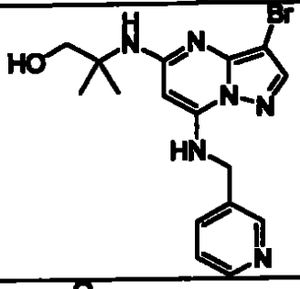
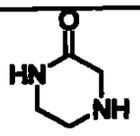
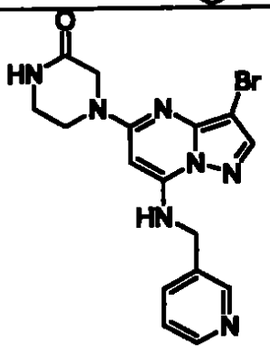
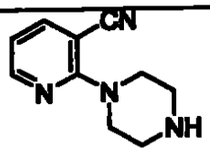
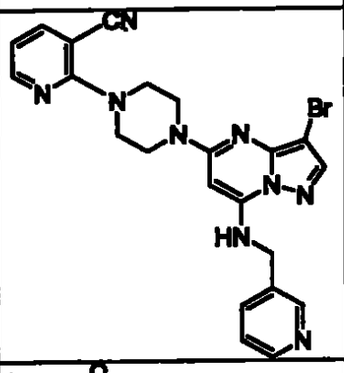
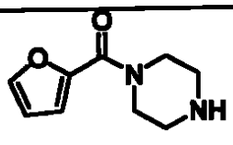
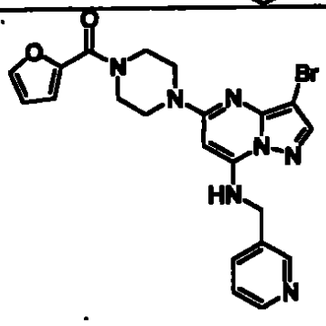
359		KOH		1. mp = 202-204 2. M+H = 418
360		TFA		1. mp = 160-162 2. M+H = 402
361		TFA		1. mp = 151-153 2. M+H = 416
362		KOH		1. mp = 140-143 2. M+H = 418
363		KOH		1. mp = 139-142 2. M+H = 418

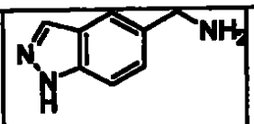
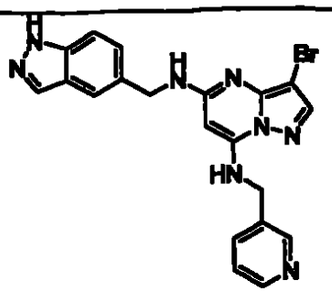
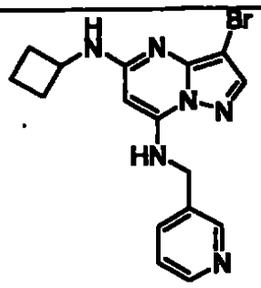
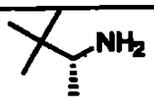
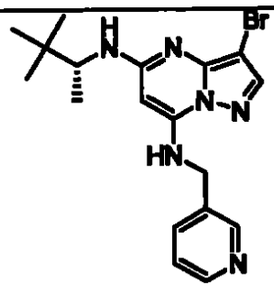
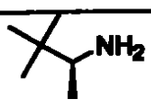
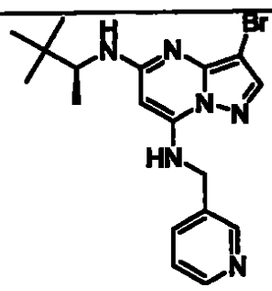
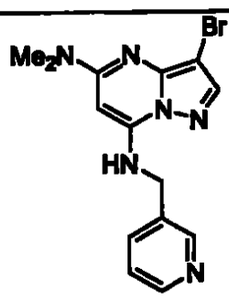
364	 (+/-)	KOH		1. mp = 115-117 2. M+H = 418
366	 (+/-)	TFA		1. mp = 102-104 2. M+H = 445
367	 (+/-)	TFA		1. mp = 118-120 2. M+H = 474
368	 (+/-)	TFA		1. mp = 106-108 2. M+H = 474
369		TFA		1. mp = 160-161 2. M+H = 464

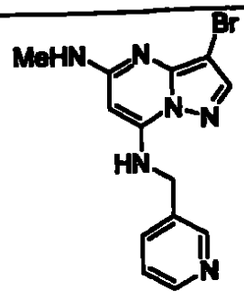
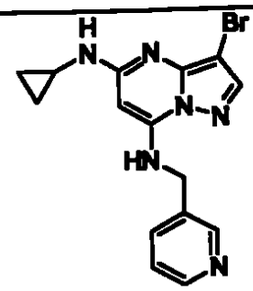
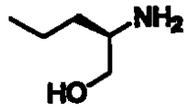
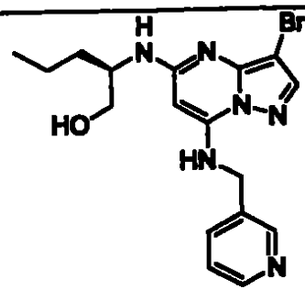
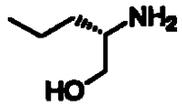
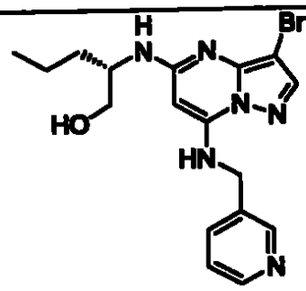
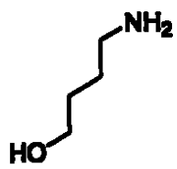
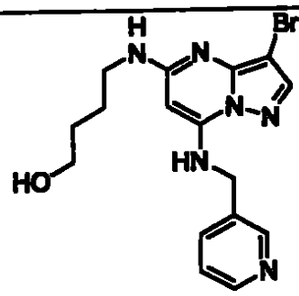
370		TFA		1. mp = 93-95 2. M+H = 432
371		KOH		1. mp = 108-110 2. M+H = 432
372		KOH		1. mp = 180-182 2. M+H = 418
373		TFA		1. mp = 169-170 2. M+H = 417
374		TFA		1. mp = 77-79 2. M+H = 479

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	$HNMe_2$	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).

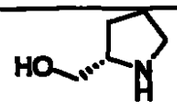
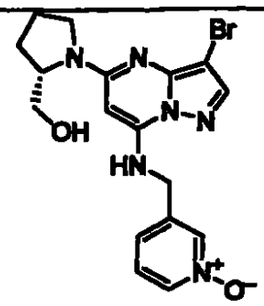
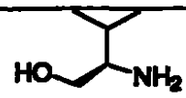
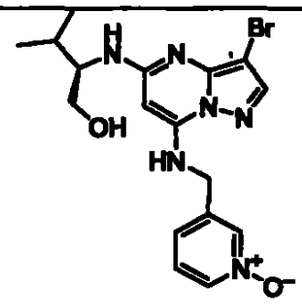
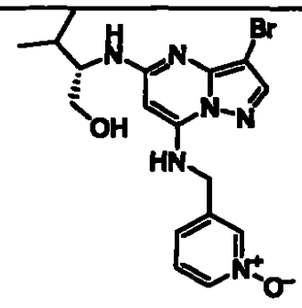
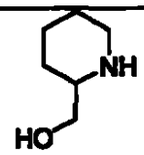
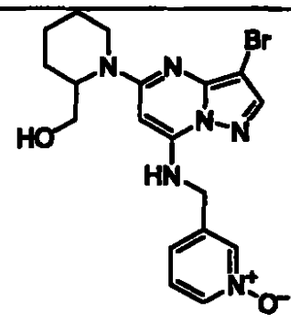
Example 396: ^{1}H NMR ($CDCl_3$) δ 8.60 (s, 1H), 8.56 (d, J = 4.2 Hz, 1H), 7.73 (s, 1H), 7.66 (m, 1H), 7.31 (dd, J = 7.8, 4.8 Hz, 1H), 6.51 (t, J = 6.0 Hz, 1H), 5.05 (s, 1H), 4.86 (d, J = 6.6 Hz, 1H), 4.50 (d, J = 6.0 Hz, 2H), 3.94 (m, 1H), 3.78 (dd, J = 11.1, 2.4 Hz, 1H), 3.57 (dd, J = 11.1, 7.2 Hz,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

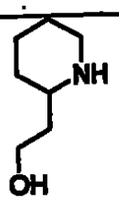
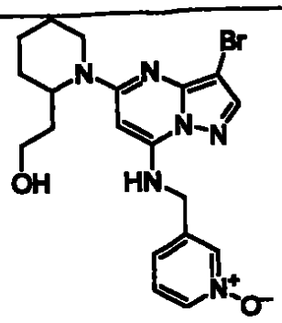
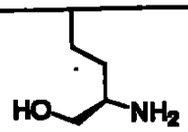
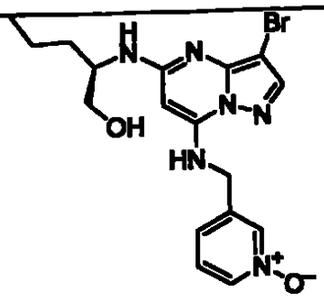
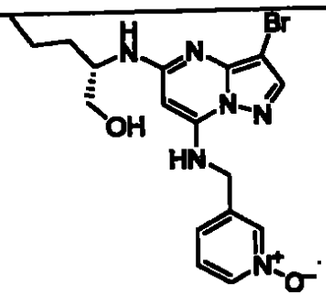
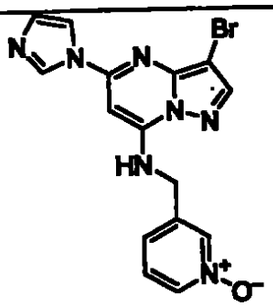
Example 397: ^{1}H NMR ($CDCl_3$) δ 8.65 (s, 1H), 8.59 (d, J = 4.5 Hz, 1H), 7.75 (s, 1H), 7.69 (m, 1H), 7.31 (m, 1H), 6.43 (t, J = 6.0 Hz, 1H), 5.06 (s, 1H), 4.88 (m, 1H), 4.55 (d, J = 6.0 Hz, 2H), 3.70 (m, 2H), 3.38 (m, 2H), 1.79-1.61 (m, 4H).

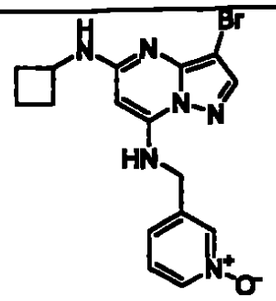
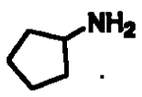
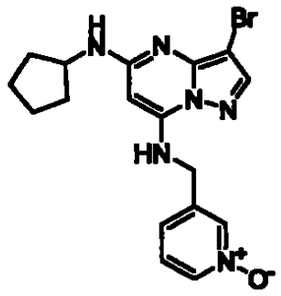
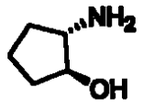
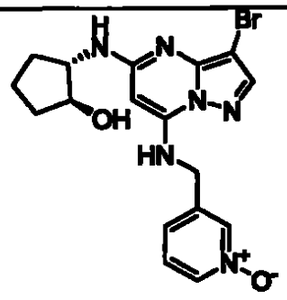
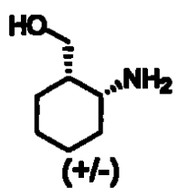
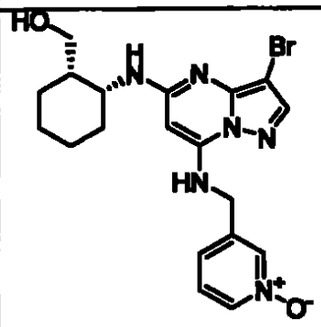
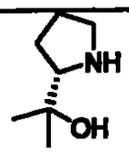
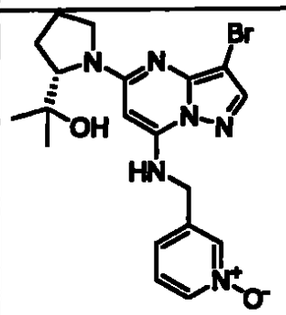
EXAMPLES 398-416:

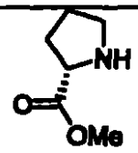
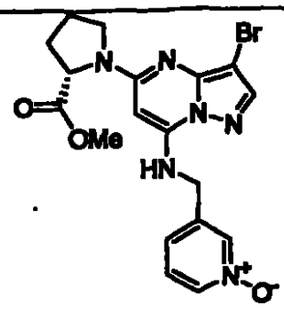
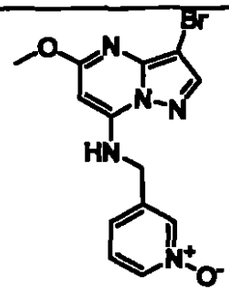
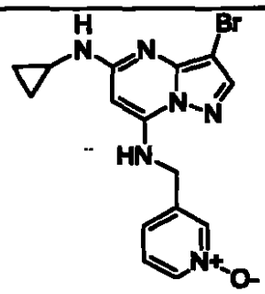
By essentially the same conditions set forth in Example 341, Steps A and B only substituting the compound prepared in Preparative Example 193.10, the compounds in Column 4 of Table 32 were prepared.

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 = 219-221 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 = 446
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).

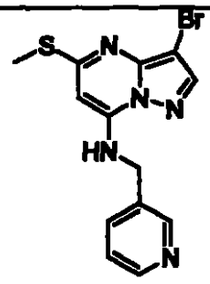
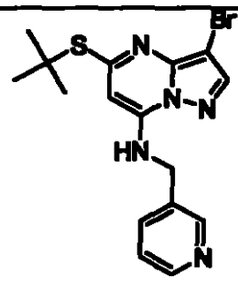
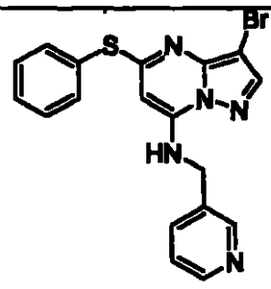
Example 403: ^{1}H NMR (DMSO-d_6+$CDCl_3$) δ 8.08 (s, 1H), 7.90 (d, J = 6.3 Hz, 1H), 7.49 (s, 1H), 7.34 (t, J = 6.3 Hz, 1H), 7.16-7.09 (m, 2H), 5.65 (d, J = 6.6 Hz, 1H), 4.97 (s, 1H), 4.90 (s, 1H), 4.29 (d, J = 6.3 Hz, 2H), 3.70 (m, 1H), 3.46 (m, 1H), 3.34 (m, 1H), 1.35-1.17 (m, 4H), 0.71 (t, J = 7.2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

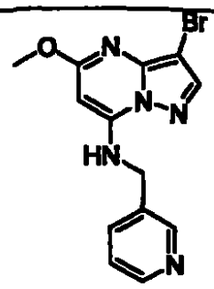
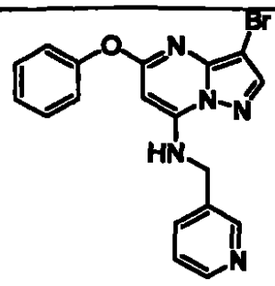
Example 404: ^{1}H NMR (DMSO-d_6) δ 8.21 (s, 1H), 8.12 (d, J = 6.6 Hz, 1H), 8.06 (m, 1H), 7.86 (s, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 6.73 (d, J = 8.7 Hz, 1H), 5.28 (s, 1H), 4.70 (t, J = 5.1 Hz, 1H), 4.41 (d, J = 6.6 Hz, 2H), 4.00 (s, 1H), 3.39 (m, 1H), 1.53 (m, 1H), 1.36-1.25 (m,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

EXAMPLES 417—421:

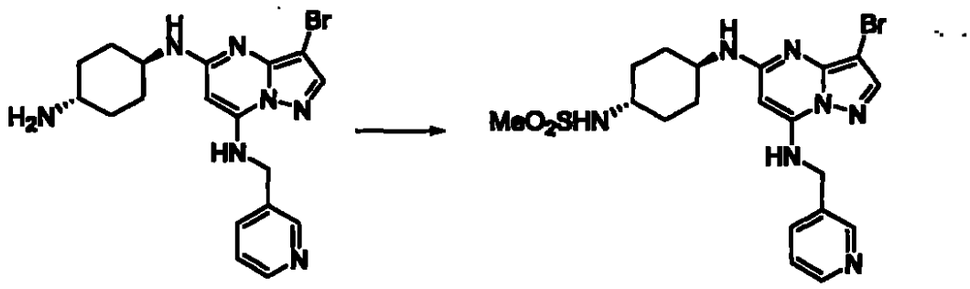
By the procedure set forth in *Chem. Pharm. Bull.* **1999**, *47*, 928-938. utilizing the oxygen or sulfur nucleophiles shown in Column 2 as described of Table 33 and by employing the cleavage method listed in Column 3 of Table 33, the compounds in Column 4 of Table 33 were prepared:

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:

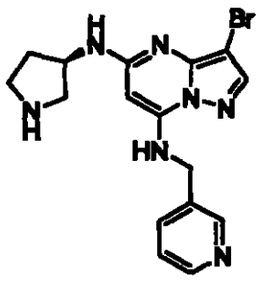
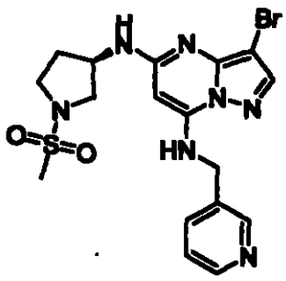
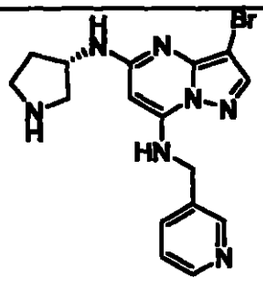
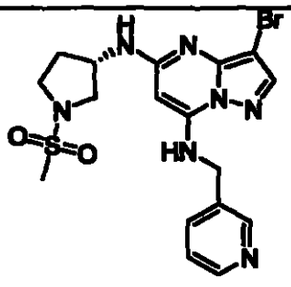


To a solution of amino compound (18 mg, 0.043 mmol) from Example 373 in CH_2Cl_2 (1 mL) at rt was added DIPEA (10 µL, 0.056 mmol) followed by $MeSO_2Cl$ (4 mL, 0.052 mmol). The mixture was stirred at rt for 12 h and was diluted with CH_2Cl_2 (2 mL) and sat. aq. $NaHCO_3$ (2 mL). The layers were separated 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:

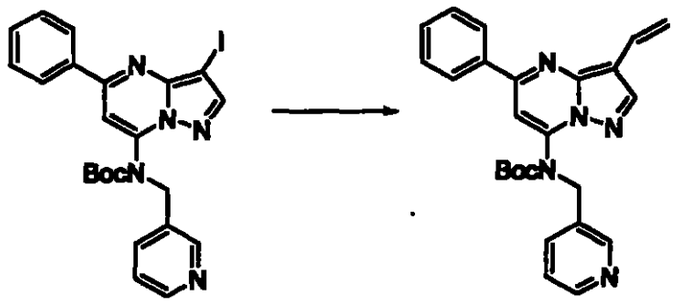
Utilizing the procedure outlined in Example 422, the amino compounds (Column 2) were converted to the corresponding methylsulfonamides (Column 3) in Table 34.

TABLE 34

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

EXAMPLE 425:

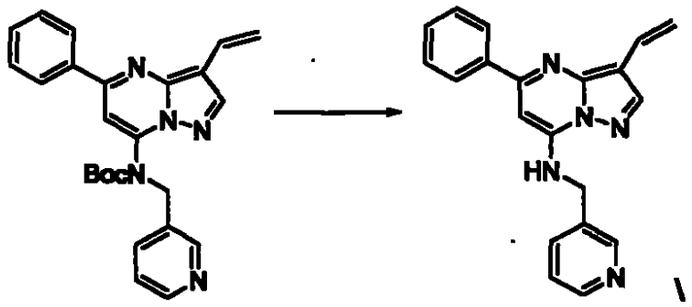
STEP A:



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.

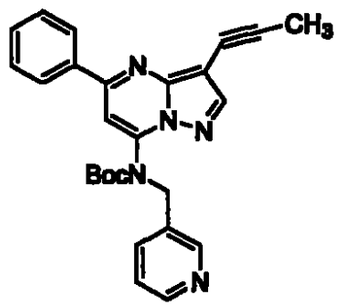
STEP B:



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.

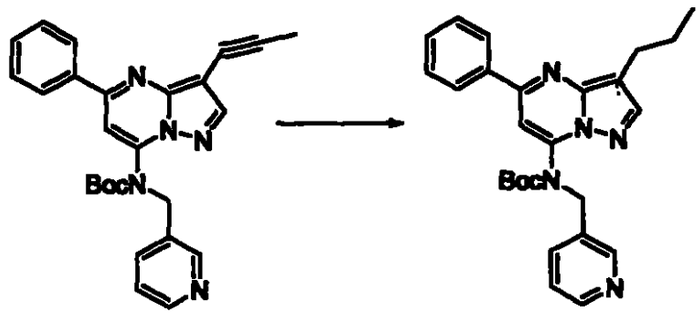
EXAMPLE 426:

STEP A:



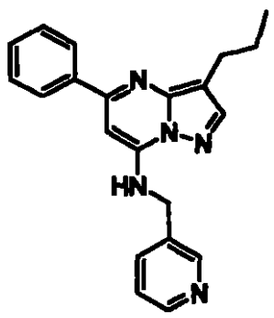
By essentially the same procedure set forth in Example 425, Step A only using tributylmethylethynyltin, the compound shown above was prepared.

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%).

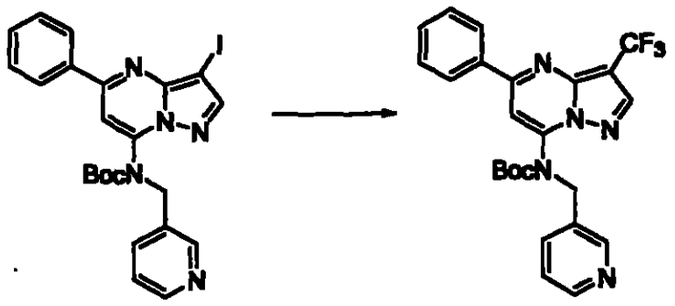
STEP C:



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.

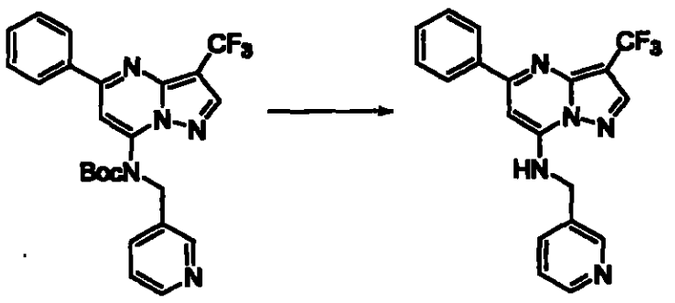
EXAMPLE 427:

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.

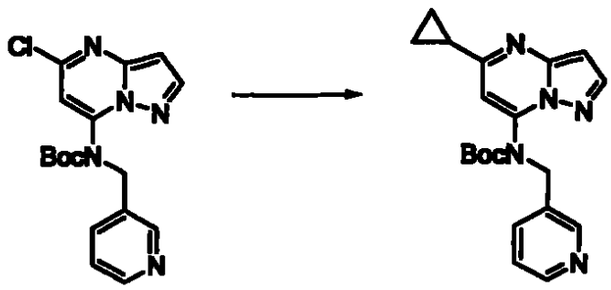
STEP B:



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.

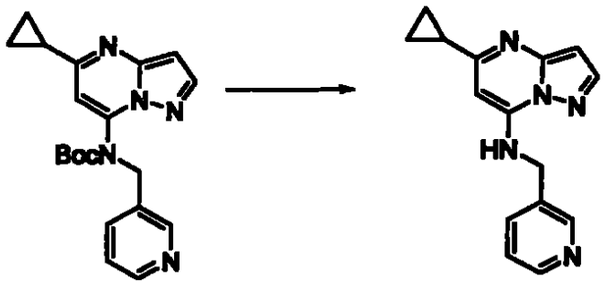
EXAMPLE 428:

STEP A:



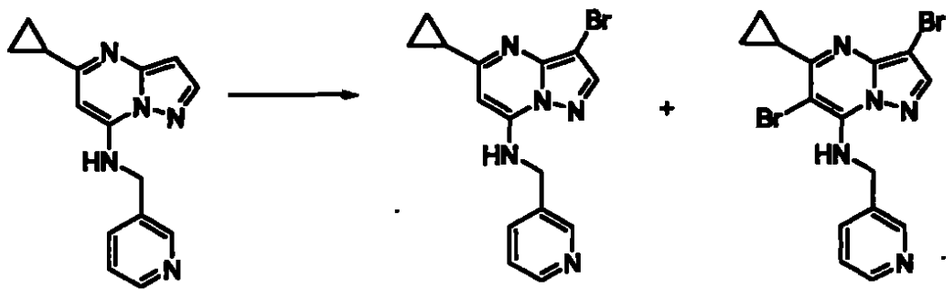
A mixture of the compound prepared in Preparative Example 193 (100 mg, 0.28 mmol), tetracyclopropylitin (91 mg, 0.32 mmol), Pd_2dba_3 (8.0 mg, 0.009 mmol) and $Pd(Pt\text{-}Bu_3)_2$ (9.0 mg, 0.017 mmol) in anhydrous dioxane (3 mL) was refluxed under N_2 for 27 hr. The solvent was evaporated and the residue 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.

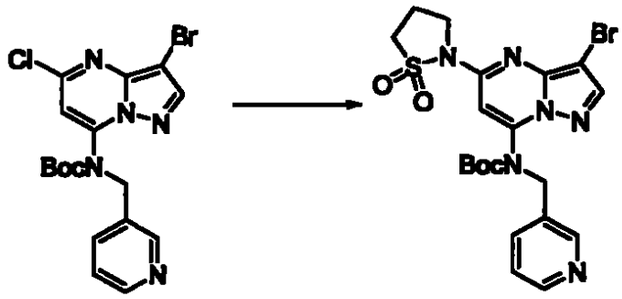
STEP C:



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).

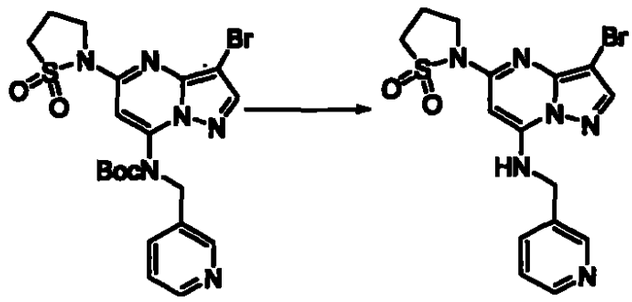
EXAMPLE 429:

STEP A:



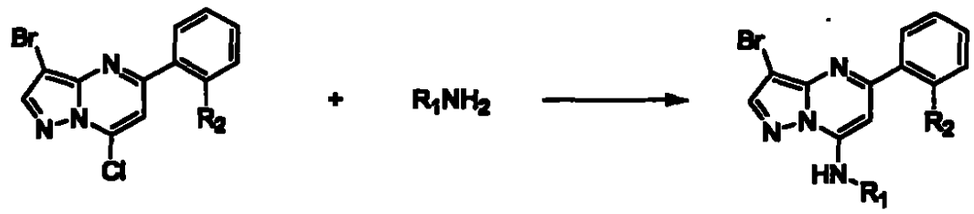
1,3-propanesultam (72 mg, 0.60 mmol) in anhydrous DMF (3 mL) was added under N_2 to 60 % NaH in mineral oil (36 mg, 0.90 mmol). The mixture was stirred for 20 min, then the compound prepared in Preparative Example 196 (200 mg, 0.46 mmol) was added. The mixture was stirred at 100°C for 30 min, the solvent 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:

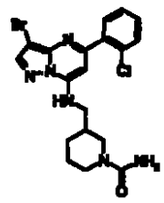
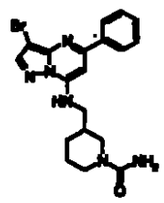
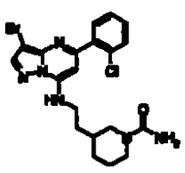
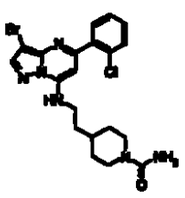
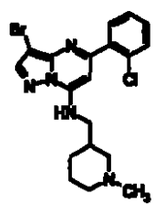


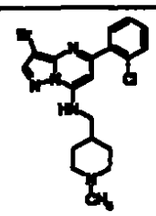
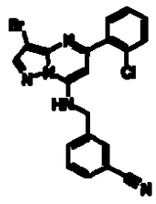
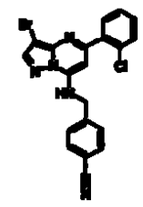
Where: R_2=H, or Cl

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.

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 $C_{18}H_{21}N_6OBrCl$: 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_8), 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.

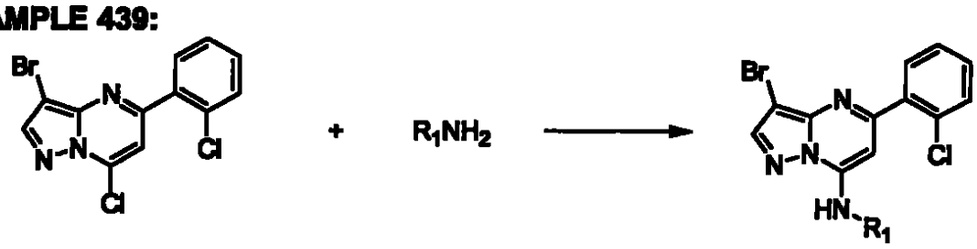
EXAMPLE 435: Reactants: 3-Bromo-7-chloro-5-phenylpyrazolo[1,5-a]pyrimidin (174mg, 0.507mmoles) (prepared as described in Preparative Example 129) and 3-(aminomethyl)-1-methylpiperidine (65mg, 0.507mmoles) (prepared as described in Preparative Example 244 above); diisopropyl ethylamine (0.178mL, 1.014mmoles); 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_8), 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_8), 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, -CH_2NH-), 6.32 (1H, s, H_6), 7.00 (1H, m, -CH_2NH-), 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.

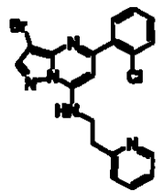
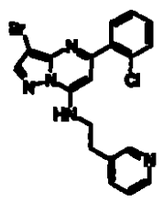
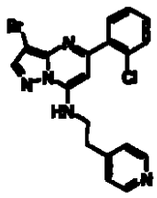
EXAMPLE 439:

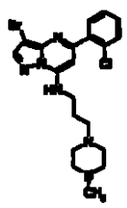
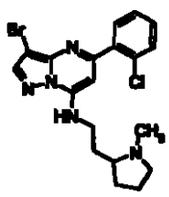
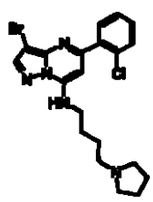
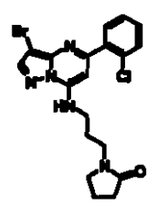
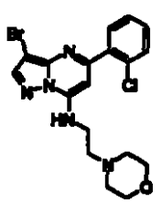


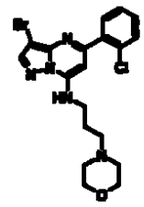
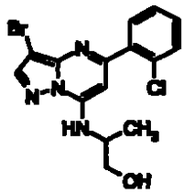
3-Bromo-7-chloro-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidine (50mg, 0.146mmoles) (prepared as described in Preparative Example 129) was dissolved in anhydrous 1,4-dioxane (5mL) in a GeneVac Technologies carousel reaction tube. PS-diisopropyl ethylamine resin (161mg, 0.5828mmoles) was

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, $C_5H_4NCH_2CH_2NH$-), 3.94 (2H, ddd, $C_5H_4NCH_2CH_2NH$-), 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, $C_5H_4NCH_2CH_2NH$-), 3.77 (2H, ddd, $C_5H_4NCH_2CH_2NH$-), 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, $C_5H_4NCH_2CH_2NH$-), 3.80 (2H, ddd, $C_5H_4NCH_2CH_2NH$-), 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 $C_{19}H_{22}N_6BrCl$: 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

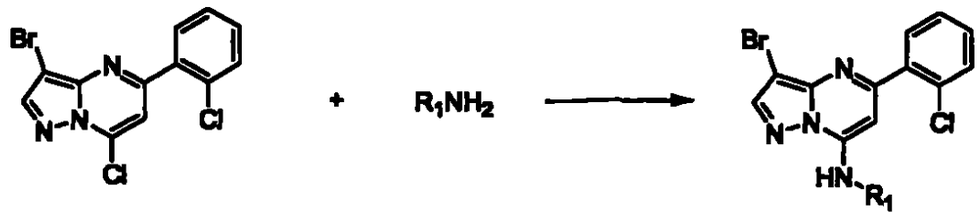
(1H, s, H_2); δ_C ($CDCl_3$) CH_2: 18.0, 26.3, 30.8, 39.2, 39.9, 47.5; CH: 87.0, 127.1, 130.1, 130.1, 131.6, 144.1; C: 82.9, 132.1, 138.9, 145.6, 146.2, 157.9, 176.2.

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($C\underline{H}_2CH_2$)$_2$O), 2.83 (2H, m, =N$C\underline{H}_2CH_2$NH-), 3.57 (2H, m, =N$CH_2C\underline{H}_2$NH-), 3.83 (4H, m, -N($CH_2C\underline{H}_2$)$_2$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) 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, =N$CH_2C\underline{H}_2CH_2$NH-), 2.58 (4H, m, -N($C\underline{H}_2CH_2$)$_2$O), 2.67 (2H,m, =N$C\underline{H}_2CH_2CH_2$NH-), 3.59 (2H, m, =N$CH_2CH_2C\underline{H}_2$NH-), 3.94 (4H, m, -N($CH_2C\underline{H}_2$)$_2$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) 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.

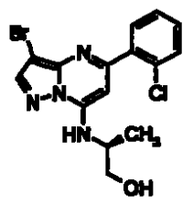
EXAMPLE 449: Physical properties: HRFABMS: m/z 381.0114 (MH^+). Calcd. for $C_{18}H_{15}N_4OBrCl$: m/z 381.0118; δ_H ($CDCl_3$) 1.39 (3H, d, CHC$\underline{H}_3$), 2.76 (1H, bm, -OH), 3.71 (1H, m, =CHC$\underline{H}_2$OH), 3.81 (1H, m, =CHC$\underline{H}_2$OH), 3.88 (1H, m, =C$\underline{H}CH_2$OH), 6.38 (1H, s, H_6), 7.38 (2H, m, Ar-H), 7.48 (1H, m, Ar-H), 7.68 (1H, m, Ar-H) 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.

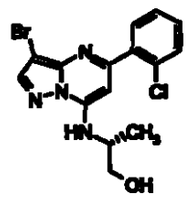
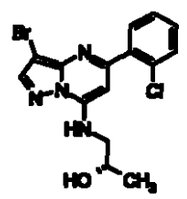
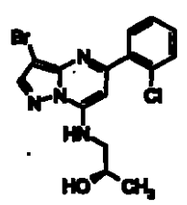
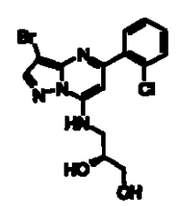
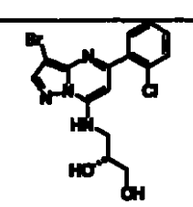
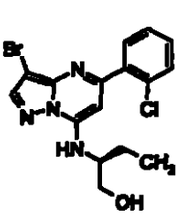
EXAMPLE 450:

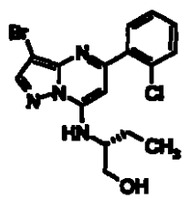
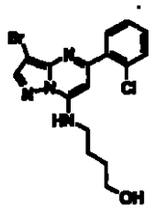


3-Bromo-7-chloro-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidine (50mg, 0.146mmoles) (prepared as described in Preparative Example 129) was dissolved in anhydrous 1,4-dioxane (5mL) in a GeneVac Technologies carousel reaction tube. PS-diisopropyl ethylamine resin (161mg, 0.5828mmoles) was added to each tube. 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 $C_{16}H_{15}N_4OBrCl$: 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_5), 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 $C_{16}H_{15}N_4O_2BrCl$: 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_5), 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_5), 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

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Date: Aug 25, 2005

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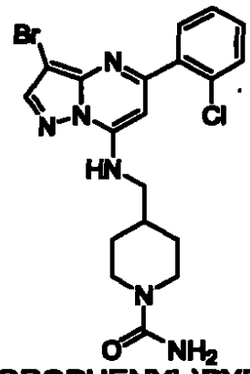
Address: Bureau international de l'OMPI 34, chemin des Colombettes Geneve 20 1211 CH

(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) 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.

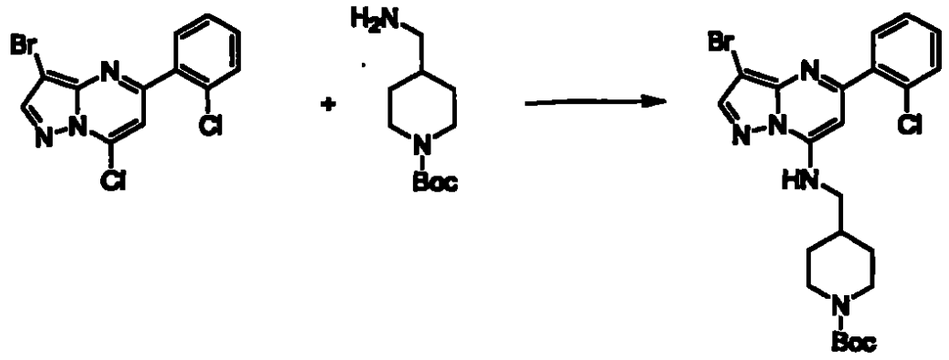
EXAMPLE 459: Physical properties: HRFABMS: m/z 395.0264 (MH^+). Calcd. for $C_{16}H_{17}N_4OBrCl$: m/z 395.0274; δ_H ($CDCl_3$) 1.77 (2H, m, $-NHCH_2CH_2C\underline{H_2}CH_2OH$), 1.90 (1H, bm, $-NHCH_2CH_2CH_2CH_2O\underline{H}$), 1.93 (2H, m, $-NHCH_2C\underline{H_2}CH_2CH_2OH$), 3.54 (2H, m, $-NHC\underline{H_2}CH_2CH_2CH_2OH$), 3.77 (2H, m, $-NHCH_2CH_2CH_2C\underline{H_2}OH$), 6.37 (1H, s, H_6), 6.72 (1H, m, $-N\underline{H}CH_2CH_2CH_2CH_2OH$), 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:

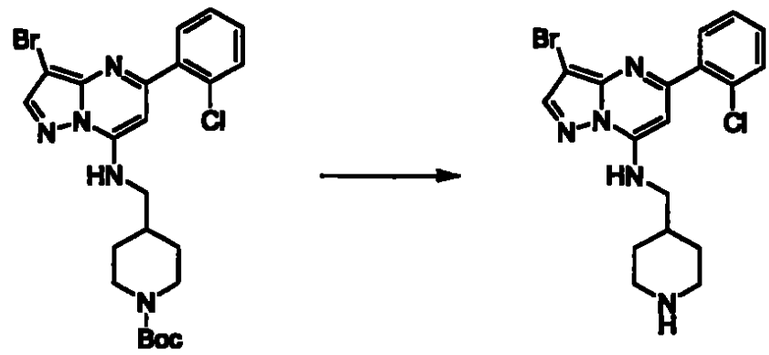


A. 4-{[3-BROMO-5-(2-CHLOROPHENYL)PYRAZOLO[1,5-a]PYRIMIDIN-7-YLAMINO]METHYL}PIPERIDINE-1-CARBOXYLIC ACID *tert*-BUTYL ESTER:



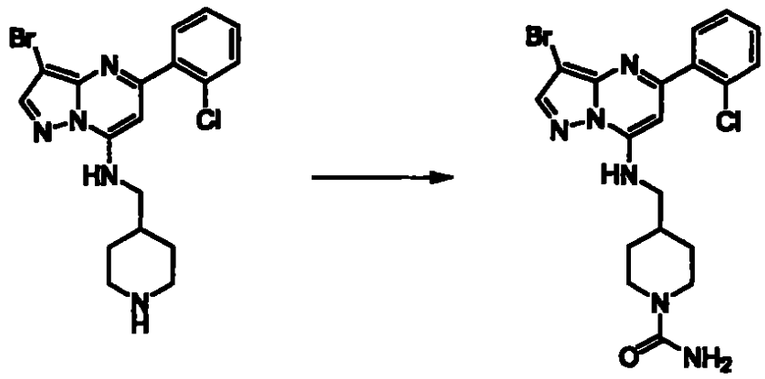
3-Bromo-7-chloro-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidine (300mg, 0.875mmoles) (prepared as described in Preparative Example 129) was dissolved in anhydrous 1,4-dioxane (6.8mL). 4-(aminomethyl)piperidine-1-carboxylic acid *tert*-butyl ester (225mg, 1.05mmoles) and diisopropyl ethylamine (0.3055mL, 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_8), 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.

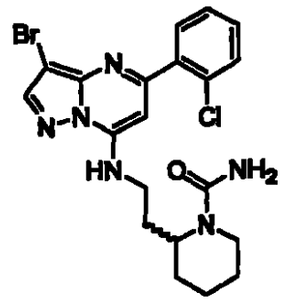
C. 4-[[3-BROMO-5-(2-CHLOROPHENYL)PYRAZOLO[1,5-a]PYRIMIDIN-7-YLAMINO]METHYL]PIPERIDINE-1-CARBOXYLIC ACID AMIDE:



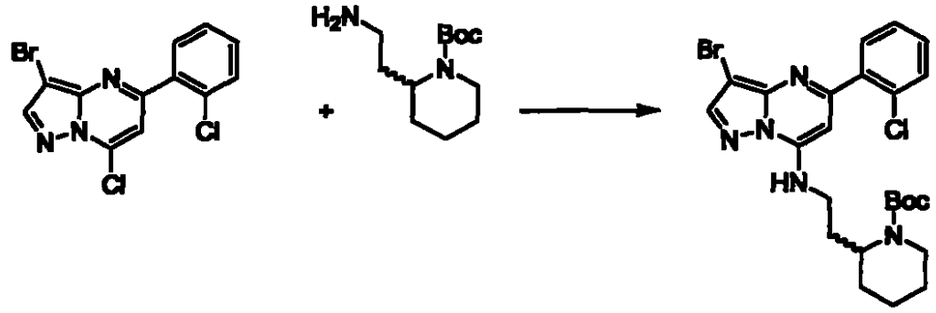
[3-Bromo-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidin-7-yl]piperidin-4-ylmethylamine (57mg, 0.136mmoles) (prepared as described in Example 460, Step B above) was dissolved in anhydrous dichloromethane (1.2mL) and trimethylsilylisocyanate (0.091mL, 0.679mmoles) was added. The mixture was stirred at 25°C 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:



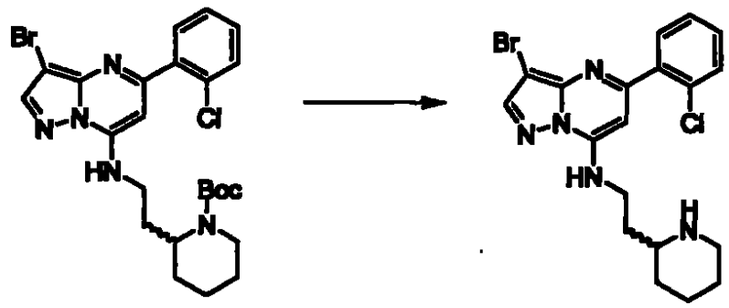
A. 2-{2-[3-BROMO-5-(2-CHLOROPHENYL)PYRAZOLO[1,5-a]PYRIMIDIN-7-YLAMINO]ETHYL}PIPERIDINE-1-CARBOXYLIC ACID *tert*-BUTYL ESTER:



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),

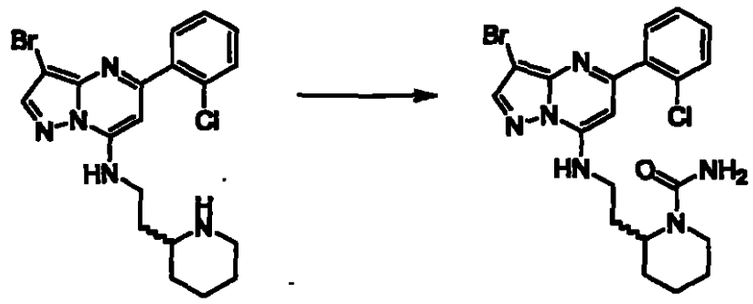
7.51 (1H, m, Ar-H), 7.76 (1H, m, Ar-H) and 8.08 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 28.5, 28.5, 28.5; CH_2: 19.2, 25.5, 29.2, 29.2, 39.2, 67.1; CH: ~47.4, 87.1, 127.1, 130.1, 130.1, 131.6, 143.9; C: 80.0, 83.0, 132.1, 138.9, 145.7, 146.2, 158.0.

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



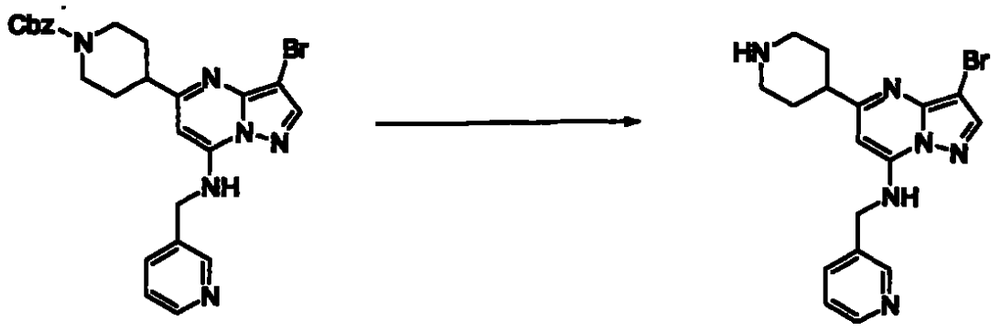
2-[[3-Bromo-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidin-7-ylamino]ethyl]piperidine-1-carboxylic acid *tert*-butyl ester (465mg, 0.869mmoles) (prepared as described in Example 461, Step A above) was dissolved in methanol (4.5mL) and 10% (v/v) conc. sulfuric acid in 1,4-dioxane (11.76mL) was added. The 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_8), 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:

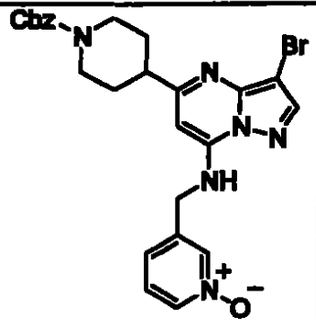
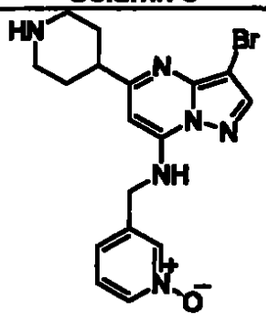


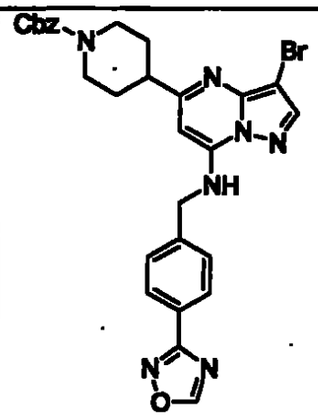
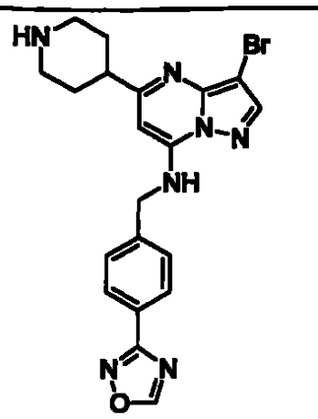
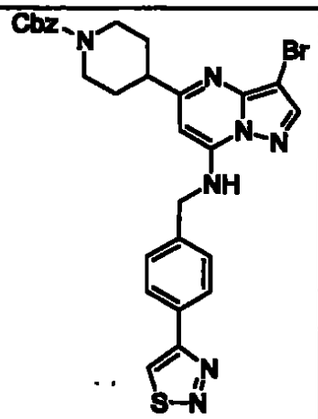
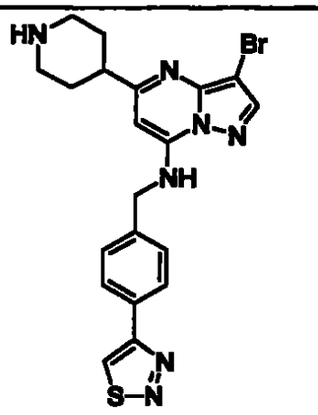
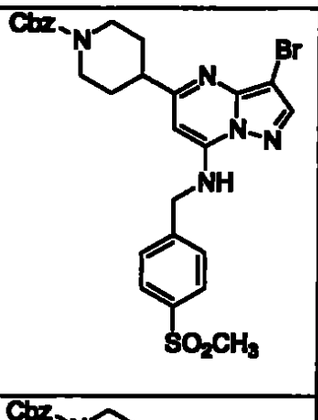
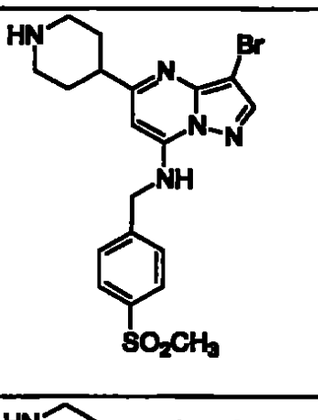
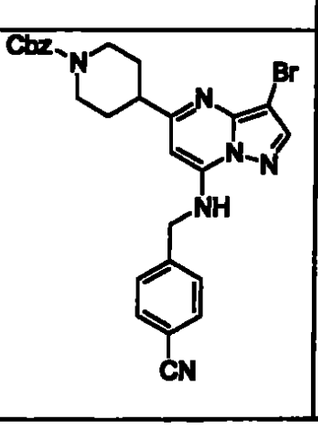
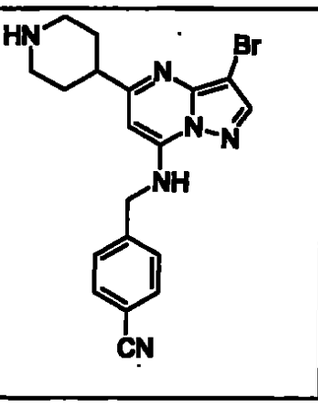
To a solution of the compound prepared in Example 204 (1.11 g, 2.12 mmol) in anhydrous acetonitrile (20 mL) was added TMSI (1.70 g, 8.52 mmol), dropwise at ambient temperature. After 10 minutes the acetonitrile was removed *in vacuo*. The resulting yellow foam was treated with 2 N HCl solution (7 mL) 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

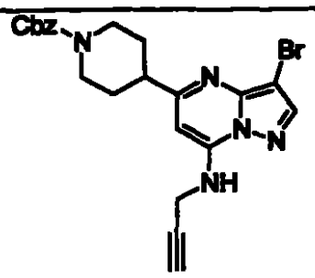
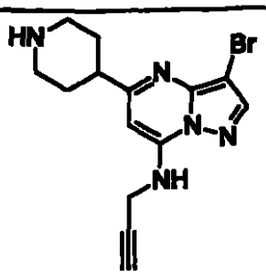
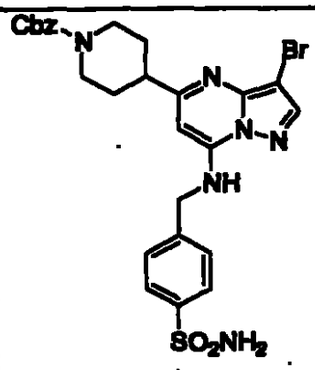
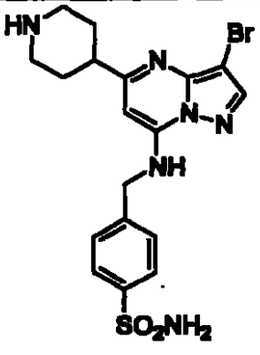
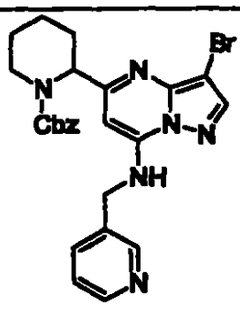
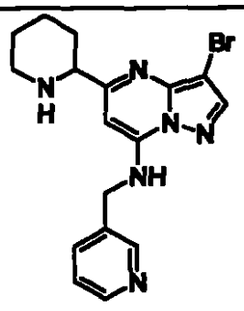
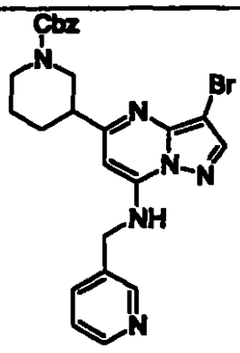
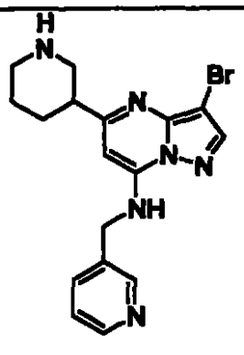
EXAMPLES 463-472:

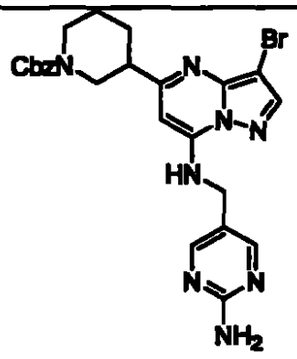
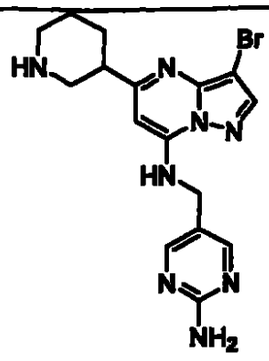
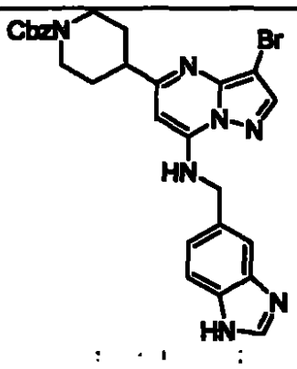
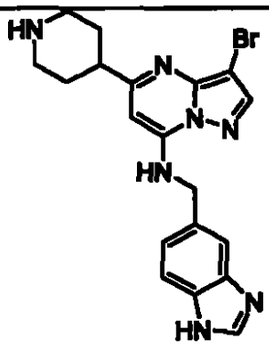
By essentially the same procedure set forth in Example 462 only substituting the compounds shown in Column 2 of Table 38, the compounds shown in Column 3 of Table 38 were prepared.

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), 2.98 – 2.70 (m, 3H), 2.05 –1.78 (m, 4H).

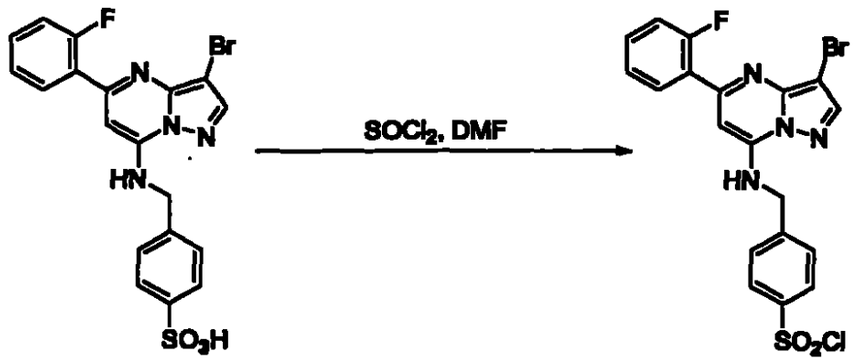
464			MH^+ = 454 m. p. = 175.4 °C
465			Yield = 87 MH^+ = 470 m. p. = 220 °C m. pt (hydrochloride salt) = 164.3 °C
466			MH^+ = 464 m. p. = 206 °C
467			MH^+ = 411 m. p. = 169.5 °C

468			MH^+ = 334 m. p. = 176.2 °C
469			MH^+ = 465 m. p. = 250.4 °C
470			MH^+ = 387 m. p. = 88.5 °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:

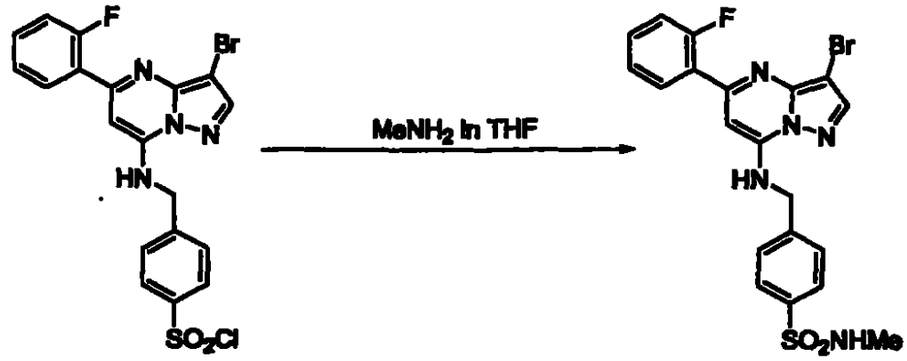
Step A:



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

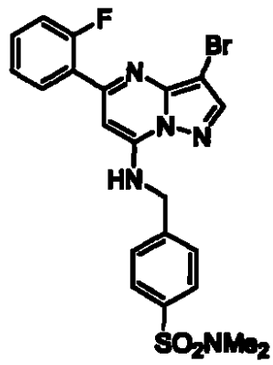
step without further purification. ^{1}H NMR ($CDCl_3$) δ 8.20-8.10 (m,1H), 8.10-7.95 (m, 3H), 7.65 (d, 2H), 7.45-7.35 (m, 1H), 7.35-7.20 (m, 1H), 7.15-7.05 (m, 1H), 6.95 (t, 1H), 4.85 (d, 2H).

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:

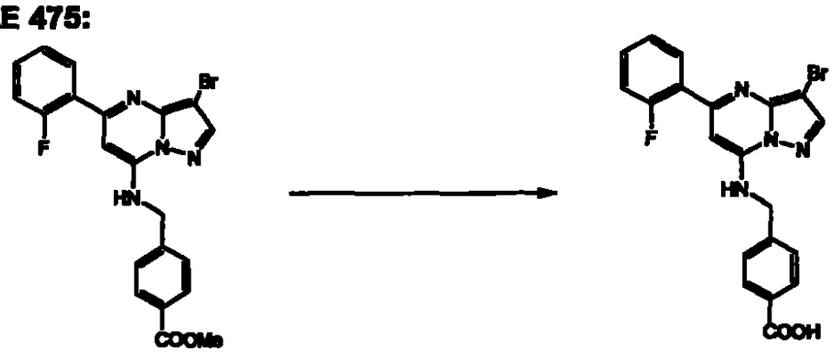


By essentially the same procedure set forth in Example 473, only substituting dimethylamine, the above compound was prepared. ^{1}H NMR ($CDCl_3$)

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:

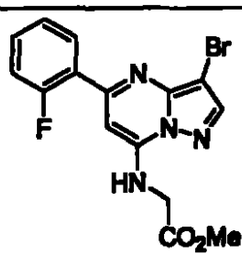
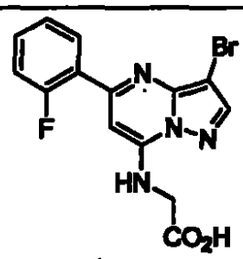


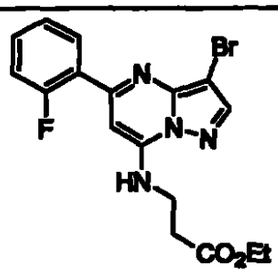
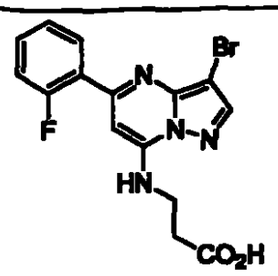
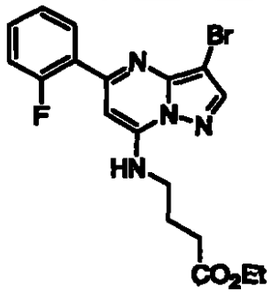
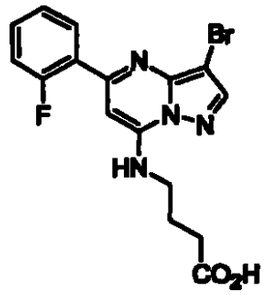
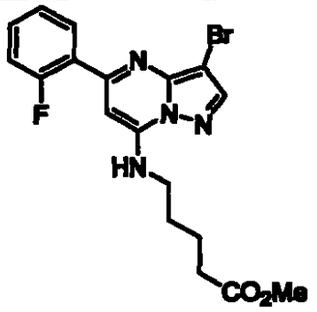
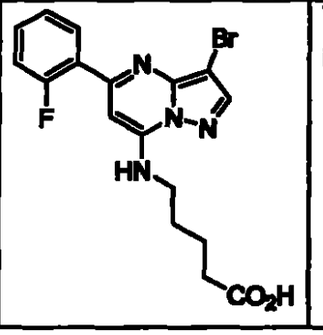
A mixture of the compound prepared in Example 129 (300 mg, 0.66 mmol), NaOH (5 g), CH_3OH –H_2O (100 mL, 90:10) was stirred at 25 C for about 15 h. Progress of hydrolysis was checked by TLC. Reaction mixture was concentrated to remove methanol. The concentrate was diluted with 50 mL water, and extracted 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

+

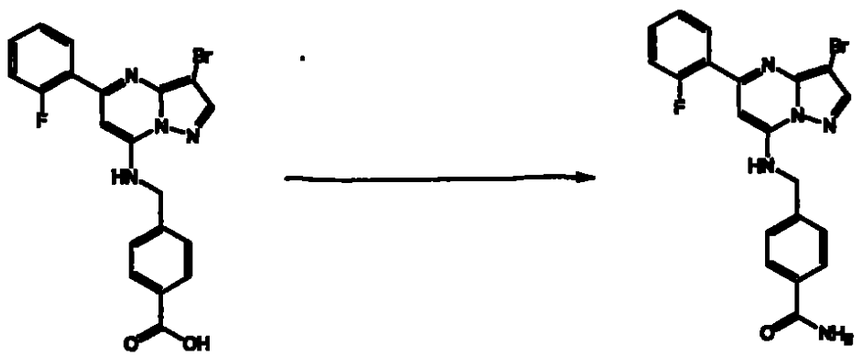
Additional data for select examples shown below:

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:

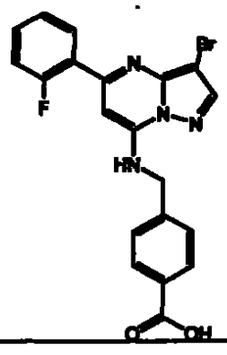
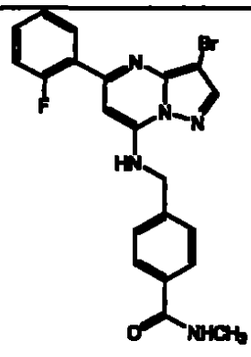


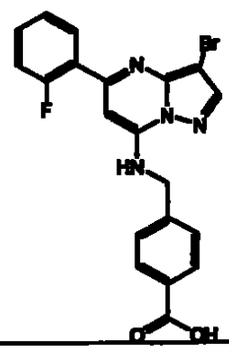
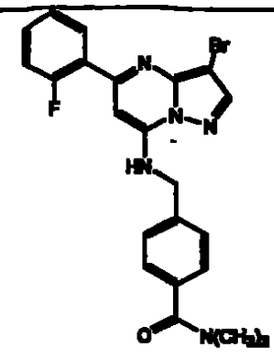
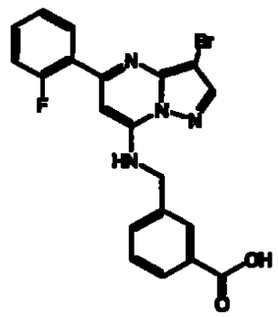
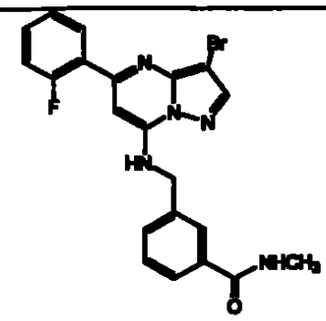
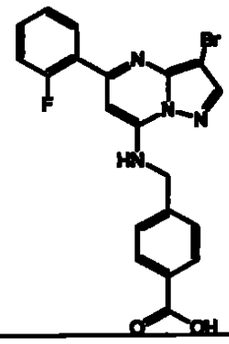
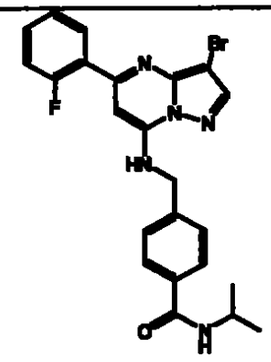
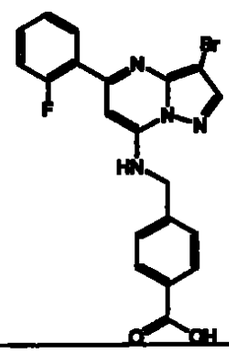
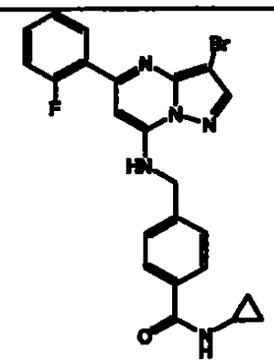
A mixture of the acid from Example 475 (85mg, 0.193 mmol) and Et_3N (20 mg, 0.193 mmol) in THF (20 mL) was stirred at 25 C for 15 min. Isobutyryl chloroformate (28mg, 0.205 mmol) was added to the reaction mixture and stirred for 10 min followed by addition of NH4OH solution (0.5 mL). The reaction mixture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

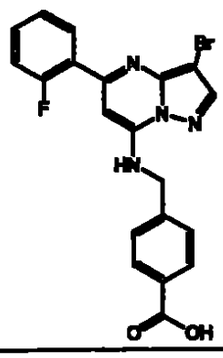
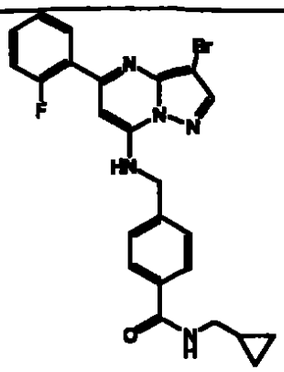
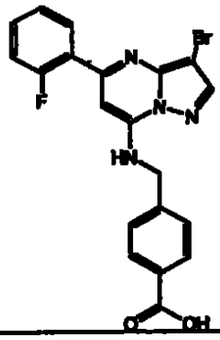
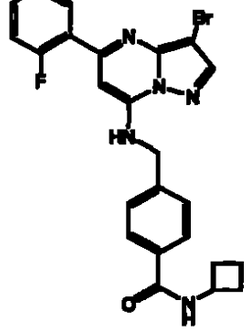
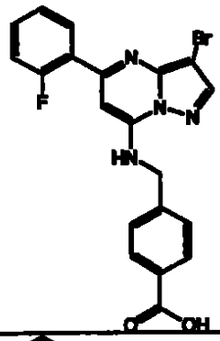
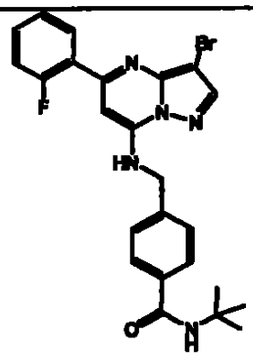
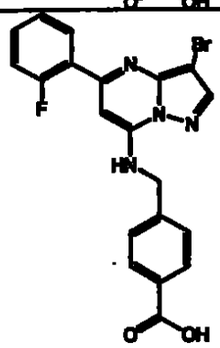
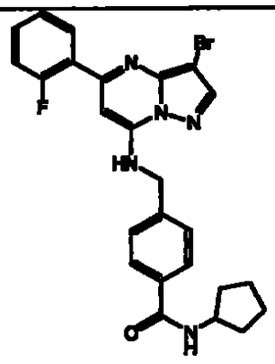
EXAMPLES 481-509:

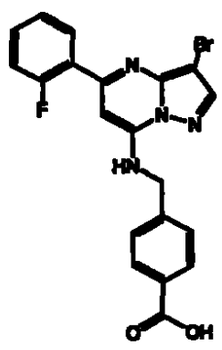
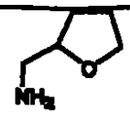
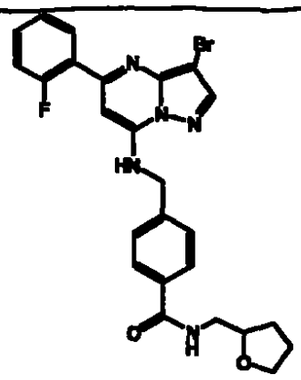
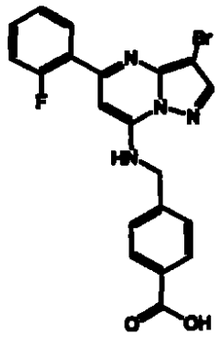
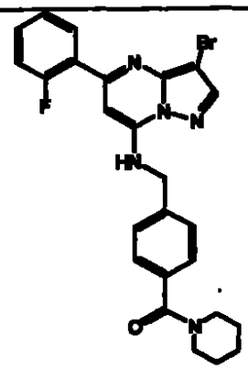
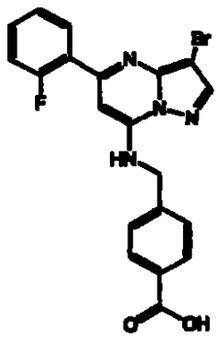
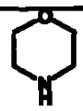
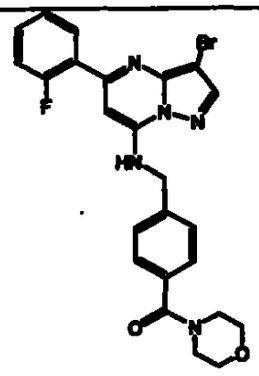
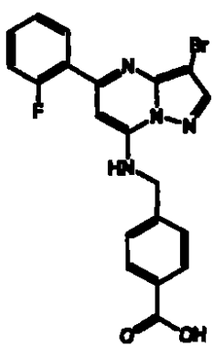
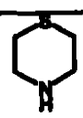
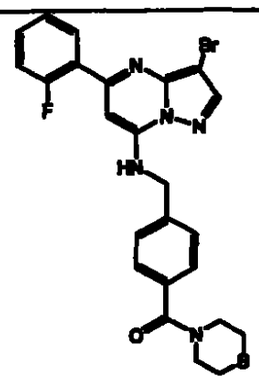
By essentially the same procedure set forth in Example 480 only substituting the carboxylic acid shown in Column 2 of Table 40 and the amine shown in Column 3 of Table 40, the compounds shown in Column 4 of Table 40 were prepared.

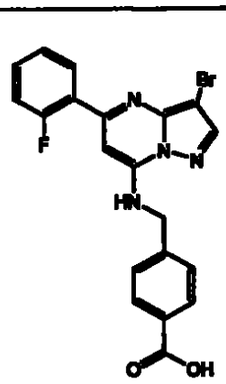
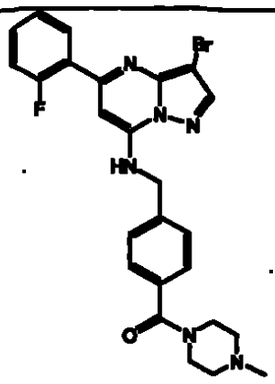
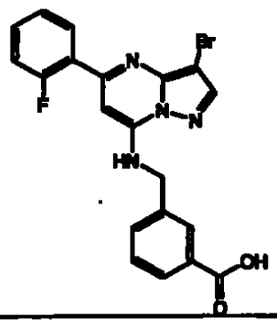
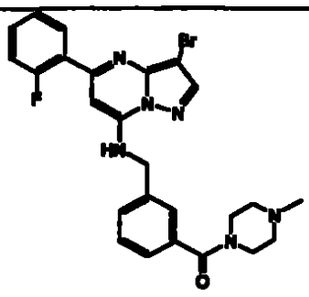
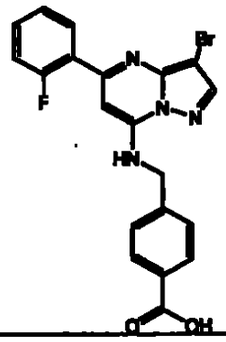
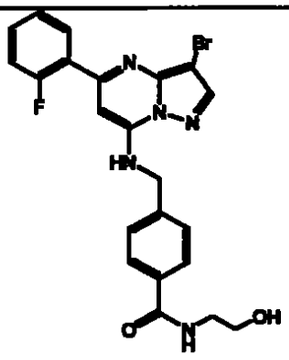
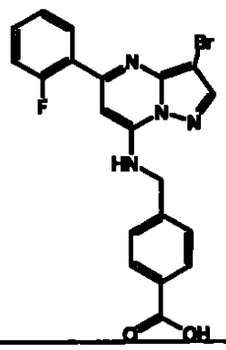
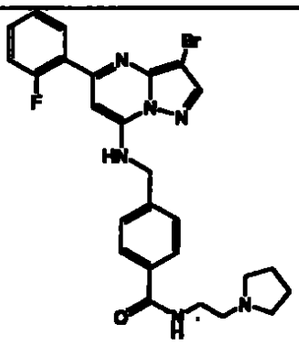
Table 40

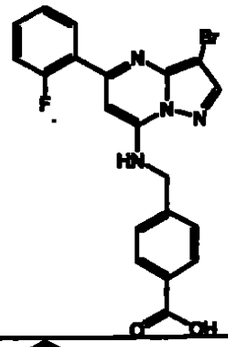
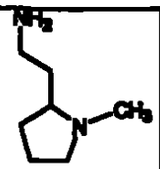
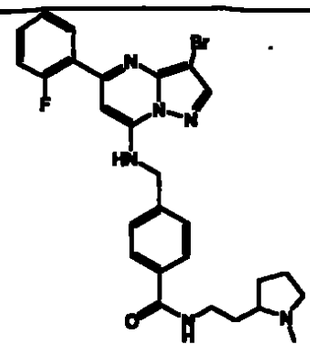
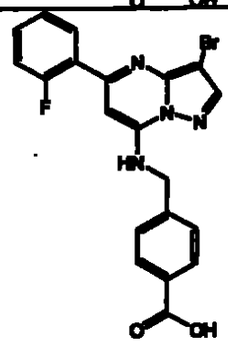
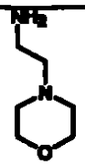
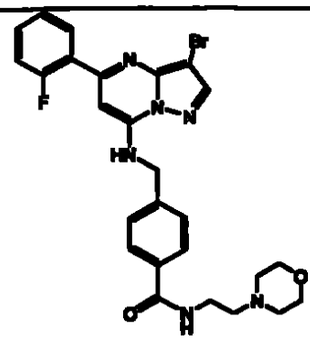
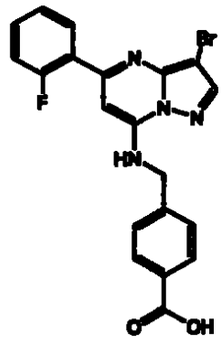
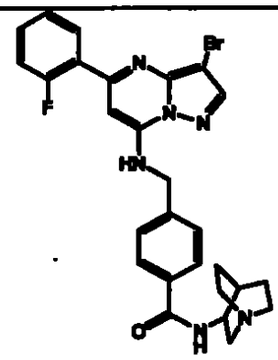
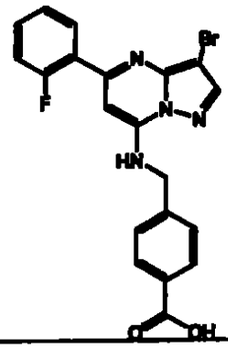
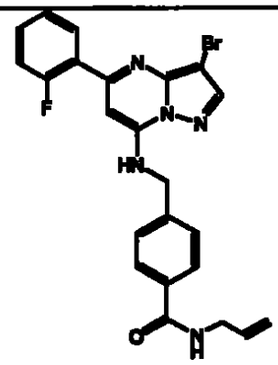
Ex.	Column 2	Column 3	Column 4	CMPD
481		CH_3NH_2		Yield = 88% LCMS: MH^+ = 454

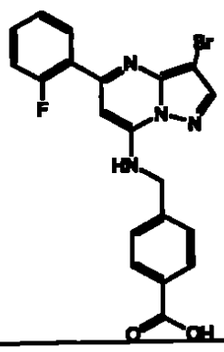
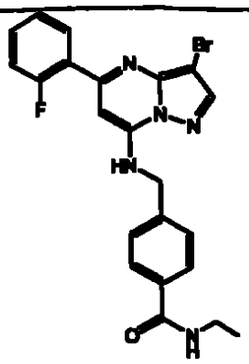
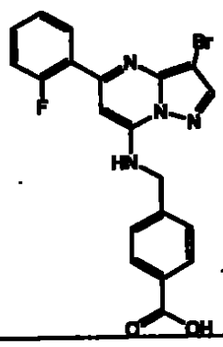
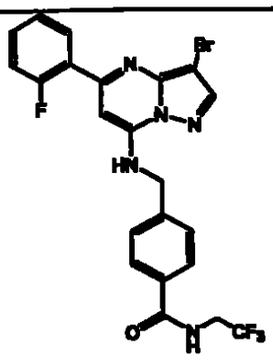
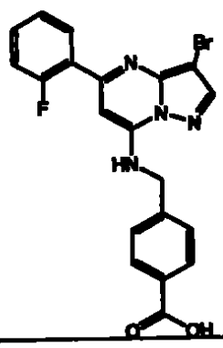
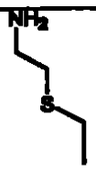
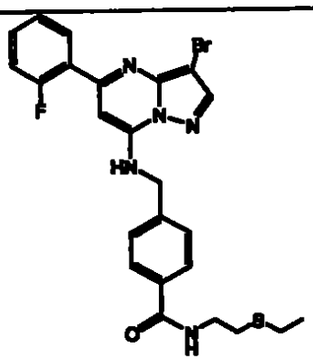
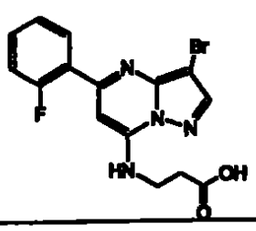
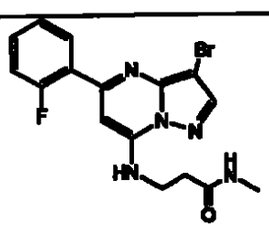
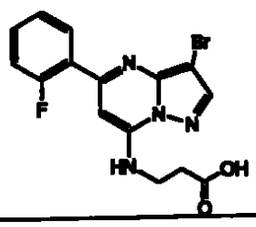
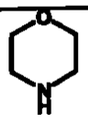
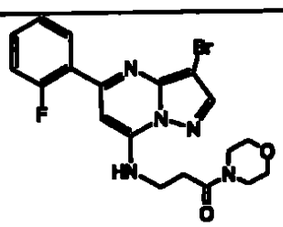
482		$(CH_3)_2NH$		Yield=80 % LCMS MH^+ = 468
483		CH_3NH_2		Yield=70 % LCMS MH^+ = 454.
484				Yield=75 % LCMS MH^+ = 482.1
485				Yield=71 % LCMS MH^+ = 480.1

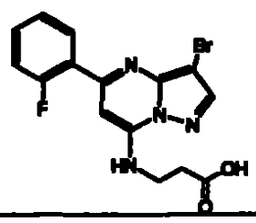
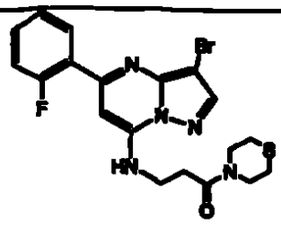
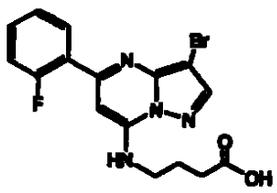
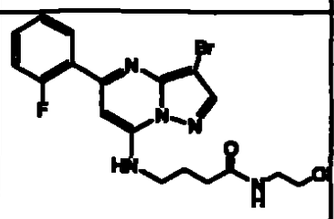
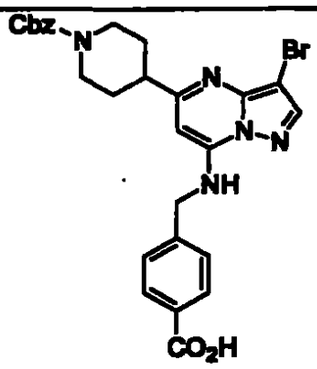
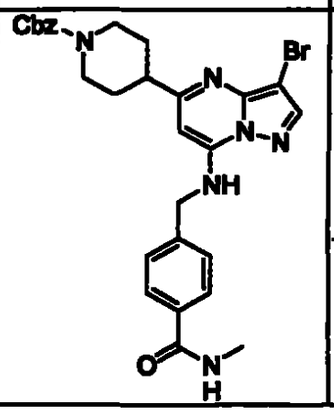
486				Yield=75 % LCMS MH^+ = 494.1
487				Yield=75 % MH^+ = 494.1
488				Yield=75 % MH^+ = 496.1
489				Yield=75 % LCMS MH^+ = 508.1

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^+ = 484.1
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), 3.8 (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).

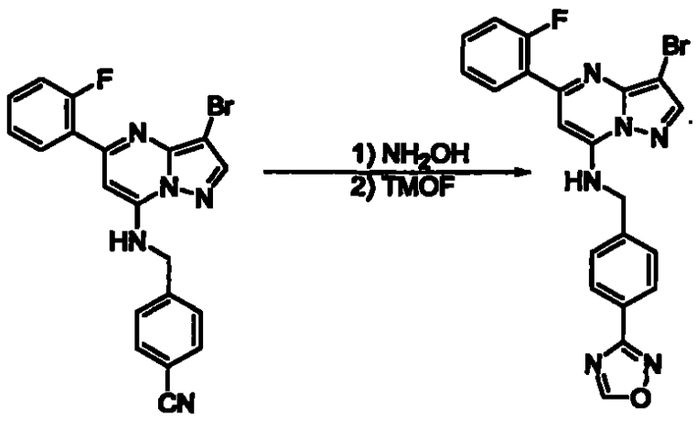
Example 505: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.4 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 7.0 (t, 1H), 6.5 (s, 1H), 3.8 (m, 2H), 2.7 (t, 2H), 3.0 (d, 3H).

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:

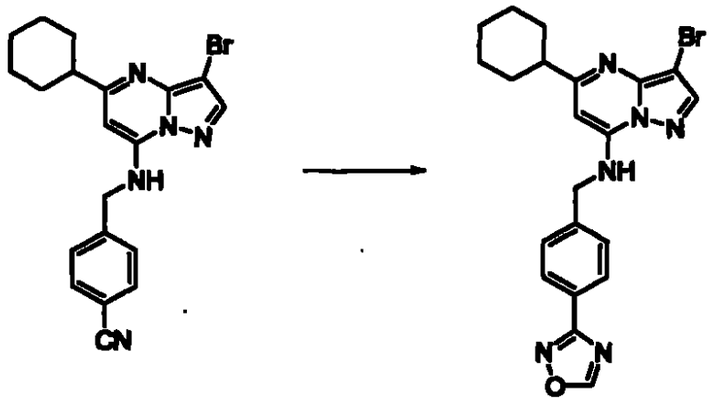


A solution of NaOH (59 mg, 1.47 mmol) in 1 mL of water was added to a suspension of $NH_2OH.HCl$ (102 mg, 1.47 mmol) in 10 mL of methanol at 0 °C. After 5 min, the compound prepared in Example 210.10 (208 mg, 0.49 mmol) was added and the reaction mixture was refluxed overnight. The solvent was removed *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).

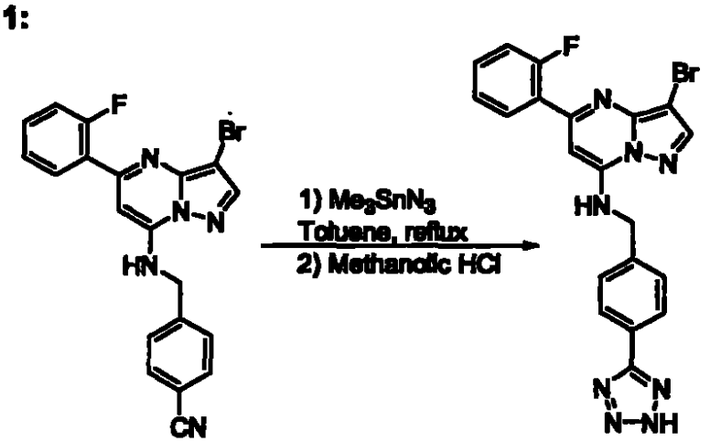
LCMS: MH^+ = 465.2

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.

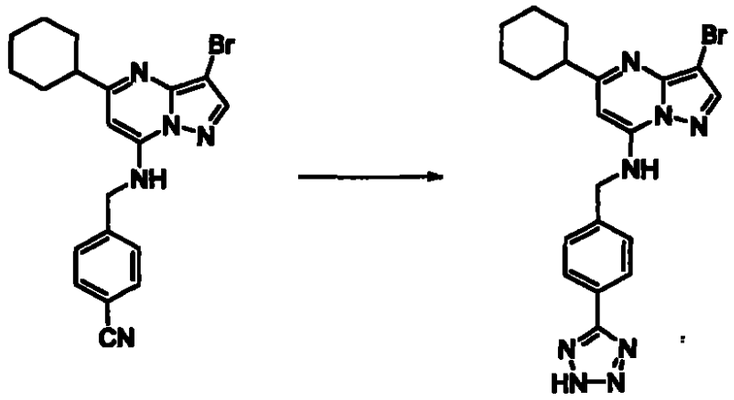
EXAMPLE 511:



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

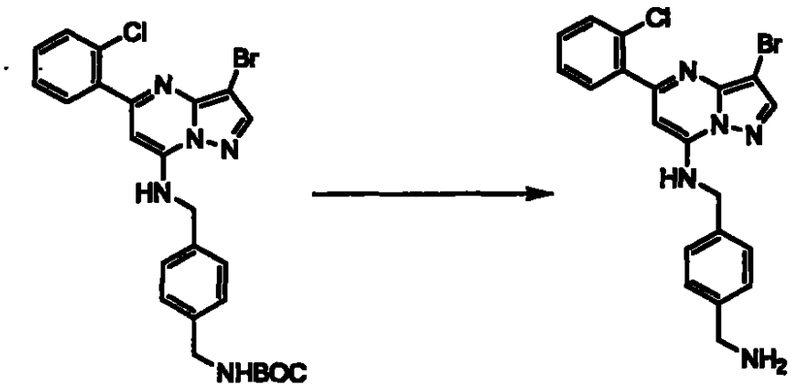
extracted into EtOAc. Evaporation of the EtOAc layer after drying (Na_2SO_4) provided the residue which was purified by chromatography (silica, DCM:MeOH (98:2→95:5)) to yield 50 mg (19%) of the pure tetrazole. ^1H NMR (CD_3OD) δ 8.10 (s, 1H), 8.00 (d, J = 9 Hz, 2H), 7.90 (t, J = 7 Hz, 1H), 7.65 (d, J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



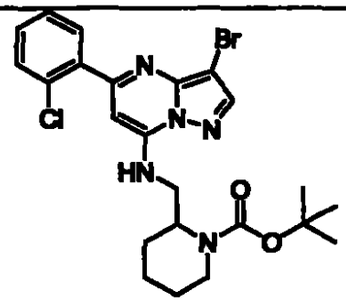
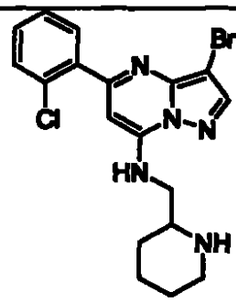
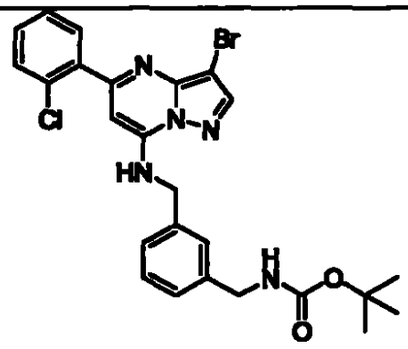
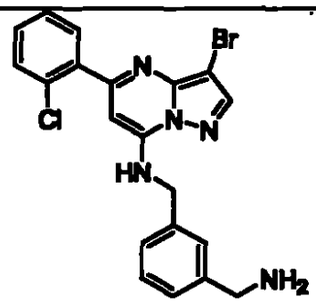
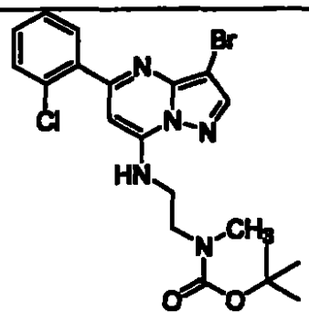
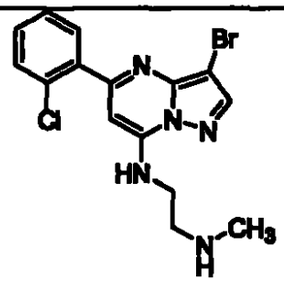
The compound prepared in Example 157 was dissolved in dioxane (30 mL) and a HCl-dioxane solution (4 M, 30 mL) was added. The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was evaporated under reduced pressure and ethyl acetate (200 mL) was added. The organic

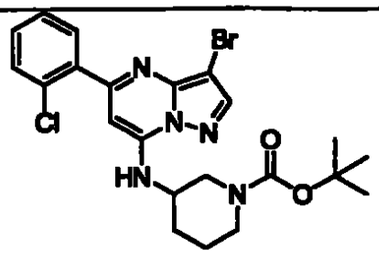
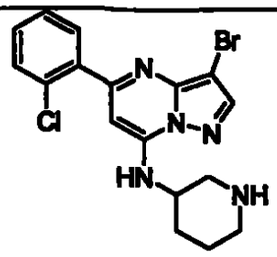
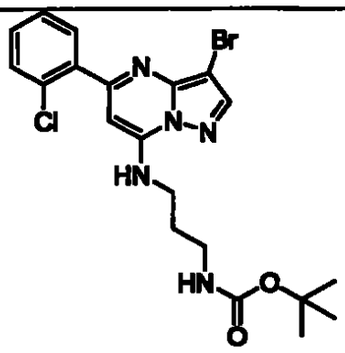
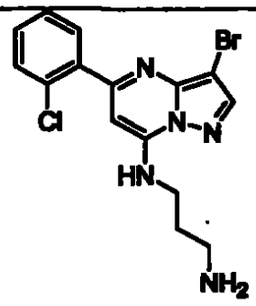
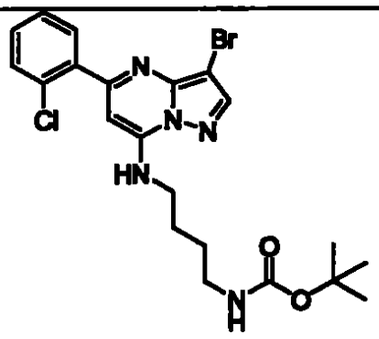
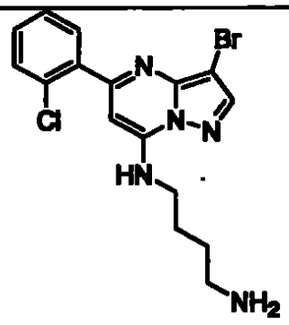
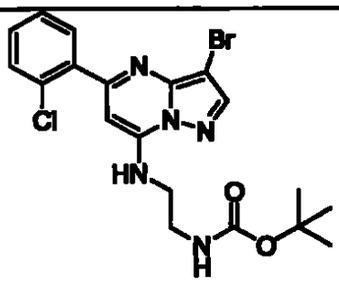
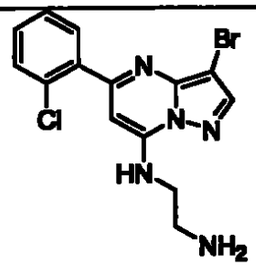
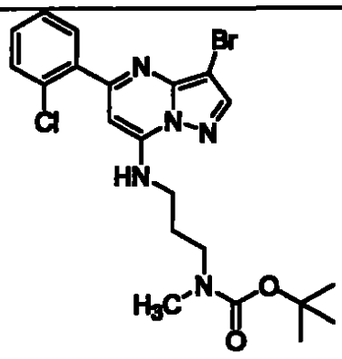
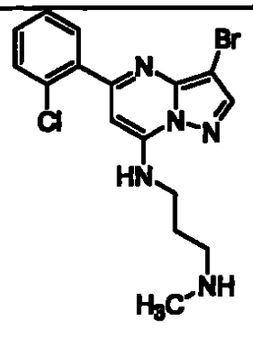
solution was washed with 1 N sodium hydroxide followed by saturated brine. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. MH^+ = 442.1

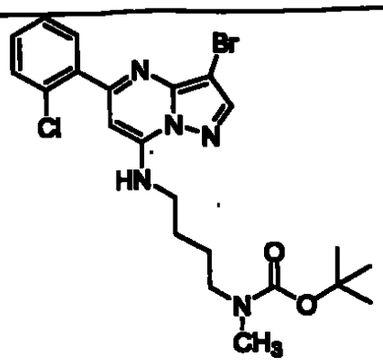
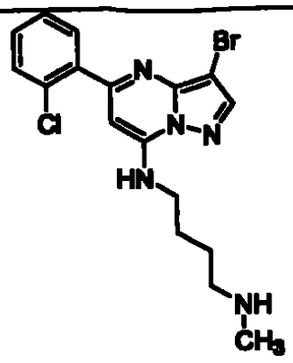
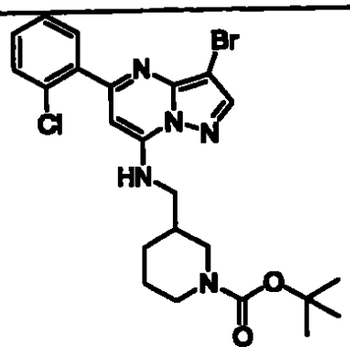
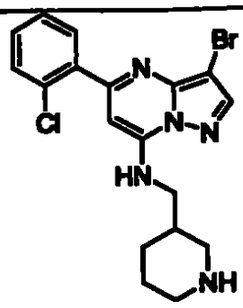
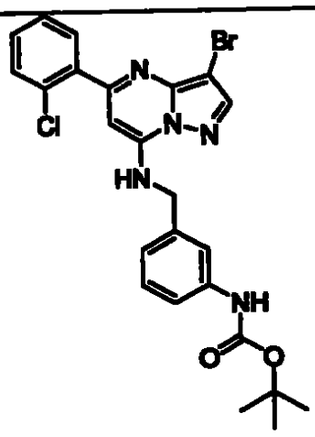
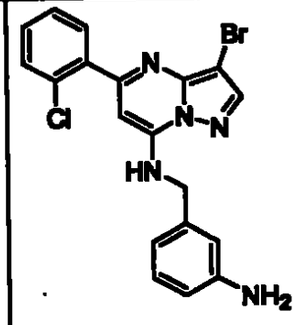
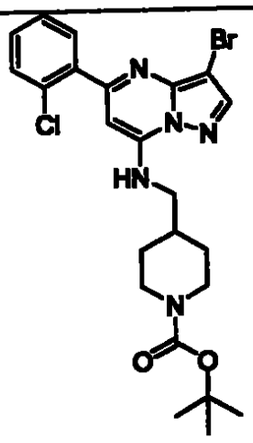
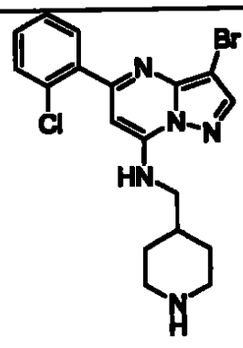
EXAMPLE 514-526:

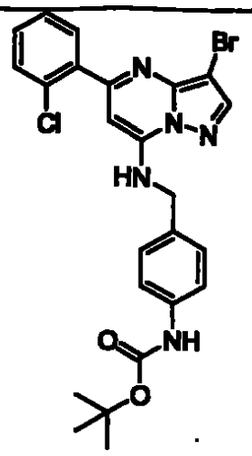
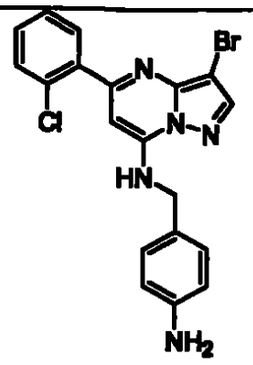
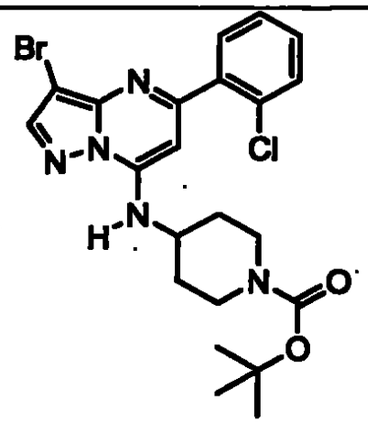
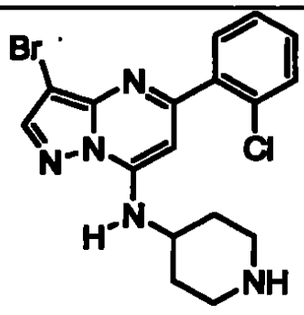
By essentially the same procedure set forth in Example 513, only substituting the compounds shown in Column 2 of Table 41, the compounds shown in Column 3 of Table 41 were prepared.

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			

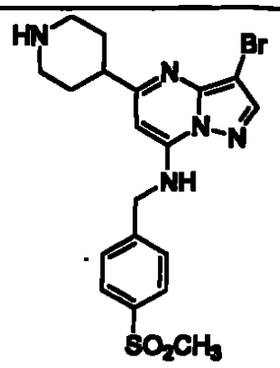
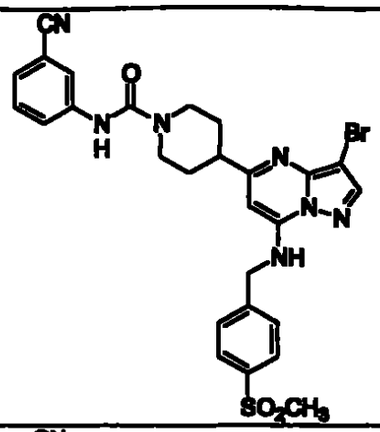
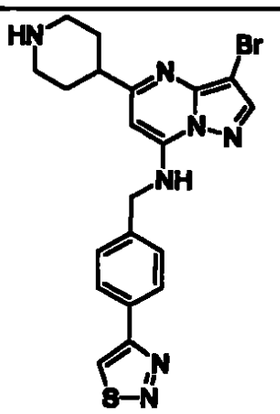
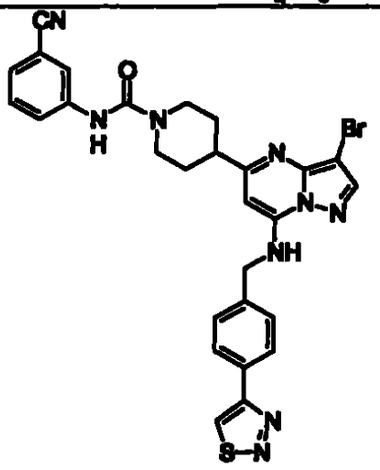
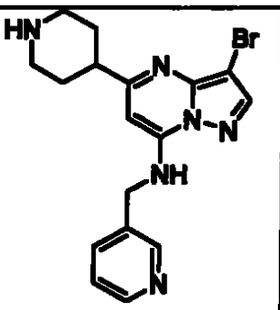
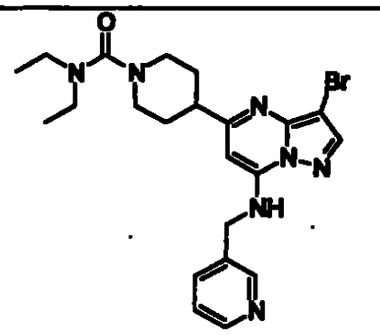
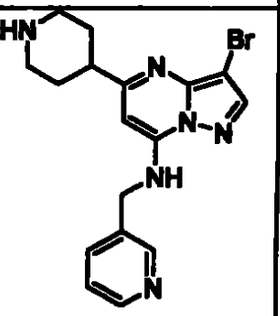
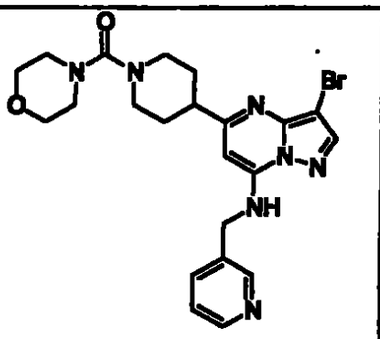
EXAMPLES 528-564:

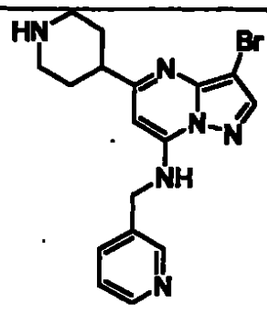
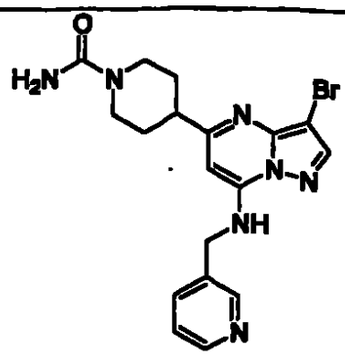
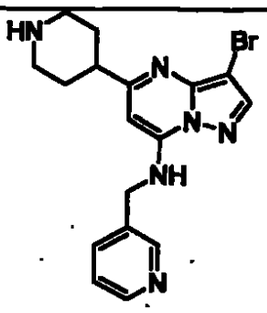
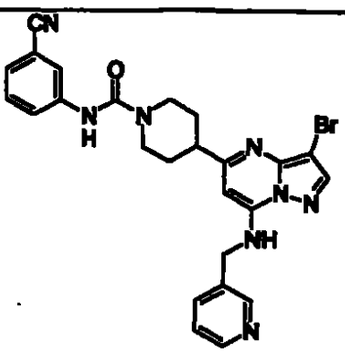
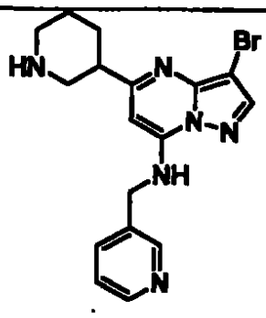
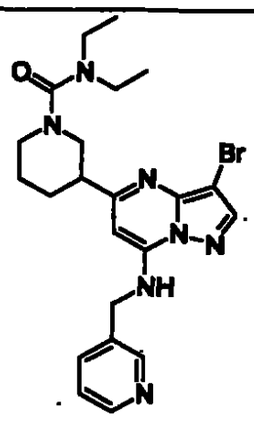
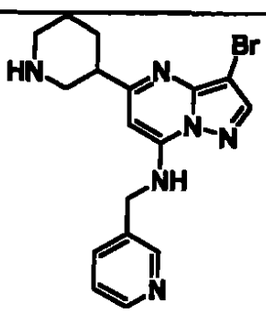
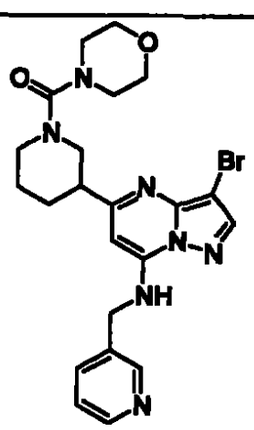
General procedure for 5-piperidinyl parallel library formation:

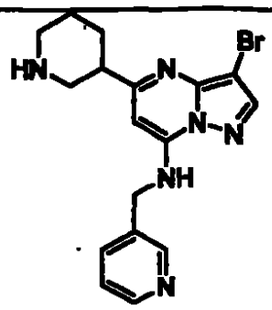
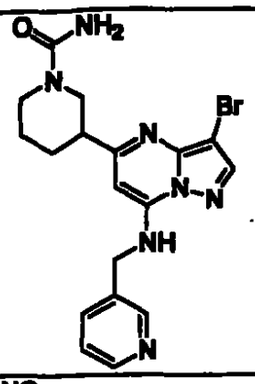
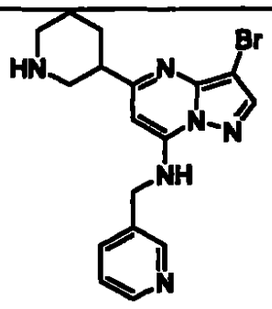
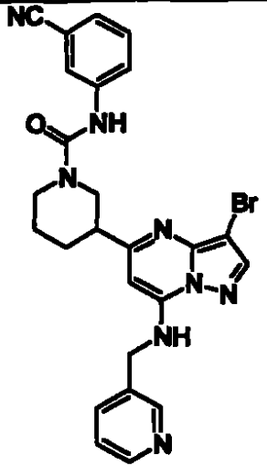
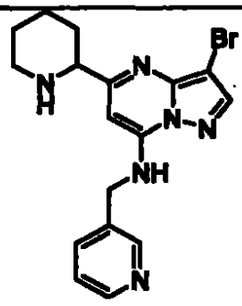
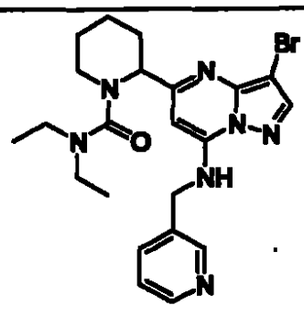
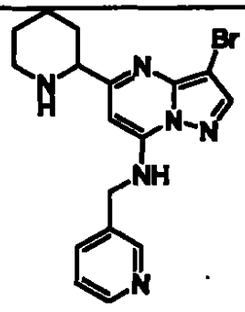
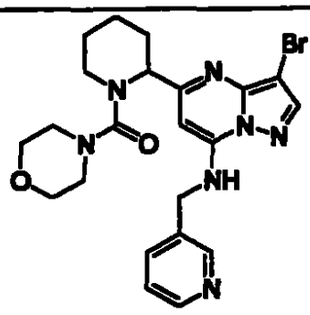
To a mixture of the starting material (80 mg, 0.21 mmol) shown in Column 2 of Table 42 in anhydrous CH_2Cl_2 (1.5 mL) was added DIPEA (75 µL, 0.42 mmol) and the appropriate capping reagent (1.1 equiv., 0.23 mmol). After 1 to 2 h, the reaction mixture was applied to 1000 micron preparatory TLC plate and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

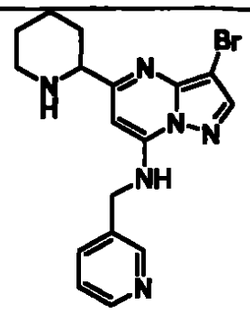
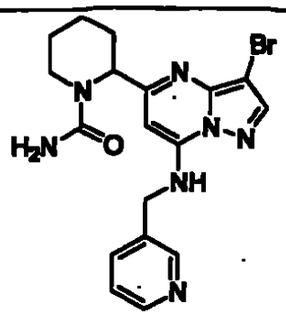
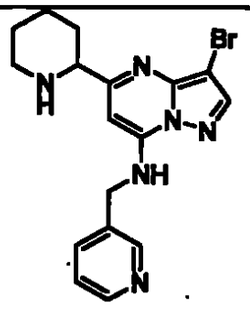
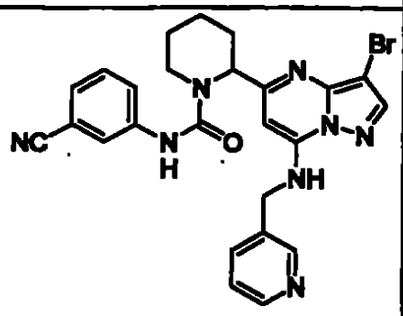
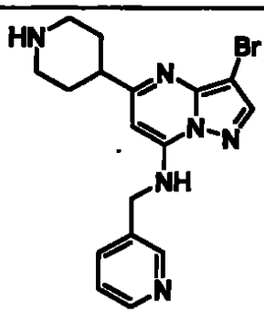
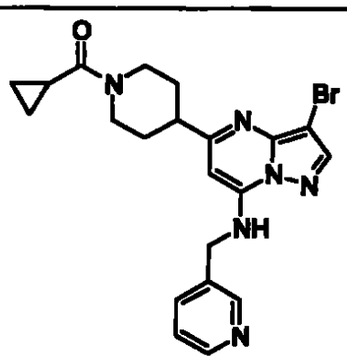
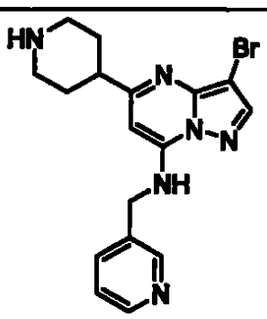
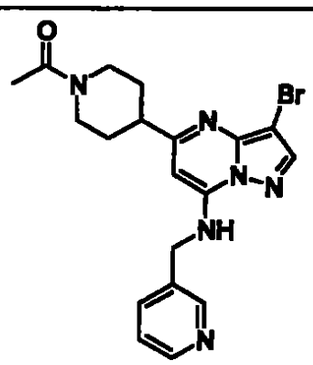
TABLE 42

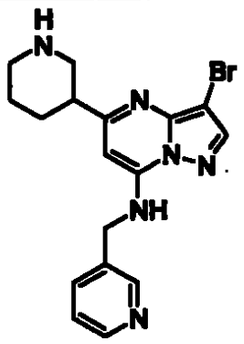
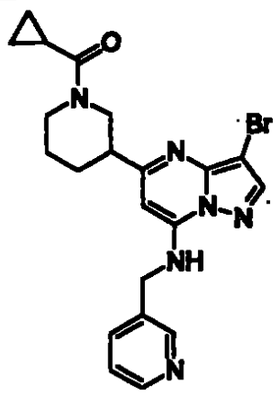
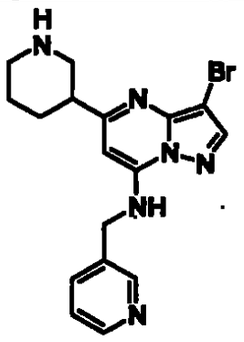
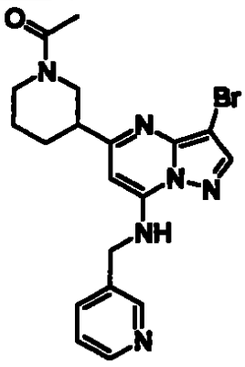
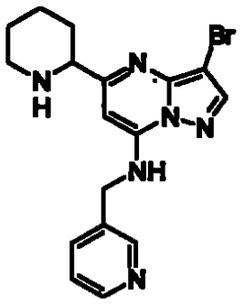
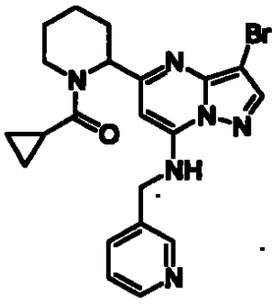
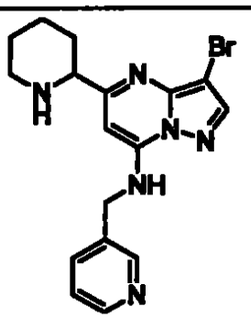
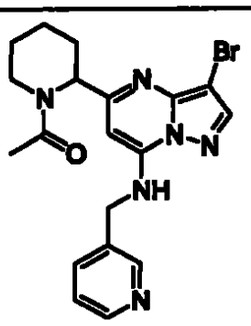
Ex.	Column 2	Column 3	CMPD

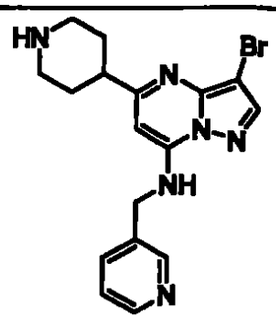
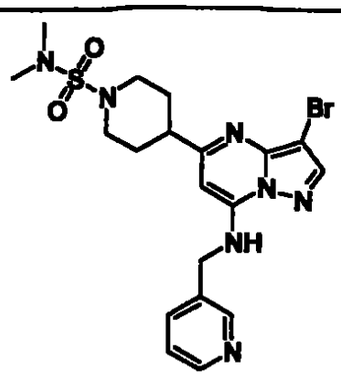
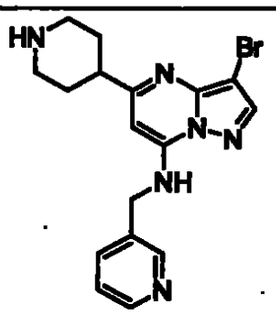
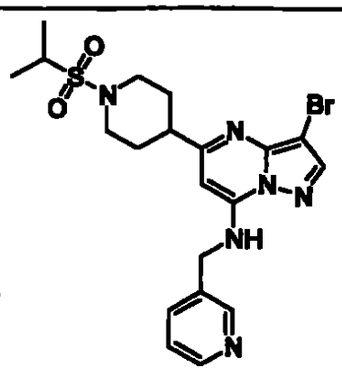
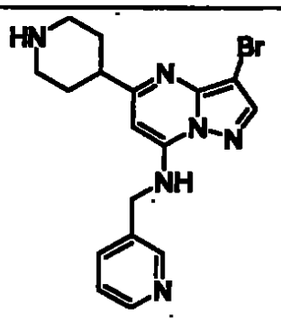
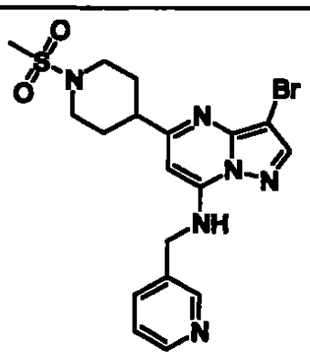
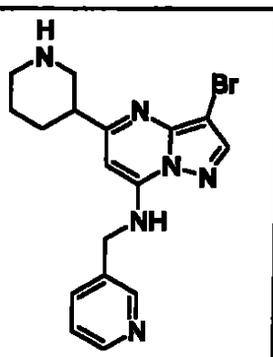
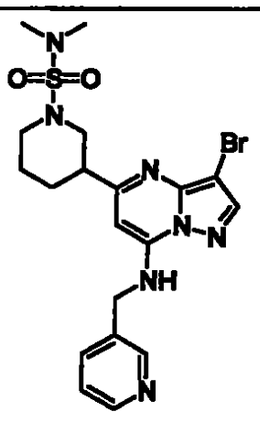
528			MH^+ = 608 m. p. = 230.1 °C
529			Yield = 82 MH^+ = 614 m. p. = 235.4 °C
530			MH^+ = 486 m. p. = 60.5 °C
531			MH^+ = 500 m. p. = 113.6 °C

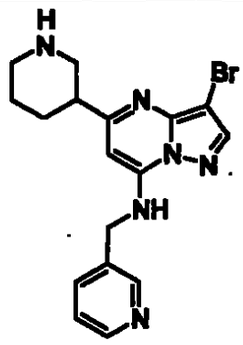
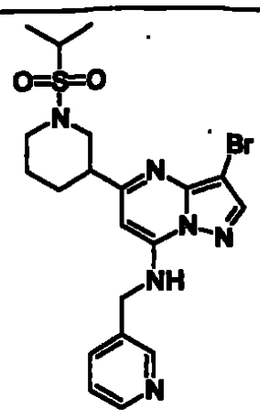
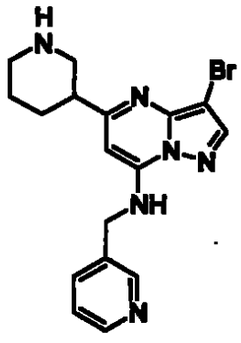
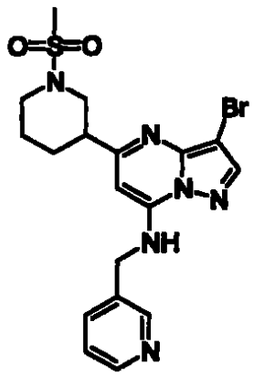
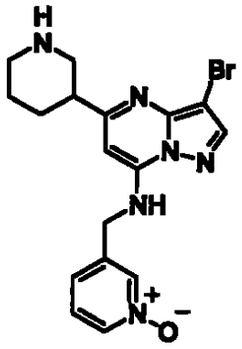
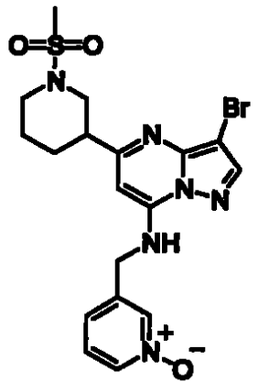
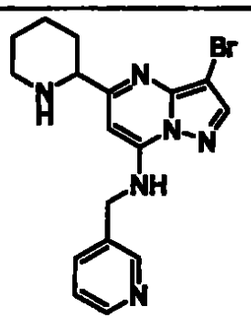
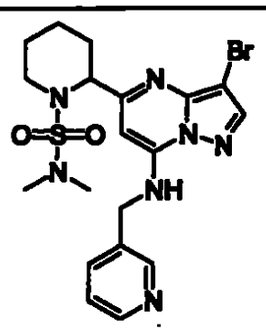
532			MH^+ = 430 m. p. = 158.3 – 159.2 °C
533			MH^+ = 531 m. p. =105.9 °C
534			MH^+ = 486
535			MH^+ = 500

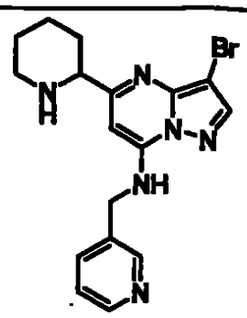
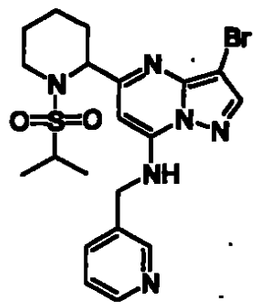
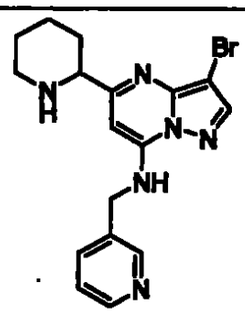
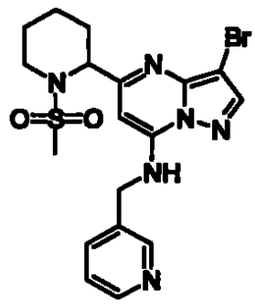
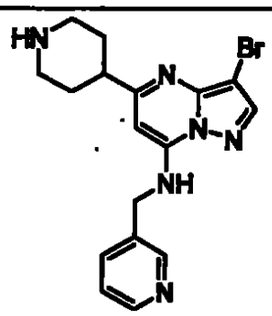
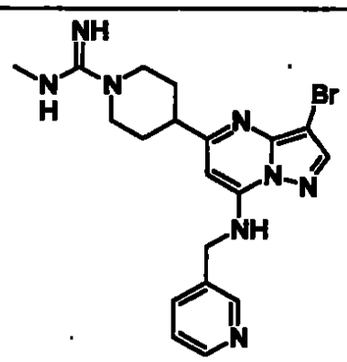
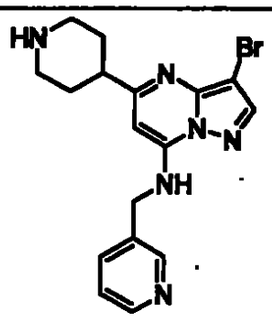
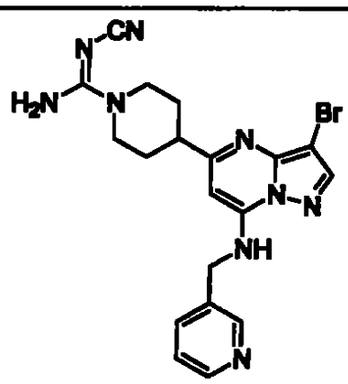
536			MH^+ = 430
537			MH^+ = 531
538			MH^+ = 486 m. p. = 69.6 °C
539			MH^+ = 500 m. p. = 82.3 °C

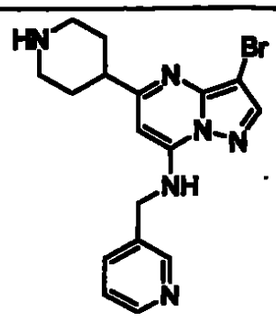
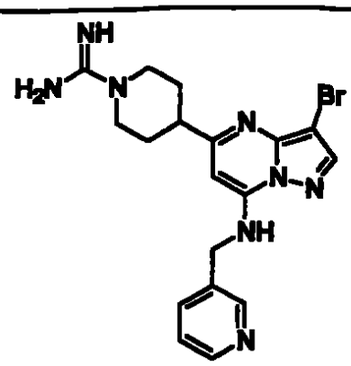
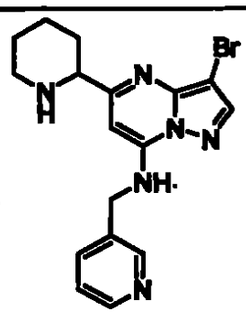
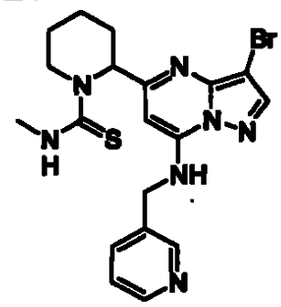
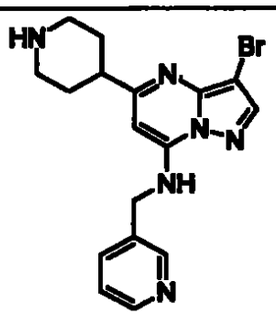
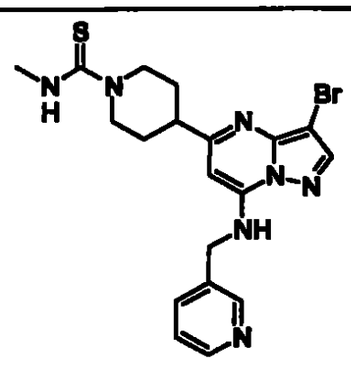
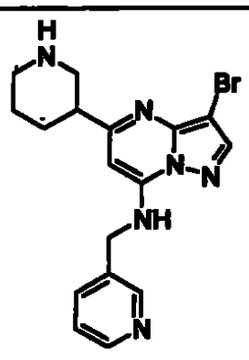
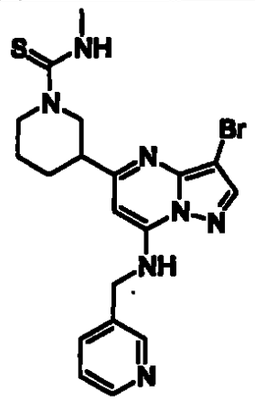
540			MH^+ = 430 m. p. = 223.6 °C
541			MH^+ = 531 m. p. = 118.1 °C
542			MH^+ = 455 m. p. = 109 – 110 °C
543			MH^+ = 429 m. p. = 111.5 °C

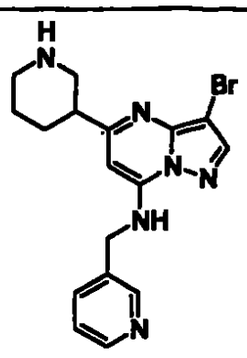
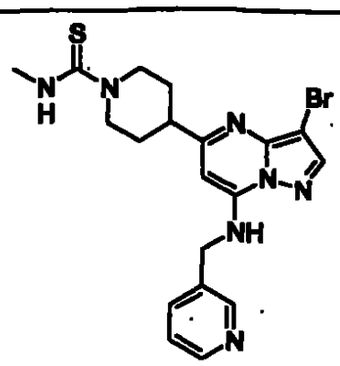
544			MH^+ = 455
545			MH^+ = 429
546			MH^+ = 455 m. p. =80.1 °C
547			MH^+ = 429 m. p. = 64.7 °C

548			MH^+ = 494 m. p. = 76.5 °C
549			MH^+ = 493 m. p. = 83.6 °C
550			MH^+ =. 485 m. p. =207.5 °C
551			MH^+ = 494

552			MH^+ = 493
553			MH^+ = 485
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).

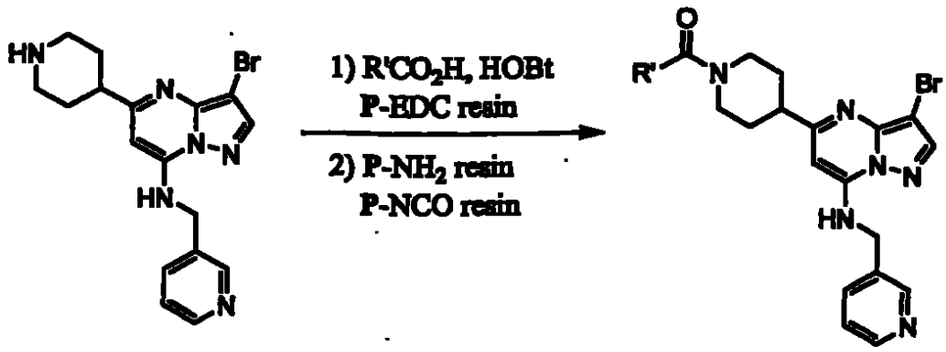
Example 552: ^{1}H NMR (300MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.62 – 8.59 (d, 1H), 7.95 (s, 1H), 7.74 – 7.69 (d, 1H), 7.36 – 7.31 (dd, 1H), 6.67 – 6.60 (t, 1H), 5.98 (s, 1H), 4.67 – 4.63 (d, 2H), 3.92 – 3.86 (m, 1H), 3.85 – 3.75 (m, 1H), 3.40 – 3.30 (dd, 1H), 3.27 – 3.16 (m, 1H), 3.10 – 2.86 (m, 2H), 2.10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

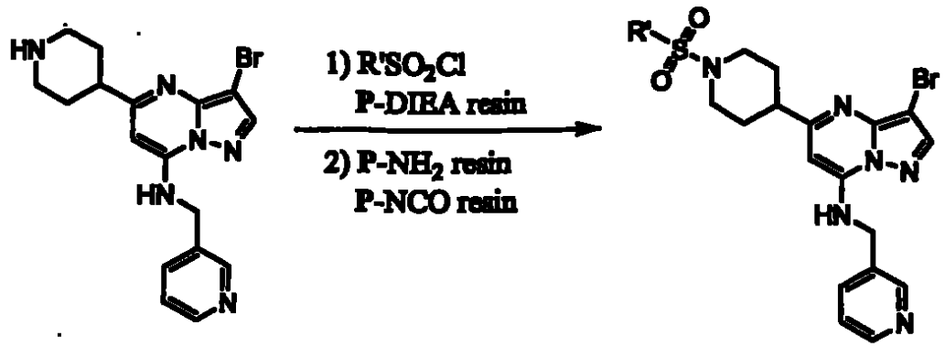
Example 563: ^{1}H NMR (300MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.62 – 8.58 (d, 1H), 7.96 (s, 1H), 7.73 – 7.68 (d, 1H), 7.36 – 7.30 (dd, 1H), 6.96 – 6.86 (br s, 1H), 6.79 – 6.74 (t, 1H), 6.00 (s, 1H), 4.67 – 4.64 (d, 2H), 4.37 – 4.30 (dd, 1H), 4.22 – 4.13 (m, 1H), 3.97 – 3.86 (dd, 1H), 3.73 – 3.64 (m, 1H),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



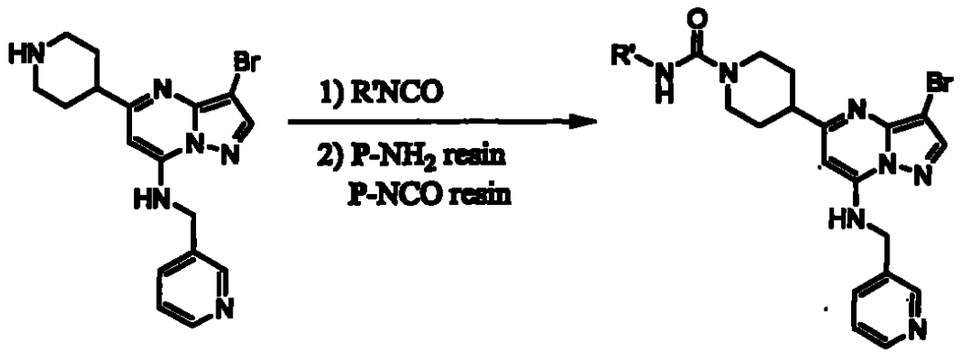
Parallel synthesis was conducted in polypropylene 96-well reaction blocks with removable top seal and fixed bottom seal. Each reaction well was fitted with a 20 micron polypropylene bottom frit and the maximum volume was 3 mL. Collection block was not fitted with bottom frit. To each reaction well was 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.

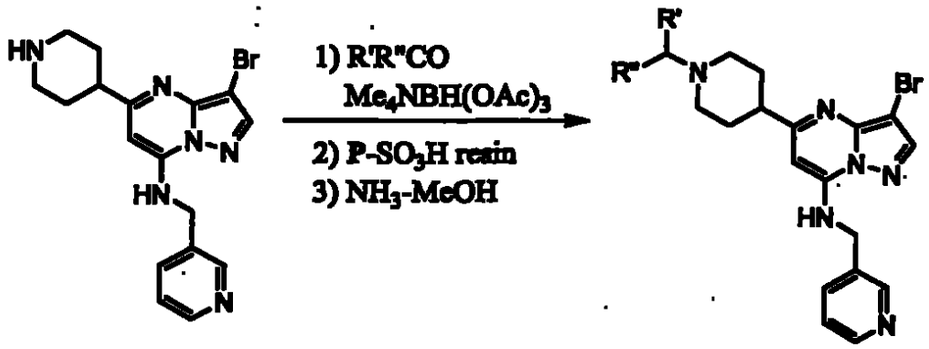
ENERAL PROCEDURE 3: Procedure for the urea formation parallel synthesis



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.

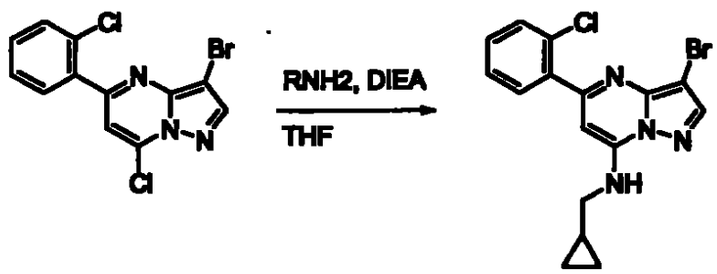
GENERAL PROCEDURE 4: Procedure for the reductive alkylation parallel synthesis



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

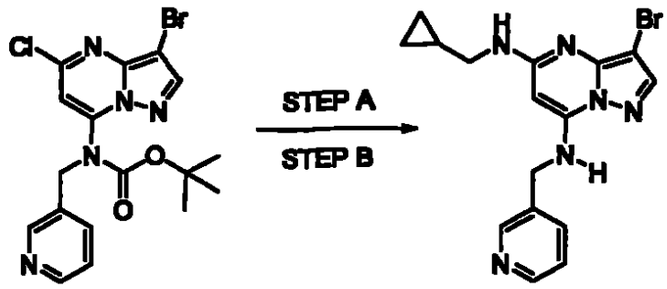


To 3-bromo-7-chloro-5-(2-chloro-phenyl)-pyrazolo[1,5-a]pyrimidine (9.0 mg, 0.03 mmol) in tetrahydrofuran were added di-*iso*-propylethylamine (12 μL, 0.07), followed by cyclopropylmethylamine (70 μL, .07 mmol; 1M solution in DMF). The reaction mixture was heated to 70 °C for 36 h and then cooled to rt. 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):

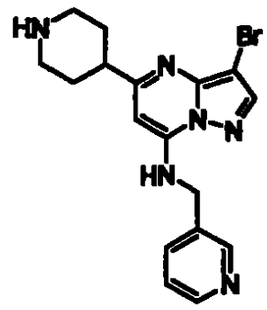
The product from STEP A was taken up in 35% TFA/DCM and agitated for 4 h followed by concentration under high vacuum. The residue was treated with 10% HCl(aq) in MeOH agitated for 2 h and then concentrated to give the desired product. . observed m/z 375.21.

STEP B(basic):

The product from step A was taken up in EtOH and treated with Amberseр® 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.

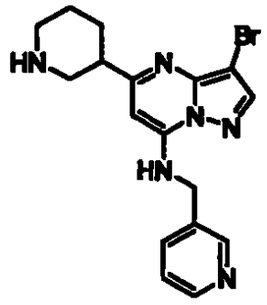
EXAMPLE 565:

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.



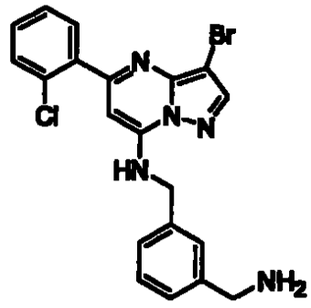
EXAMPLE 566:

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.



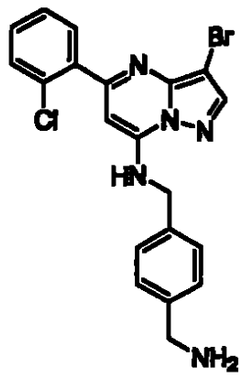
EXAMPLE 567:

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 obeerved m/z were prepared.



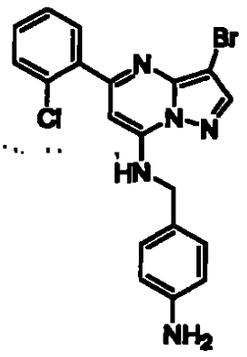
EXAMPLE 568:

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.



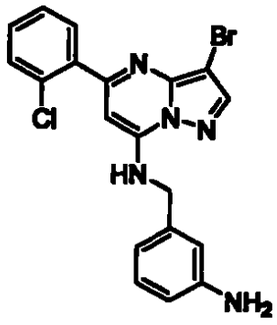
EXAMPLE 569:

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.



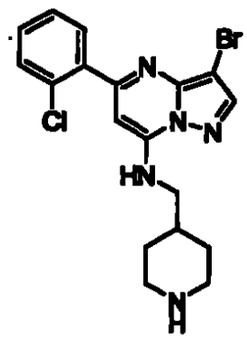
EXAMPLE 570:

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.



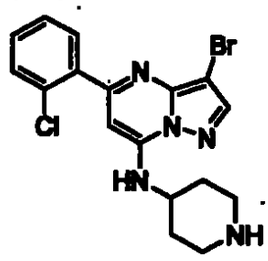
EXAMPLE 571:

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.



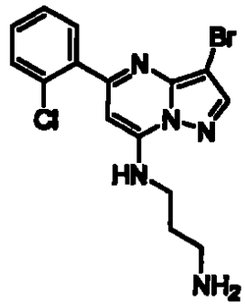
EXAMPLE 572:

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.



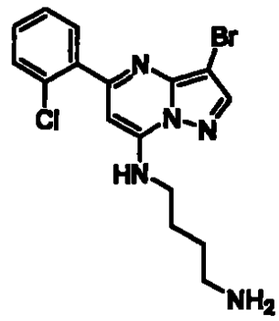
EXAMPLE 573:

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.



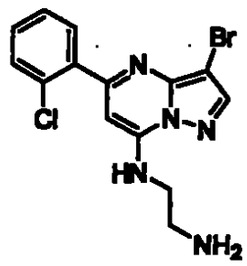
EXAMPLE 574:

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.



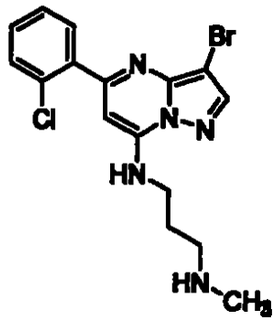
EXAMPLE 575:

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.



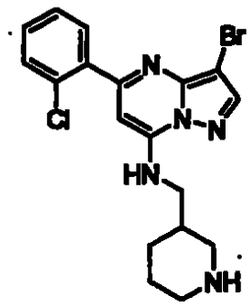
EXAMPLE 576:

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.



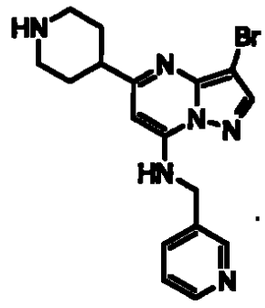
EXAMPLE 577:

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.



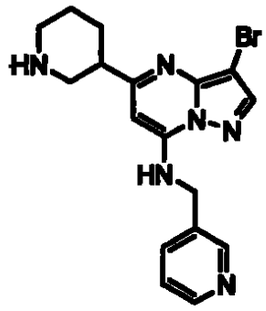
EXAMPLE 578:

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.



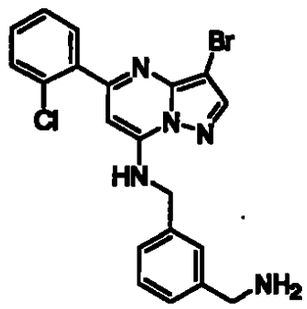
EXAMPLE 579:

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.



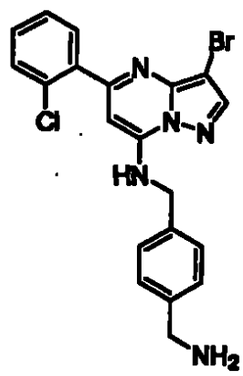
EXAMPLE 580:

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.



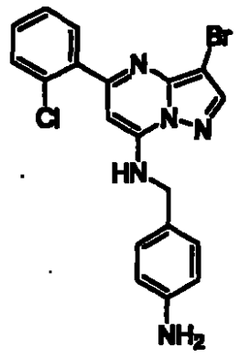
EXAMPLE 581:

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.



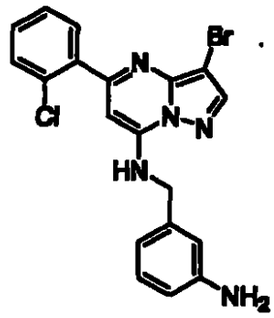
EXAMPLE 582:

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.



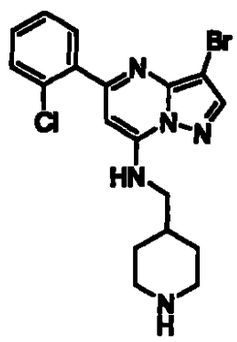
EXAMPLE 583:

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.



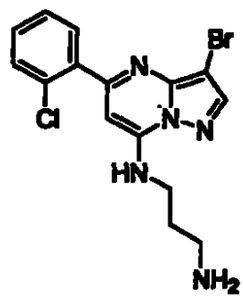
EXAMPLE 585:

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.



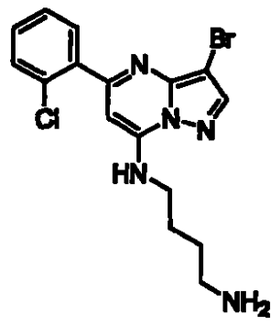
EXAMPLE 586:

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.



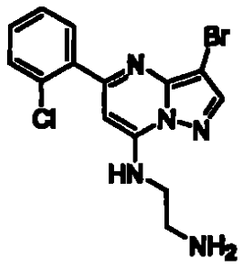
EXAMPLE 587:

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.



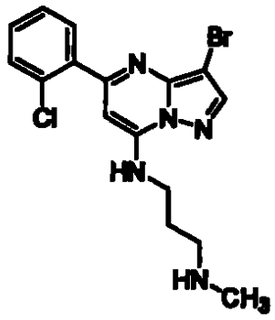
EXAMPLE 588:

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.



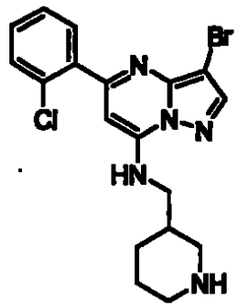
EXAMPLE 589:

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.



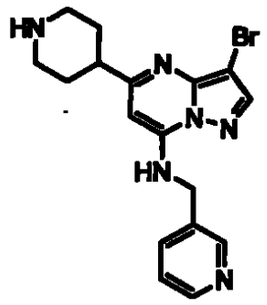
EXAMPLE 590:

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.



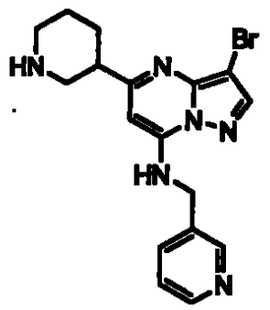
EXAMPLE 591:

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.



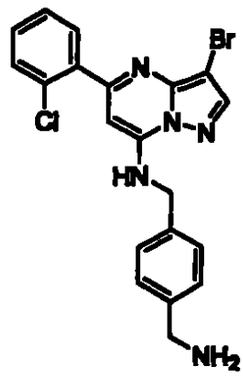
EXAMPLE 592:

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.



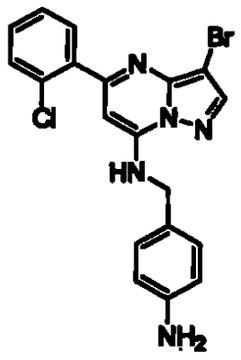
EXAMPLE 593:

By utilizing the procedure set forth in General Procedure 3 and the compound from Example 513 shown below, the compounds shown in Tabl 72 with the observed m/z were prepared.



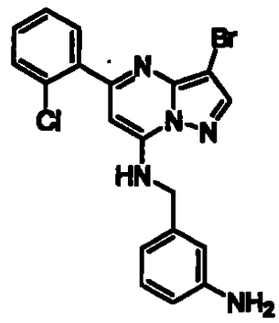
EXAMPLE 594:

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.



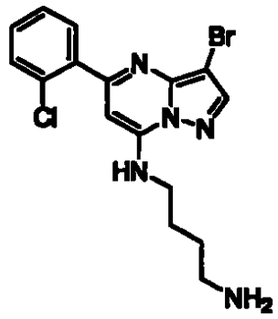
EXAMPLE 595:

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.



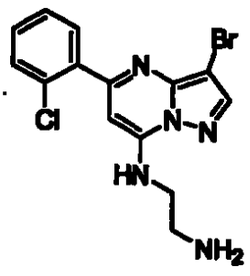
EXAMPLE 596:

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.



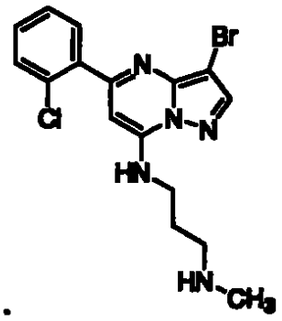
EXAMPLE 597:

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.



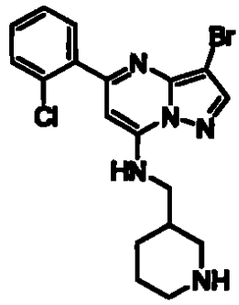
EXAMPLE 598:

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.



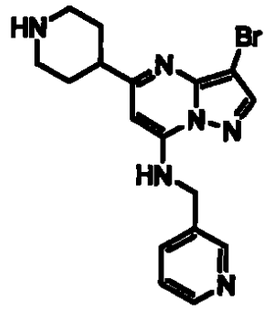
EXAMPLE 599:

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.



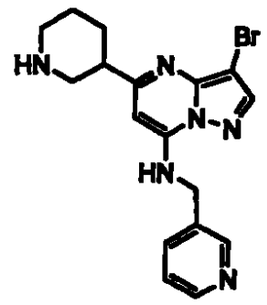
EXAMPLE 600:

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.



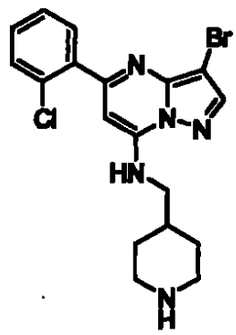
EXAMPLE 601:

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.



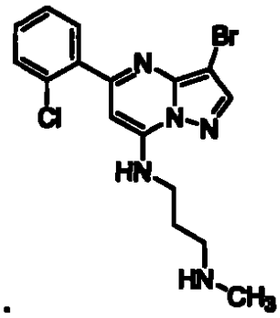
EXAMPLE 603:

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.



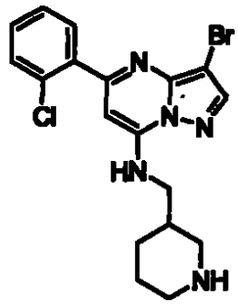
EXAMPLE 604:

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.



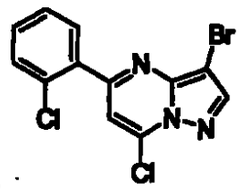
EXAMPLE 605:

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.



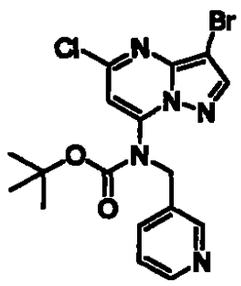
EXAMPLE 606:

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.

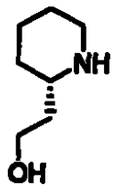


EXAMPLE 607:

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.

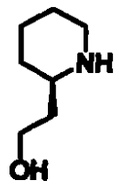


PREPARATIVE EXAMPLE 500



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).

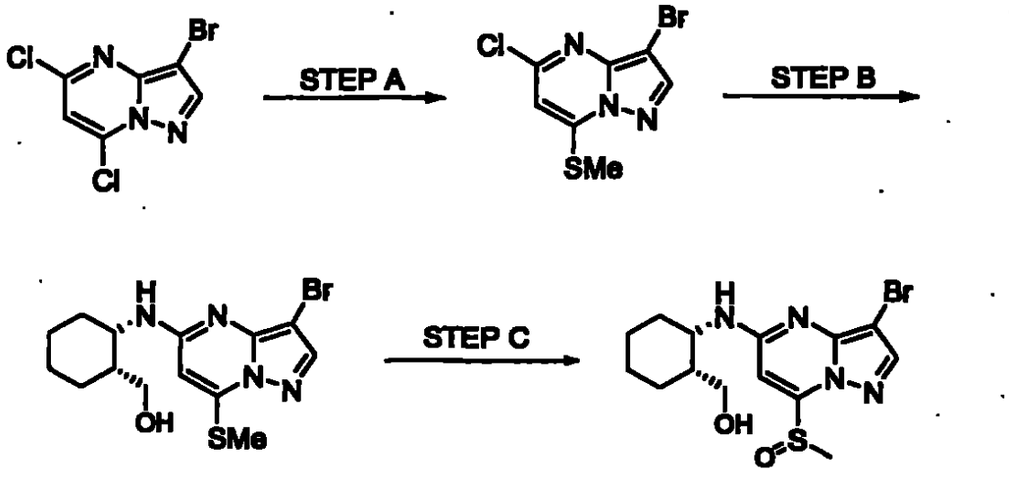
PREPARATIVE EXAMPLE 502



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.

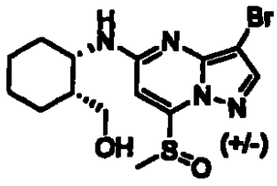
Step B:

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:

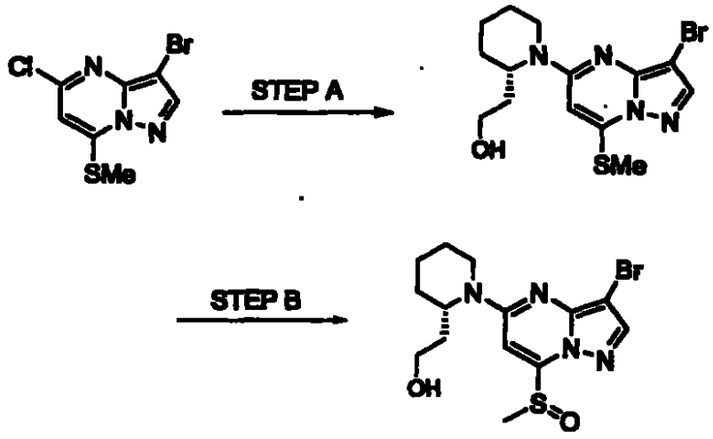
To a solution of thiomethyl derivative (2.2 g, 5.92 mmol) from Step B in CH_2Cl_2 (20 mL) at 0 °C was added MCPBA (1.53 g, 8.9 mmol) in one portion. The resulting mixture was stirred for 2h at 0 °C whereupon the mixture was diluted with CH_2Cl_2 (20 mL) and sat. aq. $NaHCO_3$ (15 mL). The layers were 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



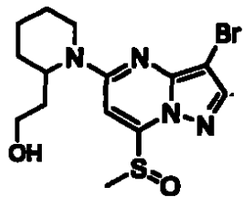
Step A:

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:

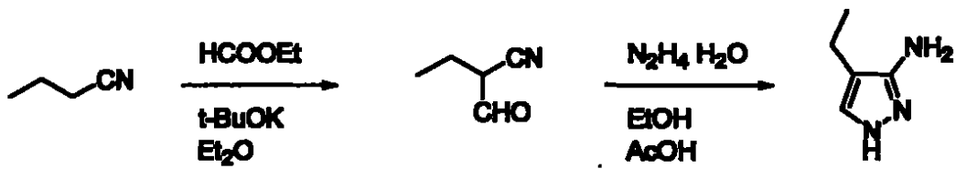
Following the procedure from Step C in Preparative Example 503, the thiomethyl derivative (0.30 g, 0.81 mmol) was treated with MCPBA (0.21 g, 1.2 mmol) to afford 0.31 g (99%) the title compound as a yellow viscous oil. M+H = 388.

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.

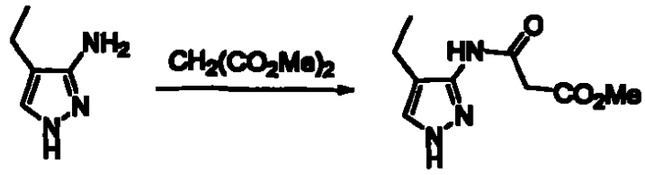
PREPARATIVE EXAMPLE 507



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.

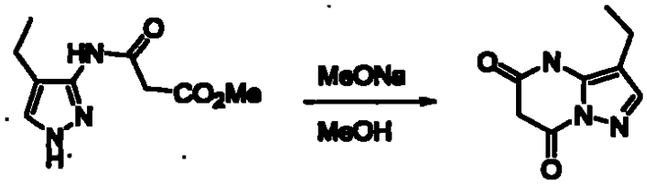
PREPARATIVE EXAMPLE 508



Step A:

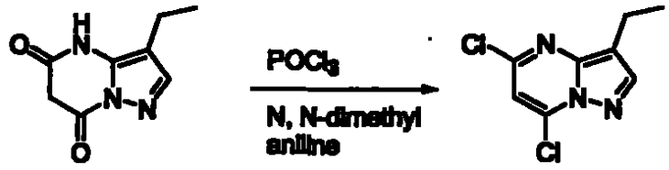
The pyrazole from Preparative Example 507 (9.80g) and dimethylmalonate (45 mL) were stirred and refluxed under N_2 for 3 hrs. The excess of dimethylmalonate was evaporated in a vacuum and the residue was chromatographed with 15:1 CH_2Cl_2:MeOH to yield pale yellow solid (10.6 g, 57%). LCMS: MH^+ = 212.

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.

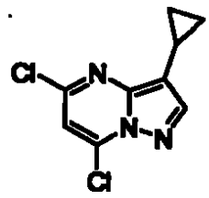
Step C:



$POCl_3$ (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

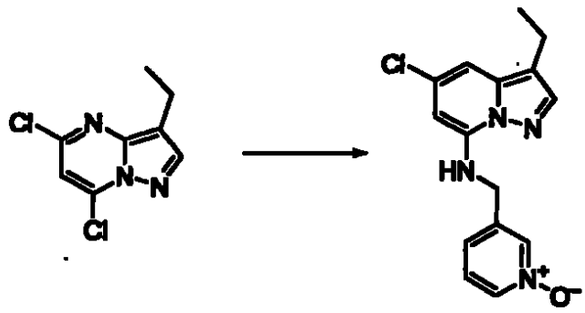
residue was chromatographed with CH_2Cl_2 to yield pale yellow solid (8.20 g, 90%). LCMS: MH^+ = 216.

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

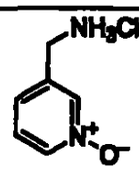
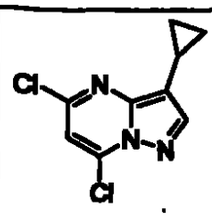
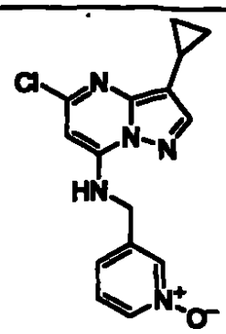
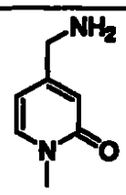
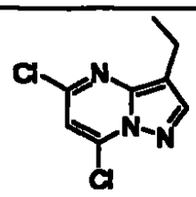
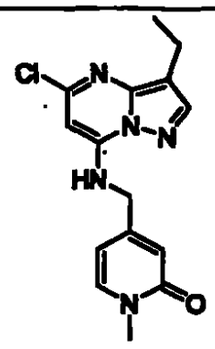
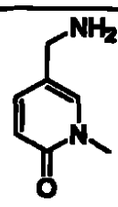
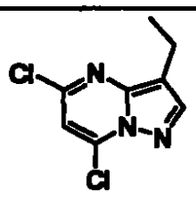
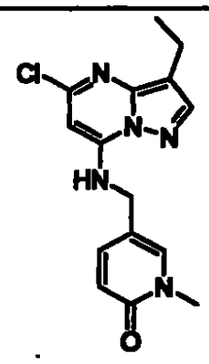
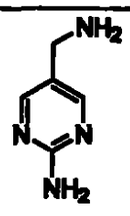
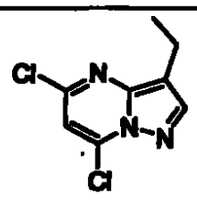
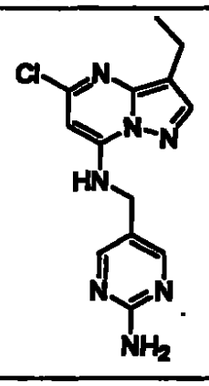


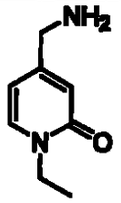
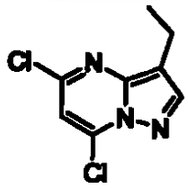
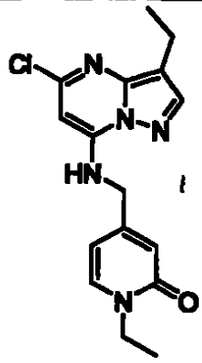
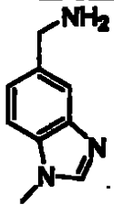
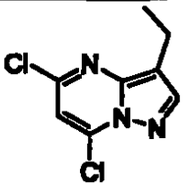
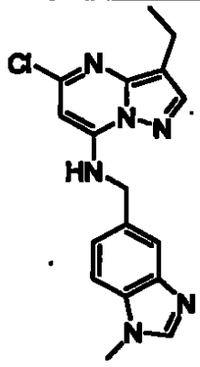
A mixture of the dichloride from Preparative Example 508 (3.13g, 14.5 mmol), the amine.HCl from Preparative Example (3.00g, 16.9 mmol), DIPEA (7.5 mL), and dry NMP (40 mL) plus dry dioxane (40 mL) was stirred at 60°C for 4 days under N_2. The solvents were then distilled off in a vacuum and the residue 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 nly 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

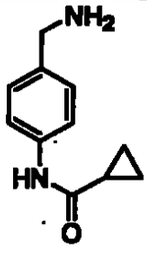
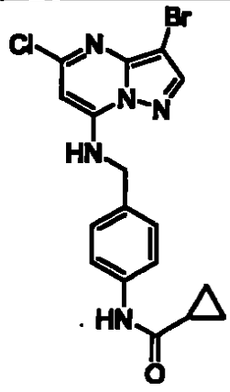
Prep. Ex.	Column 2	Column 3	Column 4	CMPD
510				M+H = 316
512				M+H = 316
513				M+H = 316
514				

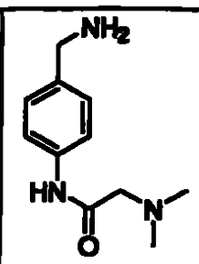
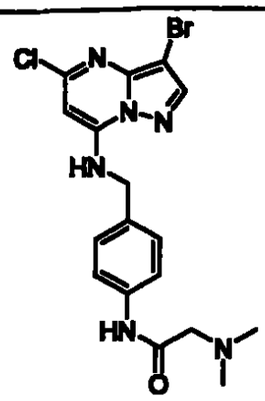
515				M+H = 332
516				

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

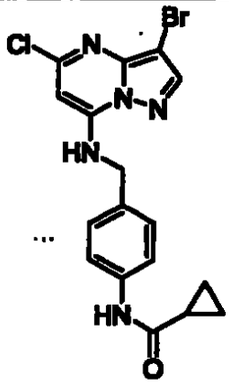
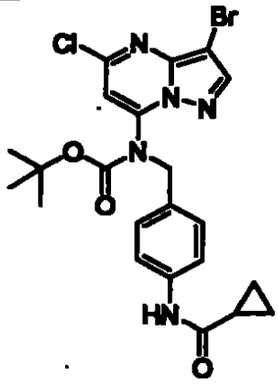
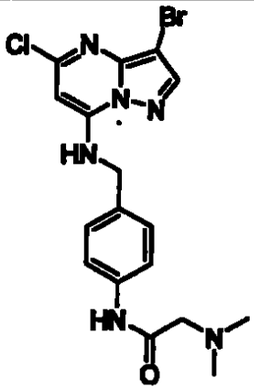
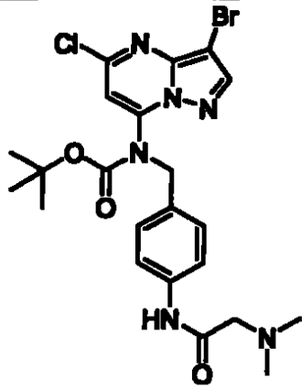
Prep. Ex.	Column 2	Column 3	CMPD
518			M+H= 422.1

519			

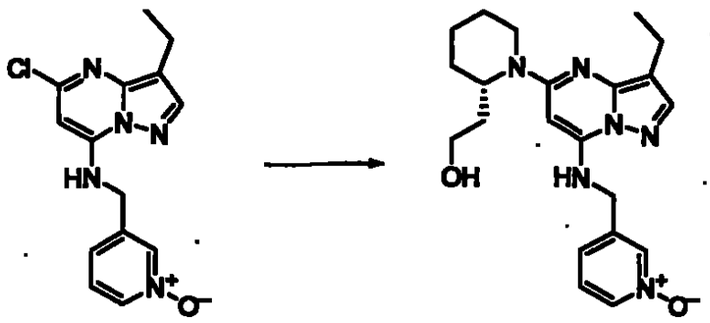
PREPARATIVE EXAMPLE 520-521:

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

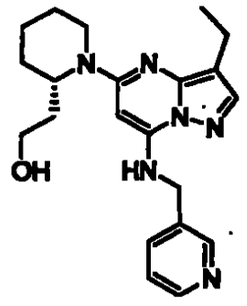
EXAMPLE 1000:



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:

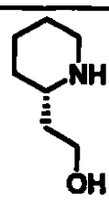
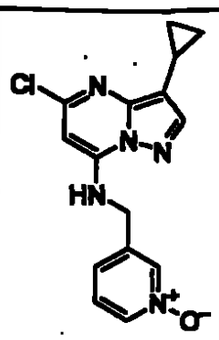
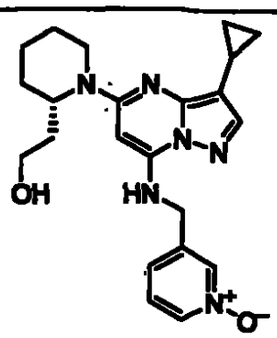
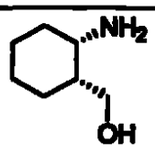
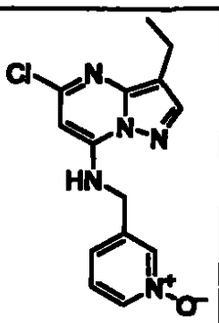
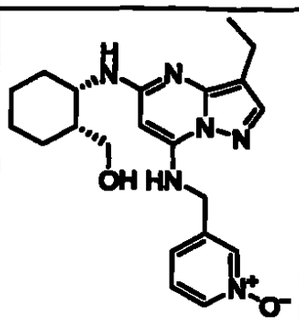
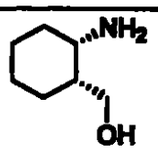
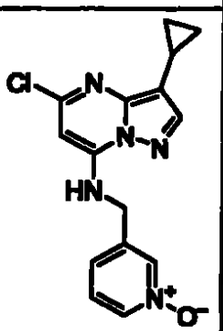
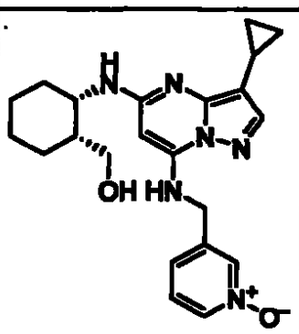
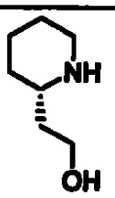
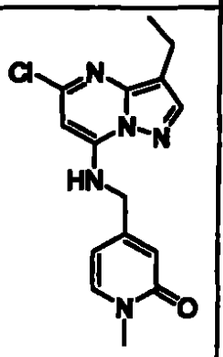
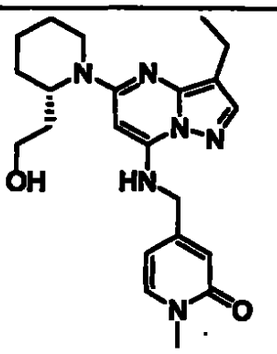


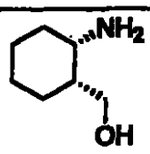
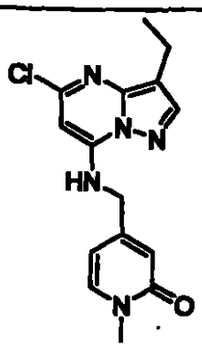
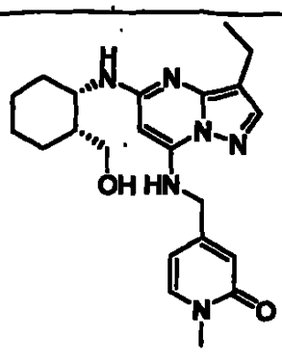
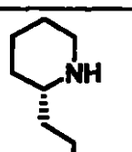
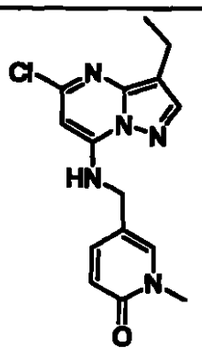
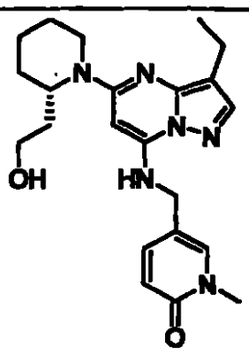
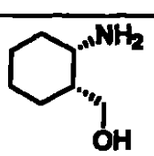
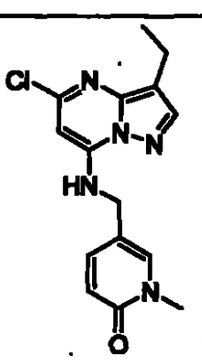
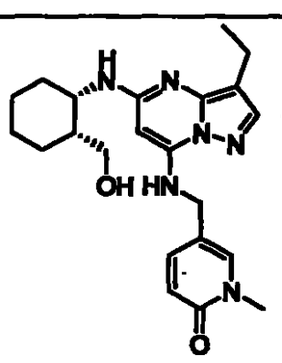
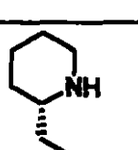
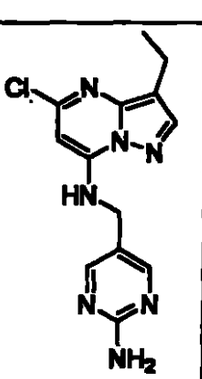
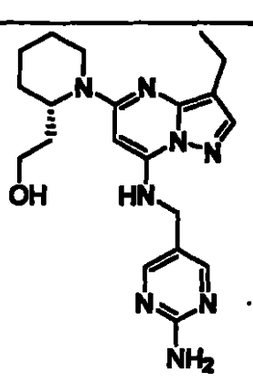
EXAMPLES 1002 – 1014:

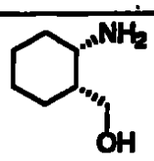
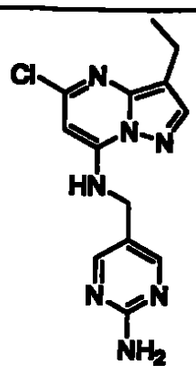
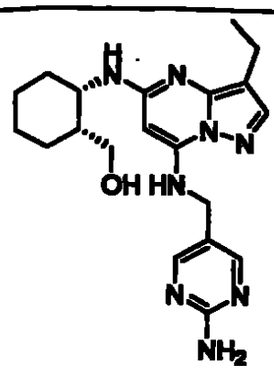
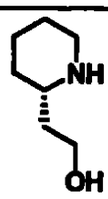
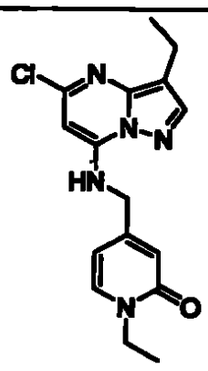
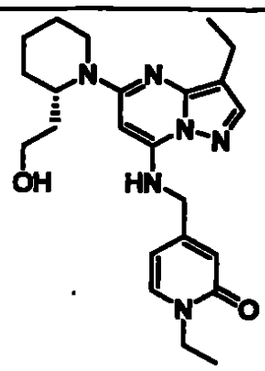
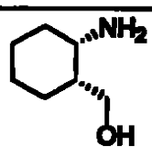
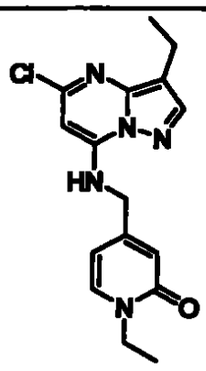
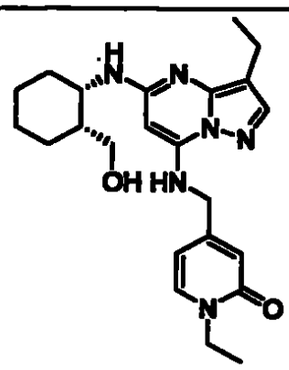
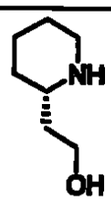
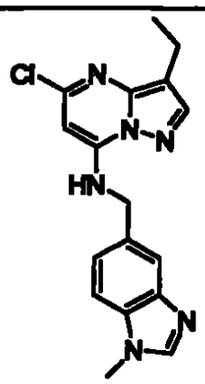
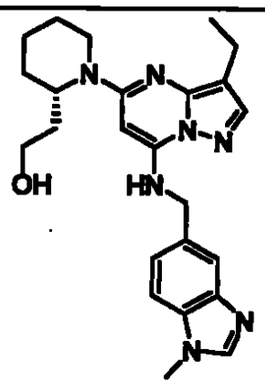
By essentially the same procedure set forth in Example 1000 only substituting the amines in Column 2 of Table 1000 and the chlorides in Column 3 of Table 1000 the compounds in column 4 of Table 1000 were prepared.

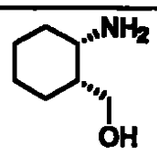
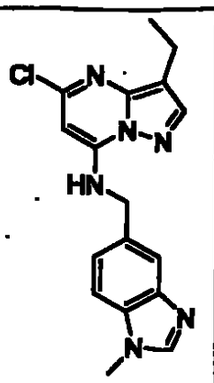
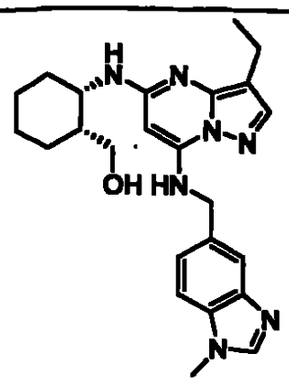
TABLE 1000

Ex.	Column 2	Column 3	Column 4	CMPD

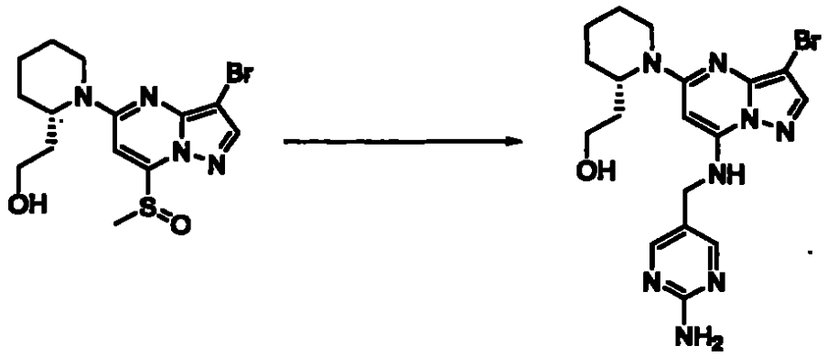
1002				MH^+ = 409; mp = 165-171 °C
1003				MH^+ = 397; mp = 219-221 °C
1004				MH^+ = 409; mp = 138-142 °C
1005				MH^+ = 411; mp = 194-196 °C

1006				MH^+ = 411; mp = 118-120 °C
1007				MH^+ = 411; mp = 86-87 °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:



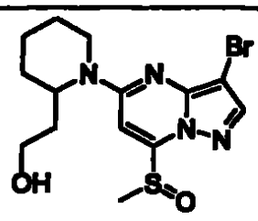
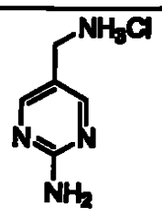
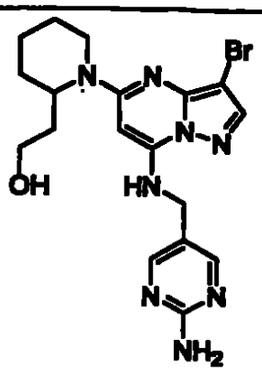
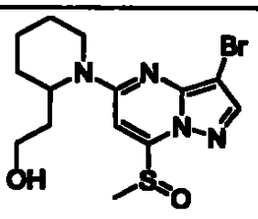
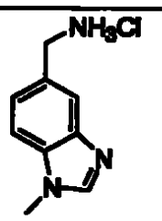
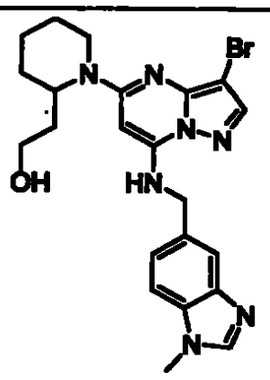
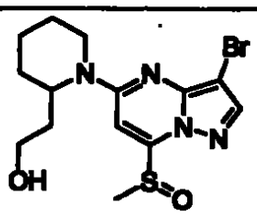
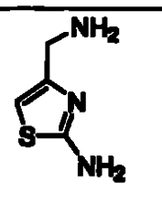
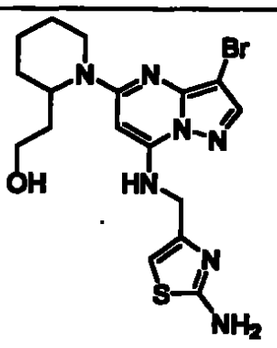
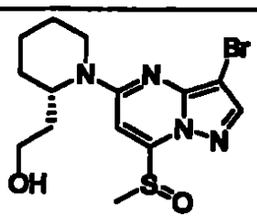
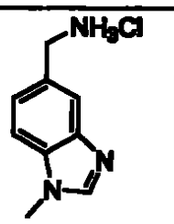
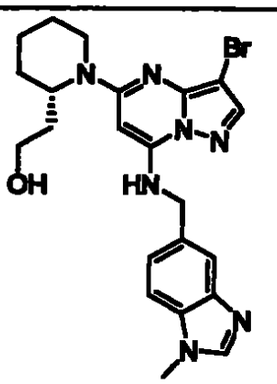
To a solution of sulfoxide from Preparative Example 505 (0.10 g, 0.28 mmol) in *n*-BuOH in a sealed tube was added Et_3N (0.13 mL, 1.0 mmol) followed by the amine dihydrochloride (0.13 g, 0.65 mmol) from Preparative Example 216. The tube was sealed and was heated to 100 °C, cooled to room temperature, 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.

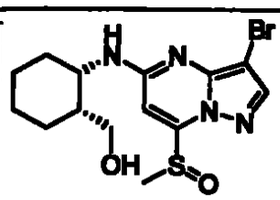
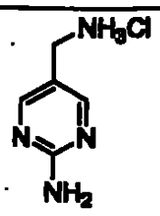
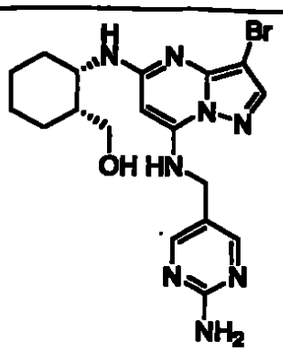
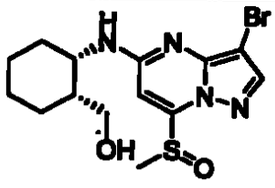
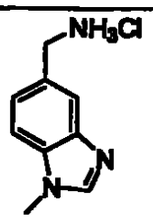
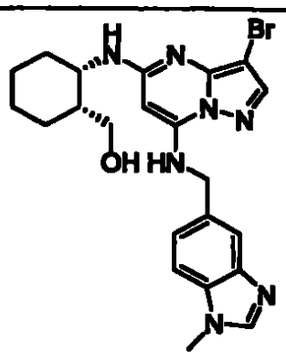
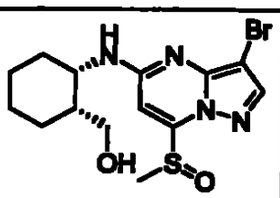
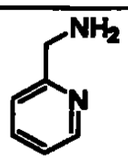
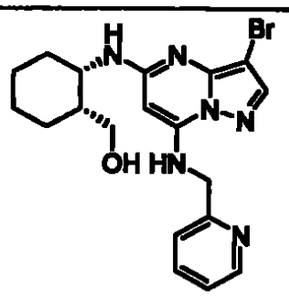
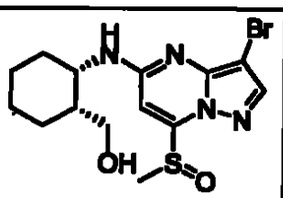
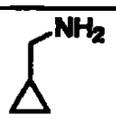
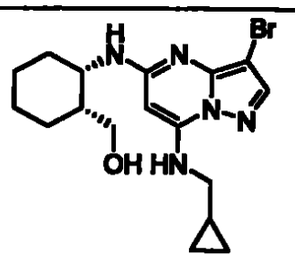
EXAMPLES 1016-1026:

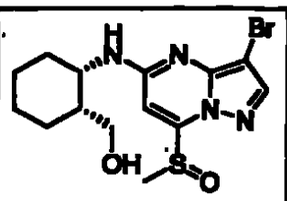
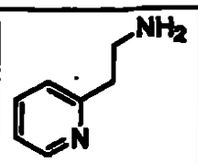
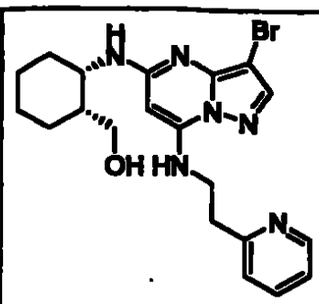
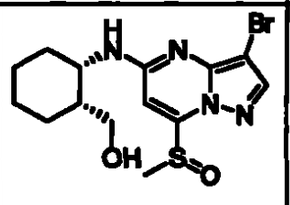
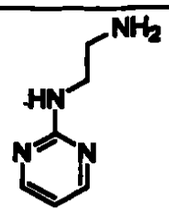
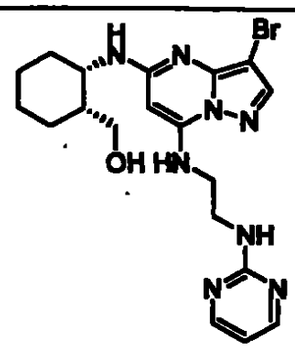
By essentially the same procedure set forth in Example 1015 only substituting the sulfoxide shown in Column 2 of Table 1001 and the amine in Column 3 of Table 1001, the compounds shown in Column 4 of Table 1001 were prepared.

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

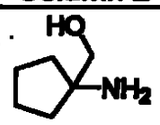
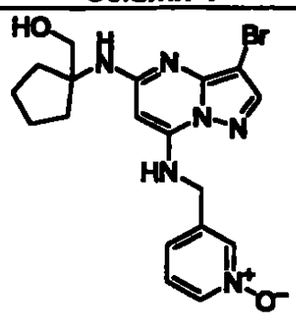
1021				mp = 154-157 °C; M+H = 448
1022				mp = 103-105 °C; M+H = 485
1023	 (±)		 (±)	mp = 203-205 °C; M+H = 432
1024	 (±)		 (±)	mp = 210-212 °C; M+H = 395

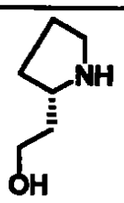
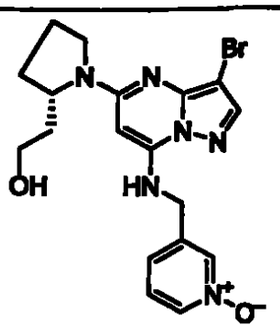
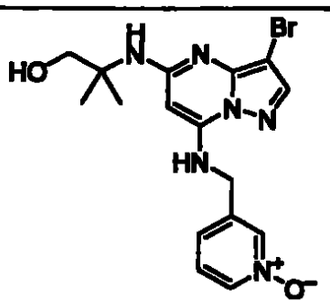
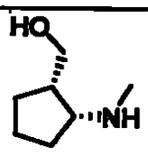
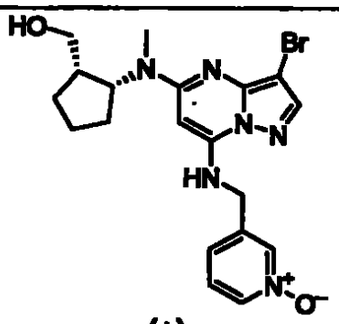
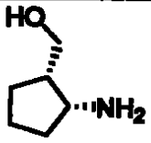
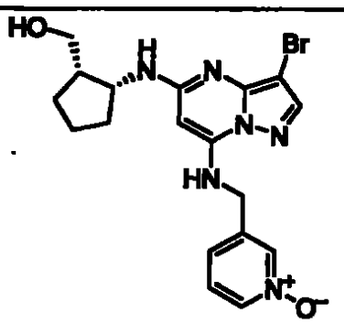
1025	 (±)		 (±)	mp = 82-84 °C; M+H = 448
1026	 (±)		 (±)	mp = 88-90 °C; M+H = 462

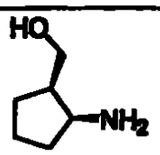
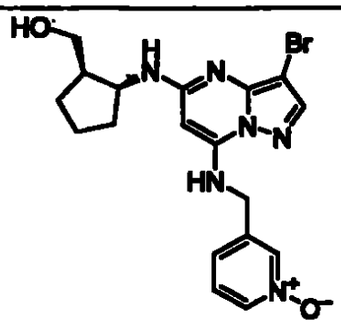
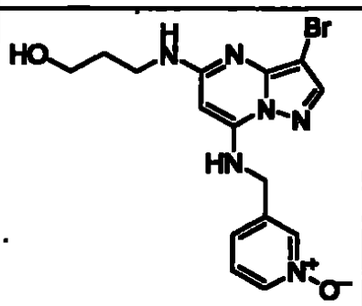
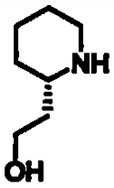
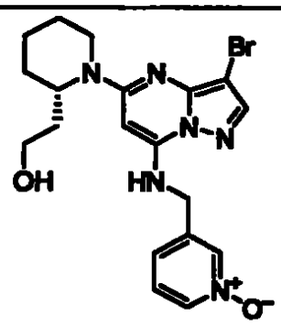
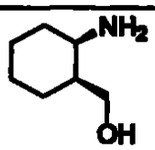
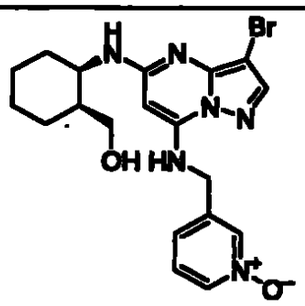
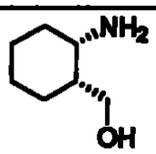
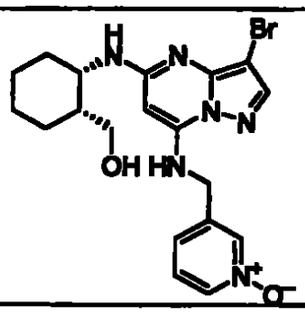
EXAMPLES 1027-1038:

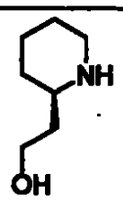
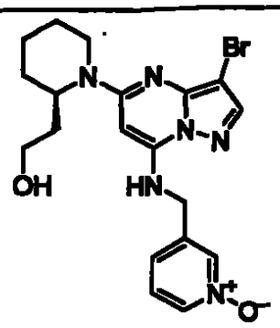
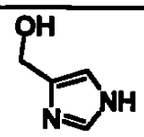
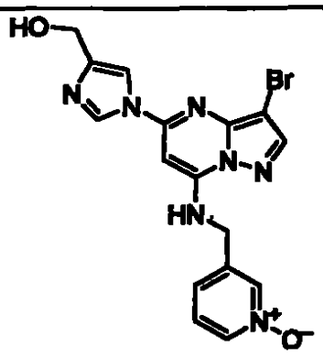
By essentially the same conditions set forth in Example 341, Steps A and B only substituting the amines in Column 2 of Table 1002 and the compound prepared in Preparative Example 193.10, the compounds in Column 4 of Table 1002 were prepared.

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

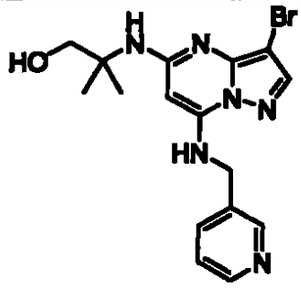
1032			mp = 167-168 °C; M+H = 434
1033			MH^+ = 393
1034			mp = 157-160 °C; M+H = 447
1035			mp = 164-168 °C; M+H = 448
1036			mp = 165-168 °C; M+H = 448

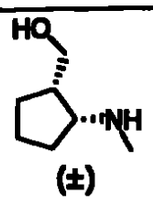
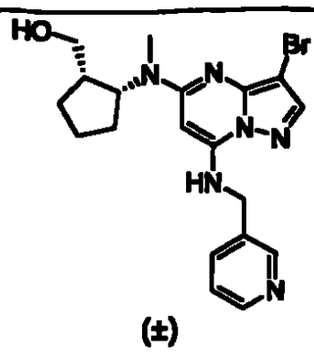
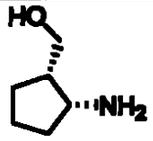
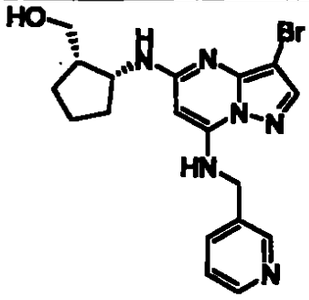
1037			mp = 131-135 °C; M+H = 447
1038			

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

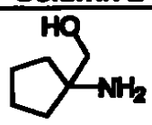
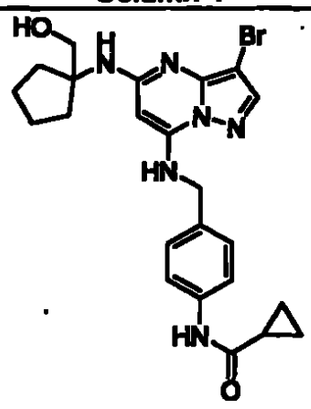
Ex.	Column 2	Column 4	CMPD
1039			mp = 210-212 °C; M+H = 392

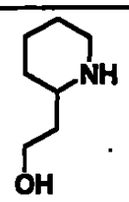
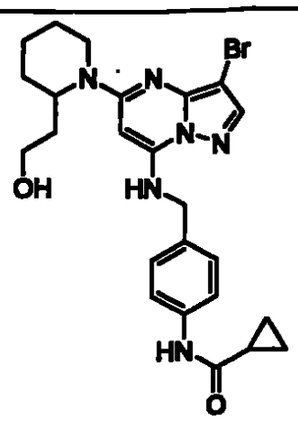
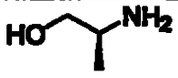
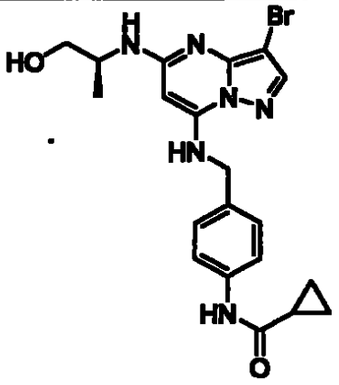
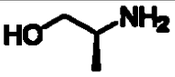
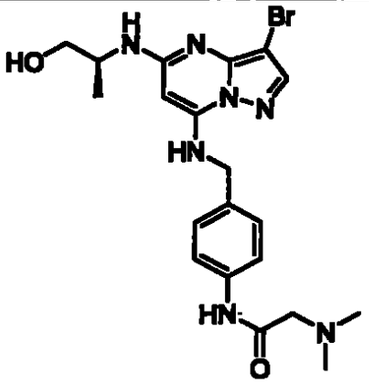
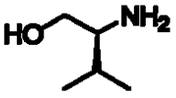
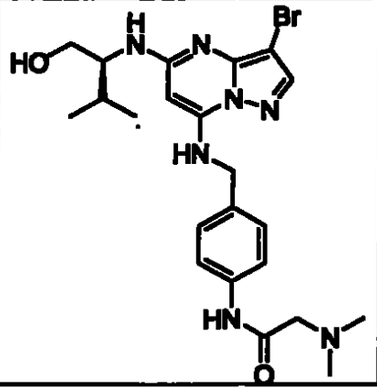
1040	 (±)	 (±)	mp = 128-130 °C; M+H = 432
1041			mp = 148-151 °C; M+H = 18

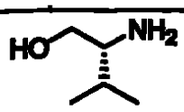
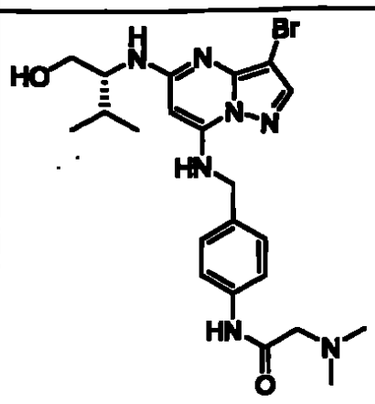
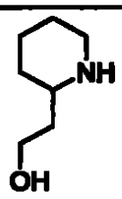
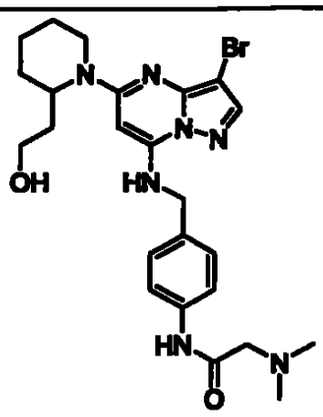
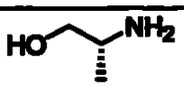
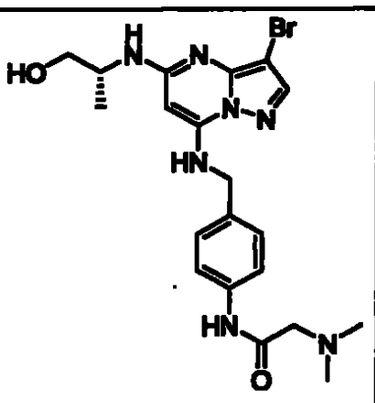
EXAMPLES 1042-1057:

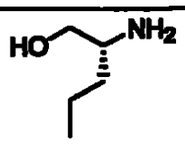
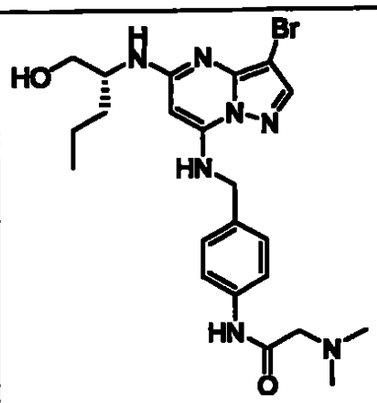
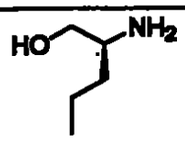
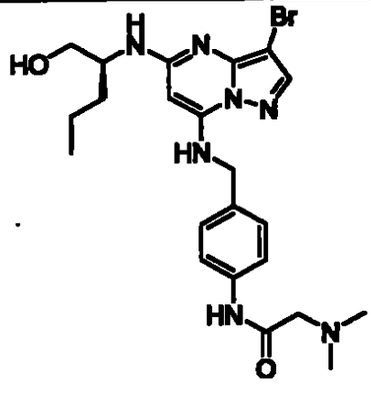
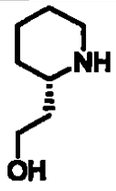
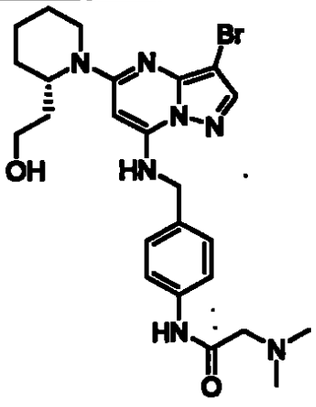
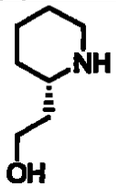
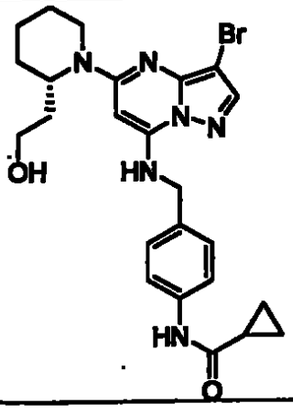
By essentially the same procedure set forth in Example 340 only using the appropriate 5-chloroderivative and substituting the amines in Column 2 of Table 1004, the compounds shown in Column 4 of Table 1004 were prepared.

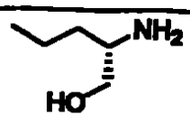
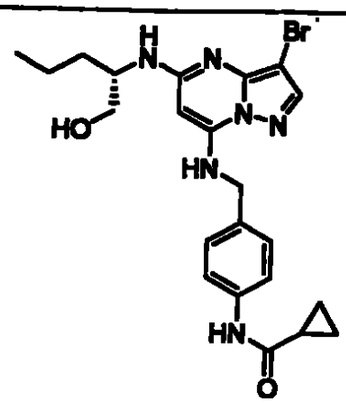
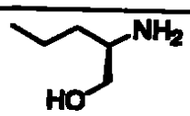
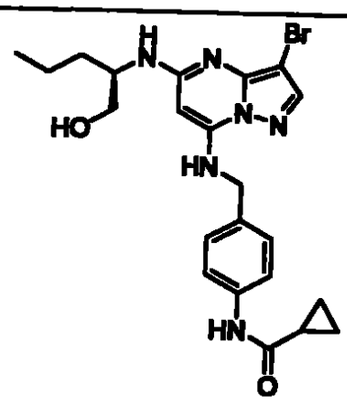
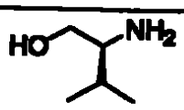
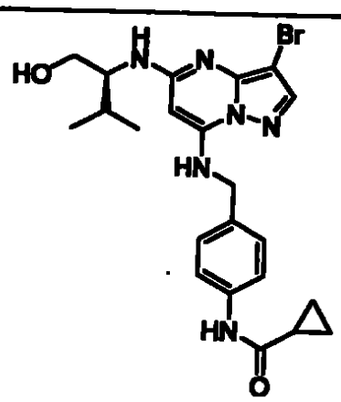
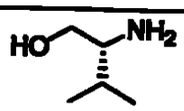
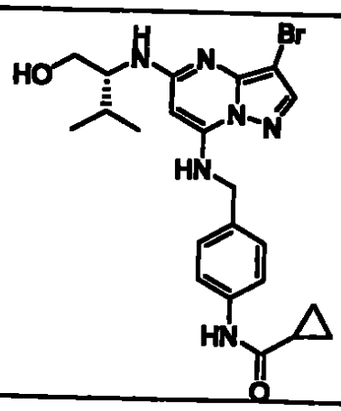
TABLE 1004

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

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.

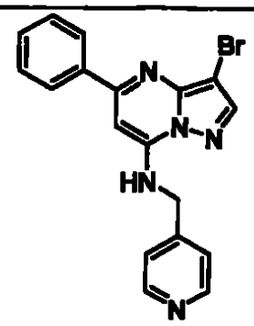
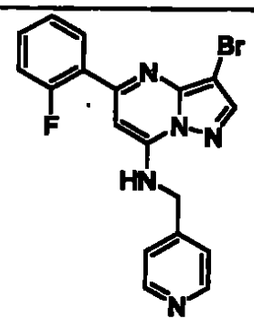
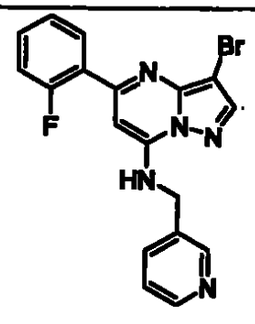
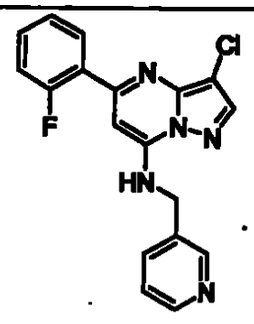
IN VITRO KINASE ASSAY: CDK2 kinase assays (either cyclin A or E-dependent) were performed in low protein binding 96-well plates (Corning Inc, Corning, New York). Enzyme was diluted to a final concentration of 50 μg/ml in kinase buffer containing 50mM Tris pH 8.0, 10mM $MgCl_2$, 1mM DTT, and 0.1mM

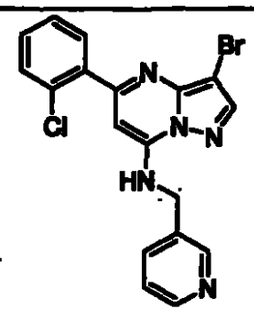
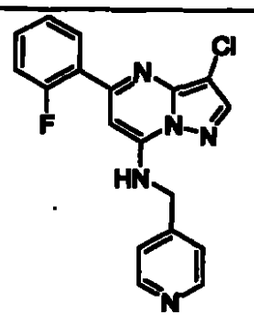
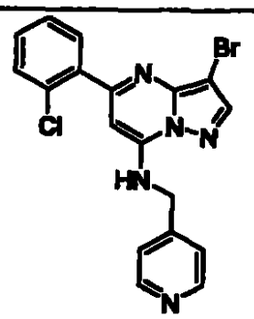
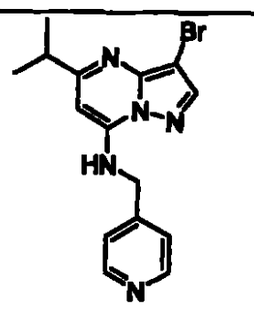
sodium orthovanadate. The substrate used in these reactions was a biotinylated peptide derived from Histone H1 (from Amersham, UK). The substrate was thawed on ice and diluted to 2 μM in kinase buffer. Compounds were diluted in 10%DMSO to desirable concentrations. For each kinase reaction, 20 μl of the 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).

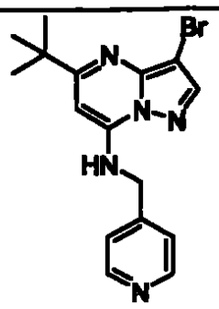
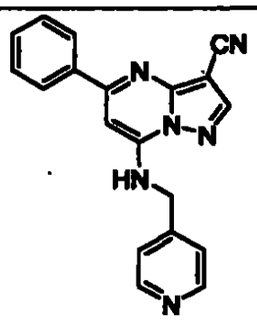
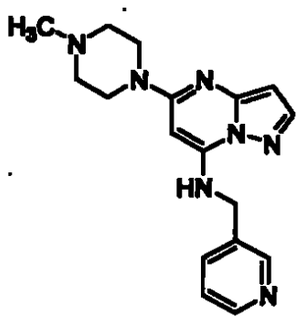
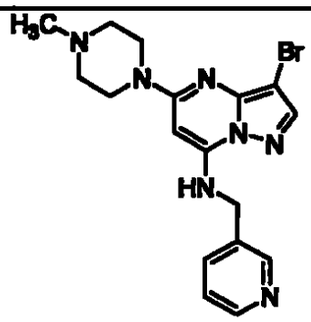
IC_{50} DETERMINATION: Dose-response curves were plotted from inhibition data generated, each in duplicate, from 8 point serial dilutions of inhibitory compounds. Concentration of compound was plotted against % kinase activity, calculated by CPM of treated samples divided by CPM of untreated samples. 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

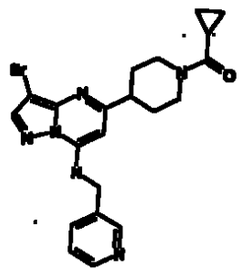
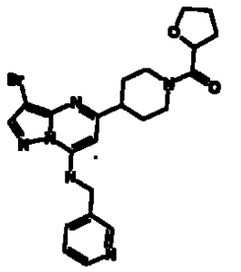
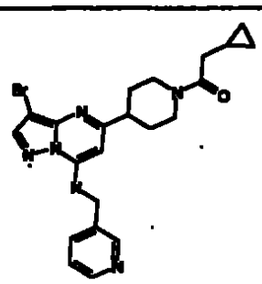
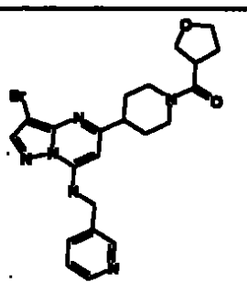
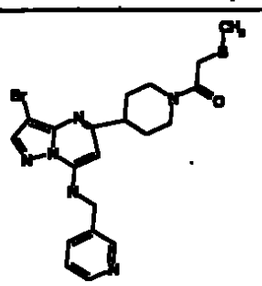
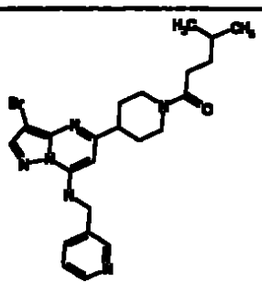
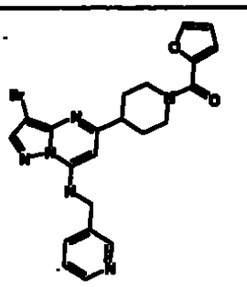
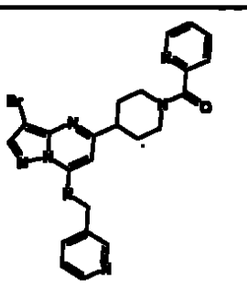
	8	0.003
	6	0.064 0.029
	7	0.01 0.006
	10	0.042

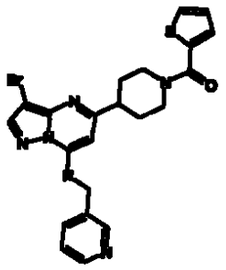
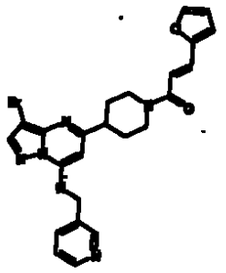
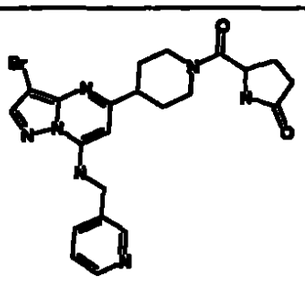
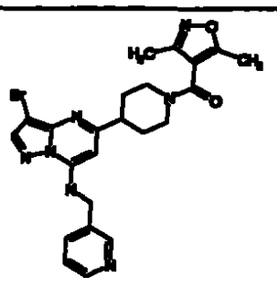
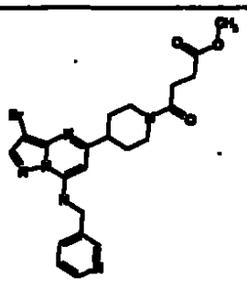
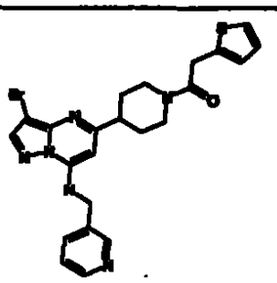
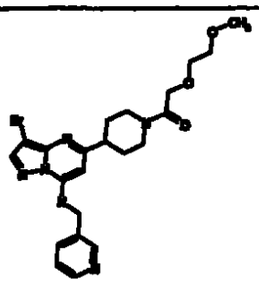
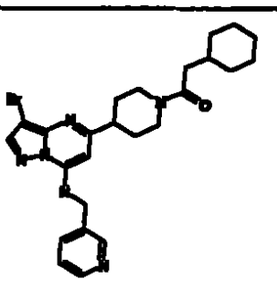
	12	0.17
	16	0.62
	1	5.6
	3	0.14

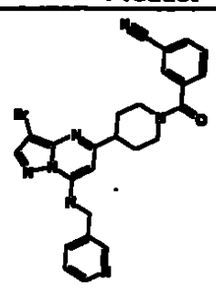
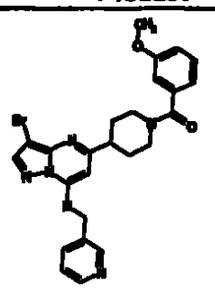
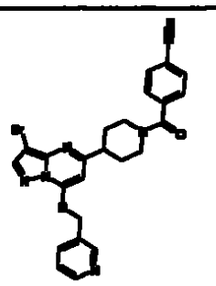
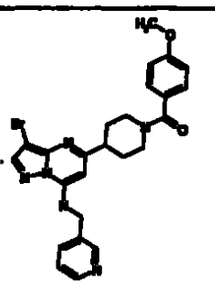
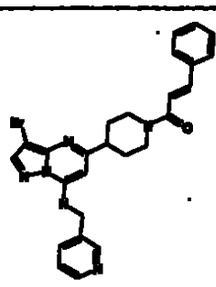
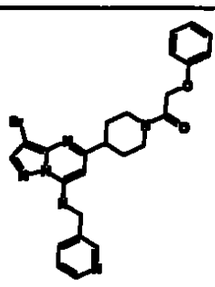
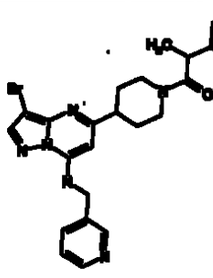
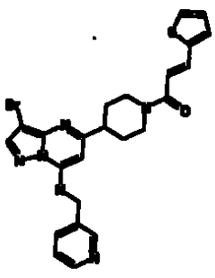
As demonstrated above by the assay values, the compounds of the present invention exhibit excellent CDK inhibitory properties.

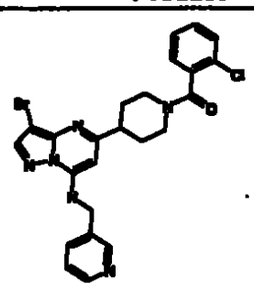
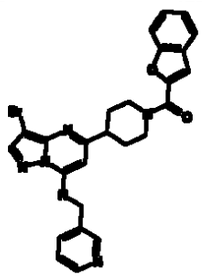
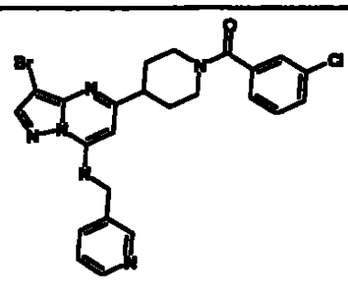
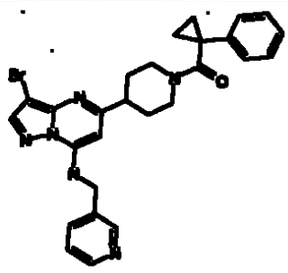
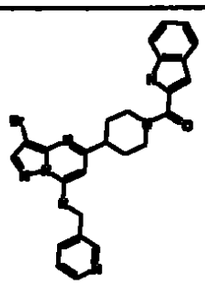
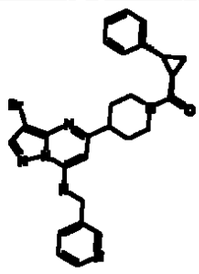
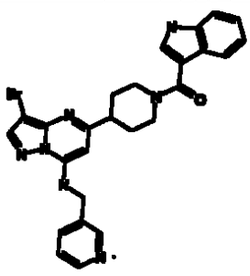
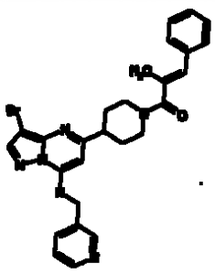
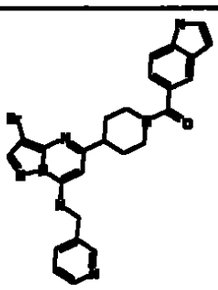
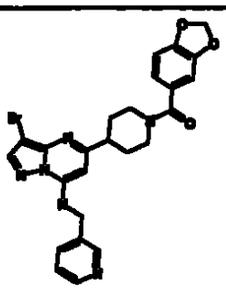
While the present invention has been described with in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

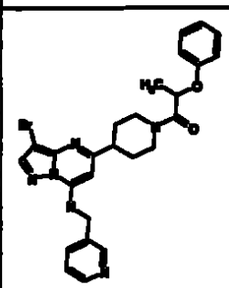
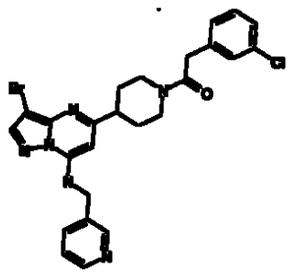
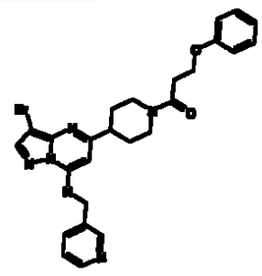
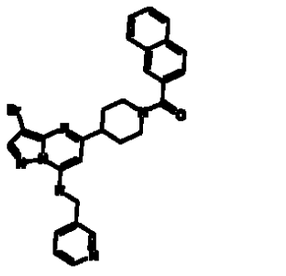
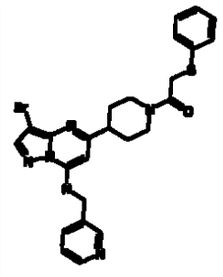
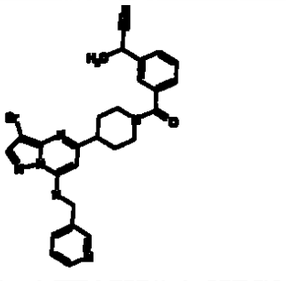
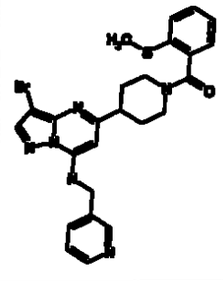
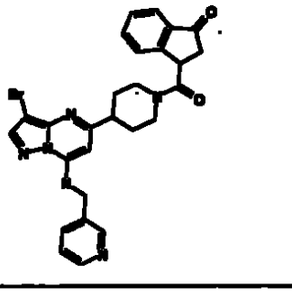
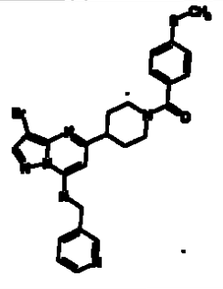
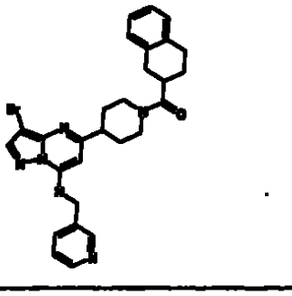
TABLE 43

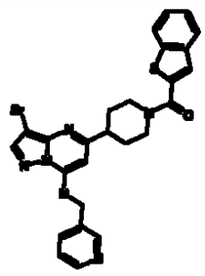
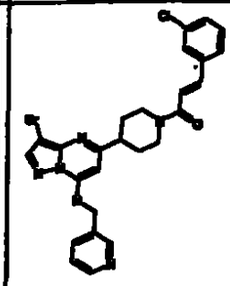
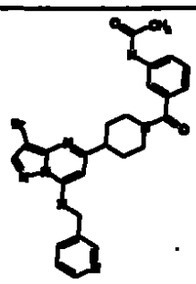
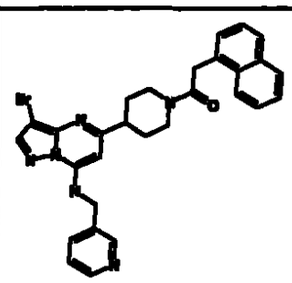
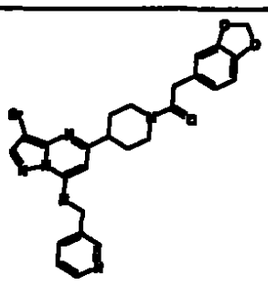
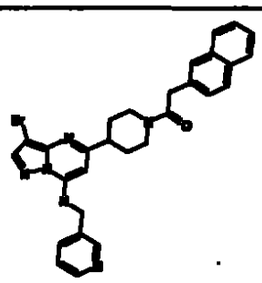
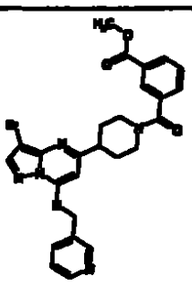
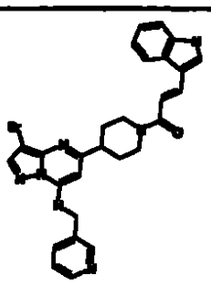
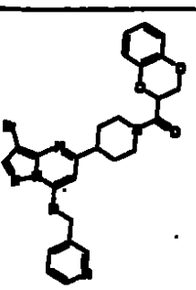
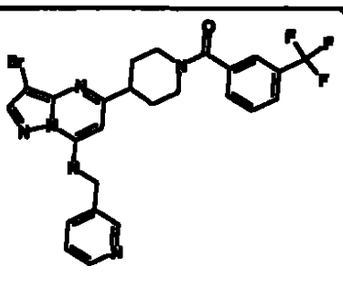
Ex.	Compound	m/z	Ex.	Compound	m/z
4301		457.25	4305		487.27
4302		471.26	4306		487.27
4303		477.26	4307		487.27
4304		483.27	4308		494.27

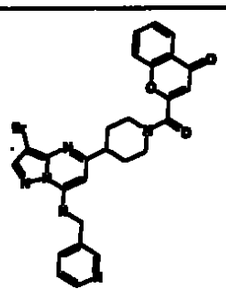
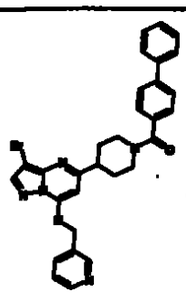
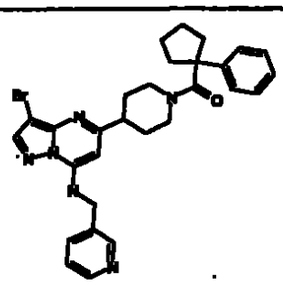
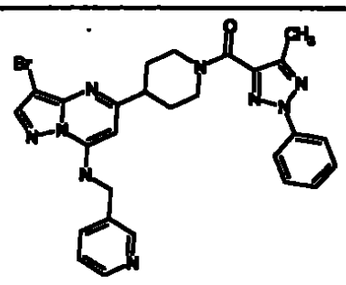
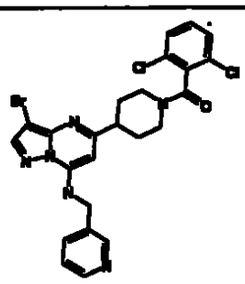
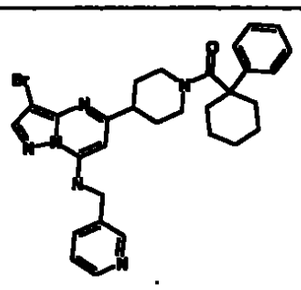
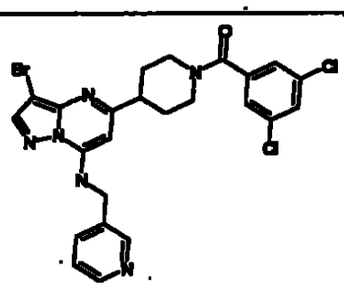
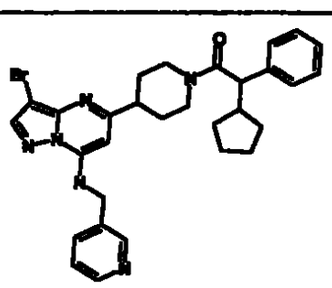
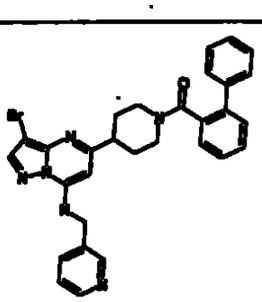
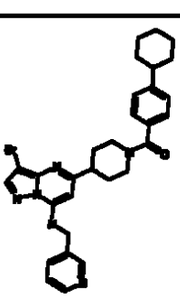
Ex.	Product	m/z	Ex.	Product	m/z
4309		499.27	4313		509.28
4310		500.27	4314		512.28
4311		503.28	4315		513.28
4312		505.28	4316		513.28

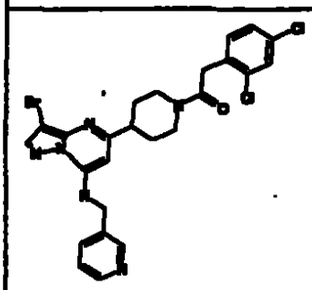
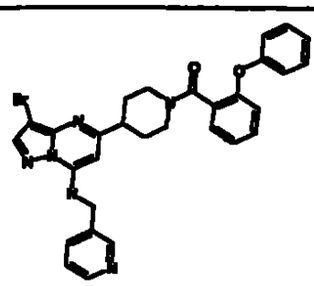
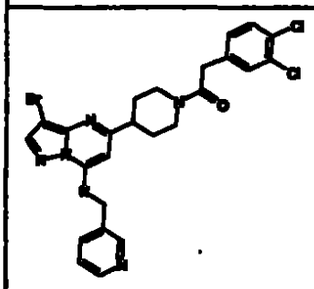
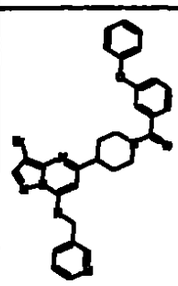
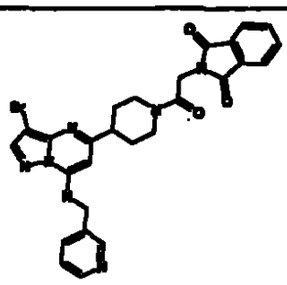
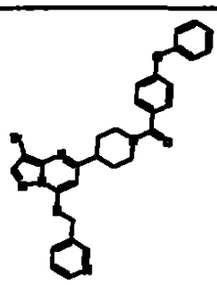
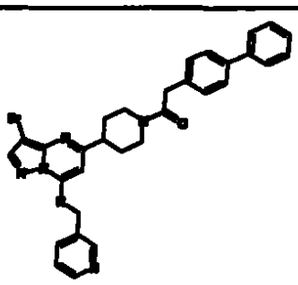
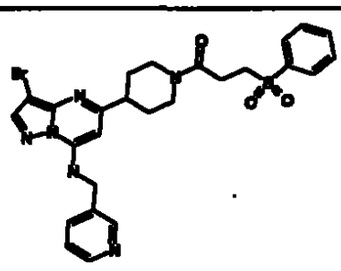
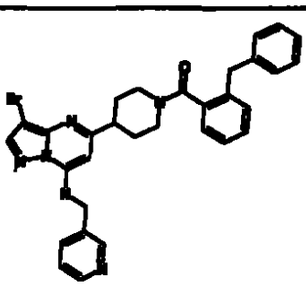
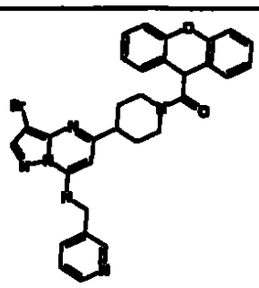
Ex.	Product	m/z	Ex.	Product	m/z
4317		518.28	4321		523.29
4318		518.28	4322		523.29
4319		519.29	4323		523.29
4320		521.29	4324		525.29

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. 548.3
	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. 563.3
	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. 581.31

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
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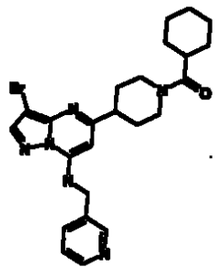
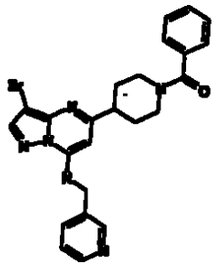
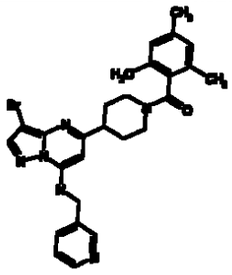
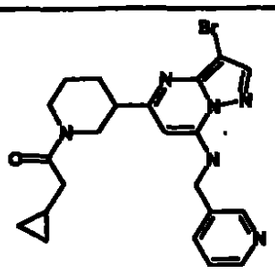
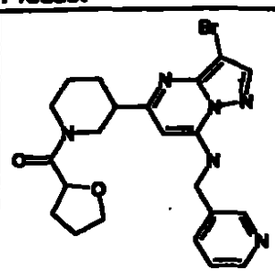
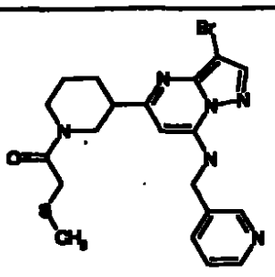
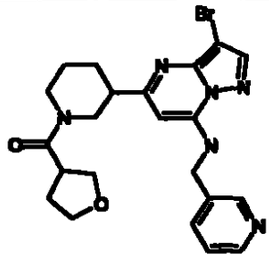
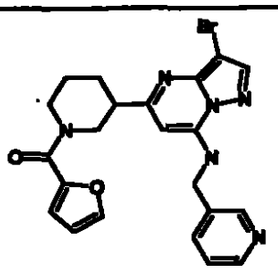
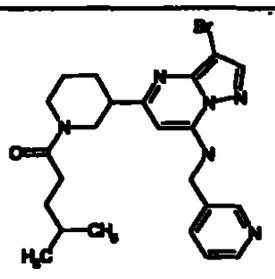
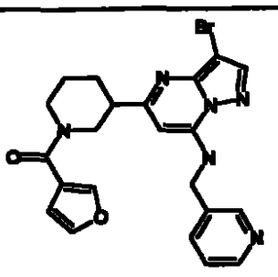
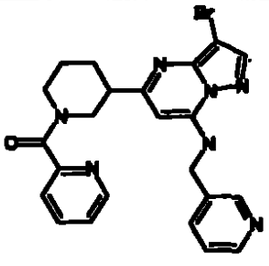
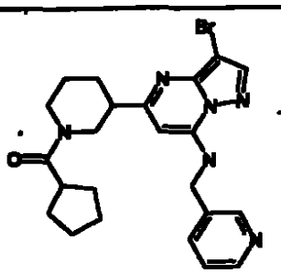
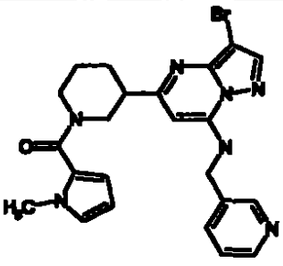
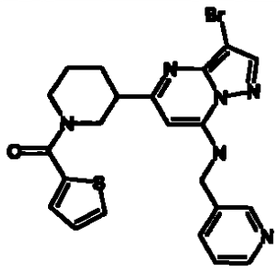
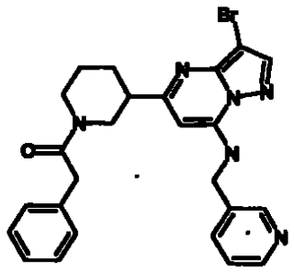
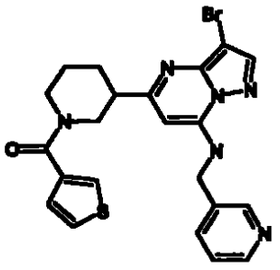
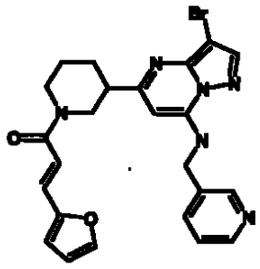
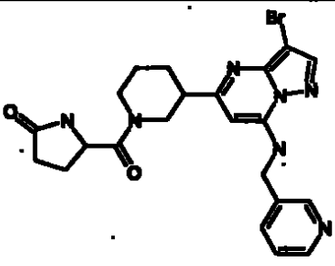
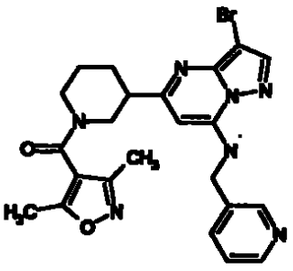
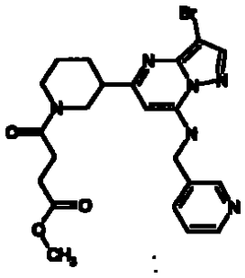
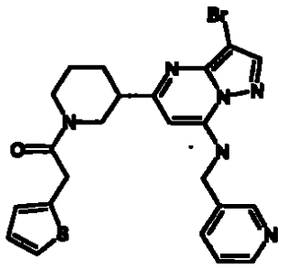
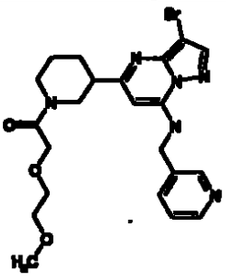
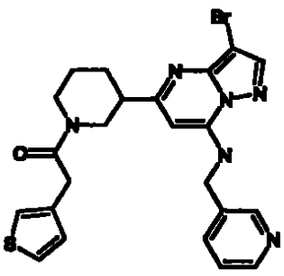
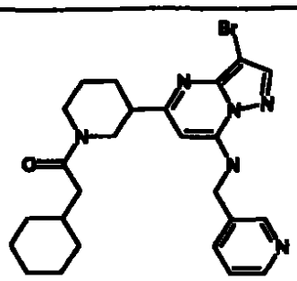
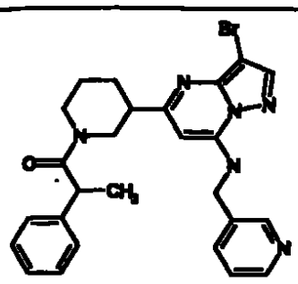
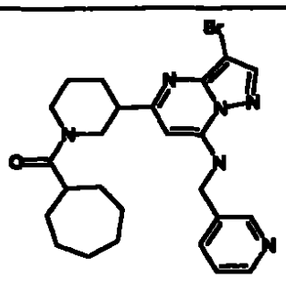
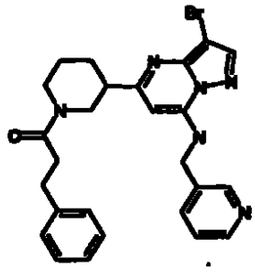
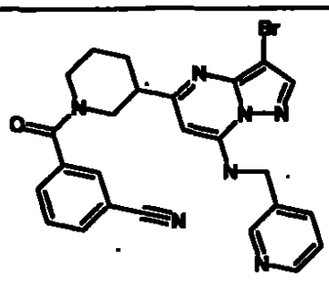
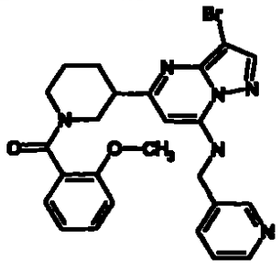
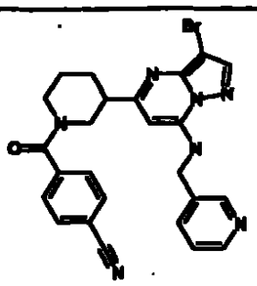
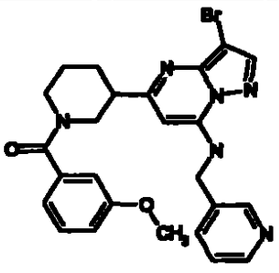
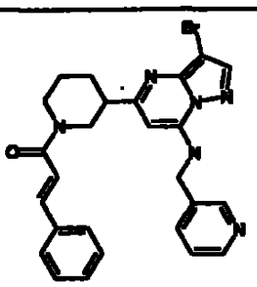
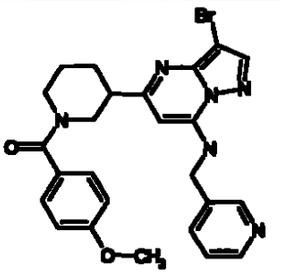
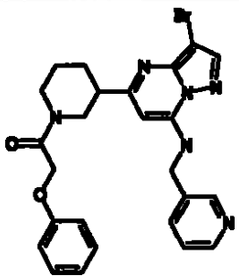
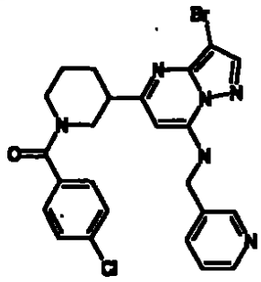
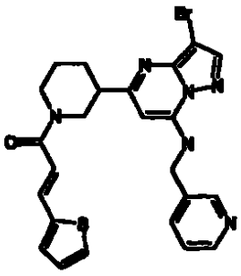
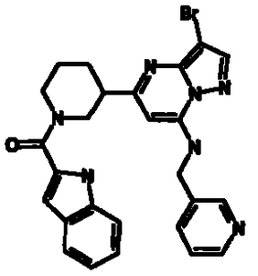
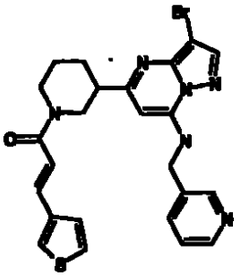
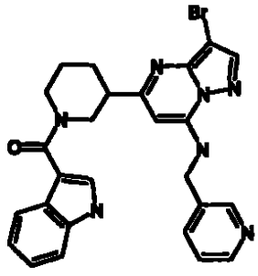
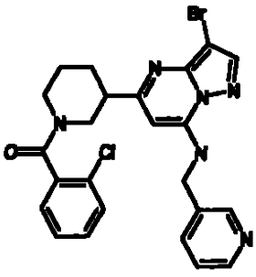
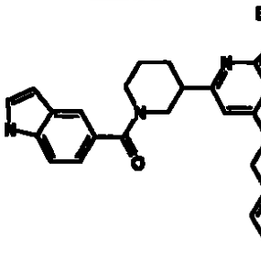
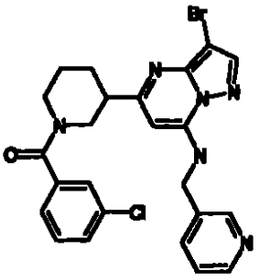
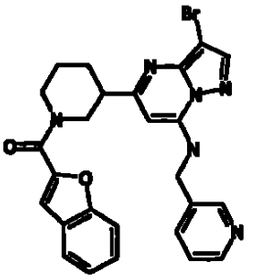
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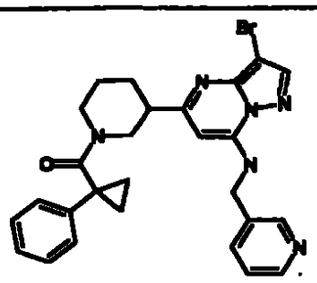
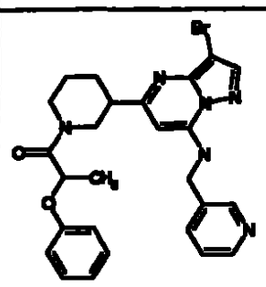
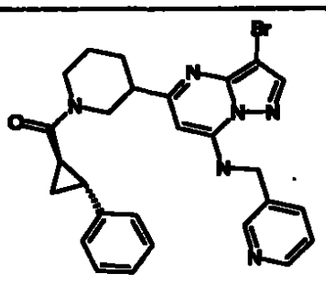
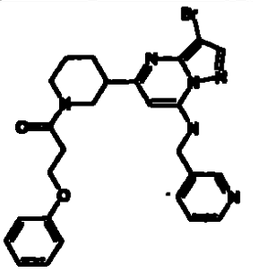
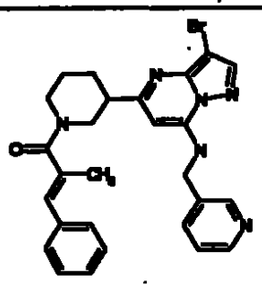
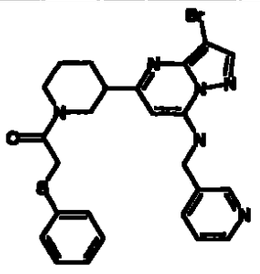
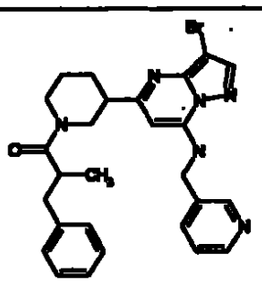
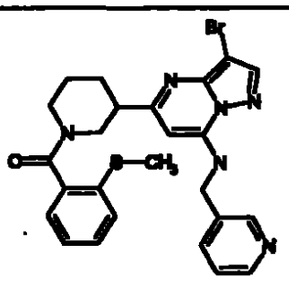
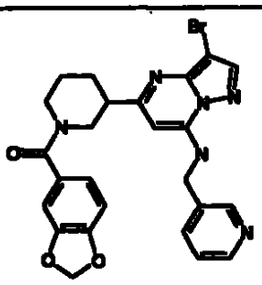
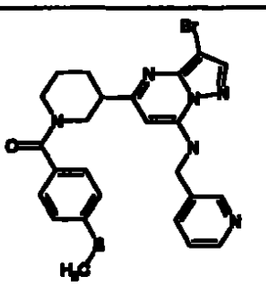
TABLE 44

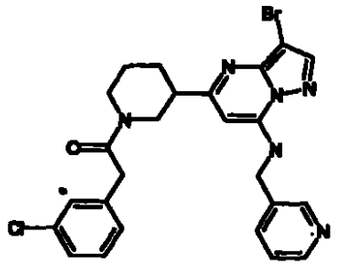
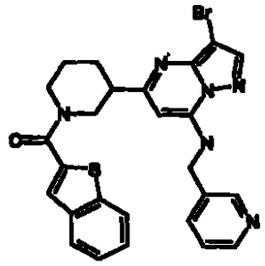
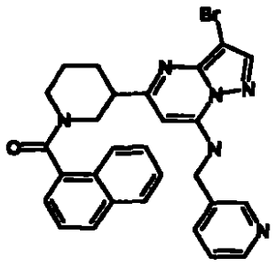
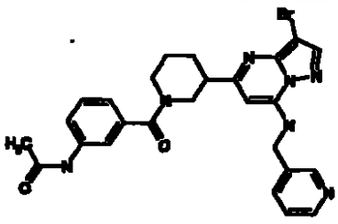
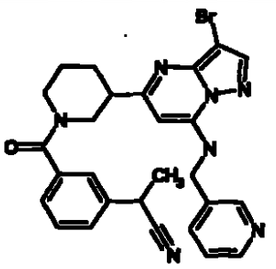
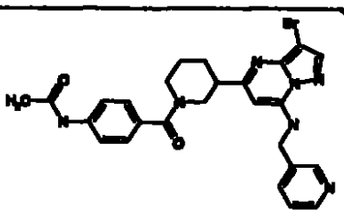
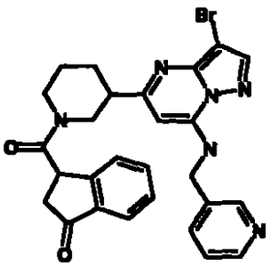
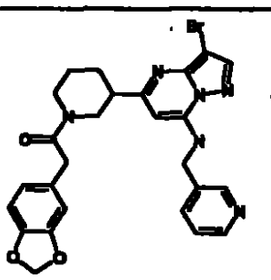
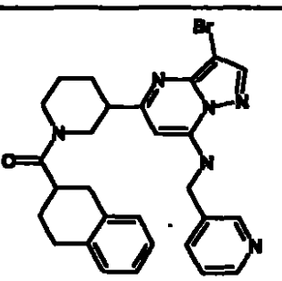
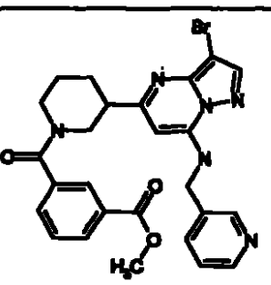
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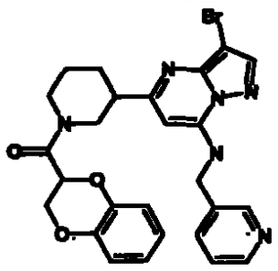
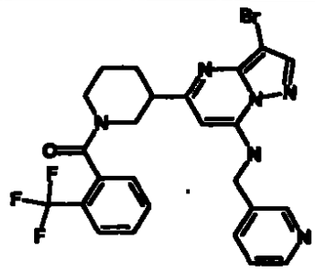
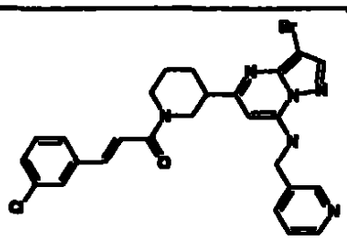
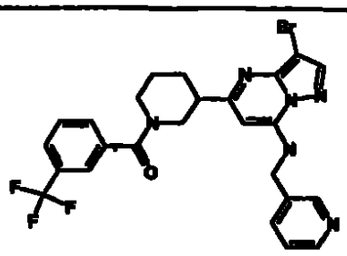
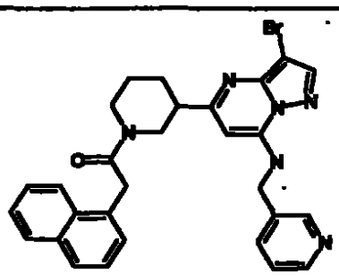
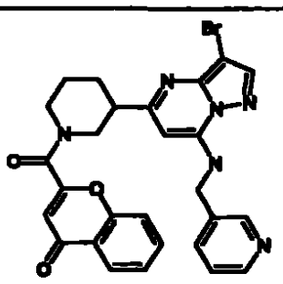
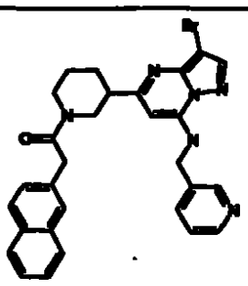
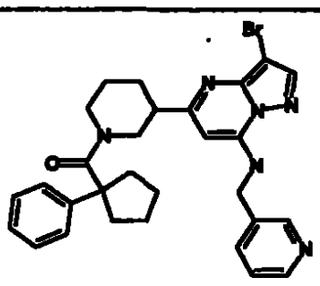
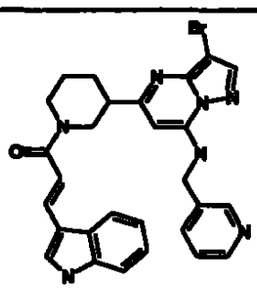
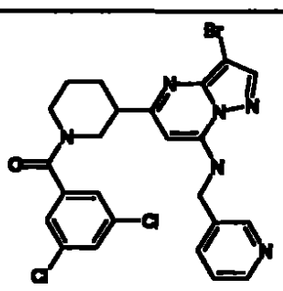
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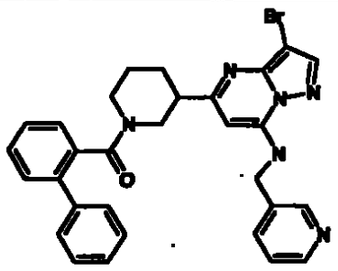
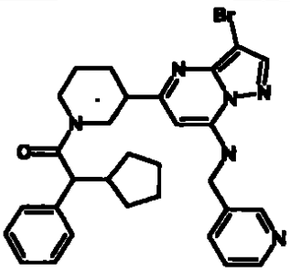
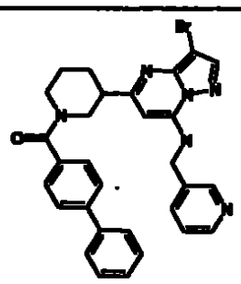
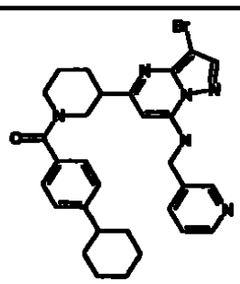
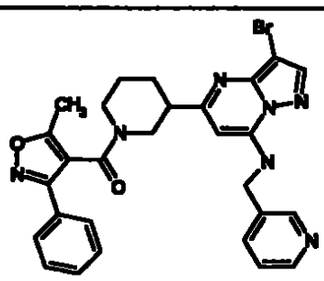
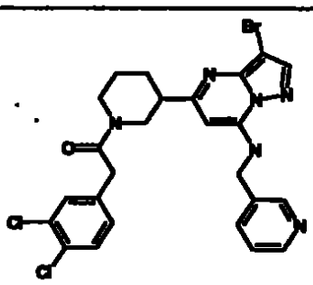
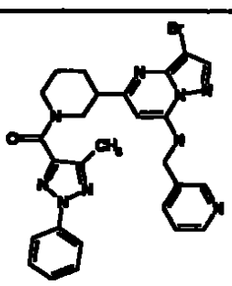
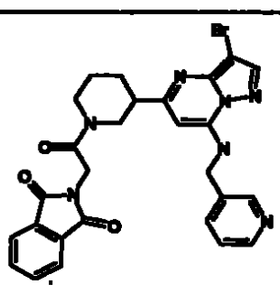
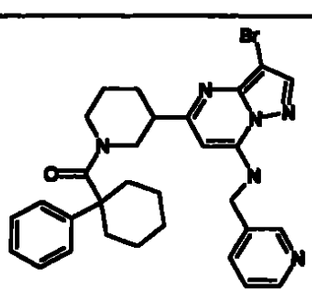
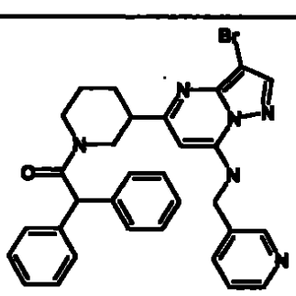
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	1. 4421 2. 513.28			1. 4426 2. 521.29
	1. 4422 2. 513.28			1. 4426 2. 521.29
	1. 4423 2. 518.28			1. 4428 2. 523.29
	1. 4424 2. 518.28			1. 4429 2. 523.29
	1. 4425 2. 519.3			1. 4430 2.523.29

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

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

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
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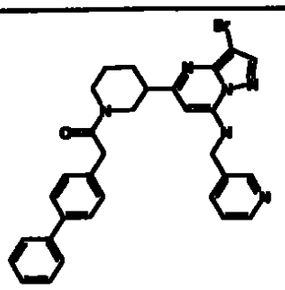
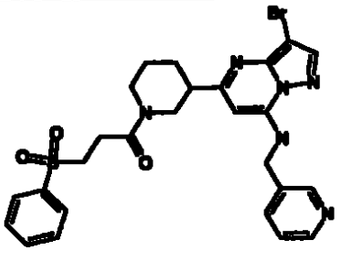
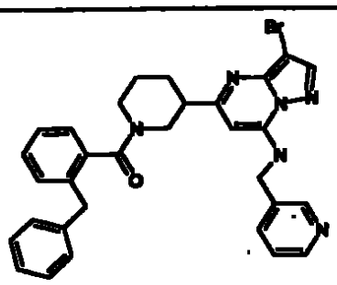
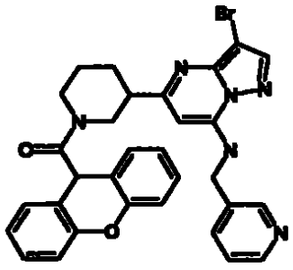
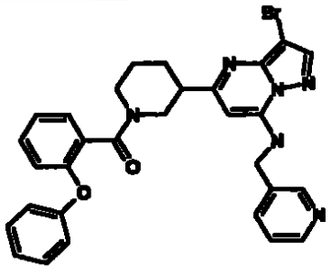
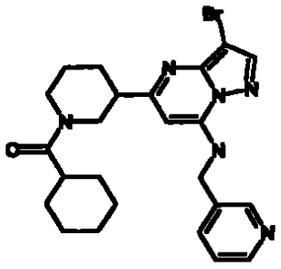
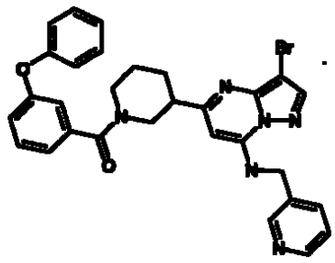
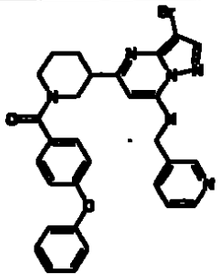
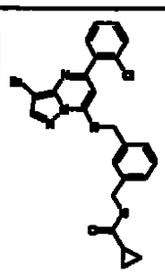
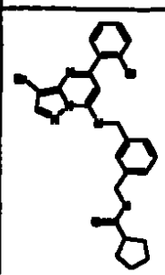
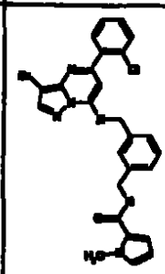
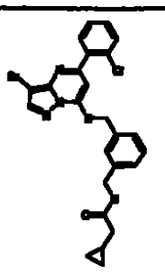
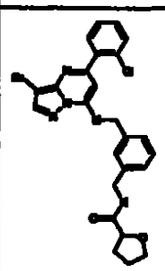
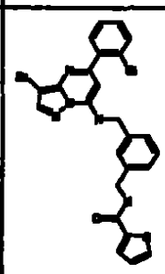
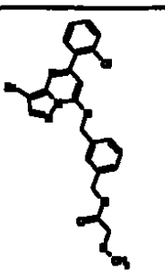
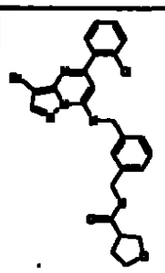
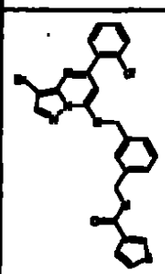
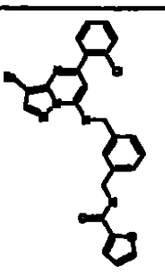
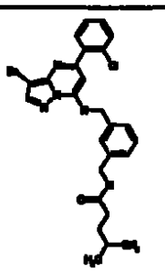
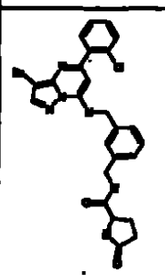
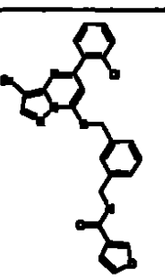
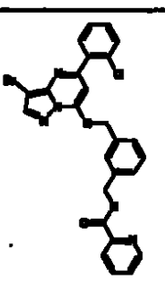
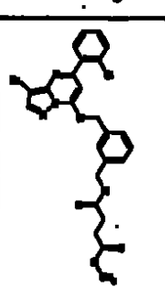
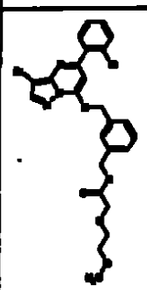
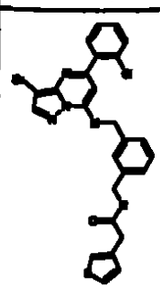
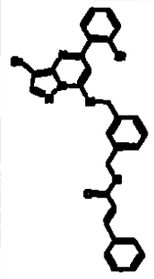
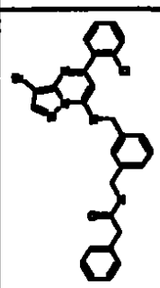
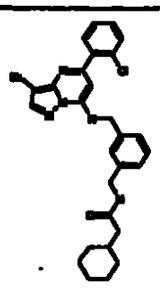
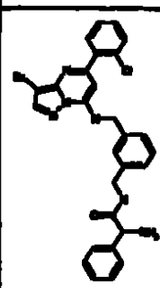
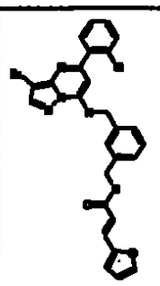
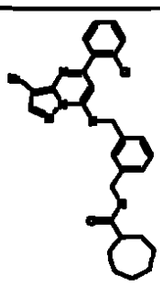
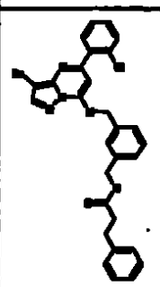
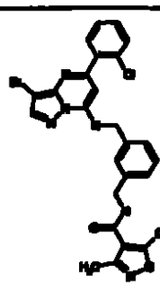
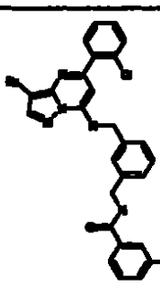
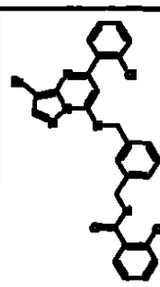
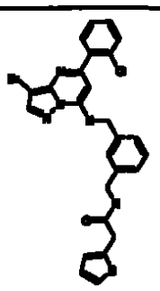
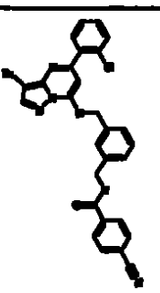
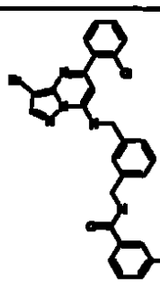
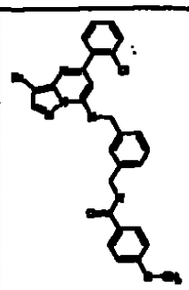
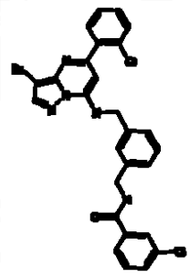
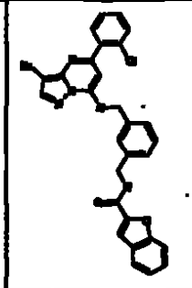
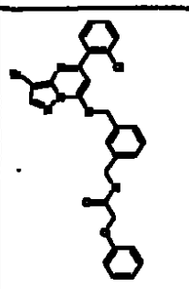
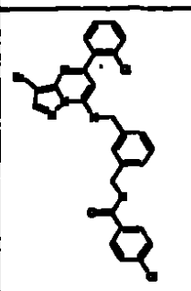
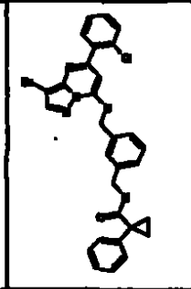
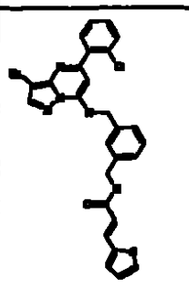
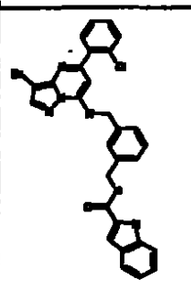
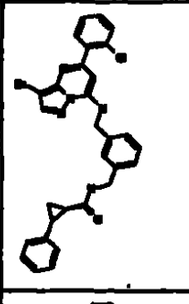
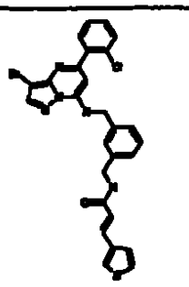
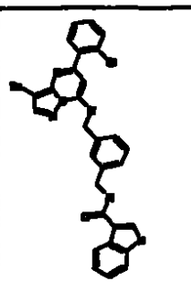
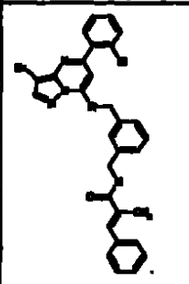
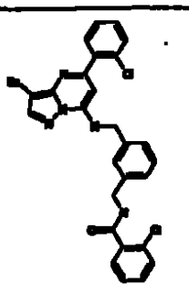
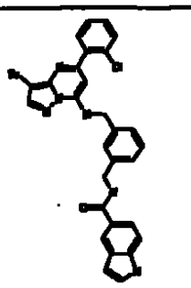
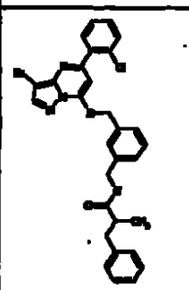
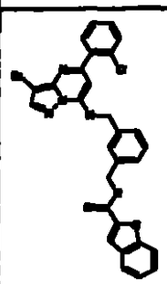
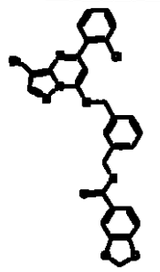
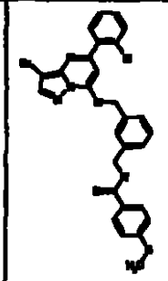
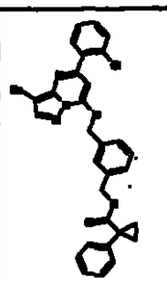
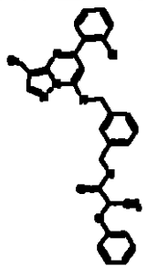
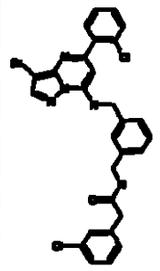
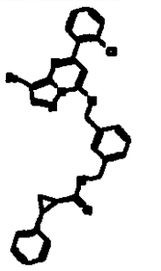
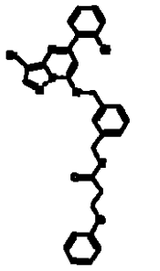
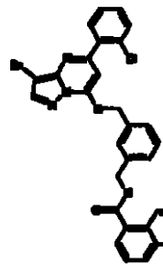
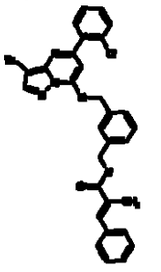
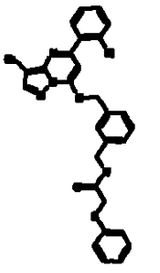
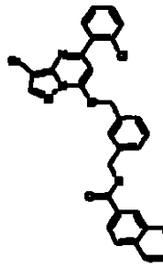
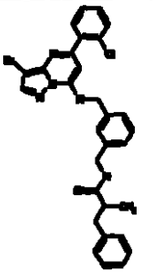
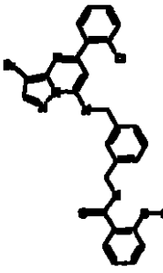
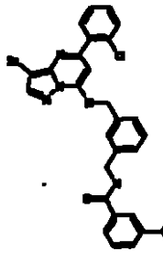
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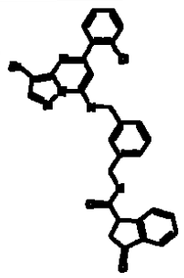
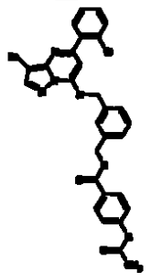
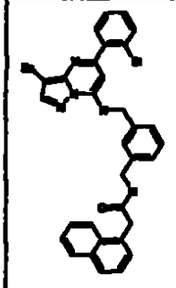
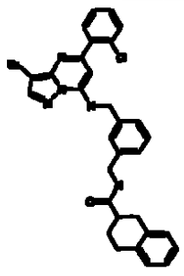
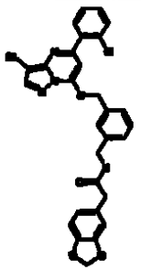
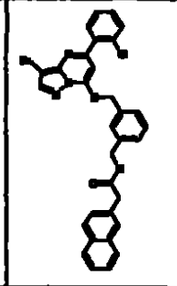
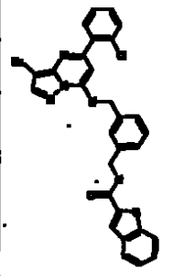
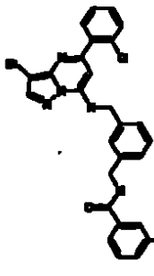
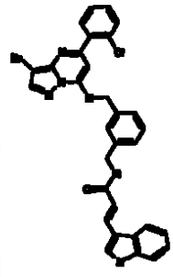
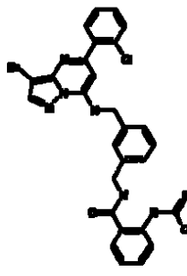
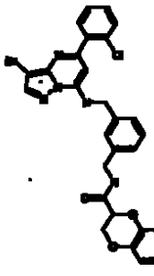
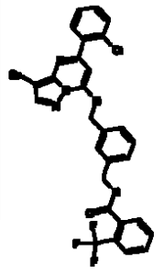
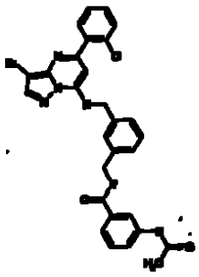
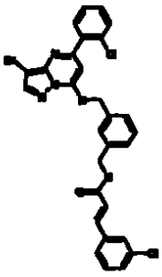
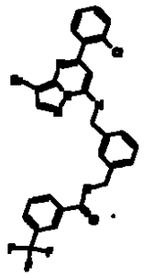
TABLE 45

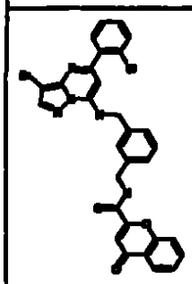
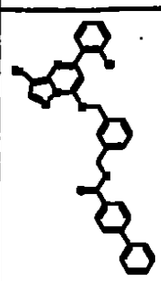
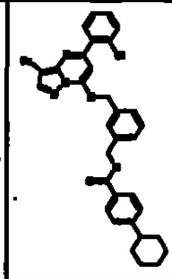
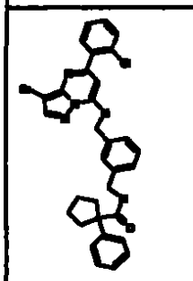
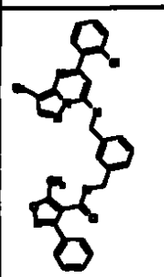
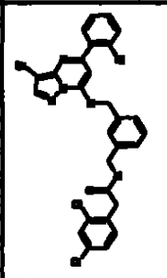
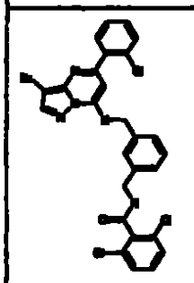
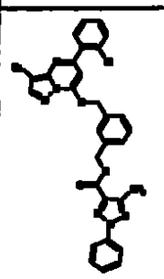
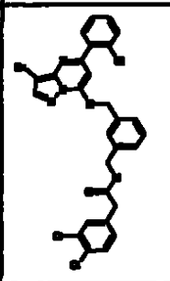
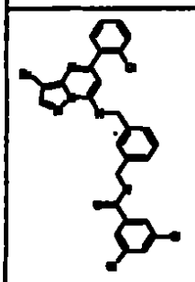
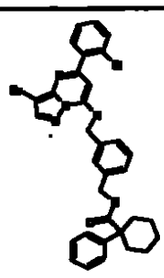
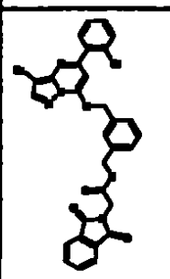
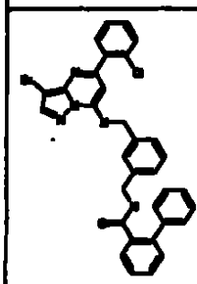
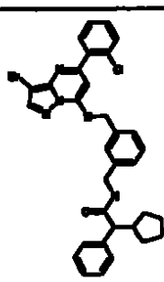
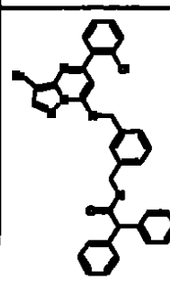
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	1. 4502 2. 526.29		1. 4507 2. 542.3		1. 4512 2. 554.3
	1. 4503 2. 532.29		1. 4508 2. 542.3		1. 4513 2. 554.3
	1. 4504 2. 538.3		1. 4509 2. 542.3		1. 4514. 2. 555.31
	1. 4505 2. 538.3		1. 4510 2. 549.3		1. 4515 2. 558.31

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. 586.32		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. 596.33
	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. Ex. 2. m/z
	1. 4561 2. 602.33		1. 4566 2. 606.33		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. 606.33		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
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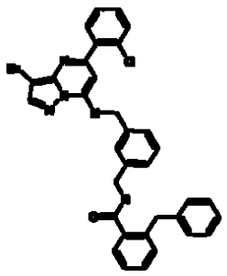
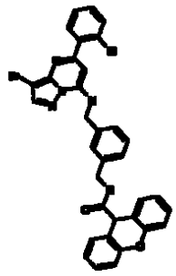
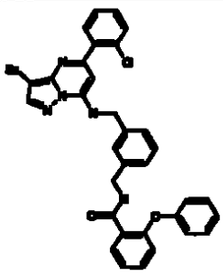
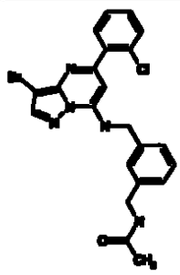
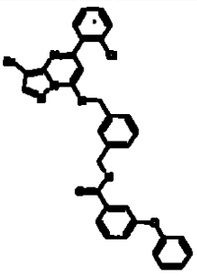
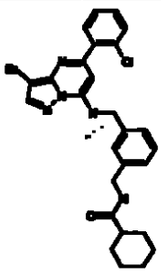
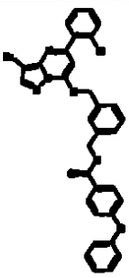
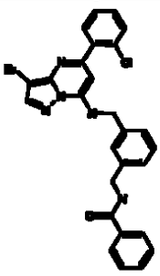
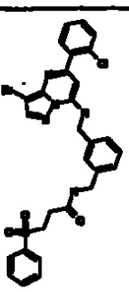
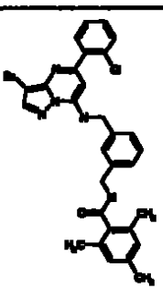
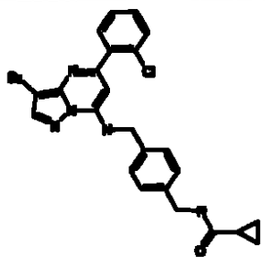
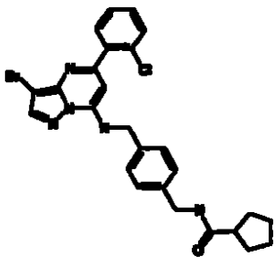
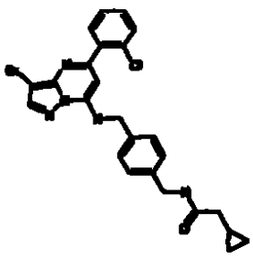
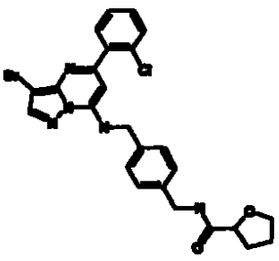
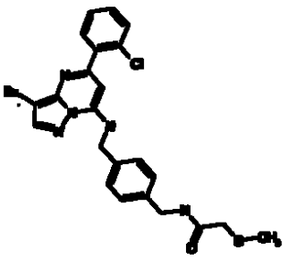
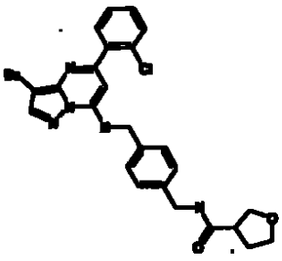
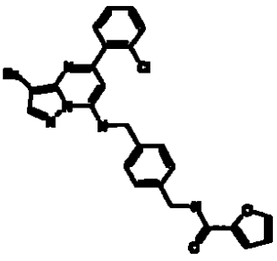
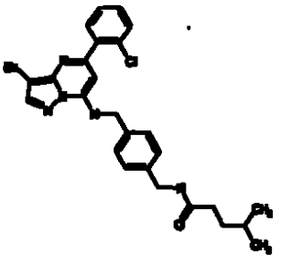
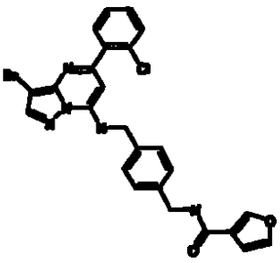
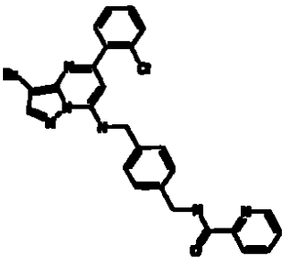
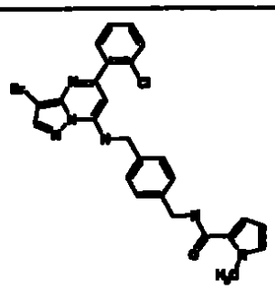
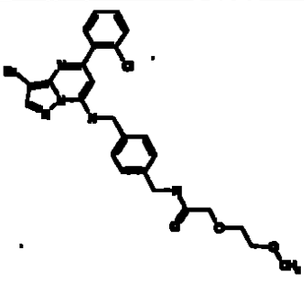
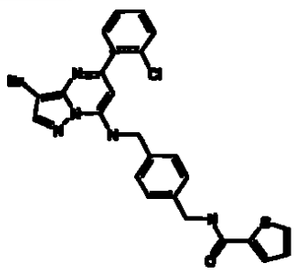
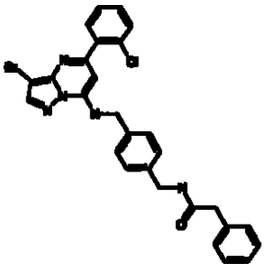
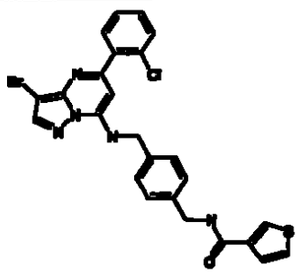
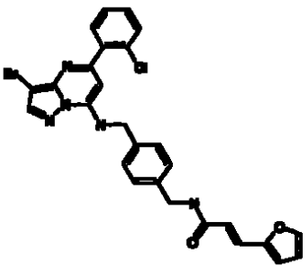
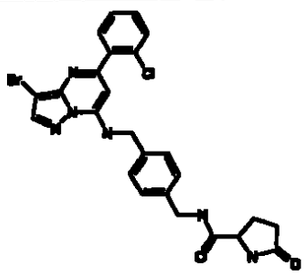
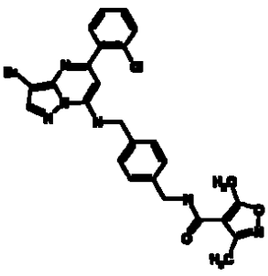
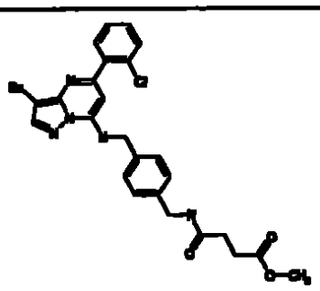
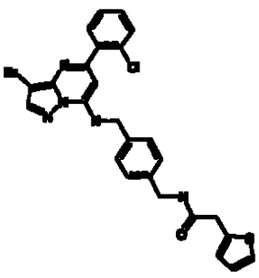
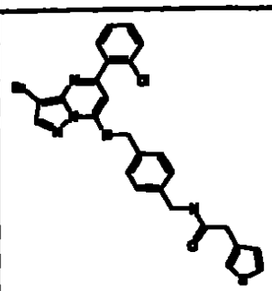
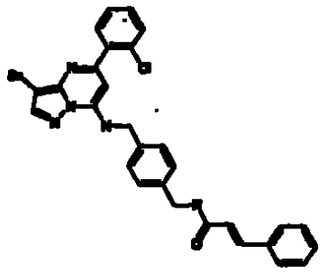
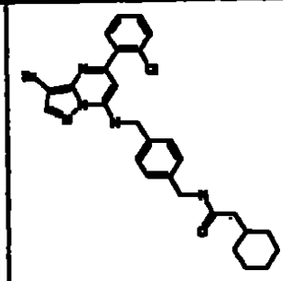
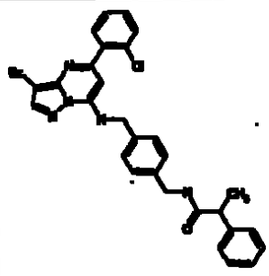
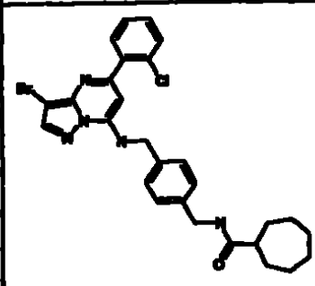
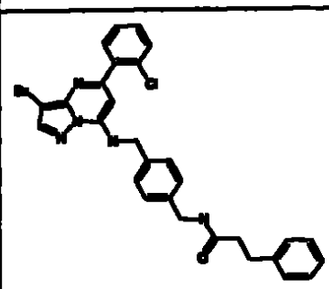
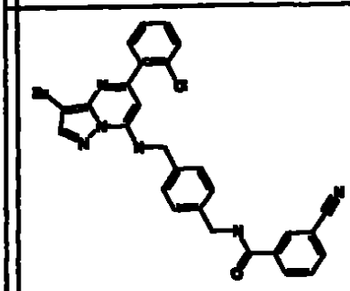
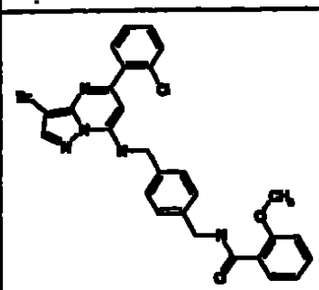
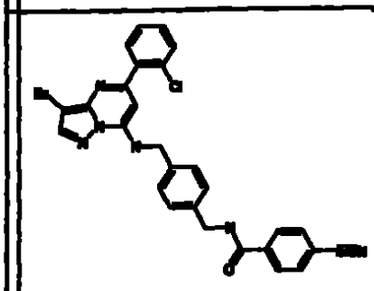
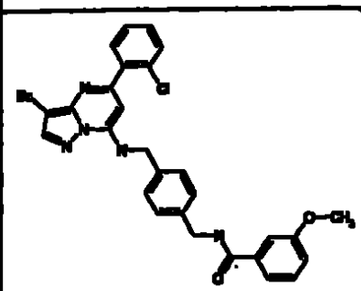
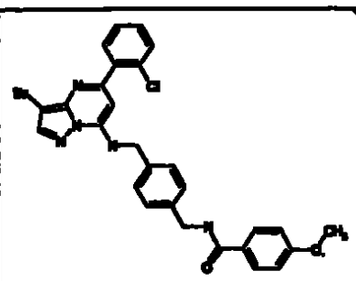
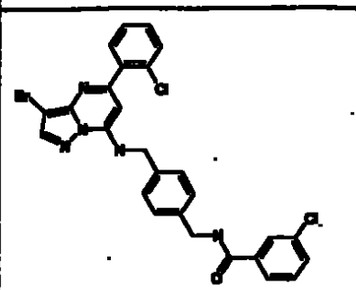
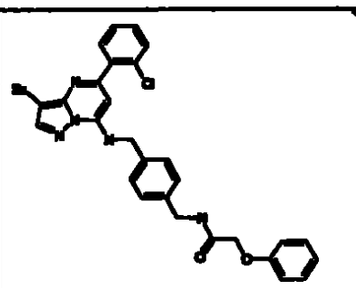
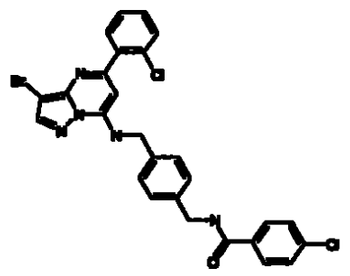
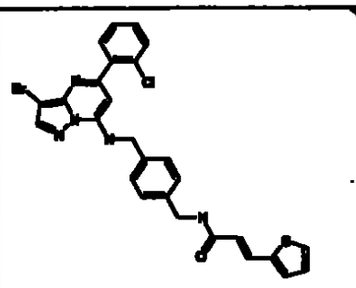
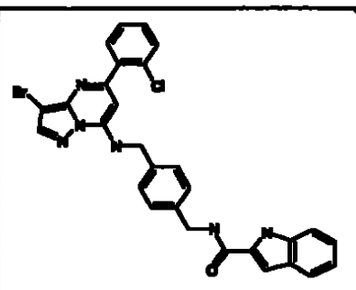
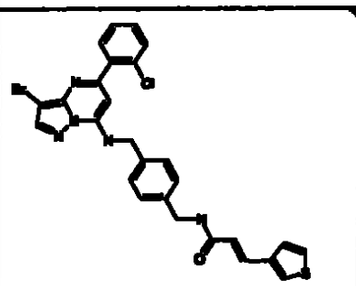
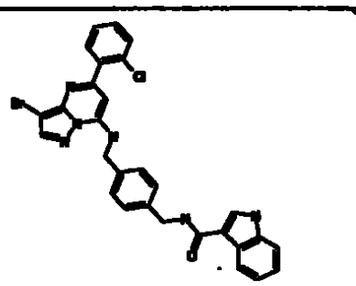
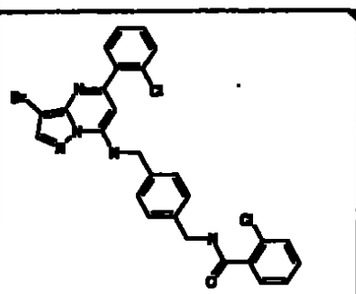
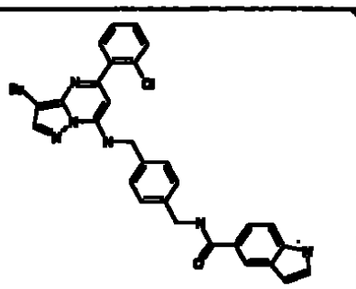
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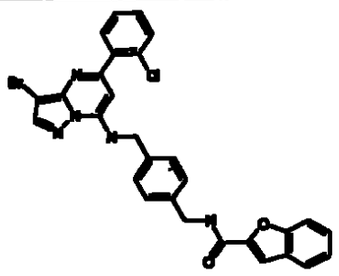
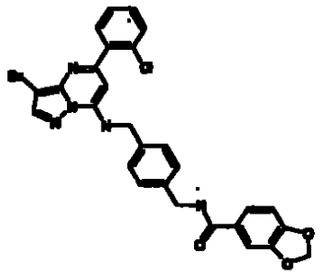
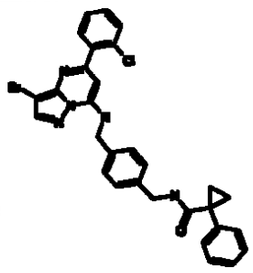
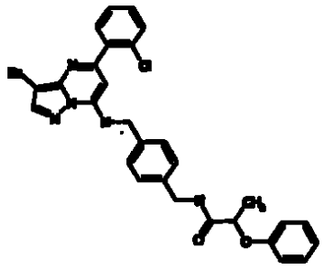
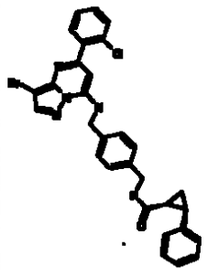
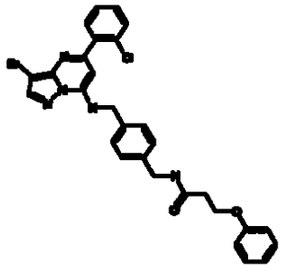
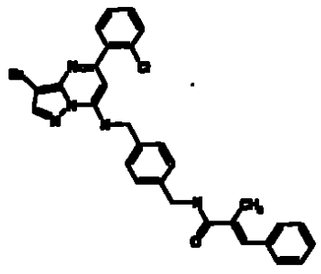
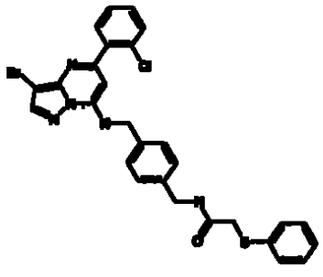
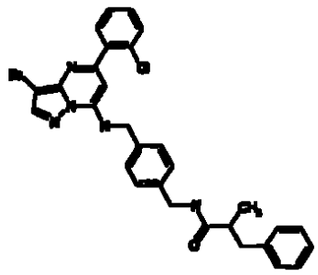
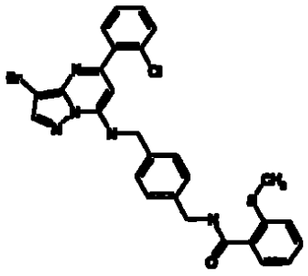
TABLE 46

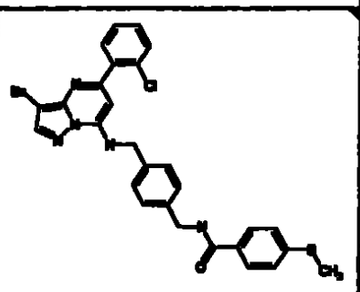
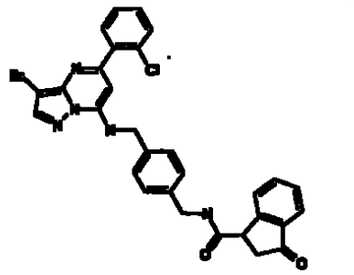
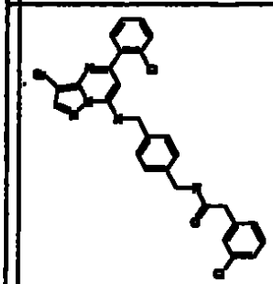
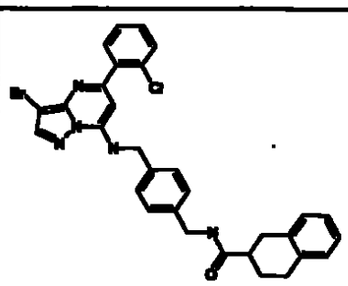
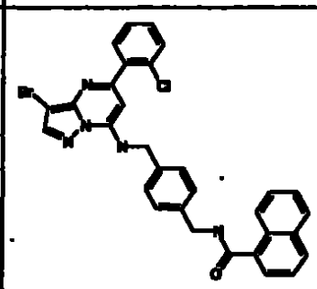
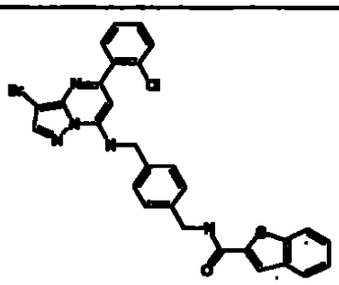
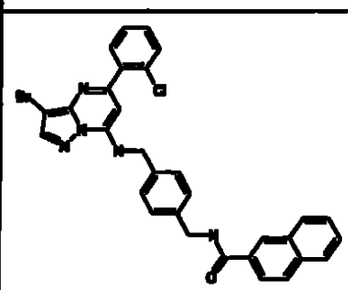
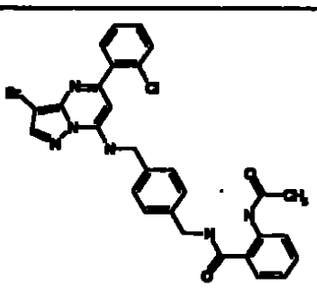
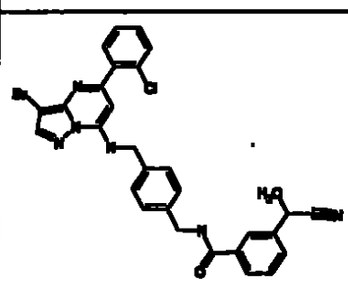
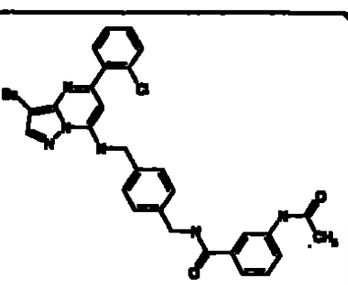
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	1. 4602 2. 526.29		1. 4607 2. 542.3
	1. 4603 2. 532.29		1. 4608 2. 542.3
	1. 4604 2. 538.3		1. 4609 2. 542.3
	1. 4605 2. 538.3		1. 4610 2. 547.3

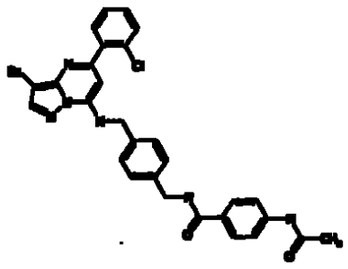
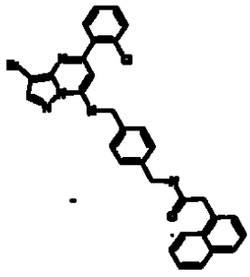
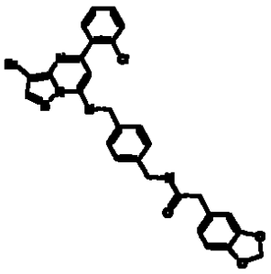
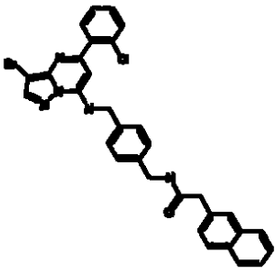
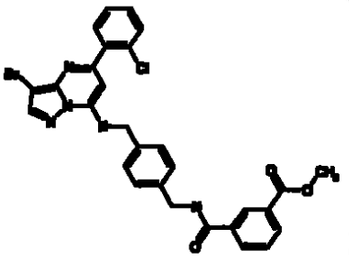
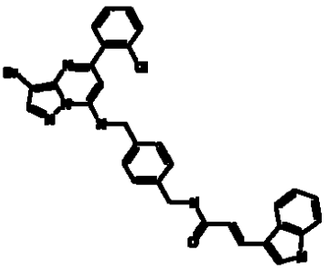
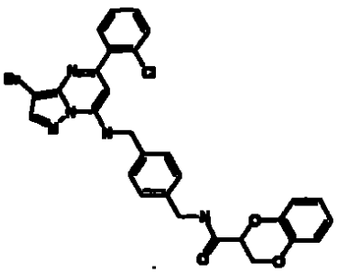
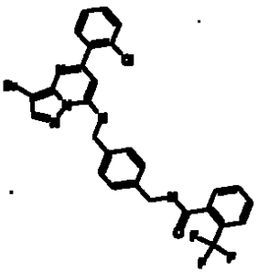
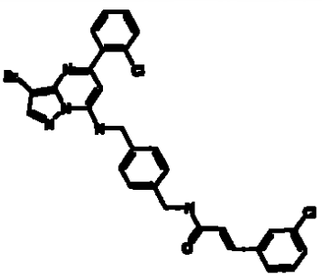
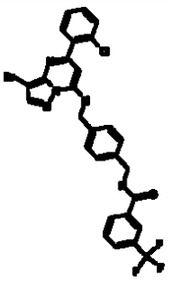
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	1. 4611 2. 551.3			1. 4616 2. 560.31
	1. 4612 2. 552.3			1. 4617 2. 562.31
	1. 4613 2. 552.3			1. 4618 2. 562.3
	1. 4614 2. 555.31			1. 4619 2. 567.31
	1. 4615 2. 558.31			1. 4620 2. 568.31

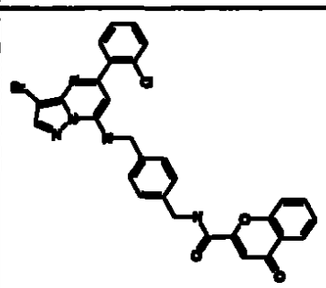
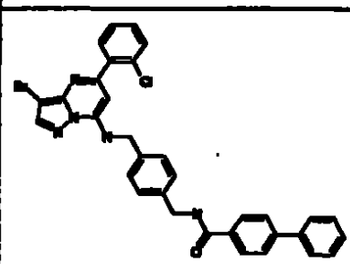
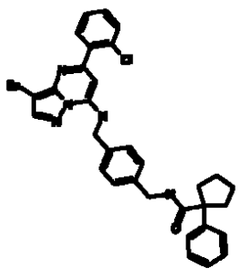
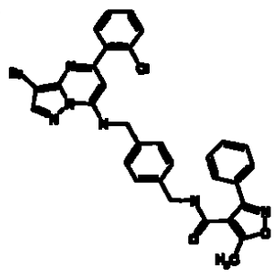
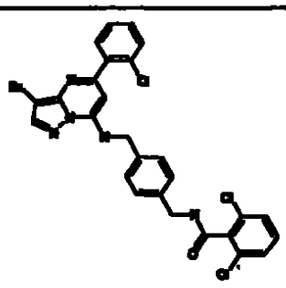
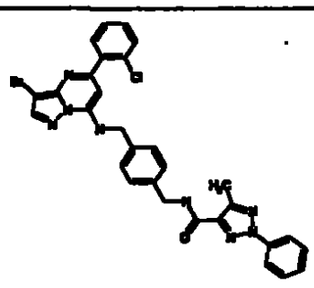
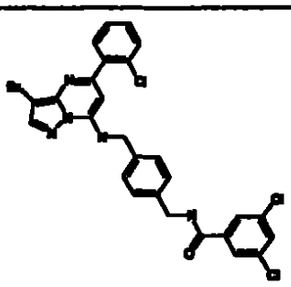
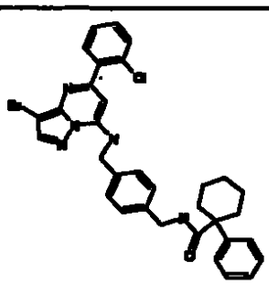
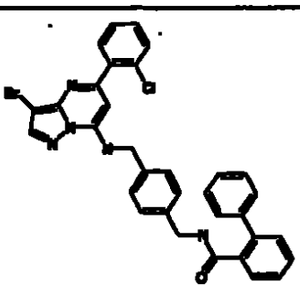
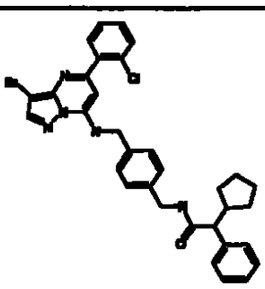
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	1. 4622 2. 568.31			1. 4627 2. 576.32
	1. 4623 2. 568.31			1. 4628 2. 576.32
	1. 4624 2. 573.32			1. 4629 2. 576.32
	1. 4625 2. 573.32			1. 4630 2. 576.32

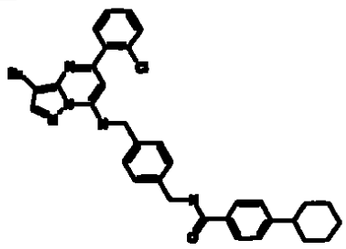
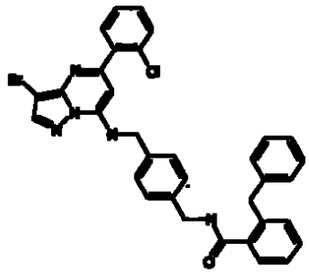
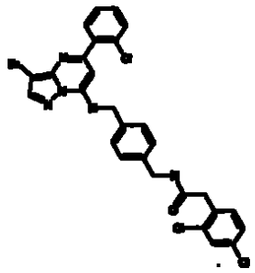
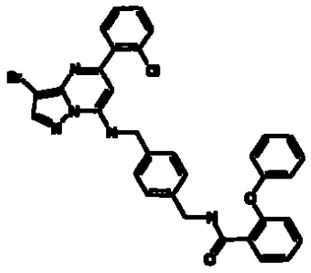
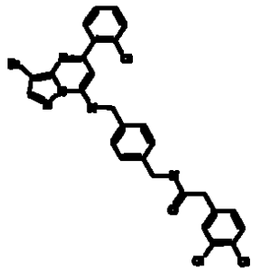
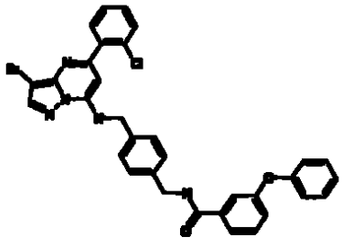
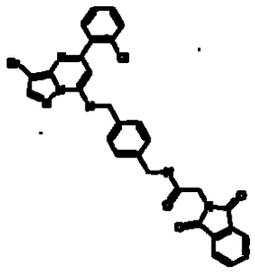
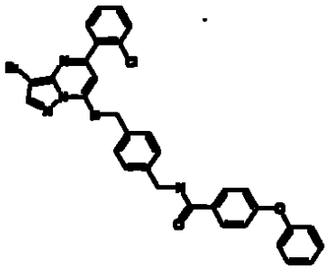
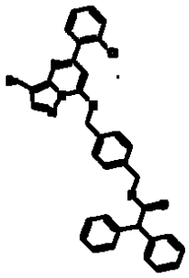
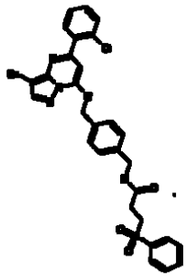
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	1. 4632 2. 578.32			1. 4637 2. 582.32
	1. 4633 2. 580.32			1. 4638 2. 587.32
	1. 4634 2. 580.32			1. 4639 2. 585.3
	1. 4635 2. 582.32			1. 4640 2. 585.3

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. 606.33		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

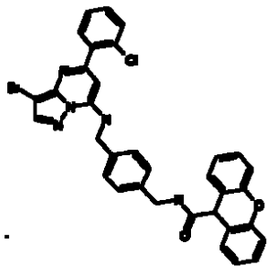
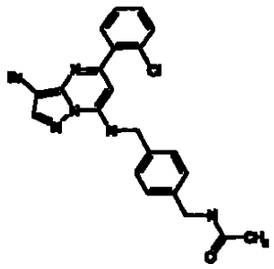
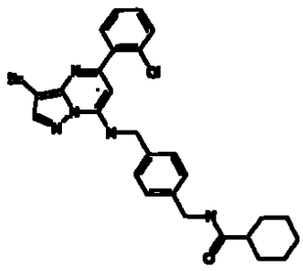
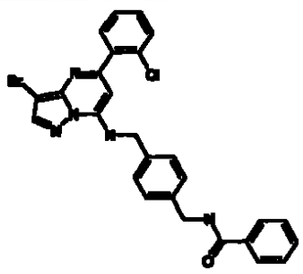
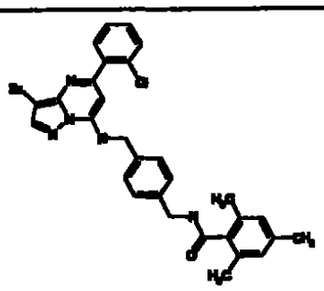
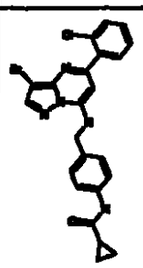
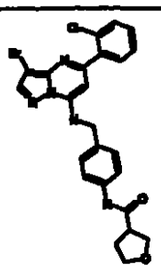
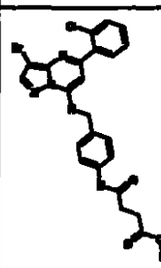
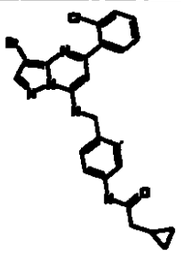
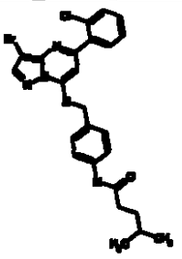
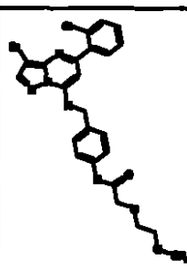
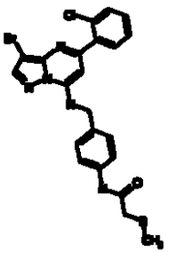
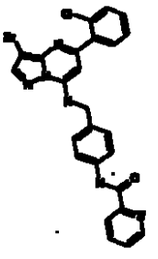
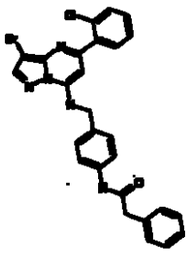
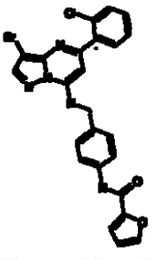
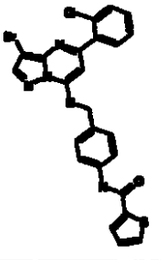
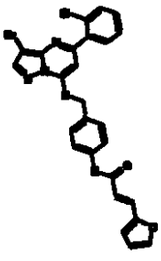
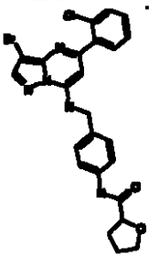
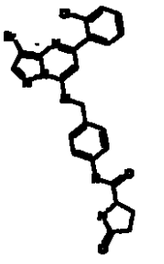
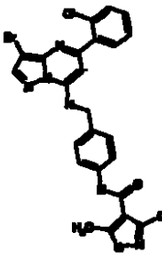
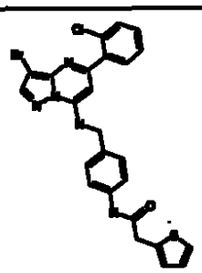
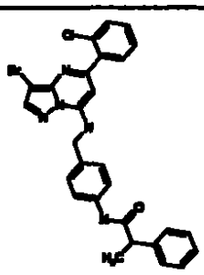
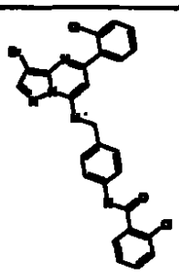
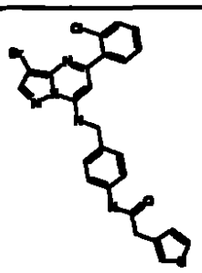
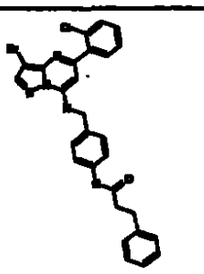
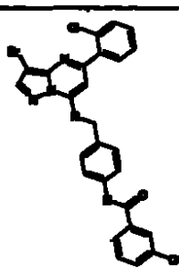
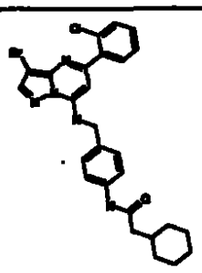
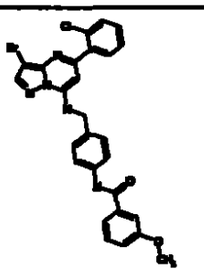
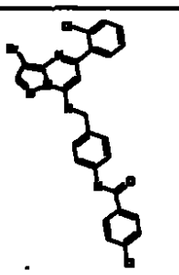
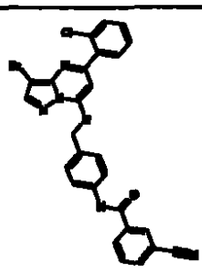
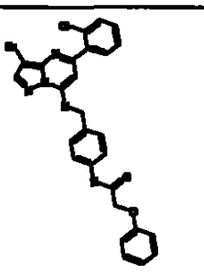
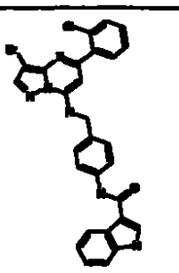
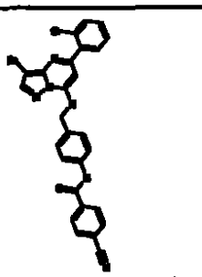
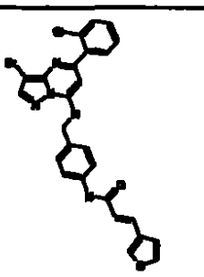
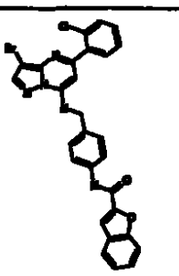
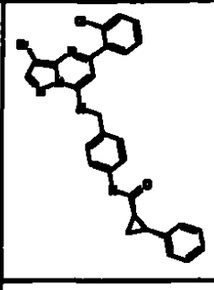
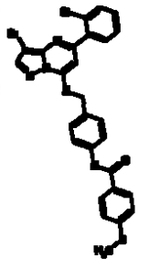
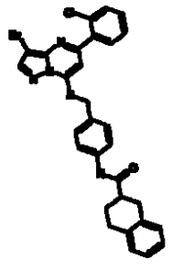
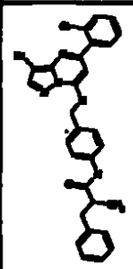
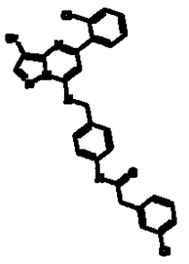
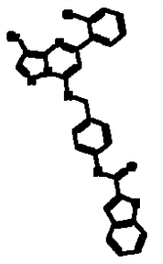
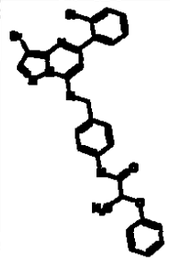
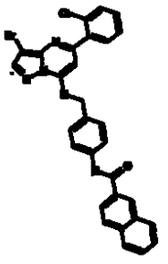
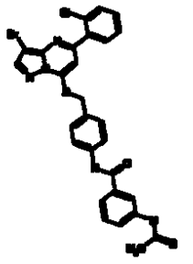
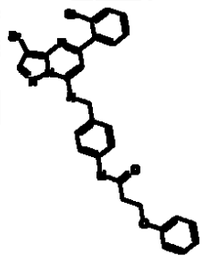
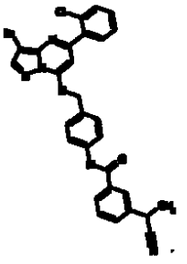
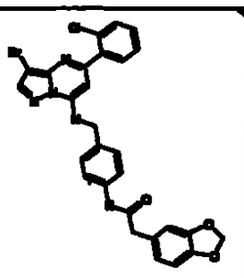
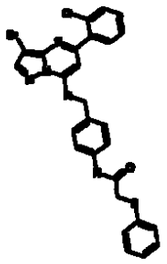
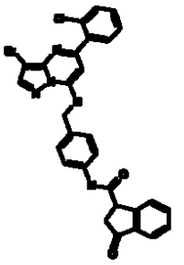
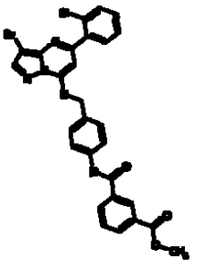
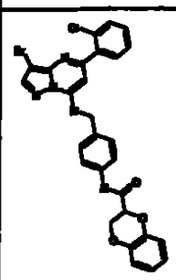
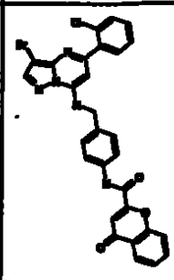
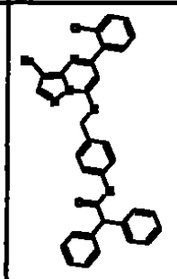
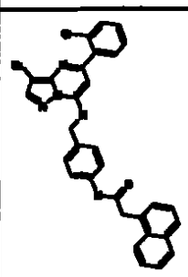
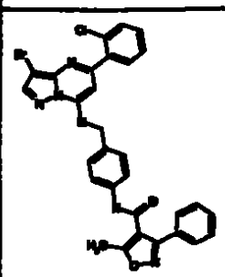
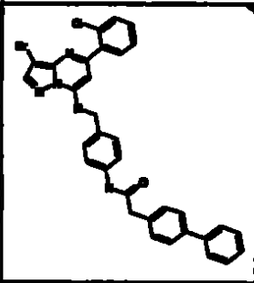
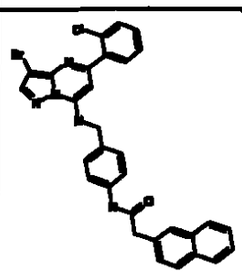
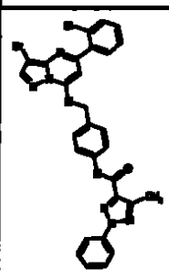
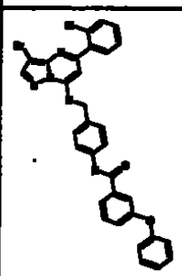
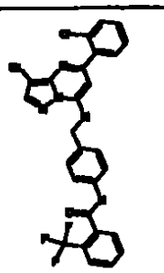
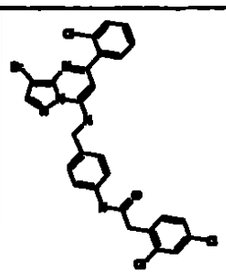
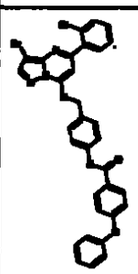
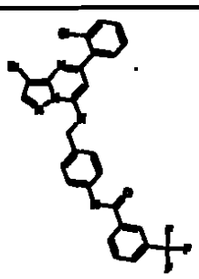
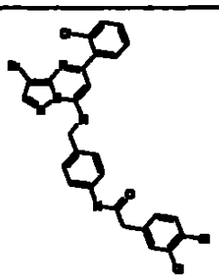
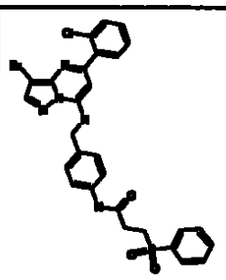
Product	1. Ex. 2. m/z
	1. 4691 2. 652.36
	1. 4692 2. 484.3
	1. 4693 2. 554.3
	1. 4694 2. 548.3
	1. 4695 2. 590.32

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. 526.29		1. 4711 2. 544.3
	1. 4702 2. 512.28		1. 4707 2. 526.29		1. 4712 2. 548.3
	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. 526.29		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. 586.32		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

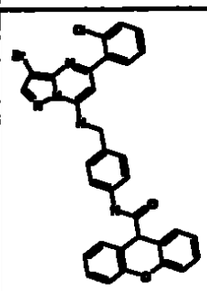
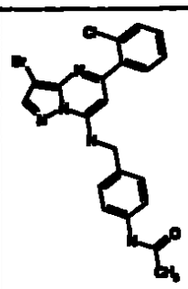
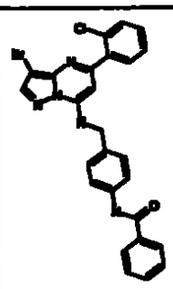
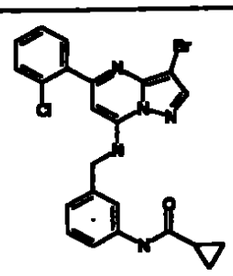
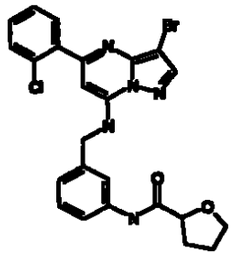
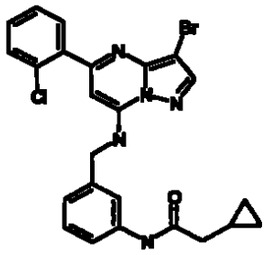
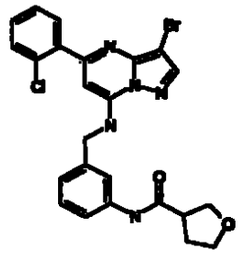
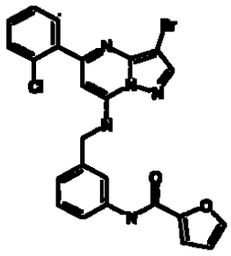
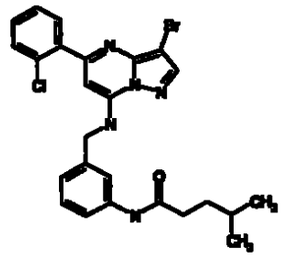
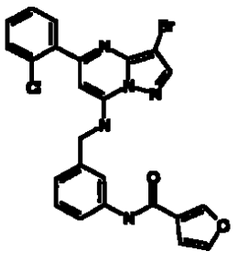
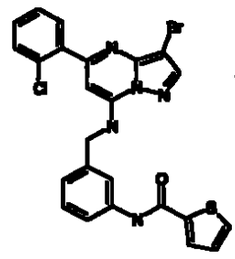
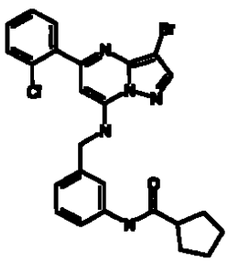
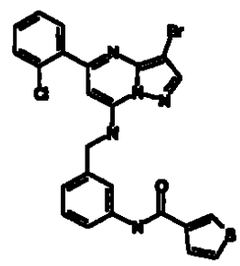
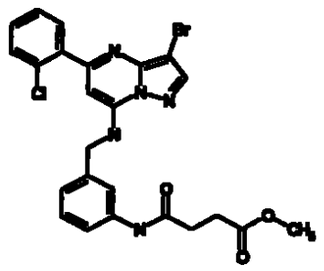
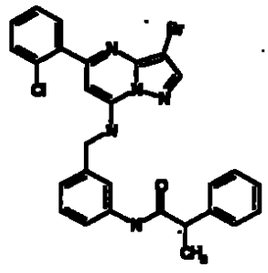
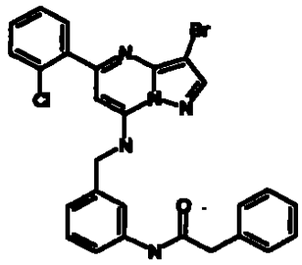
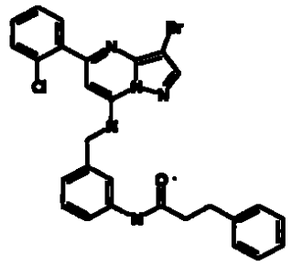
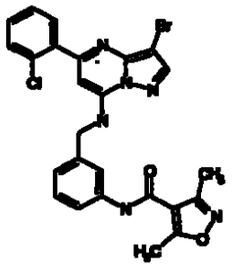
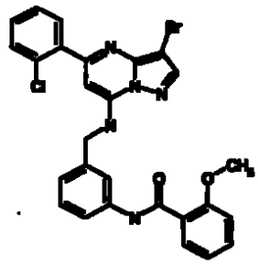
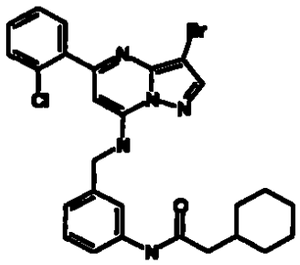
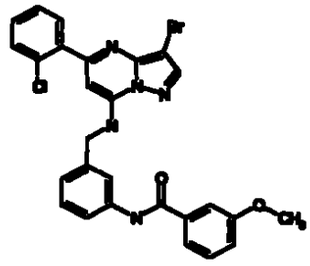
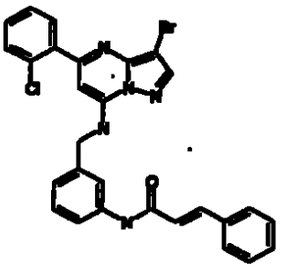
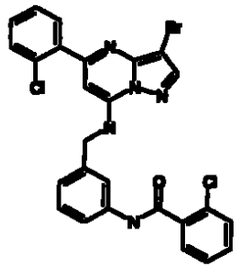
Product	1. Ex. 2. m/z
	1. 4761 2. 638.35
	1. 4762 2. 472.26
	1. 4763 2. 534.29

TABLE 48

Product	1. Ex. 2. m/z		Product	1. Ex. 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

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

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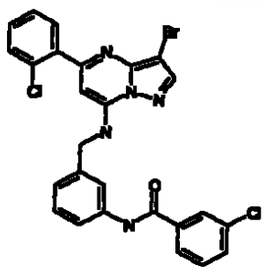
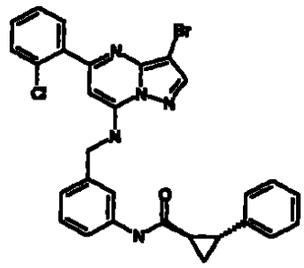
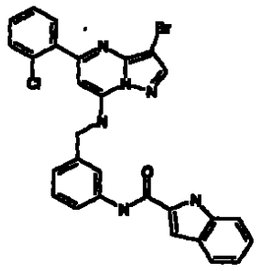
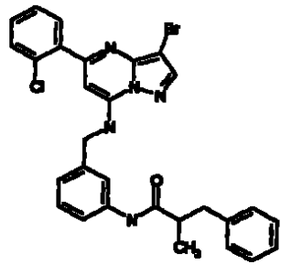
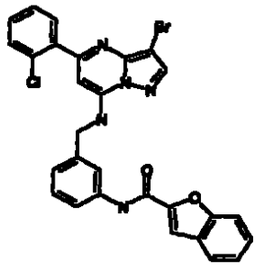
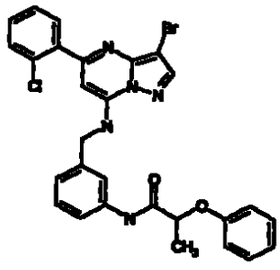
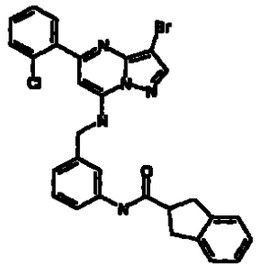
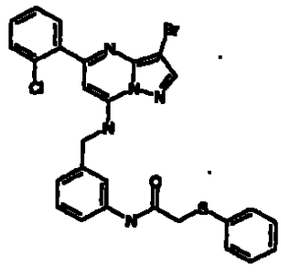
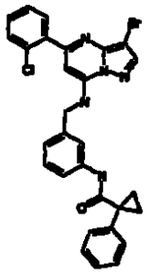
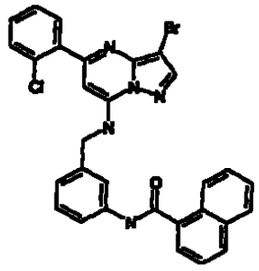
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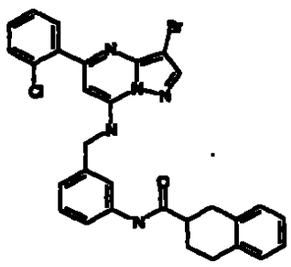
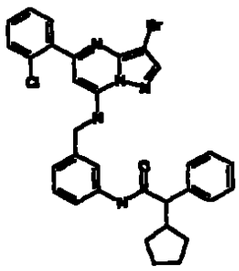
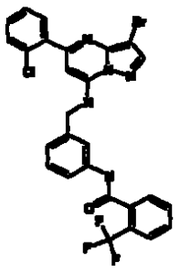
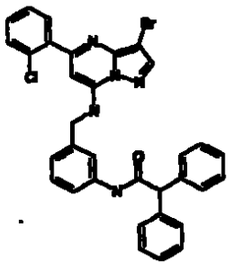
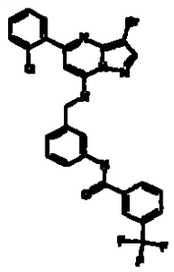
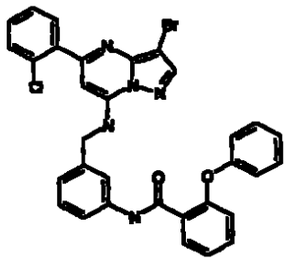
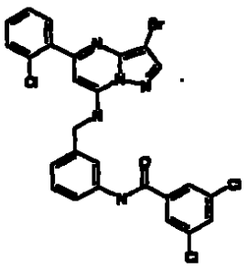
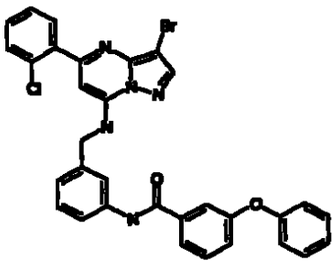
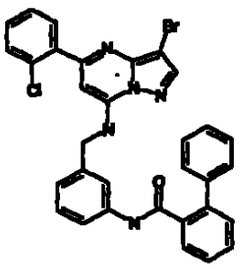
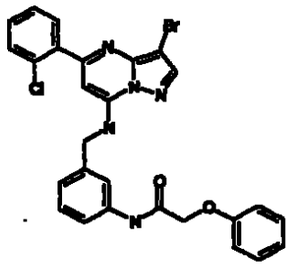
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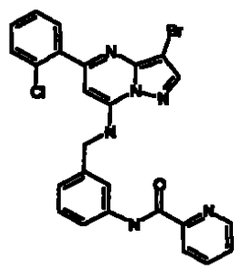
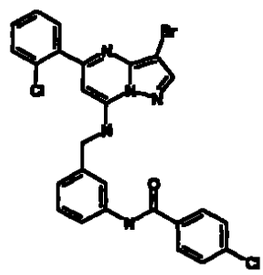
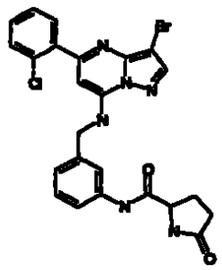
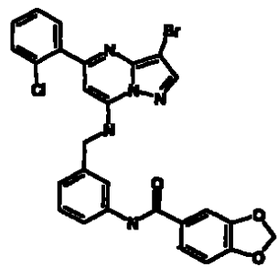
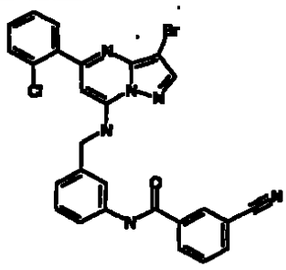
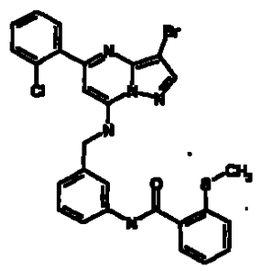
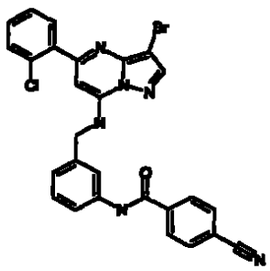
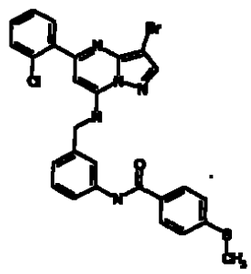
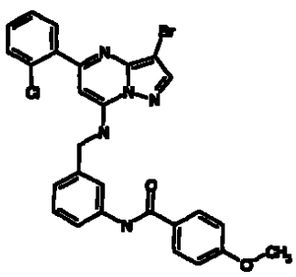
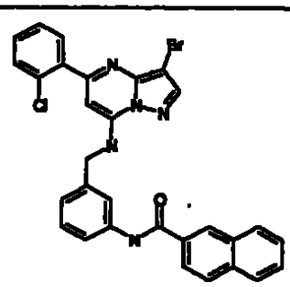
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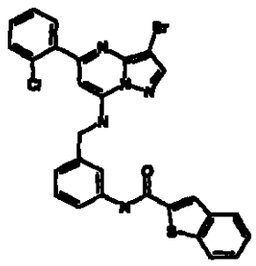
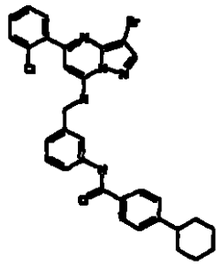
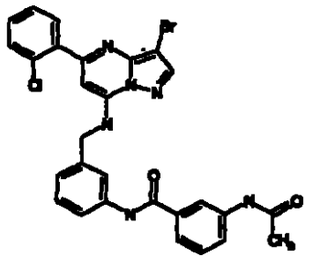
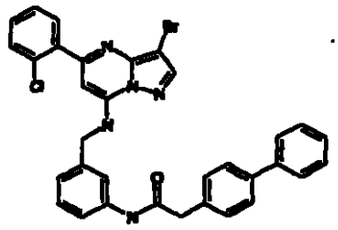
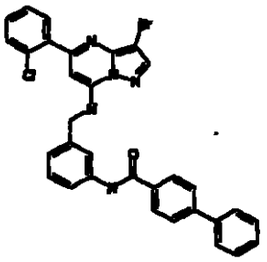
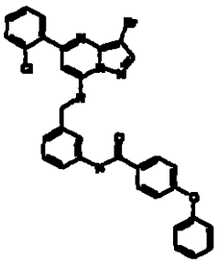
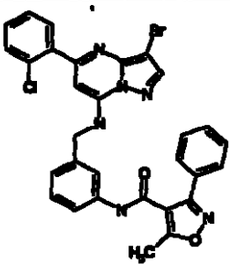
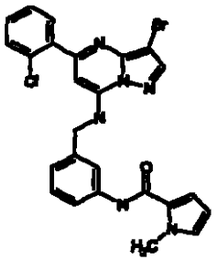
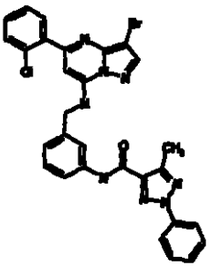
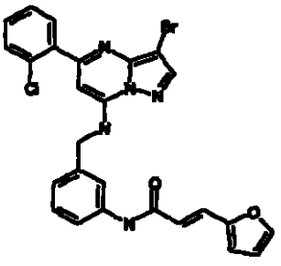
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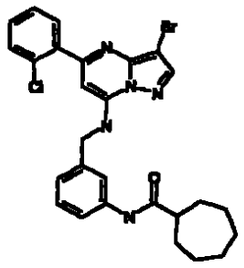
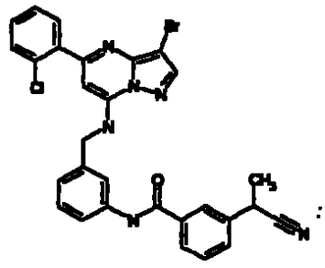
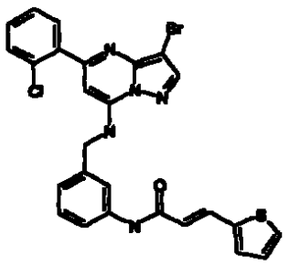
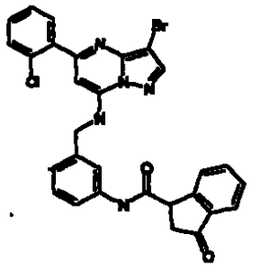
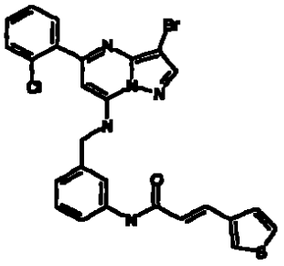
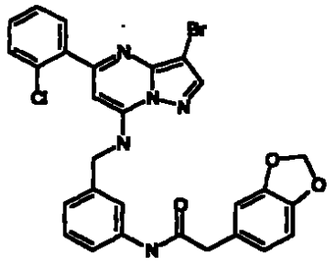
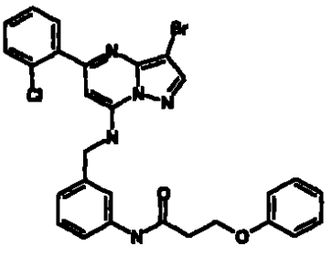
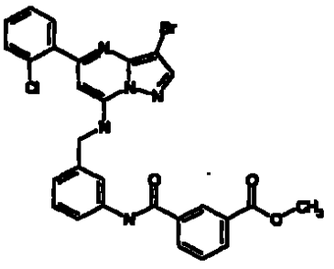
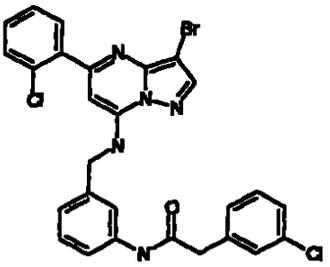
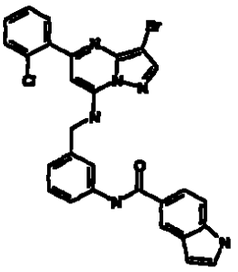
Address: Bureau international de l'OMPI 34, chemin des Colombettes Geneve 20 1211 CH

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	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
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	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
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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. 586.32
	1. 4863 2. 566.31		1. 4868 2. 592.33
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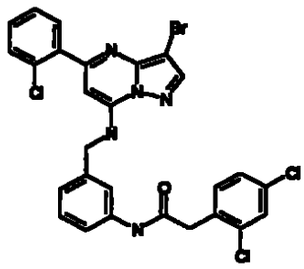
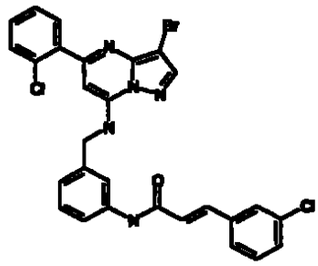
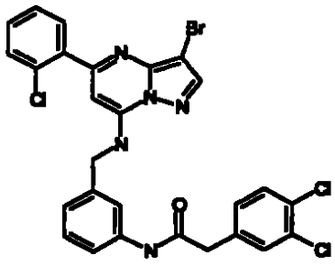
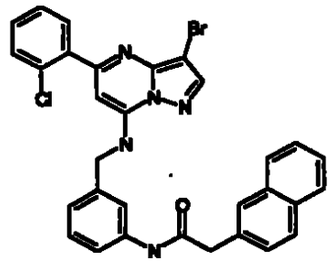
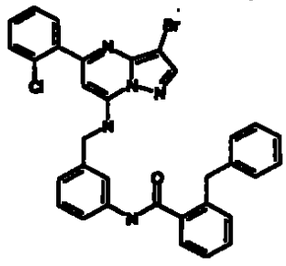
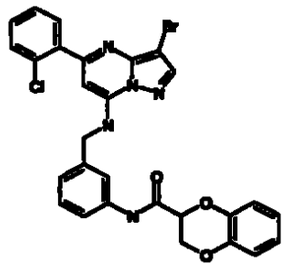
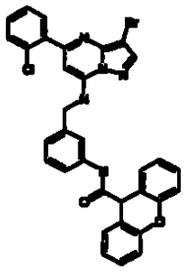
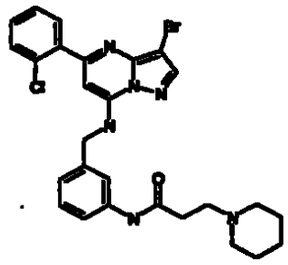
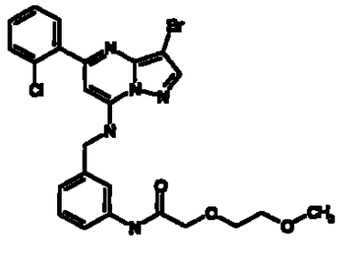
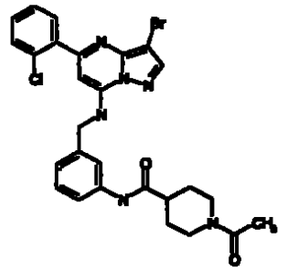
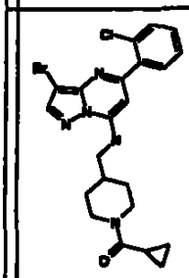
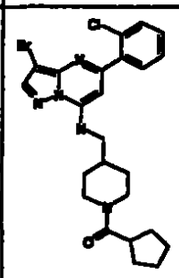
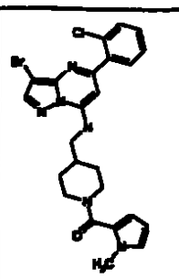
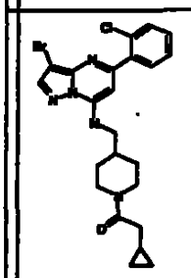
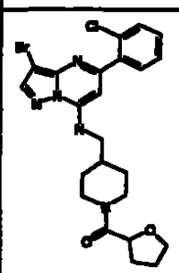
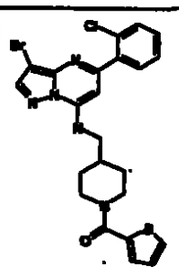
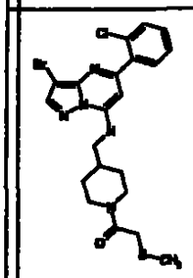
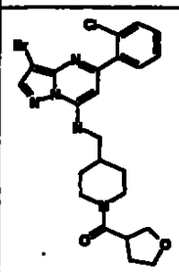
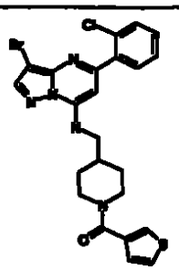
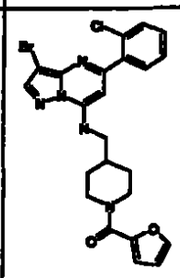
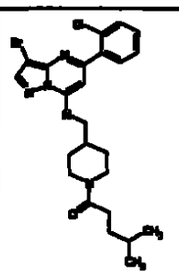
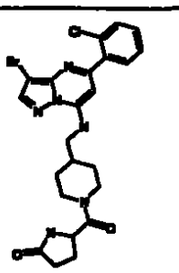
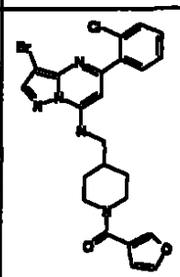
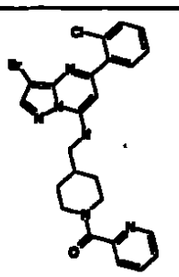
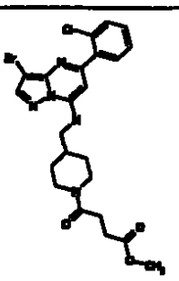
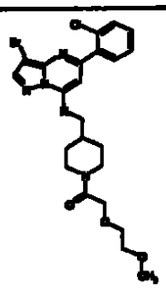
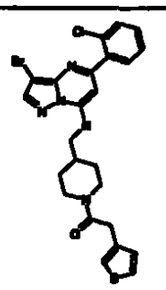
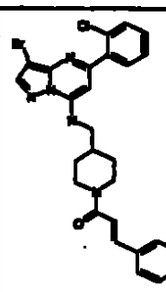
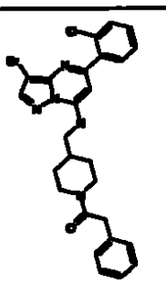
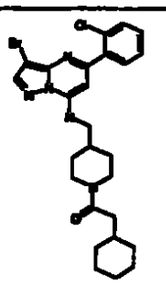
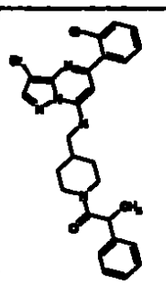
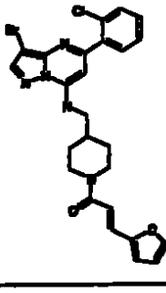
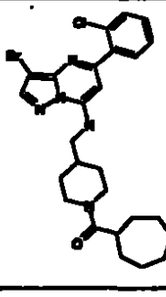
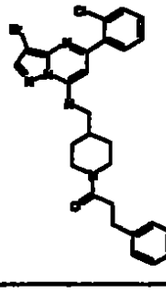
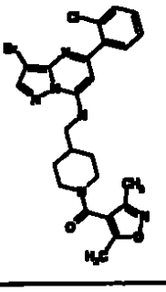
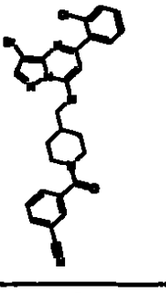
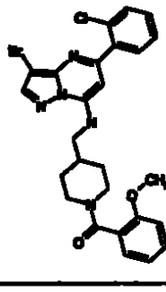
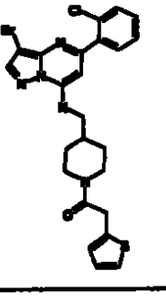
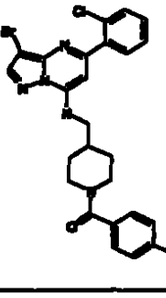
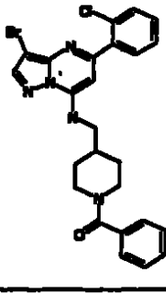
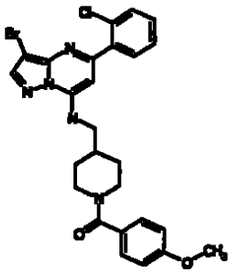
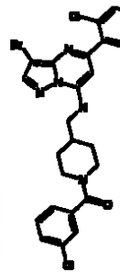
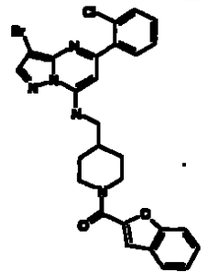
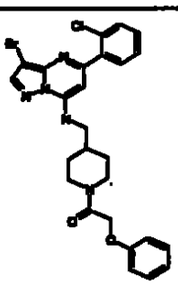
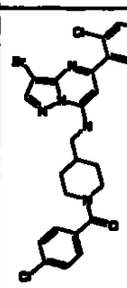
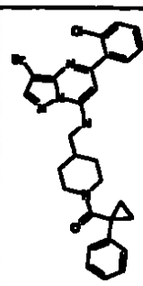
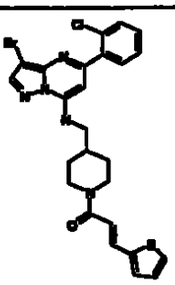
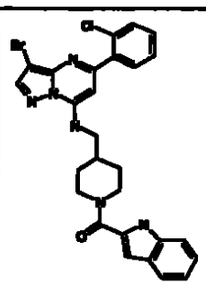
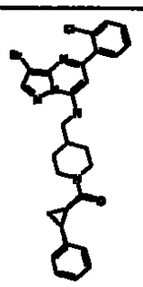
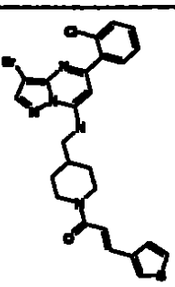
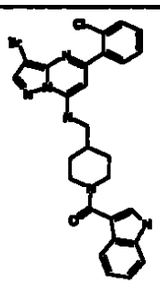
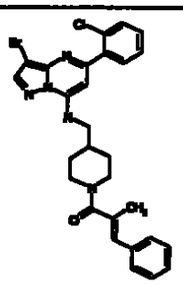
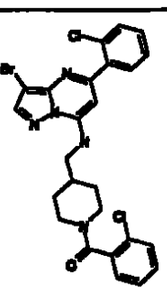
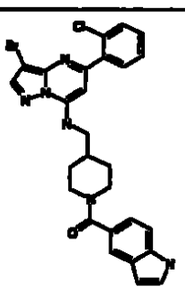
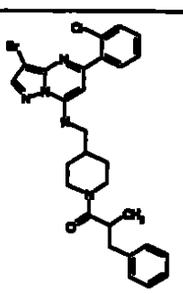
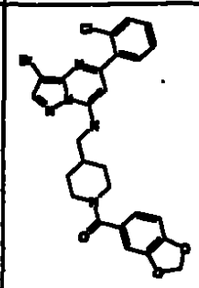
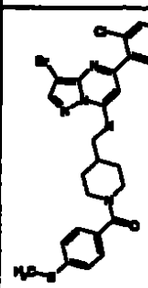
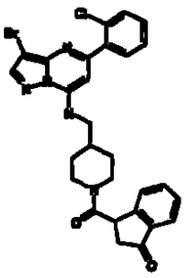
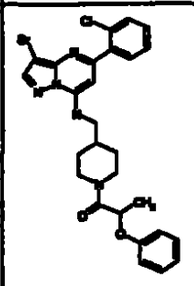
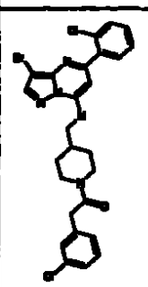
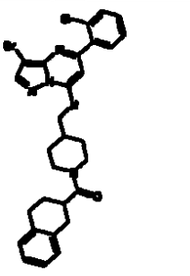
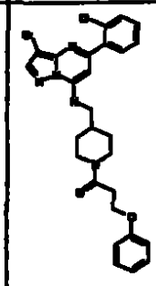
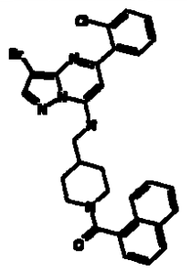
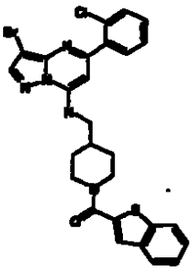
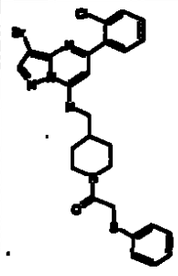
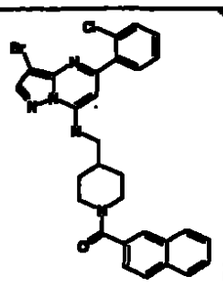
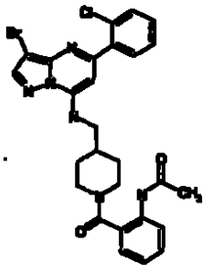
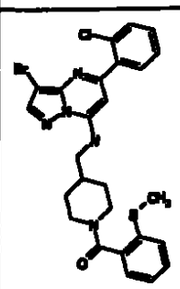
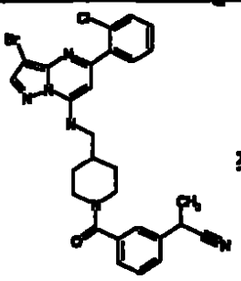
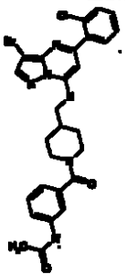
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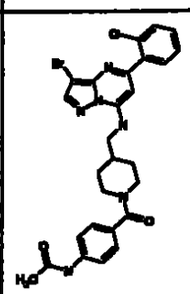
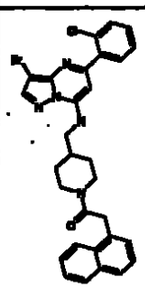
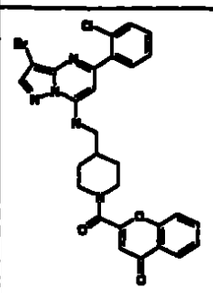
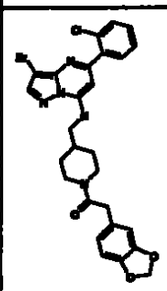
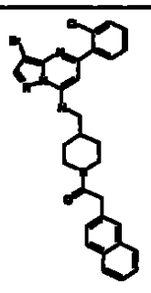
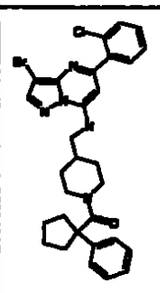
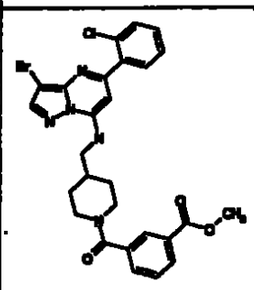
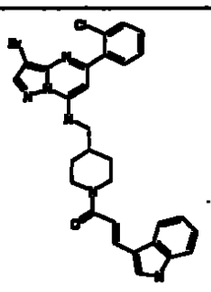
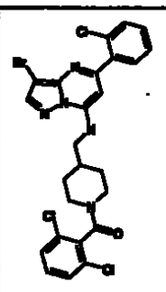
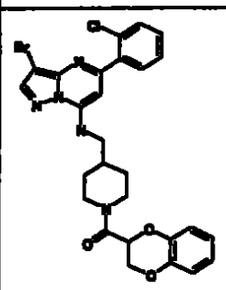
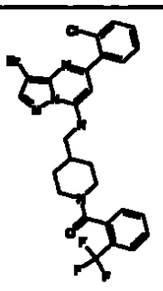
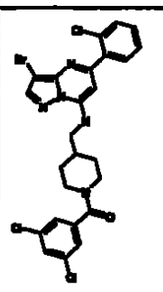
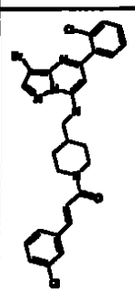
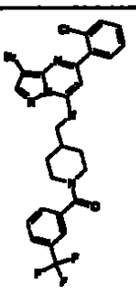
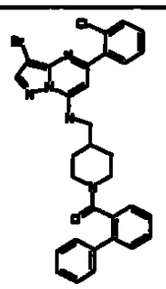
TABLE 49

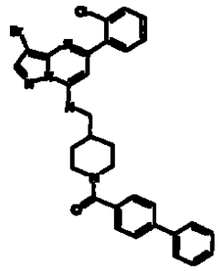
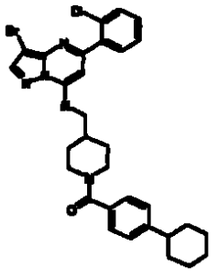
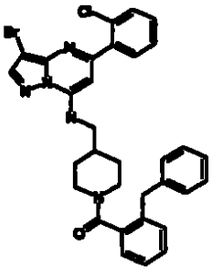
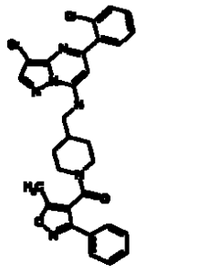
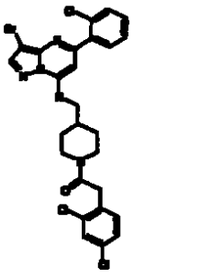
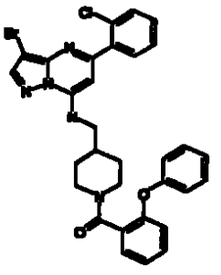
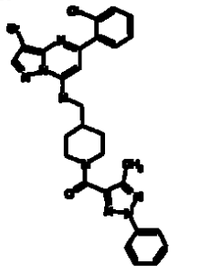
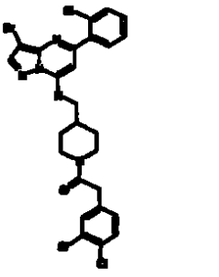
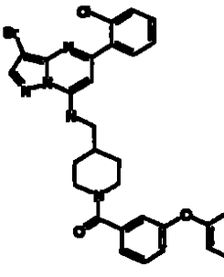
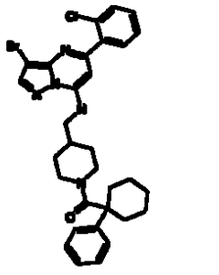
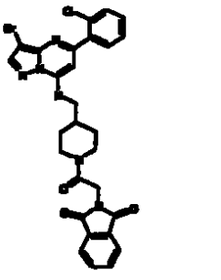
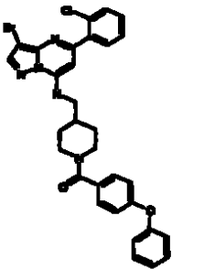
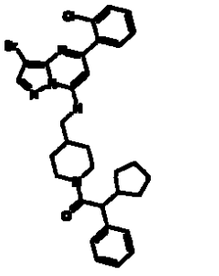
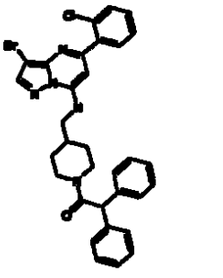
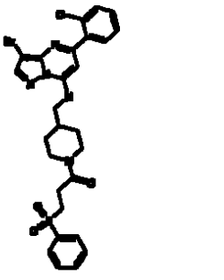
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	1. 4901 2. 490.27		1. 4906 2. 518.28		1. 4911 2. 529.29
	1. 4902 2. 504.28		1. 4907 2. 520.29		1. 4912 2. 532.29
	1. 4903 2. 510.28		1. 4908 2. 520.29		1. 4913 2. 532.29
	1. 4904 2. 516.28		1. 4909 2. 520.29		1. 4914 2. 533.29
	1. 4905 2. 516.28		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. 546.3		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. 566.31
	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. 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		1. 4955 2. 579.32		1. 4960 2. 583.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 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

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. 4089 2. 618.34
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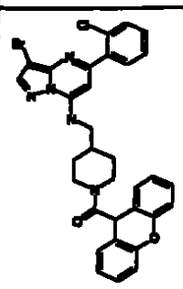
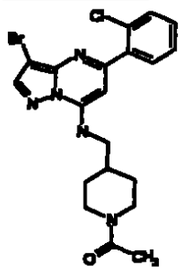
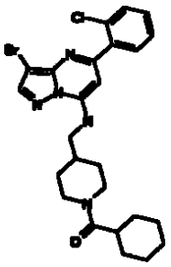
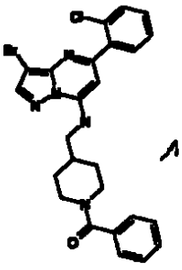
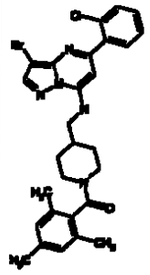
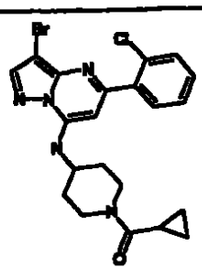
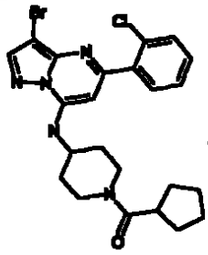
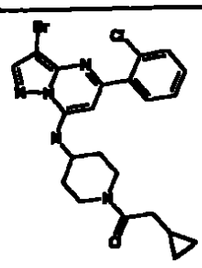
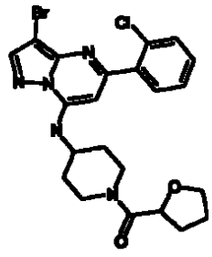
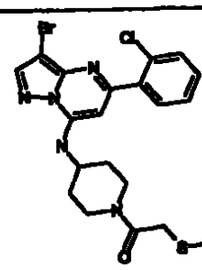
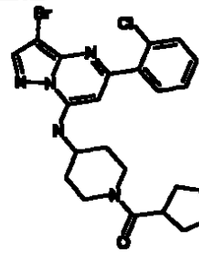
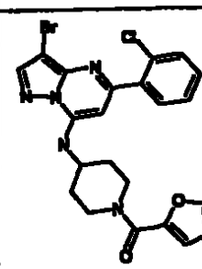
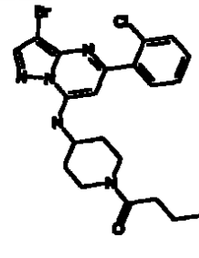
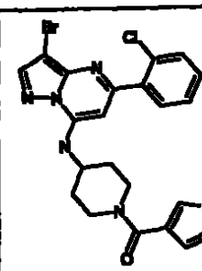
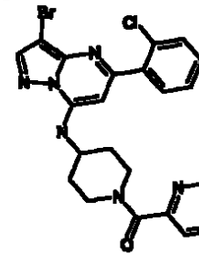
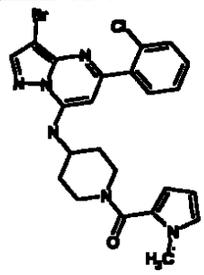
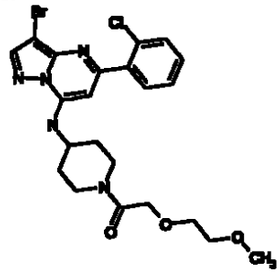
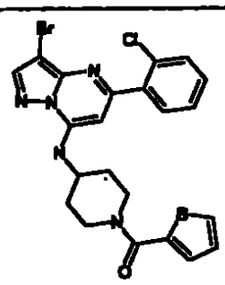
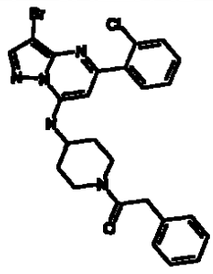
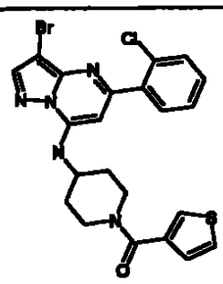
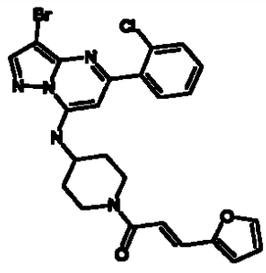
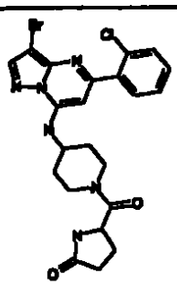
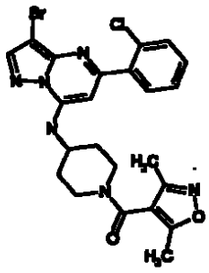
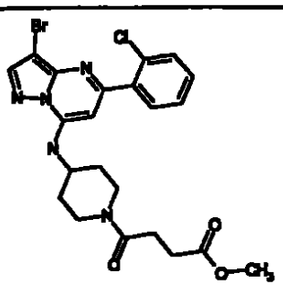
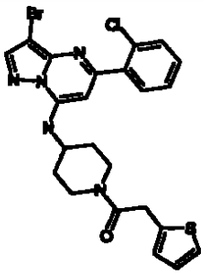
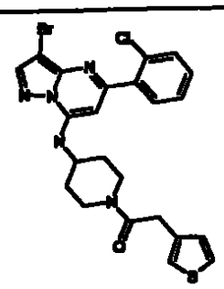
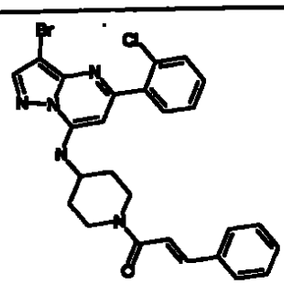
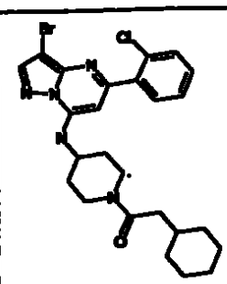
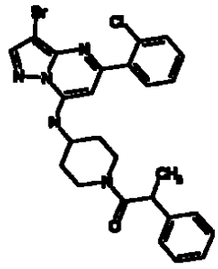
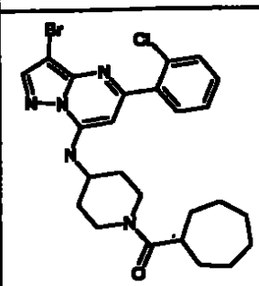
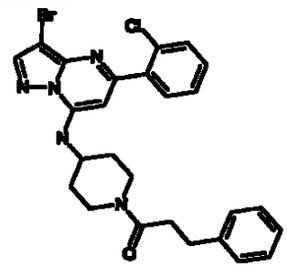
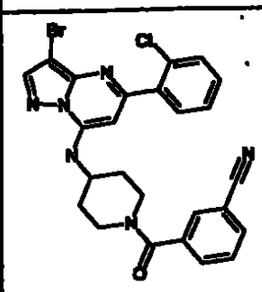
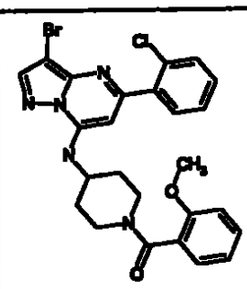
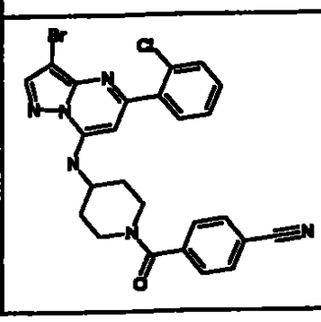
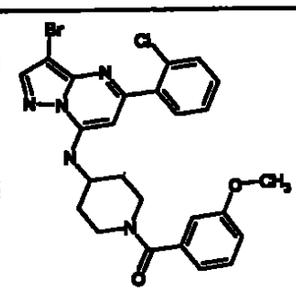
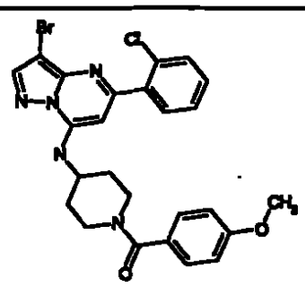
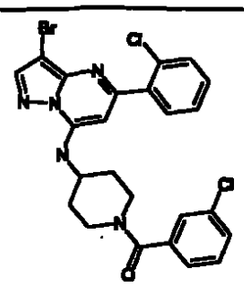
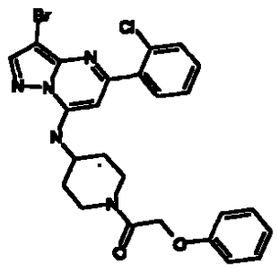
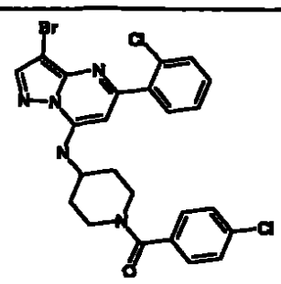
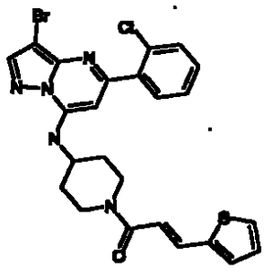
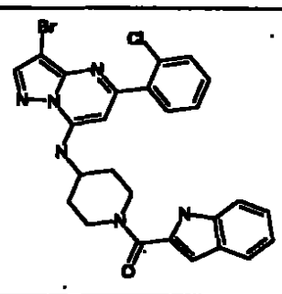
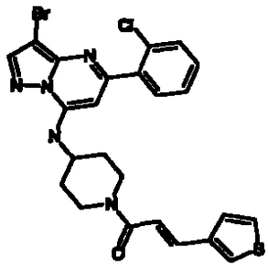
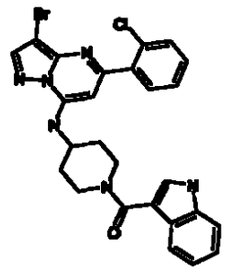
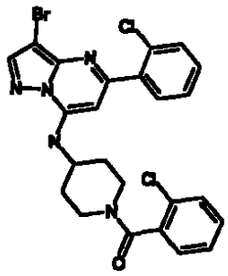
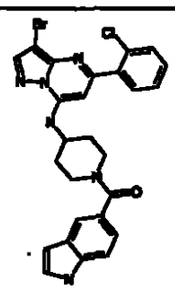
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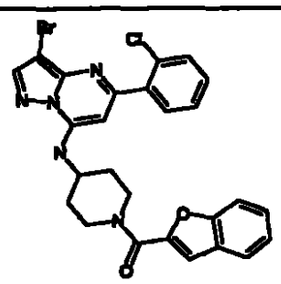
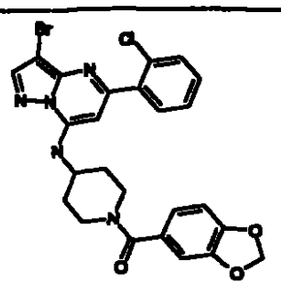
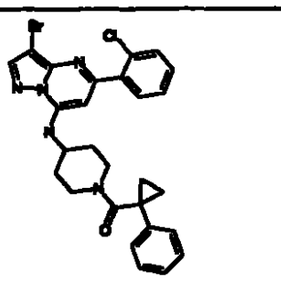
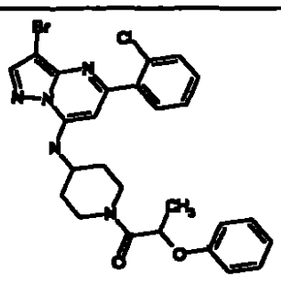
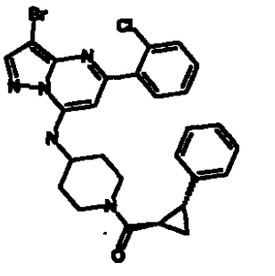
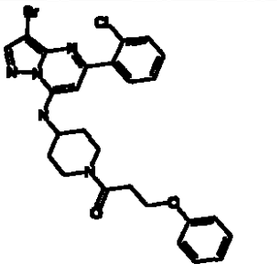
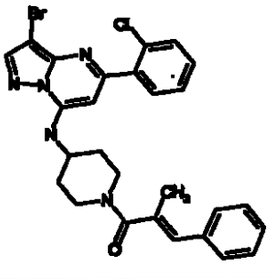
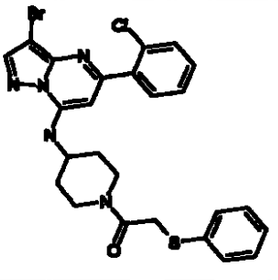
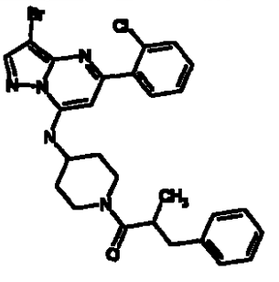
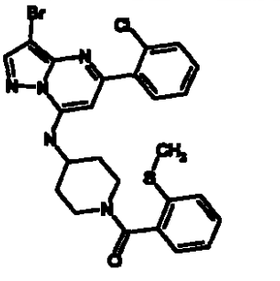
TABLE 50

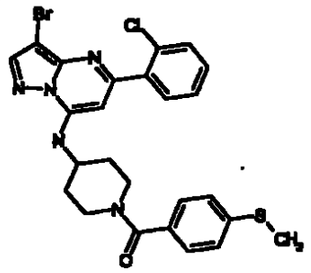
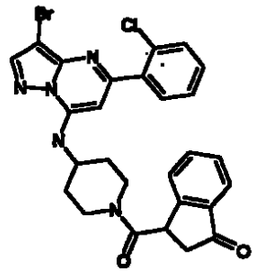
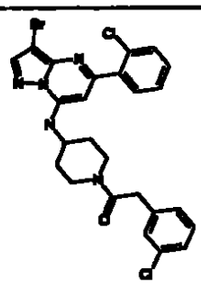
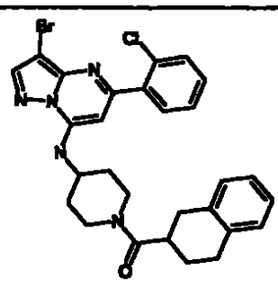
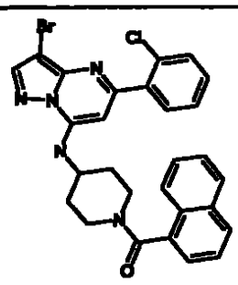
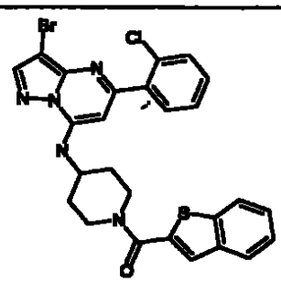
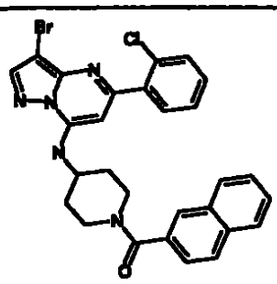
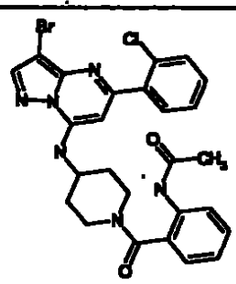
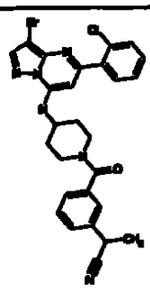
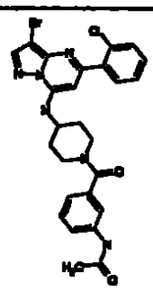
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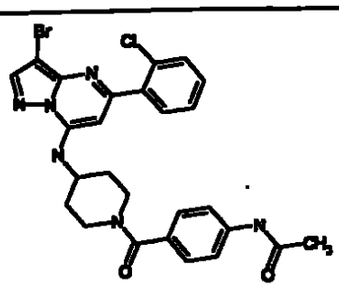
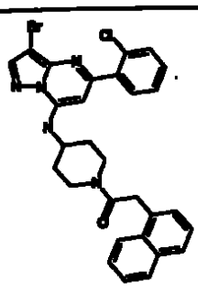
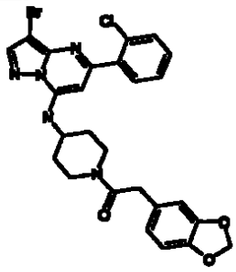
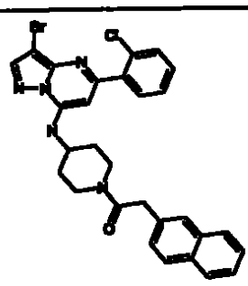
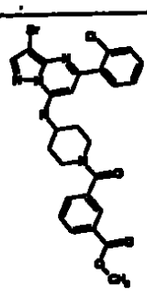
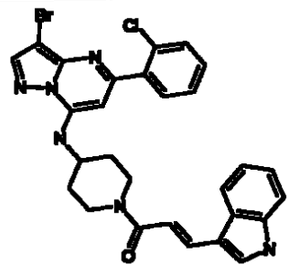
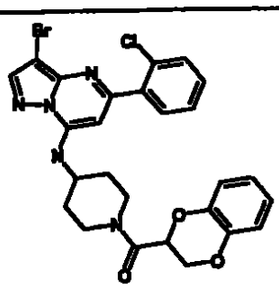
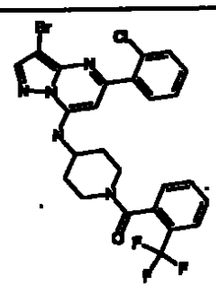
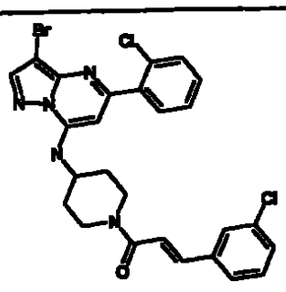
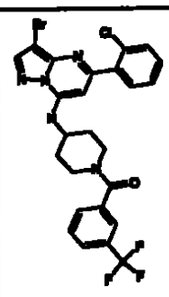
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	1. 5013 2. 518.28			1. 5018 2. 528.29
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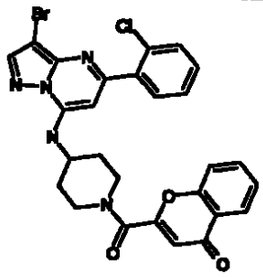
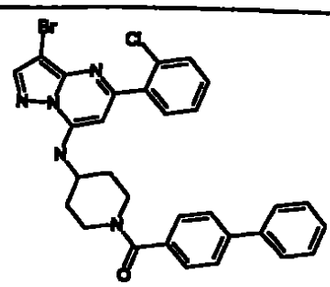
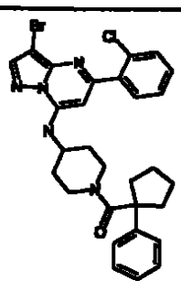
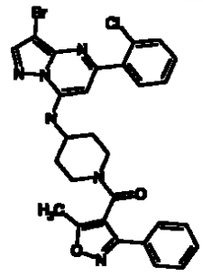
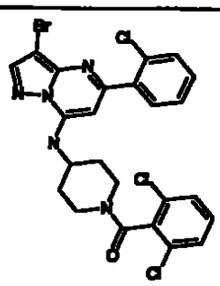
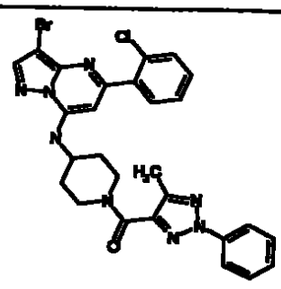
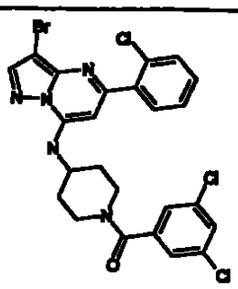
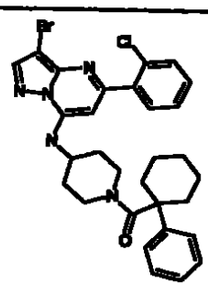
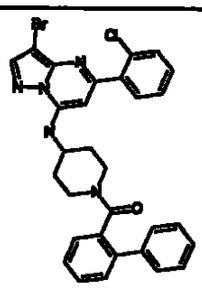
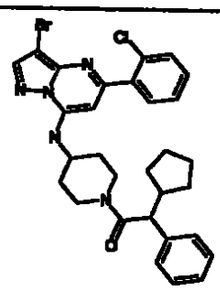
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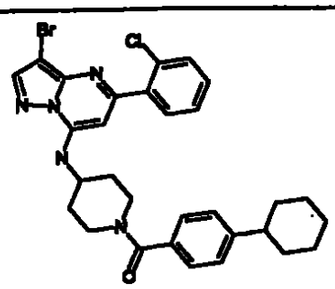
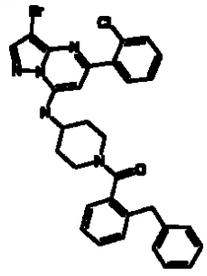
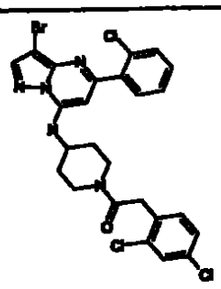
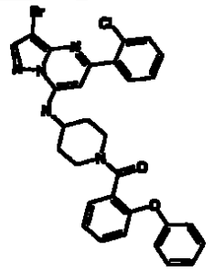
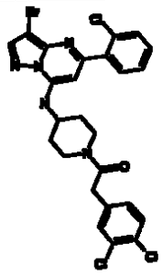
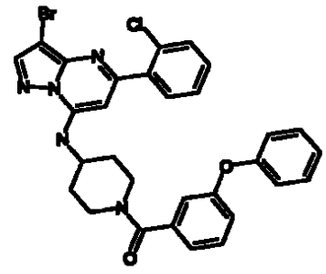
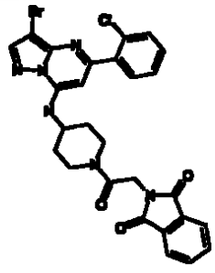
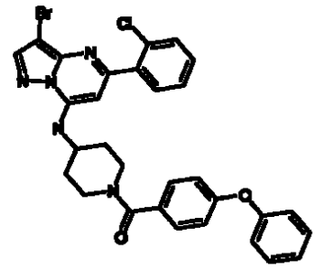
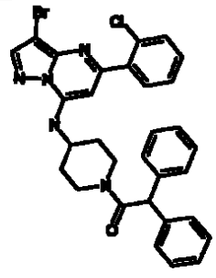
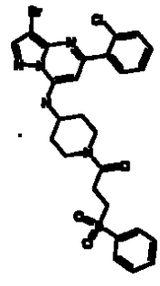
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	1. 5032 2. 542.3			1. 5037 2 .548.3
	1. 5033 2. 544.3			1. 5038 2. 551.3
	1. 5034 2. 544.3			1. 5039 2. 551.3
	1. 5035 2 .546.3			1. 5040

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. 556.31
	1. 5045 2. 554.3			1. 5050 2. 556.31

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
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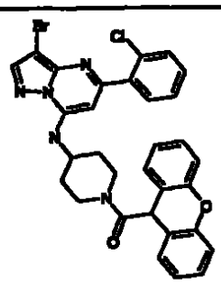
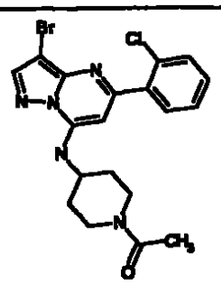
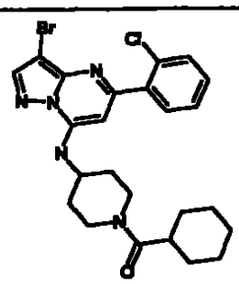
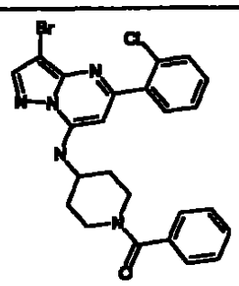
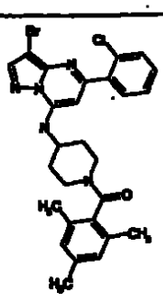
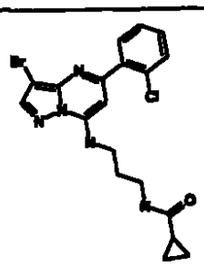
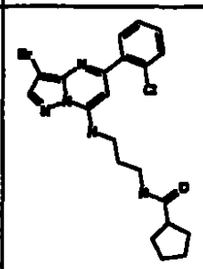
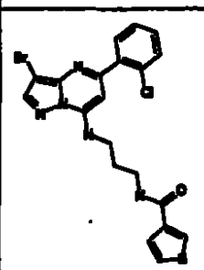
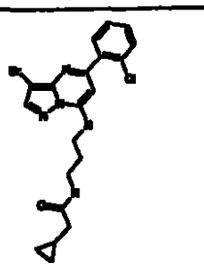
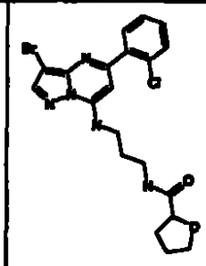
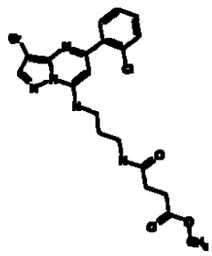
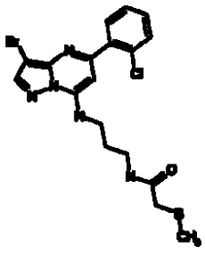
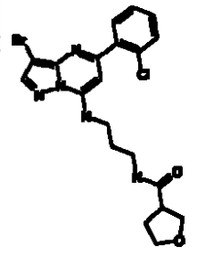
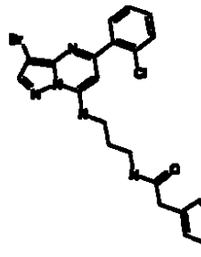
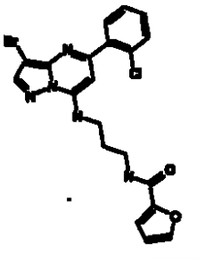
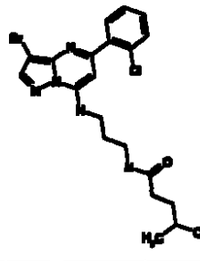
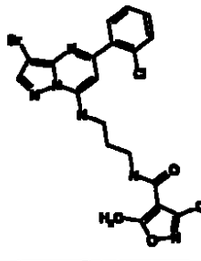
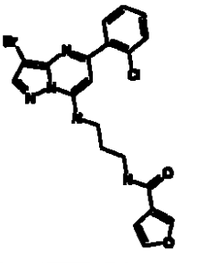
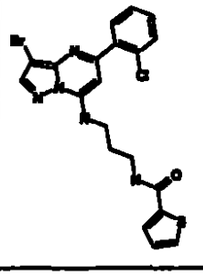
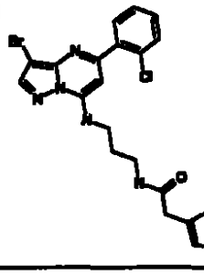
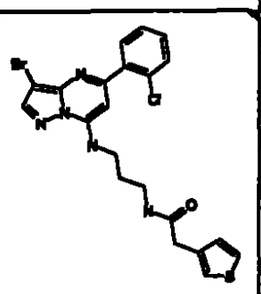
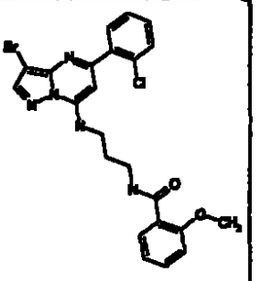
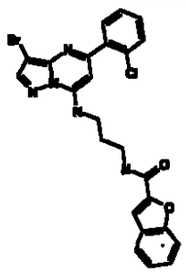
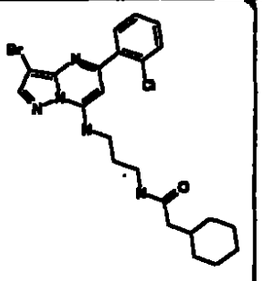
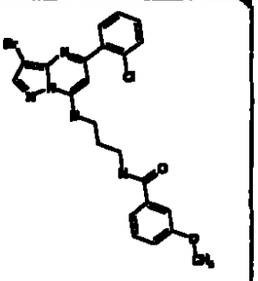
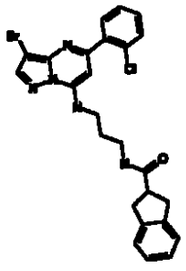
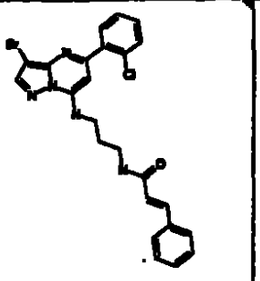
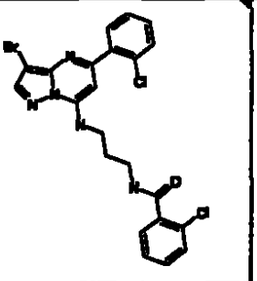
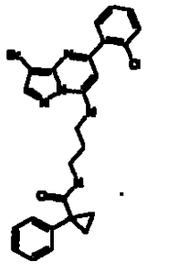
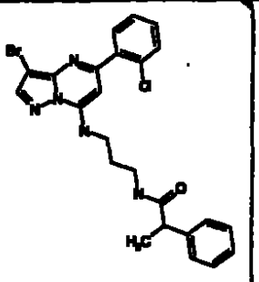
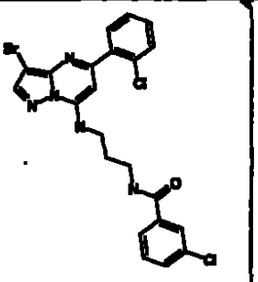
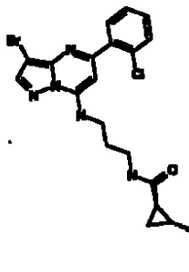
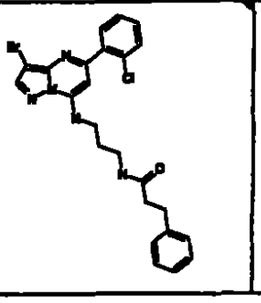
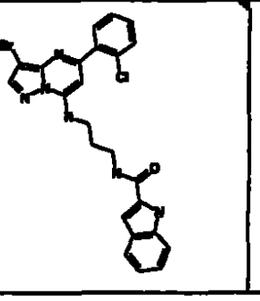
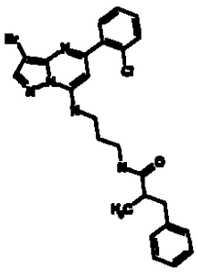
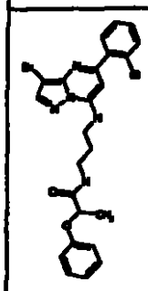
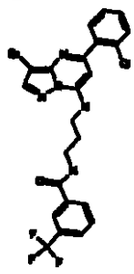
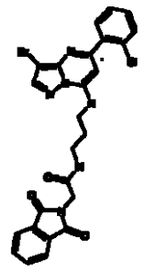
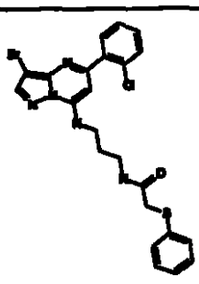
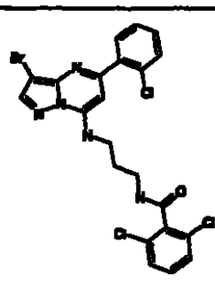
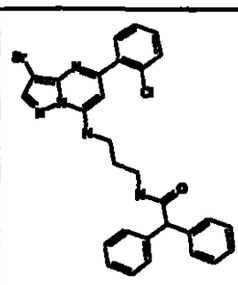
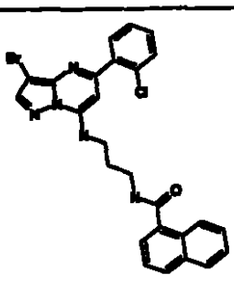
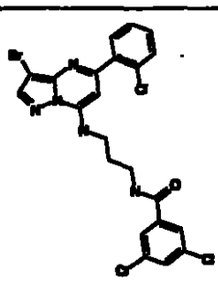
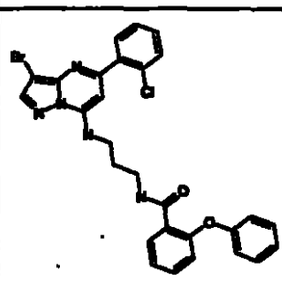
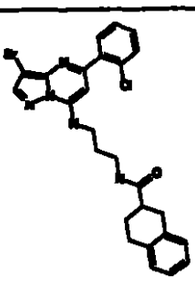
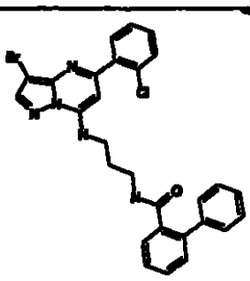
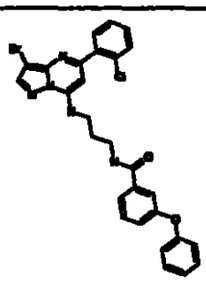
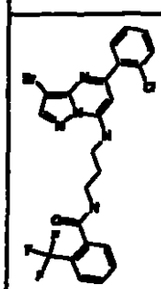
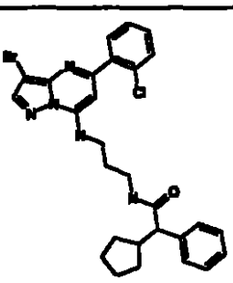
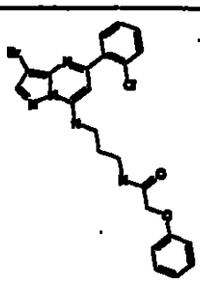
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	1. 5091 2. 616.34
	1. 5092 2. 450.25
	1. 5093 2. 518.28
	1. 5094 2. 512.28
	1. 5095 2.554.3

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. 476.8		1. 5112 2. 494.8
	1. 5103 2. 466.8		1. 5108 2. 476.8		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

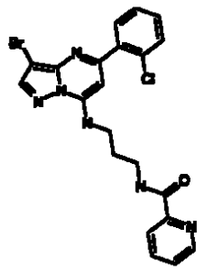
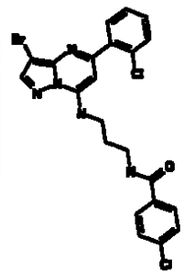
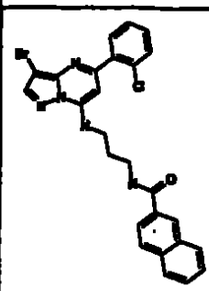
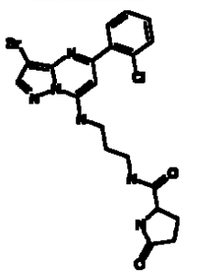
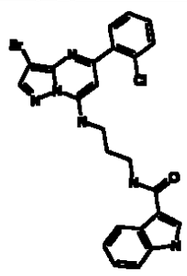
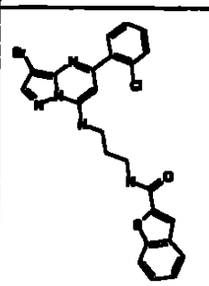
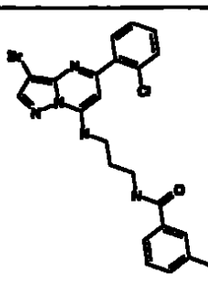
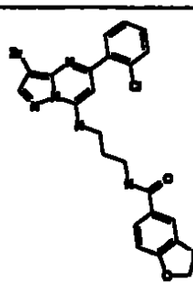
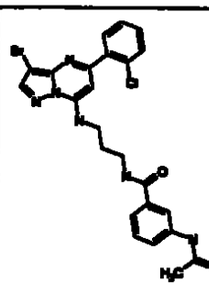
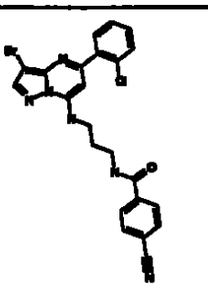
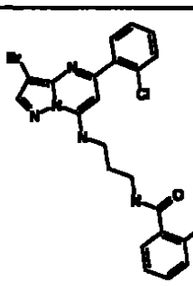
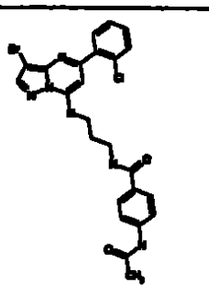
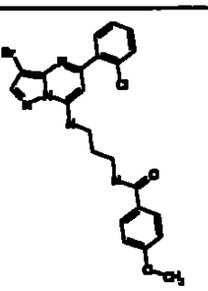
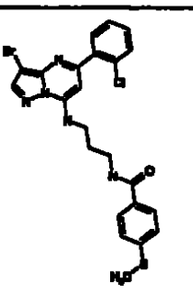
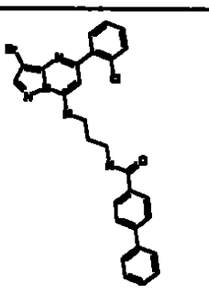
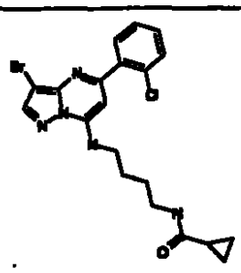
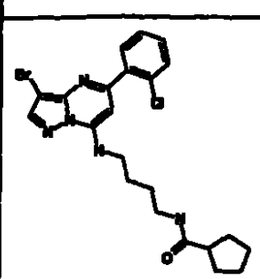
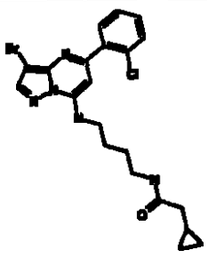
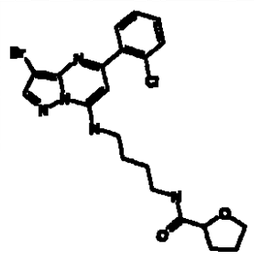
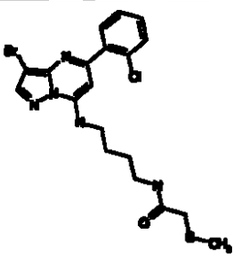
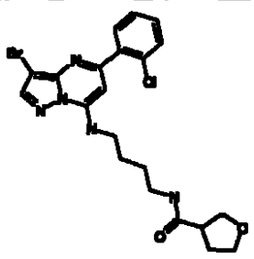
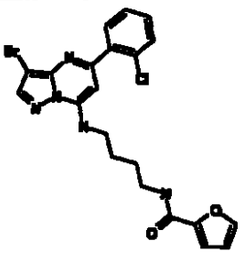
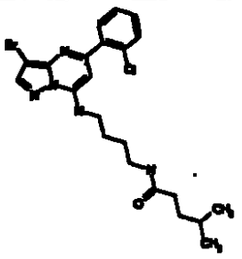
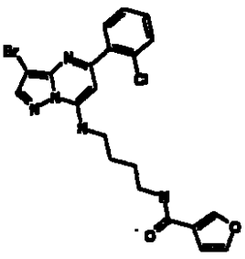
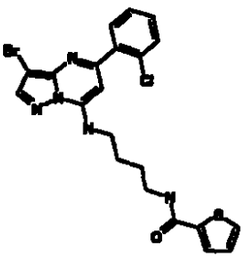
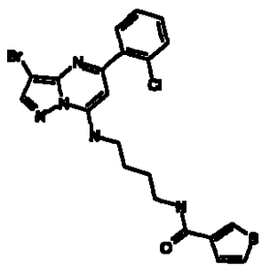
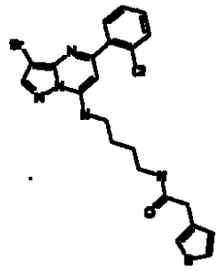
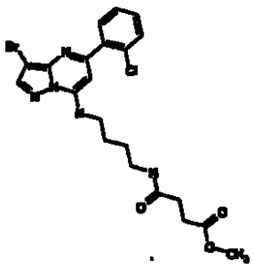
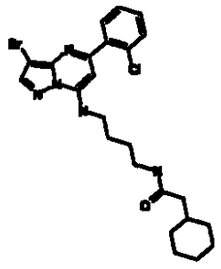
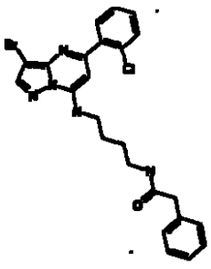
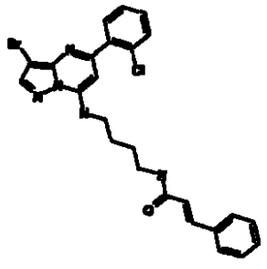
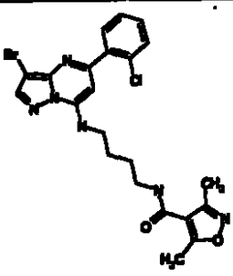
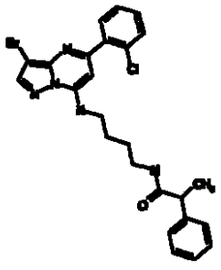
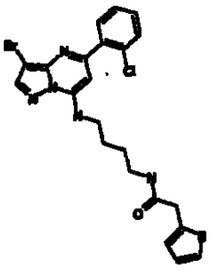
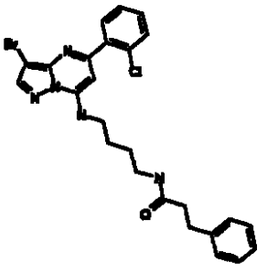
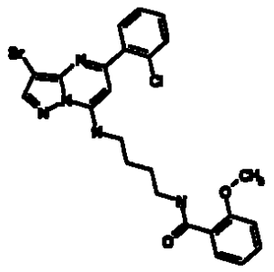
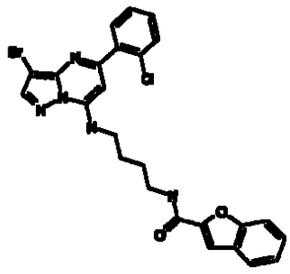
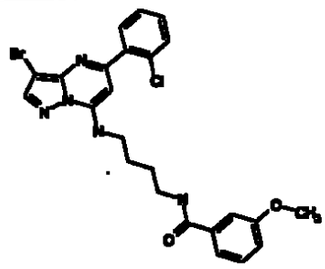
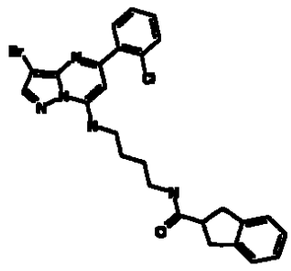
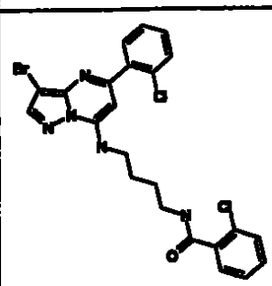
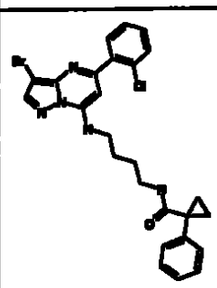
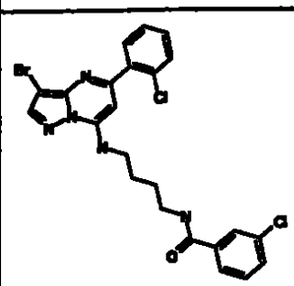
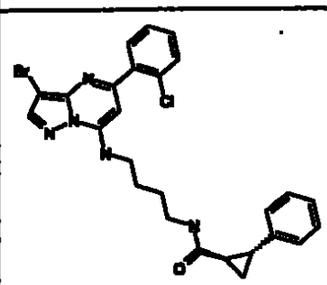
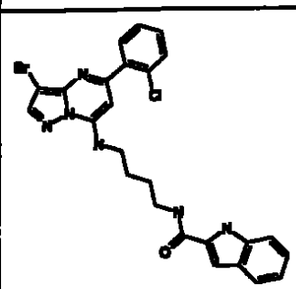
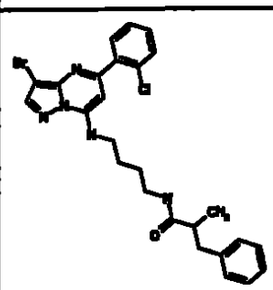
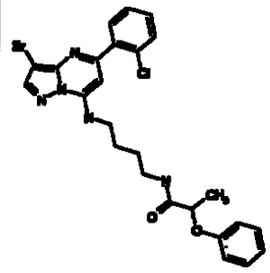
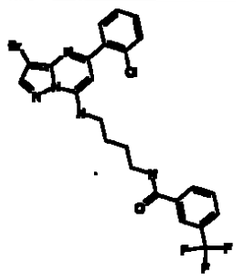
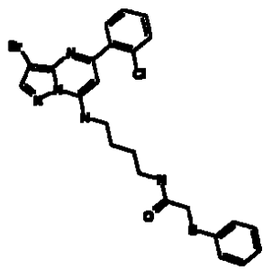
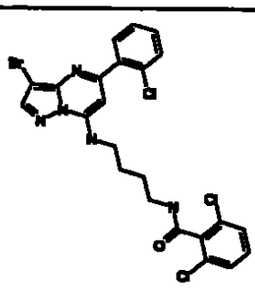
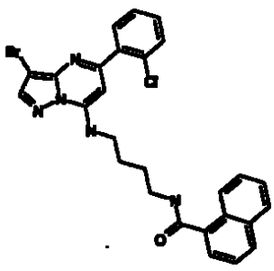
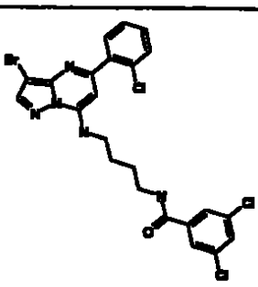
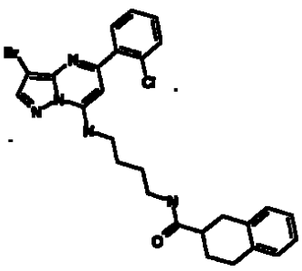
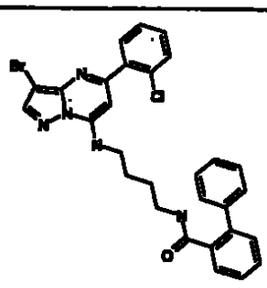
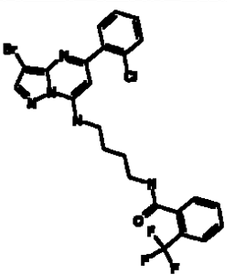
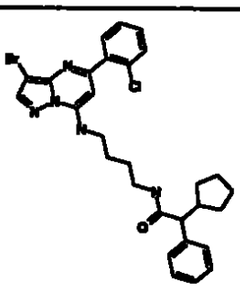
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	1. 5146 2. 485.8		1. 5151 2. 519.2		1. 5156 2. 534.8
	1. 5147 2. 491.8		1. 5152 2. 523.8		1. 5157 2. 540.9
	1. 5148 2. 509.8		1. 5153 2. 528.8		1. 5158 2. 541.8
	1. 5149 2. 509.8		1. 5154 2. 530.9		1. 5159 2. 541.8
	1. 5150 2. 514.8		1. 5155 2. 530.9		1. 5160 2. 560.9

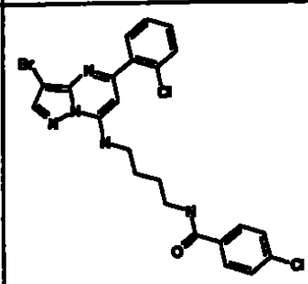
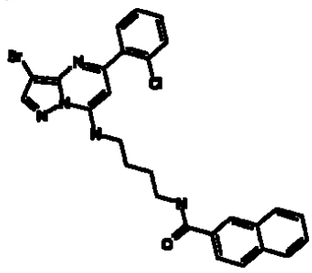
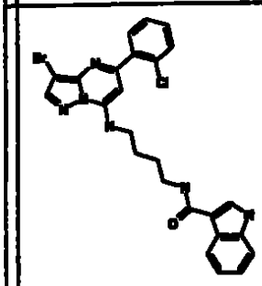
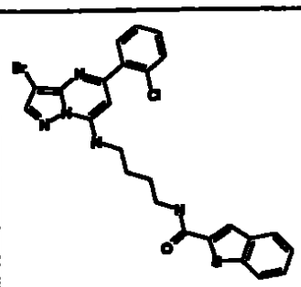
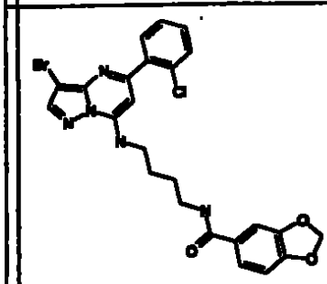
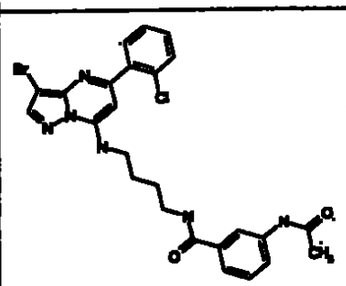
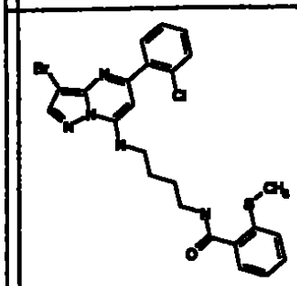
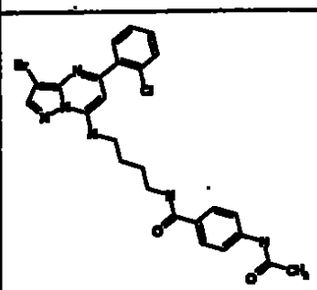
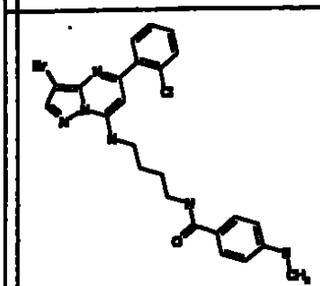
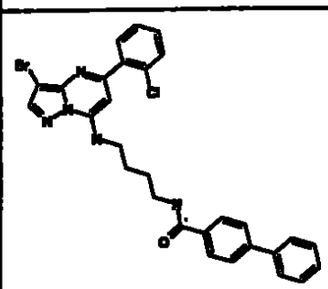
TABLE 52

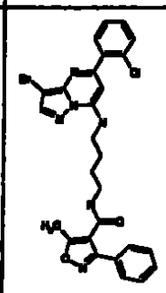
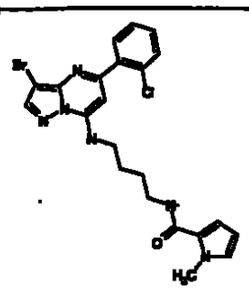
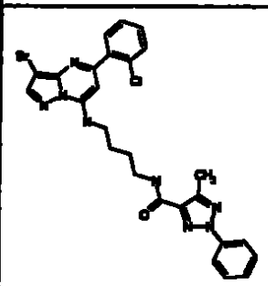
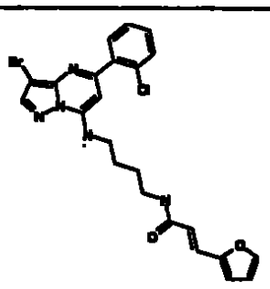
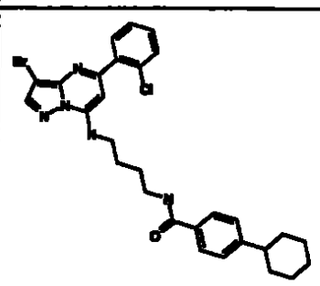
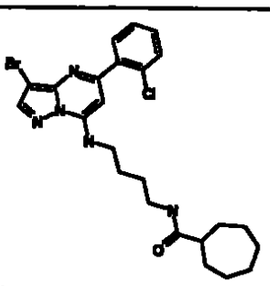
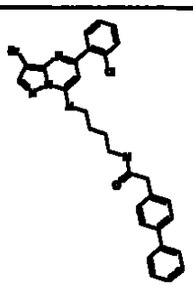
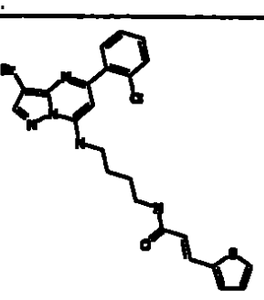
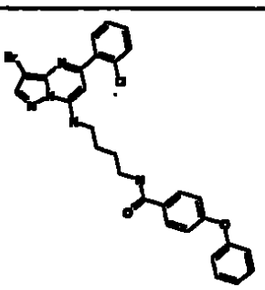
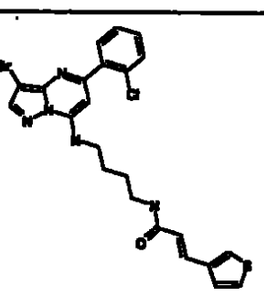
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	1. 5202 2. 476.8		1. 5207 2. 492.8
	1. 5203 2. 482.8		1. 5208 2. 492.8
	1. 5204 2. 488.8		1. 52009 2. 492.9
	1. 5205 2. 488.8		1. 5210 2. 504.8

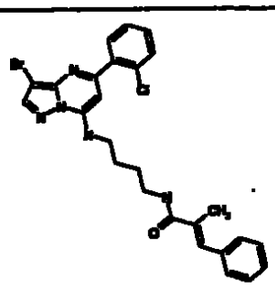
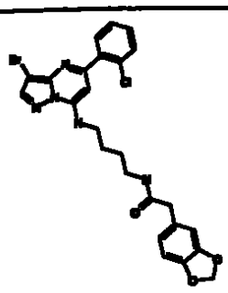
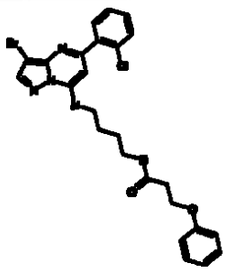
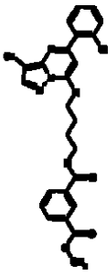
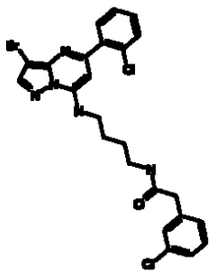
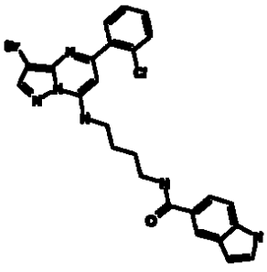
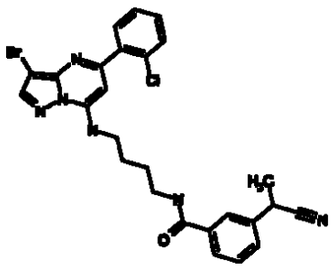
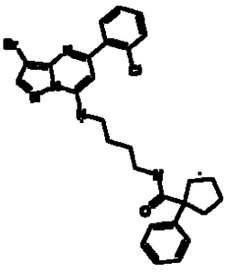
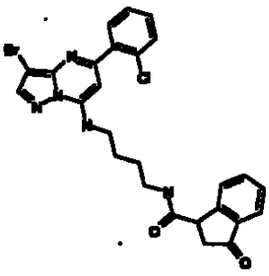
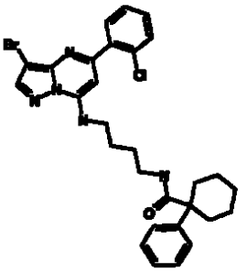
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	2. 5212 2. 508.8			1. 5217 2. 518.9
	1. 5213 2. 512.8			1. 5218 2. 524.9
	1. 5214 2. 517.8			1. 5219 2. 526.9
	1. 5215 2. 518.9			1. 5220 2. 526.9

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. 536.9
	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		Product	1. Ex. 2. m/z
	1. 5231 2. 542.9			1. 5236 2. 566.8
	1. 5232 2. 544.9			1. 5237 2. 567.7
	1. 5233 2. 548.9			1. 5238 2. 567.7
	1. 5234 2. 552.9			1. 5239 2. 574.9
	1. 5235 2. 566.8			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
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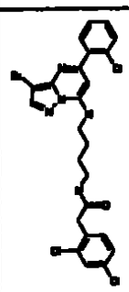
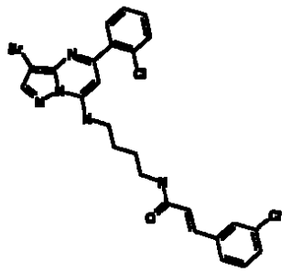
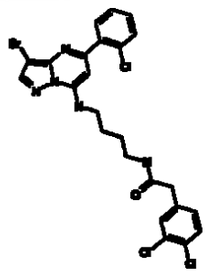
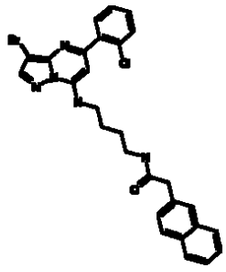
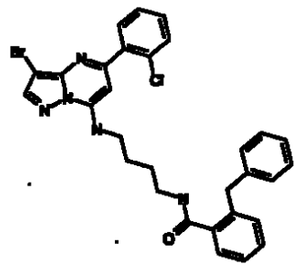
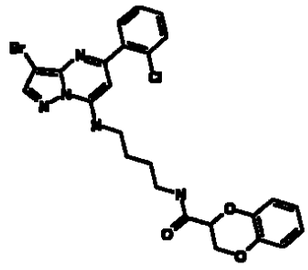
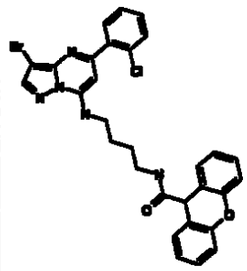
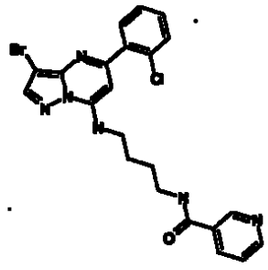
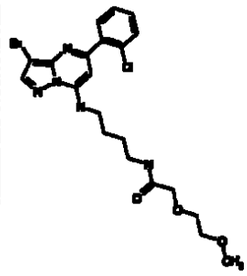
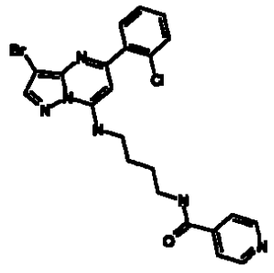
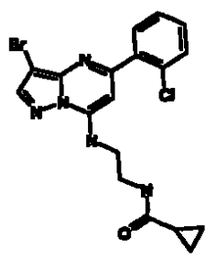
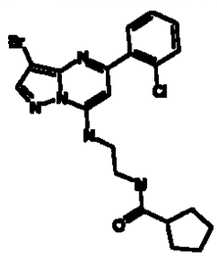
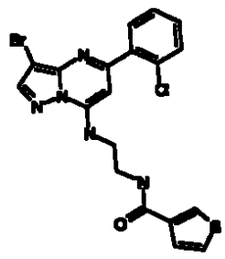
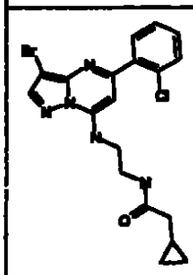
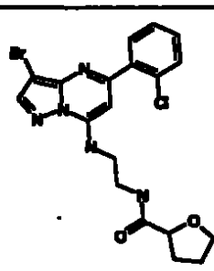
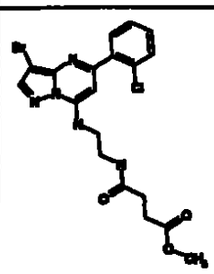
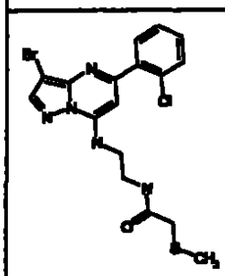
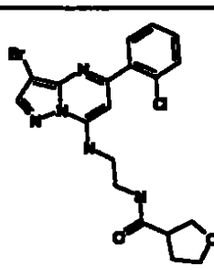
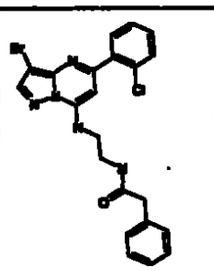
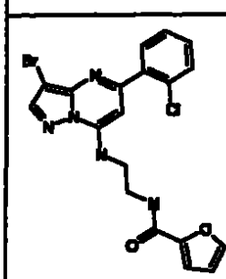
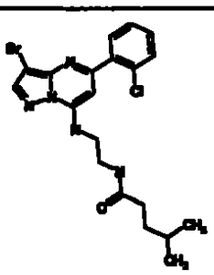
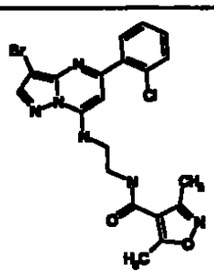
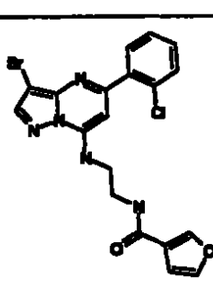
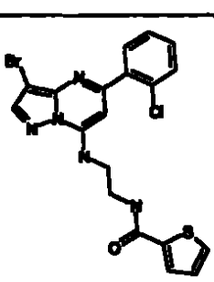
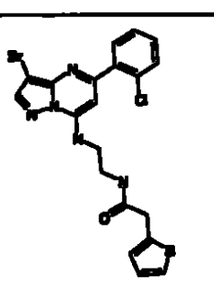
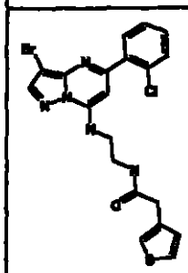
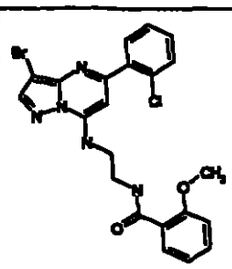
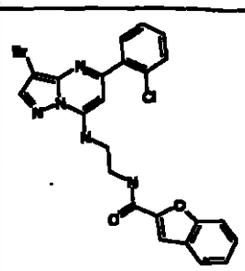
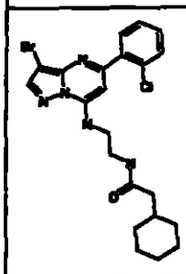
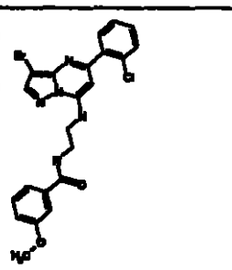
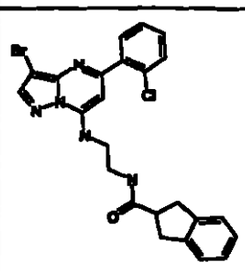
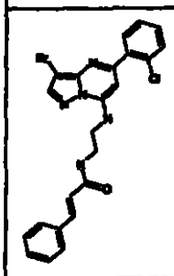
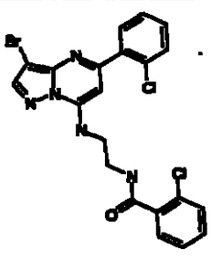
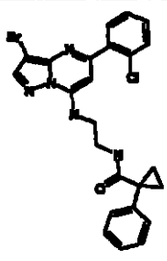
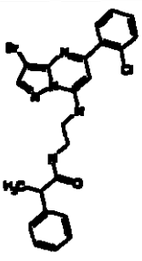
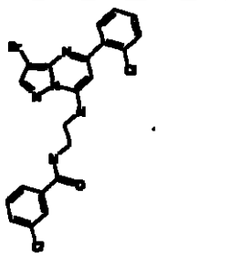
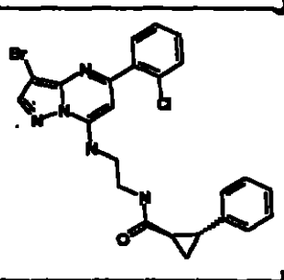
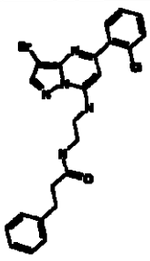
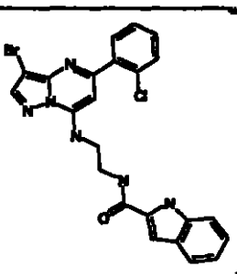
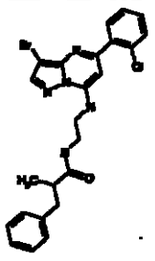
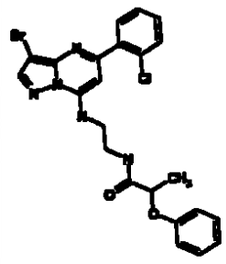
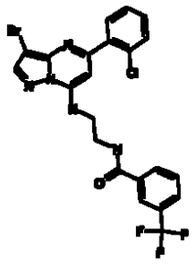
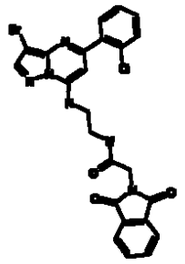
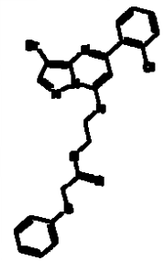
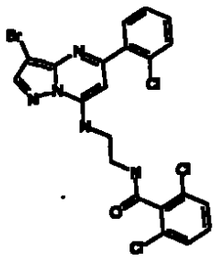
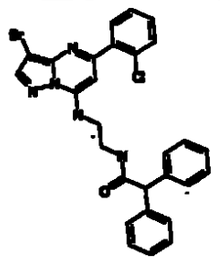
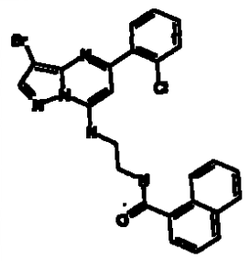
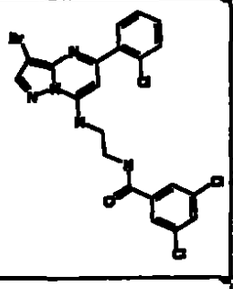
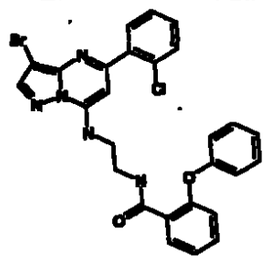
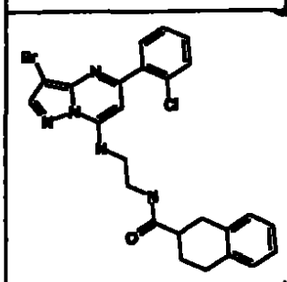
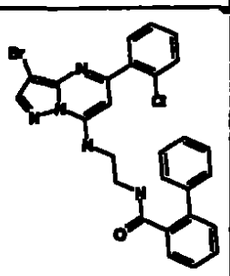
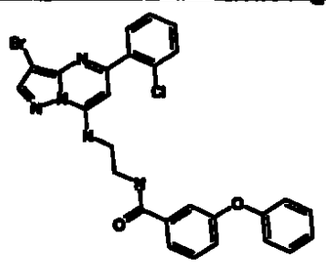
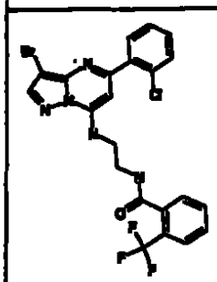
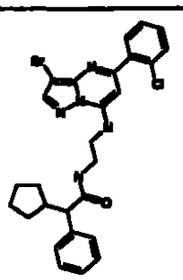
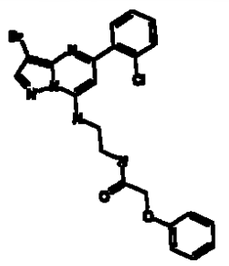
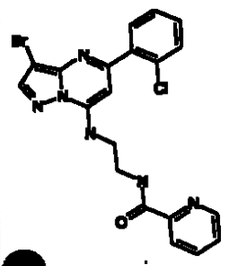
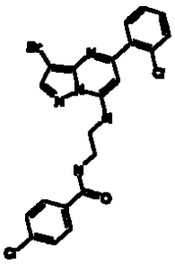
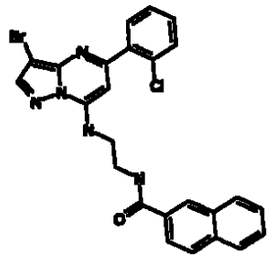
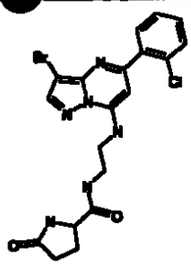
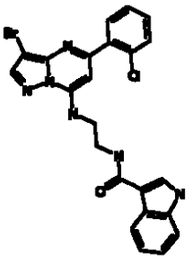
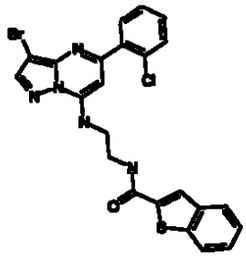
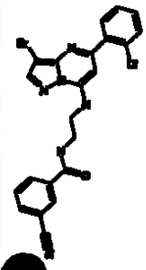
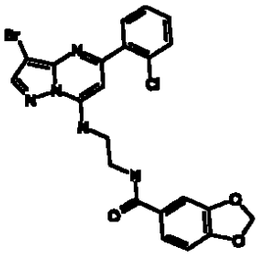
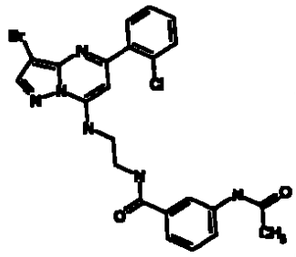
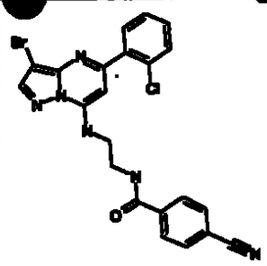
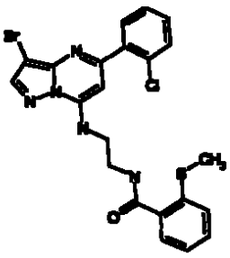
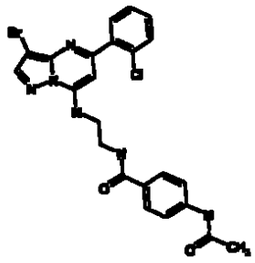
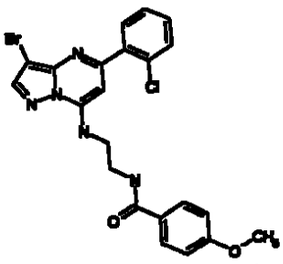
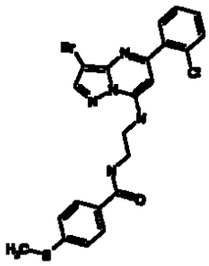
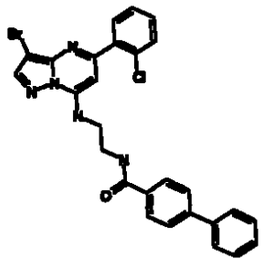
Product	1. Ex. 2. m/z		Product	1. Ex. 2. m/z
	1. 5271 2. 581.7			1. 5276 2. 559.3
	1. 5272 2. 581.7			1. 5277 2. 562.9
	1. 5273 2. 588.9			1. 5278 2. 556.9
	1. 5274 2. 602.9			1. 5279 2. 499.8
	1. 5275 2. 510.8			1. 5280 2. 499.8

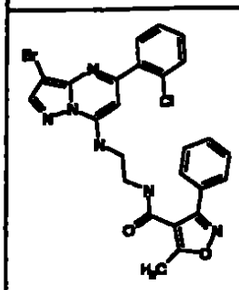
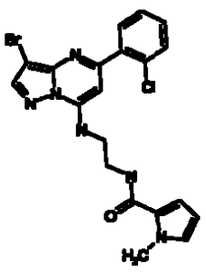
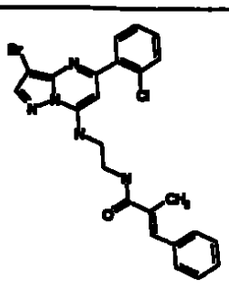
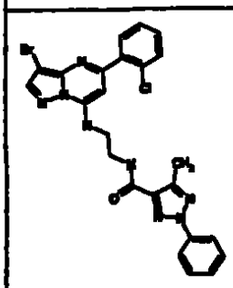
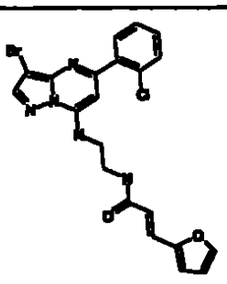
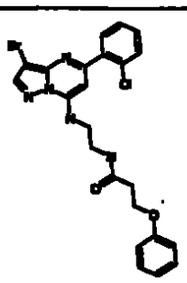
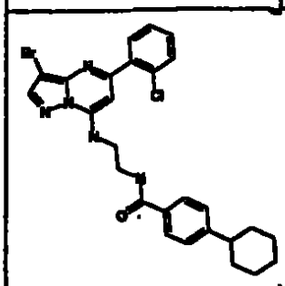
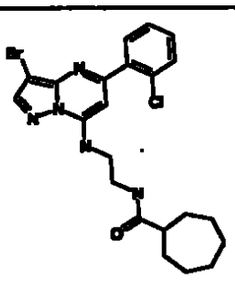
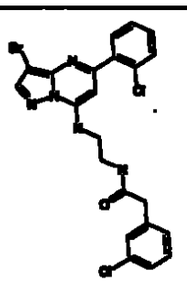
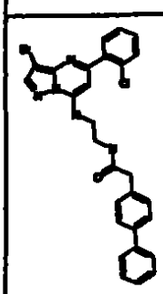
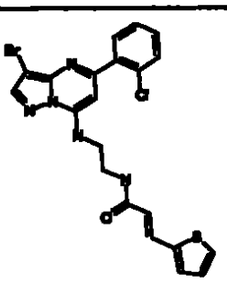
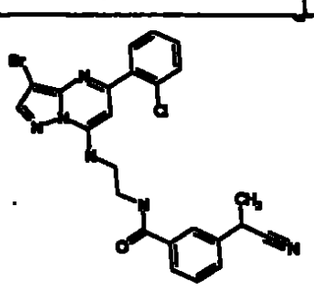
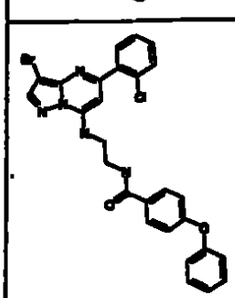
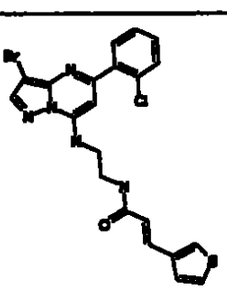
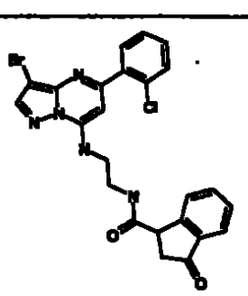
TABLE 53

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. 464.8
	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. 496.8		1. 5324 2. 505.2		1. 5329 2. 510.8
	1. 5320 2. 496.8		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. 536.8		1. 5341 2. 553.8
	1. 5332 2. 516.9		1. 5337 2. 539.8		1. 5342 2. 580.9
	1. 5333 2. 520.8		1. 5338 2. 539.6		1. 5343 2. 582.9
	1. 5334 2. 524.9		1. 5339 2. 546.9		1. 5344 2. 582.9
	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 . 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

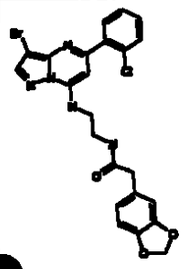
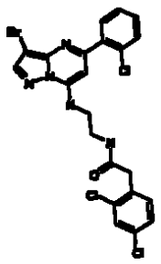
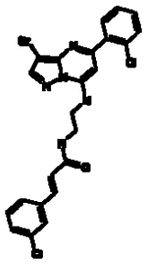
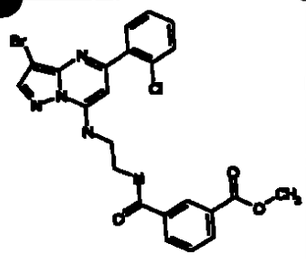
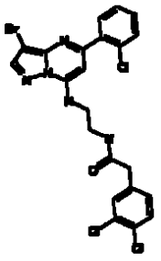
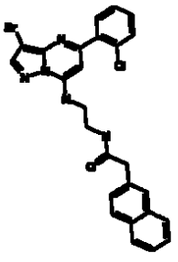
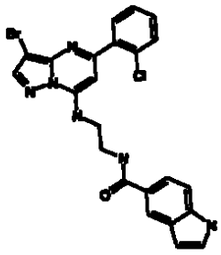
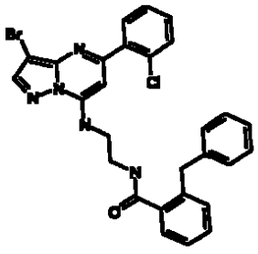
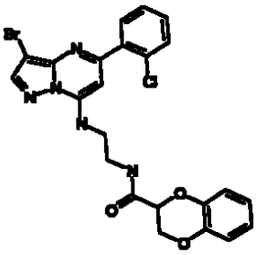
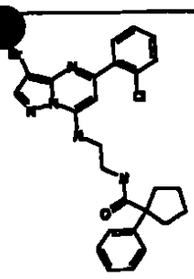
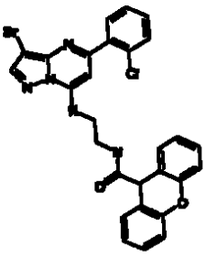
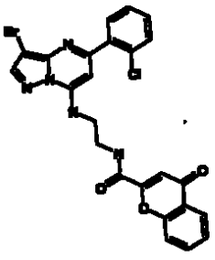
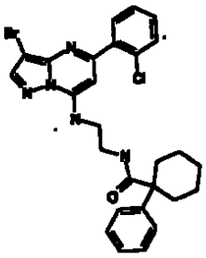
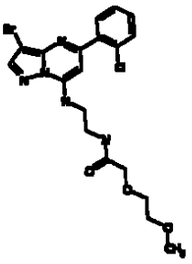
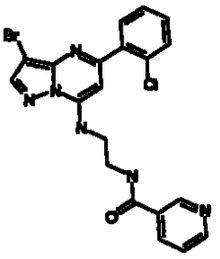
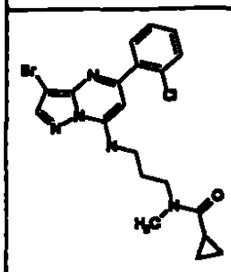
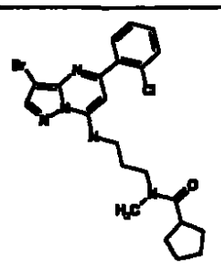
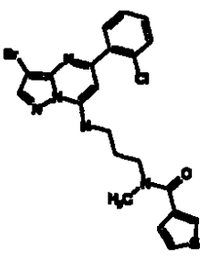
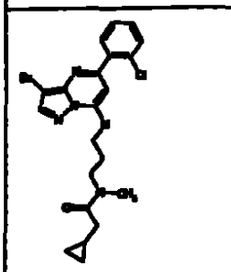
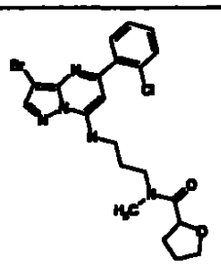
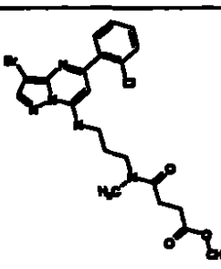
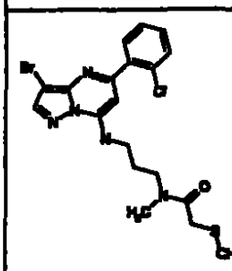
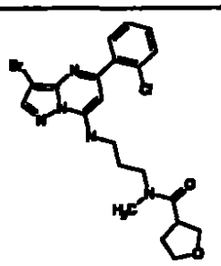
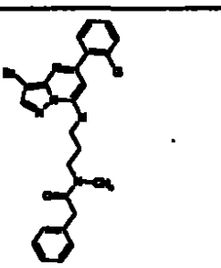
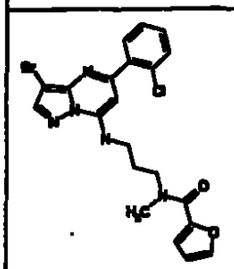
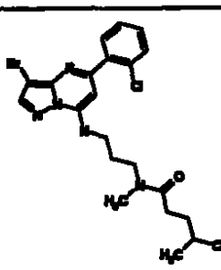
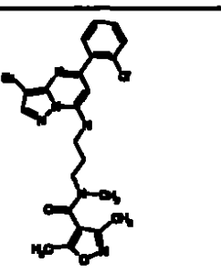
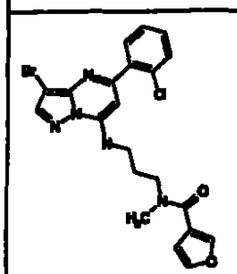
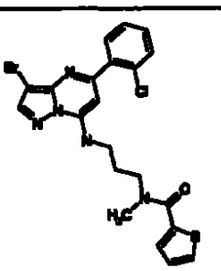
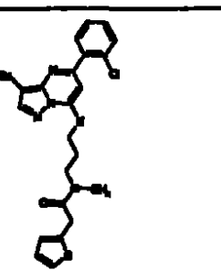
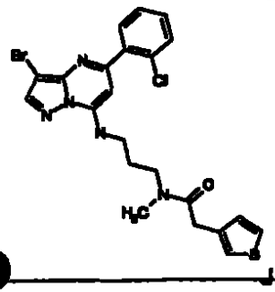
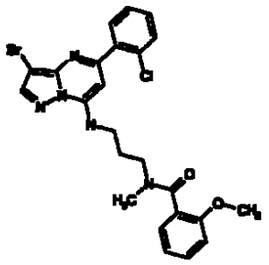
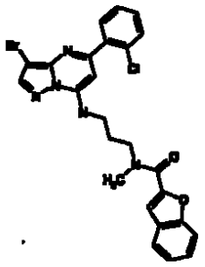
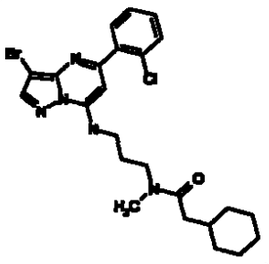
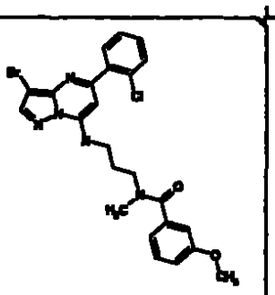
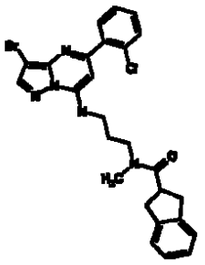
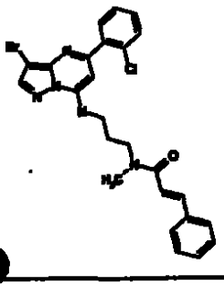
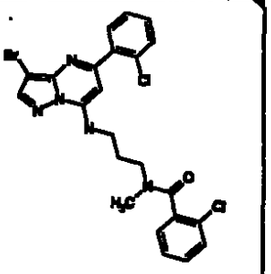
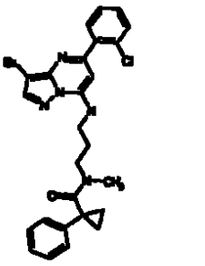
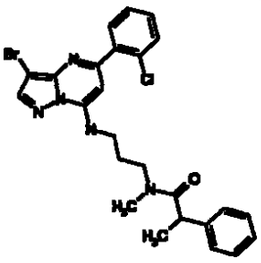
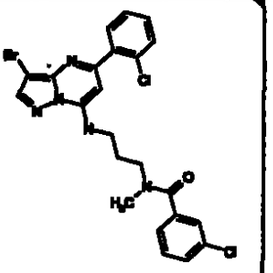
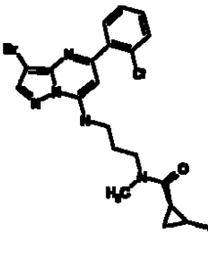
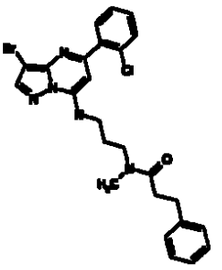
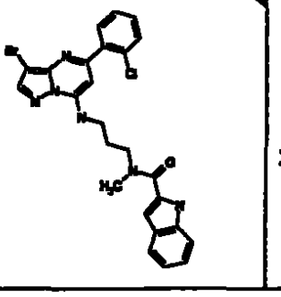
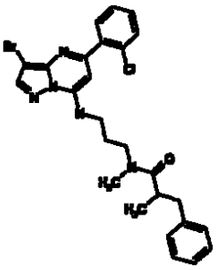
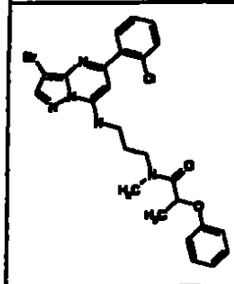
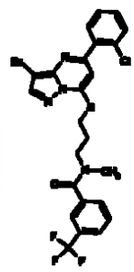
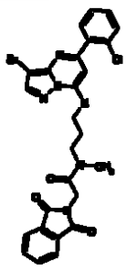
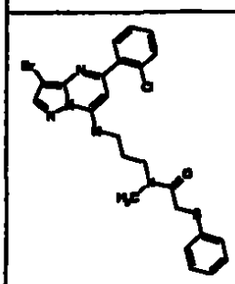
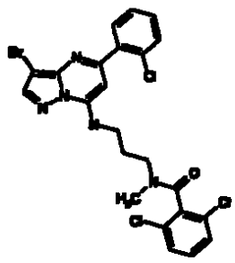
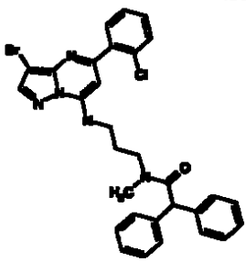
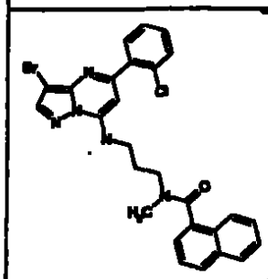
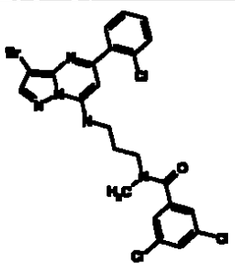
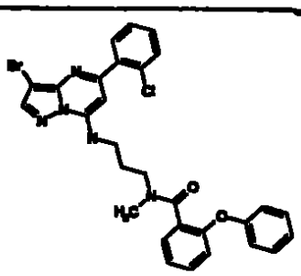
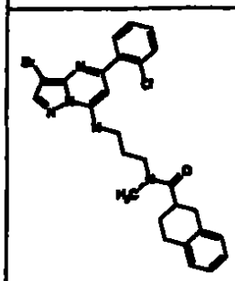
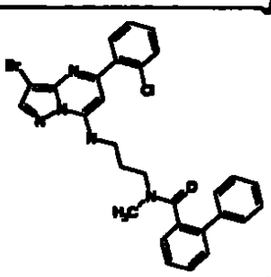
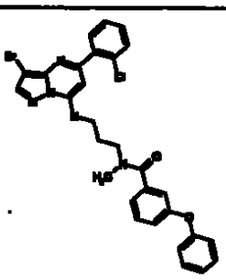
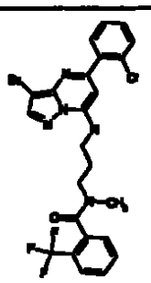
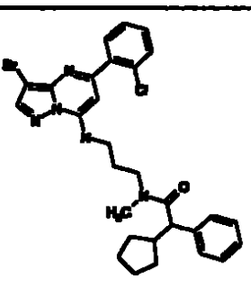
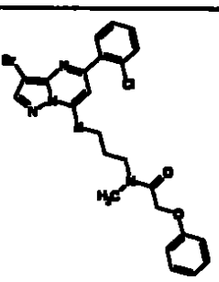
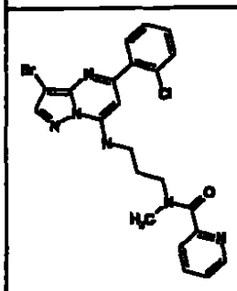
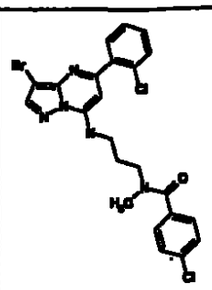
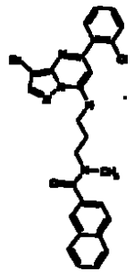
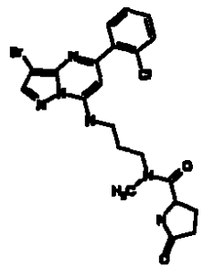
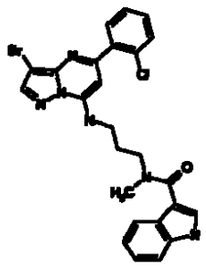
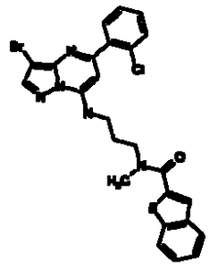
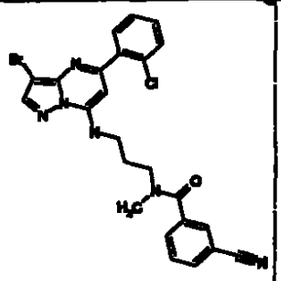
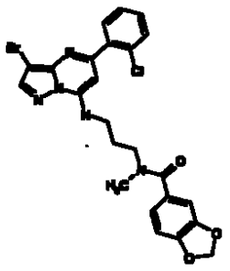
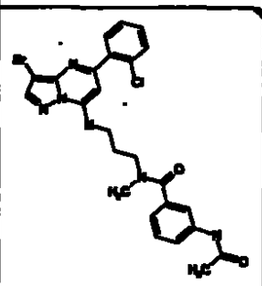
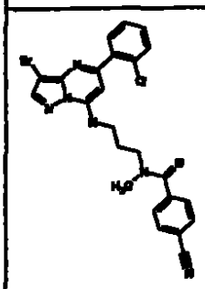
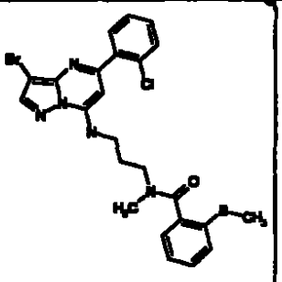
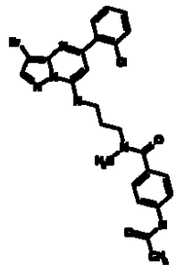
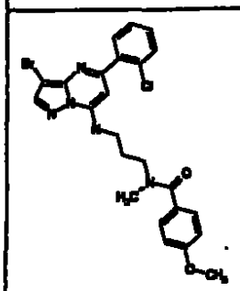
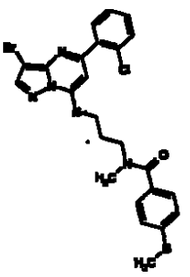
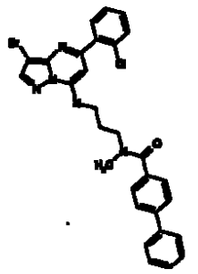
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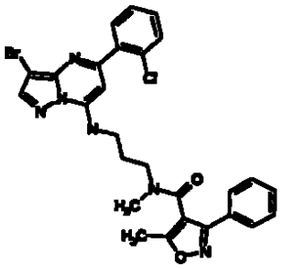
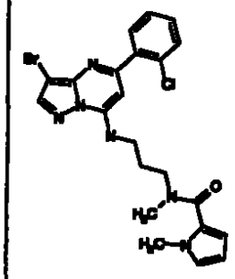
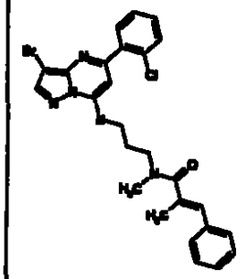
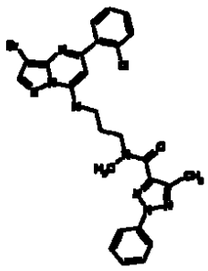
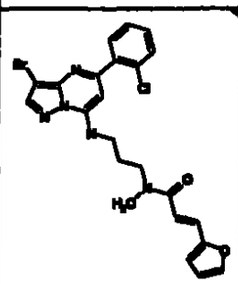
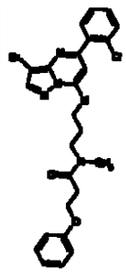
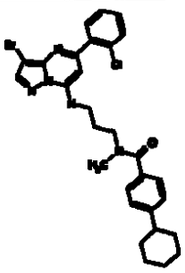
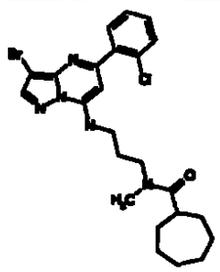
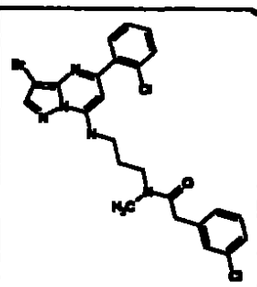
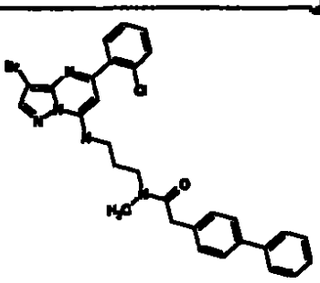
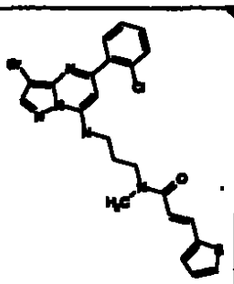
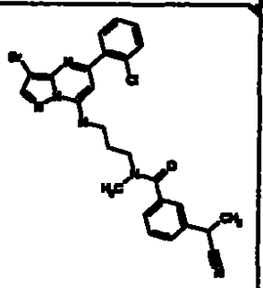
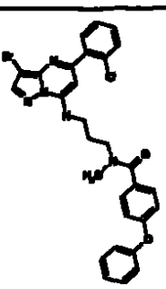
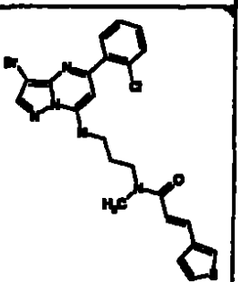
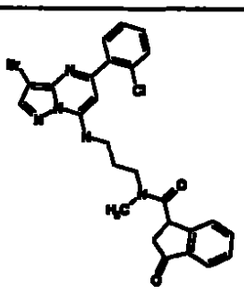
TABLE 54

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. 536.3		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 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

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

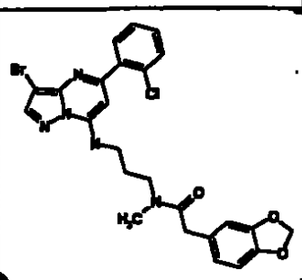
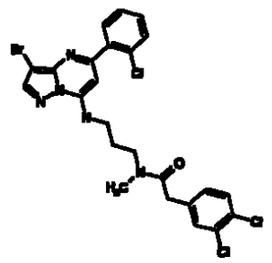
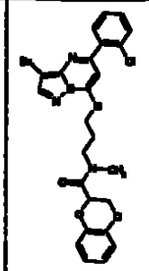
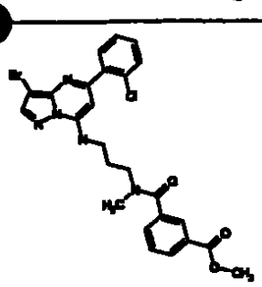
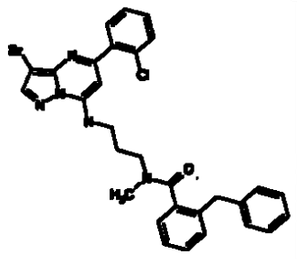
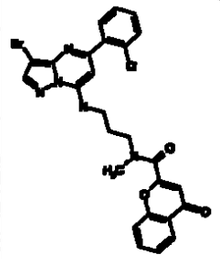
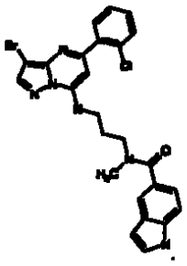
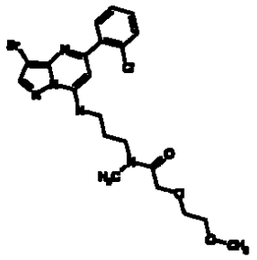
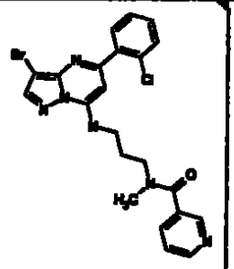
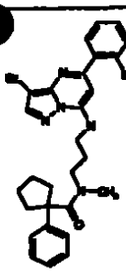
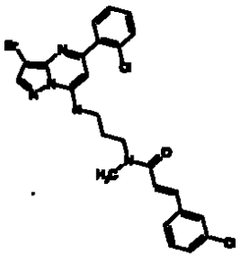
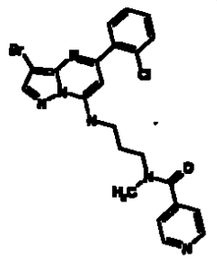
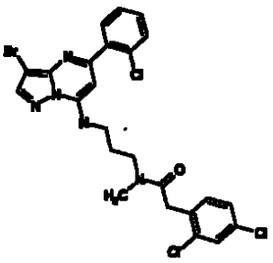
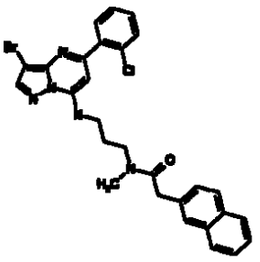
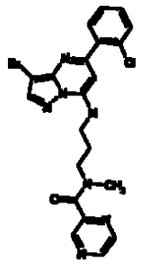
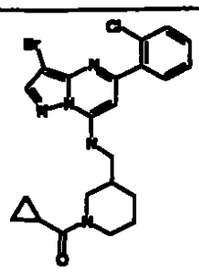
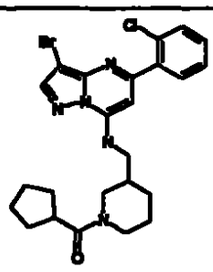
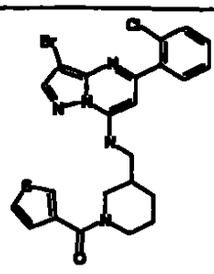
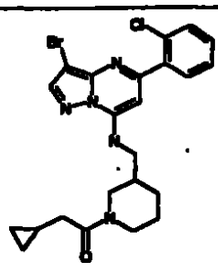
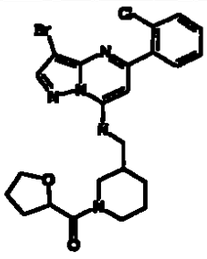
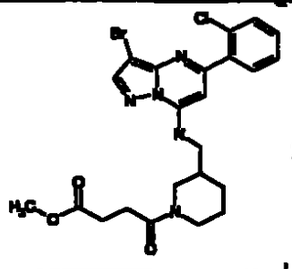
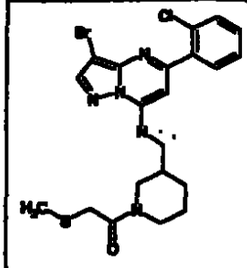
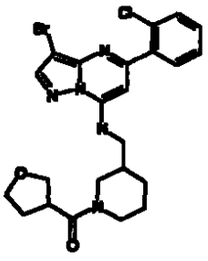
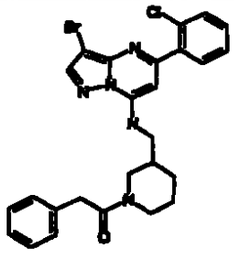
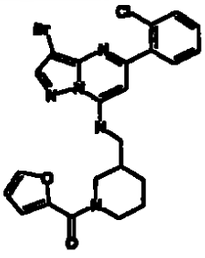
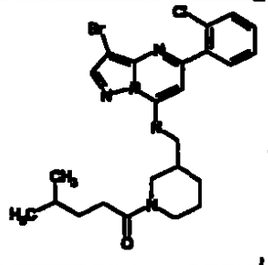
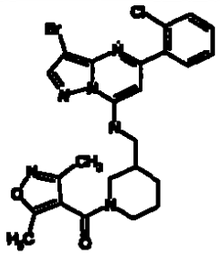
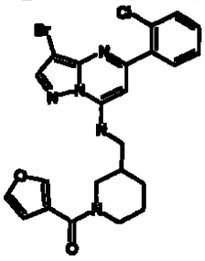
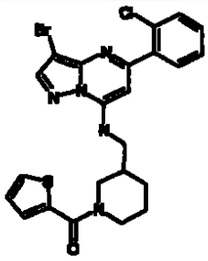
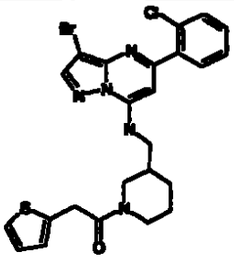
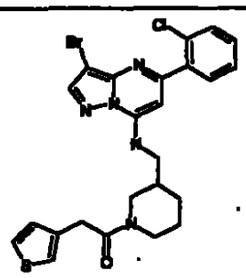
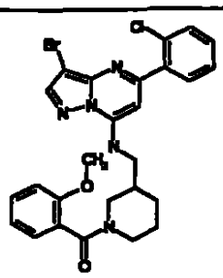
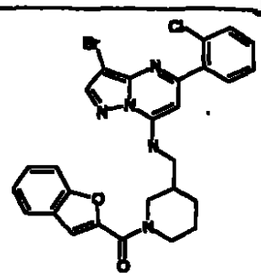
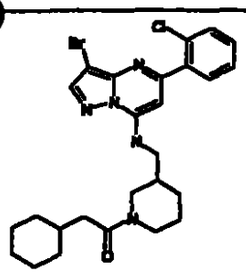
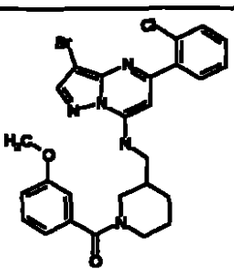
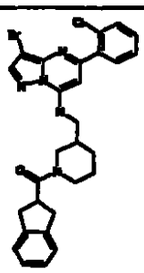
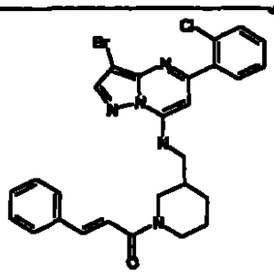
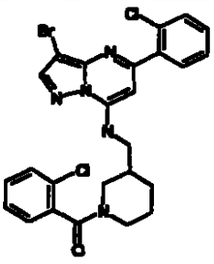
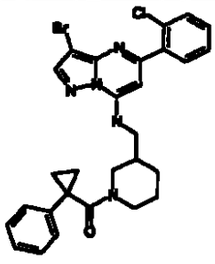
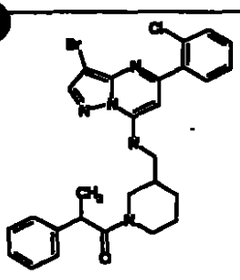
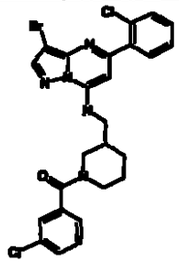
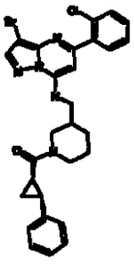
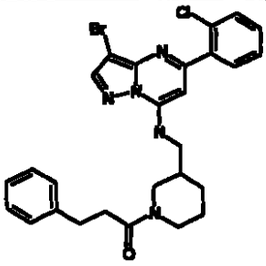
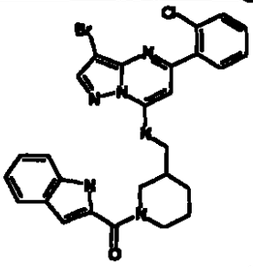
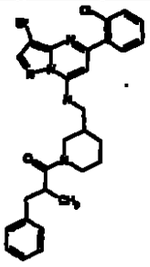
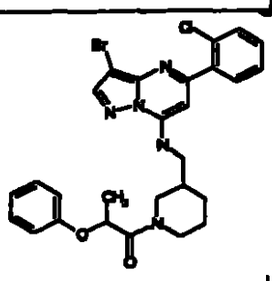
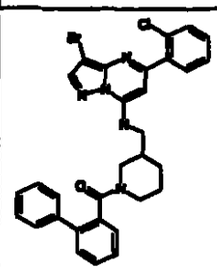
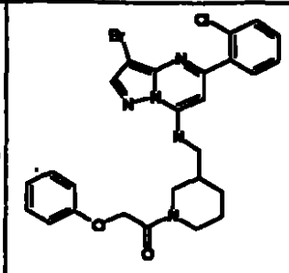
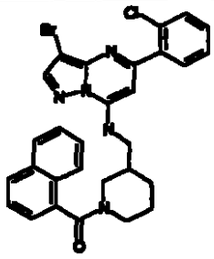
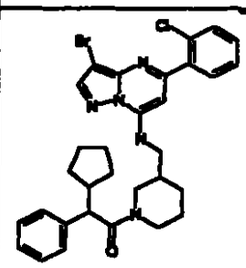
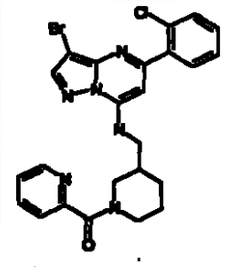
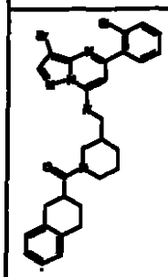
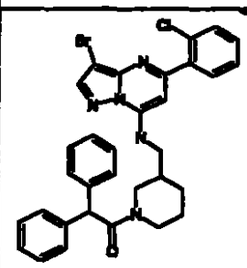
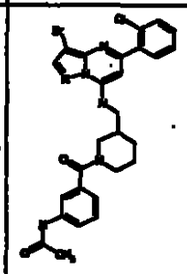
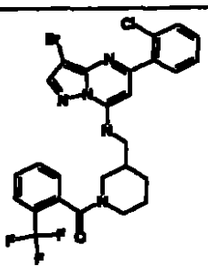
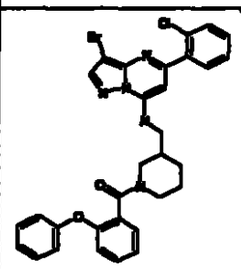
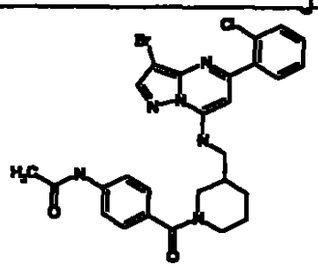
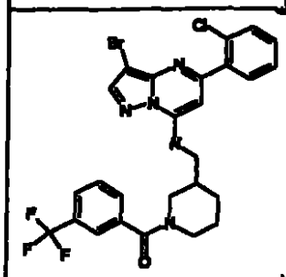
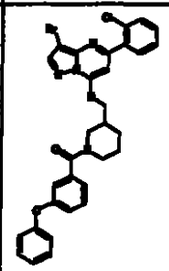
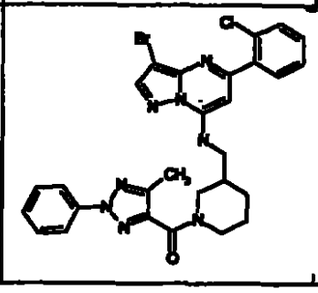
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	1. 5476 2. 557.3		1. 5481 2. 581.3		. 5486 2.
	1. 5477 2. 557.3		1. 5482 2. 589.3		1. 5487 2. 891.5
	1. 5478 2. 538.3		1. 5483 2. 511.3		1. 5488 2. 500.3
	1. 5479 2. 567.3		1. 5484 2. 559.3		1. 5489 2. 500.3
	1. 5480 2. 581.3		1. 5485 2. 563.3		1. 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. 536.87
	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. 566.9		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
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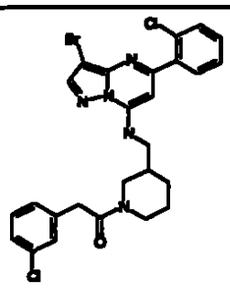
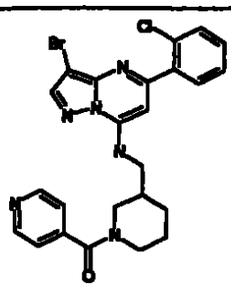
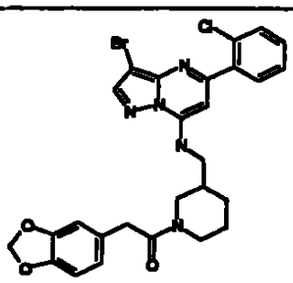
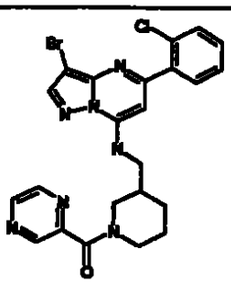
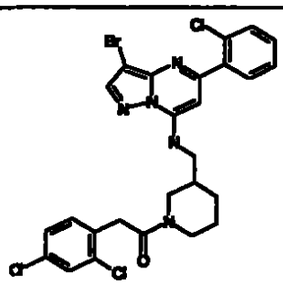
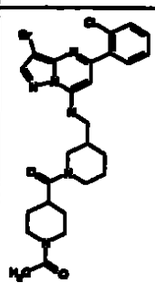
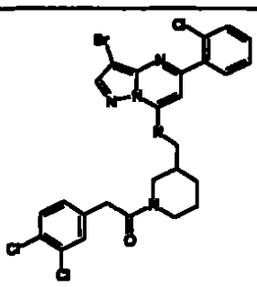
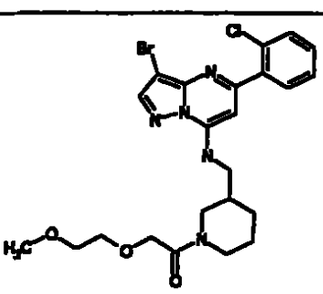
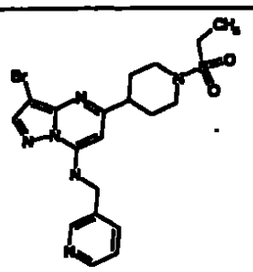
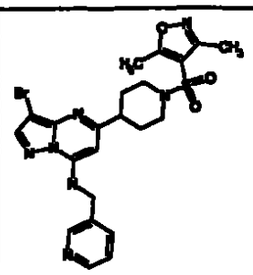
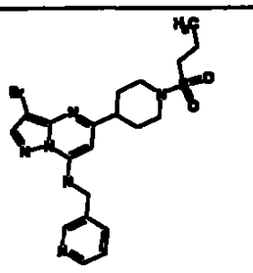
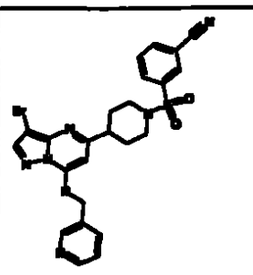
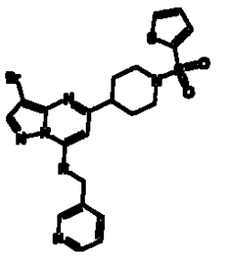
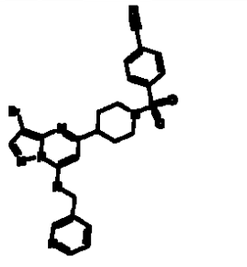
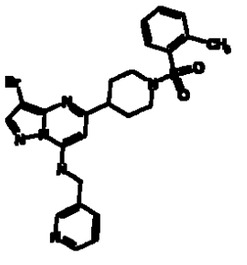
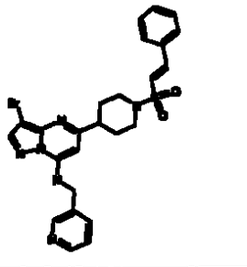
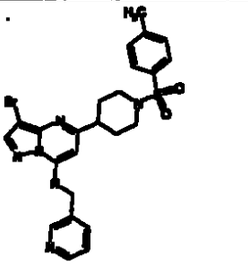
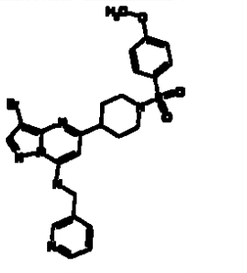
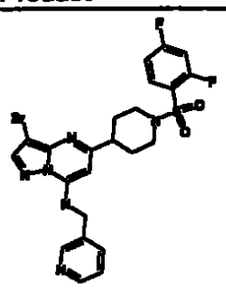
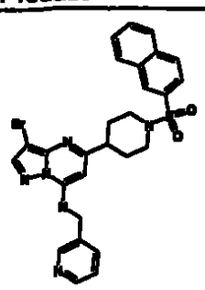
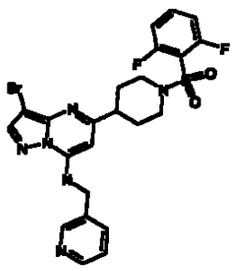
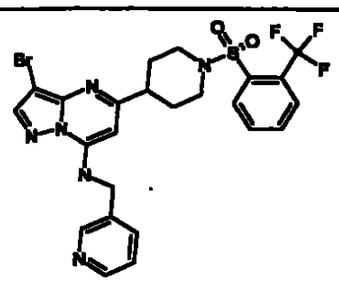
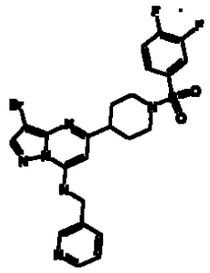
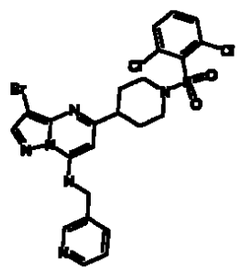
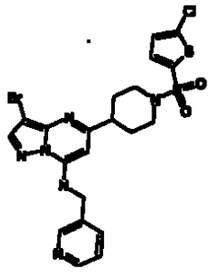
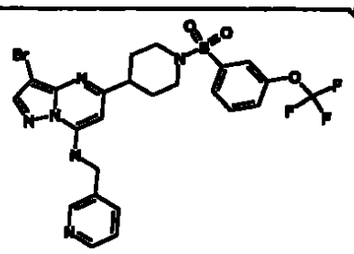
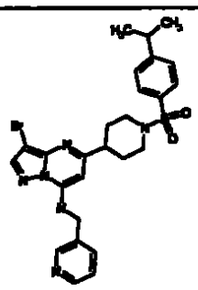
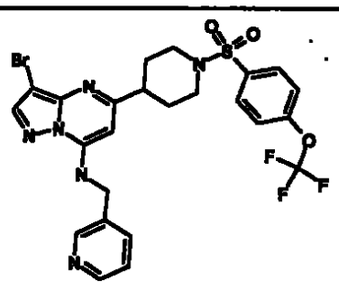
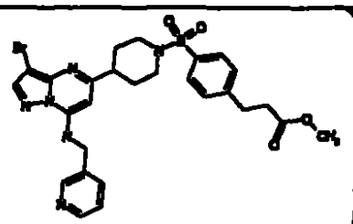
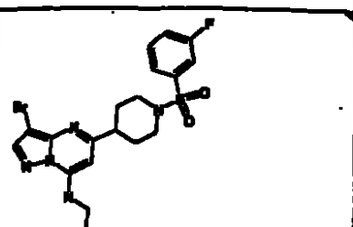
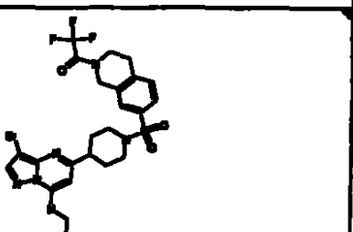
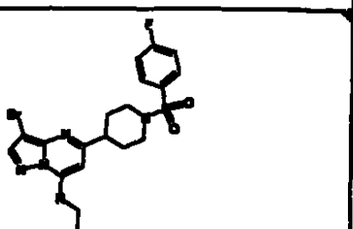
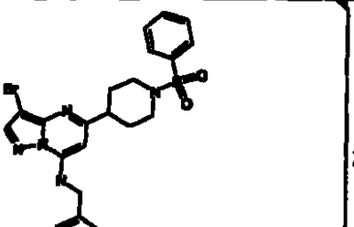
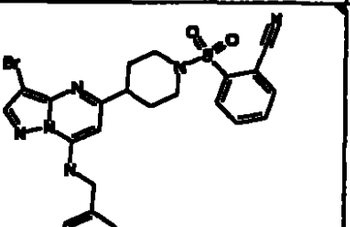
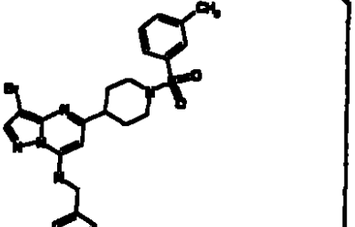
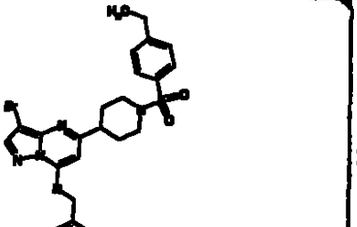
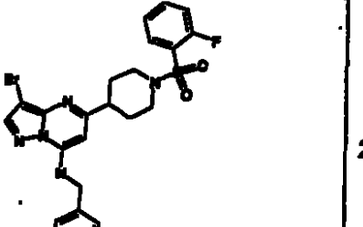
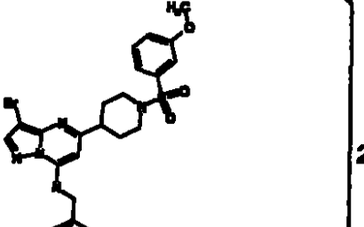
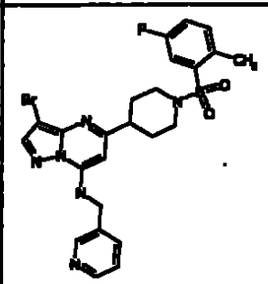
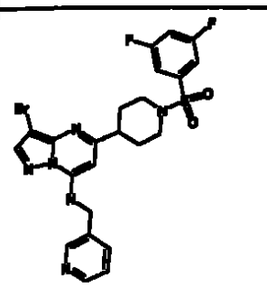
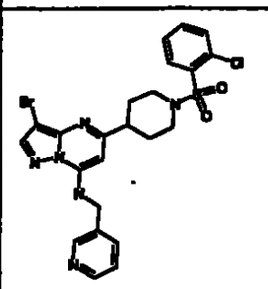
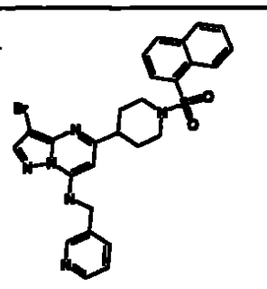
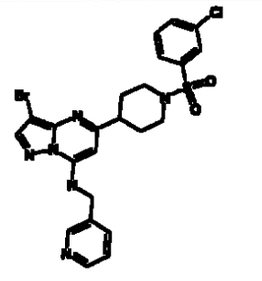
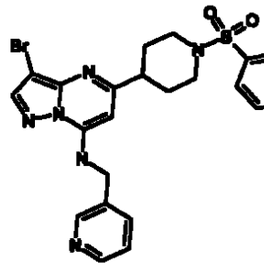
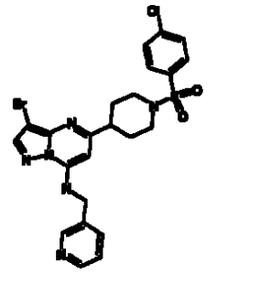
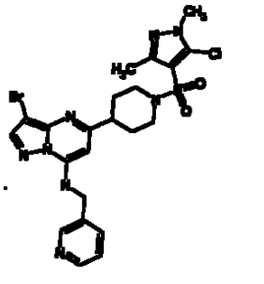
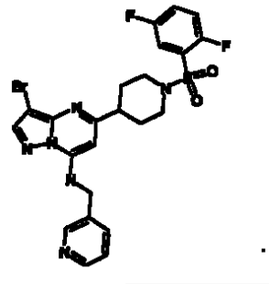
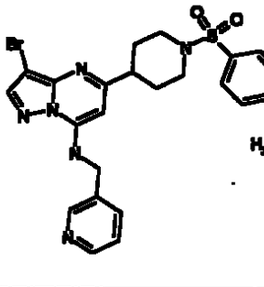
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	1. 5547 2. 582.88			1. 5552 2. 526.82
	1. 5548 2. 607.76			1. 5553 2. 573.92
	1. 5549 2. 607.76			
	1. 5550 2. 536.86			

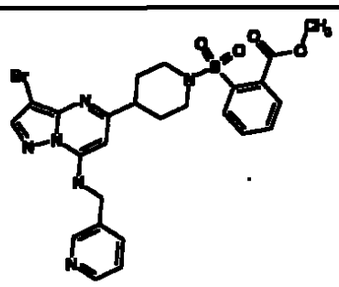
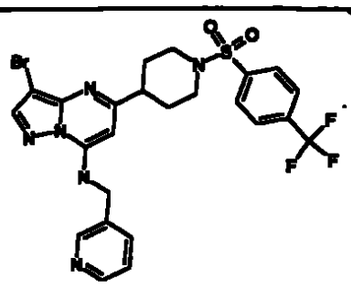
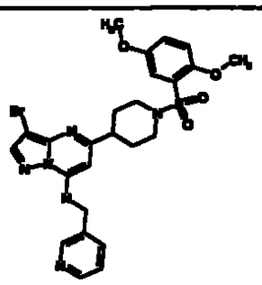
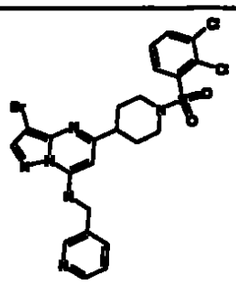
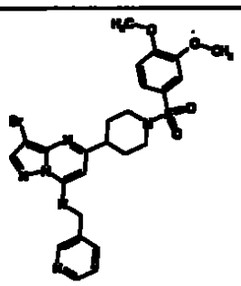
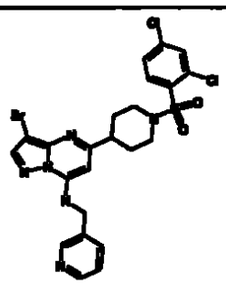
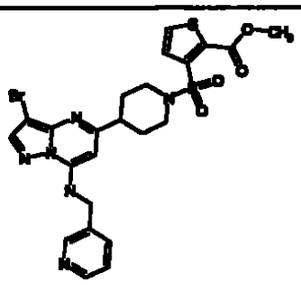
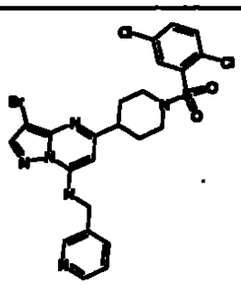
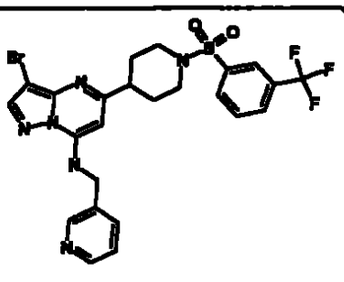
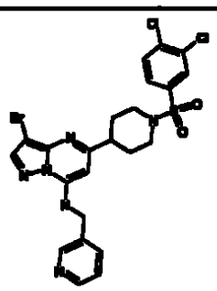
TABLE 56

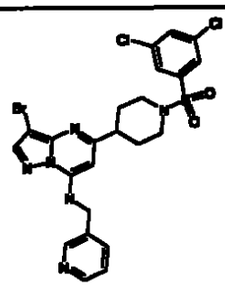
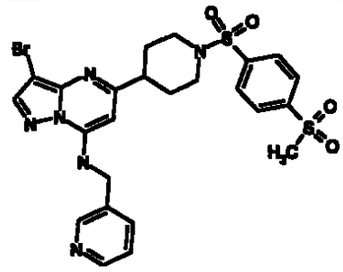
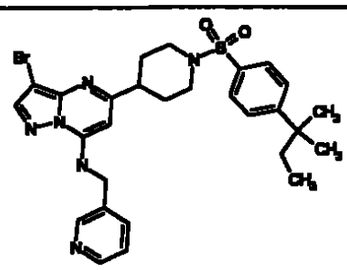
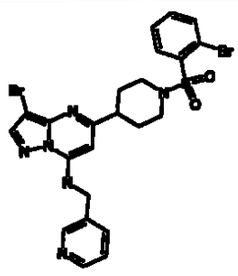
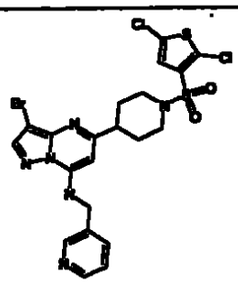
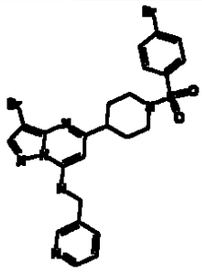
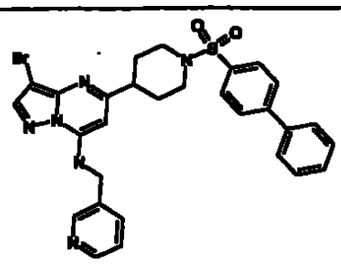
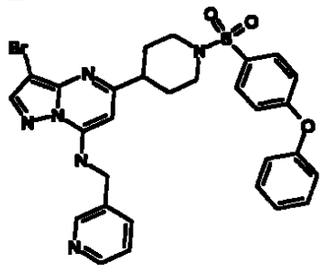
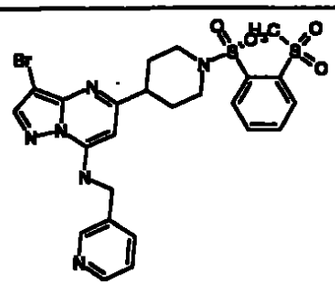
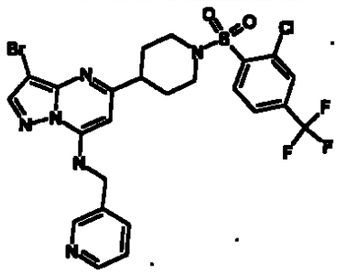
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	1. 5802 2. 495.27			1. 5807 2. 554.3
	1. 5803 2. 535.29			1. 5808 2. 554.3
	1. 5804 2. 543.3			1. 5809 2. 555.31
	1. 5805 2. 543.3			1. 5810 2. 559.31

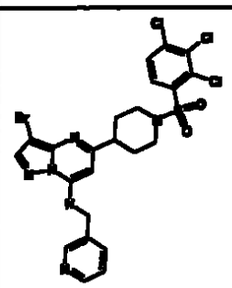
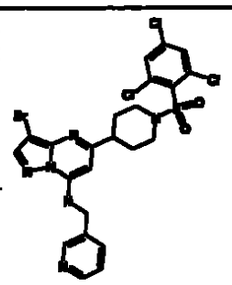
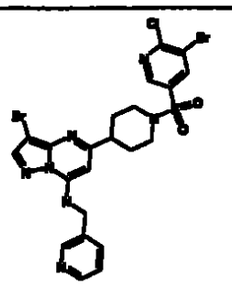
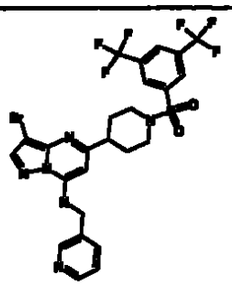
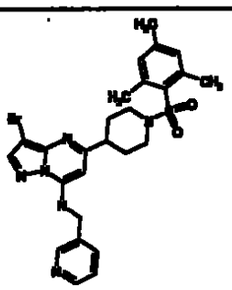
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	1. 5612 2. 565.31			1. 5617
	1. 5613 2. 565.31			1. 5618
	1. 5614 2. 569.31			1. 5619
	1. 5615 2. 571.31			1. 5620

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. 565.31
	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. 585.31
	1. 5632 2. 563.31			1. 5637 2. 579.32
	1. 5633 2. 563.31			1. 5638 2. 581.32
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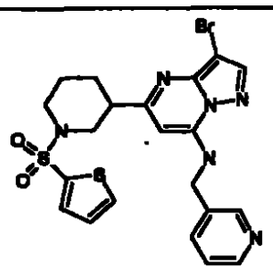
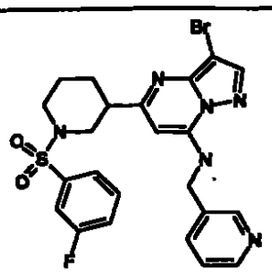
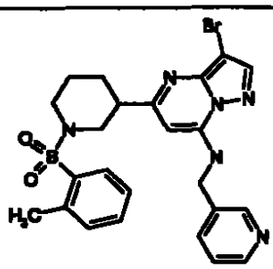
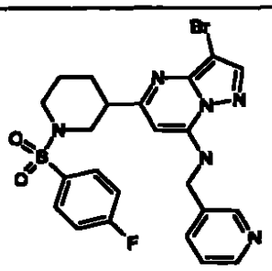
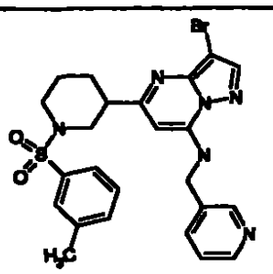
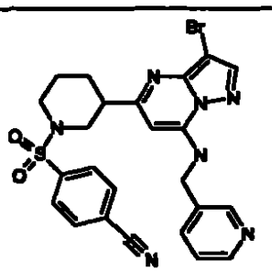
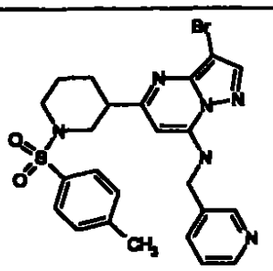
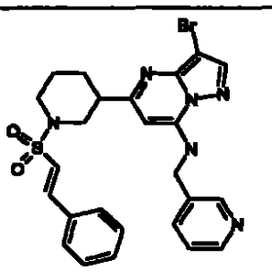
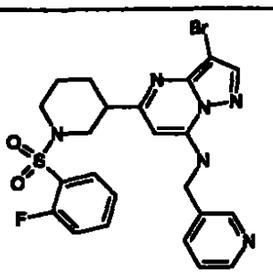
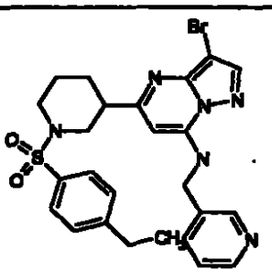
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	1. 5642 2. 589.32			1. 5647 2. 597.33
	1. 5643 2. 589.32			1. 5648 2. 597.33
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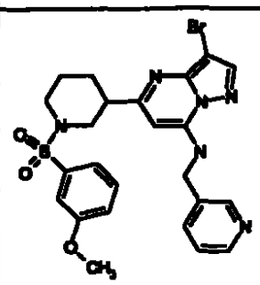
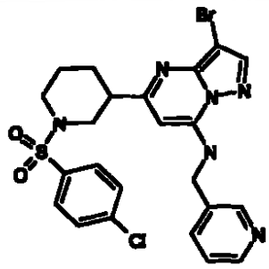
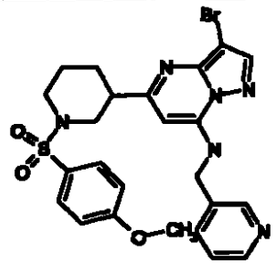
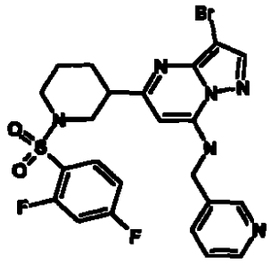
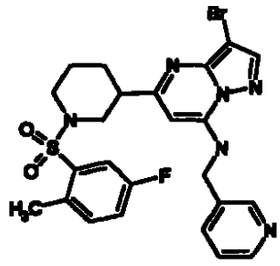
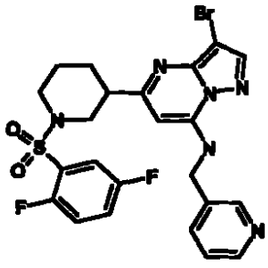
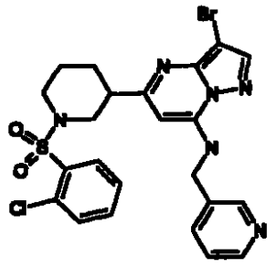
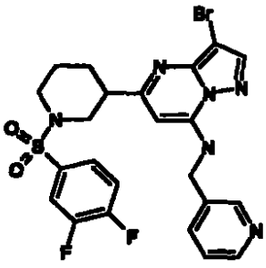
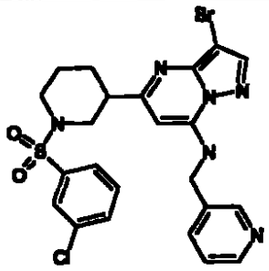
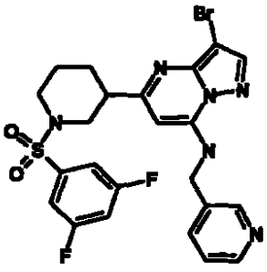
Product	1. Ex. 2. m/z		Product	1. Ex. 2. m/z
	1. 5651 2. 597.33			1. 5656 2. 607.33
	1. 5652 2. 599.33			1. 5657 2. 607.33
	1. 5653 2. 603.33			1. 5658 2. 607.33
	1. 5654 2. 605.33			1. 5659 2. 621.34
	1. 5655 2. 607.33			1. 5660 2. 631.35

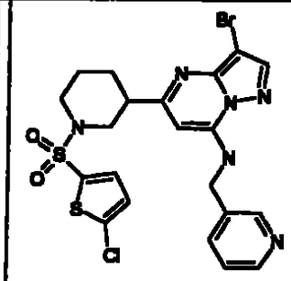
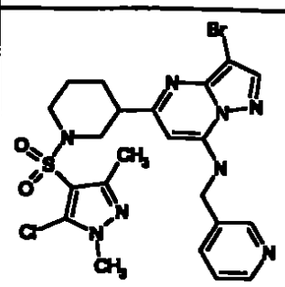
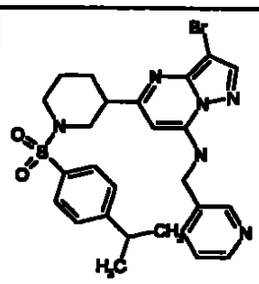
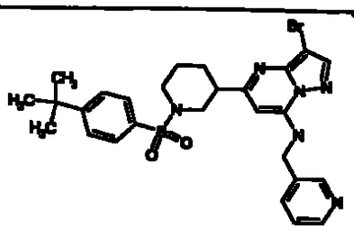
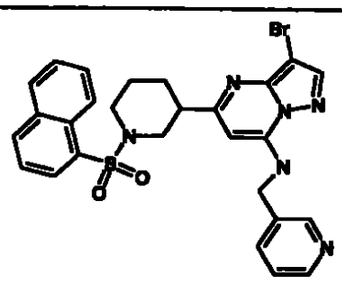
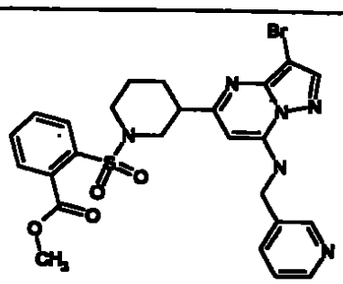
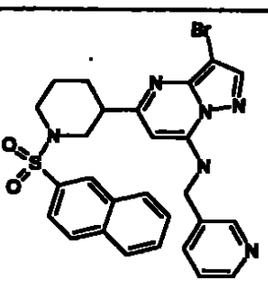
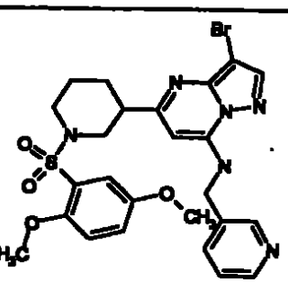
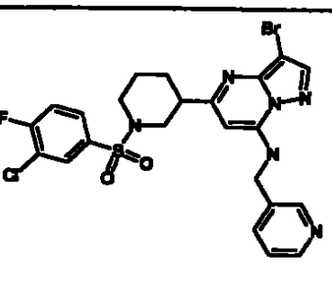
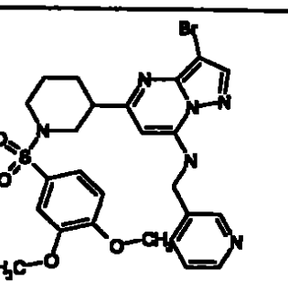
Product	1. Ex. 2. m/z
	1. 5661 2. 631.35
	1. 5662 2. 631.35
	1. 5663 2. 642.35
	1. 5664 2. 665.37
	1. 5665 2. 571.31

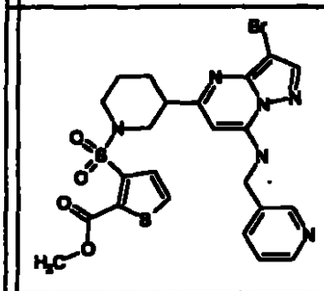
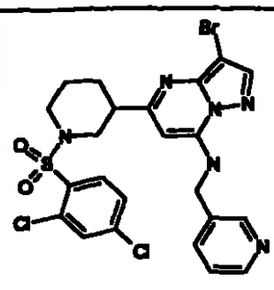
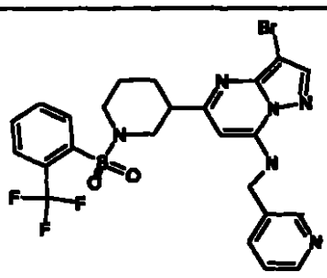
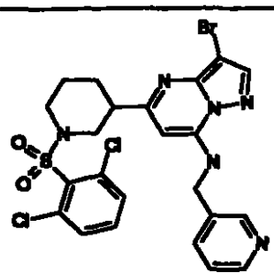
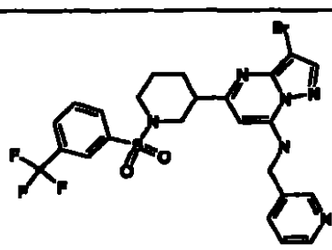
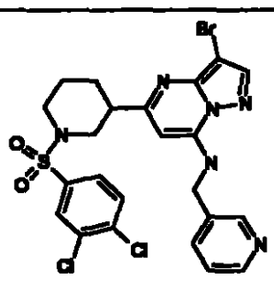
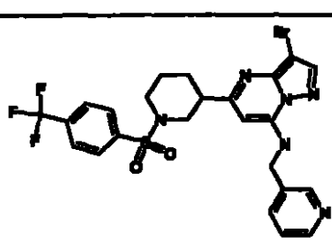
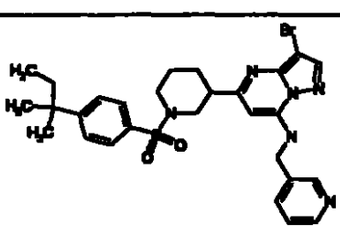
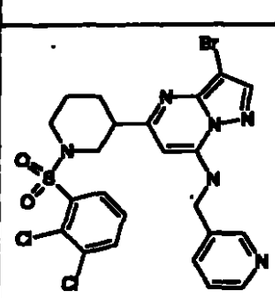
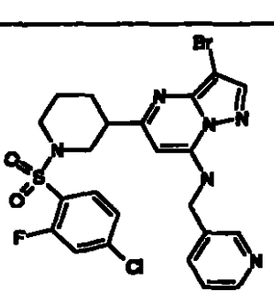
5

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

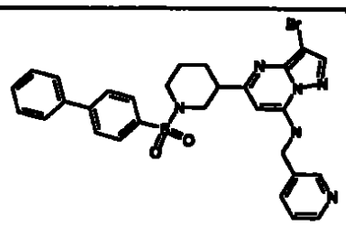
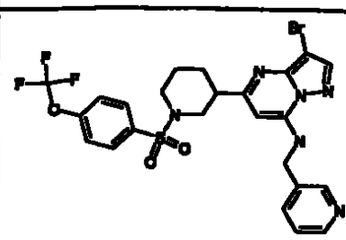
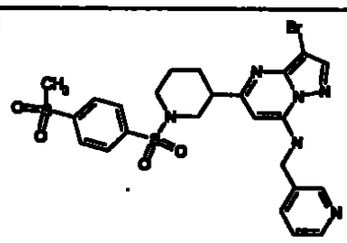
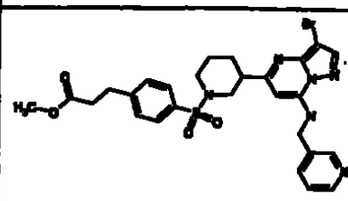
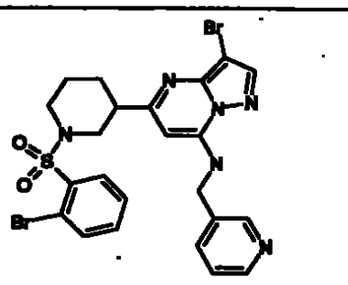
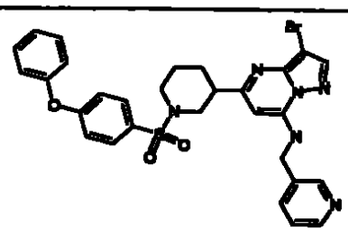
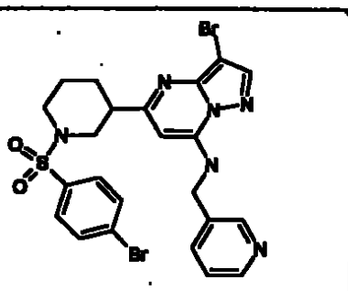
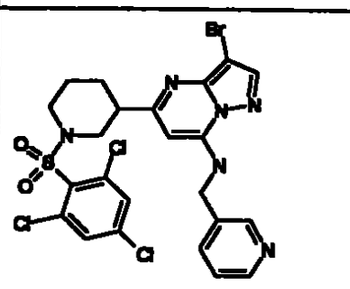
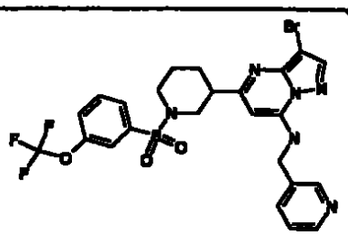
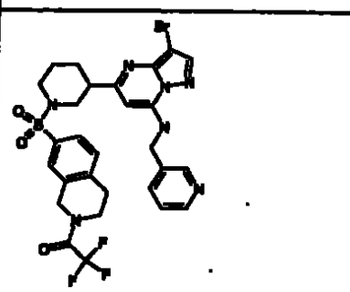
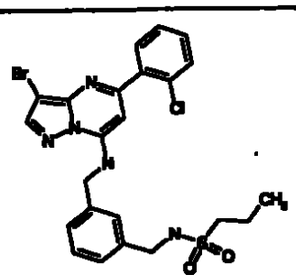
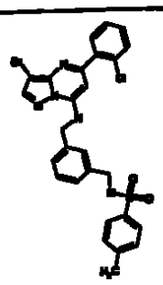
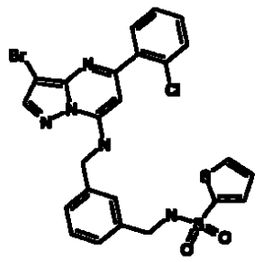
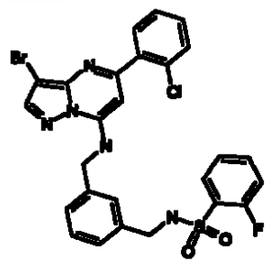
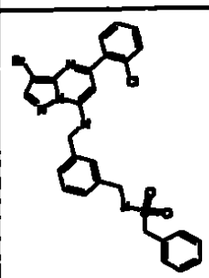
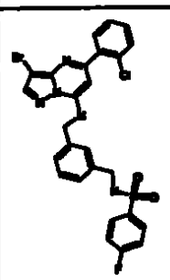
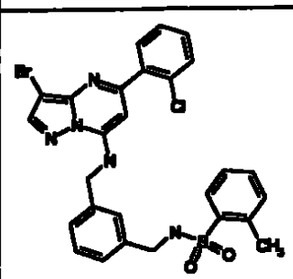
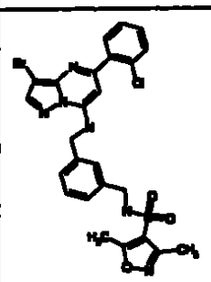
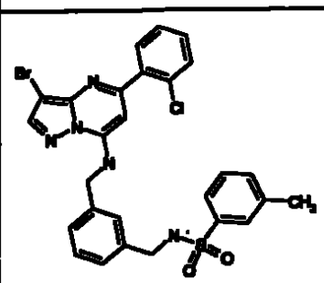
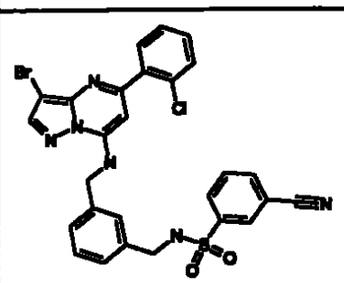
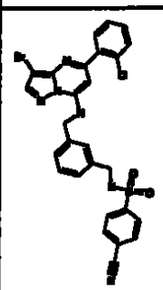
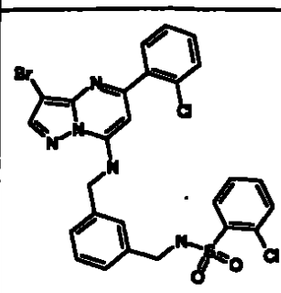
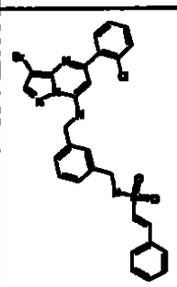
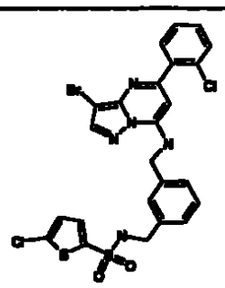
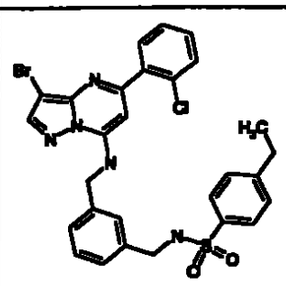
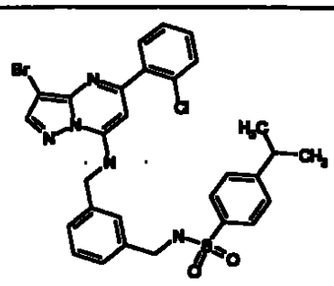
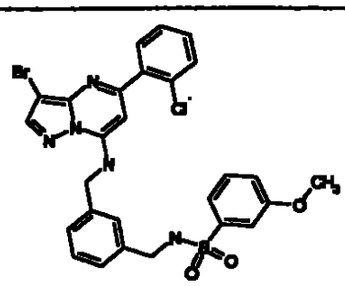
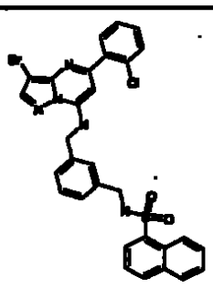
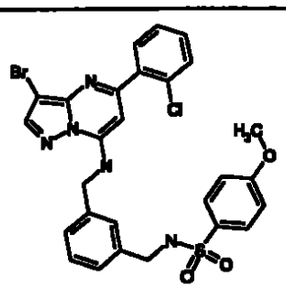
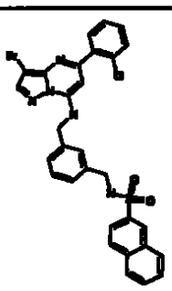
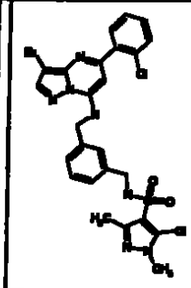
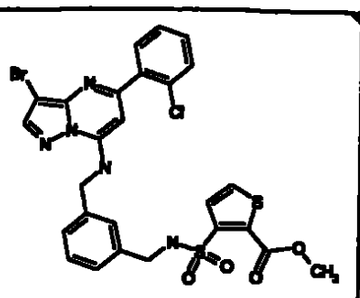
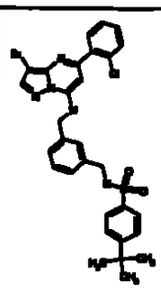
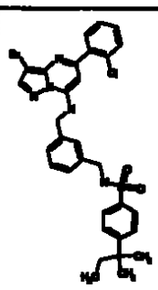
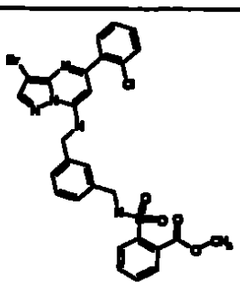
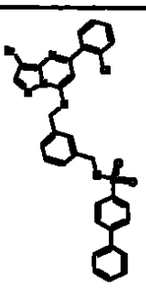
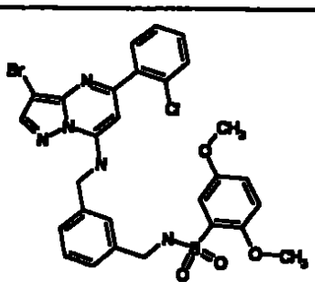
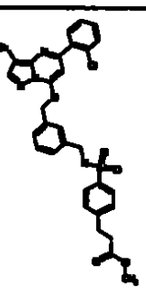
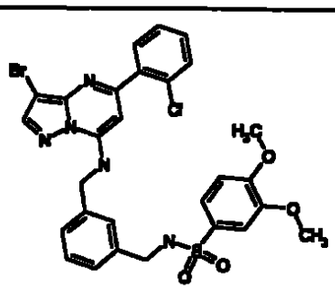
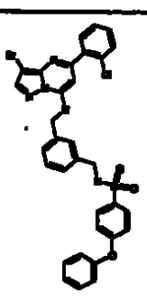
Product	1. Ex. 2. m/z		Product	1. Ex. 2. m/z
	1. 5741 2. 605.33			1. 5746 2. 613.34
	1. 5742 2. 607.33			1. 5747 2. 615.34
	1. 5743 2. 607.33			1. 5748 2. 621.34
	1. 5744 2. 607.33			1. 5749 2. 631.35
	1. 57454 2. 613.34			1. 5750 2. 680.37

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

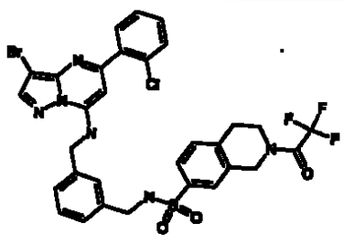
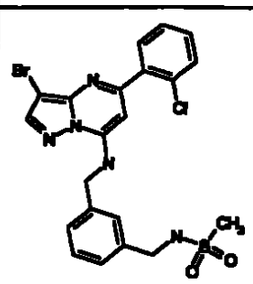
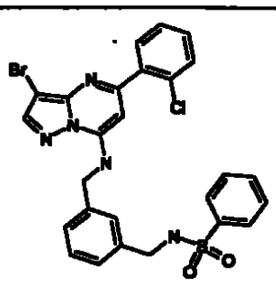
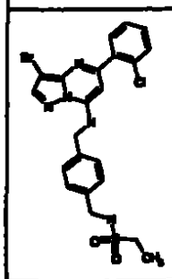
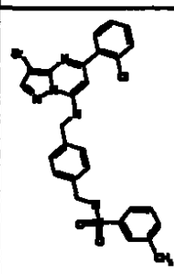
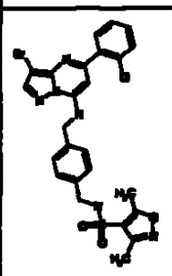
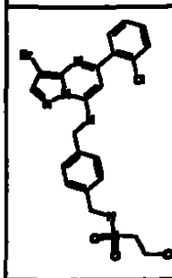
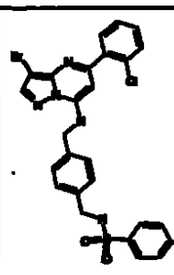
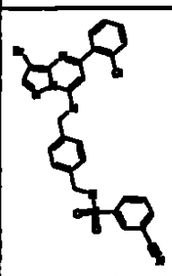
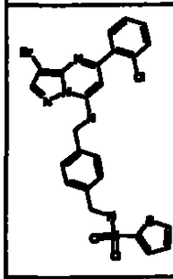
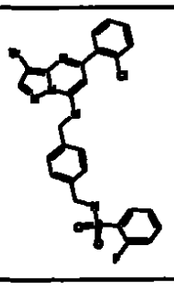
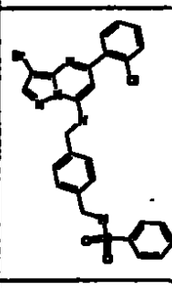
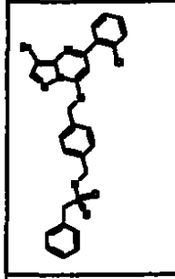
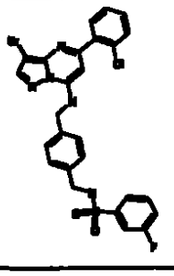
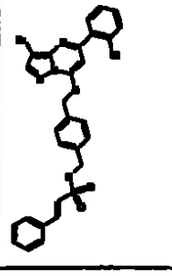
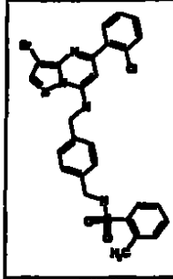
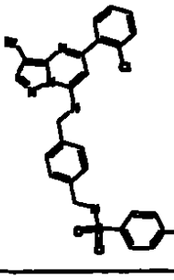
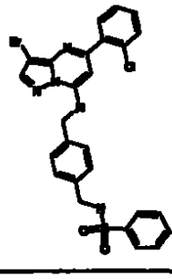
Product	1. Ex. 2. m/z
	1. 5831 2. 735.4
	1. 5832 2. 522.29
	1. 5833 2. 584.32

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	

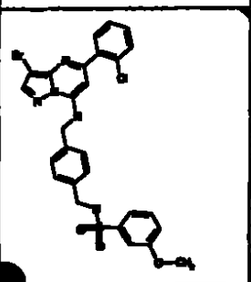
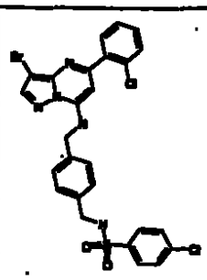
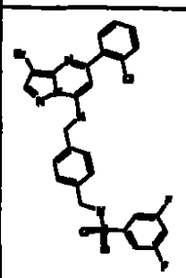
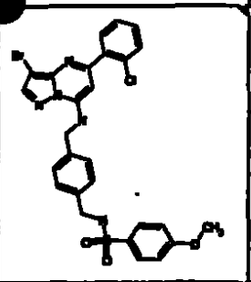
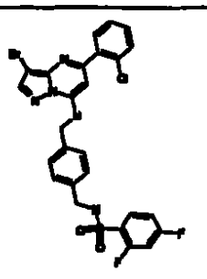
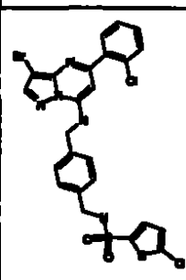
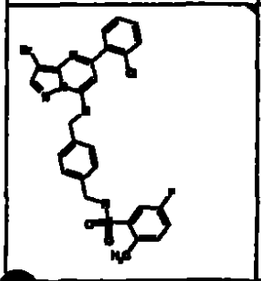
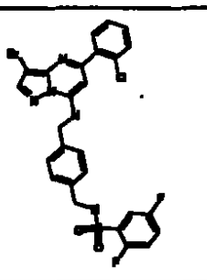
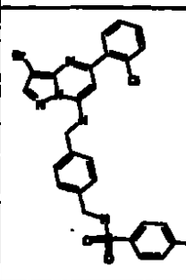
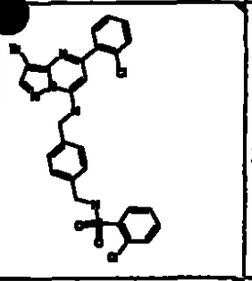
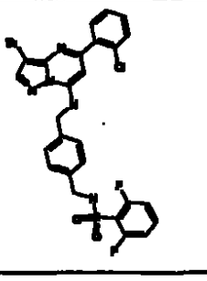
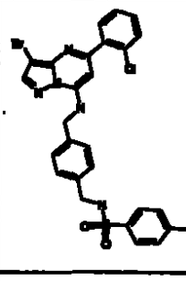
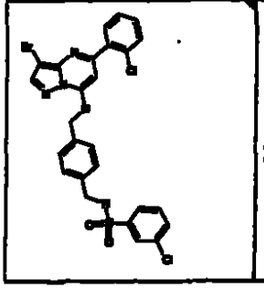
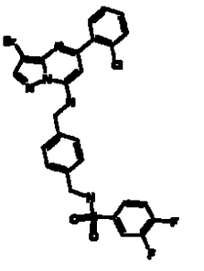
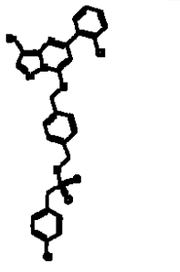
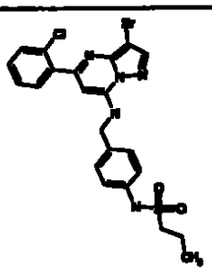
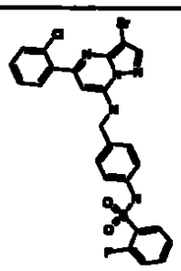
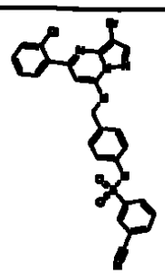
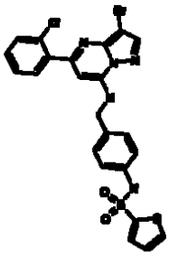
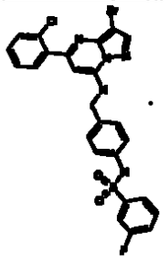
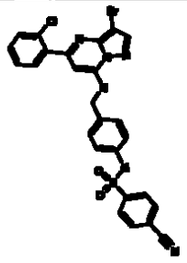
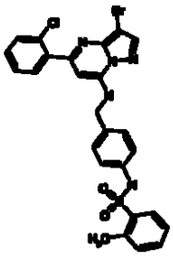
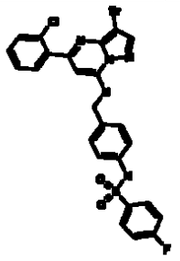
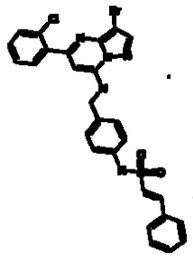
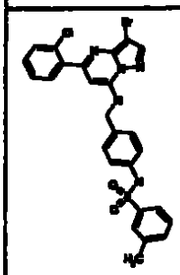
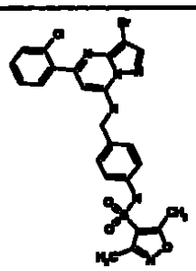
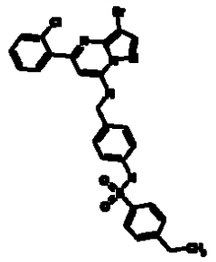
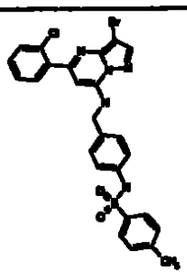
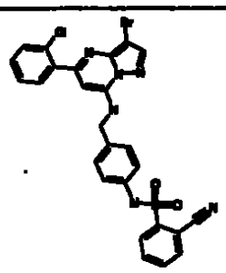
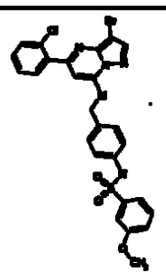
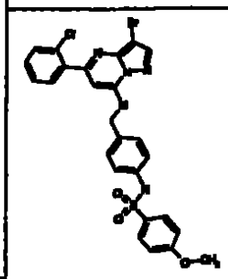
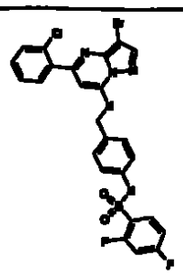
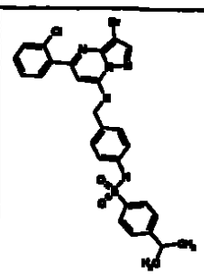
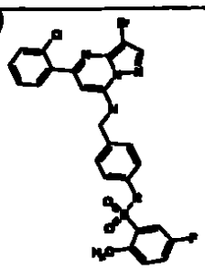
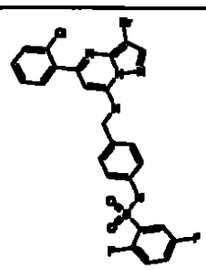
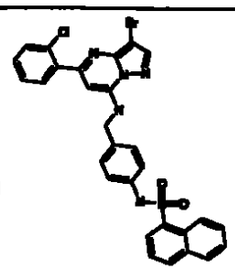
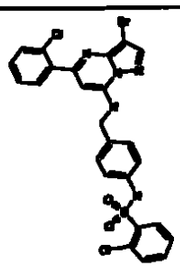
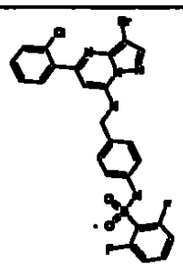
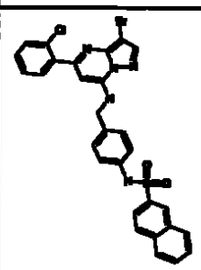
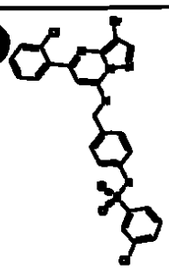
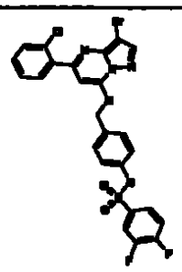
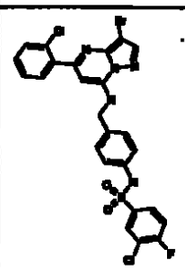
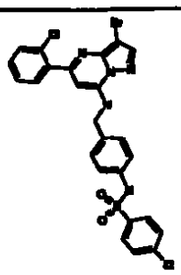
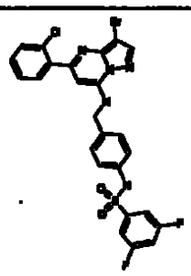
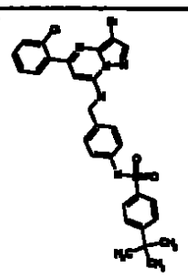
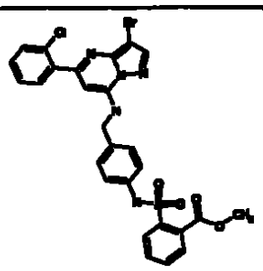
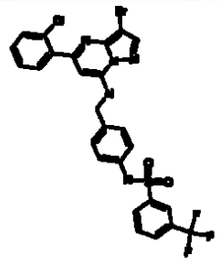
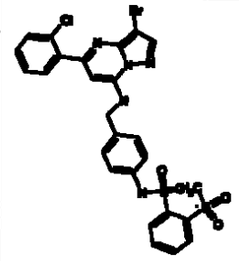
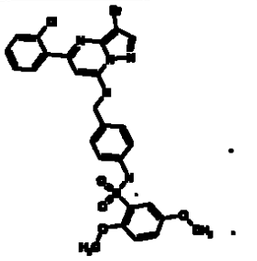
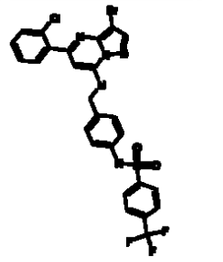
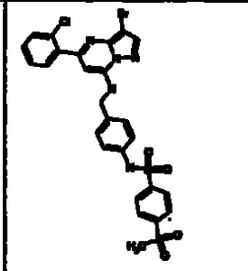
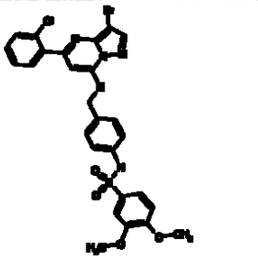
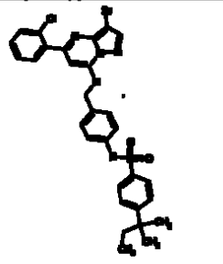
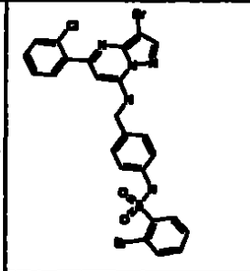
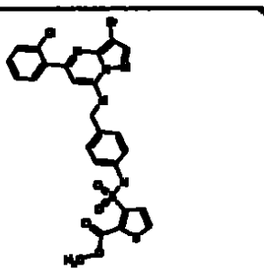
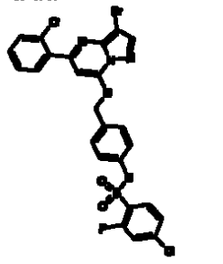
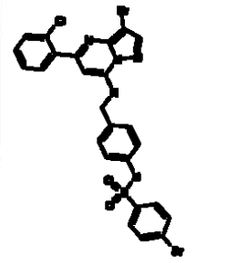
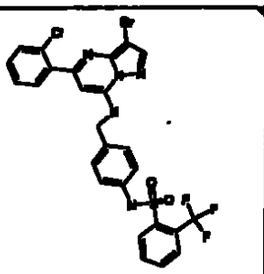
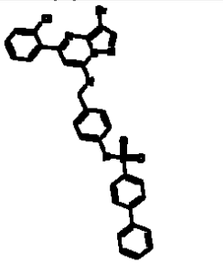
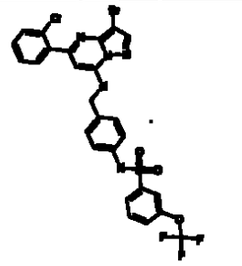
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	1. 5916 2. 614.34		1. 5921 2. 618.34		1. 5926 2. 620.34	
	1. 5917 2. 614.34		1. 5922 2. 620.34		1. 5927 2. 624.34	
	1. 5918 2. 616.34		1. 5923 2. 620.34		1. 5928 2. 626.34	
	1. 5919 2. 618.34		1. 5924 2. 620.34		1. 5929 2. 626.34	
	1. 5920 2. 618.34		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. 596.33
	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. 648.36		1. 6045 2. 654.36

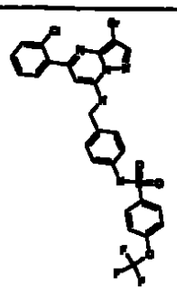
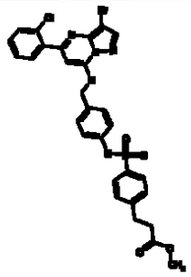
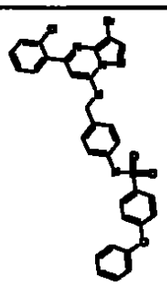
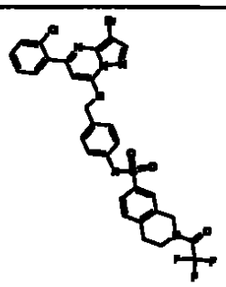
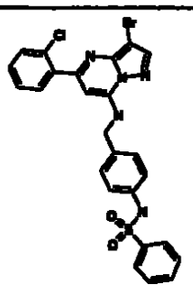
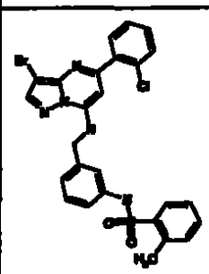
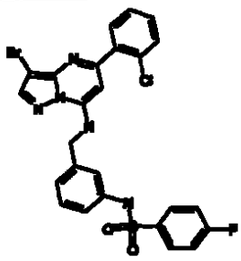
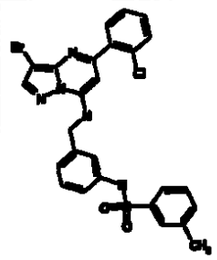
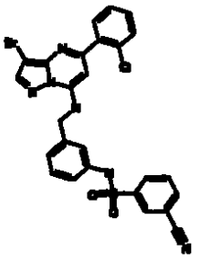
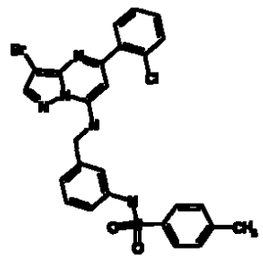
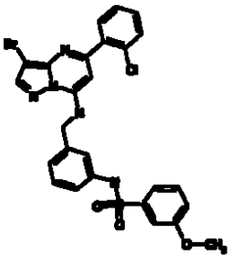
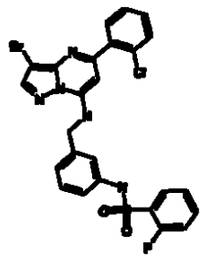
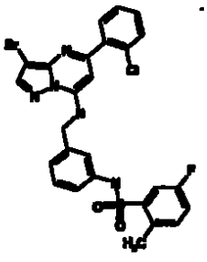
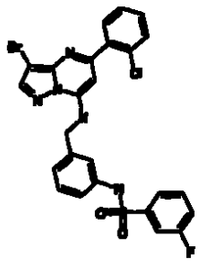
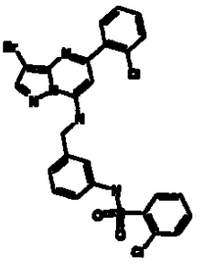
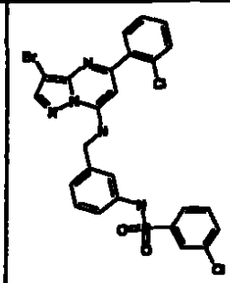
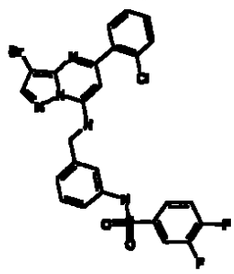
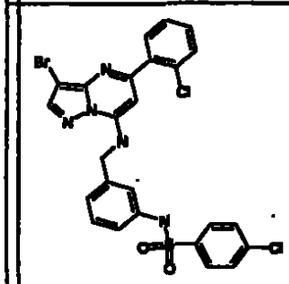
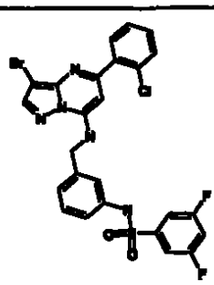
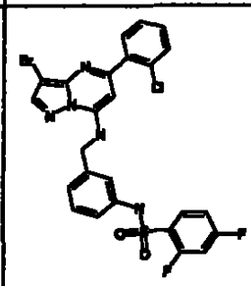
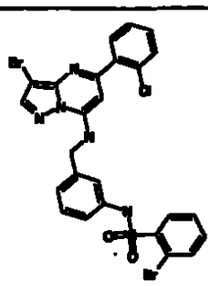
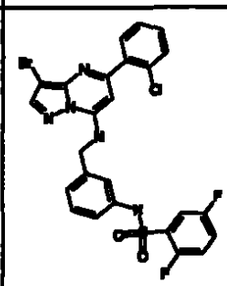
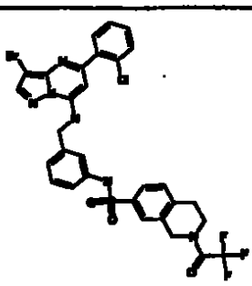
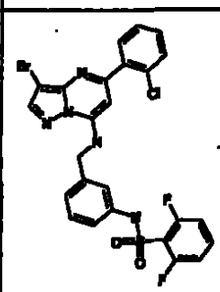
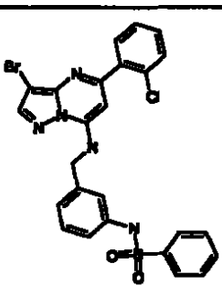
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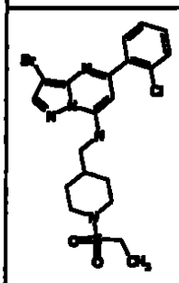
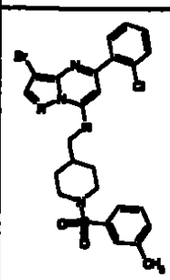
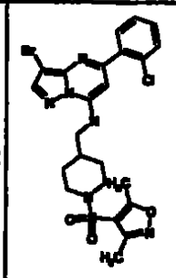
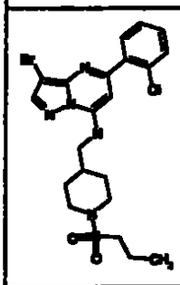
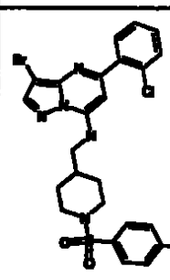
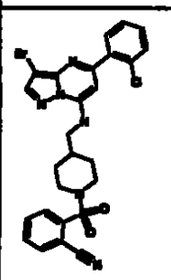
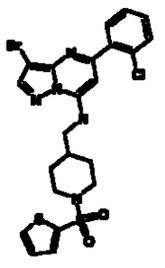
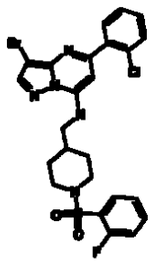
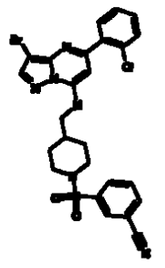
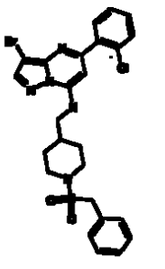
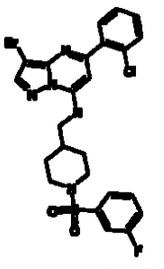
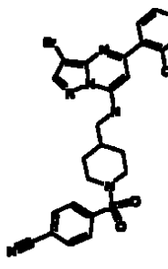
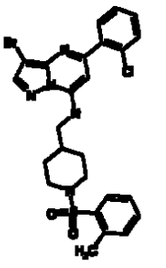
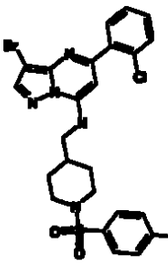
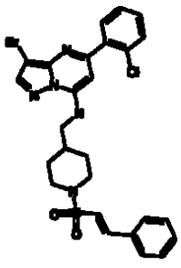
TABLE 61

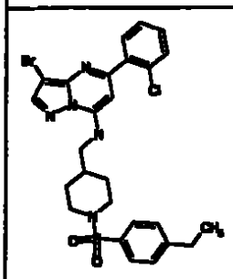
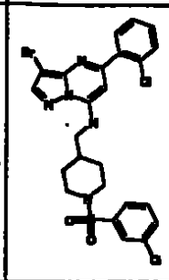
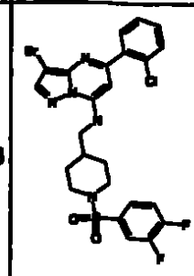
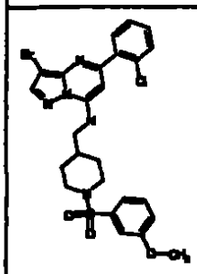
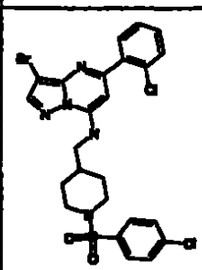
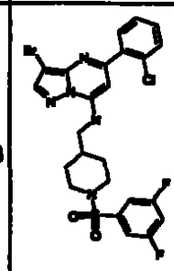
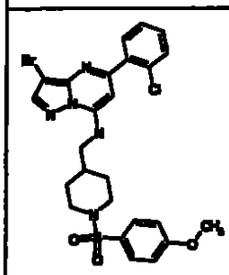
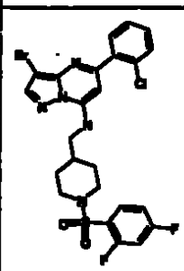
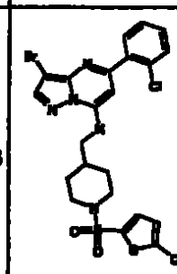
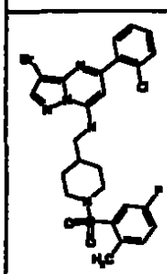
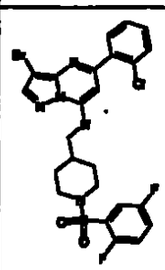
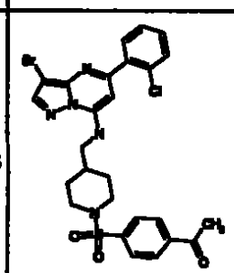
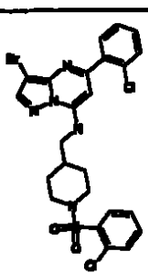
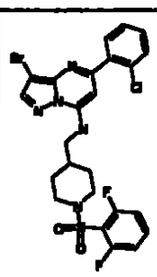
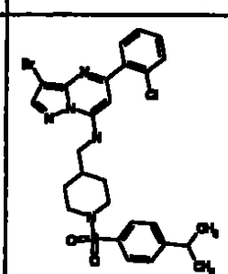
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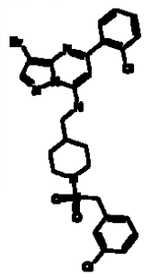
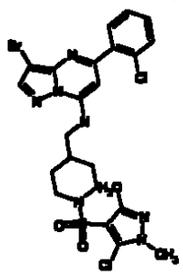
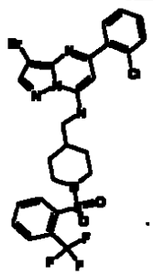
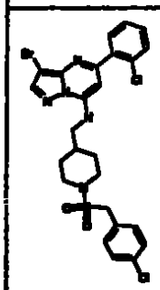
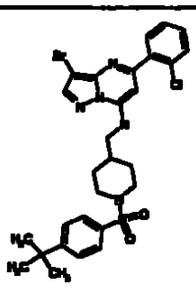
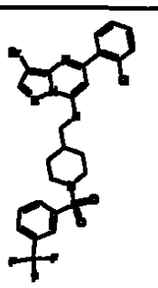
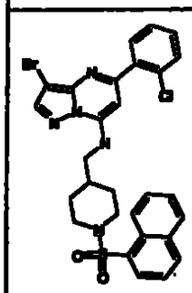
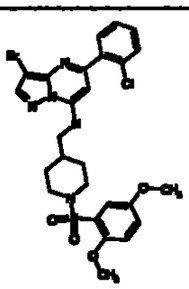
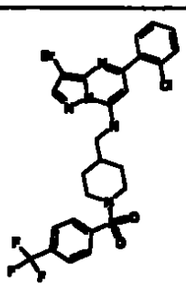
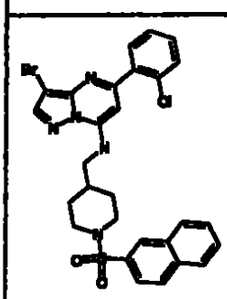
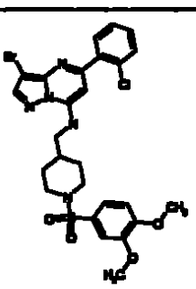
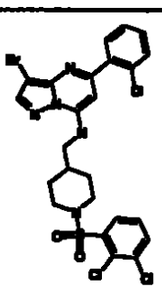
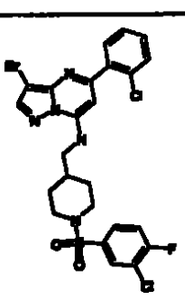
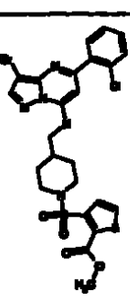
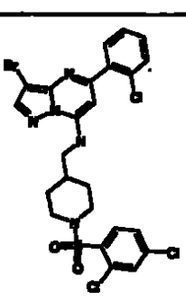
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	1. 6113 2. 606.33			1. 6118 2. 648.36
	1. 6114 2. 606.33			1. 6119 2. 721.4
	1. 6115 2. 606.33			1. 6120 2. 570.31

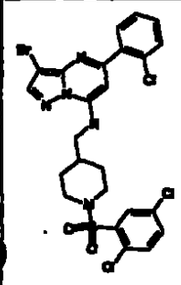
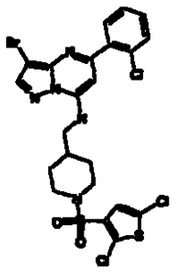
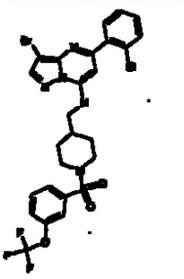
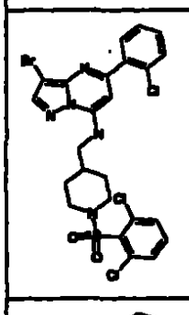
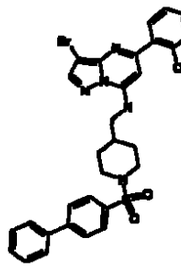
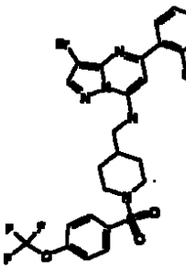
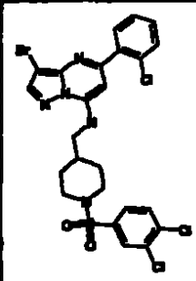
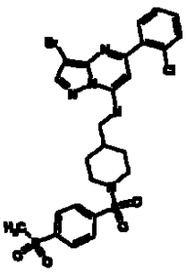
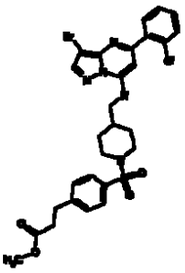
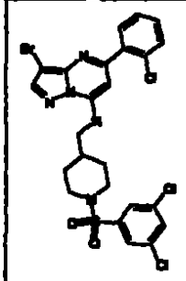
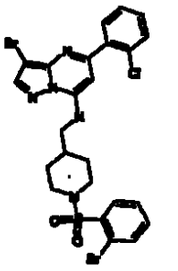
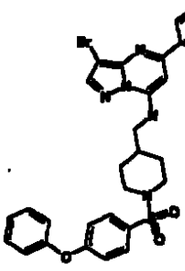
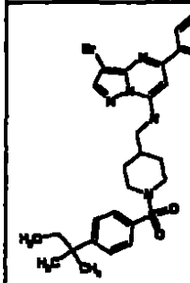
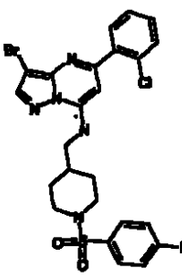
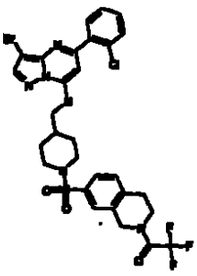
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TABLE62

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 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

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6216 2. 590.32		1. 6221 2. 596.33		1. 6226 2. 596.33
	1. 6217 2. 592.33		1. 6222 2. 596.33		1. 6227 2. 596.33
	1. 6218 2. 592.33		1. 6223 2. 596.33		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. 596.33		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. 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

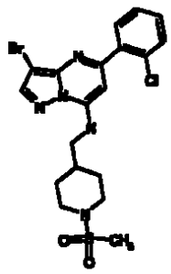
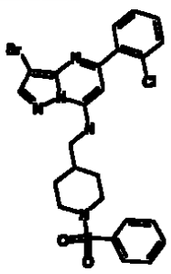
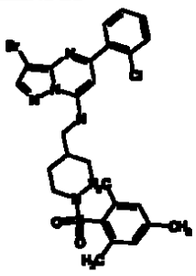
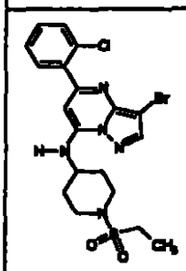
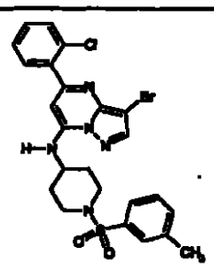
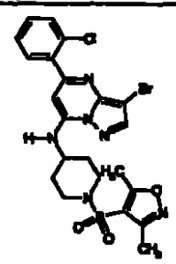
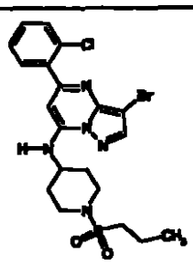
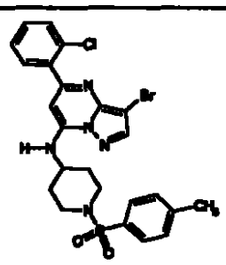
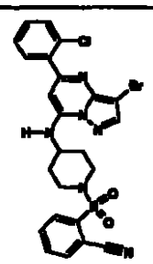
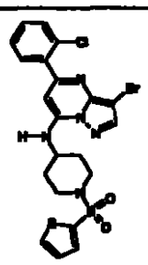
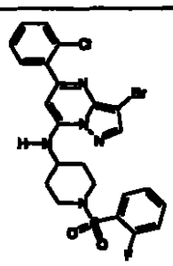
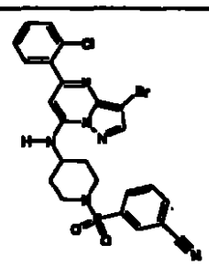
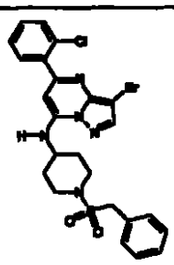
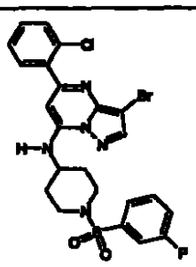
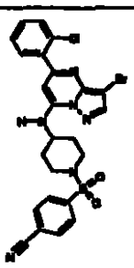
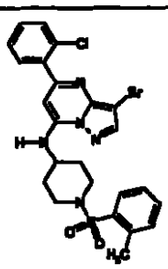
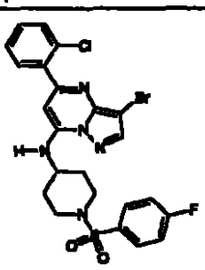
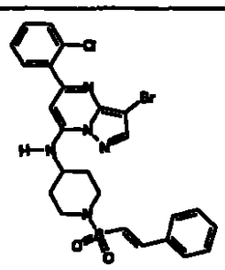
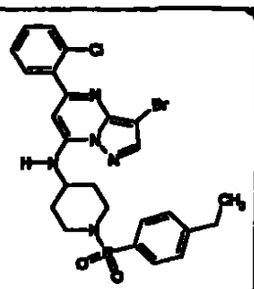
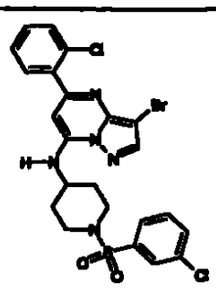
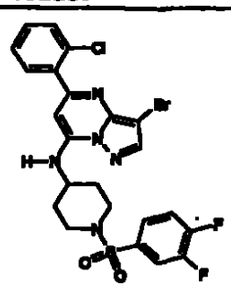
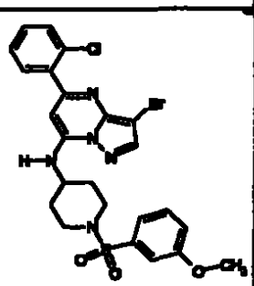
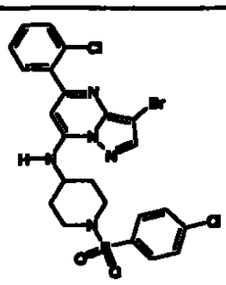
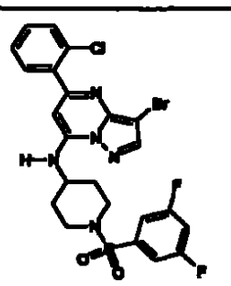
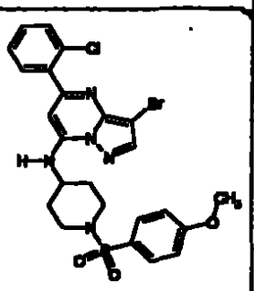
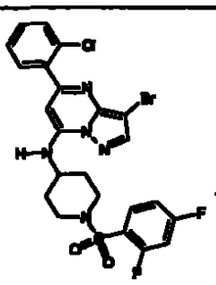
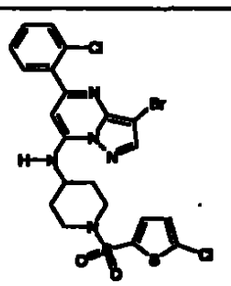
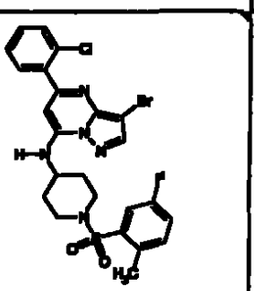
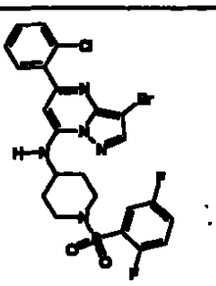
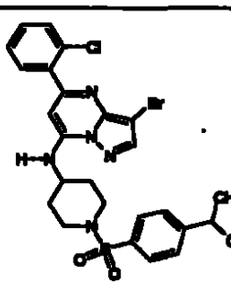
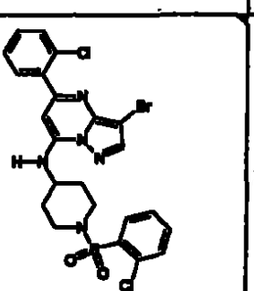
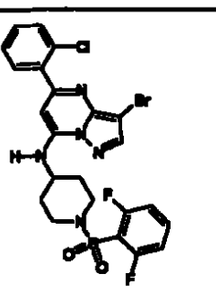
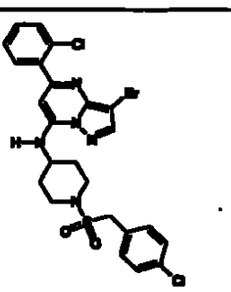
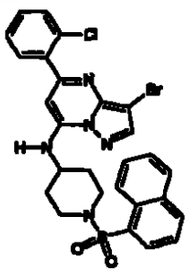
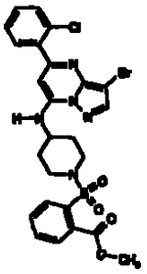
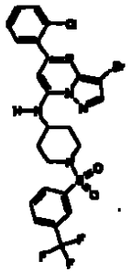
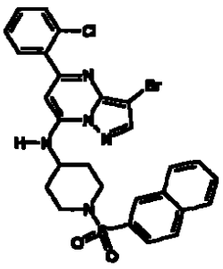
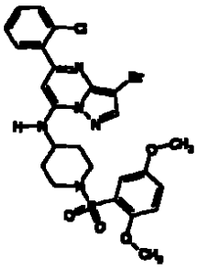
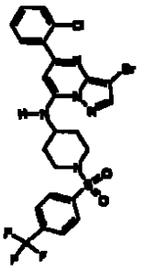
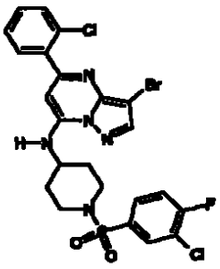
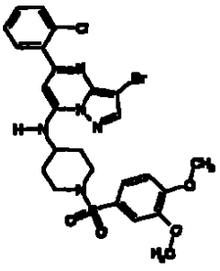
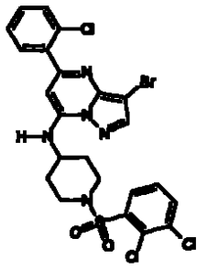
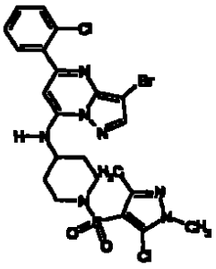
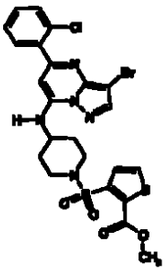
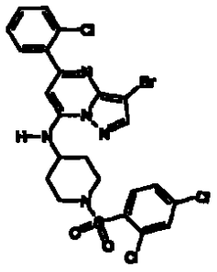
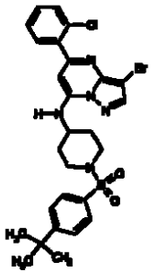
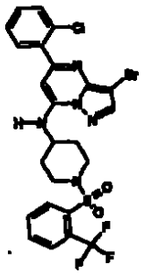
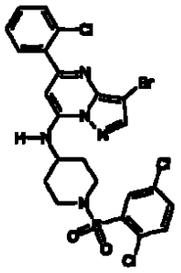
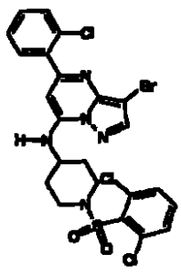
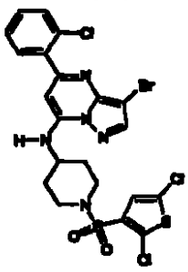
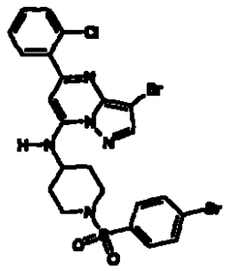
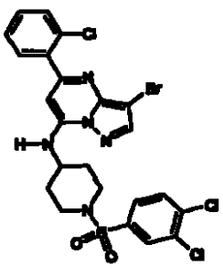
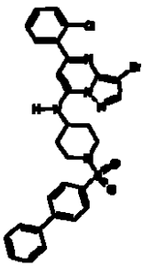
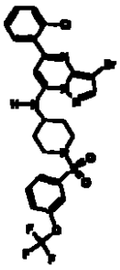
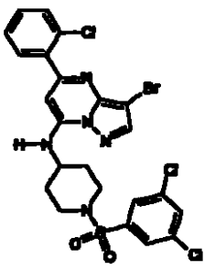
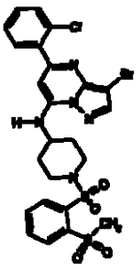
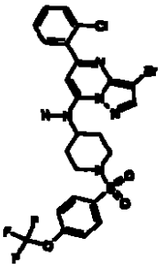
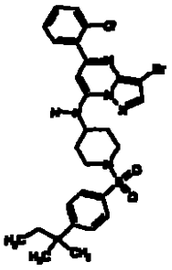
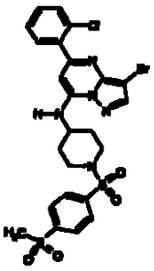
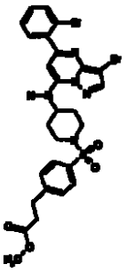
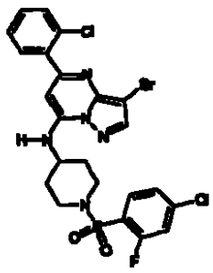
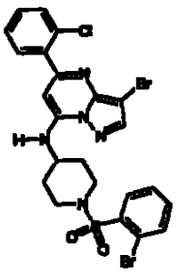
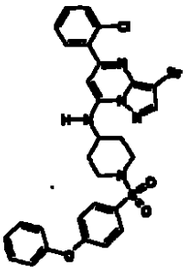
Product	1. Ex. 2. m/z
	1. 6261 2. 500.27
	1. 6262 2. 562.31
	1. 6263 2. 604.33

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. 586.32
	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

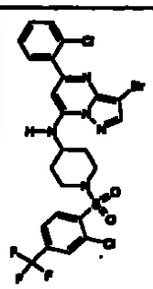
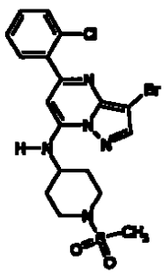
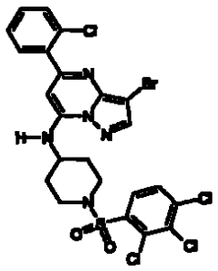
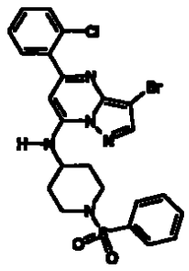
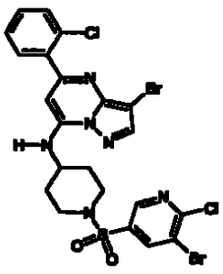
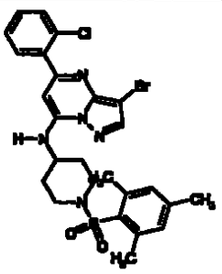
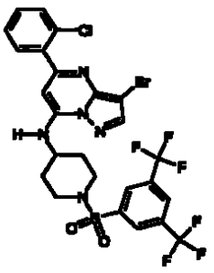
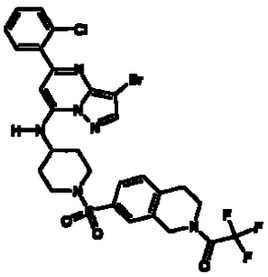
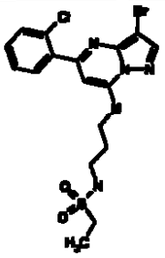
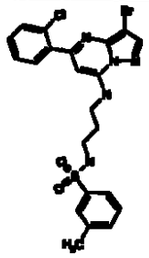
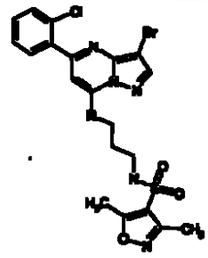
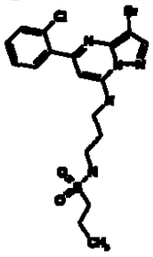
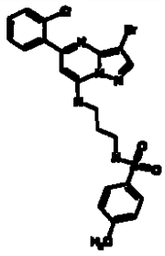
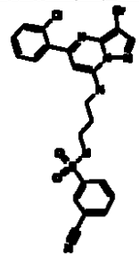
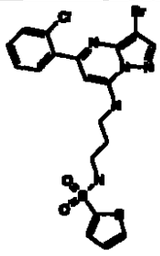
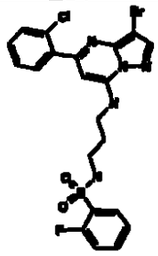
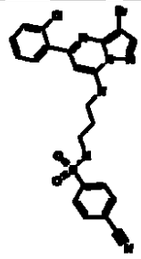
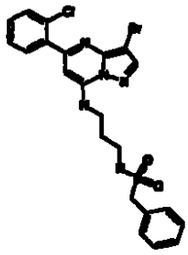
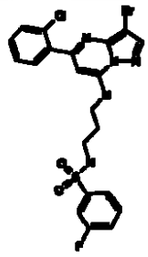
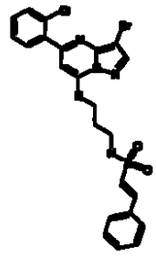
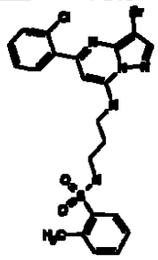
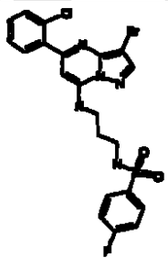
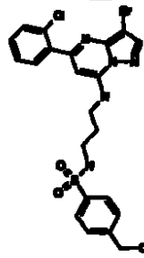
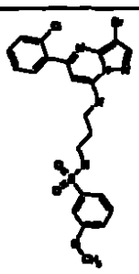
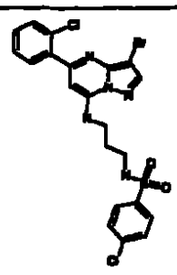
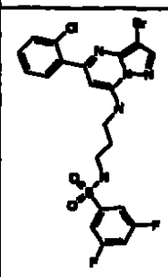
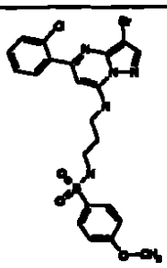
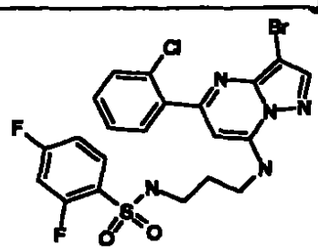
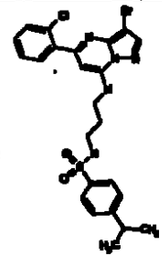
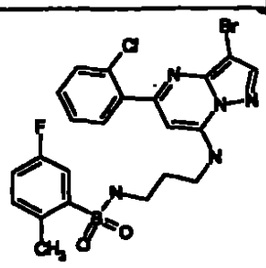
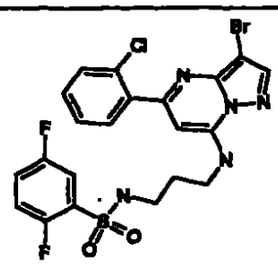
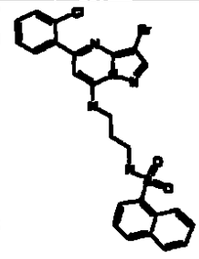
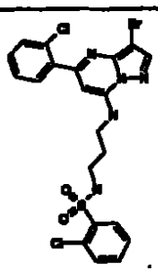
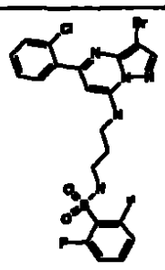
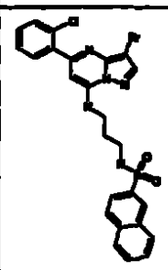
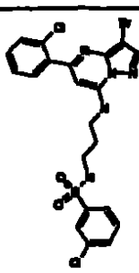
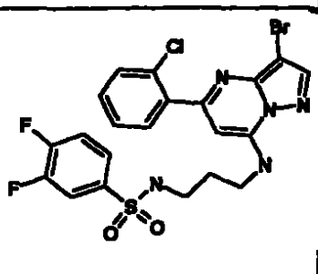
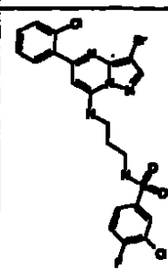
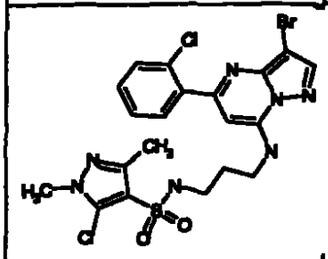
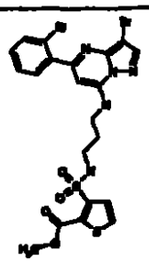
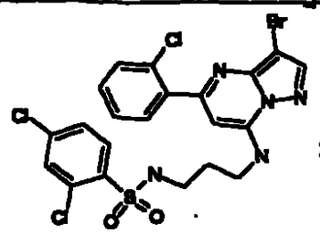
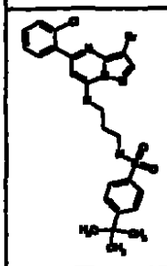
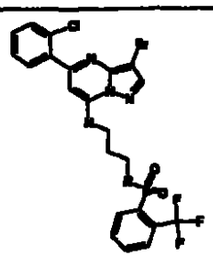
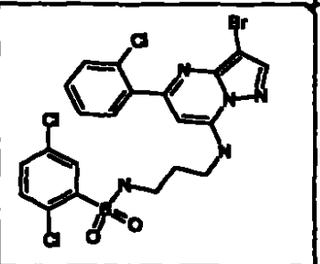
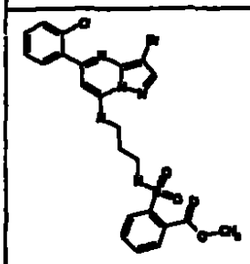
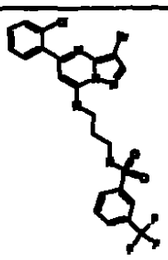
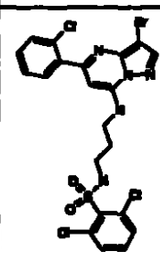
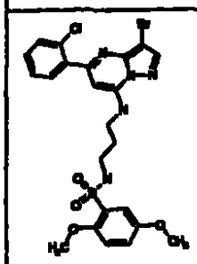
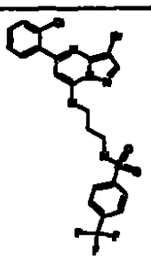
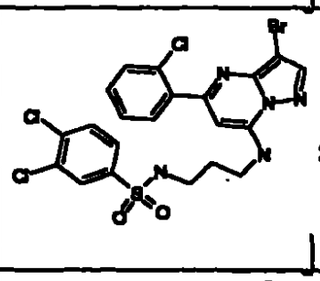
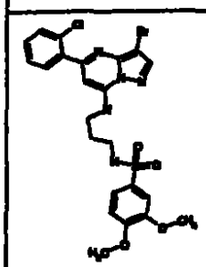
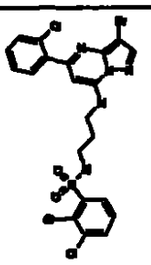
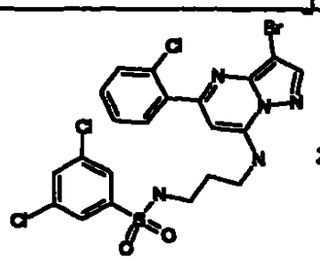
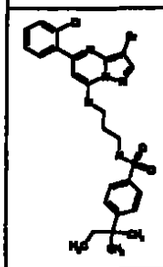
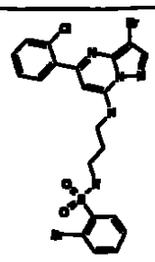
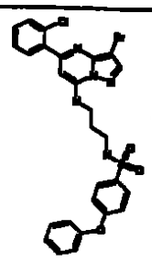
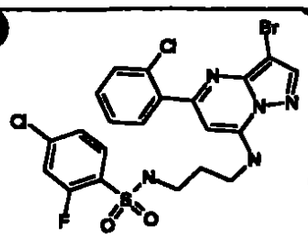
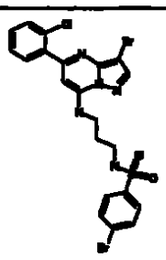
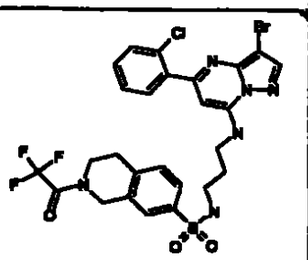
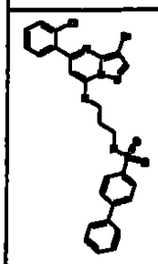
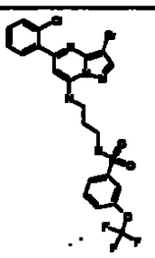
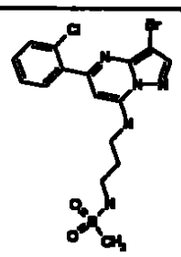
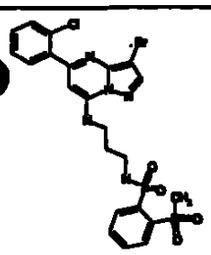
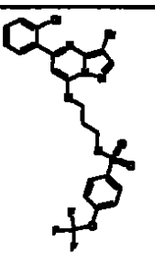
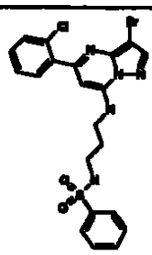
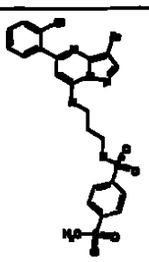
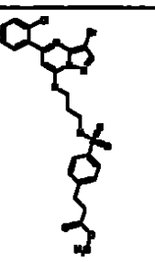
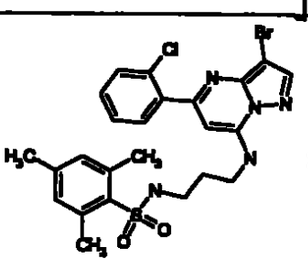
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	1. 6361 2. 650.36			1. 6366 2. 486.27
	1. 6362 2. 650.36			1. 6367 2. 548.3
	1. 6363 2. 661.36			1. 6368 2. 590.32
	1. 6364 2. 684.38			
	1. 6365 2. 699.38			

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
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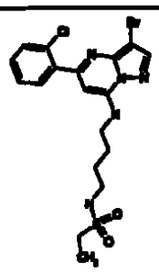
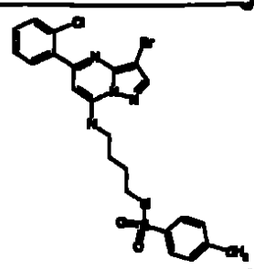
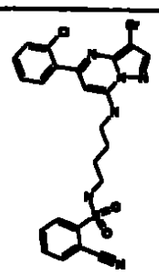
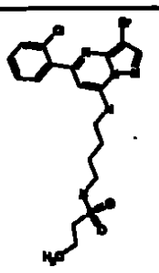
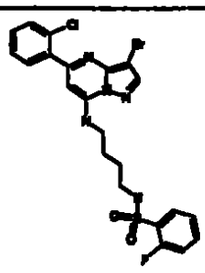
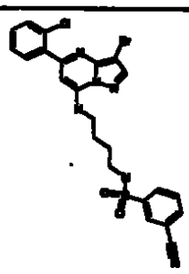
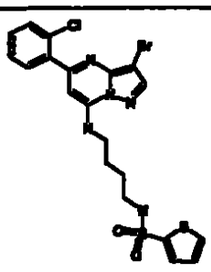
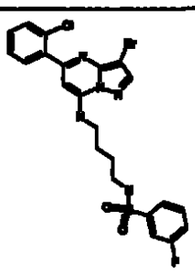
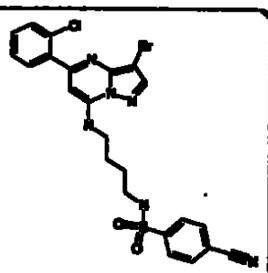
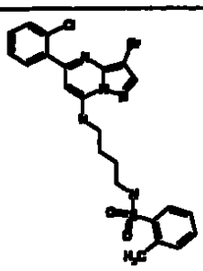
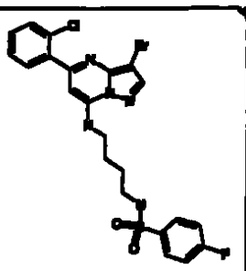
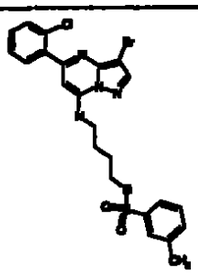
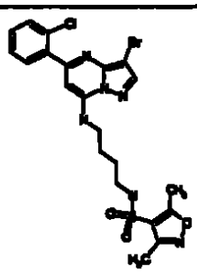
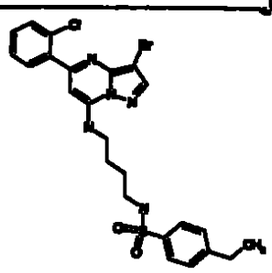
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	1. 6416 2. 552.3		1. 6421 2. 556.31		1. 6426 2. 568.31
	1. 6417 2. 552.3		1. 6122 2. 558.31		1. 6427 2. 584.31
	1. 6418 2. 554.3		1. 6423 2. 568.31		1. 6428 2. 572.31
	1. 6419 2. 568.31		1. 6424 2. 568.31		1. 6429 2. 572.31
	1. 6420 2. 568.31		1. 6425 2. 568.31		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. 566.32		1. 6441 2. 590.32
	1. 6432 2. 576.32		1. 6437 2. 590.32		1. 6442 2. 590.32
	1. 6433 2. 590.32		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

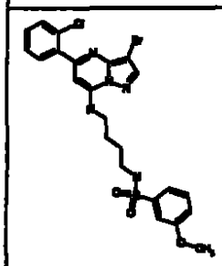
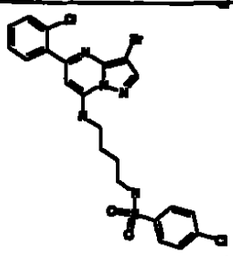
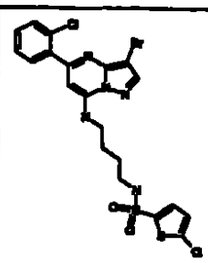
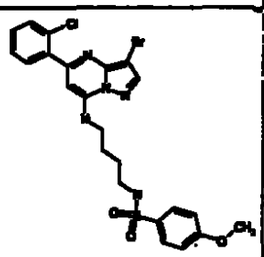
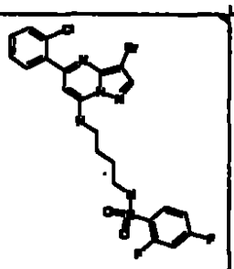
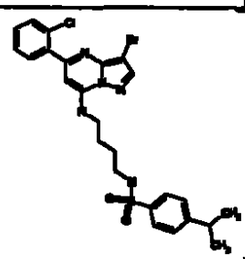
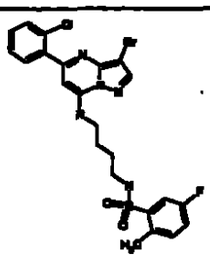
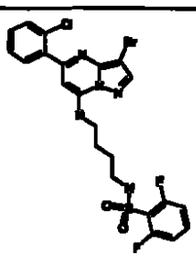
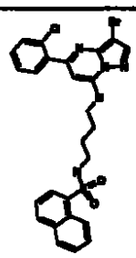
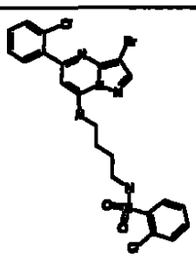
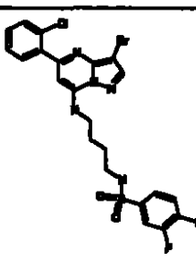
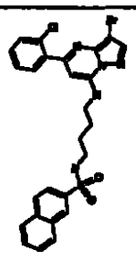
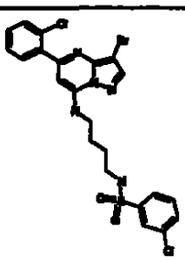
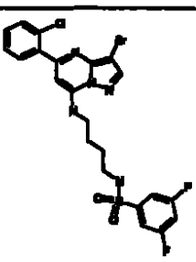
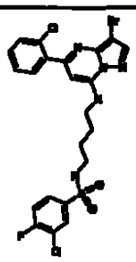
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6446 2. 592.33		1. 6451 2. 600.33		1. 6456 2. 614.34
	1. 6447 2. 574.32		1. 6452 2. 600.33		1. 6447 2. 573.37
	1. 6448 2. 598.33		1. 6453 2. 606.33		1. 6458 2. 460.25
	1. 6449 2. 600.33		1. 6454 2. 606.33		6459 2.
	1. 6450 2. 600.33		1. 6455 2. 608.33		1. 6460 2. 564.31

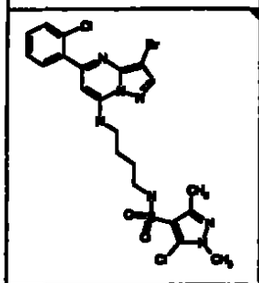
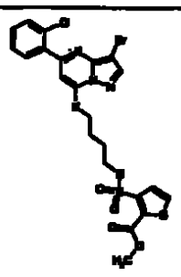
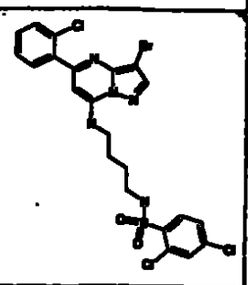
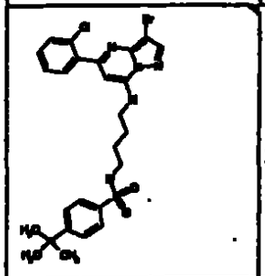
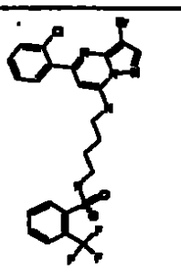
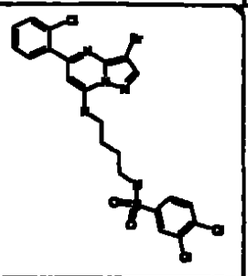
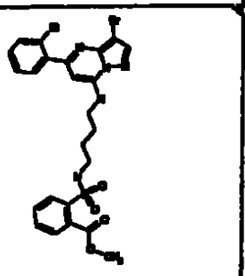
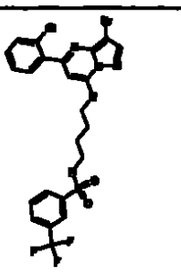
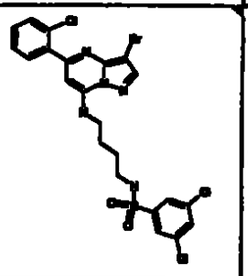
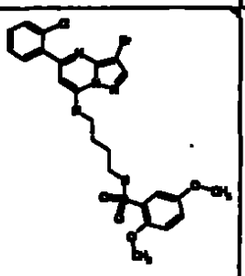
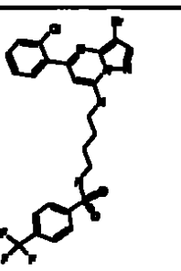
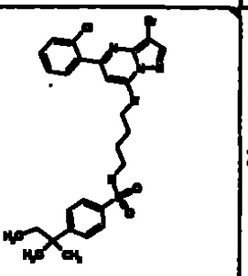
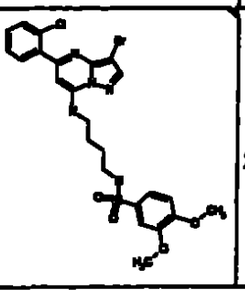
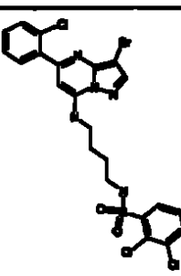
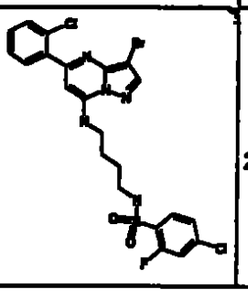
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TABLE 65

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. 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

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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. 576.32
	1. 6518 2. 566.31		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. 586.32

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

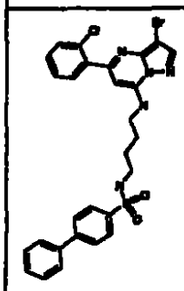
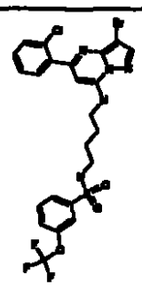
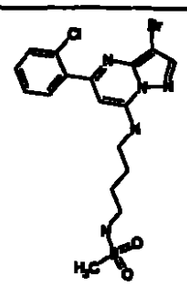
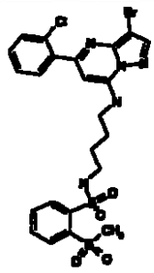
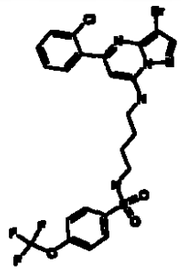
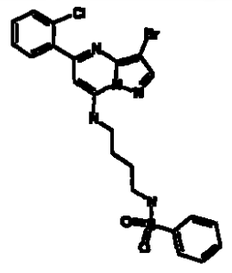
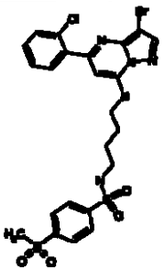
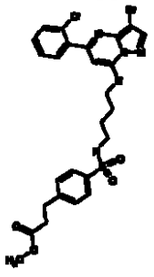
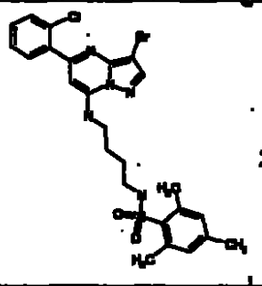
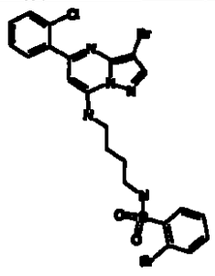
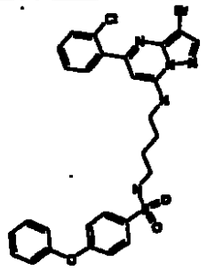
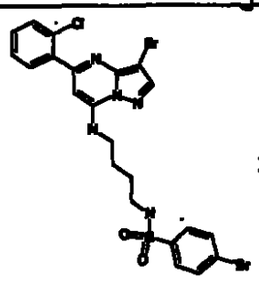
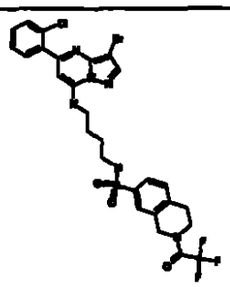
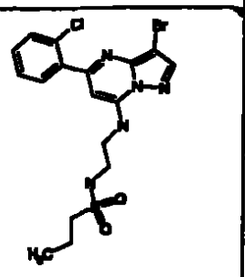
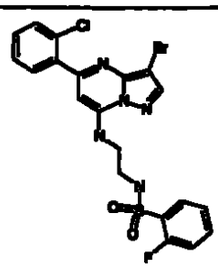
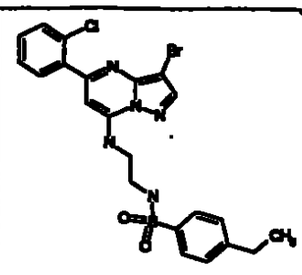
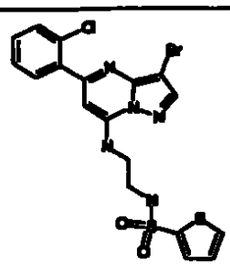
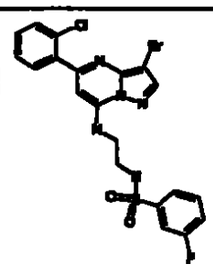
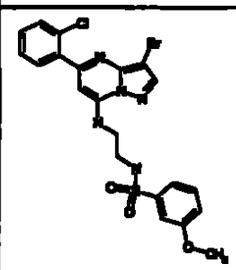
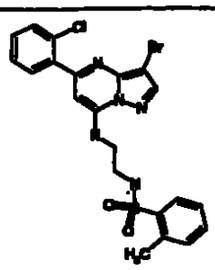
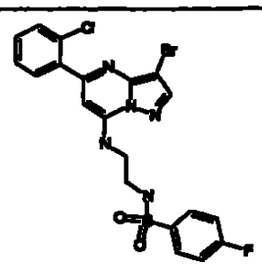
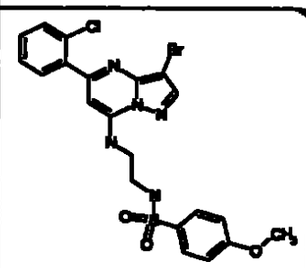
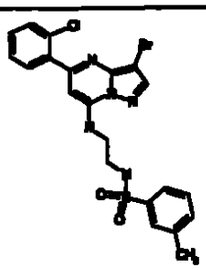
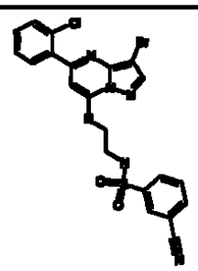
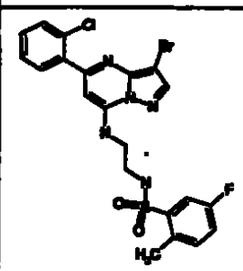
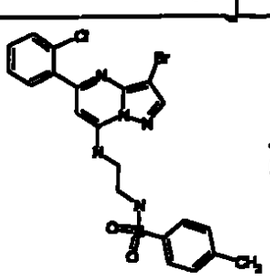
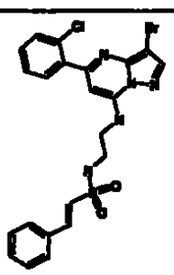
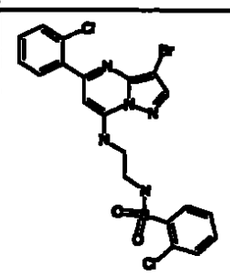
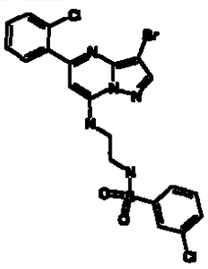
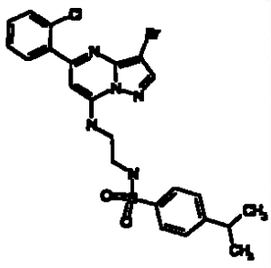
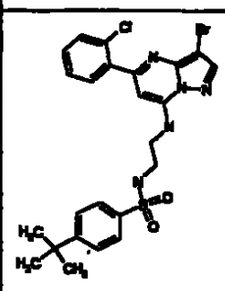
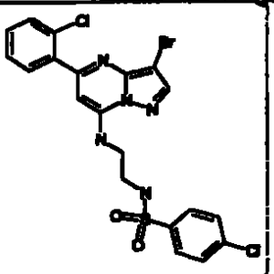
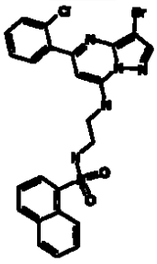
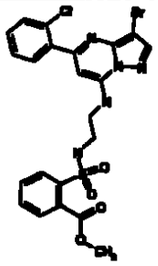
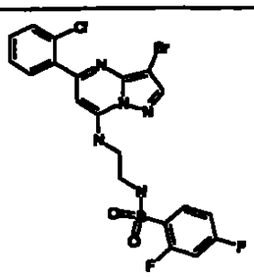
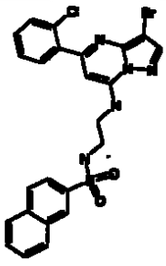
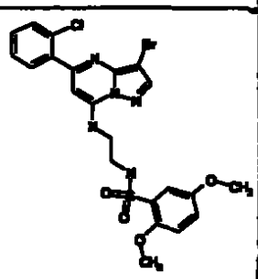
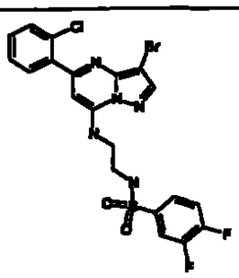
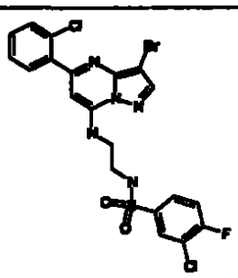
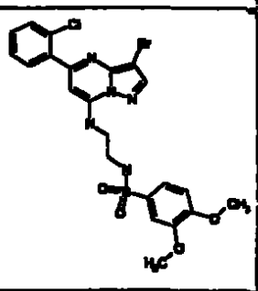
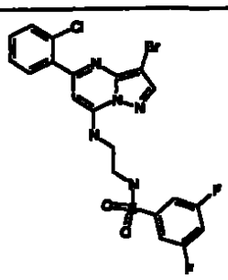
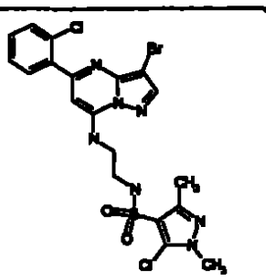
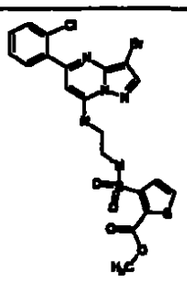
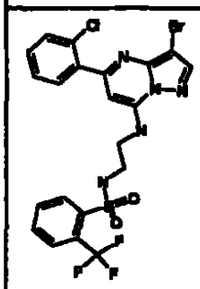
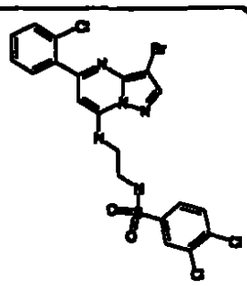
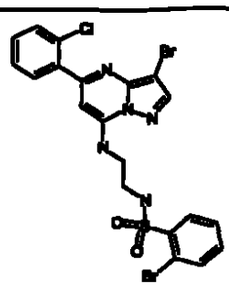
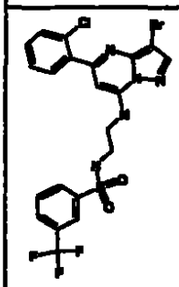
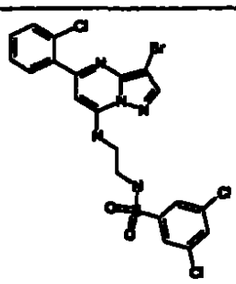
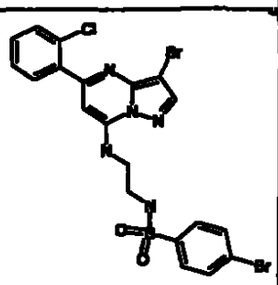
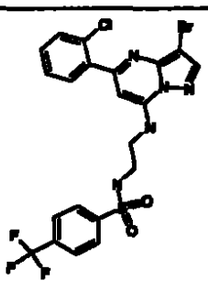
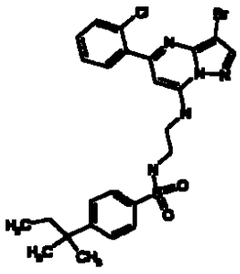
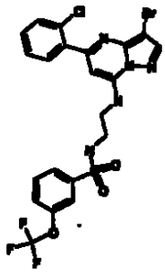
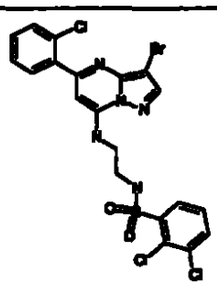
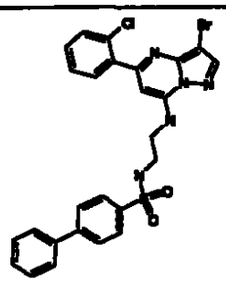
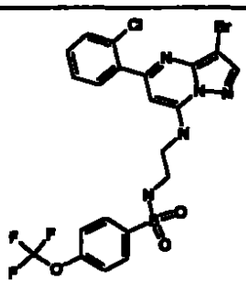
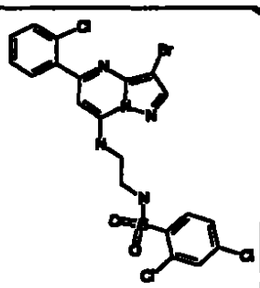
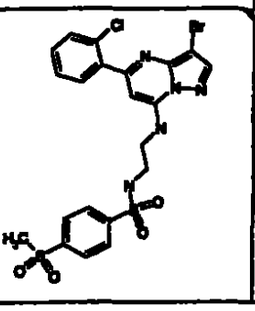
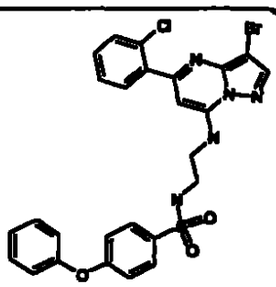
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	1. 6546 2. 612.34		1. 6551 2. 620.34		1. 6556 2. 474.28
	1. 6547 2. 614.34		1. 6552 2. 620.34		1. 6557 2. 536.29
	1. 6548 2. 614.34		1. 6553 2. 622.34		1. 6558 2. 578.32
	1. 6549 2. 614.34		1. 6554 2. 628.35		
	1. 6550 2. 614.34		1. 6555 2. 667.38		

TABLE 67

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6701 2. 474.26		1. 6706 2. 526.29		1. 6711 2. 536.2
	1. 6702 2. 514.26		1. 6707 2. 526.29		1. 6712 2. 536.3
	1. 6703 2. 522.29		1. 6708 2. 526.29		1. 6713 2. 536.3
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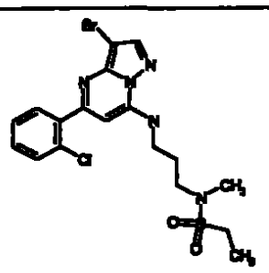
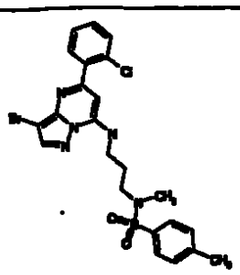
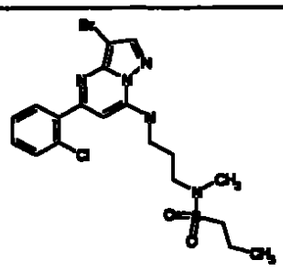
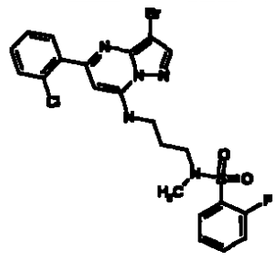
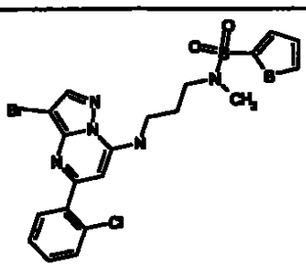
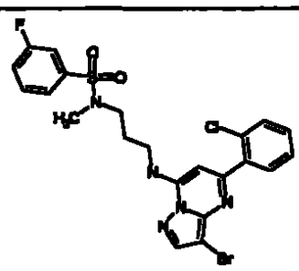
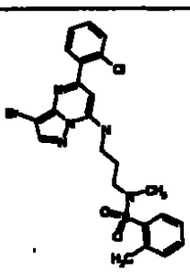
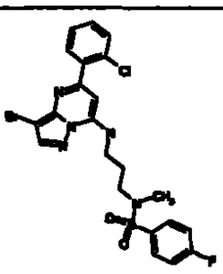
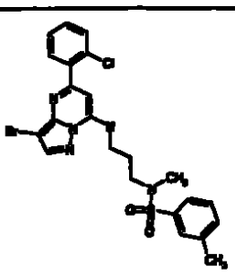
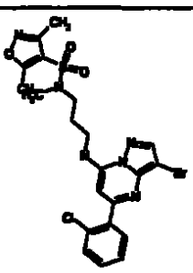
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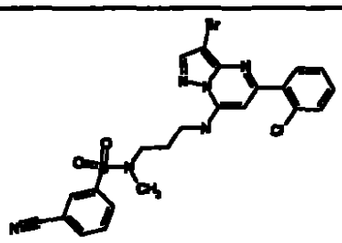
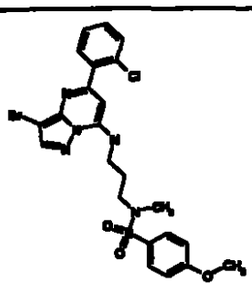
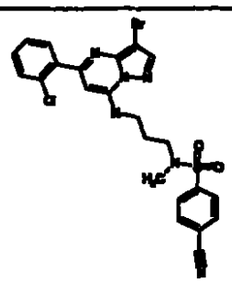
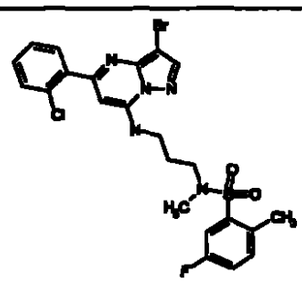
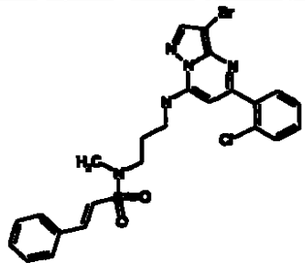
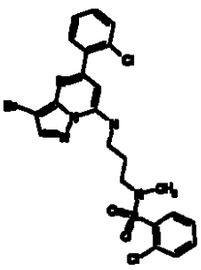
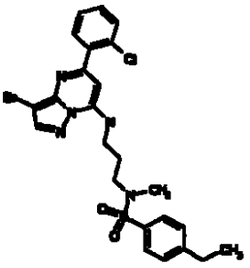
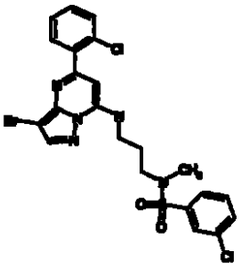
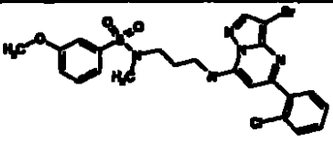
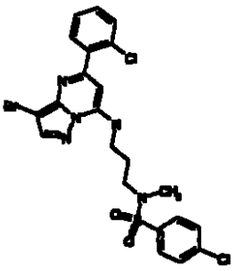
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	1. 6716 2. 542.3		1. 6721 2. 550.3		1. 6726 2. 564.31
	1. 6717 2. 542.3		1. 6722 2. 558.31		1. 6727 2. 566.31
	1. 6718 2. 544.3		1. 6723 2. 558.31		1. 6728 2. 568.31
	1. 6719 2. 544.3		1. 6724 2. 560.31		1. 6729 2. 568.31
	1. 6720 2. 544.3		1. 6725 2. 560.31		1. 6730 2. 572.31

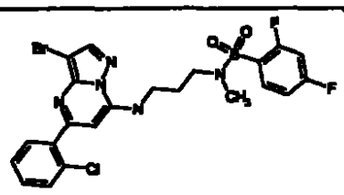
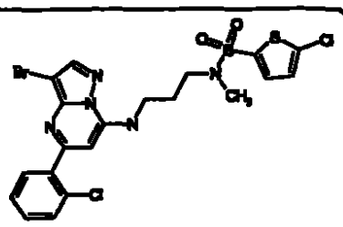
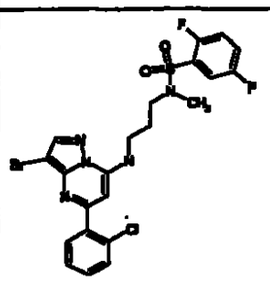
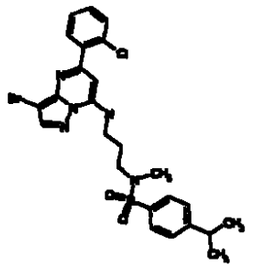
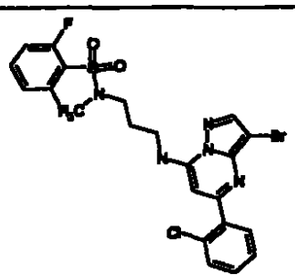
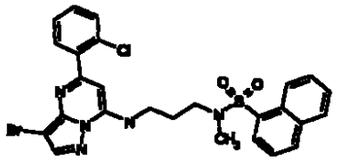
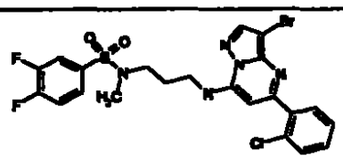
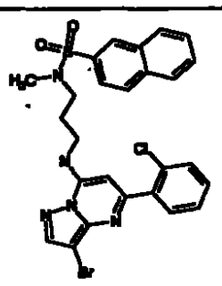
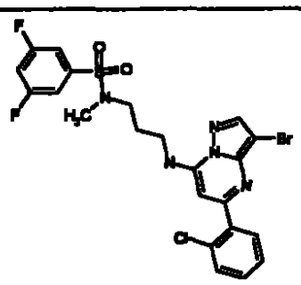
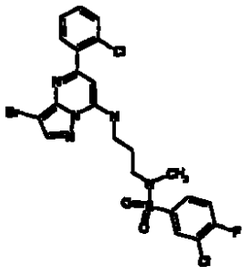
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6731 2. 576.32		1. 6736 2. 576.32		1. 6741 2. 586.32
	1. 6732 2. 576.32		1. 6737 2. 576.32		1. 6742 2. 586.32
	1. 6733 2. 576.32		1. 6738 2. 576.32		1. 6743 2. 592.33
	1. 6734 2. 576.32		1. 6739 2. 584.32		1. 6744 2. 592.33
	1. 6735 2. 576.32		1. 6740 2. 586.32		1. 6745 2. 600.33

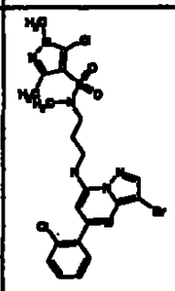
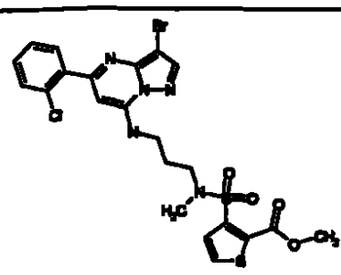
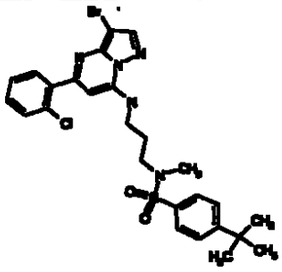
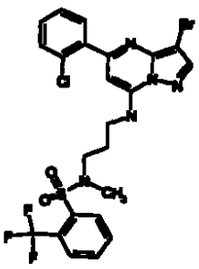
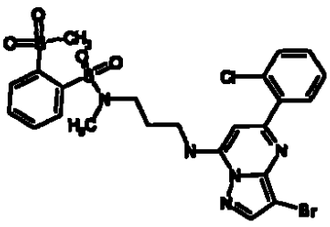
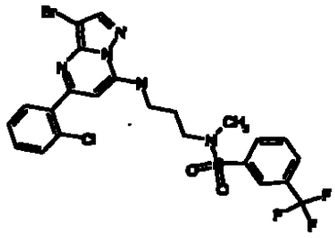
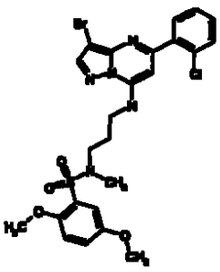
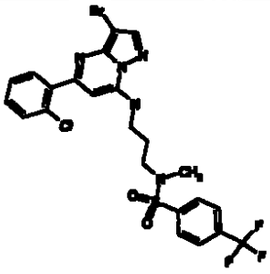
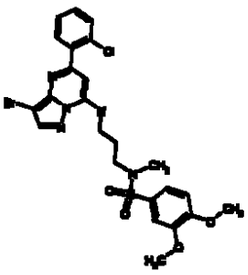
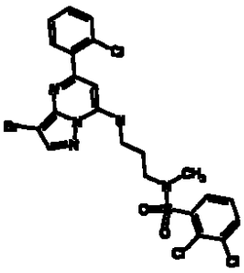
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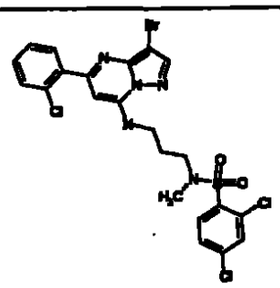
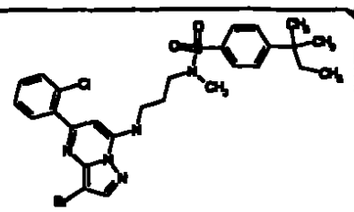
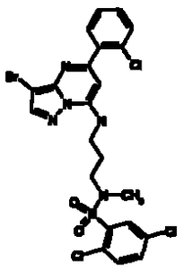
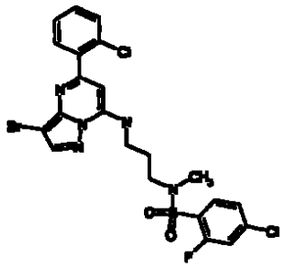
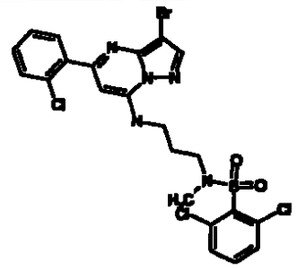
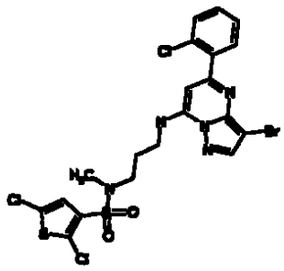
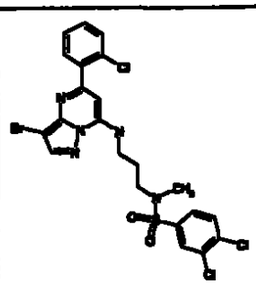
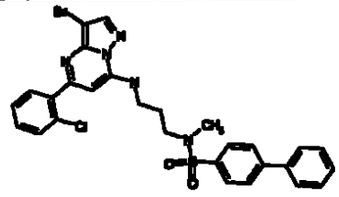
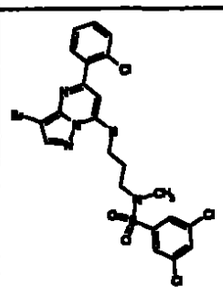
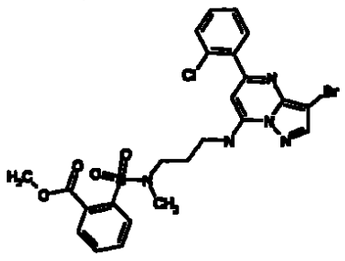
TABLE 68

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

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			1. 6850 2. 594.33

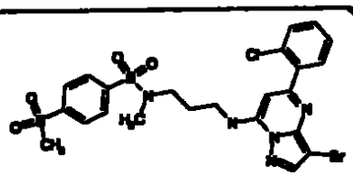
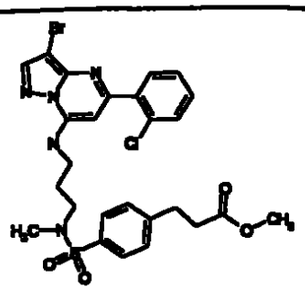
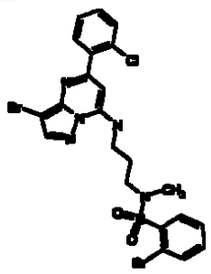
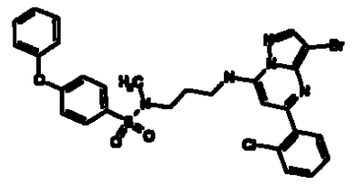
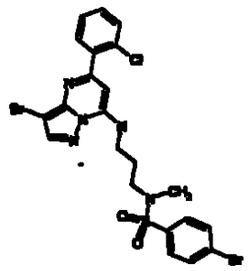
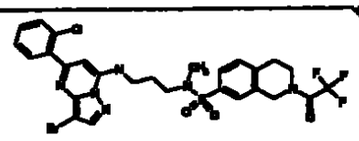
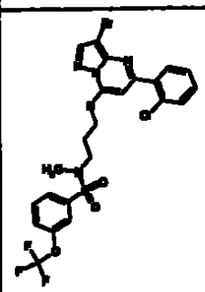
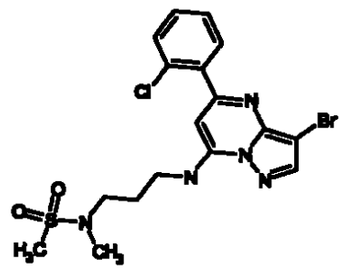
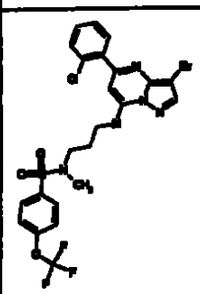
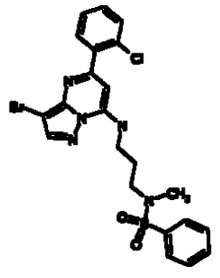
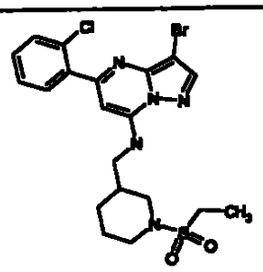
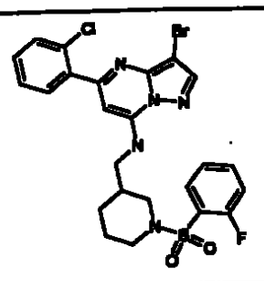
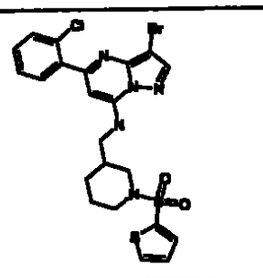
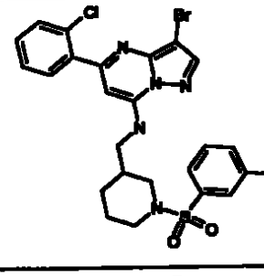
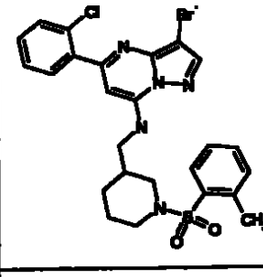
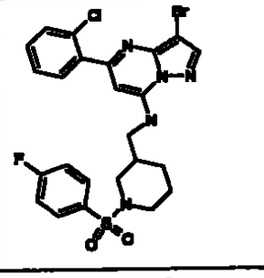
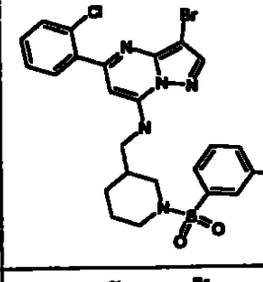
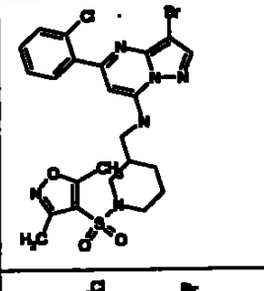
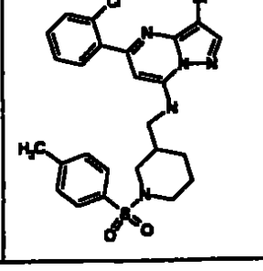
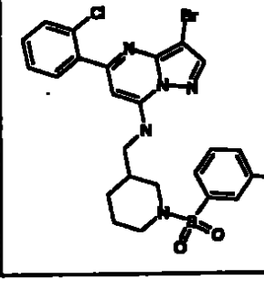
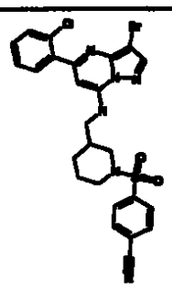
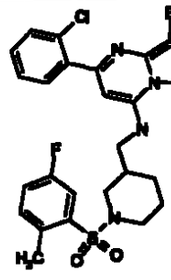
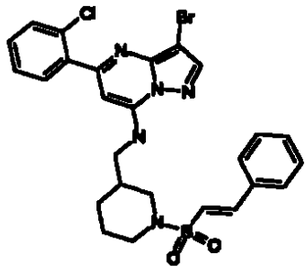
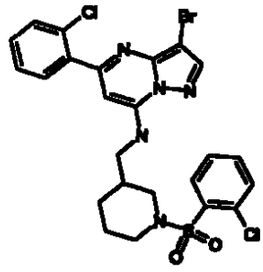
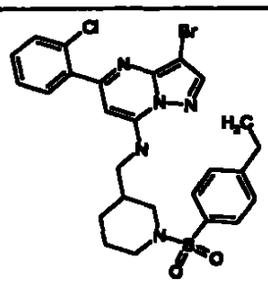
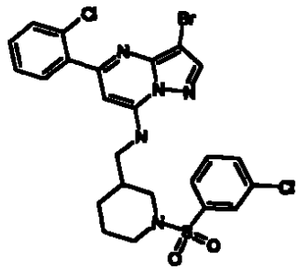
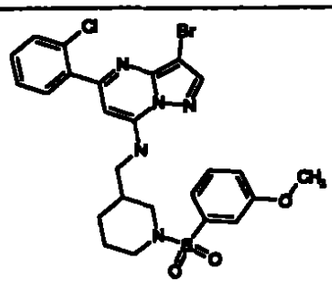
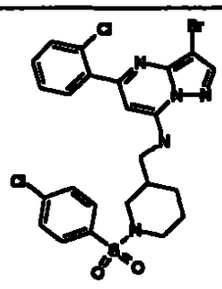
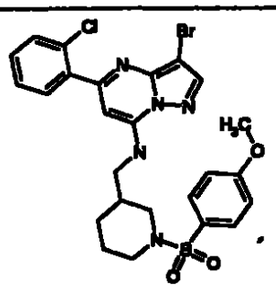
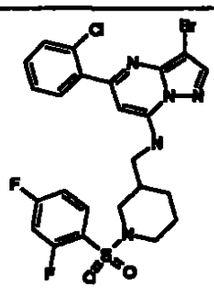
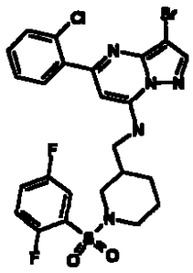
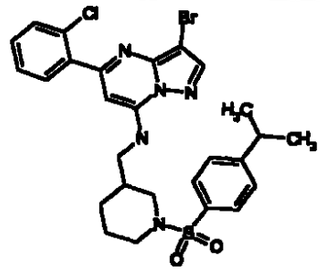
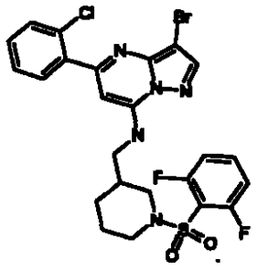
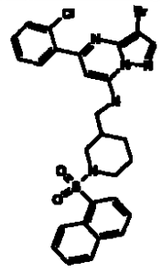
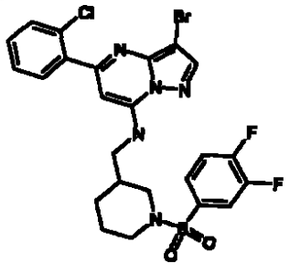
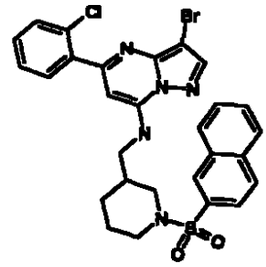
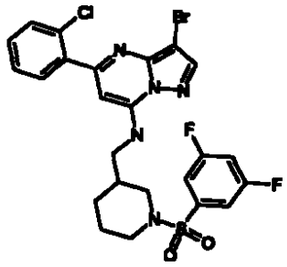
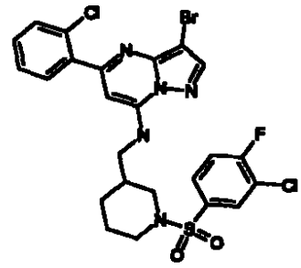
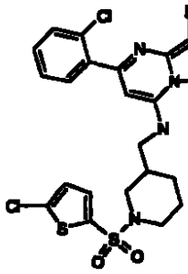
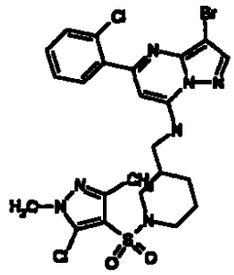
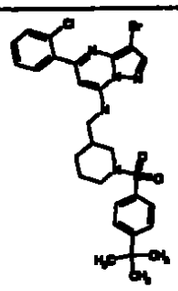
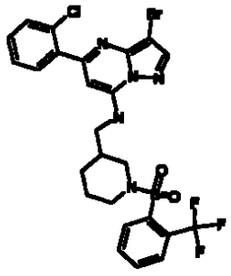
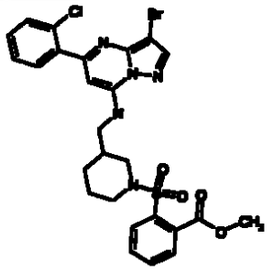
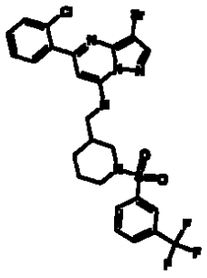
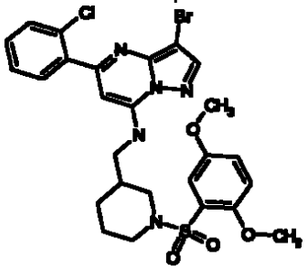
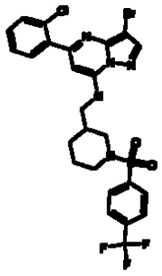
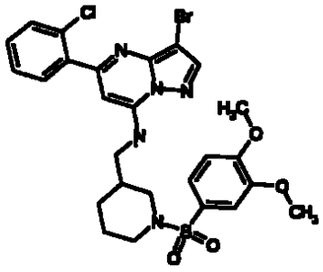
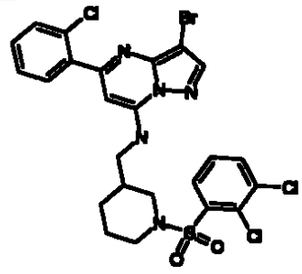
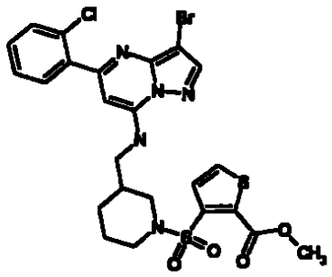
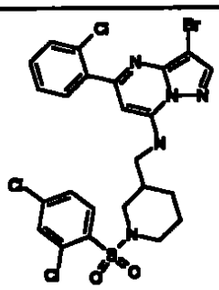
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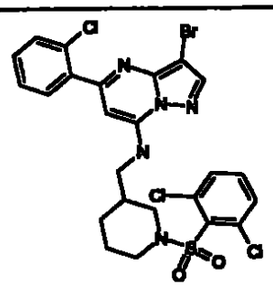
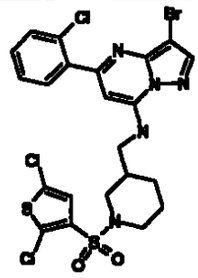
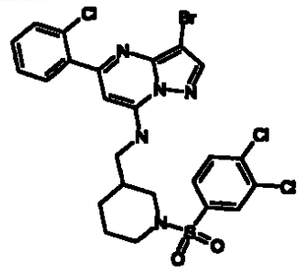
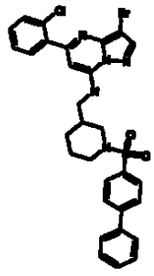
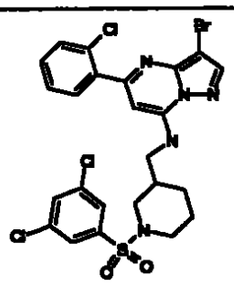
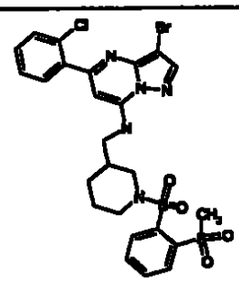
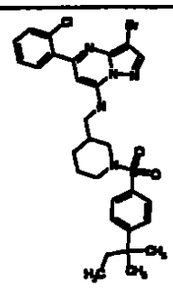
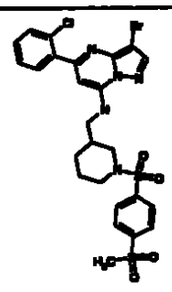
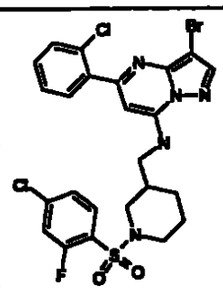
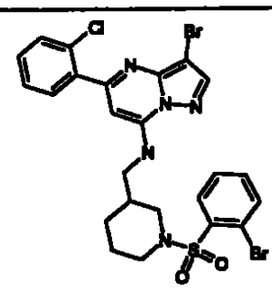
TABLE 69

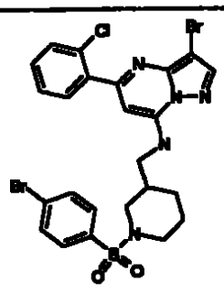
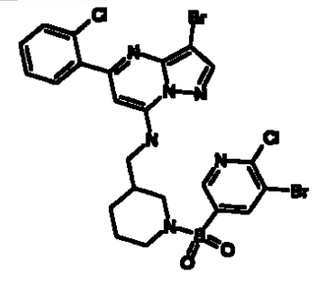
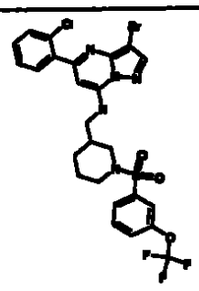
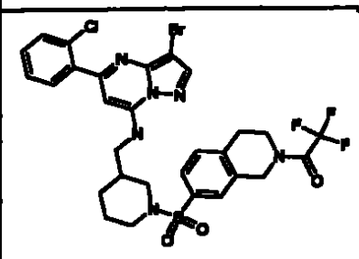
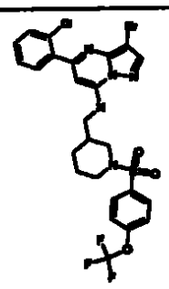
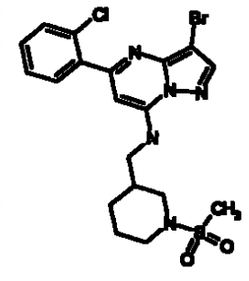
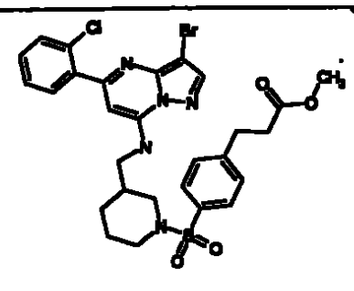
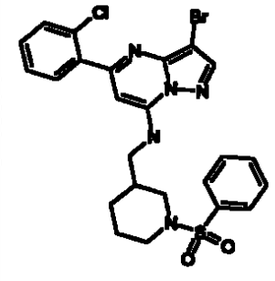
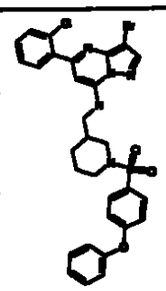
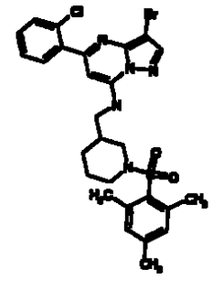
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	1 .6901 2. 514.28			1. 6906 2. 580.32
	1. 6902 2. 568.31			1. 6907 2. 580.32
	1. 6903 2. 576.32			1. 6908 2. 580.32
	1. 6904 2. 576.32			1. 6909 2. 581.32
	1. 6905 2. 576.32			1. 6910 2. 587.32

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

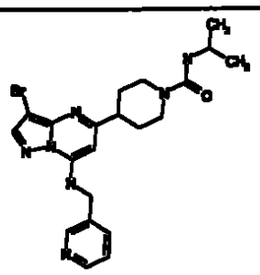
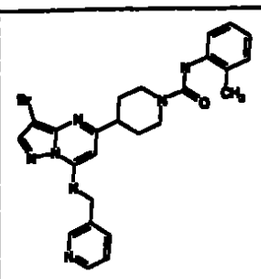
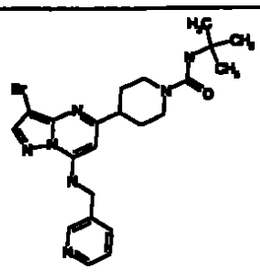
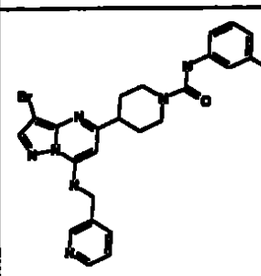
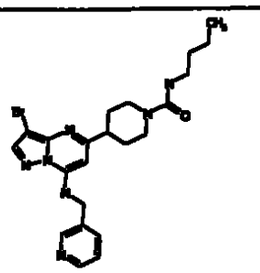
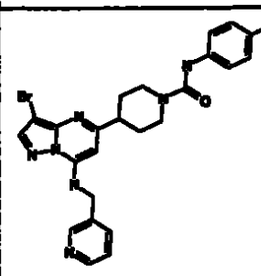
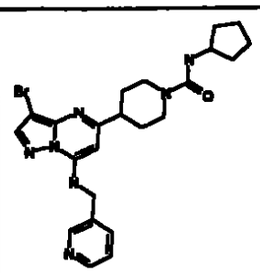
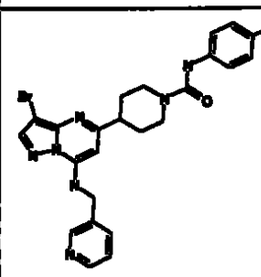
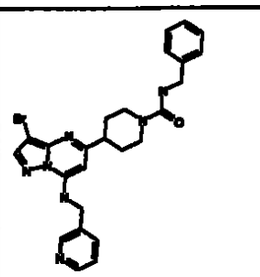
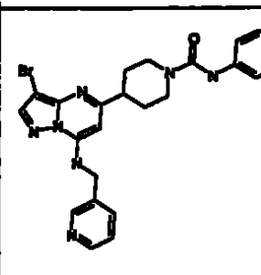
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	1. 6932 2. 620.34			1. 6937 2. 630.35
	1. 6933 2. 622.34			1. 6938 2. 630.35
	1. 6934 2. 622.34			1. 6939 2. 630.35
	1. 6935 2. 626.34			1. 6940 2. 630.35

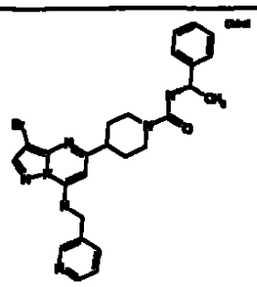
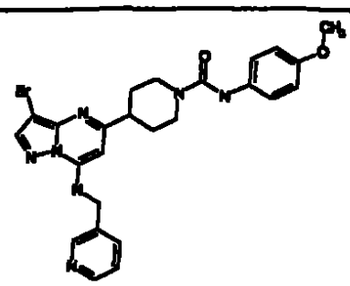
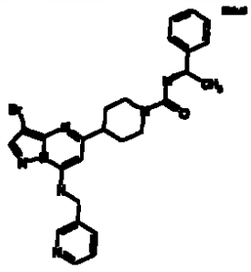
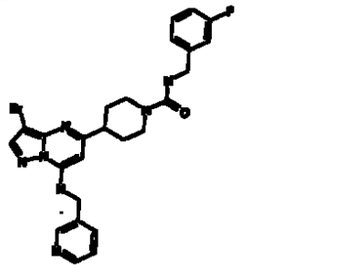
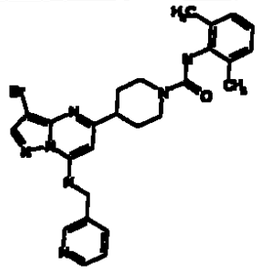
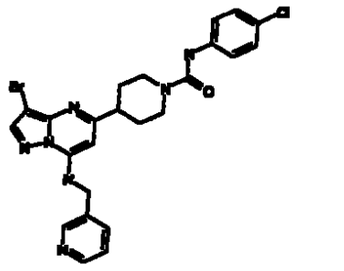
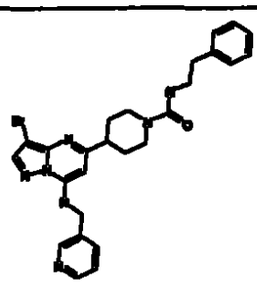
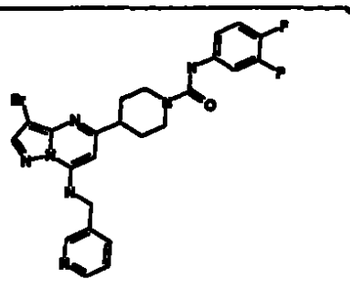
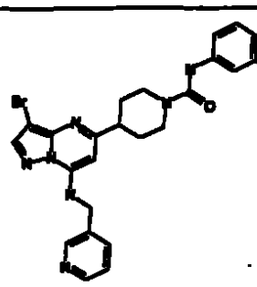
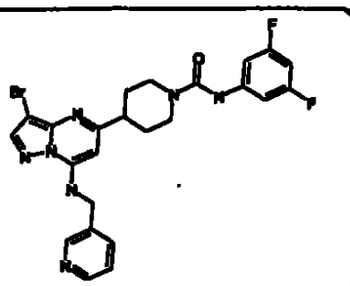
Product	1. Ex. 2. m/z		Product	1. Ex. 2. m/z
	1. 6941 2. 630.35			1. 6946 2. 636.35
	1. 6942 2. 630.35			1. 6947 2. 638.35
	1. 6943 2. 630.35			1. 6948 2. 640.35
	1. 6944 2. 632.35			1. 6949 2. 640.35
	1. 6945 2. 614.34			1. 6950 2. 640.35

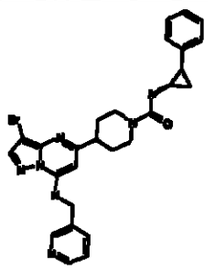
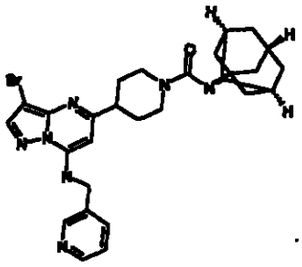
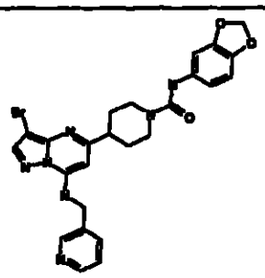
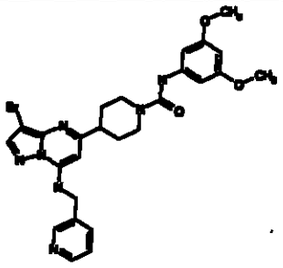
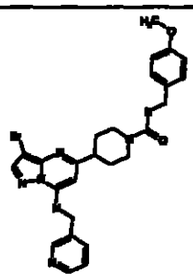
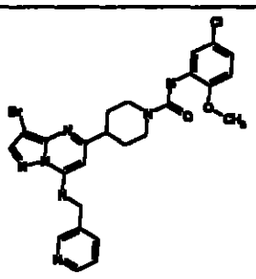
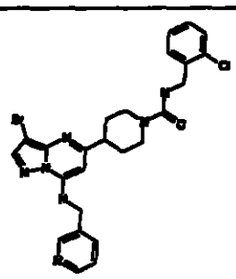
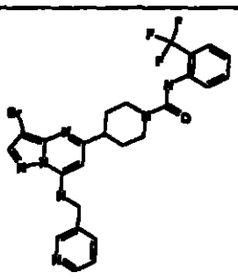
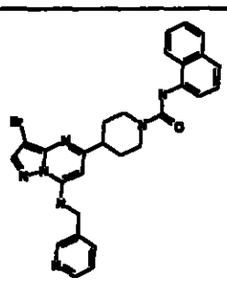
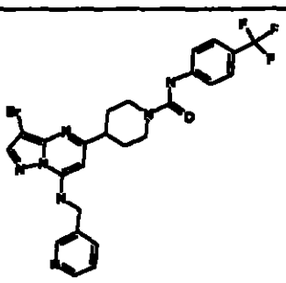
Product	1. Ex. 2. m/z		Product	1. Ex. 2. m/z
	1. 6951 2. 640.35			1. 6956 2. 675.23
	1. 6952 2. 646.36			1. 6957 2. 713.39
	1. 6953 2. 646.36			1. 6958 2. 500.27
	1. 6954 2. 648.36			1. 6959 2. 562.31
	1. 6955 2. 654.36			1. 6960 2. 604.33

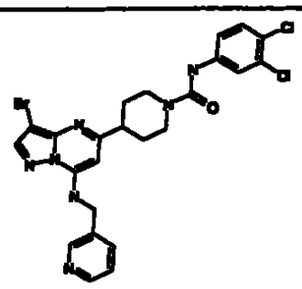
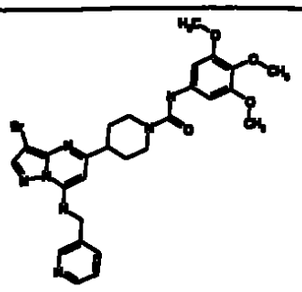
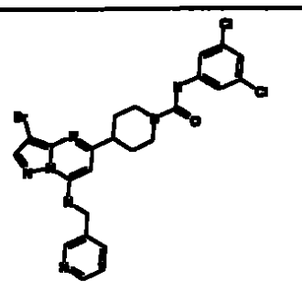
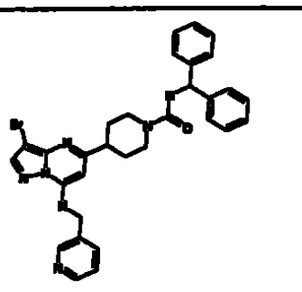
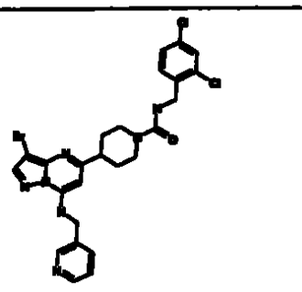
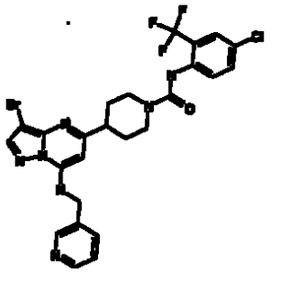
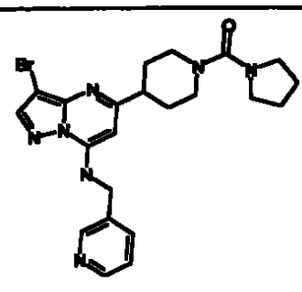
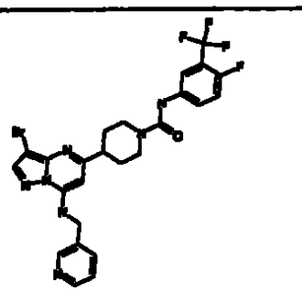
5

TABLE 70

Product	1. Ex. 2. m/z		Product	1. Ex. 2. m/z
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	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

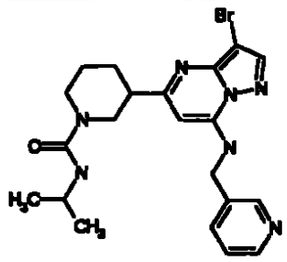
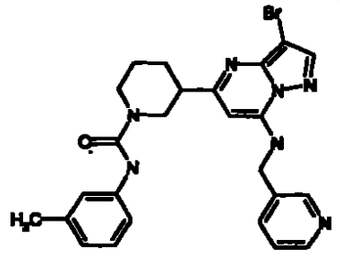
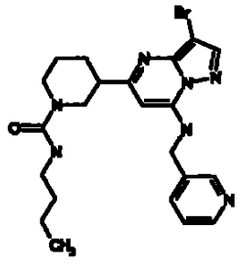
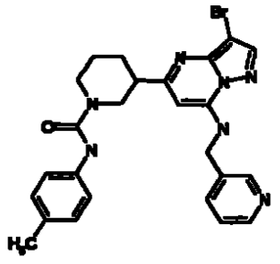
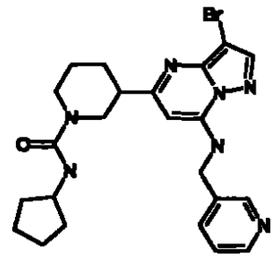
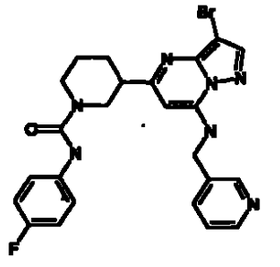
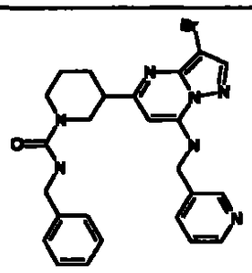
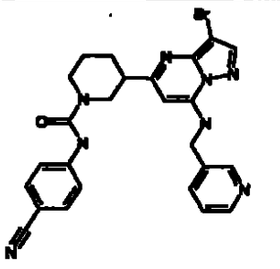
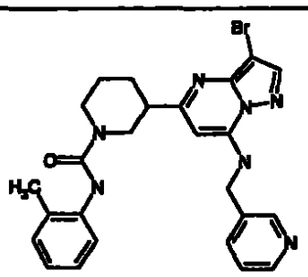
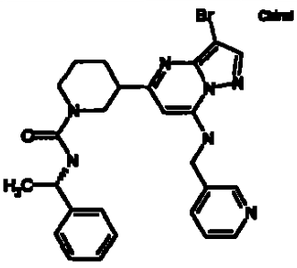
Product	1. Ex. 2. m/z		Product	1. Ex. 2. m/z
	1. 7011 2. 536.29			1. 7016 2. 538.3
	1. 7012 2. 536.29			1. 7017 2. 540.3
	1. 7013 2. 536.29			1. 7018 2. 542.3
	1. 7014 2. 536.29			1. 7019 2. 544.3
	1. 7015 2. 536.29			1. 7020 2. 544.3

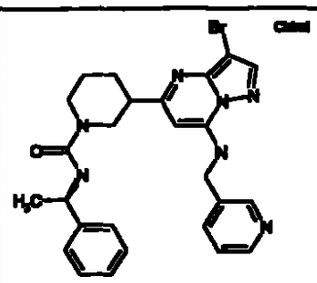
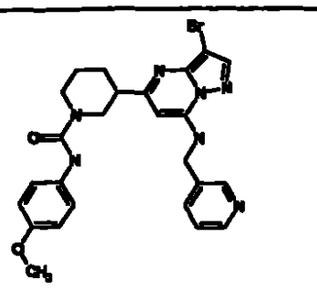
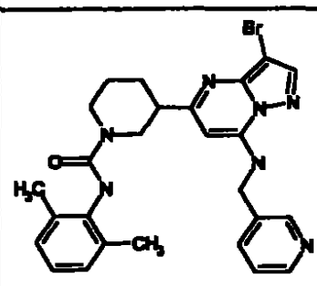
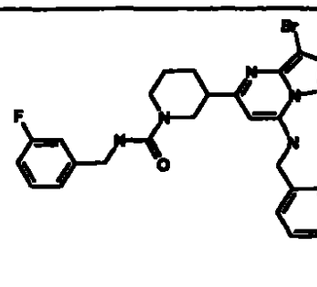
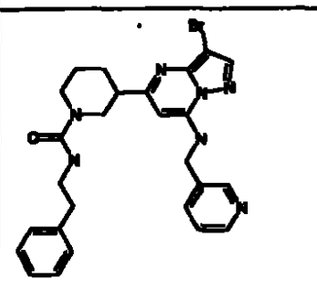
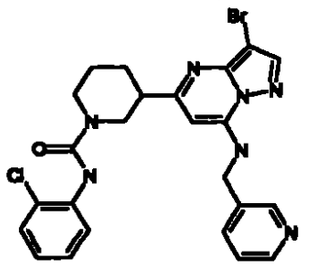
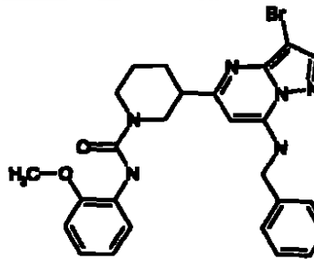
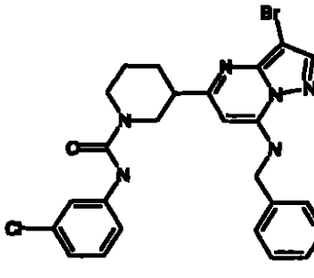
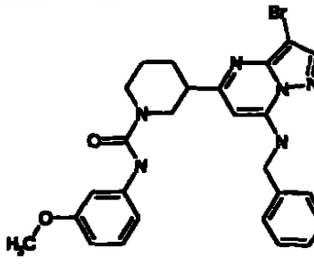
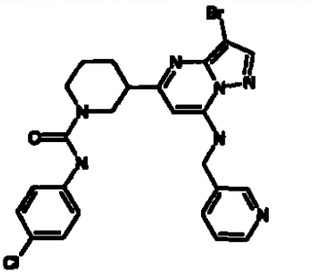
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	1. 7022 2. 552.3			1. 7027 2. 568.31
	1. 7023 2. 552.3			1. 7028 2. 572.31
	1. 7024 2. 556.31			1. 7029 2. 576.32
	1. 7025 2. 556.31			1. 7030 2. 576.32

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			

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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

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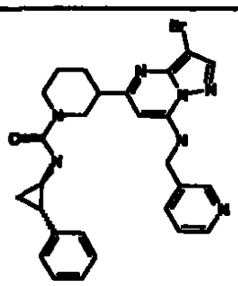
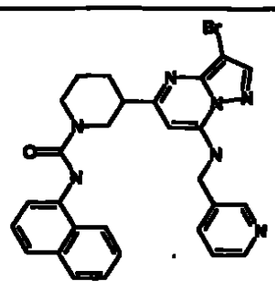
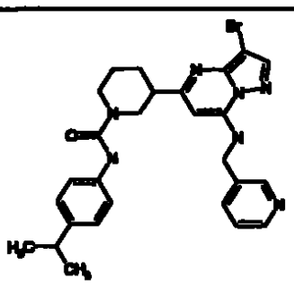
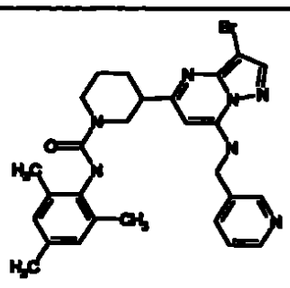
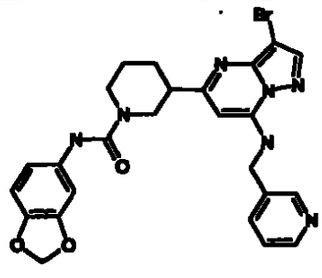
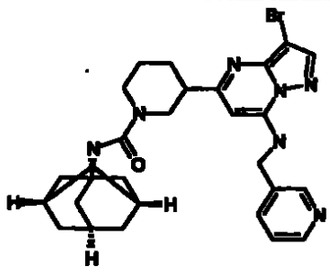
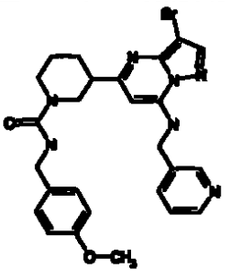
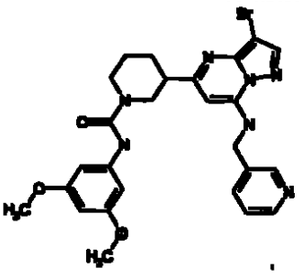
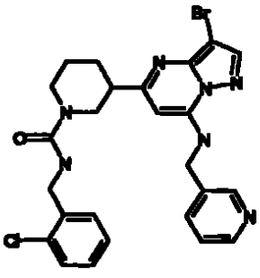
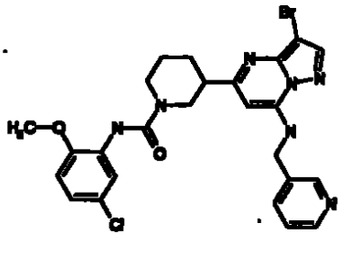
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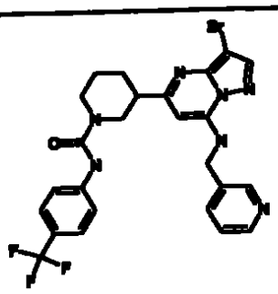
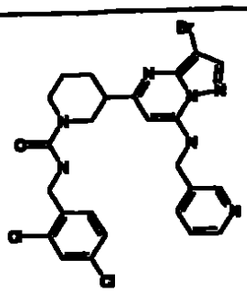
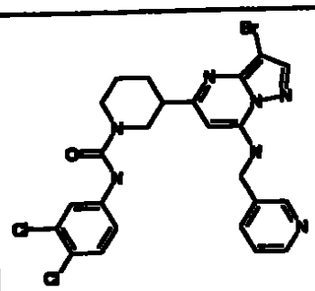
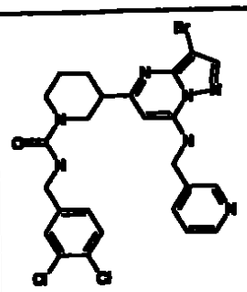
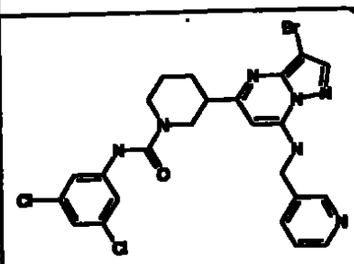
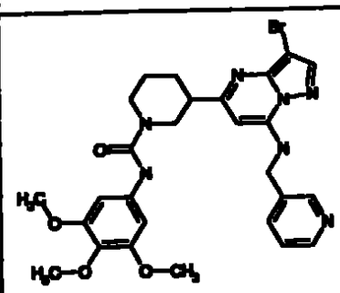
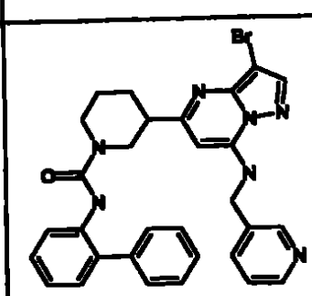
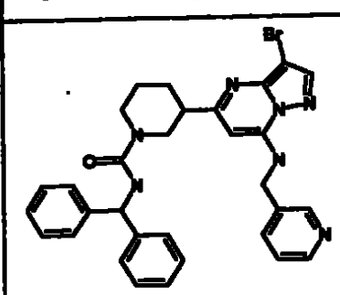
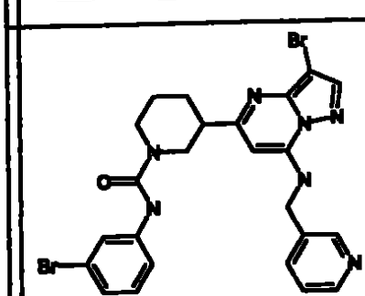
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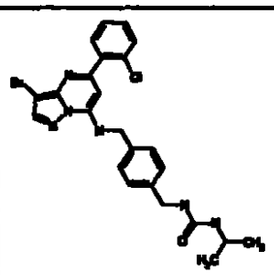
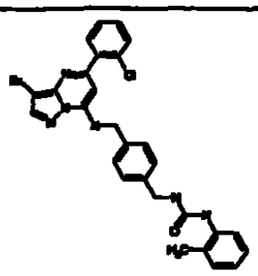
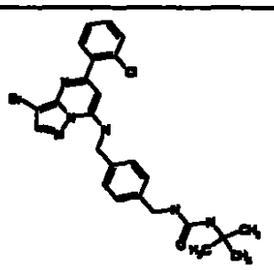
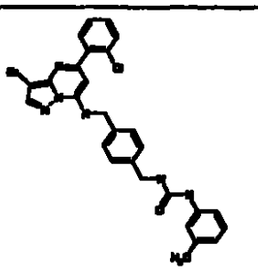
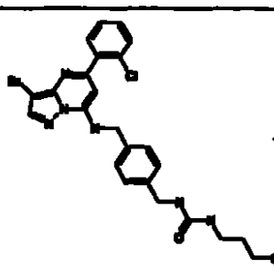
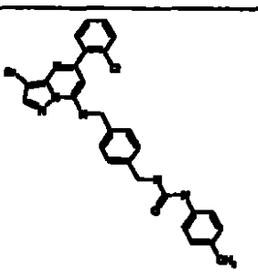
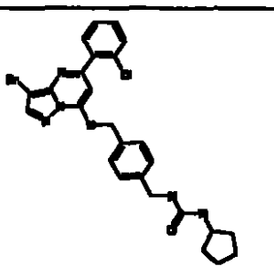
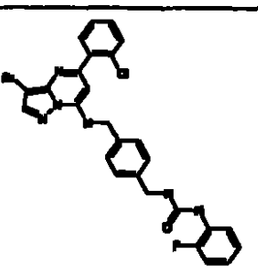
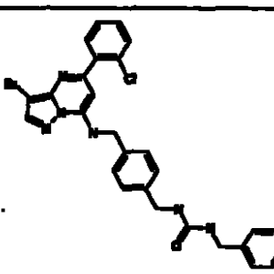
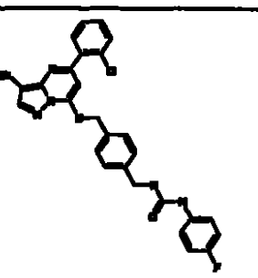
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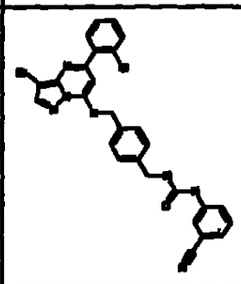
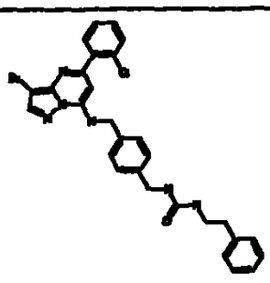
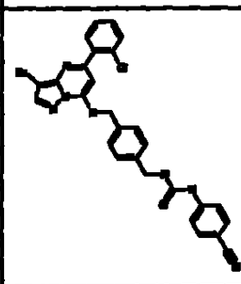
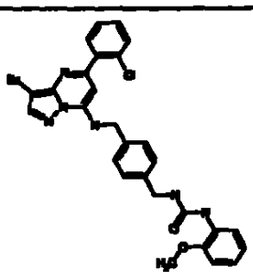
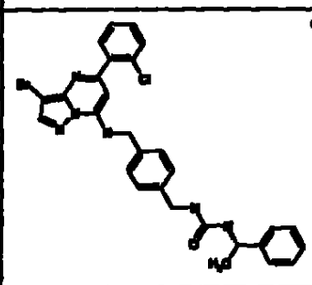
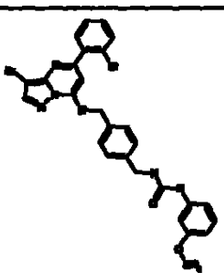
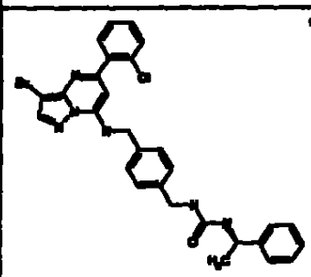
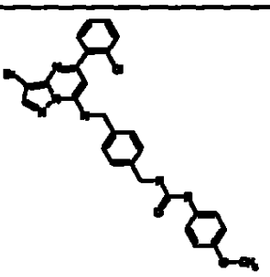
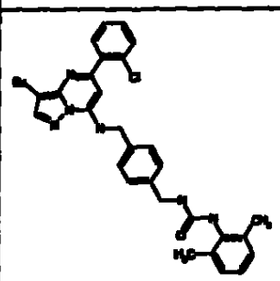
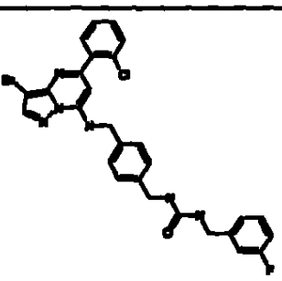
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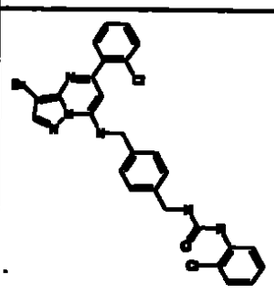
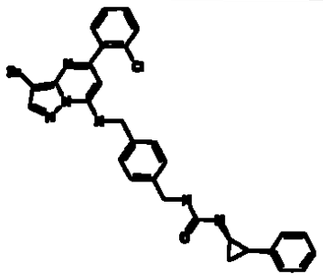
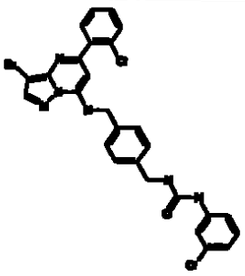
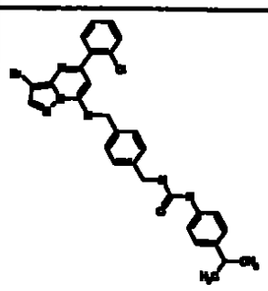
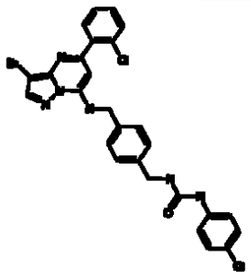
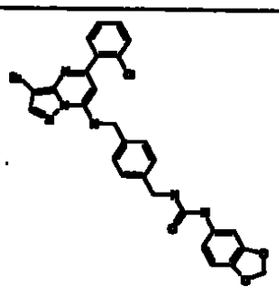
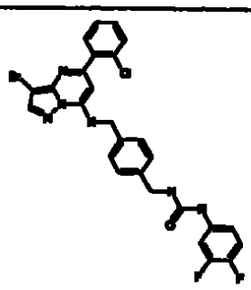
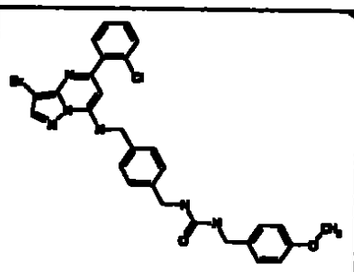
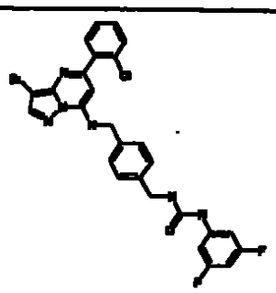
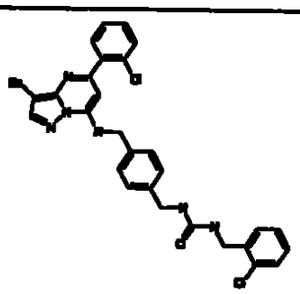
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	1. 7132 2. 576.32			1. 7137 2. 590.32
	1. 7133 2. 576.32			1. 7138 2. 598.33
	1. 7134 2. 584.32			1. 7139 2. 598.33
	1. 7135 2. 585.3			

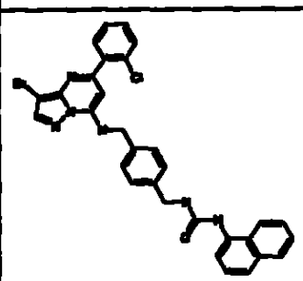
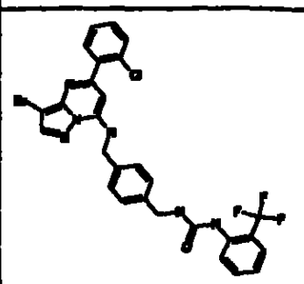
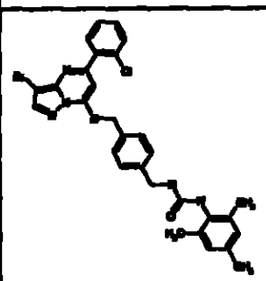
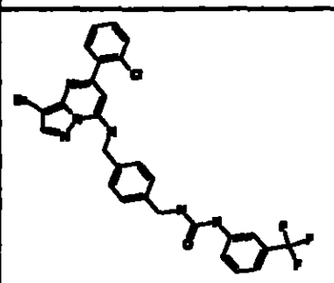
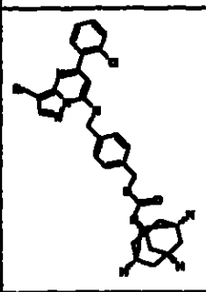
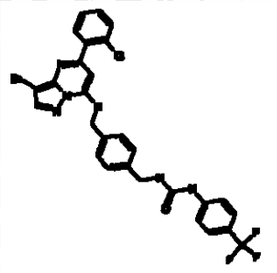
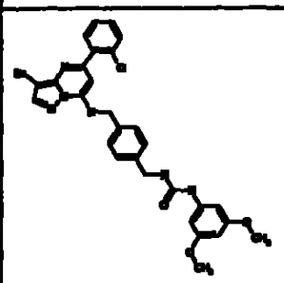
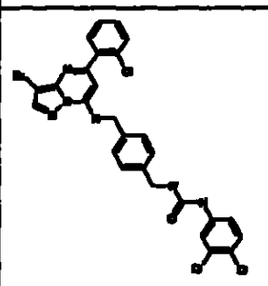
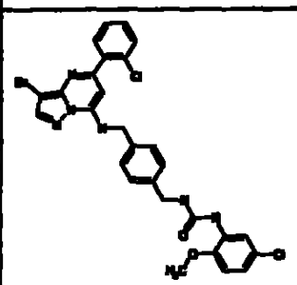
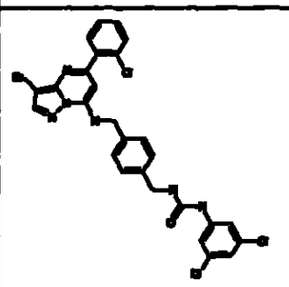
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TABLE 72

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. 586.32			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
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	1. 7235 2. 627.34			1. 7240 2. 631.35

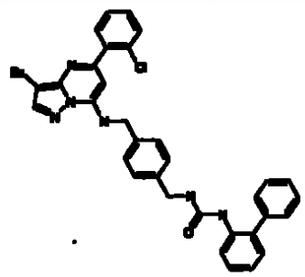
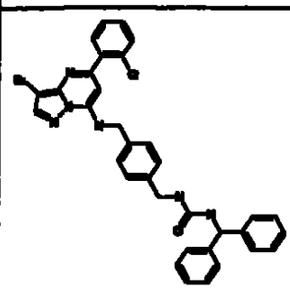
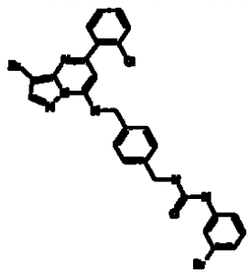
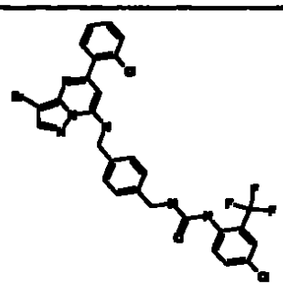
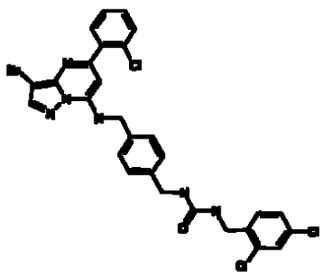
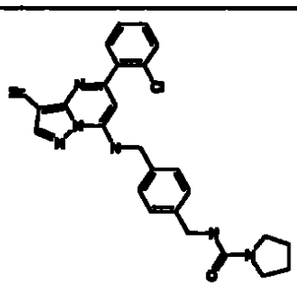
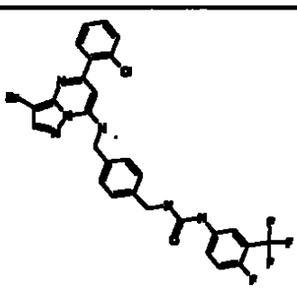
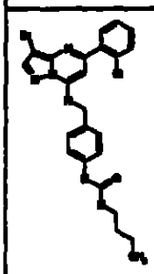
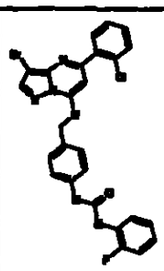
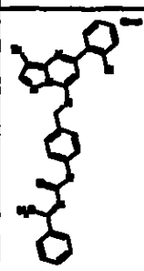
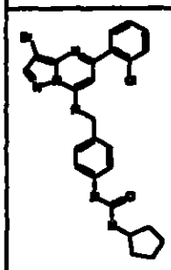
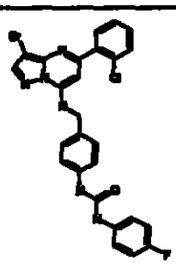
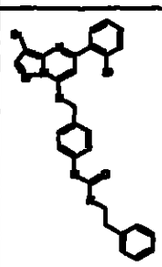
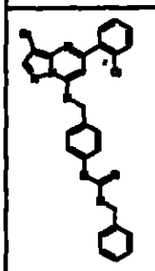
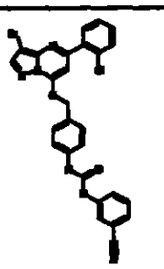
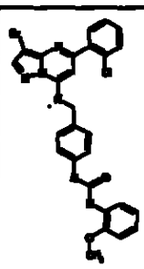
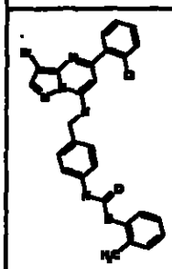
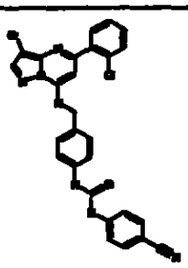
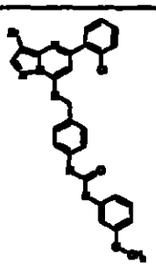
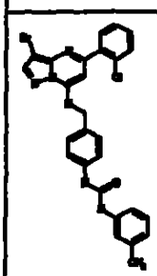
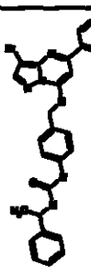
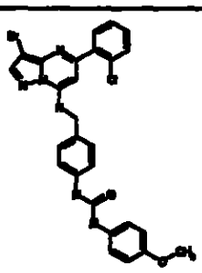
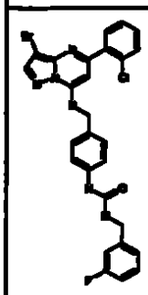
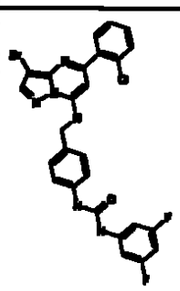
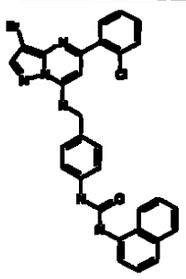
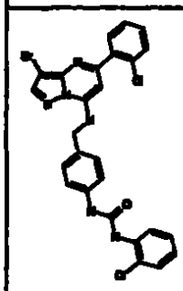
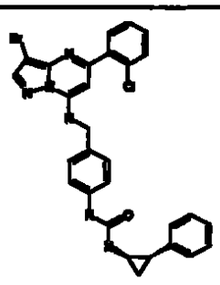
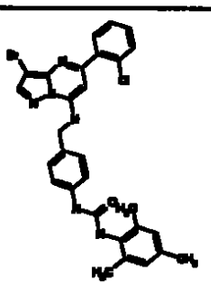
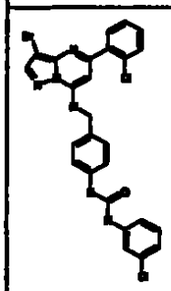
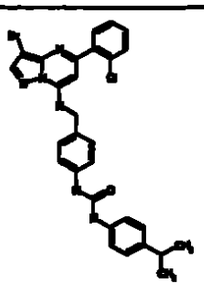
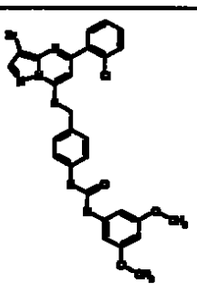
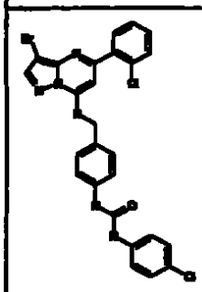
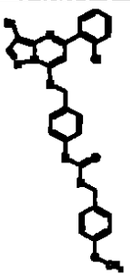
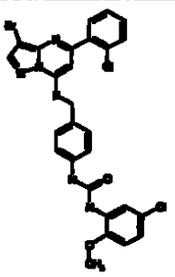
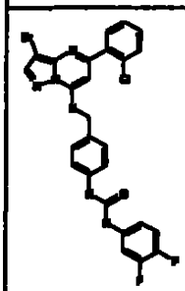
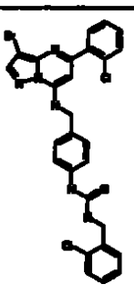
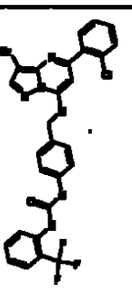
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	1. 7242 2. 641.35			1. 7247 2. 685.37
	1. 7243 2. 645.35			
	1. 7244 2. 541.3			
	1. 7245 2. 649.36			

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

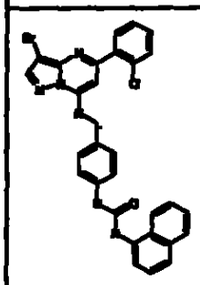
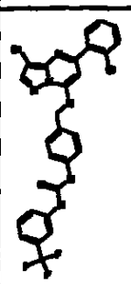
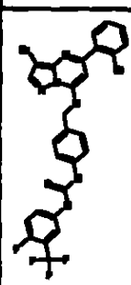
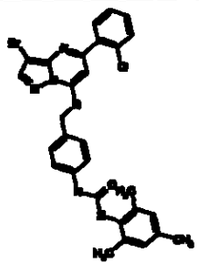
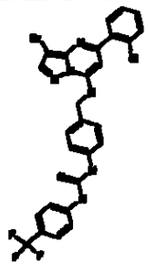
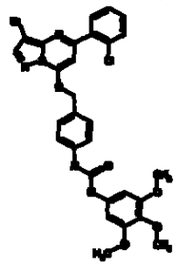
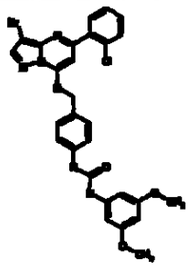
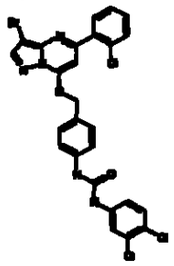
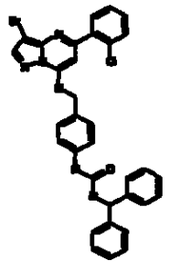
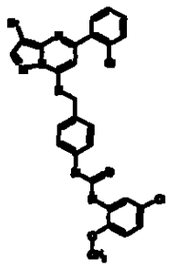
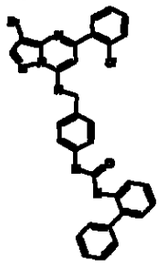
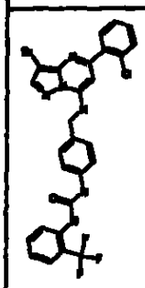
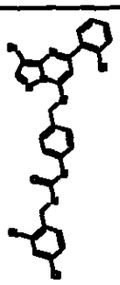
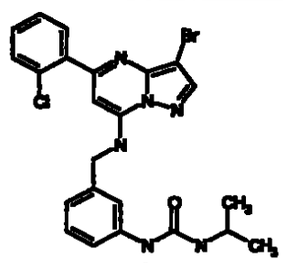
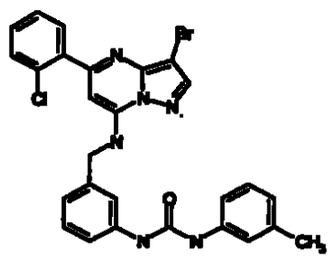
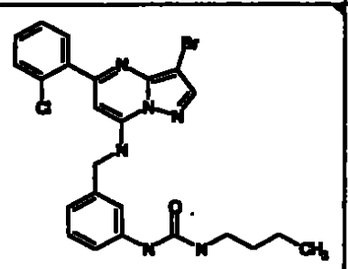
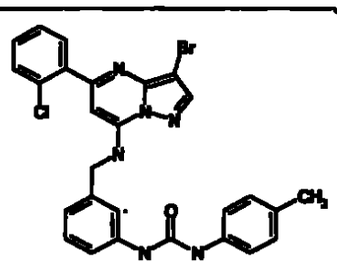
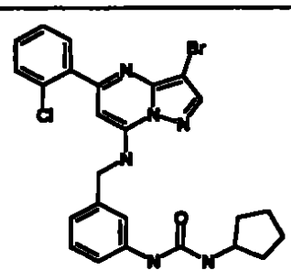
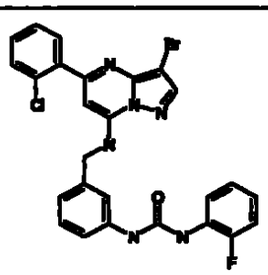
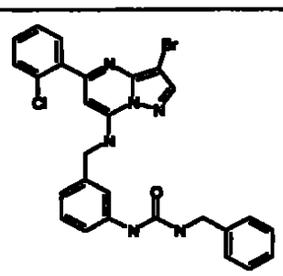
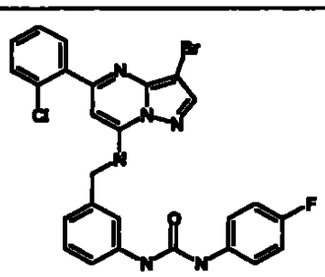
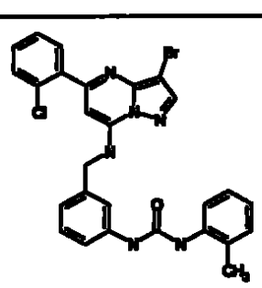
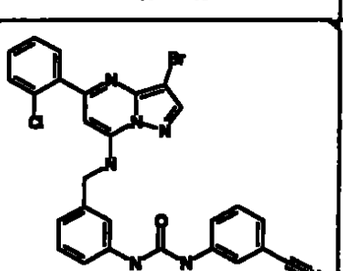
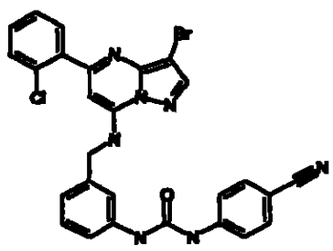
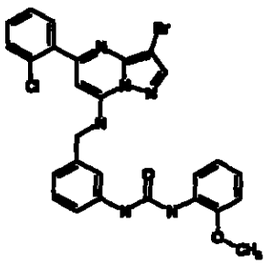
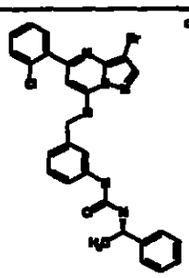
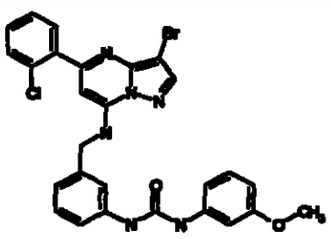
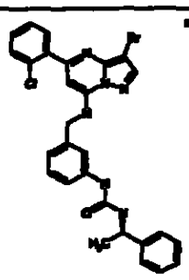
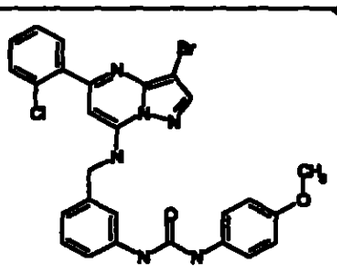
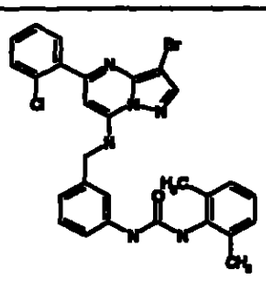
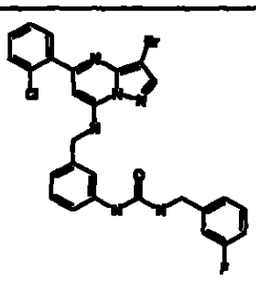
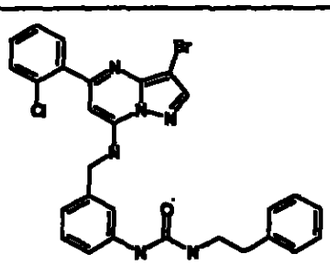
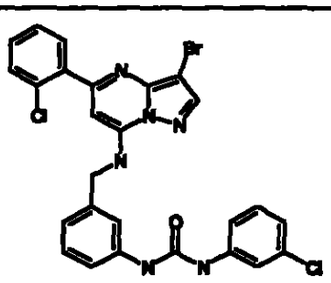
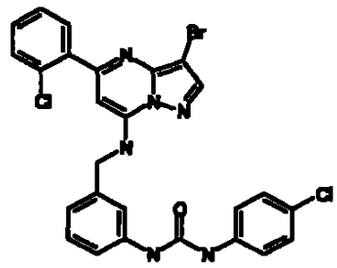
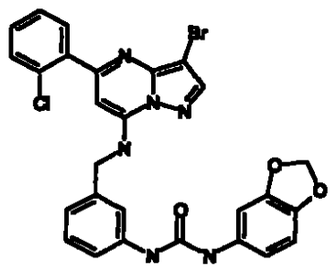
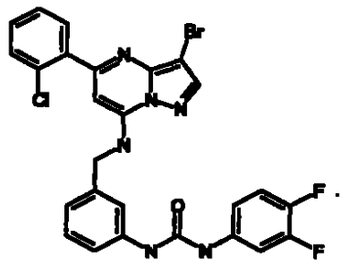
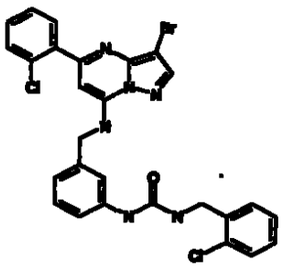
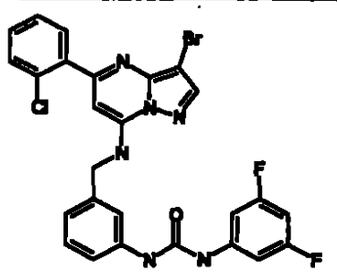
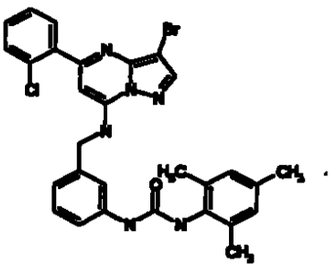
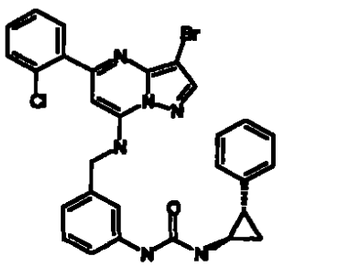
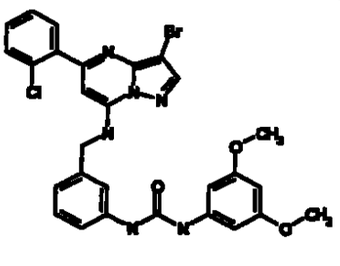
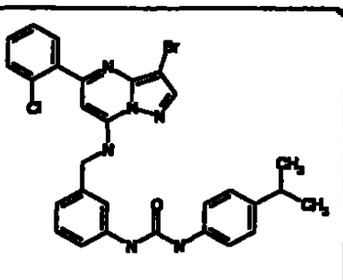
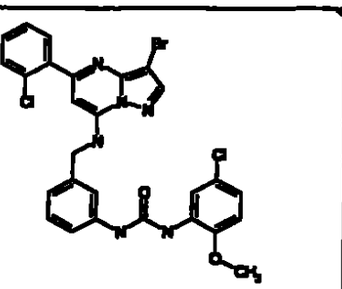
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7331 2. 599.33		1. 7336 2. 617.34		1. 73412. 635.35
	1. 7332 2. 591.33		1. 7337 2. 617.34		1. 7342 2. 639.35
	1. 7333 2. 609.33		1. 7338 2. 617.34		1. 7343 2. 639.35
	1. 7334 2. 613.34		1. 7339 2. 625.34		
	1. 7335 2. 617.34		1. 7340 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

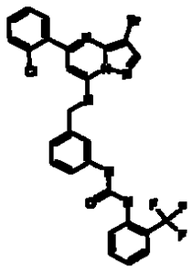
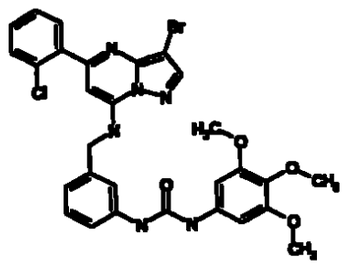
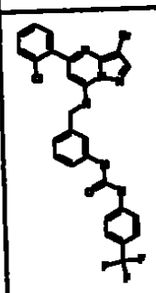
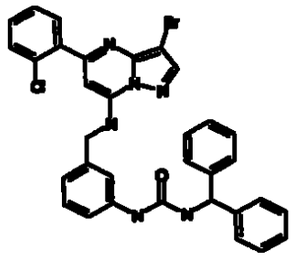
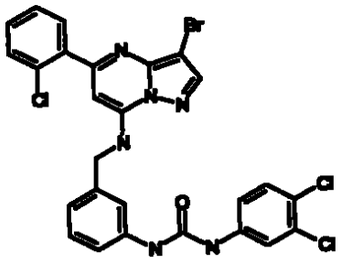
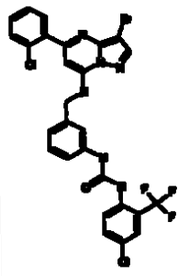
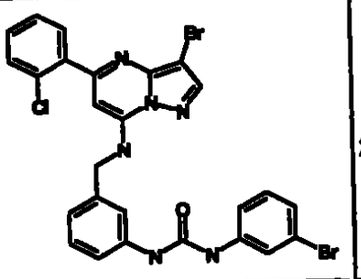
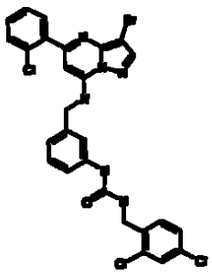
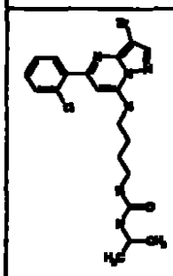
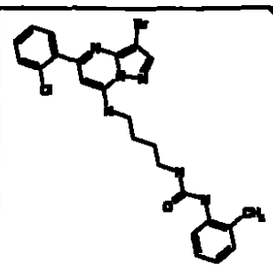
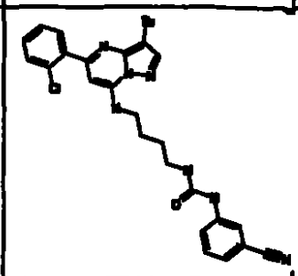
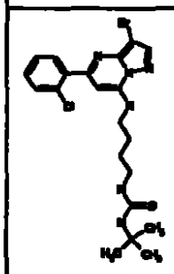
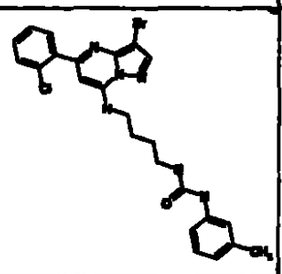
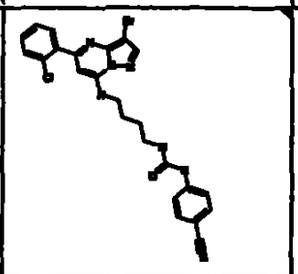
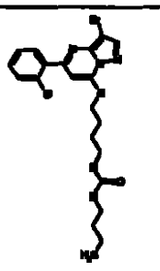
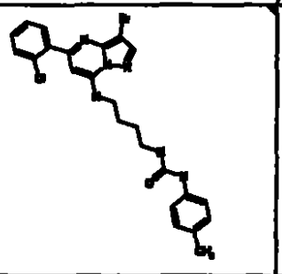
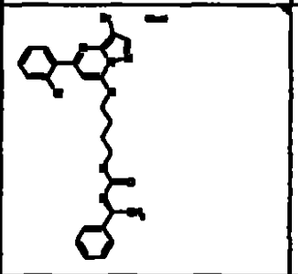
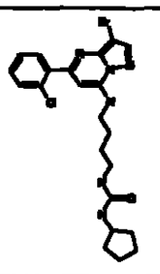
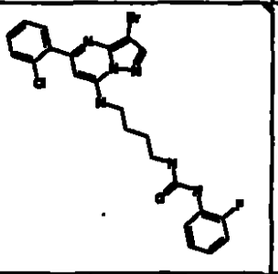
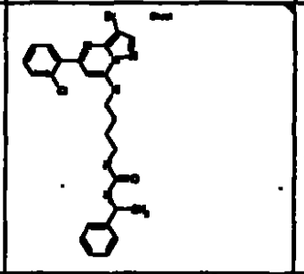
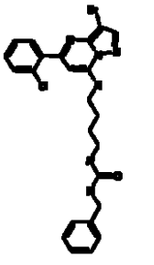
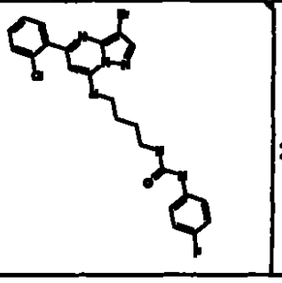
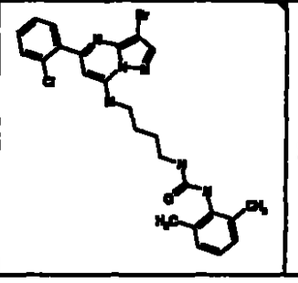
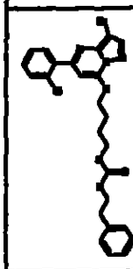
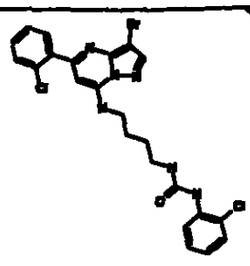
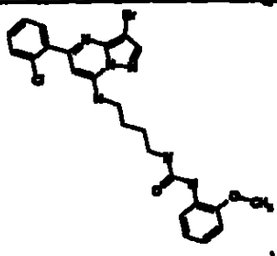
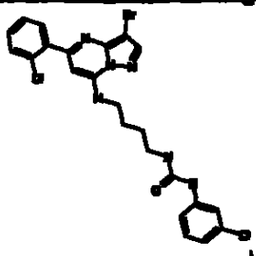
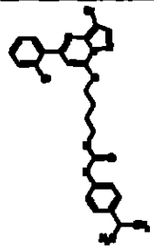
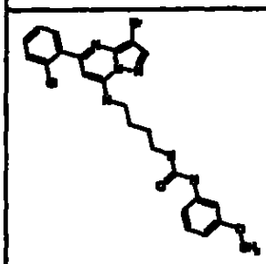
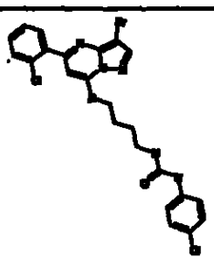
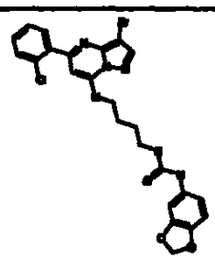
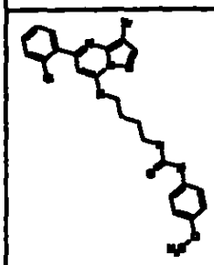
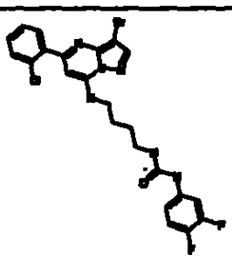
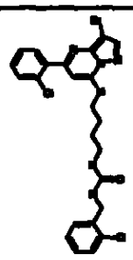
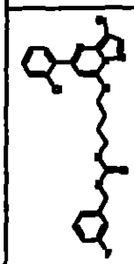
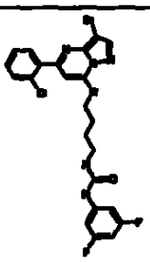
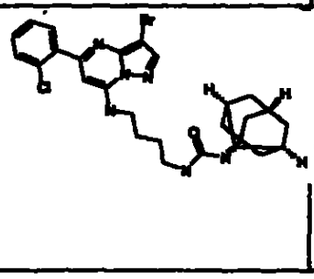
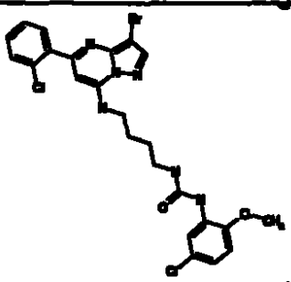
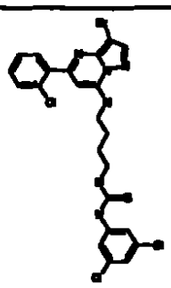
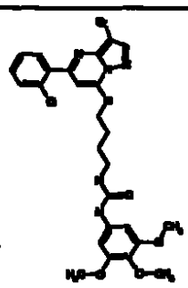
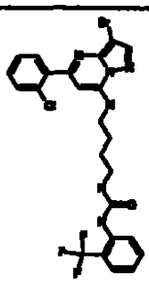
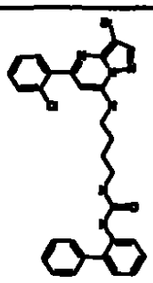
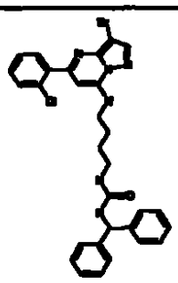
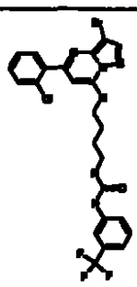
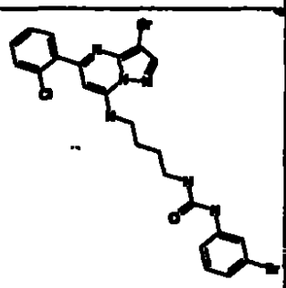
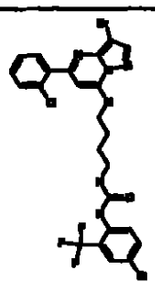
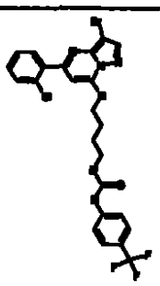
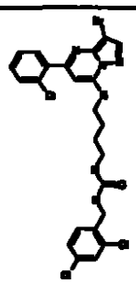
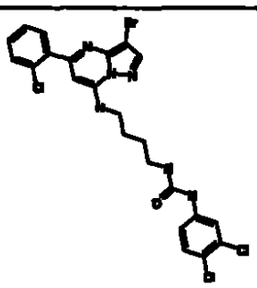
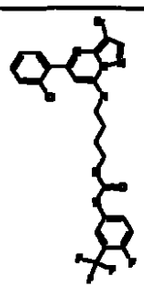
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TABLE75

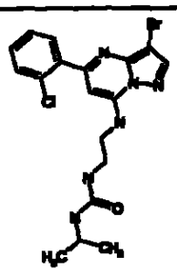
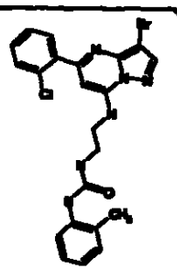
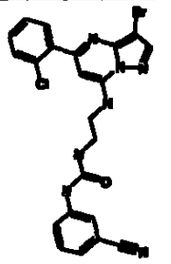
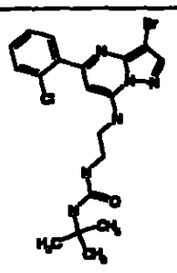
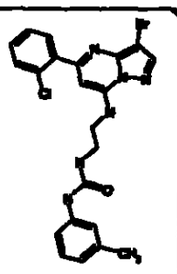
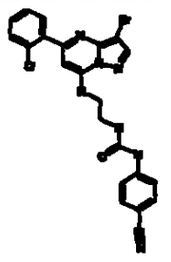
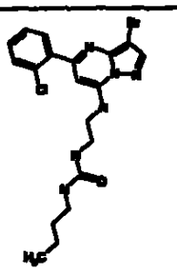
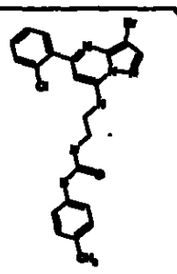
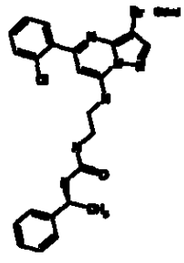
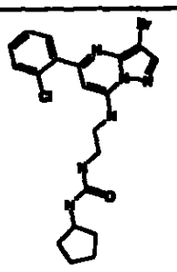
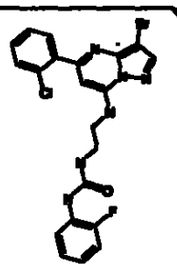
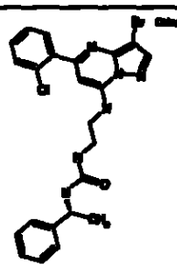
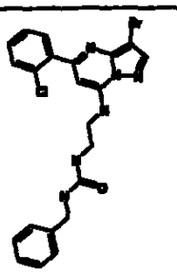
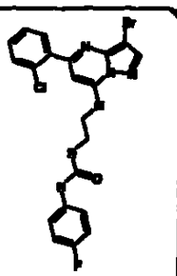
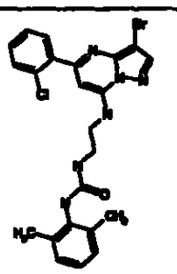
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	1. 7504 2. 507.28		1. 7509 2. 533.29		1. 7514 2. 543.3
	1. 7505 2. 529.29		1. 7510 2. 533.29		1. 7515 2. 543.3

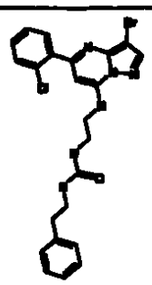
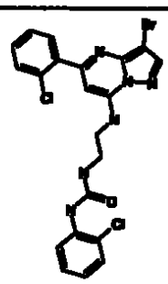
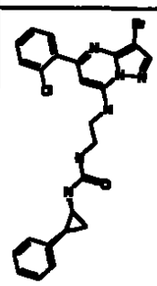
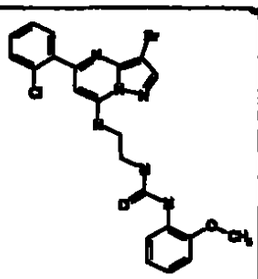
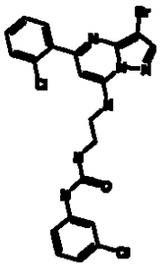
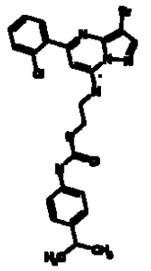
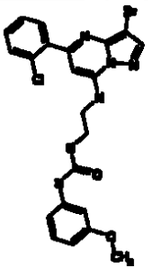
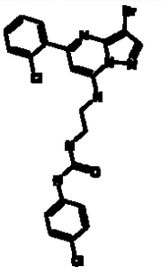
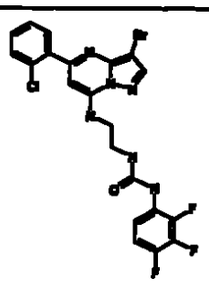
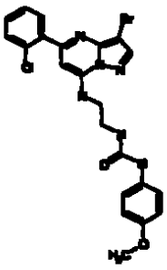
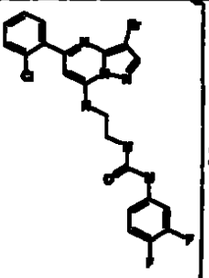
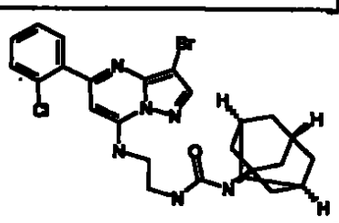
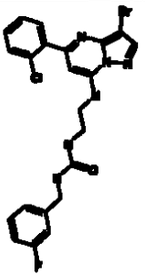
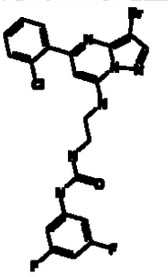
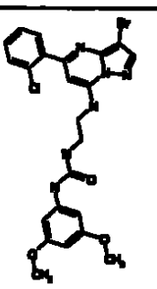
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	1. 7516 2. 543.3		1. 7521 2. 549.3		1. 7526 2. 555.31
	1. 7517 2. 545.3		1. 7522 2. 549.3		1. 7527 2. 557.31
	1. 7518 2. 545.3		1. 7523 2. 549.3		1. 7528 2. 559.31
	1. 7519 2. 545.3		1. 7524 2. 551.3		1. 7529 2. 560.31
	1. 7520 2. 547.3		1. 7525 2. 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		

5

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
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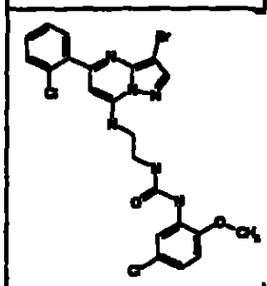
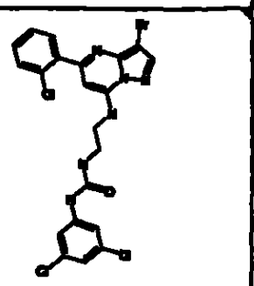
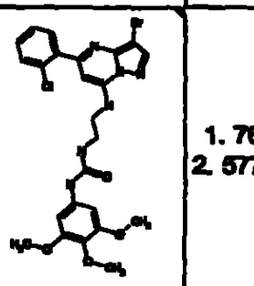
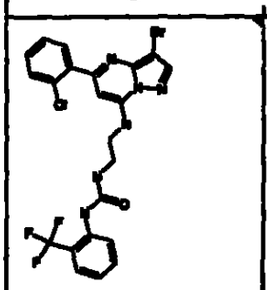
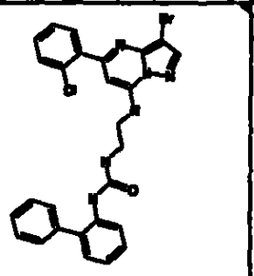
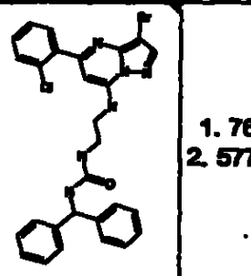
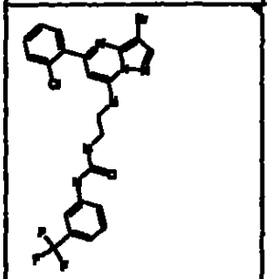
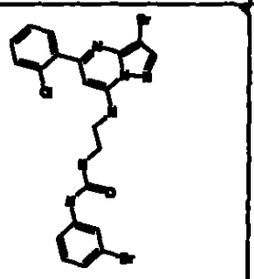
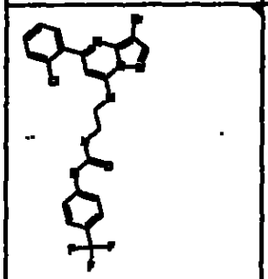
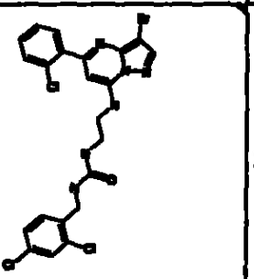
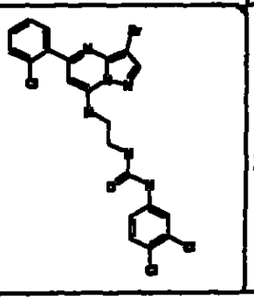
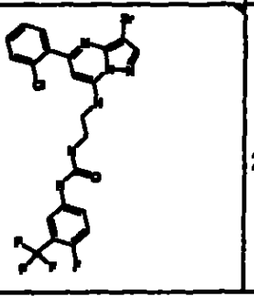
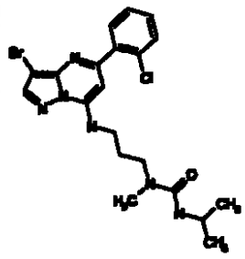
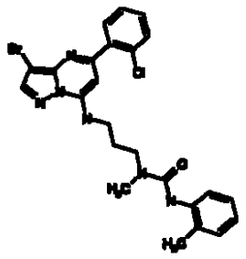
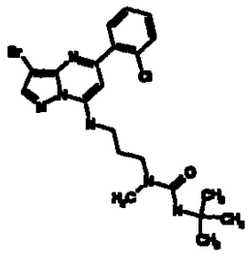
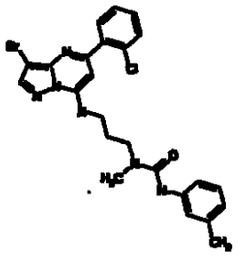
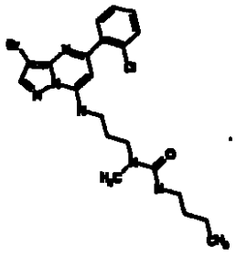
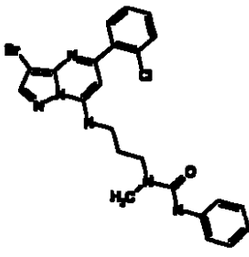
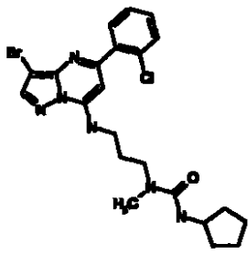
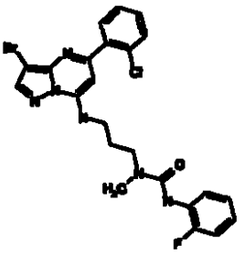
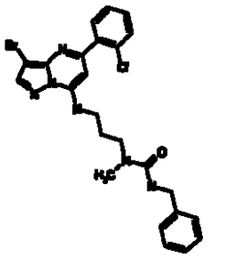
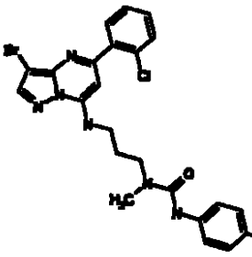
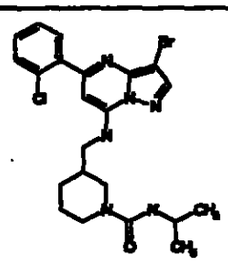
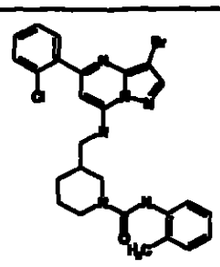
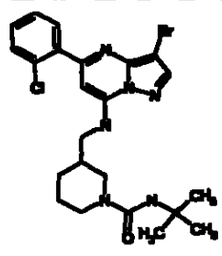
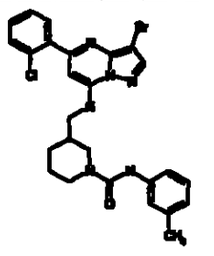
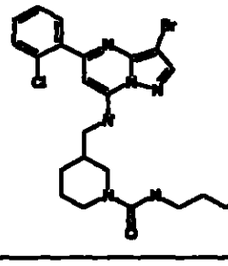
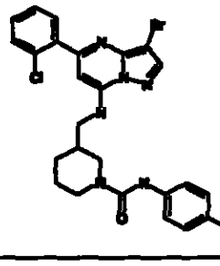
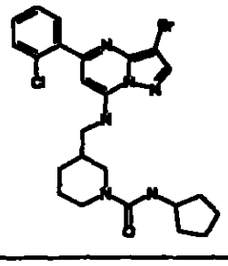
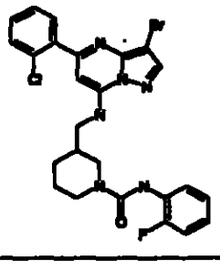
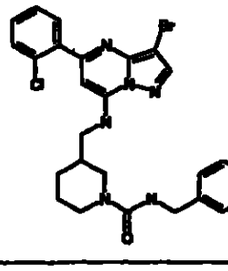
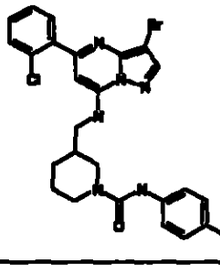
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	1. 7632 2. 555.31		1. 7637 2. 563.31		1. 7642 2. 577.32
	1. 7633 2. 555.31		1. 7636 2. 585.31		
	1. 7634 2. 555.31		1. 7639 2. 569.31		
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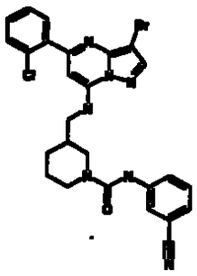
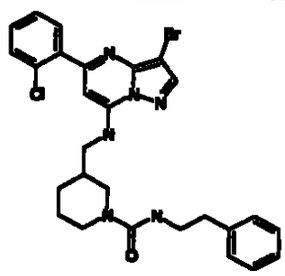
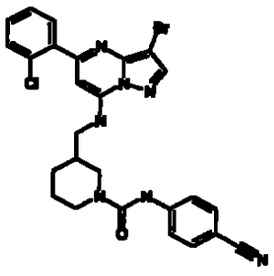
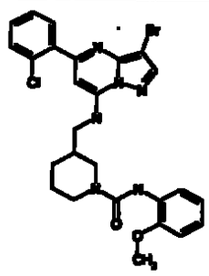
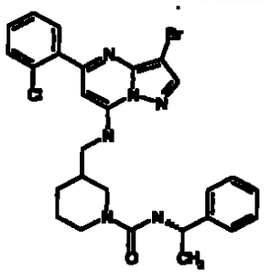
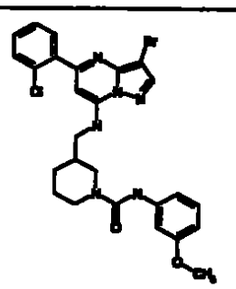
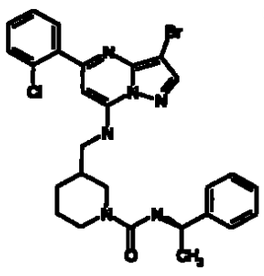
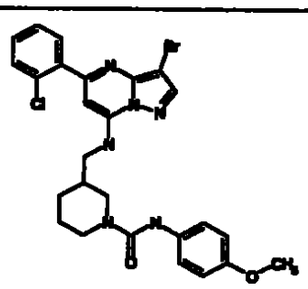
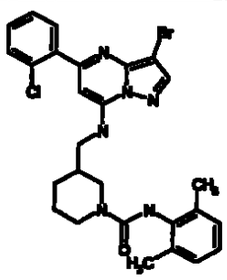
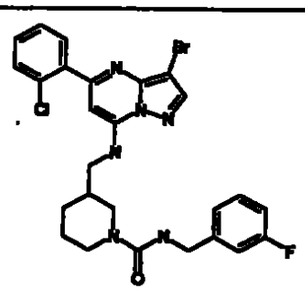
TABLE 77

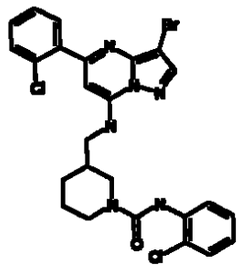
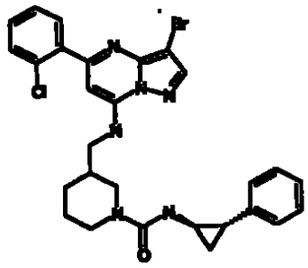
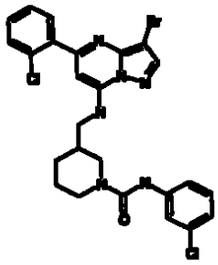
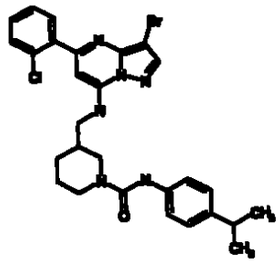
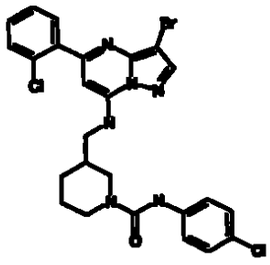
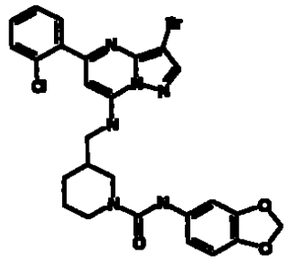
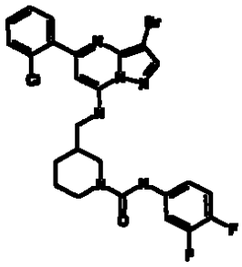
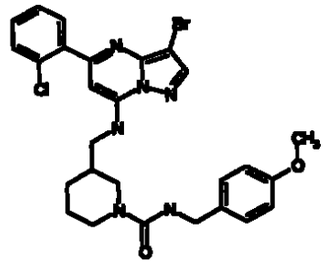
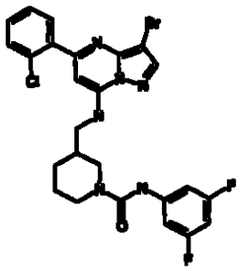
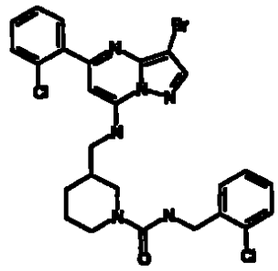
Product	1. Ex. 2. m/z		Product	1. Ex. 2. m/z
	1. 7701 2. 481.26			1. 7706 2. 529.29
	1. 7702 2. 495.27			1. 7707 2. 529.29
	1. 7703 2. 495.27			1. 7708 2. 529.29
	1. 7704 2. 507.28			1. 7709 2. 533.29
	1. 7705 2. 529.29			1. 7710 2. 533.29

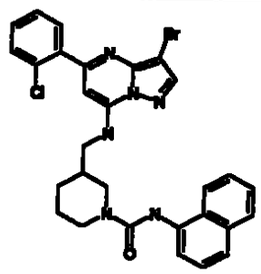
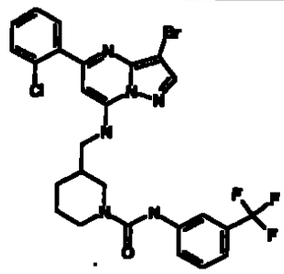
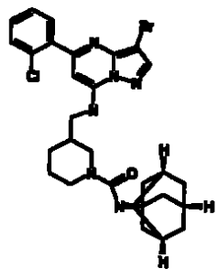
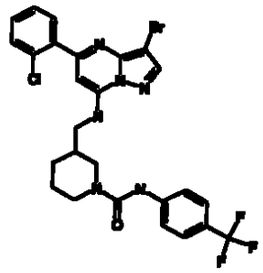
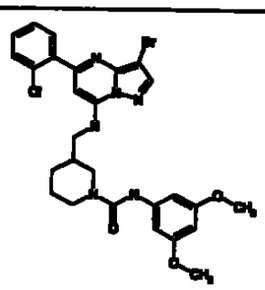
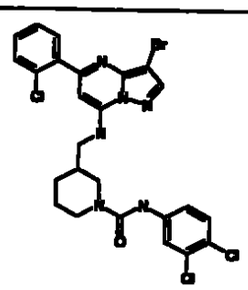
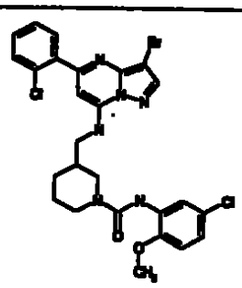
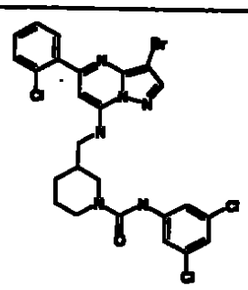
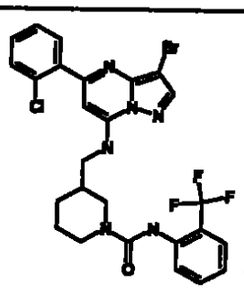
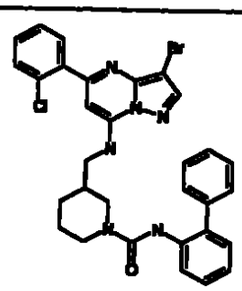
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TABLE 78

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

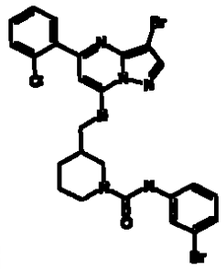
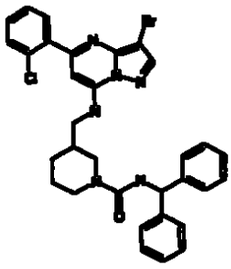
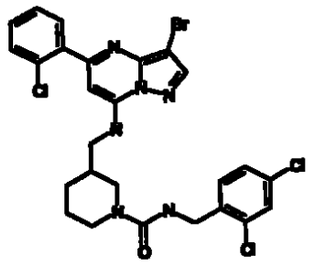
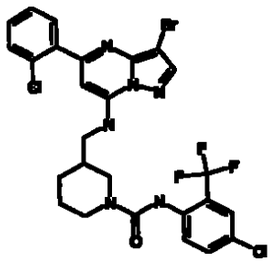
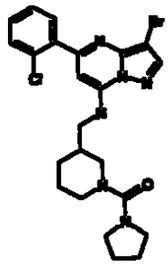
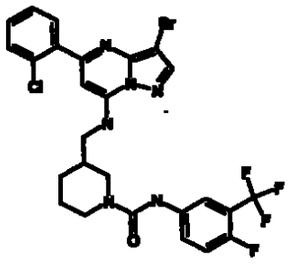
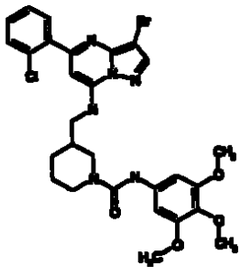
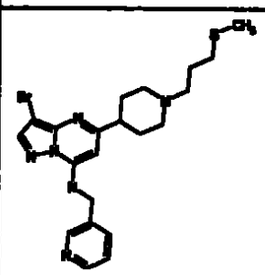
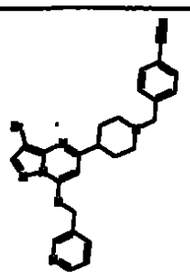
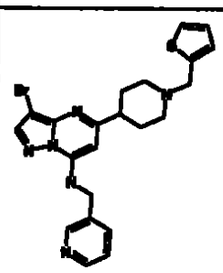
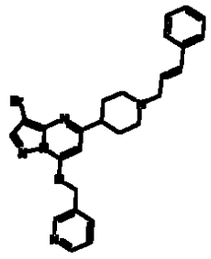
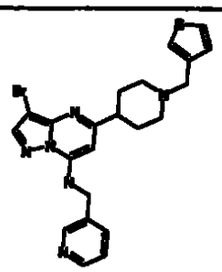
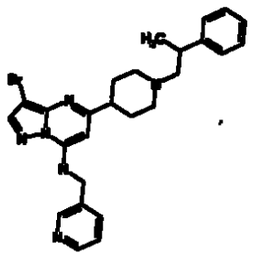
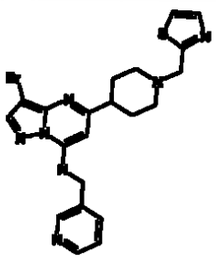
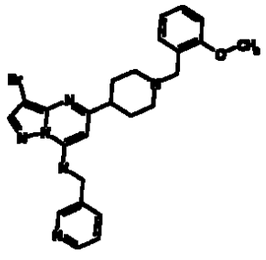
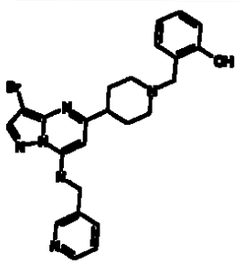
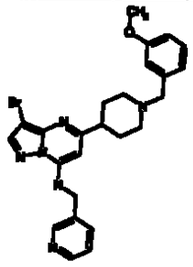
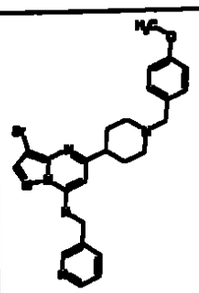
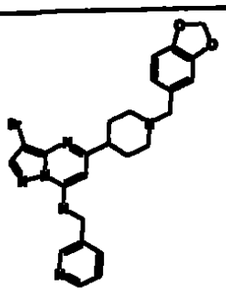
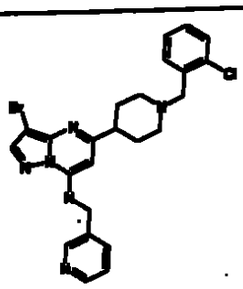
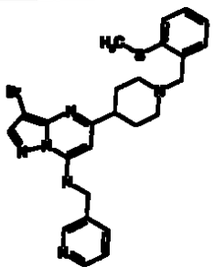
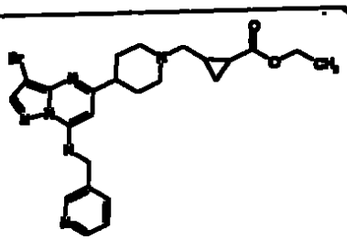
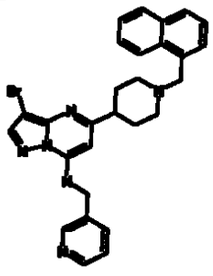
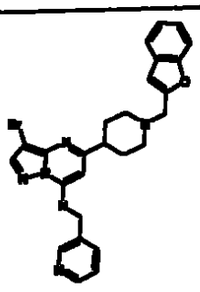
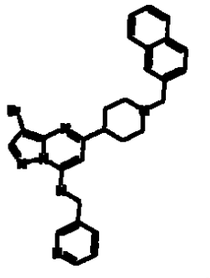
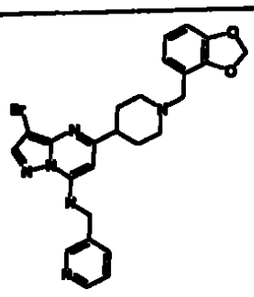
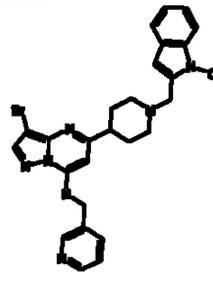
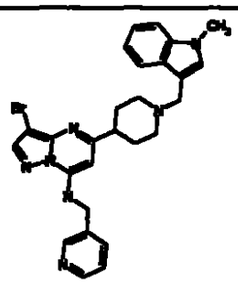
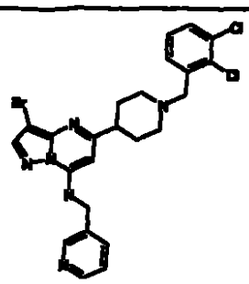
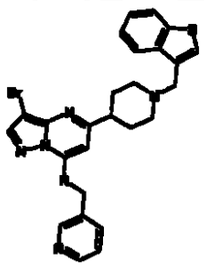
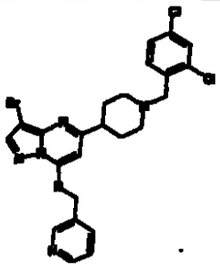
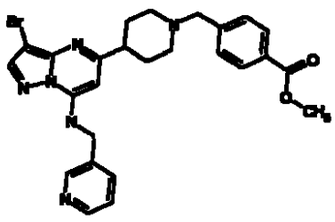
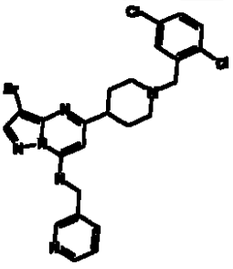
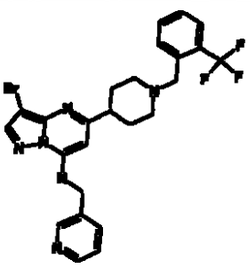
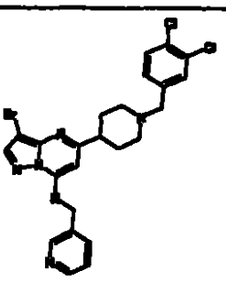
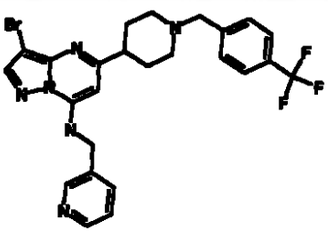
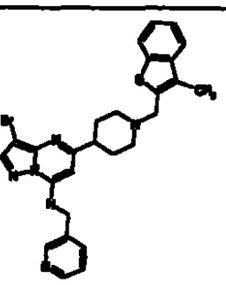
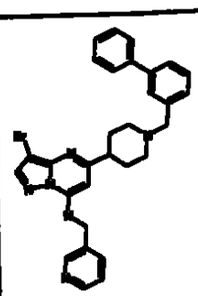
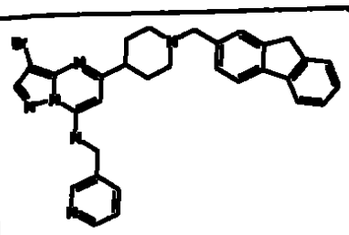
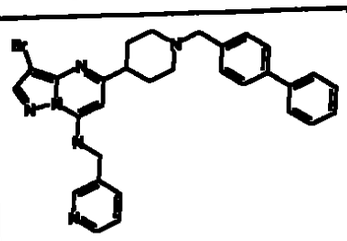
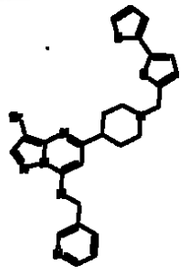
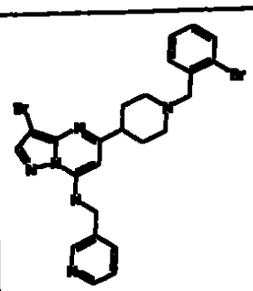
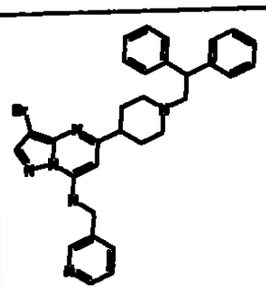
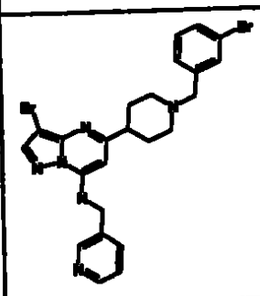
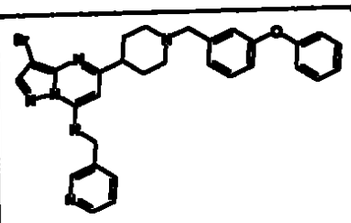
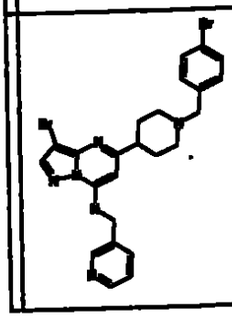
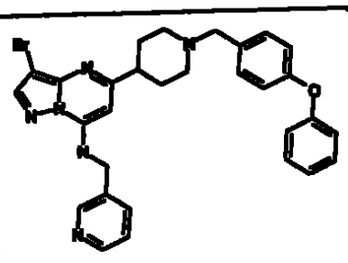
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	1. 7841 2. 619.34			1. 7846 2. 631.35
	1. 7842 2. 623.34			1. 7847 2. 643.35
	1. 7843 2. 519.29			
	1. 7844 2. 627.34			
	1. 7845 2. 631.35			

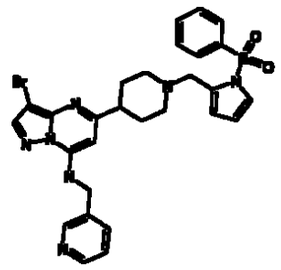
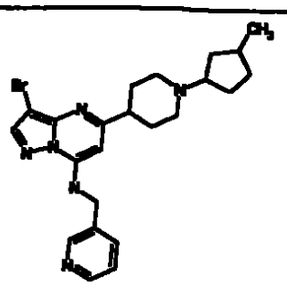
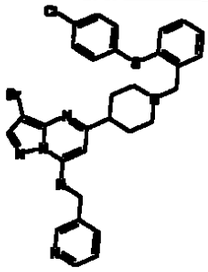
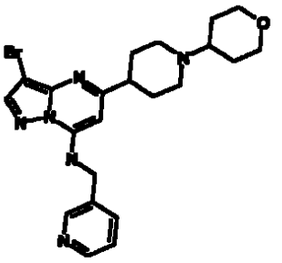
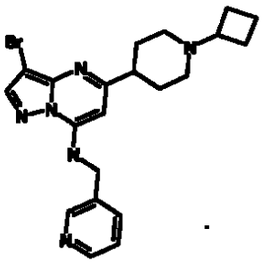
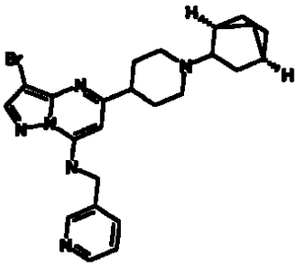
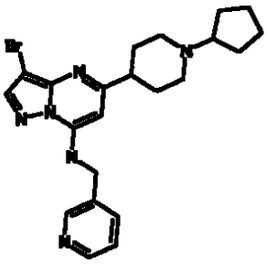
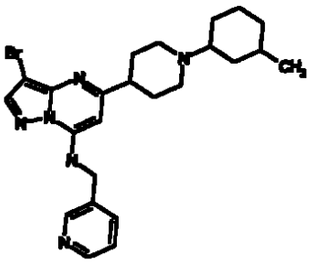
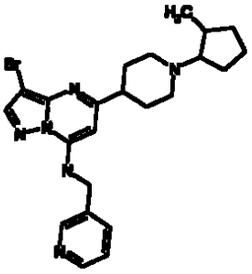
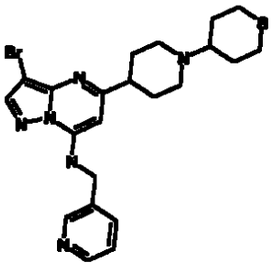
TABLE 79

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

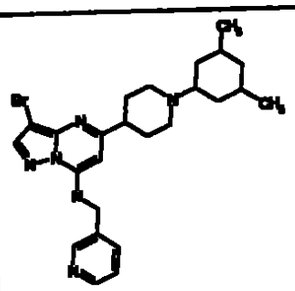
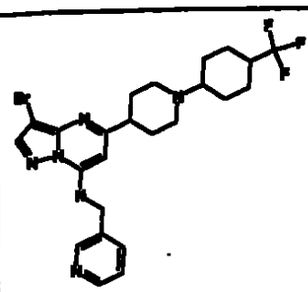
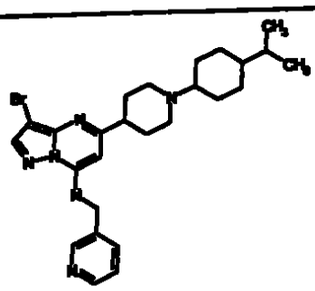
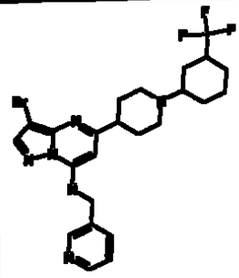
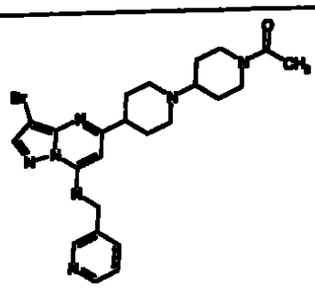
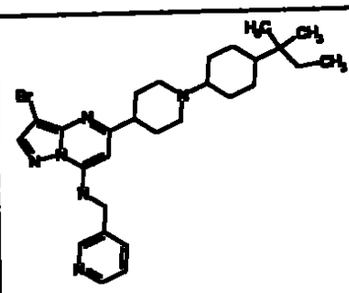
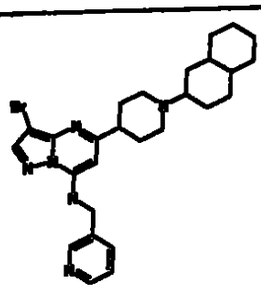
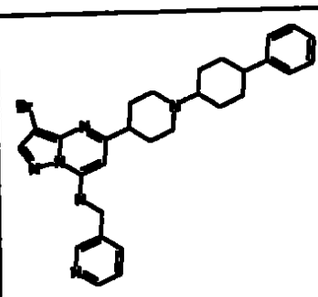
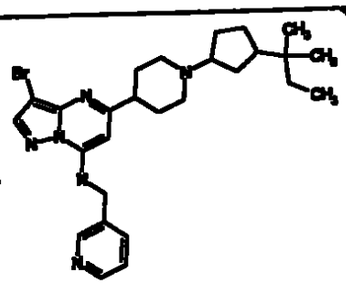
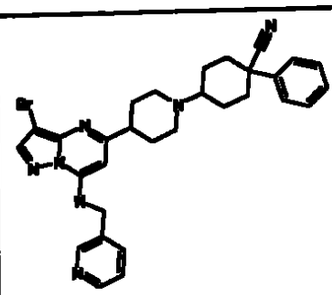
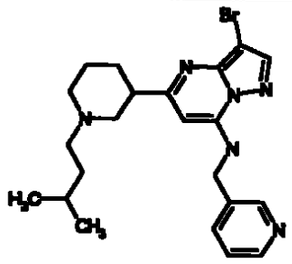
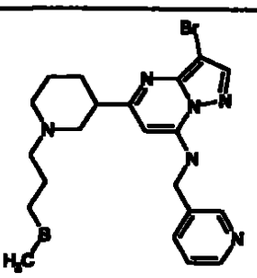
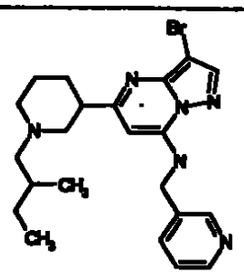
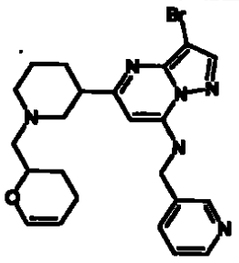
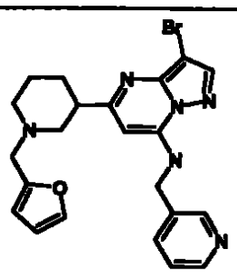
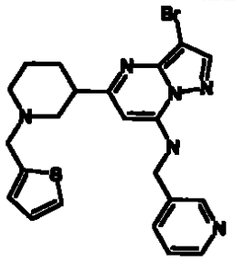
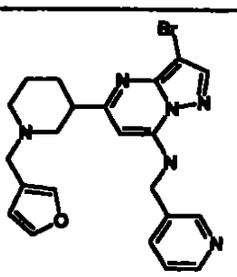
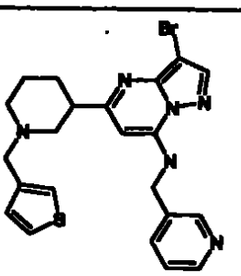
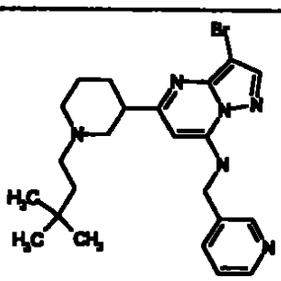
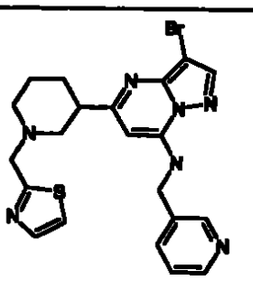
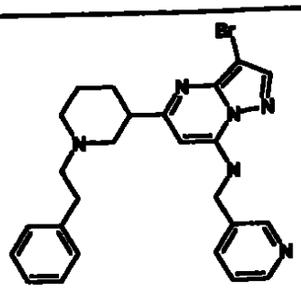
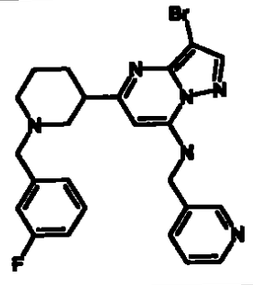
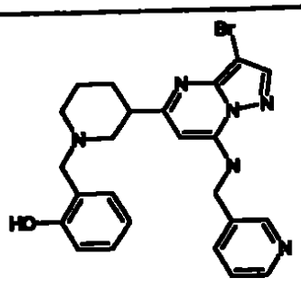
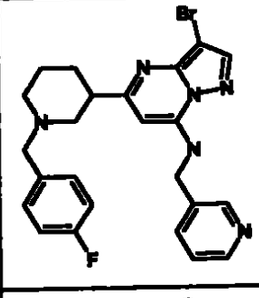
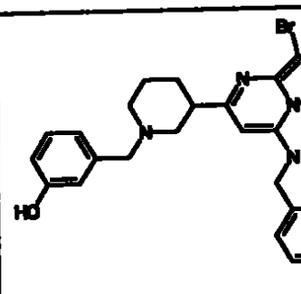
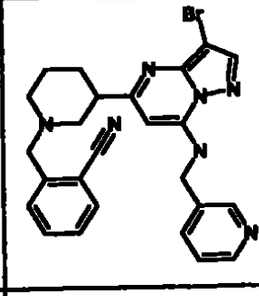
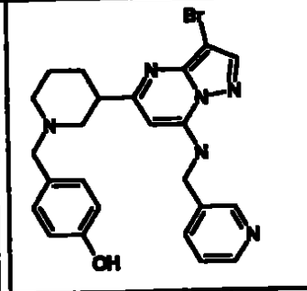
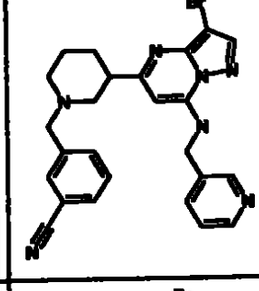
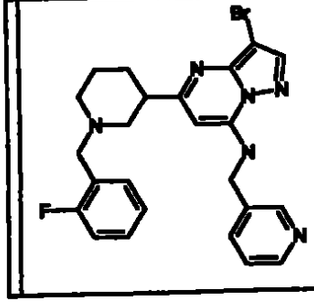
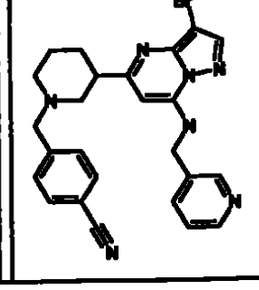
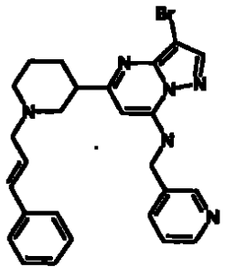
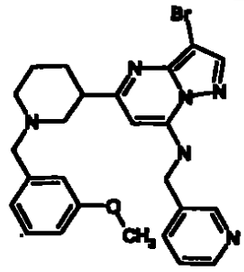
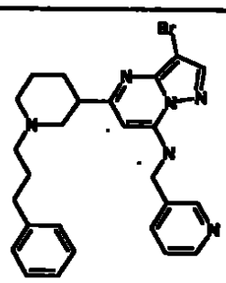
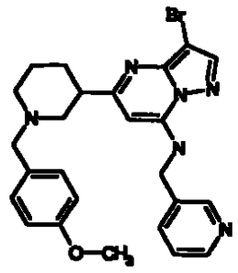
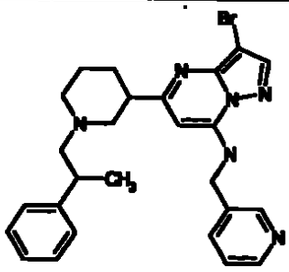
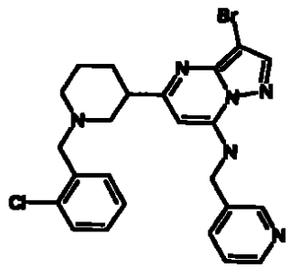
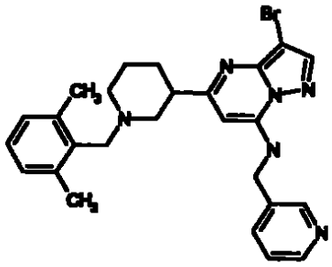
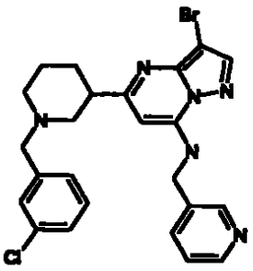
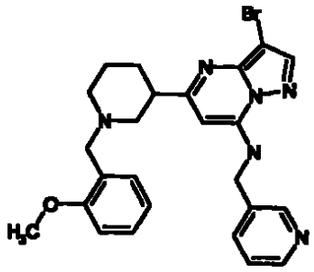
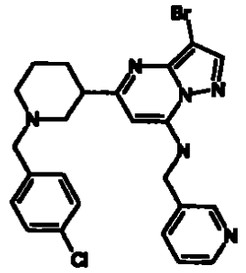
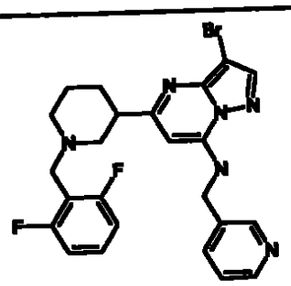
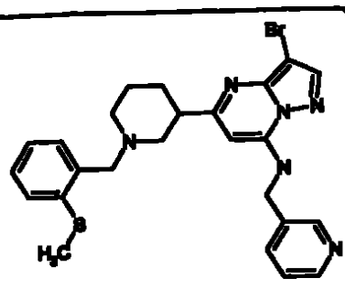
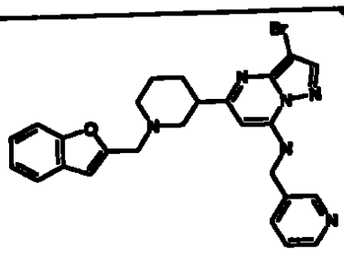
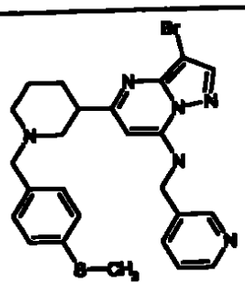
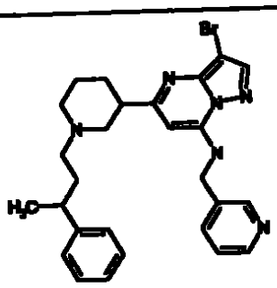
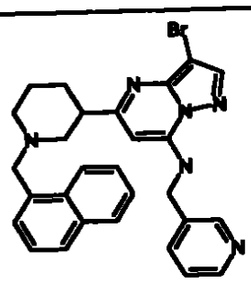
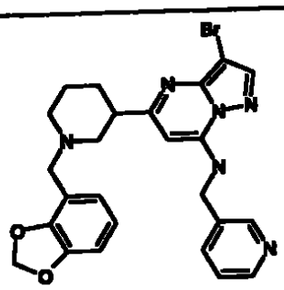
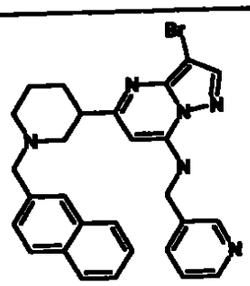
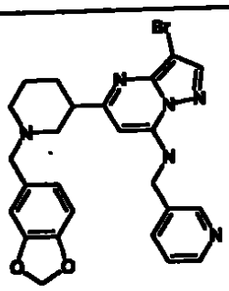
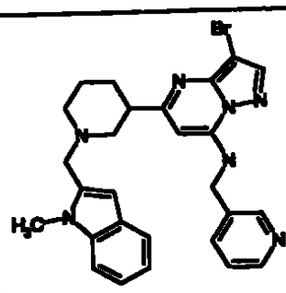
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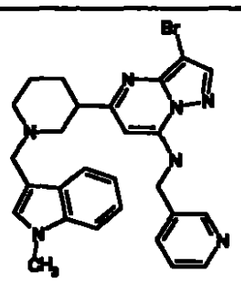
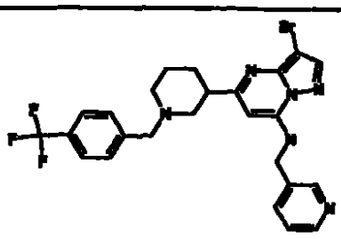
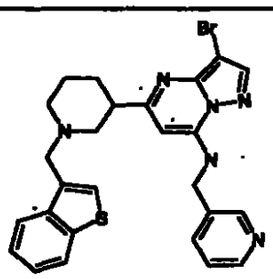
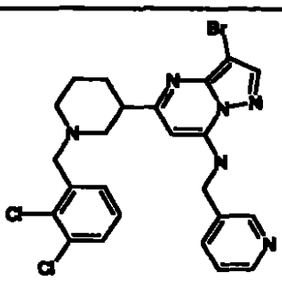
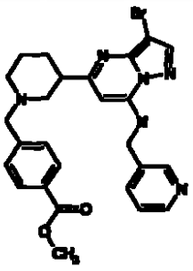
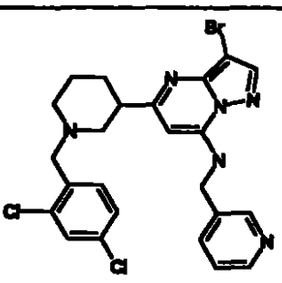
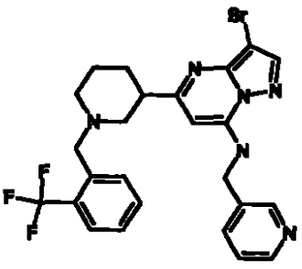
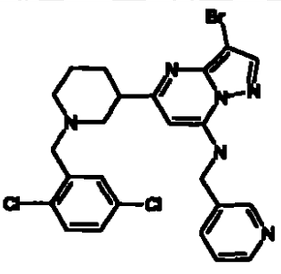
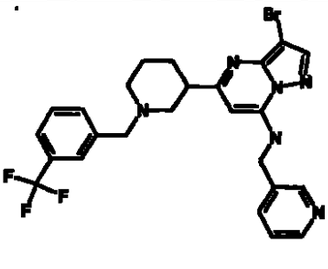
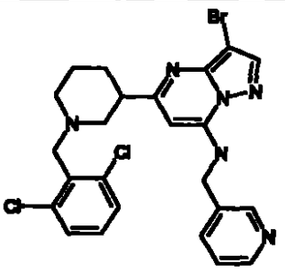
TABLE 80

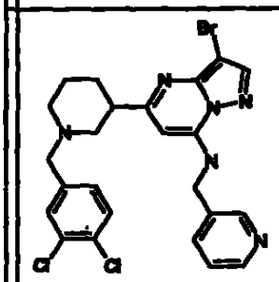
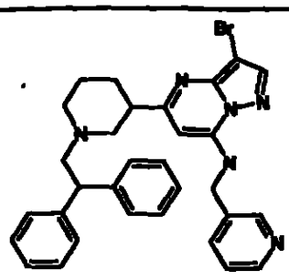
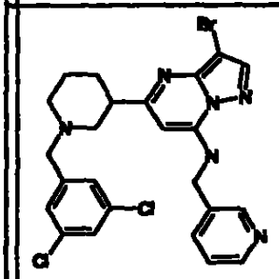
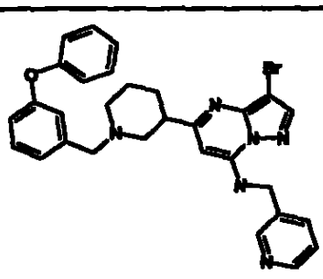
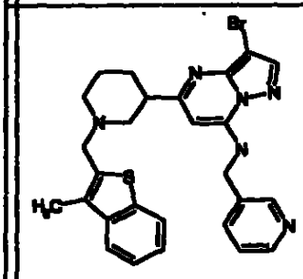
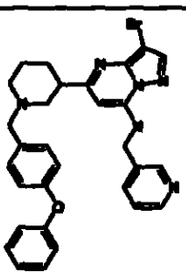
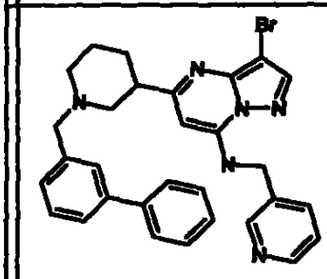
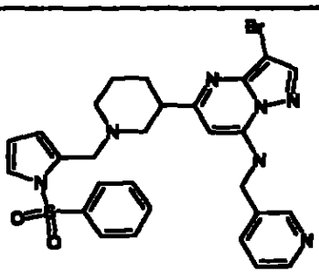
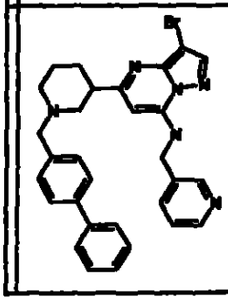
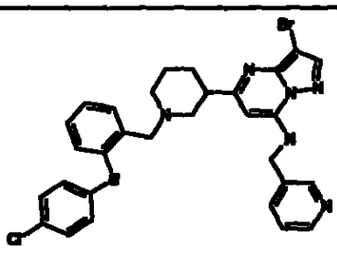
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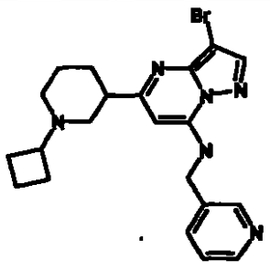
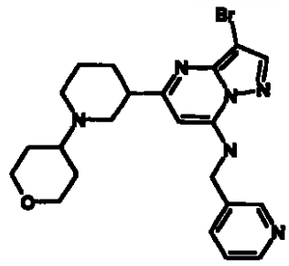
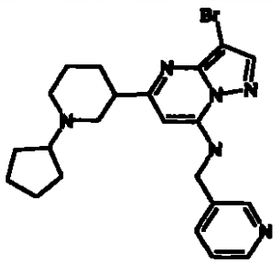
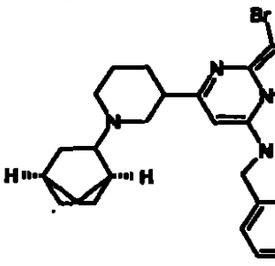
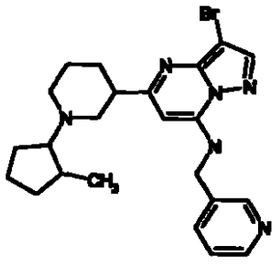
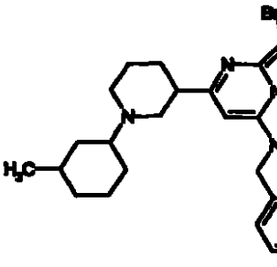
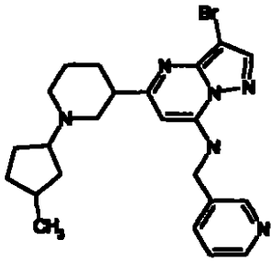
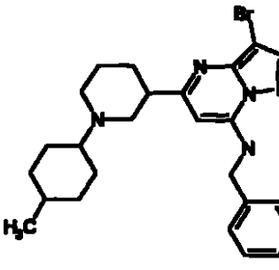
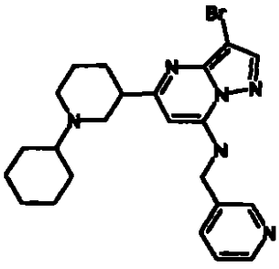
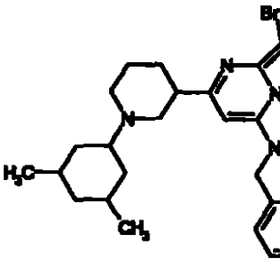
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	1. 8012 2. 495.27			1. 8017 2. 495.27
	1. 8013 2. 495.27			1. 8018 2. 502.28
	1. 8014 2. 495.27			1. 8019 2. 502.28
	1. 8015 2. 495.27			1. 8020 2. 502.28

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. 556.31			1. 8059 2. 606.33
	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
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	1. 8065 2. 469.26			1. 8070 2. 499.27

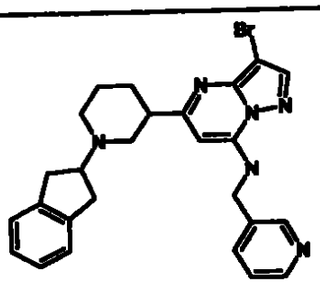
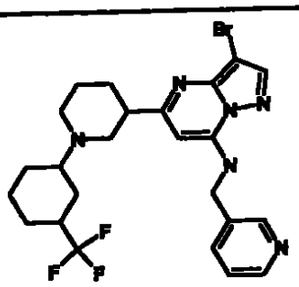
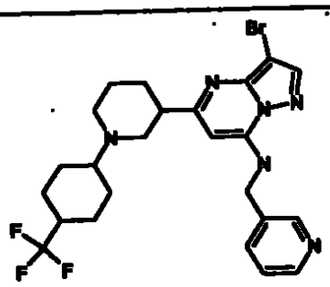
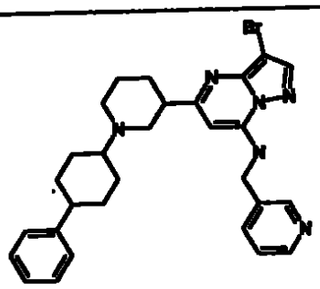
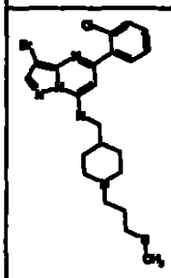
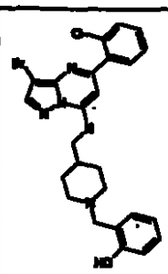
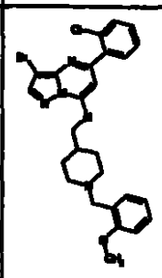
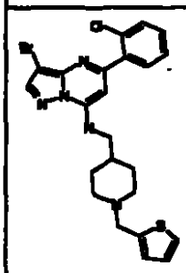
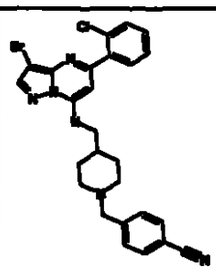
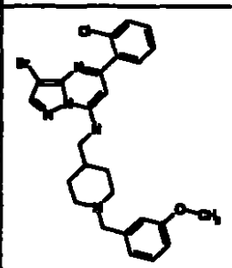
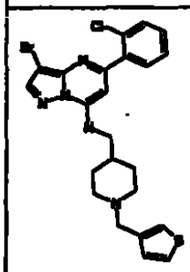
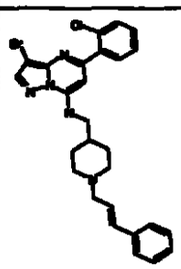
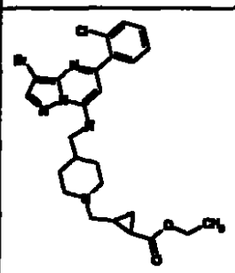
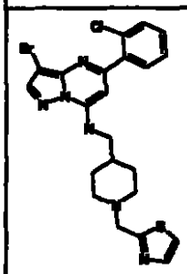
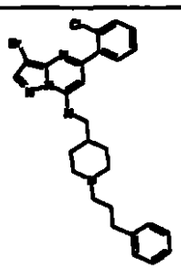
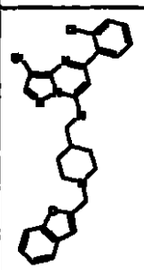
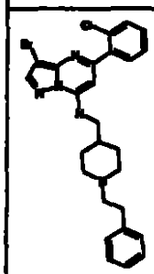
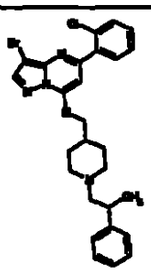
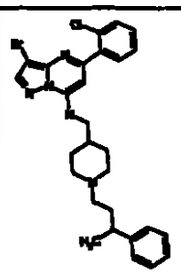
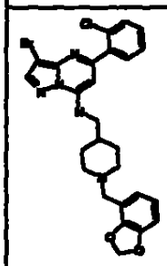
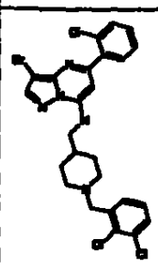
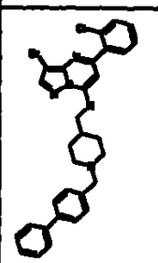
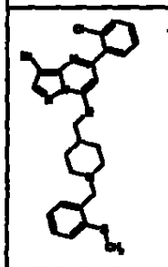
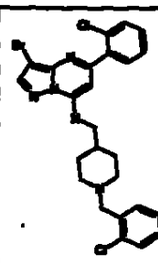
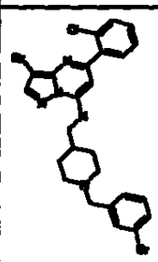
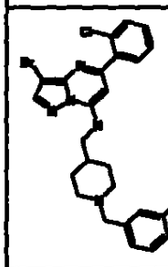
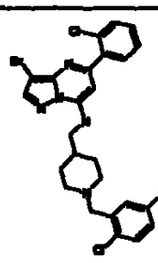
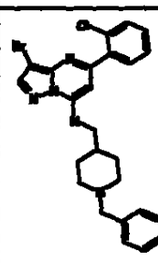
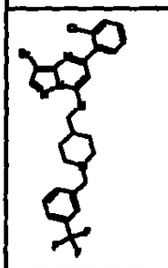
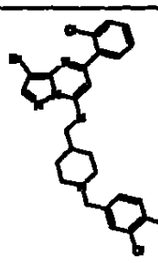
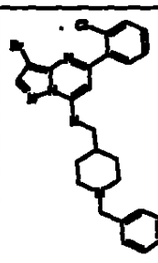
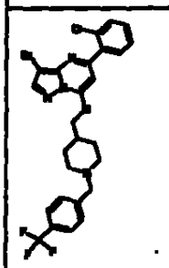
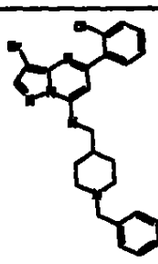
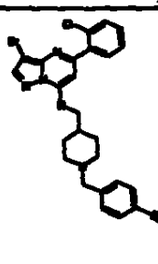
Product	1. Ex. 2. m/z
	1. 8071 2. 505.28
	1. 8072 2. 537.3
	1. 8073 2. 537.3
	1. 8074 2. 547.3

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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. 526.29		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. 566.32
	1. 8117 2. 556.31		1. 8122 2. 580.32		1. 8127 2. 580.32
	1. 8118 2. 562.31		1. 8123 2. 580.32		1. 8128 2. 580.32
	1. 8119 2. 580.32		1. 8125 2. 580.32		1. 8129 2. 604.33
	1. 8120 2. 580.32		1. 8126 2. 566.32		1. 8130 2. 612.34

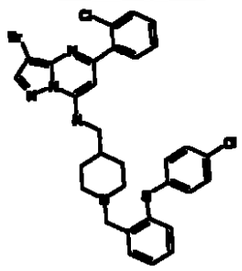
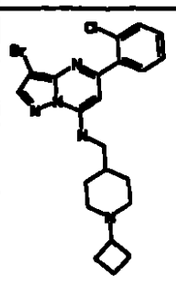
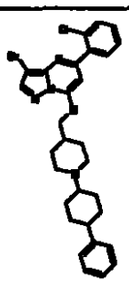
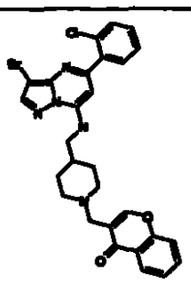
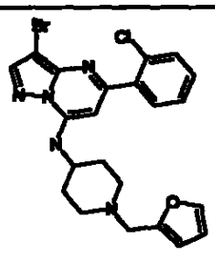
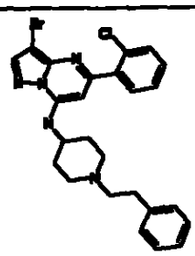
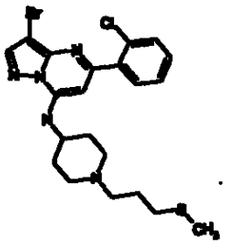
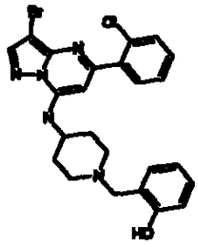
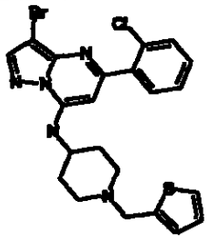
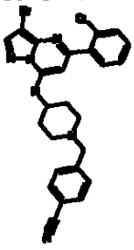
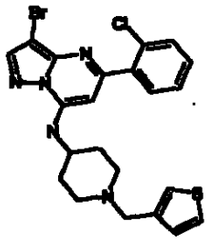
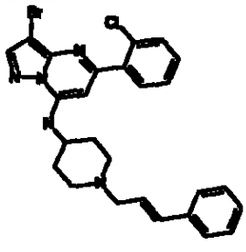
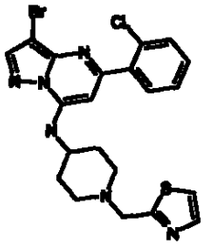
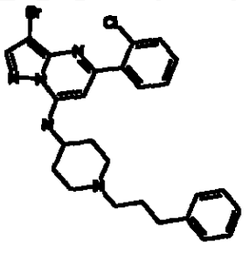
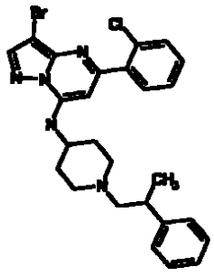
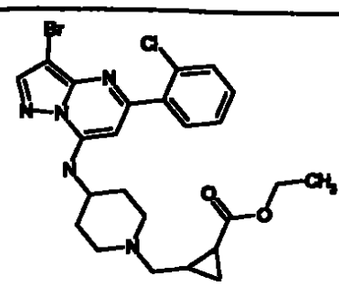
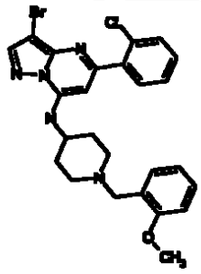
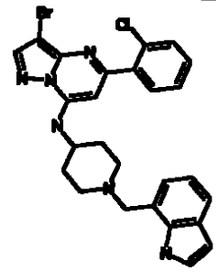
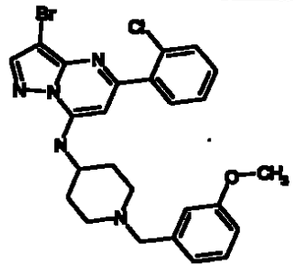
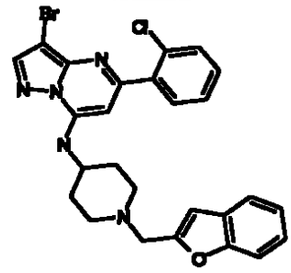
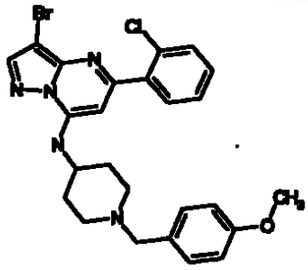
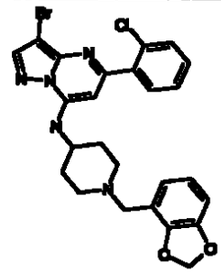
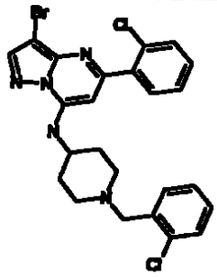
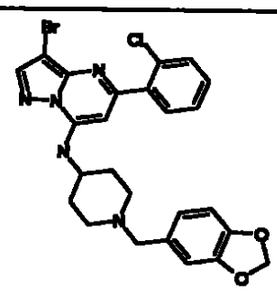
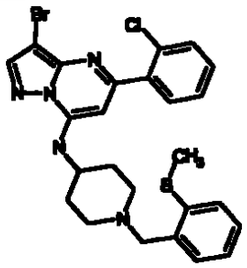
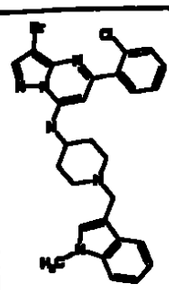
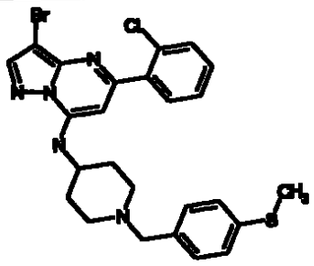
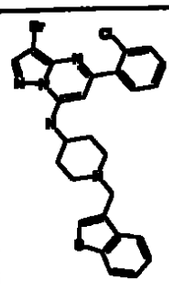
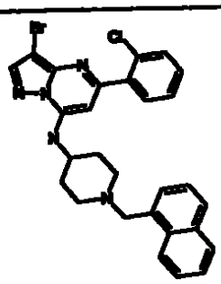
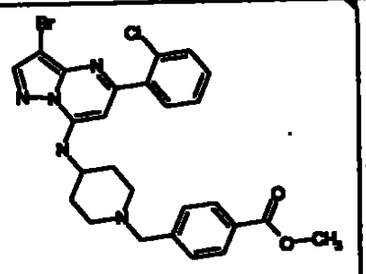
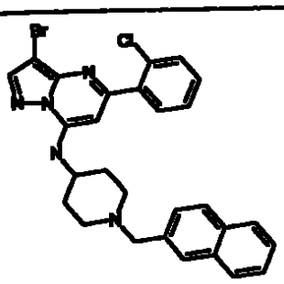
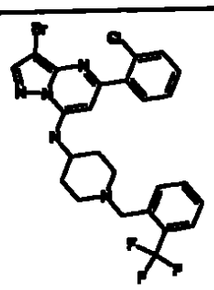
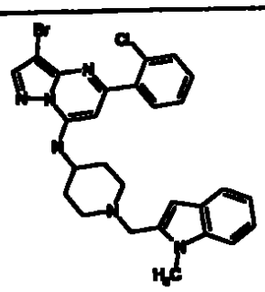
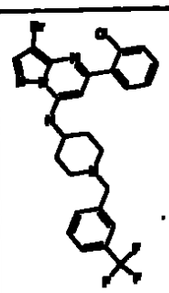
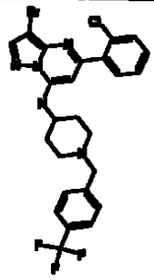
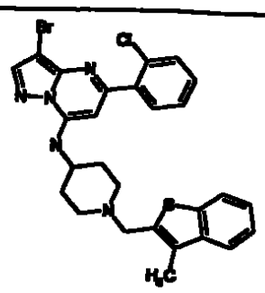
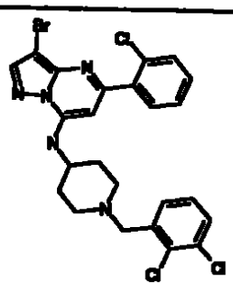
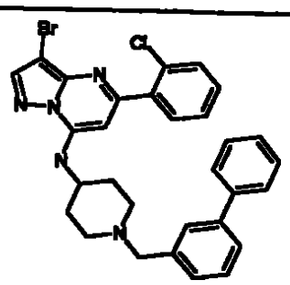
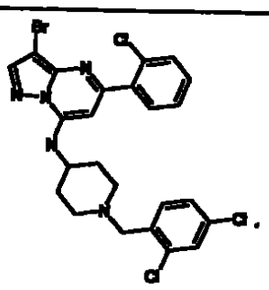
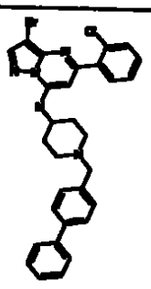
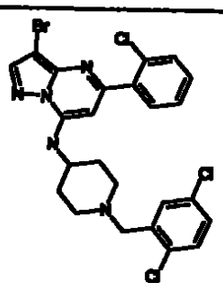
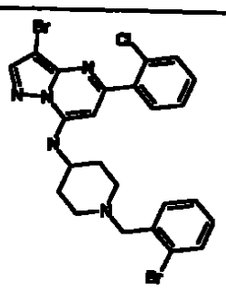
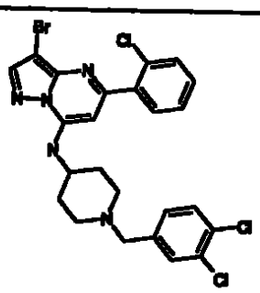
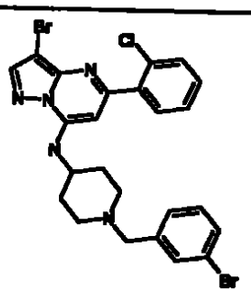
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	1. 8132 2. 476.26
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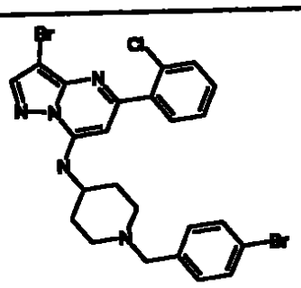
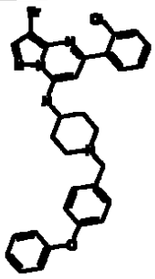
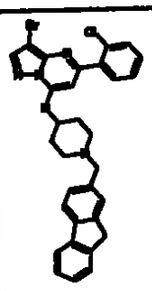
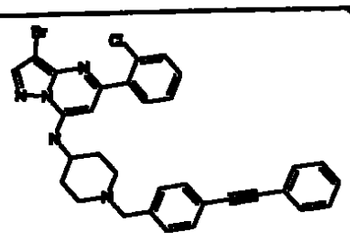
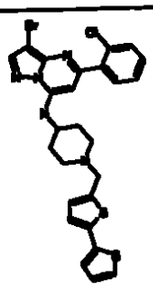
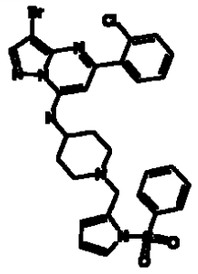
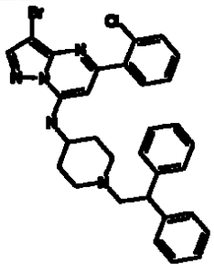
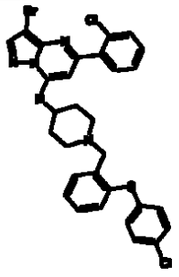
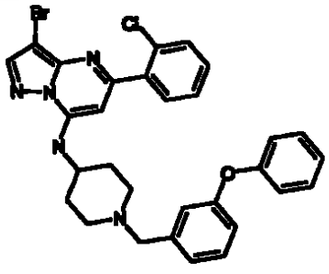
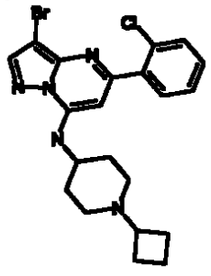
TABLE 82

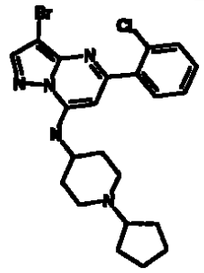
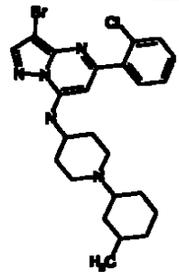
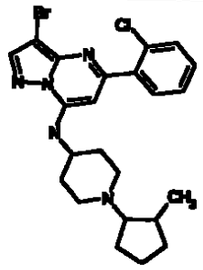
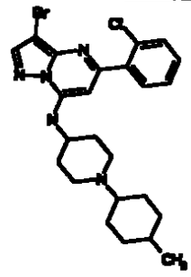
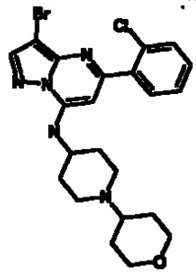
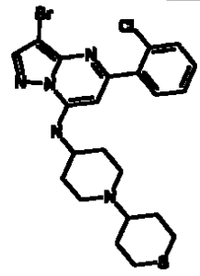
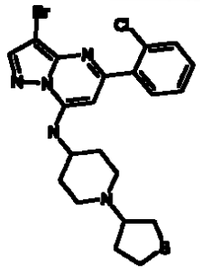
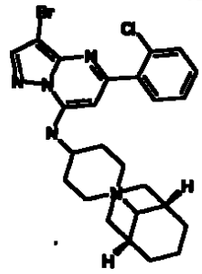
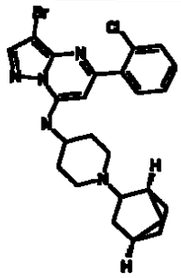
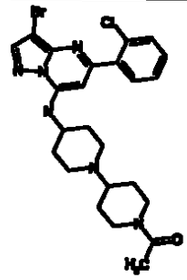
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	1. 8202 2. 496.27		1. 8207 2. 514.28
	1. 8203 2. 504.28		1. 8208 2. 523.29
	1. 8204 2. 504.28		1. 8209 2. 524.29
	1. 8205 2. 505.28		1. 8210 2. 526.29

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. 526.29			1. 8217 2. 537.3
	1. 8213 2. 526.29			1. 8218 2. 536.3
	1. 8214 2. 526.29			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. 558.31
	1. 8224 2. 548.3			1. 8229 2. 586.31
	1. 8225 2. 551.3			1. 8230 2. 586.31

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. 586.32			1. 8247 2. 598.33
	1. 8243 2. 586.32			1. 8248 2. 627.34
	1. 8244 2. 586.32			1. 8249 2. 640.35
	1. 8245 2. 590.32			1. 8250 2. 462.25

Product	1. Ex. 2. m/z		Product	1. Ex. 2. m/z
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	1. 8252 2. 490.27			1. 8257 2. 504.28
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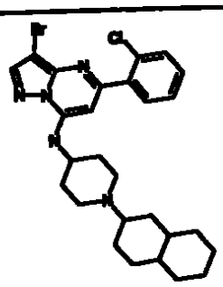
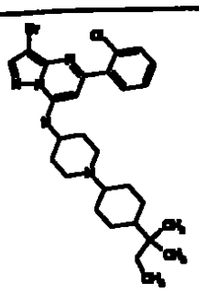
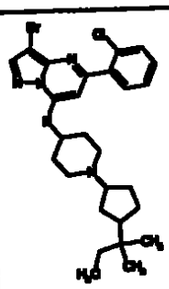
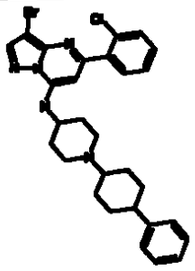
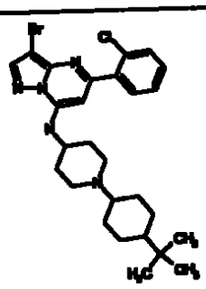
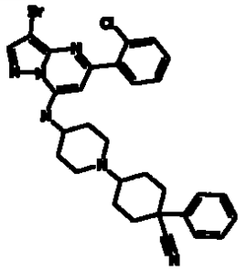
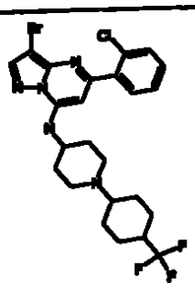
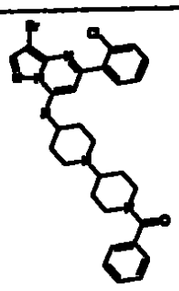
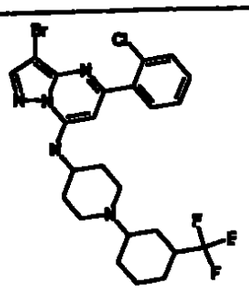
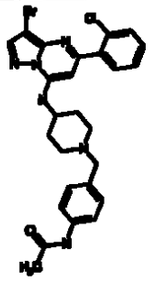
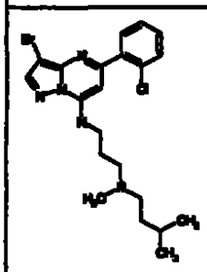
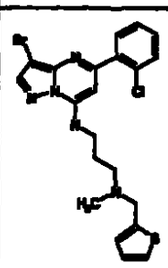
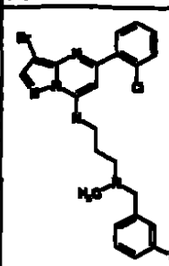
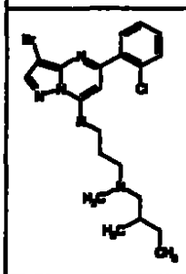
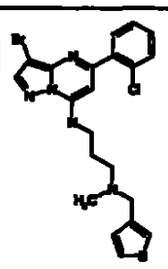
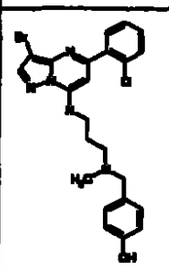
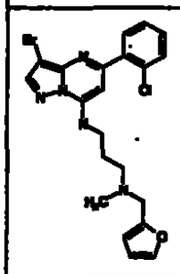
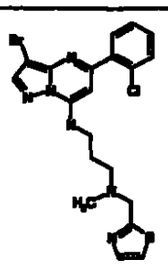
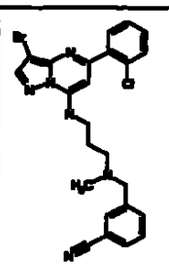
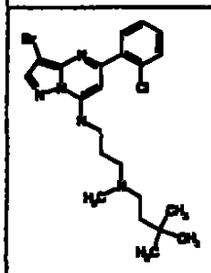
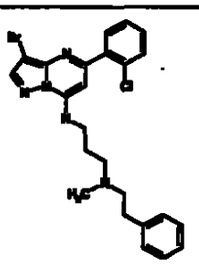
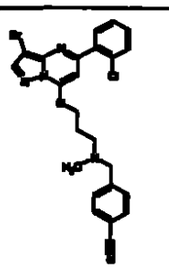
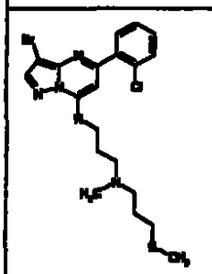
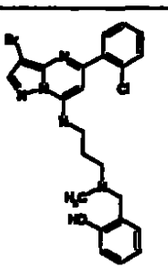
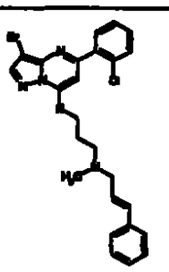
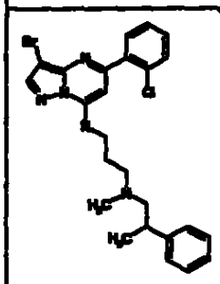
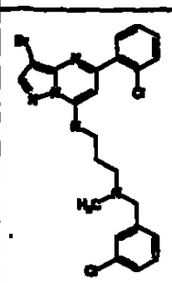
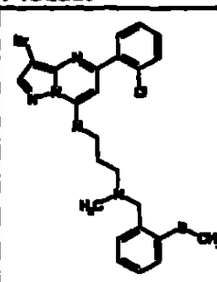
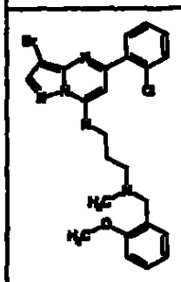
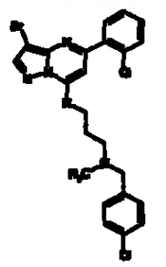
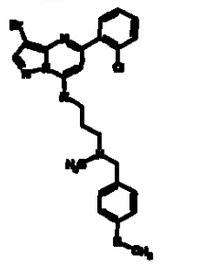
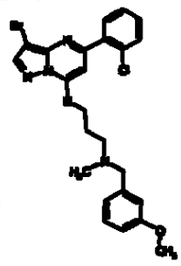
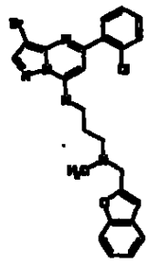
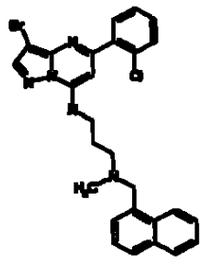
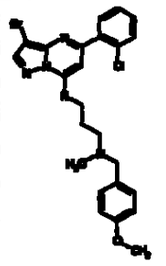
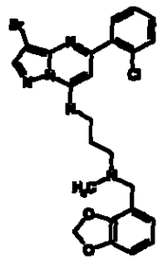
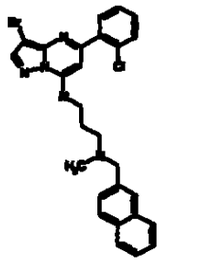
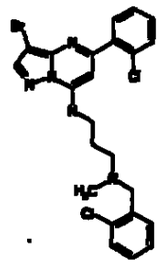
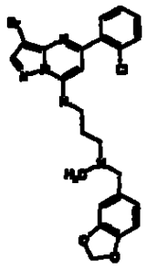
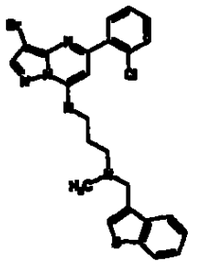
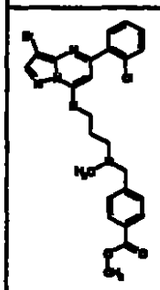
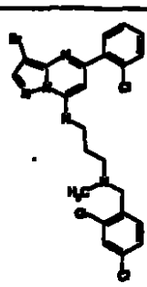
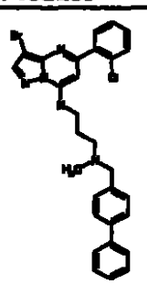
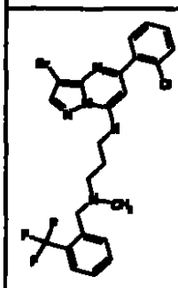
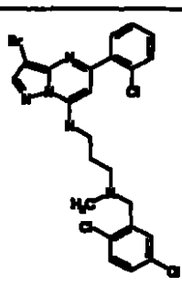
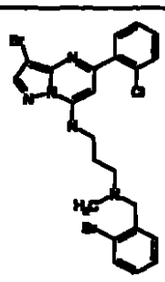
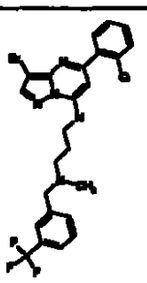
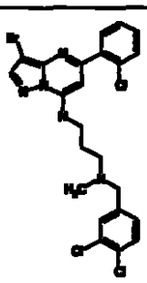
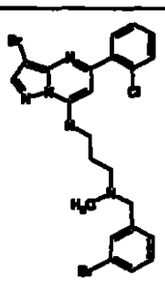
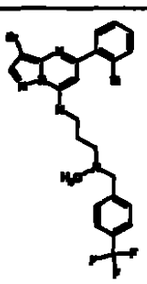
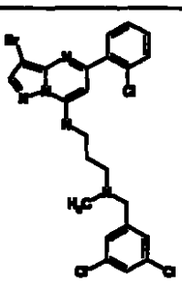
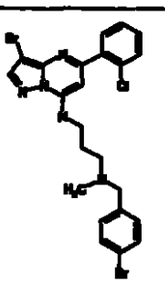
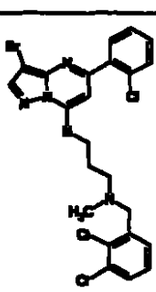
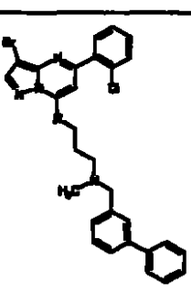
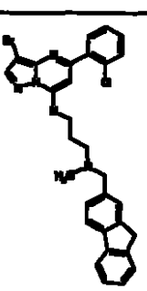
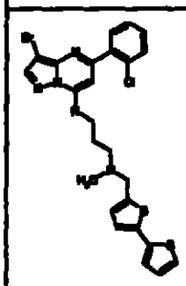
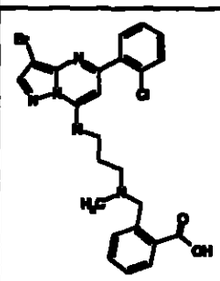
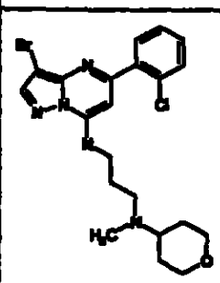
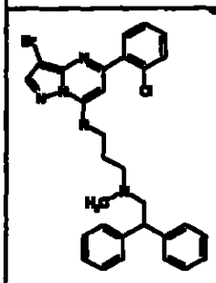
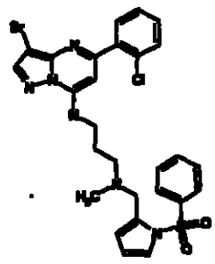
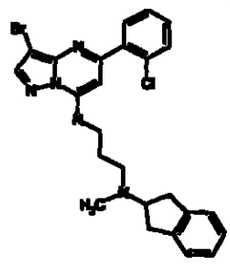
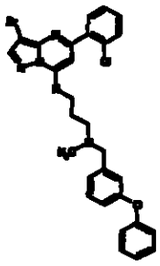
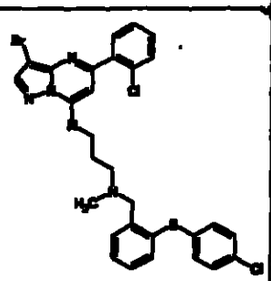
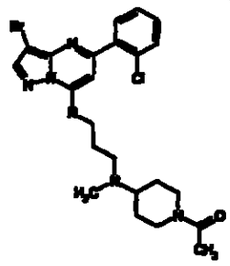
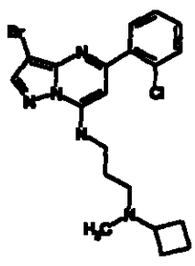
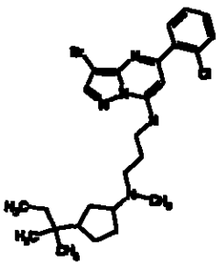
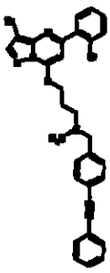
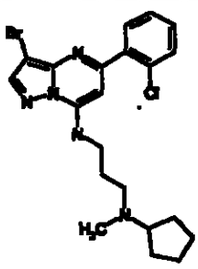
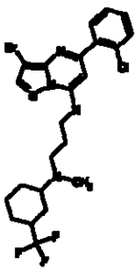
Product	1. Ex. 2. m/z		Product	1. Ex. 2. m/z
	1. 8261 2. 544.3			1. 8266 2. 560.31
	1. 8262 2. 546.3			1. 8267 2. 566.31
	1. 8263 2. 546.3			1. 8268 2. 591.33
	1. 8264 2. 558.31			1. 8269 2. 595.33
	1. 8265 2. 558.31			1. 8270 2. 565.31

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. 529.808		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. 561.836
	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. 529.806		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. 520.869
	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

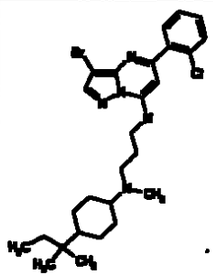
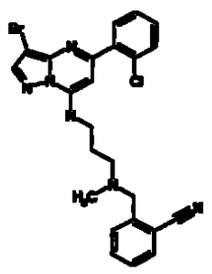
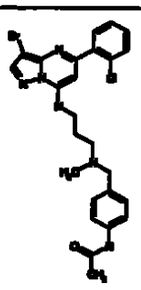
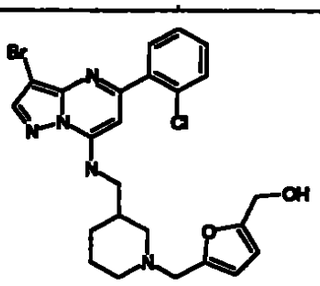
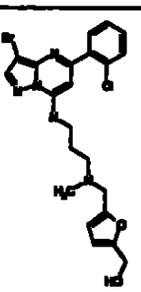
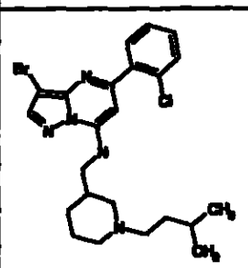
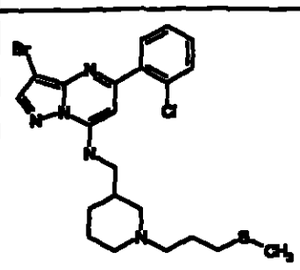
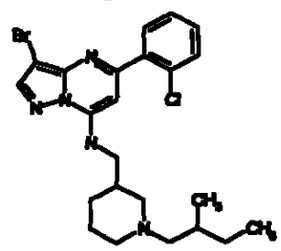
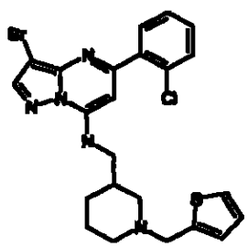
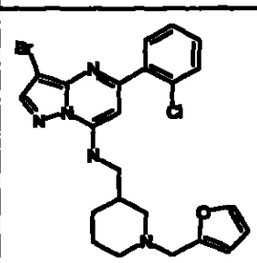
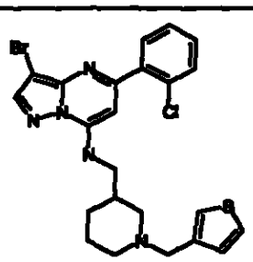
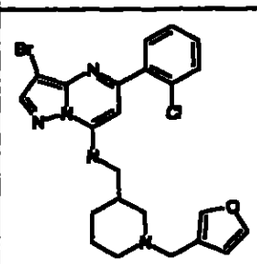
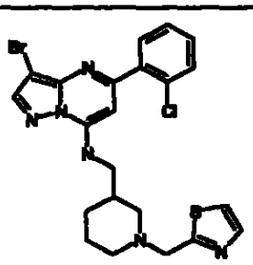
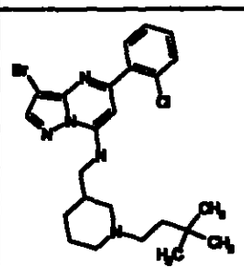
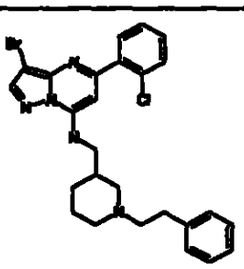
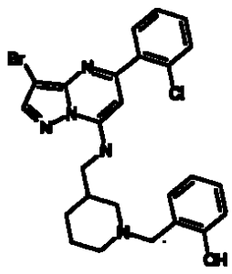
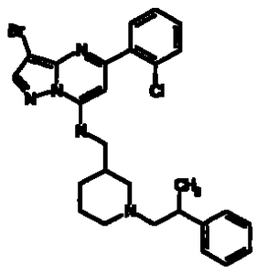
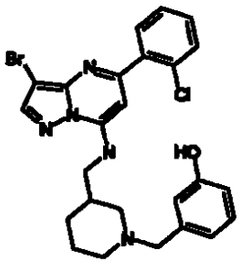
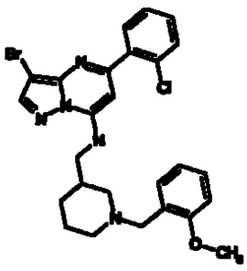
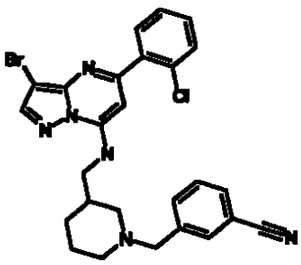
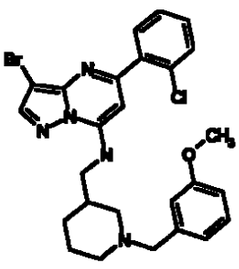
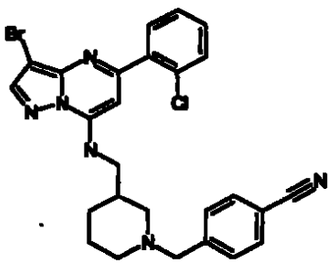
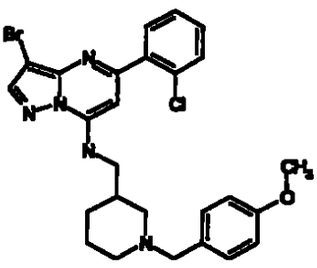
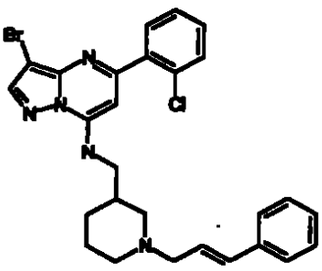
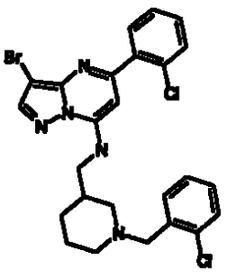
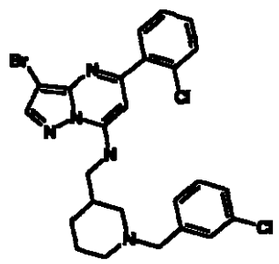
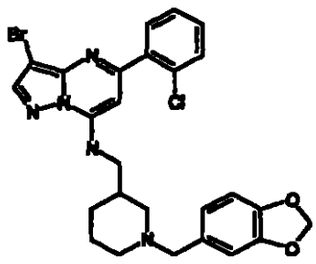
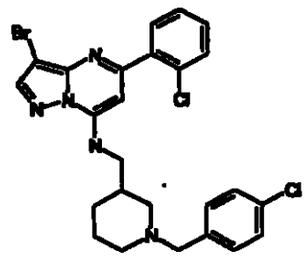
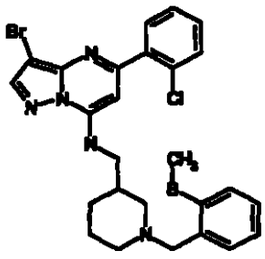
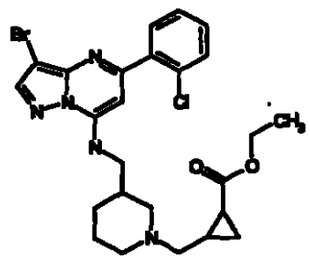
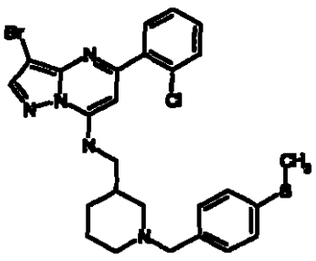
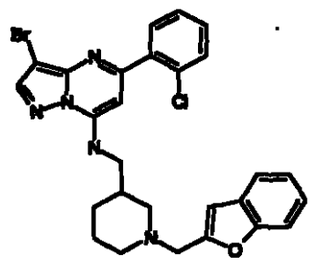
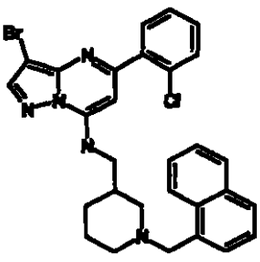
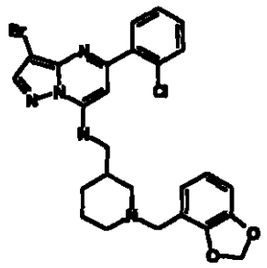
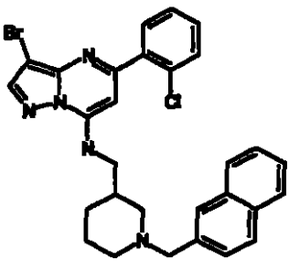
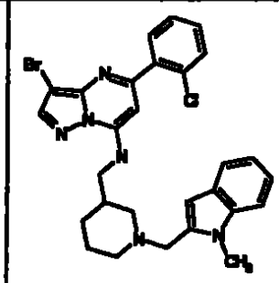
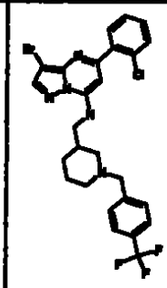
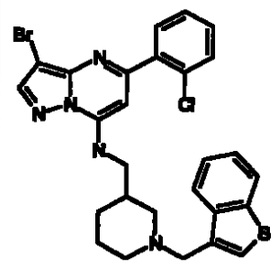
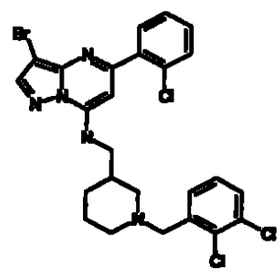
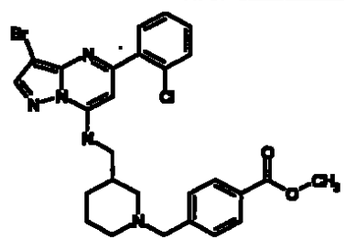
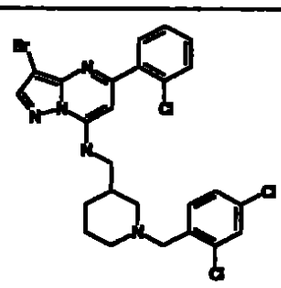
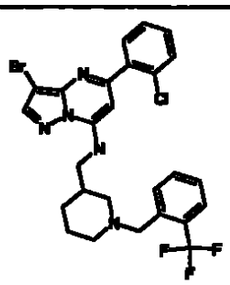
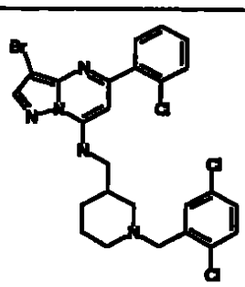
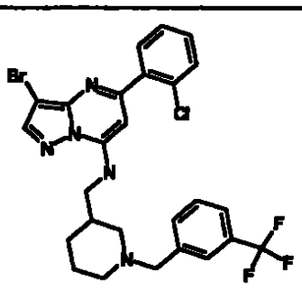
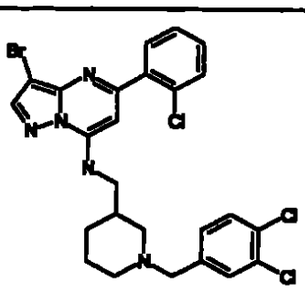
Product	1. Ex. 2. m/z
	1. 8361 2. 547.909
	1. 8362 2. 510.817
	1. 8363 2. 542.833
	1. 8364 2. 573.815
	1. 8365 2. 547.798

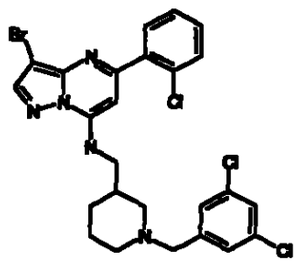
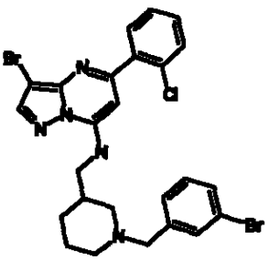
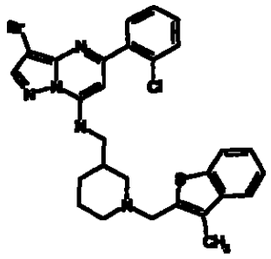
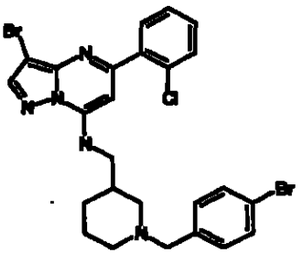
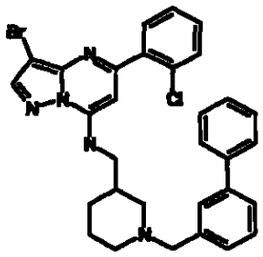
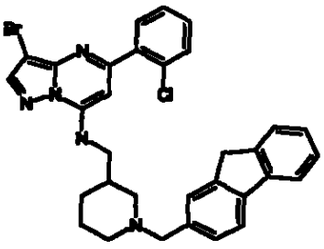
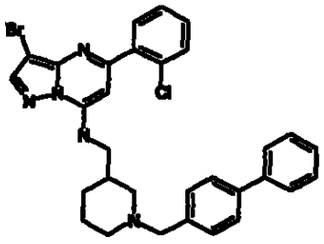
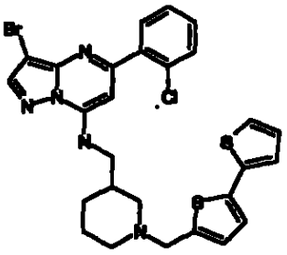
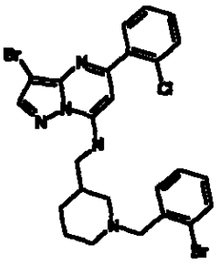
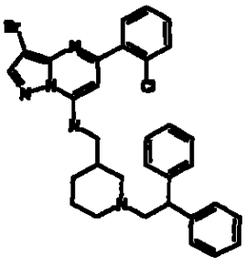
TABLE 84

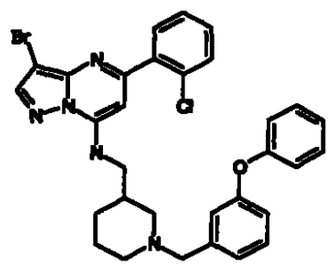
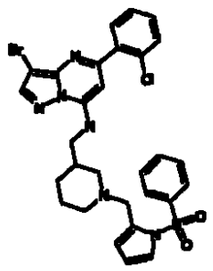
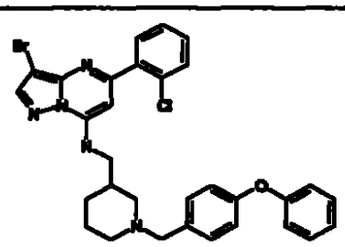
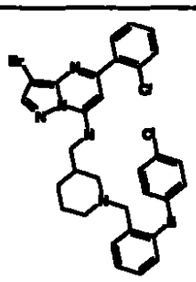
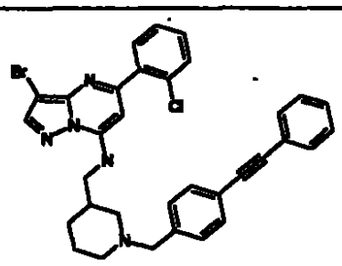
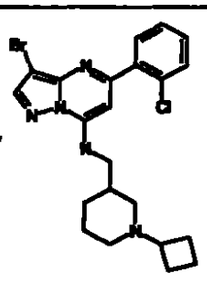
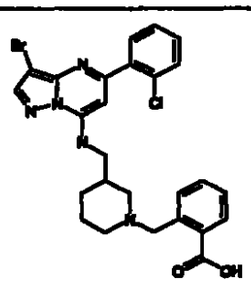
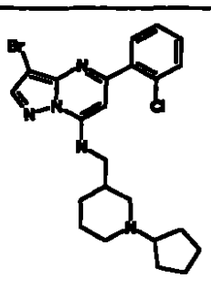
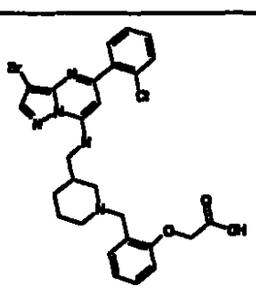
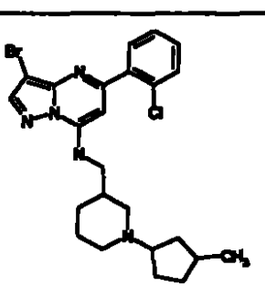
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	1. 8401 2. 491.883			1. 8406 2. 509.829
	1. 8402 2. 491.883			1. 8407 2. 517.795
	1. 8403 2. 501.823			1. 8408 2. 517.799
	1. 8404 2. 501.827			1. 8409 2. 518.798
	1. 8405 2. 505.89			1. 8410 2. 525.851

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

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. 476.871
	1. 8454 2. 555.824			1. 8459 2. 489.879
	1. 8455 2. 585.817			1. 8460 2. 503.885

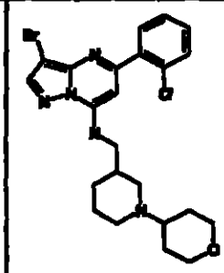
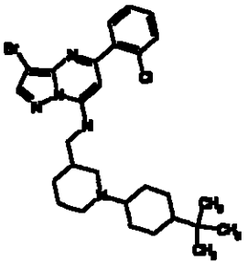
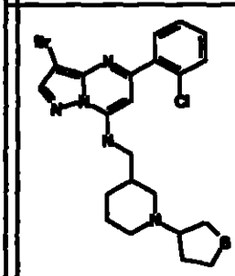
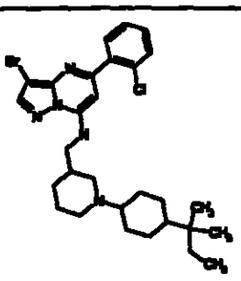
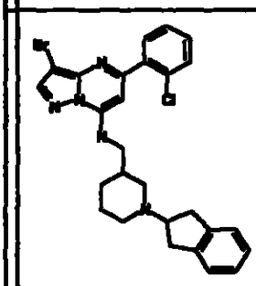
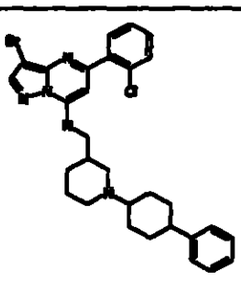
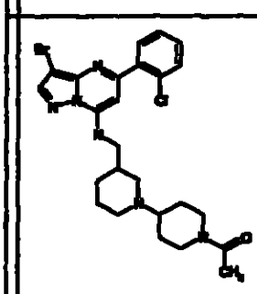
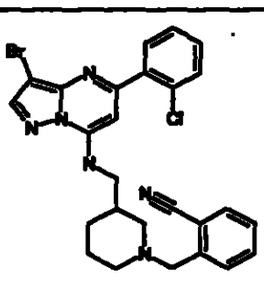
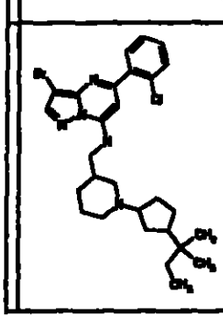
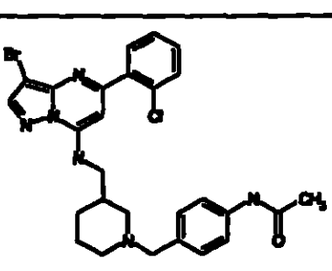
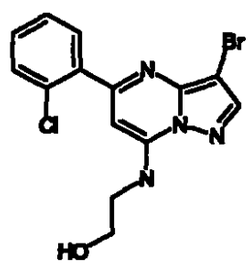
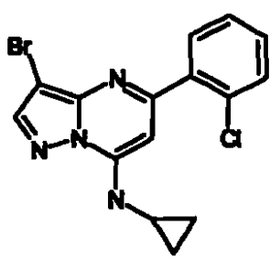
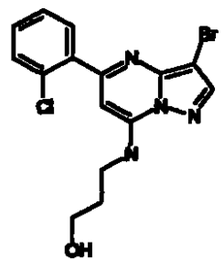
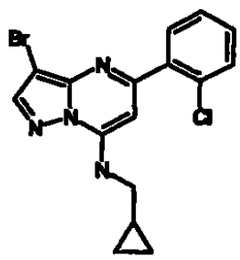
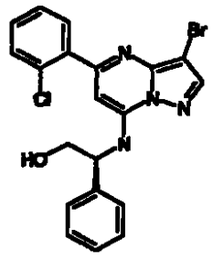
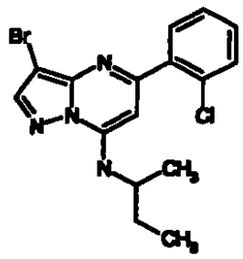
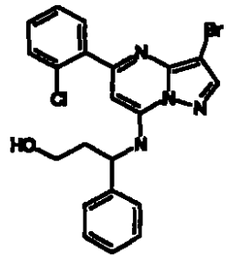
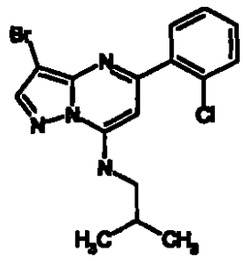
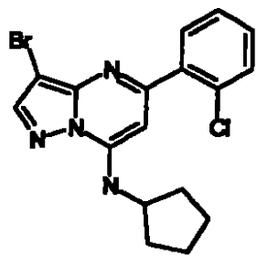
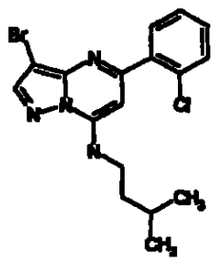
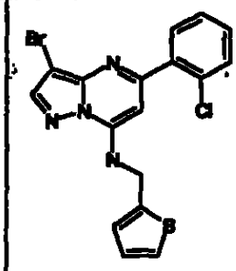
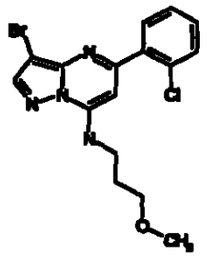
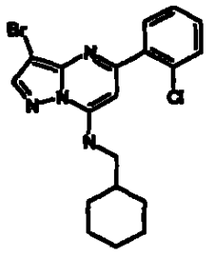
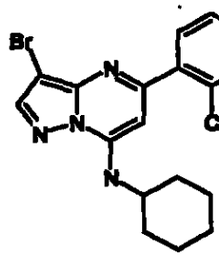
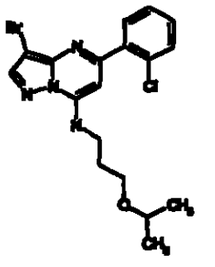
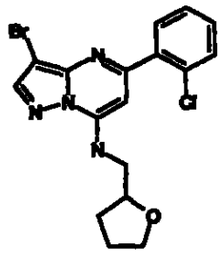
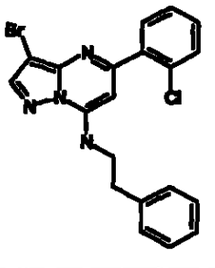
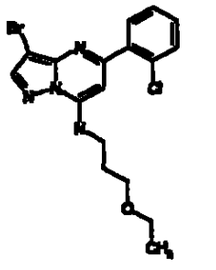
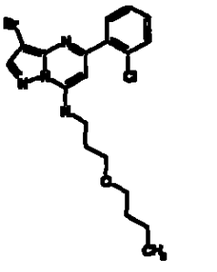
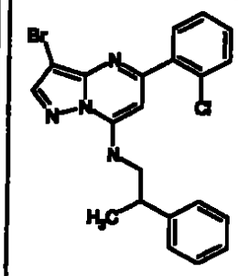
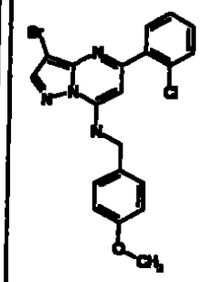
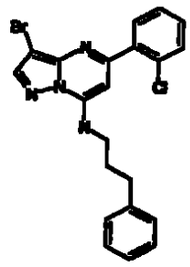
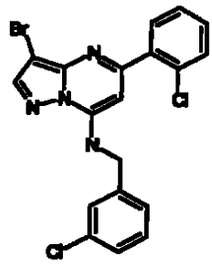
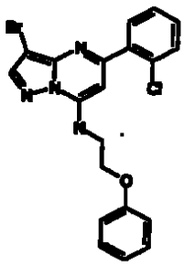
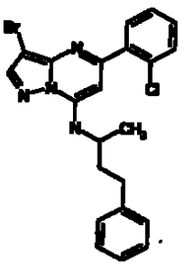
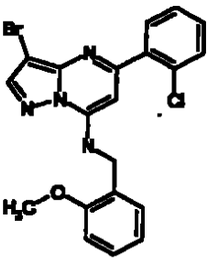
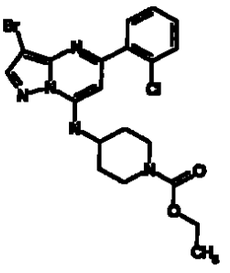
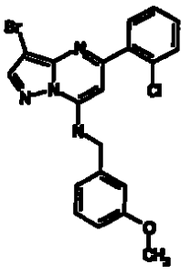
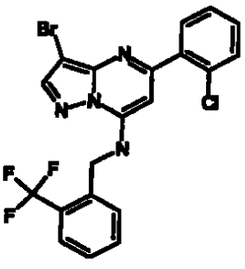
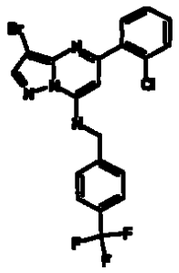
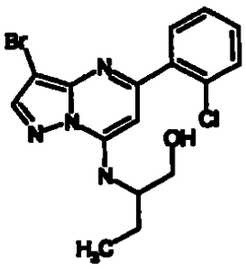
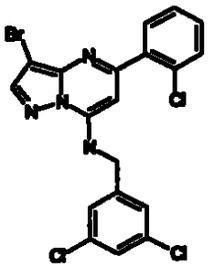
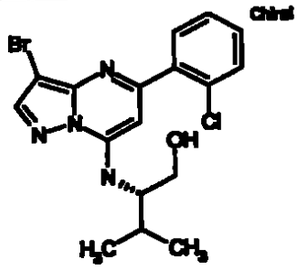
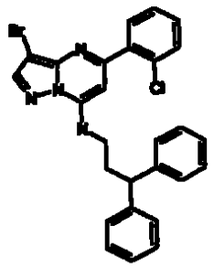
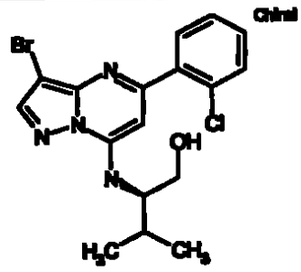
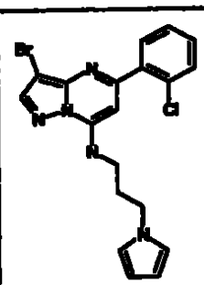
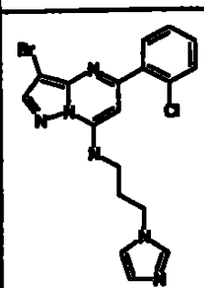
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	1. 8461 2. 505.886			1. 8466 2. 559.919
	1. 8462 2. 507.828			1. 8467 2. 573.925
	1. 8463 2. 537.859			1. 8468 2. 579.876
	1. 8464 2. 546.877			1. 8469 2. 536.831
	1. 8465 2. 559.921			1. 8470 2. 568.843

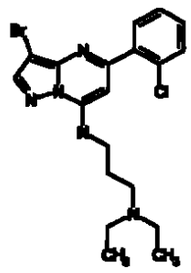
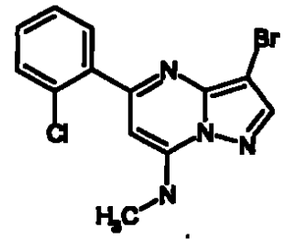
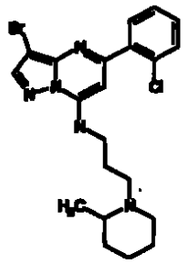
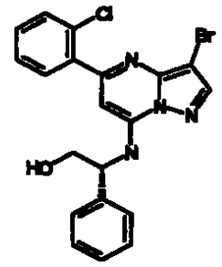
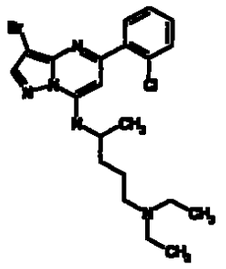
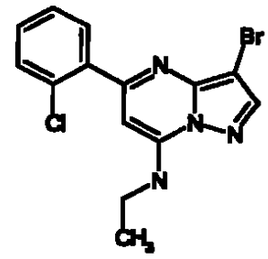
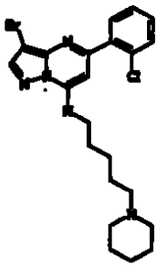
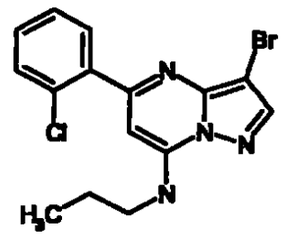
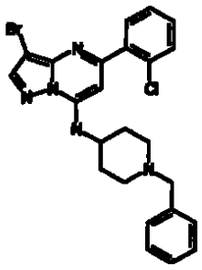
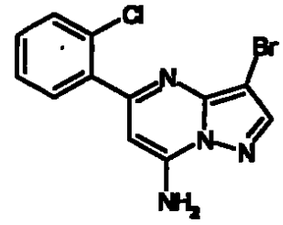
TABLE 65

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. 385.2
	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

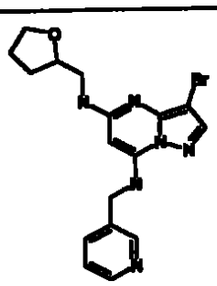
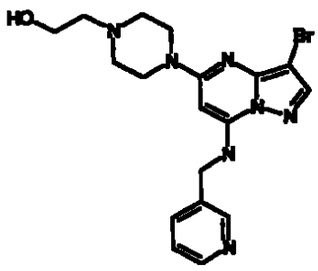
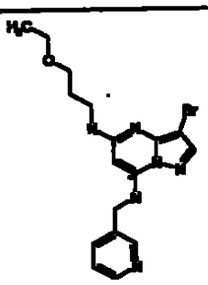
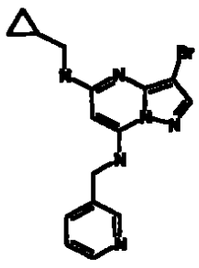
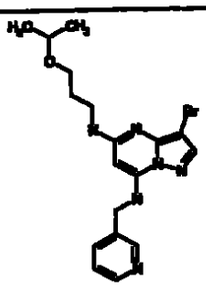
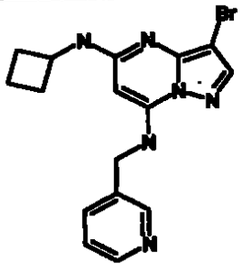
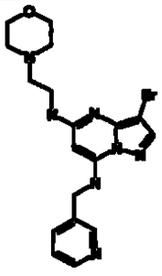
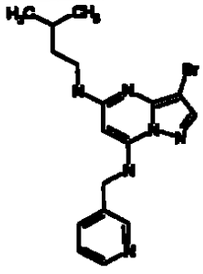
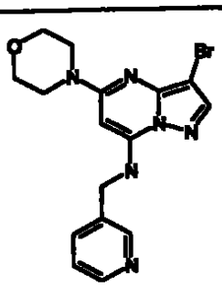
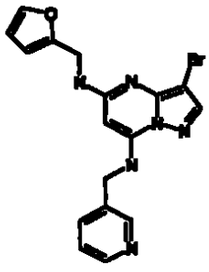
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8521 2. 429.24		1. 8526 2. 445.24
	1. 8522 2. 439.24		1. 8527 2 .444.24
	1. 8523 2. 443.24		1. 8528 2. 444.24
	1. 8524 2. 443.24		1. 8529 2. 446.25
	1. 8525 2. 445.24		1. 8530 2. 457.25

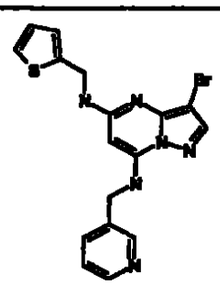
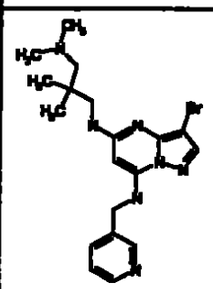
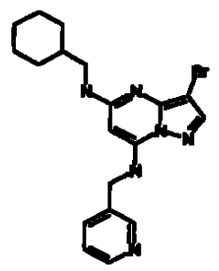
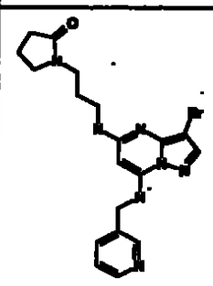
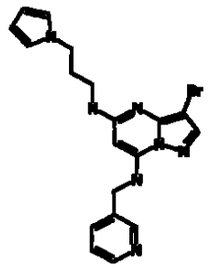
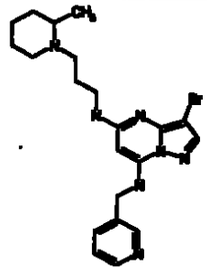
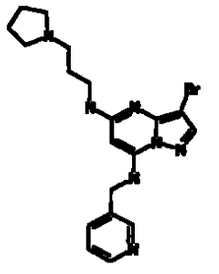
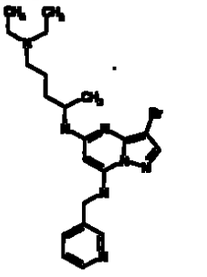
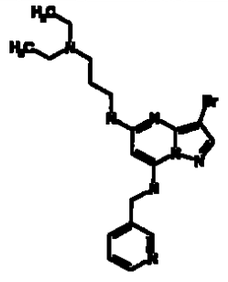
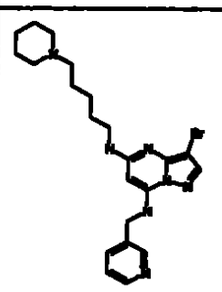
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8531 2. 480.26		1. 8536 2. 431.24
	1. 8532 2. 483.27		1. 8537 2. 429.24
	1. 8533 2. 483.27		1. 8538 2. 397.22
			1. 8539 2. 411.23
			1. 8540 2. 411.23

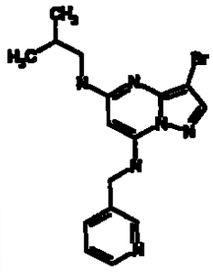
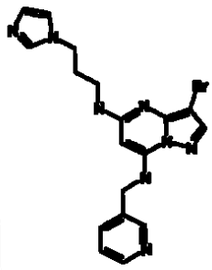
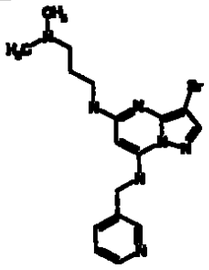
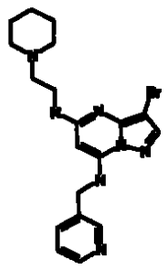
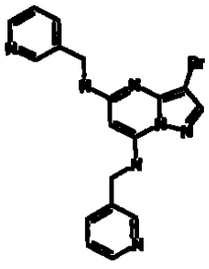
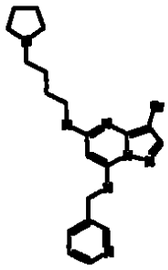
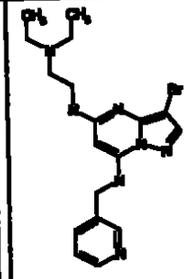
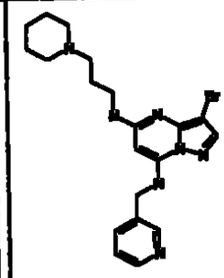
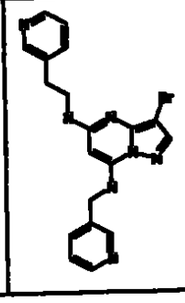
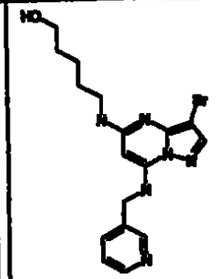
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	1. 8542 2. 433.24		1. 8548 2. 498.27
	1. 8543 2. 436.24		1. 8549 2. 365.1
	1. 8545 2. 464.26		1. 8549 2. 337.1
	1. 8546 2. 466.26		1. 8550 2. 351.1

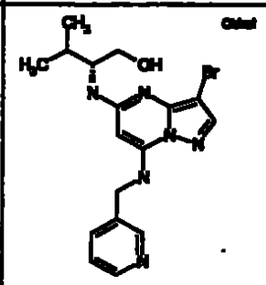
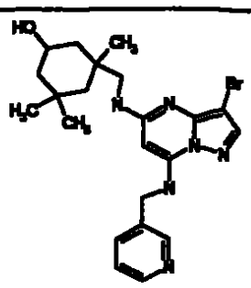
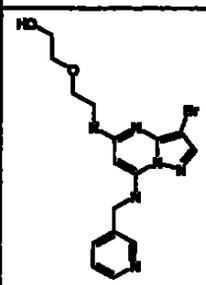
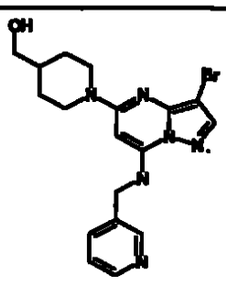
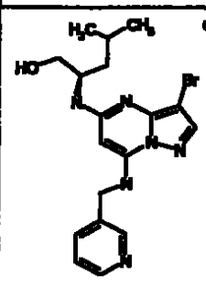
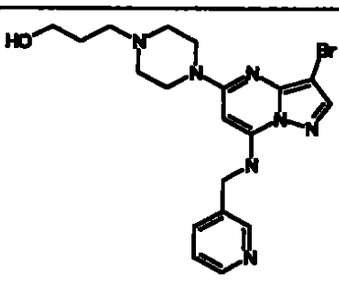
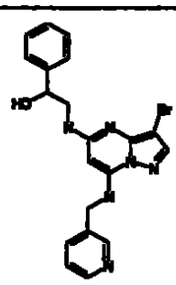
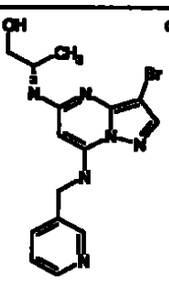
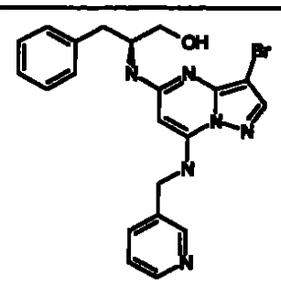
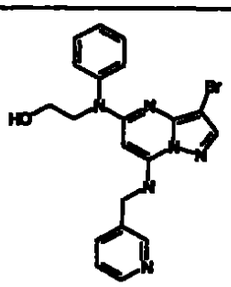
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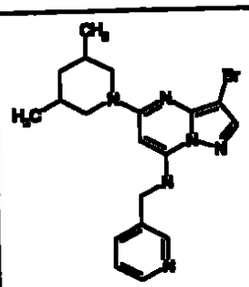
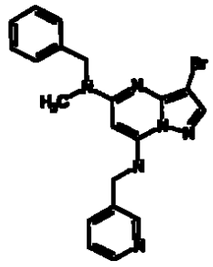
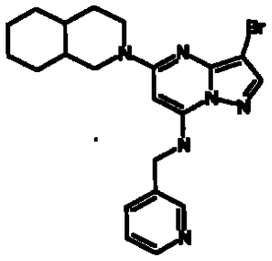
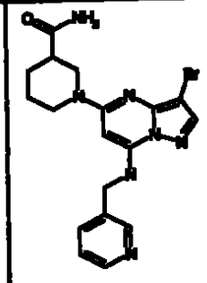
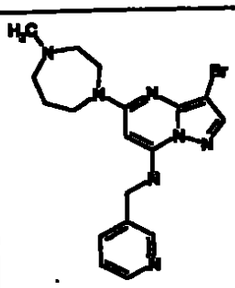
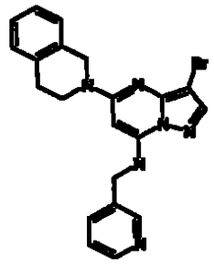
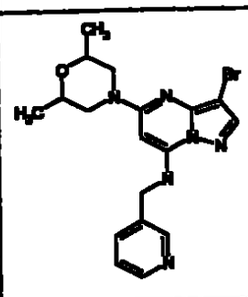
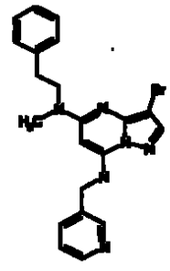
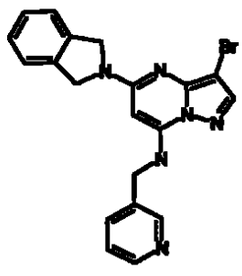
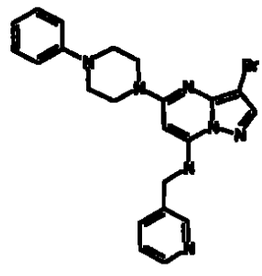
TABLE 86

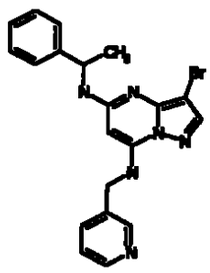
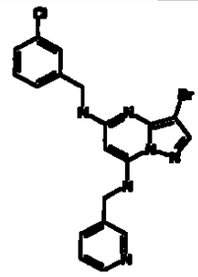
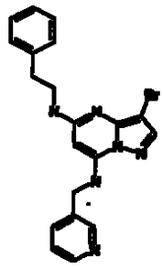
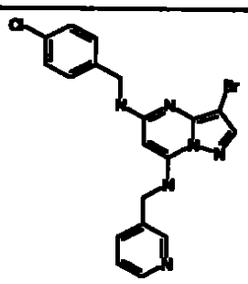
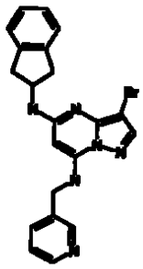
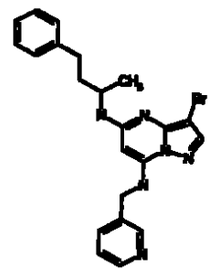
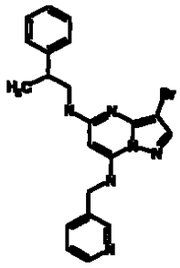
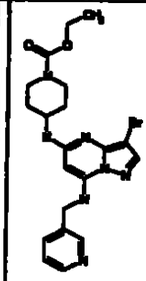
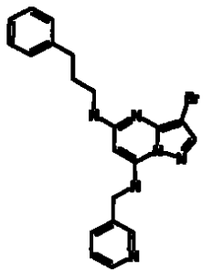
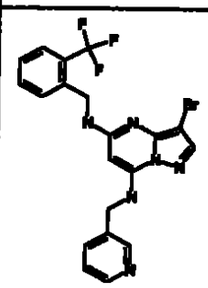
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	1. 8601 2. 403.22		1. 8606 2. 434.24
	1. 8602 2. 407.22		1. 8607 2. 375.21
	1. 8603 2. 421.23		1. 8608 2. 375.21
	1. 8604 2. 434.24		1. 8609 2. 391.22
	1. 8605 2. 391.22		1. 8610 2. 399.22

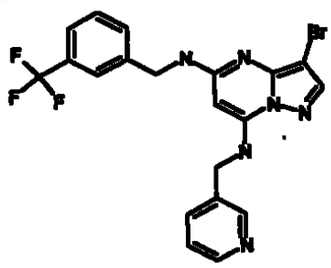
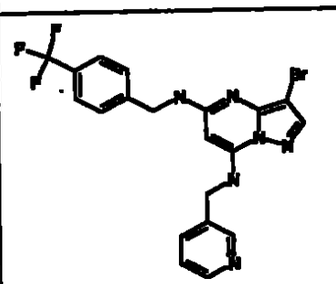
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8611 2. 417.23		1. 8616 2. 434.24
	1. 8612 2. 415.23		1. 8617 2. 446.25
	1. 8613 2. 428.24		1. 8618 2. 460.25
	1. 8614 2. 430.24		1. 8619 2. 459.25
	1. 8615 2. 434.24		1. 8620 2. 474.26

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

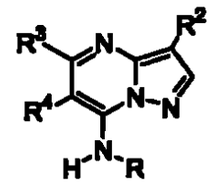
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8651 2. 423.23		1. 8656 2. 445.24
	1. 8652 2. 425.23		1. 8657 2. 445.24
	1. 8653 2. 437.24		1. 8658 2. 451.25
	1. 8654 2. 437.24		1. 8659 2. 476.26
	1. 8655 2. 437.24		1. 8660 2. 479.26

Product	1. Ex. 2. m/z		
	1. 8661 2. 477.26		
	1. 8662 2. 479.26		

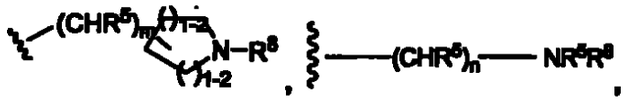
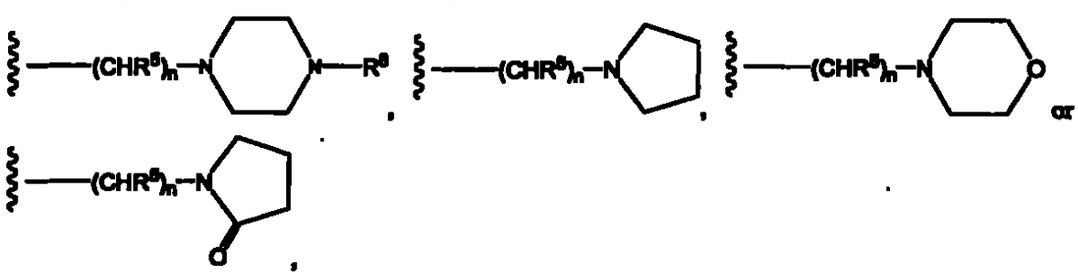
CLAIMS

What is claimed is:

1. A compound represented by the structural formula:

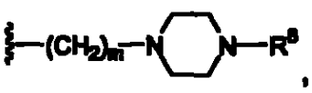


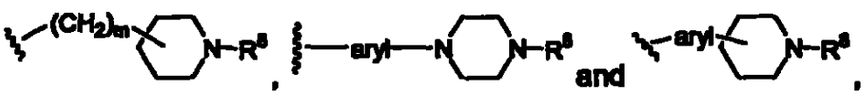
or a pharmaceutically acceptable salt or solvate of said compound, wherein:

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,  ,  , or ,

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 -$N(R^5)C(O)NR^5R^{10}$;

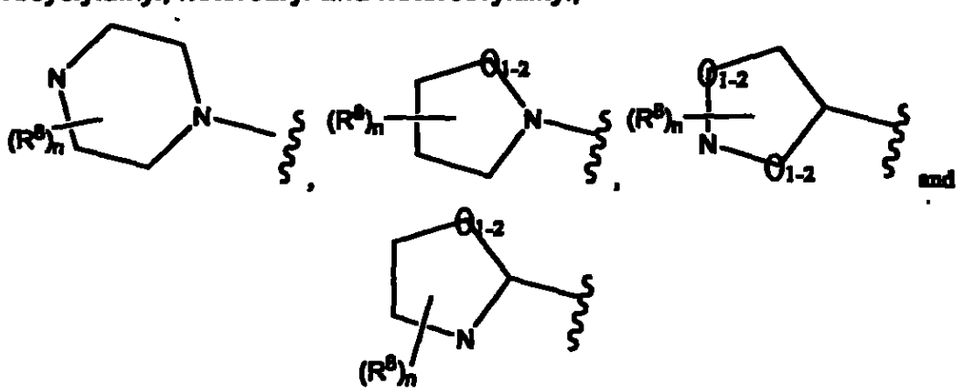
R^2 is selected from the group consisting of R^9, alkyl, alkenyl, alkynyl, CF_3, heterocyclyl, heterocyclylalkyl, halogen, haloalkyl, aryl, arylalkyl, heteroarylalkyl, alkynylalkyl, cycloalkyl, heteroaryl, alkyl substituted with 1-6 R^9 groups which can be the same or different and are independently 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, $-OR^5$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-NR^5R^6$, $-C(O)NR^5R^6$, 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,



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, $-OCF_3$,

$-(CR^4R^5)_pOR^5$, $-OR^5$, $-NR^5R^6$, $-(CR^4R^5)_pNR^5R^6$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^6$, 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 or cycloalkyl;

R^6 is selected from the group consisting of H, 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, $-OR^5$, $-NR^5R^{10}$, $-C(R^4R^5)_p-R^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^{10}$, $-SO_3H$, $-SR^{10}$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^{10}$;

R^{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, $-OR^5$, $-NR^4R^5$, $-C(R^4R^5)_p-R^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)NR^4R^6$, $-C(O)R^5$, $-SO_3H$, $-SR^5$, $-S(O_2)R^7$, $-S(O_2)NR^4R^5$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ 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^6 is selected from the group consisting of R^5, $-OR^5$, $-C(O)NR^5R^{10}$, $-S(O_2)NR^5R^{10}$, $-C(O)R^7$, $-C(=N-CN)-NH_2$, $-C(=NH)-NHR^5$, heterocyclyl, and $-S(O_2)R^7$;

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

m is 0 to 4;

n is 1 to 4; and

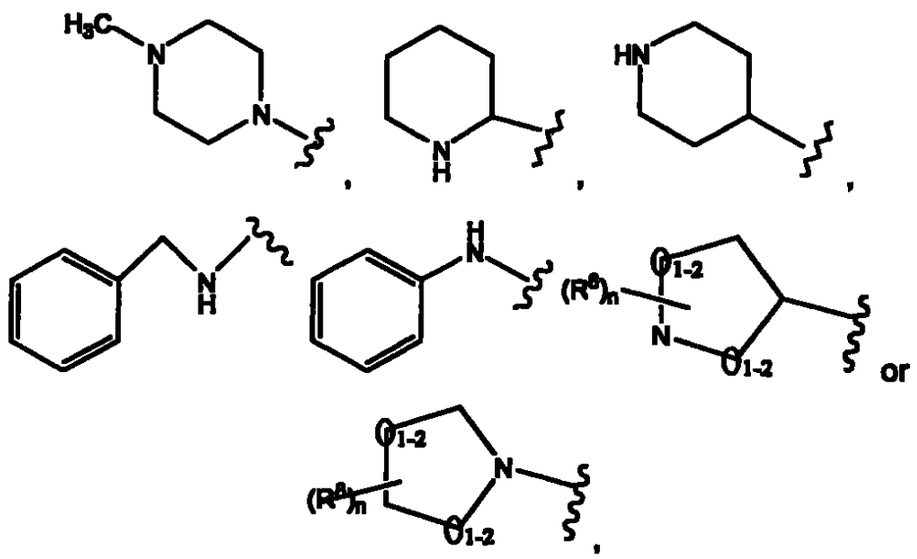
p is 1 to 4,

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.

2. The compound of claim 1, wherein R is $-(CHR^5)_n$-aryl, $-(CHR^5)_n$-heteroaryl, alkyl, cycloalkyl, heterocyclyl, or heteroarylalkyl (including N-oxide of said heteroaryl), wherein each of said alkyl, aryl, cycloalkyl, heterocyclyl and heteroaryl can be unsubstituted or optionally substituted with one or more moieties as stated in claim 1;

R^2 is halogen, alkyl, haloalkyl, CN, cycloalkyl, heterocyclyl or alkynyl;

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 $-OR^5$ moiety;

R^4 is H or lower alkyl;

R^5 is H, lower alkyl or cycloalkyl;

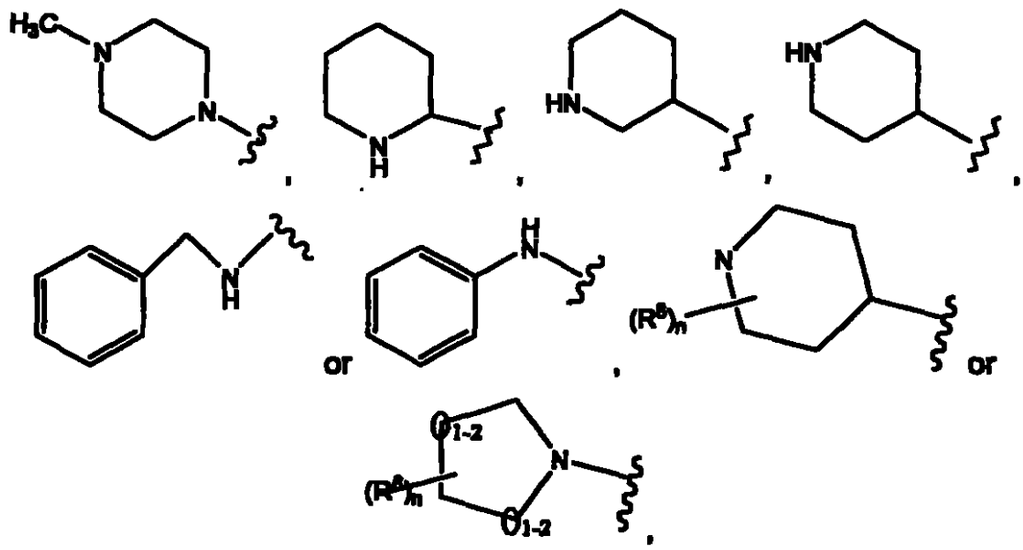
n is 1 to 2; and

p is 1 or 2.

3. The compound of claim 2, wherein R is hydroxyalkyl, $-(CHR^5)_n$-aryl, or $-(CHR^5)_n$-heteroaryl, wherein each of said aryl and heteroaryl is unsubstituted or substituted with one or more groups which can be the same or different, each group being independently selected from the group consisting of heteroaryl, amine, heterocyclyl, $-C(O)N(R^5R^6)$, $-S(O_2)R^5$, $-S(O_2)N(R^5R^6)$, alkoxy and halo.

4. The compound of claim 2, wherein R^2 is Br, Cl, CF_3, CN, lower alkyl, cyclopropyl, alkynyl, alkyl substituted with $-OR^6$ or tetrahydrofuranyl.

5. The compound of claim 2, wherein R^3 is H, lower alkyl, aryl, heteroaryl, cycloalkyl,



wherein each of said alkyl, aryl, heteroaryl, cycloalkyl and the heterocyclyl structures shown immediately above for R^3 are optionally substituted with one or more moieties which moieties can be the same or different, each moiety being independently selected from the group consisting of halogen, CF_3, OCF_3, lower alkyl, CN and OR^5, with the proviso that no carbon adjacent to a nitrogen atom on a heterocyclyl ring carries a $-OR^5$ moiety.

6. The compound of claim 2, wherein R^4 is H or lower alkyl.

7. The compound of claim 2, wherein R^5 is H.

8. The compound of claim 2, wherein n is 1.

9. The compound of claim 1, wherein p is 1.

10. The compound of claim 2, wherein R is benzyl or hydroxyalkyl.

11. The compound of claim 2, wherein R is pyrid-3-ylmethyl, wherein said pyridyl may be unsubstituted or optionally independently substituted with one or more moieties as stated in claim 1.

12. The compound of claim 2, wherein R is pyrid-4-ylmethyl, wherein said pyridyl may be unsubstituted or optionally independently substituted with one or more moieties as stated in claim 1.

13. The compound 2, wherein R is the N-oxide of pyrid-2-ylmethyl, pyrid-3-ylmethyl, or pyrid-4-ylmethyl, wherein each of said pyridyl may be unsubstituted or optionally independently substituted with one or more moieties as stated in claim 1.

14. The compound of claim 4, wherein said R^2 is Br.

15. The compound of claim 4, wherein said R^2 is Cl.

16. The compound of claim 4, wherein R^2 is ethyl.

17. The compound of claim 4, wherein R^2 is cyclopropyl.

18. The compound of claim 4, wherein R^2 is ethynyl.

19. The compound of claim 2, wherein R^3 is lower alkyl, cycloalkyl, heterocyclyl, aryl or $-N(R^5R^6)$.

20. The compound of claim 19, wherein R^3 is isopropyl.

21. The compound of claim 19, wherein R^3 is cyclohexyl or norbornyl wherein each of said cyclohexyl or norbornyl can be unsubstituted or substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of alkyl and hydroxyalkyl.

22. The compound of claim 19, wherein R^3 is unsubstituted phenyl.

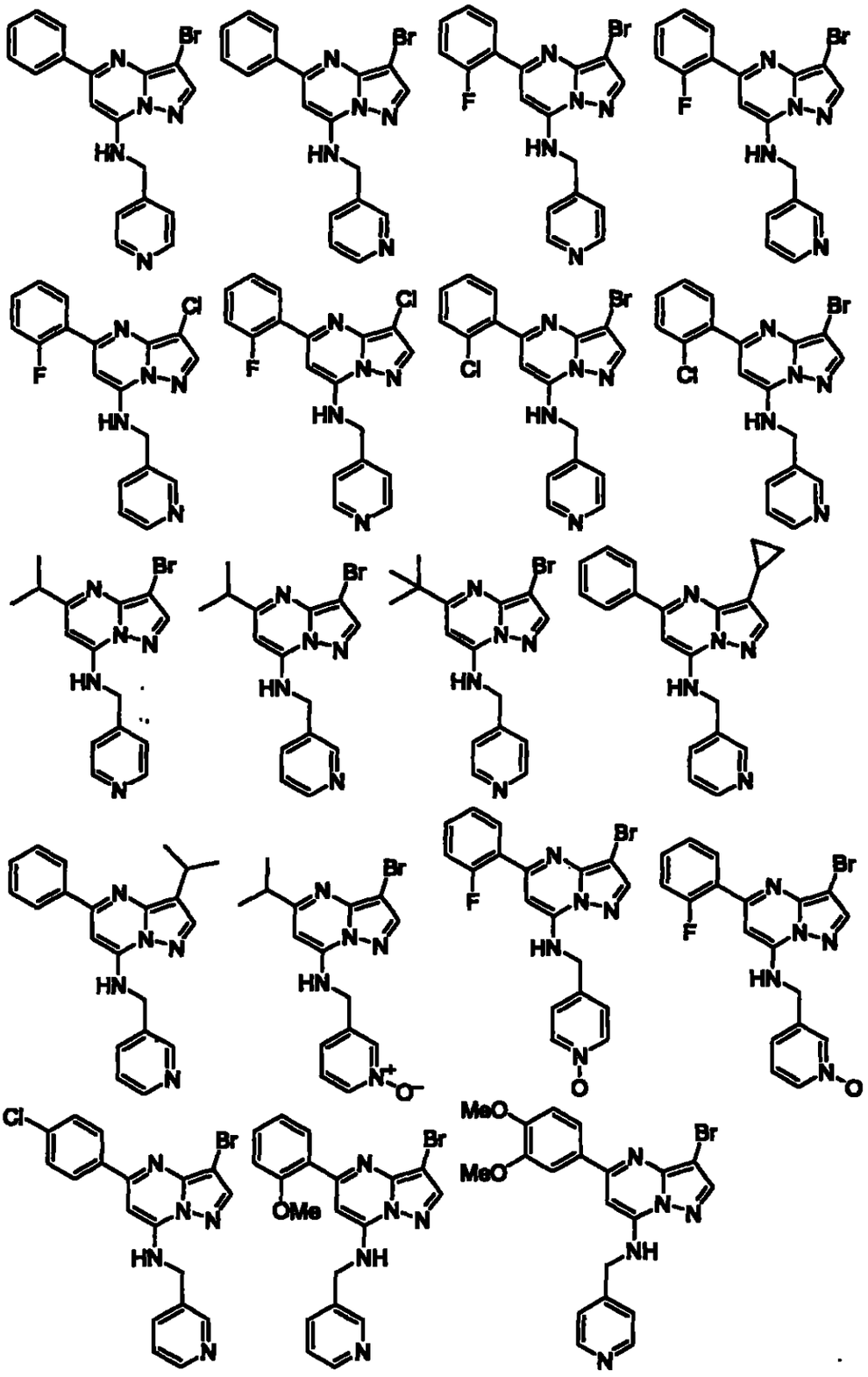
23. The compound of claim 19, wherein R^3 is a phenyl substituted with one or moieties which can be the same or different, each moiety being independently selected from the group consisting of F, Br, Cl and CF_3.

24. The compound of claim 19, wherein R^5 of said $-N(R^5R^6)$ is H or hydroxyalkyl, and R^6 of said $-N(R^5R^6)$ is selected from the group consisting of alkyl, hydroxyalkyl, cycloalkyl and methylenedioxy, wherein each of said alkyl and cycloalkyl can be unsubstituted or substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of amine, ethoxycarbonyl, amide, hydroxyalkyl, hydroxy,

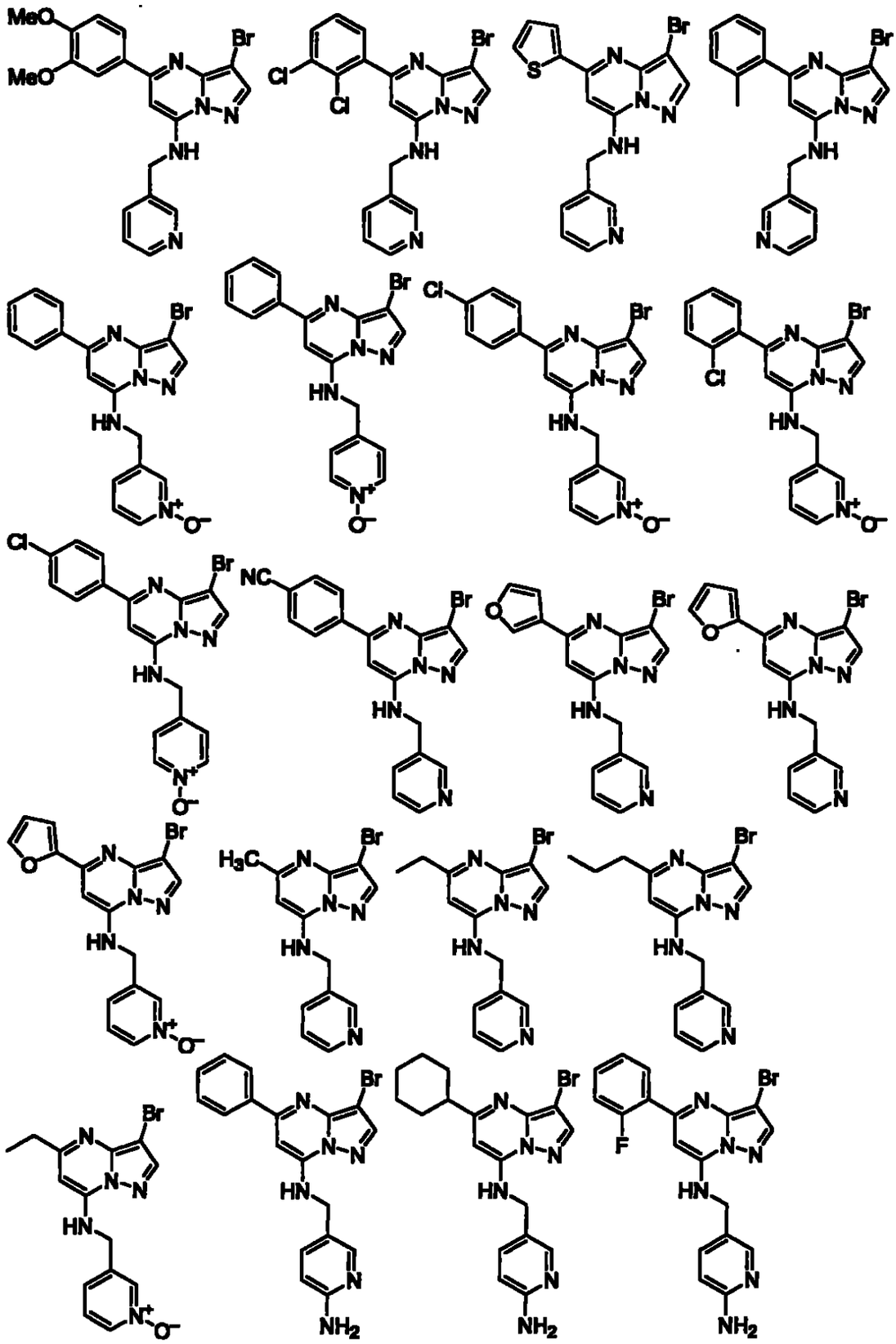
25. The compound of claim 19, wherein R^5 and R^6 of said $-N(R^5R^6)$ are joined together to form a heterocyclyl moiety, wherein said heterocyclyl moiety can be unsubstituted or optionally independently substituted with one or more groups which can be the same or different, each group being selected from the group consisting of hydroxyalkyl, amide, $-C(O)R^5$, $>C(CH_3)_2$, $-S(O_2)R^5$, $-S(O_2)N(R^5R^6)$, $-C(=NH)N(R^5R^6)$ and $-C(=N-CN)N(R^5R^6)$.

26. The compound of claim 25, wherein said heterocyclyl moiety formed by R^5 and R^6 is a pyrrolidine or piperidine ring.

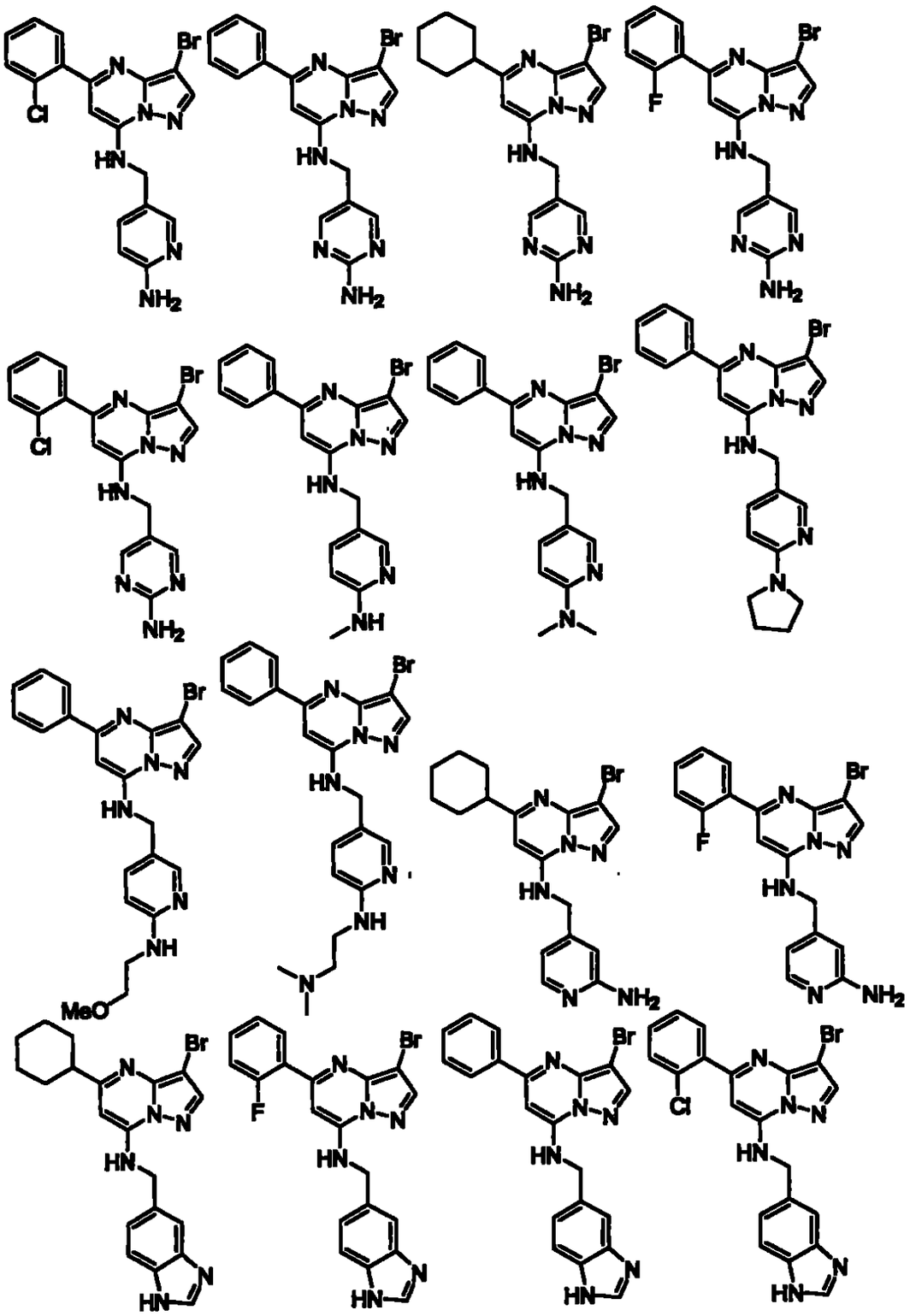
27. A compound of the formula:

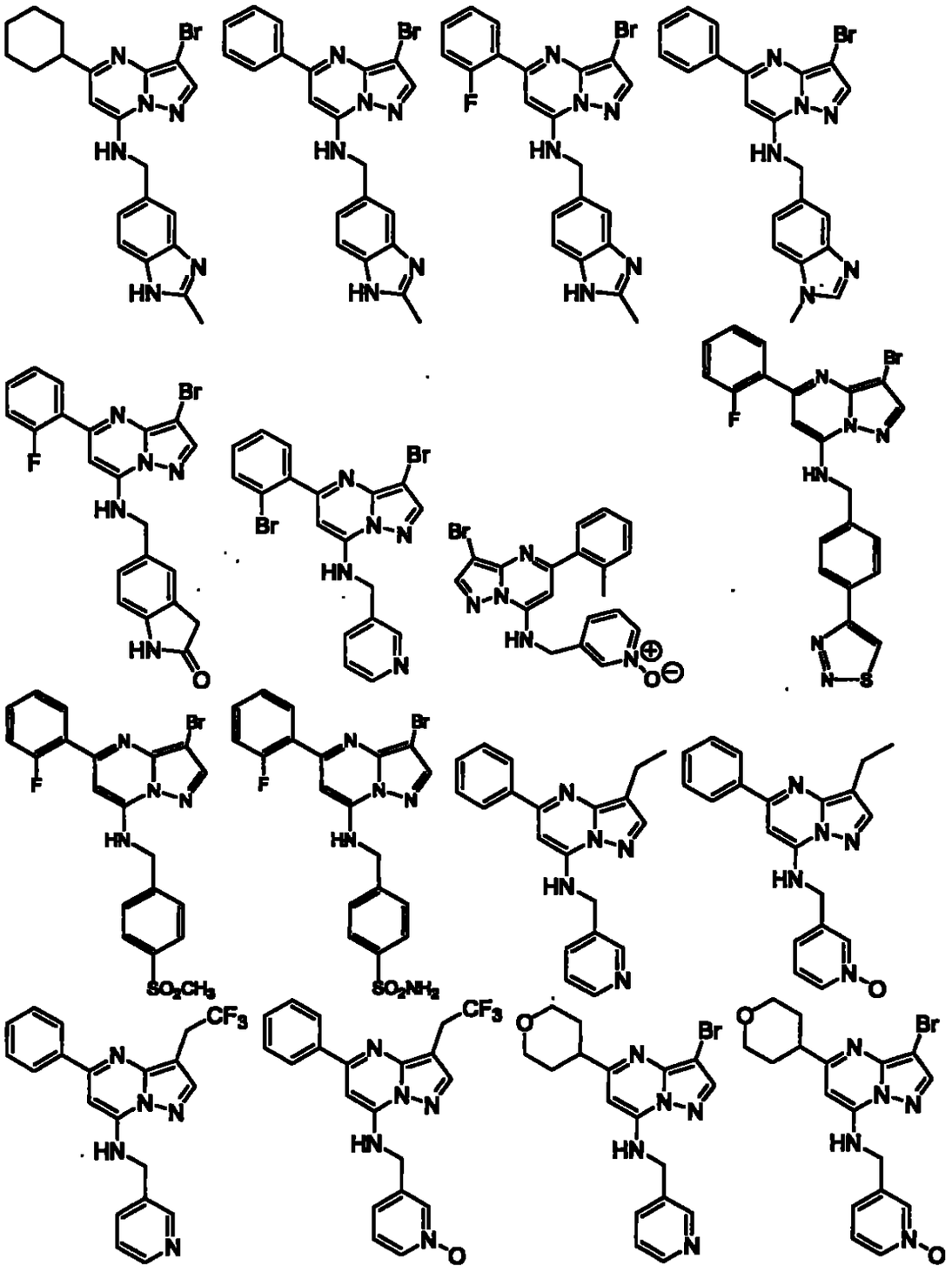


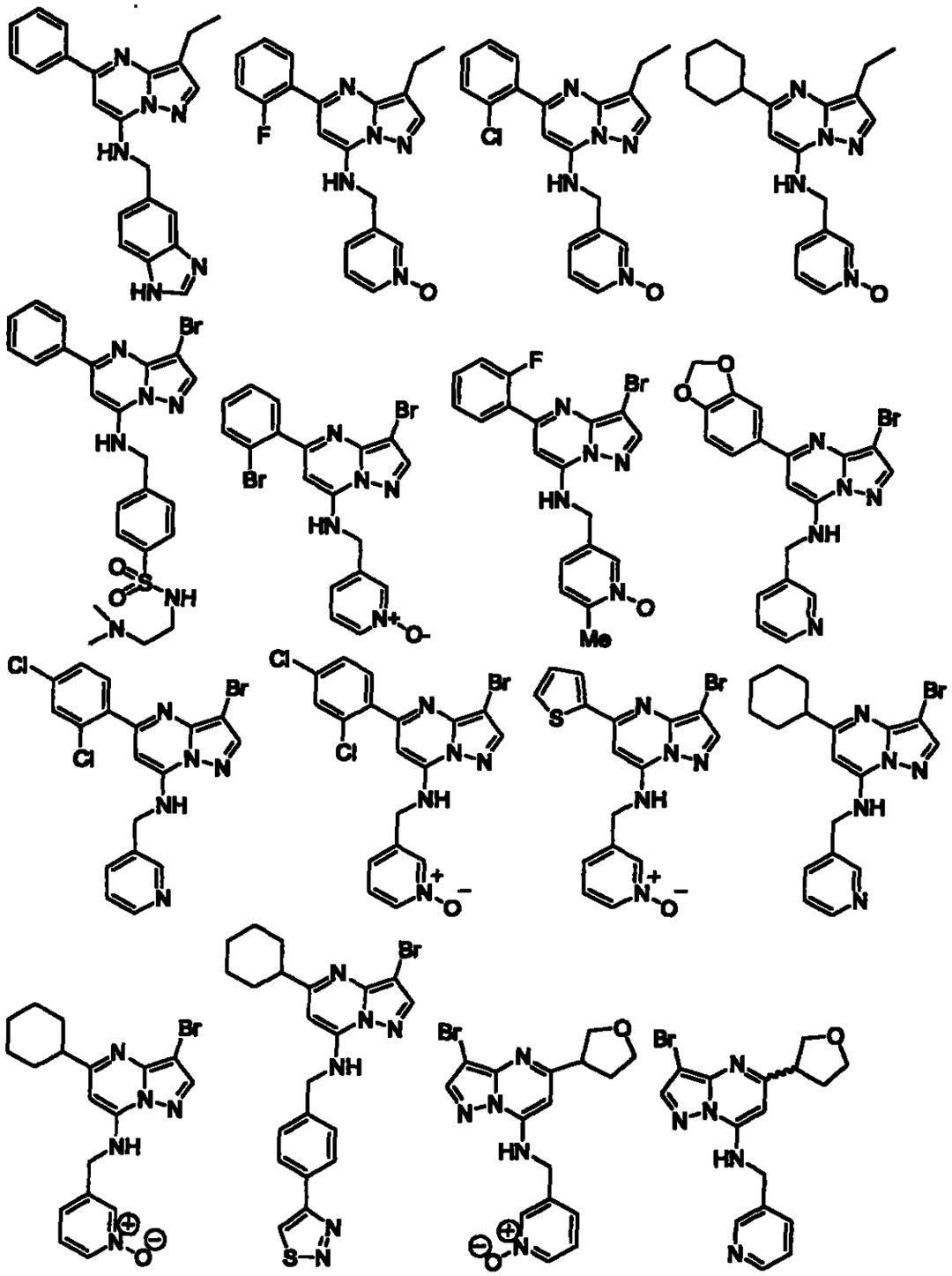
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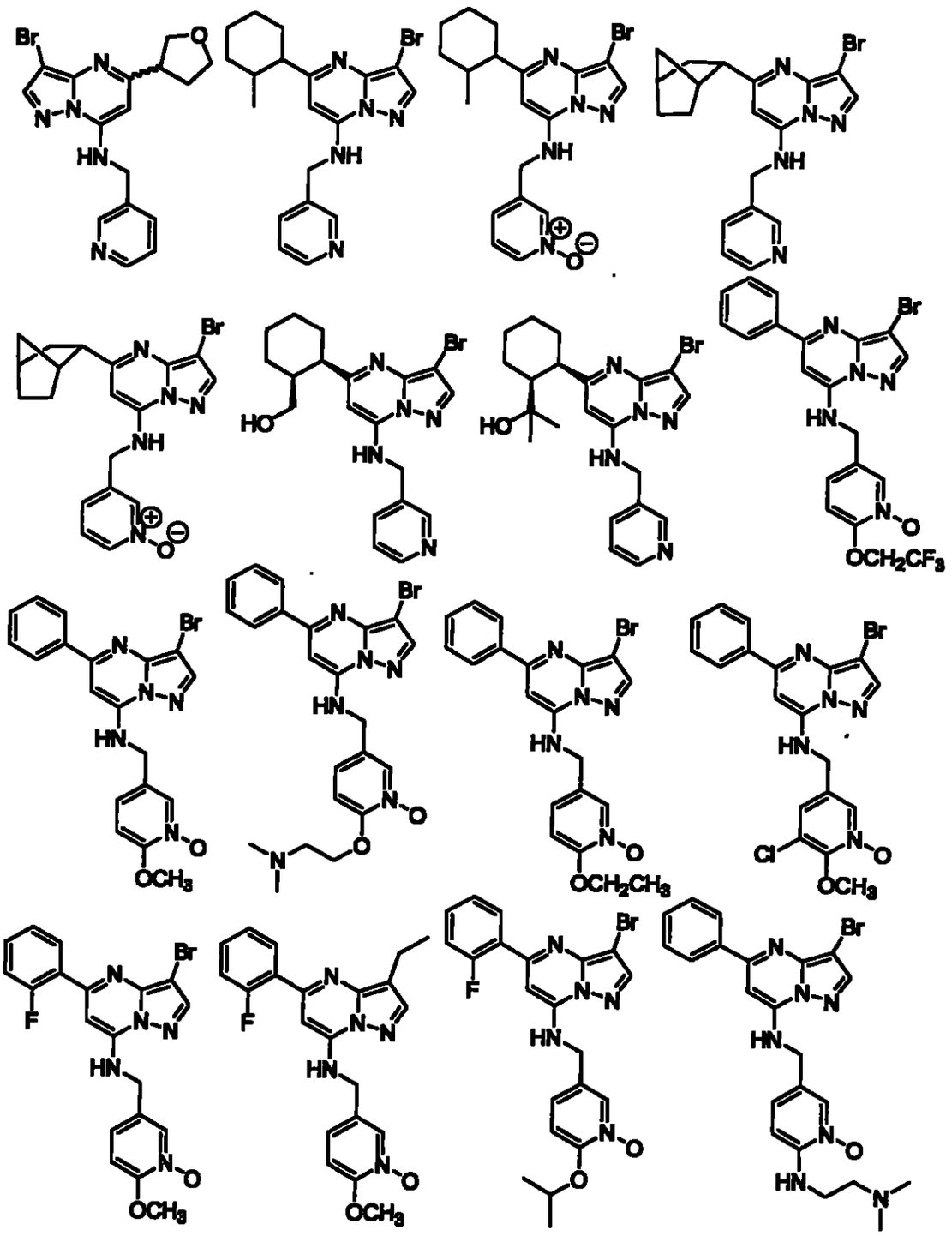


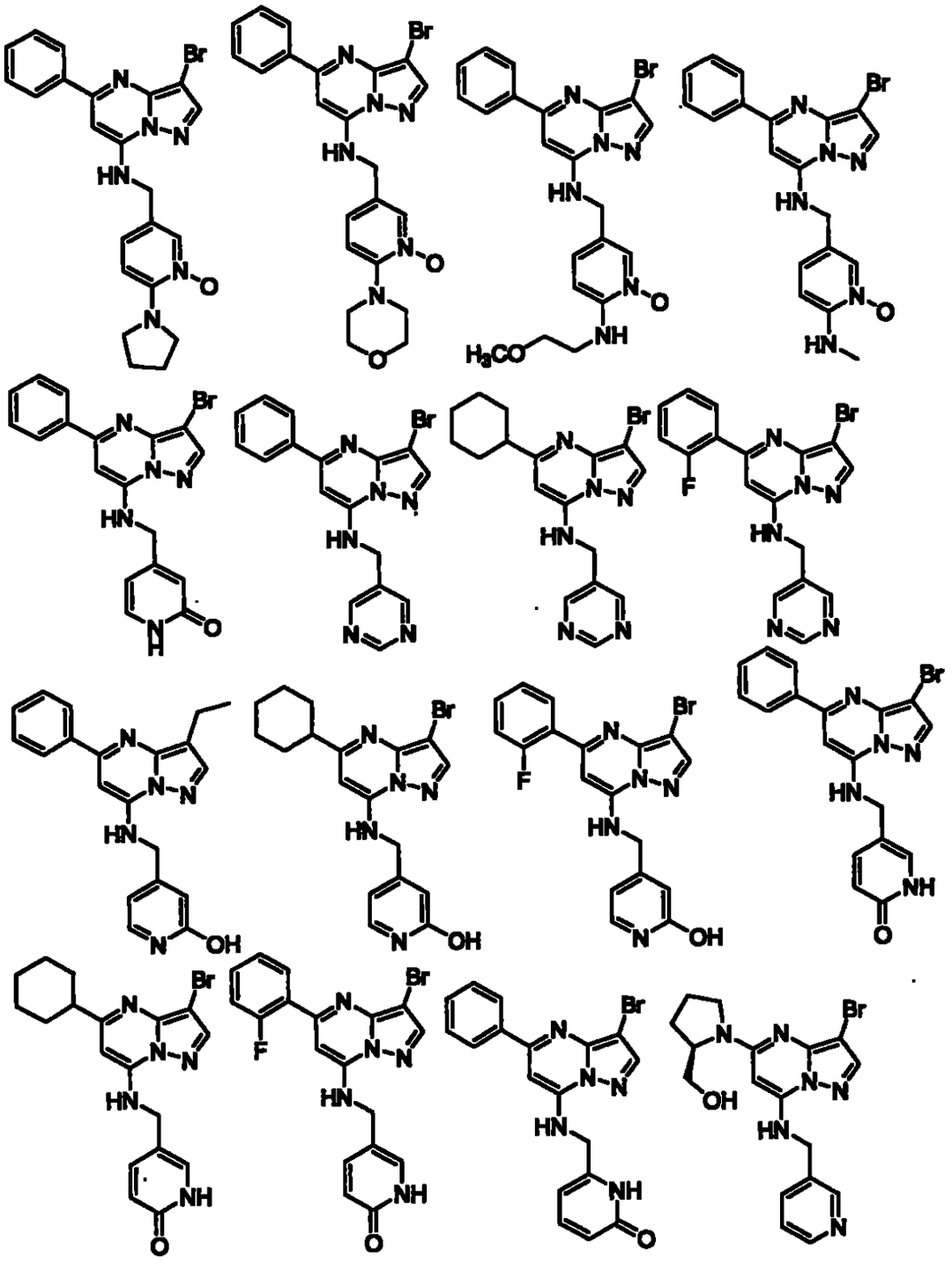
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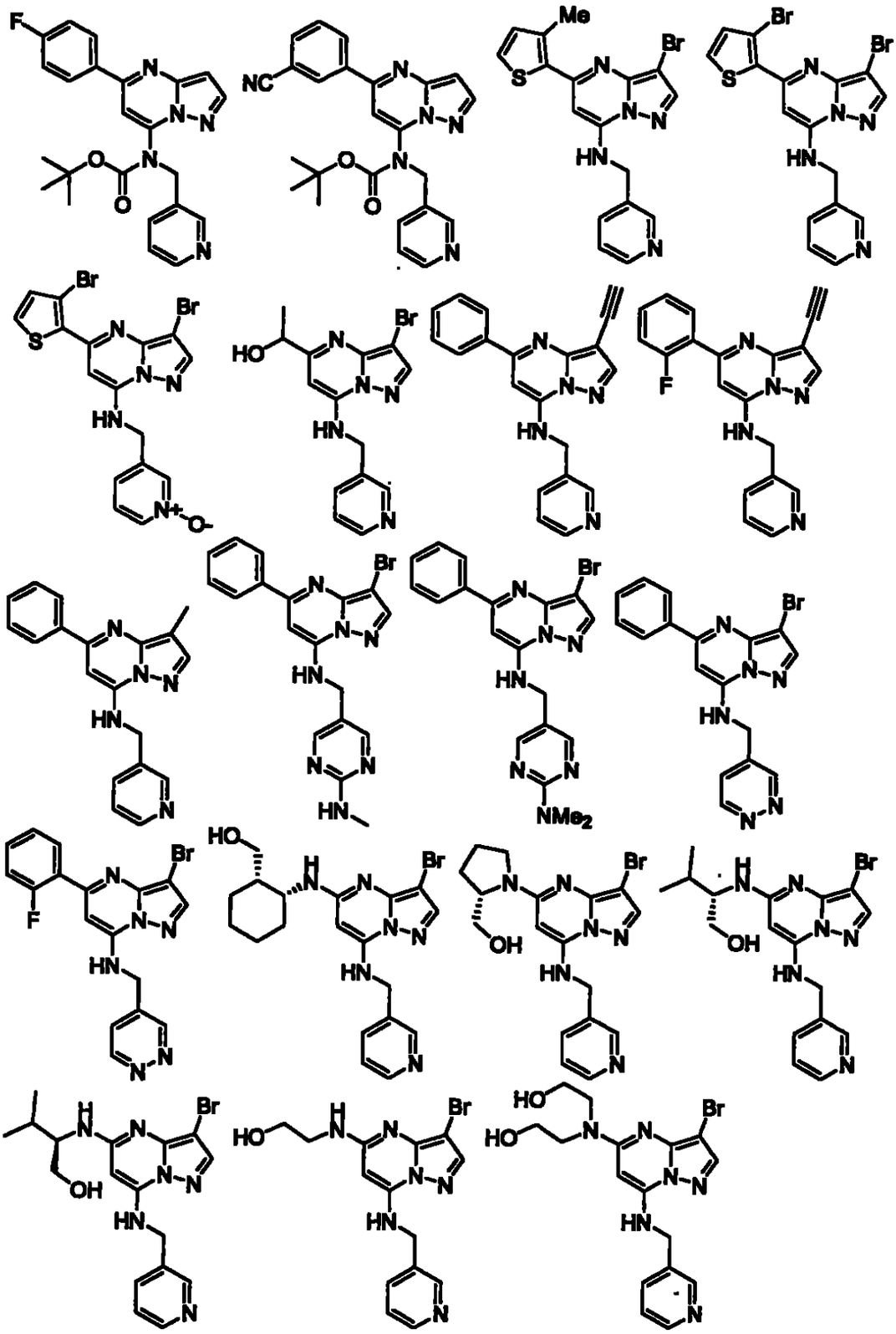




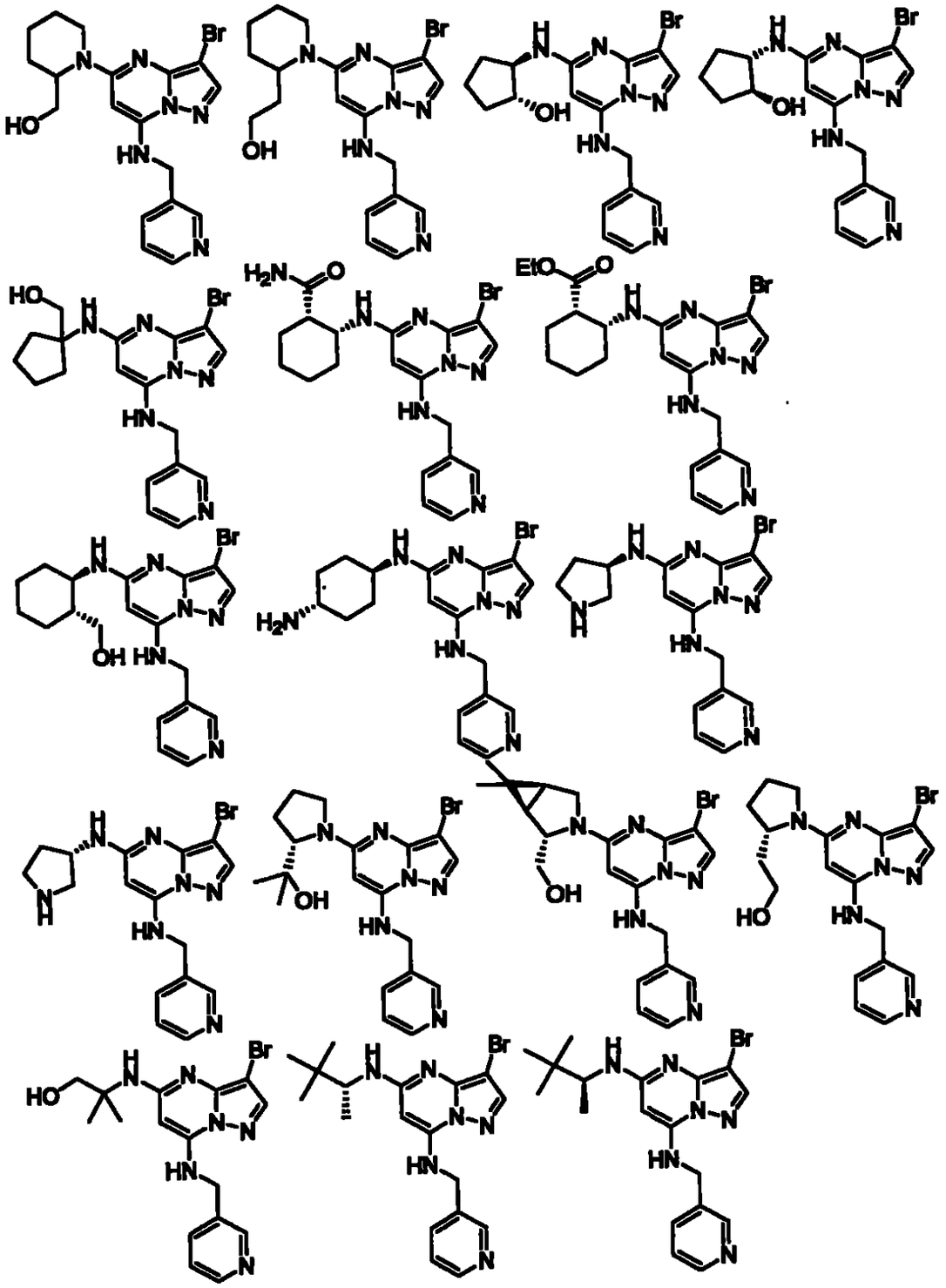




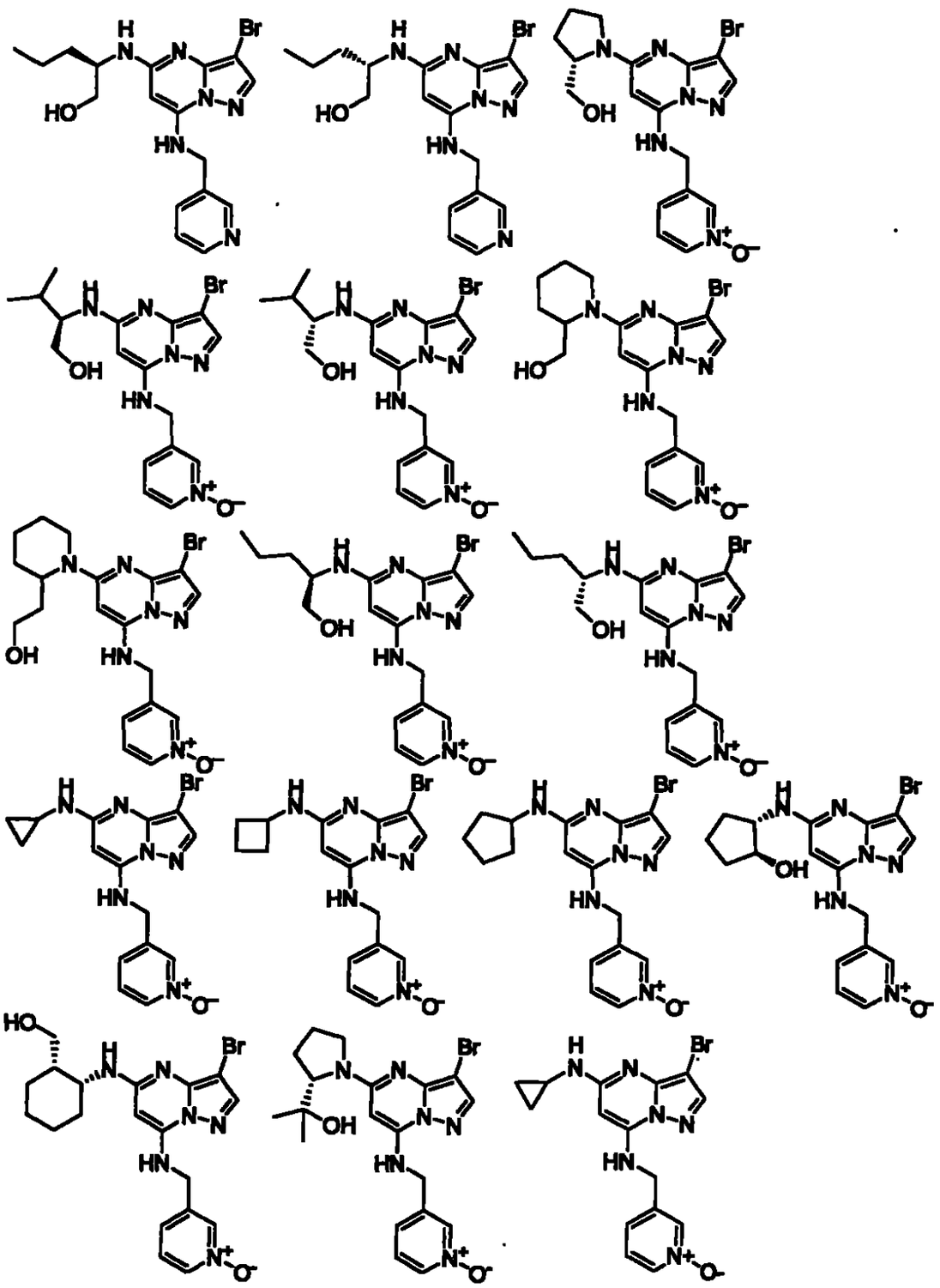




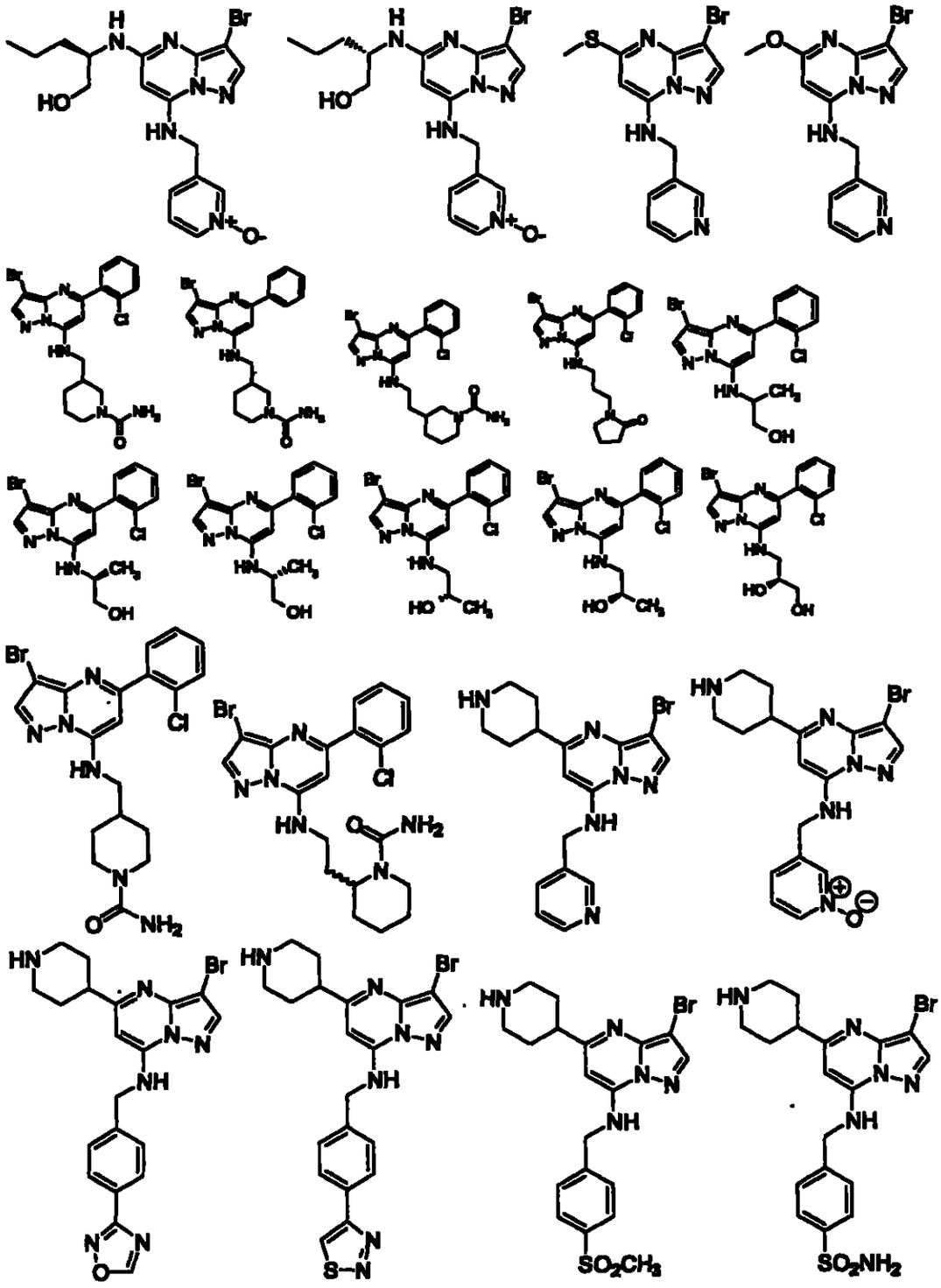
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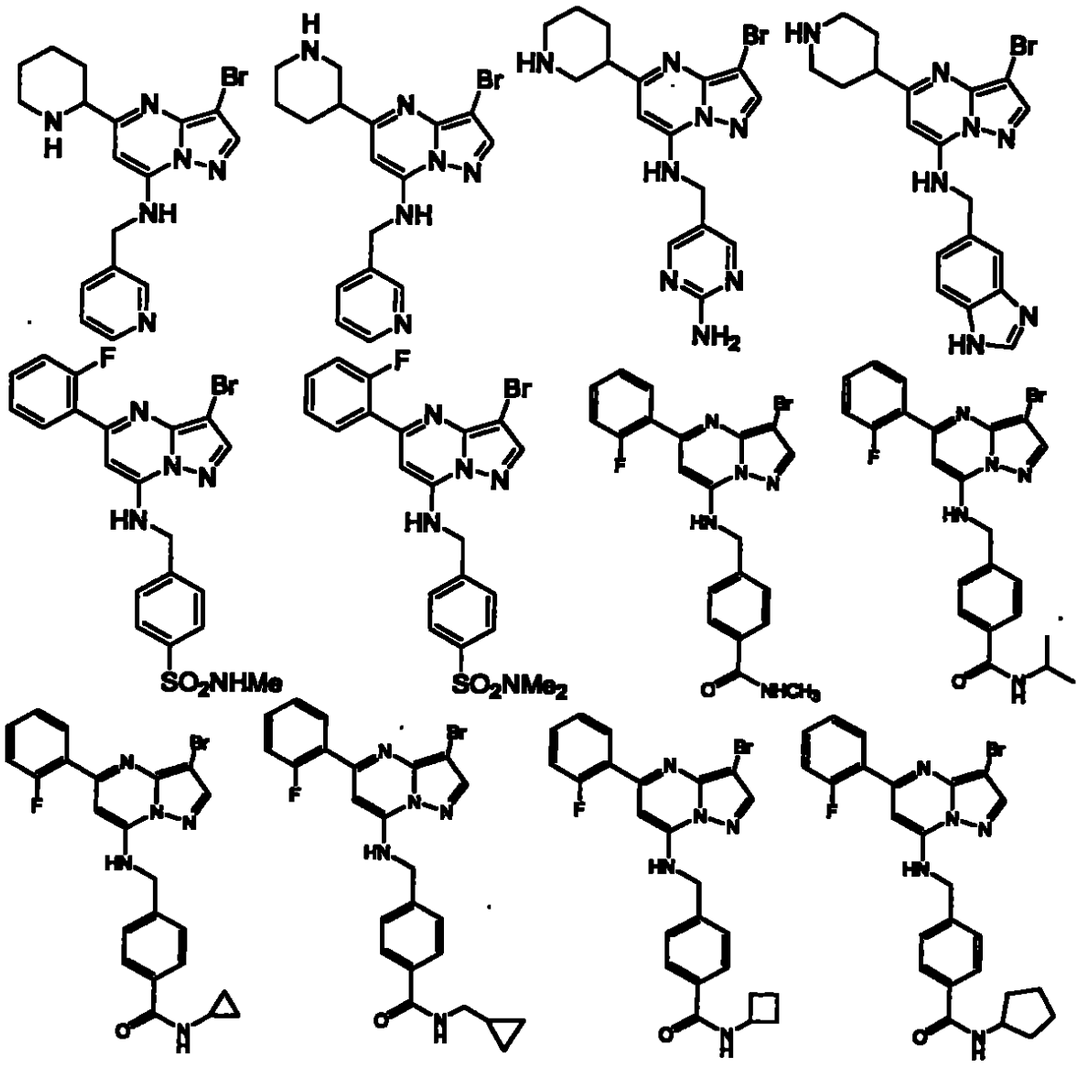


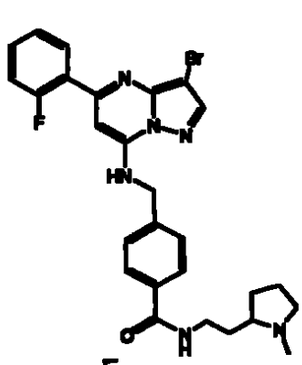
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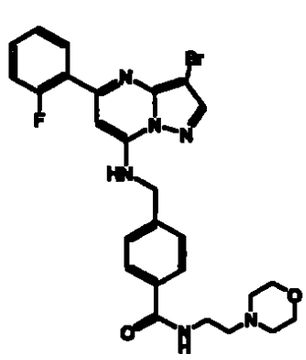


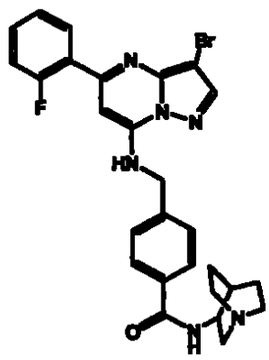
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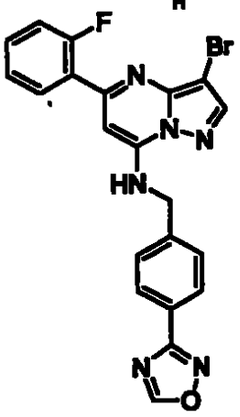


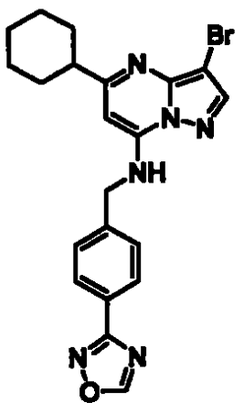

Br
NH
HN
F
SO_2NHMe
SO_2NMe_2
NH_2

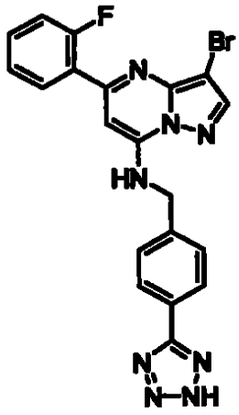


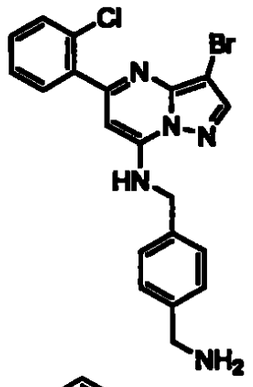


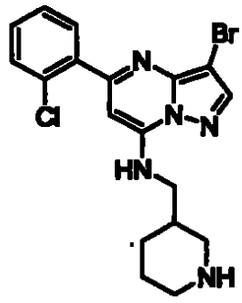


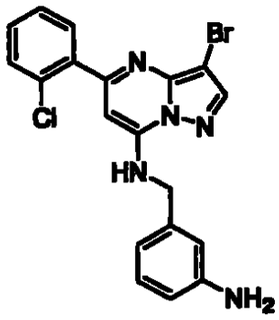


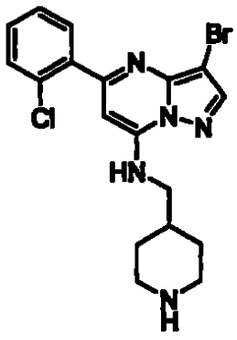


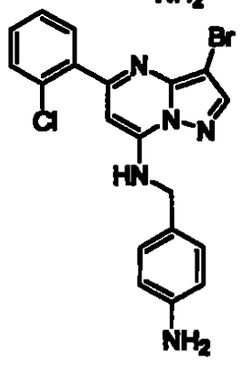




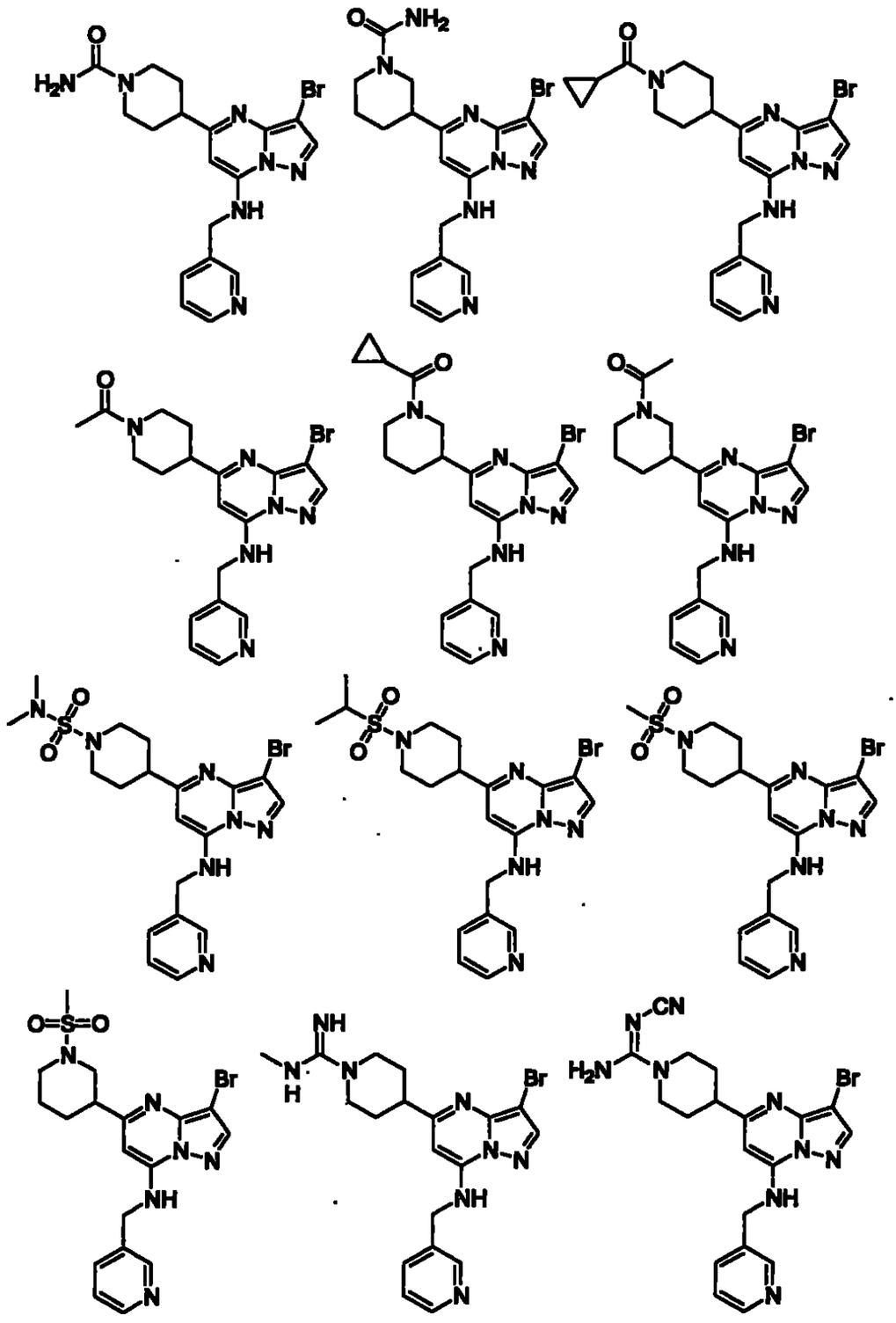


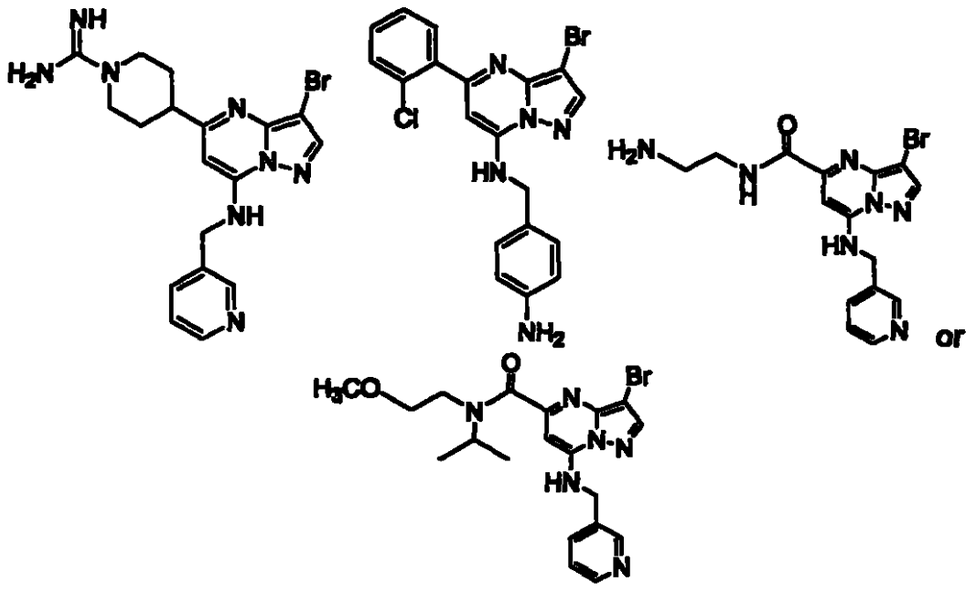






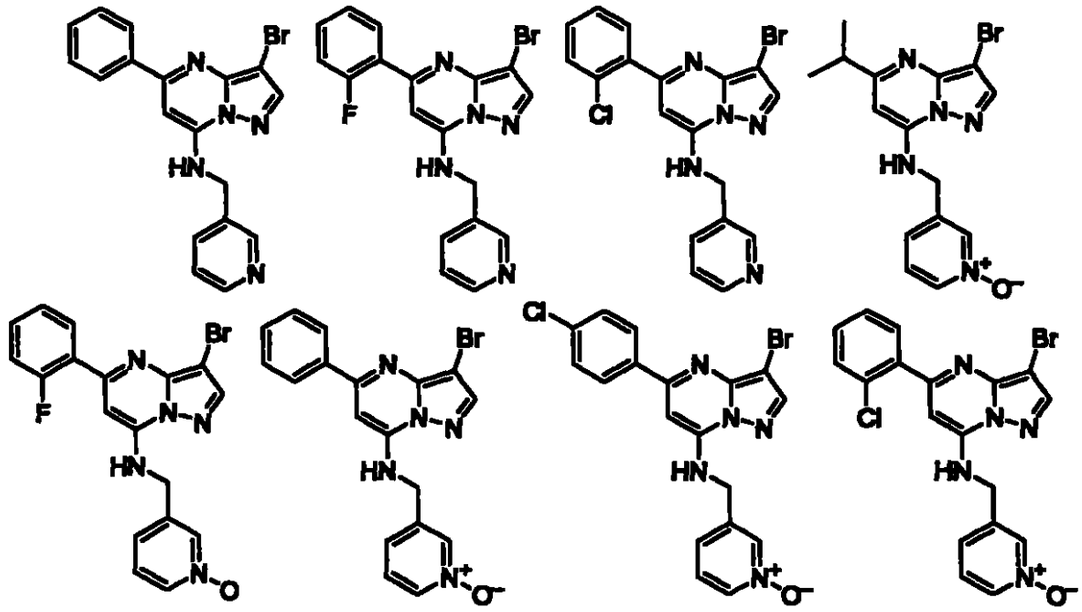
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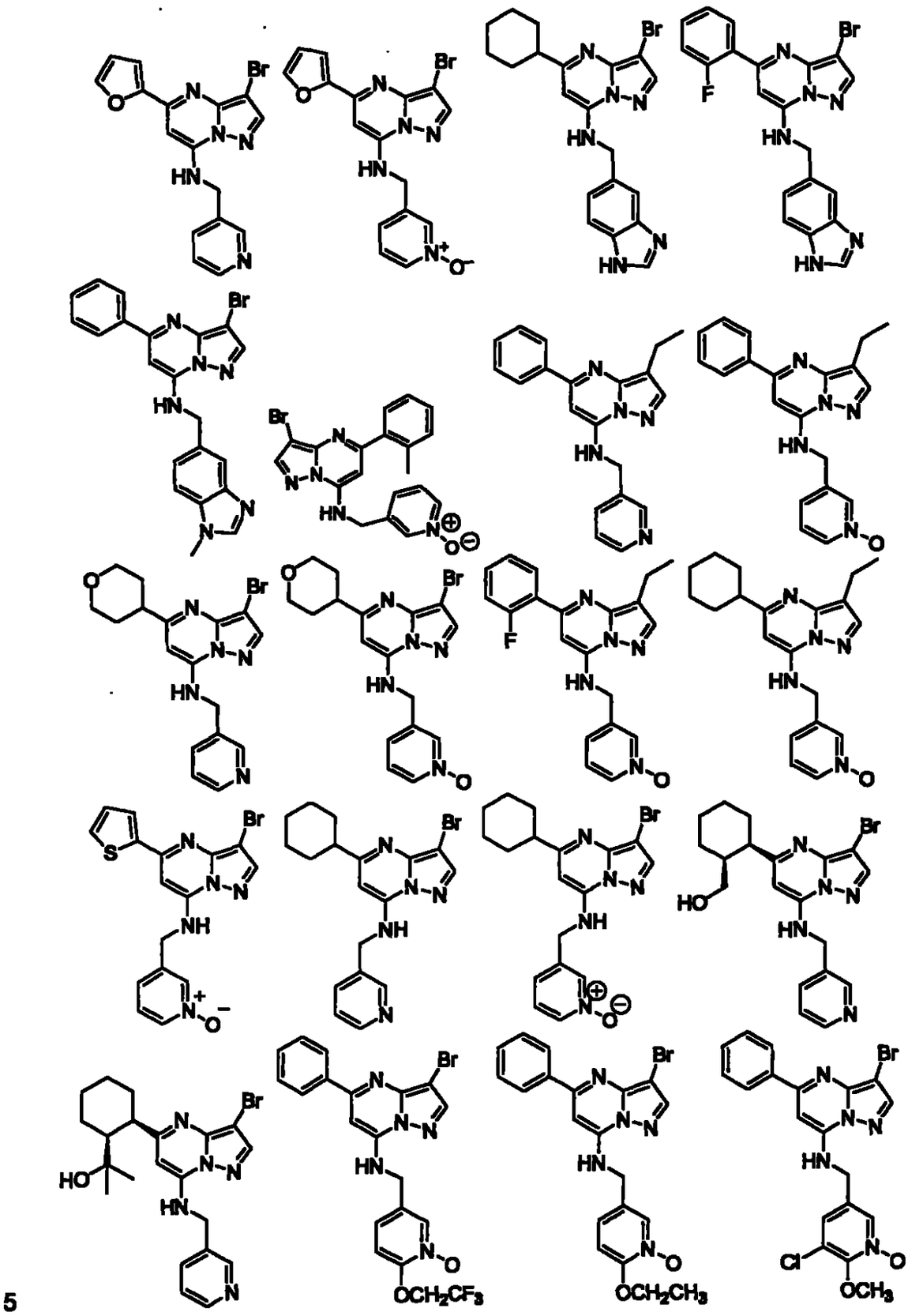




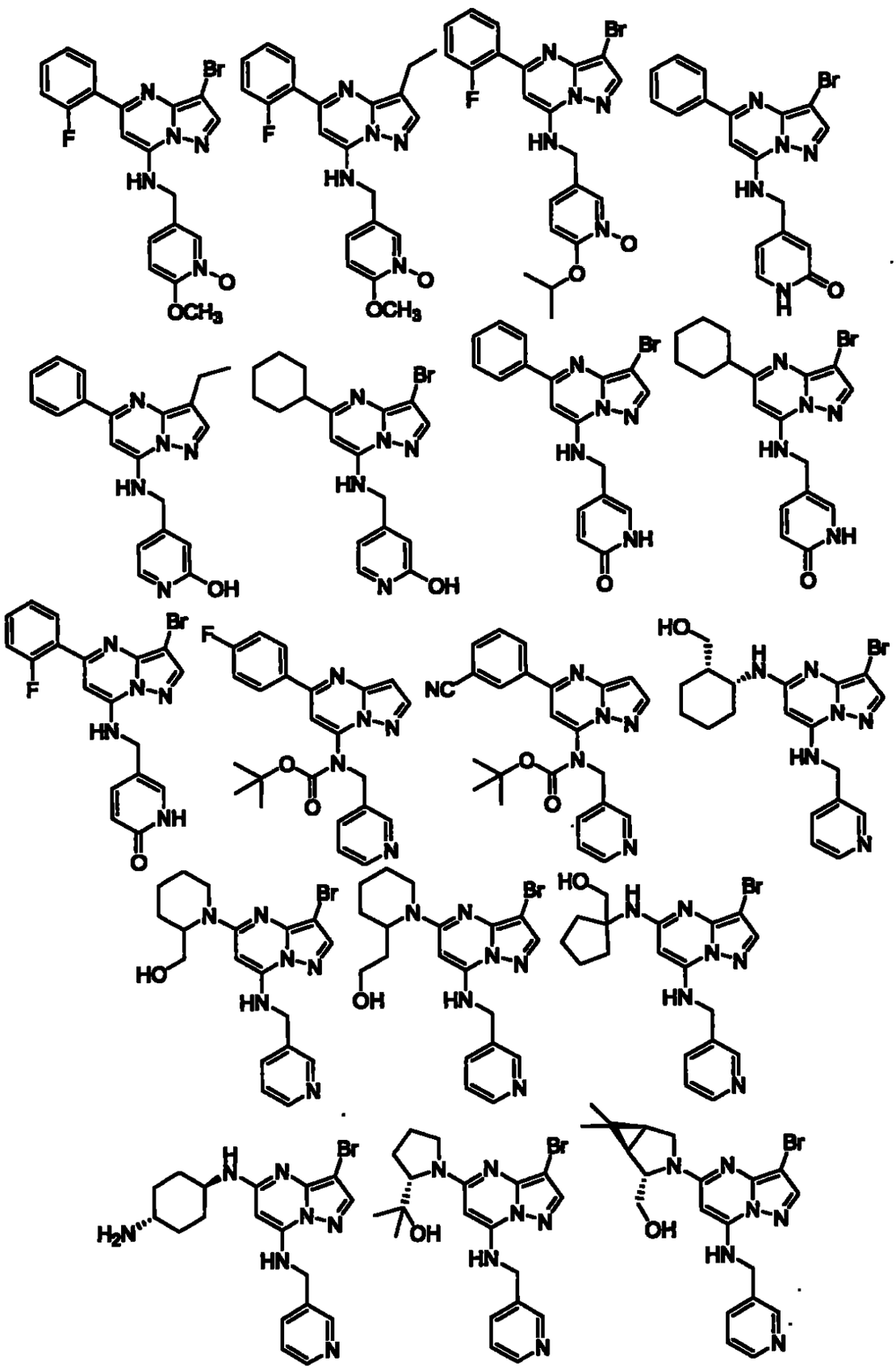
or a pharmaceutically acceptable salt or solvate thereof.

28. A compound of the formula:

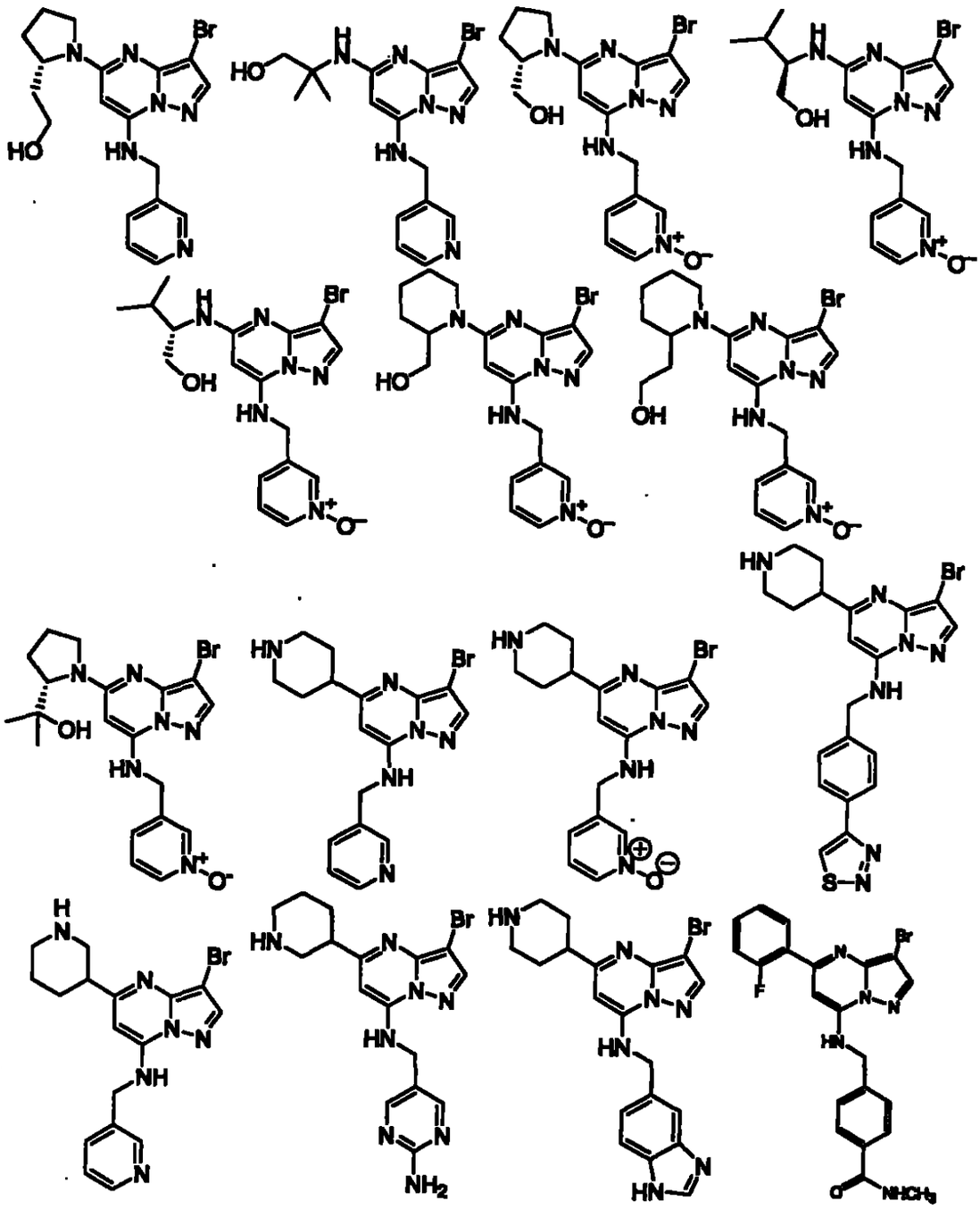


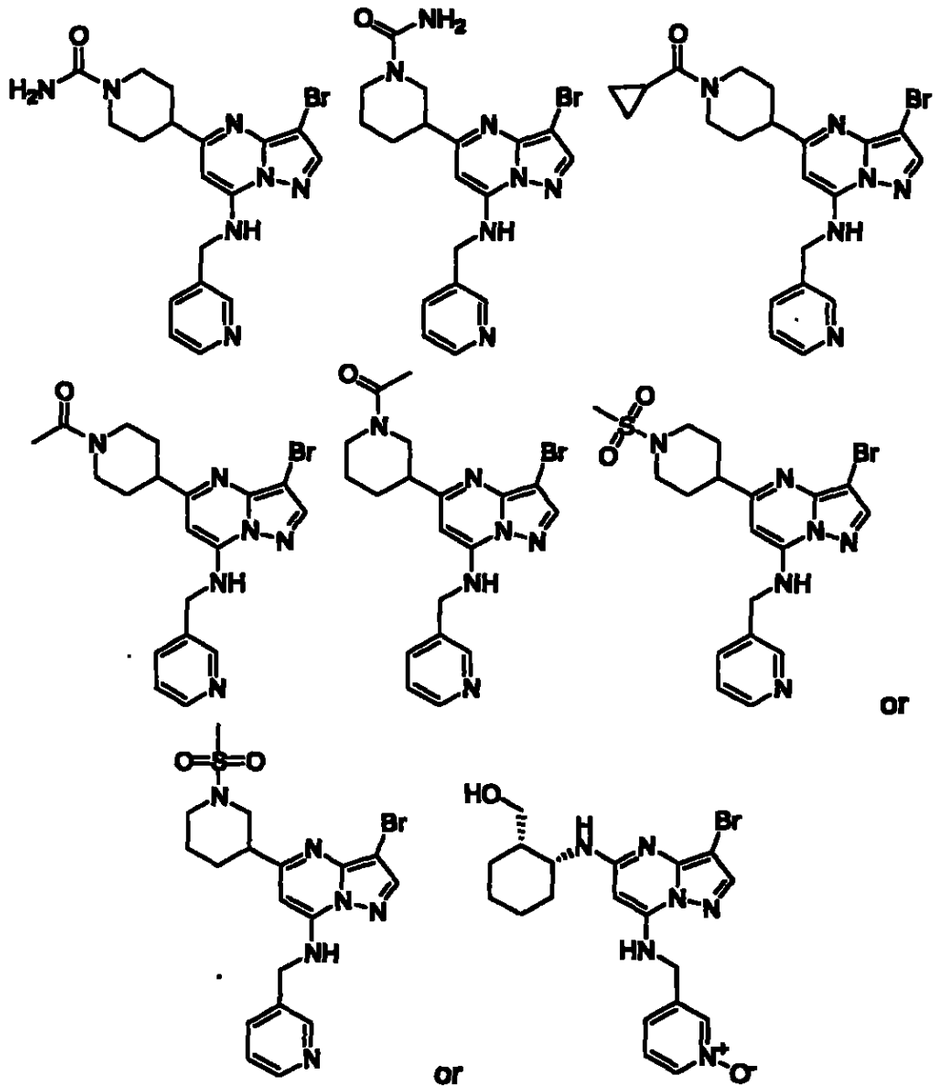


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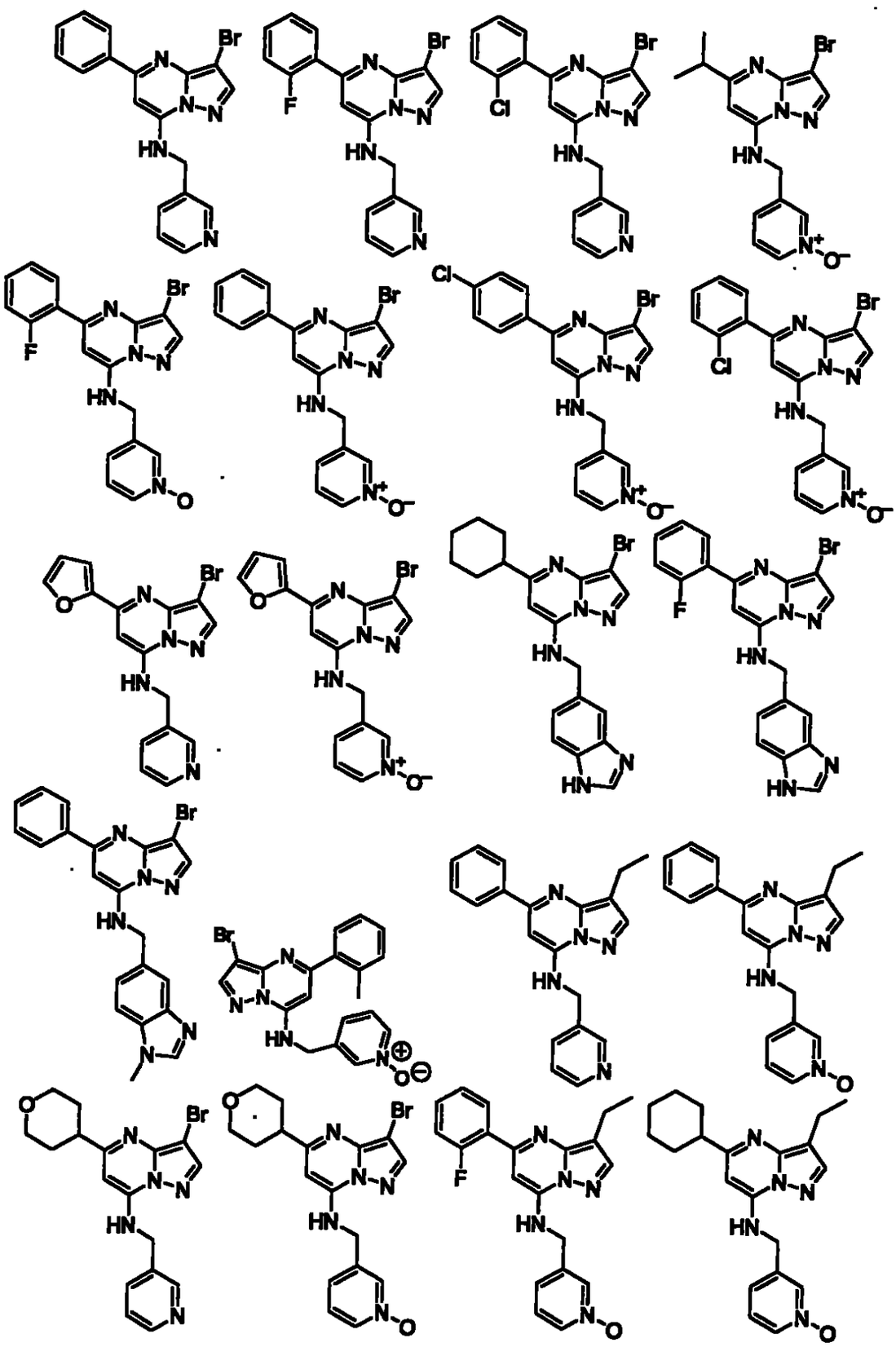


or

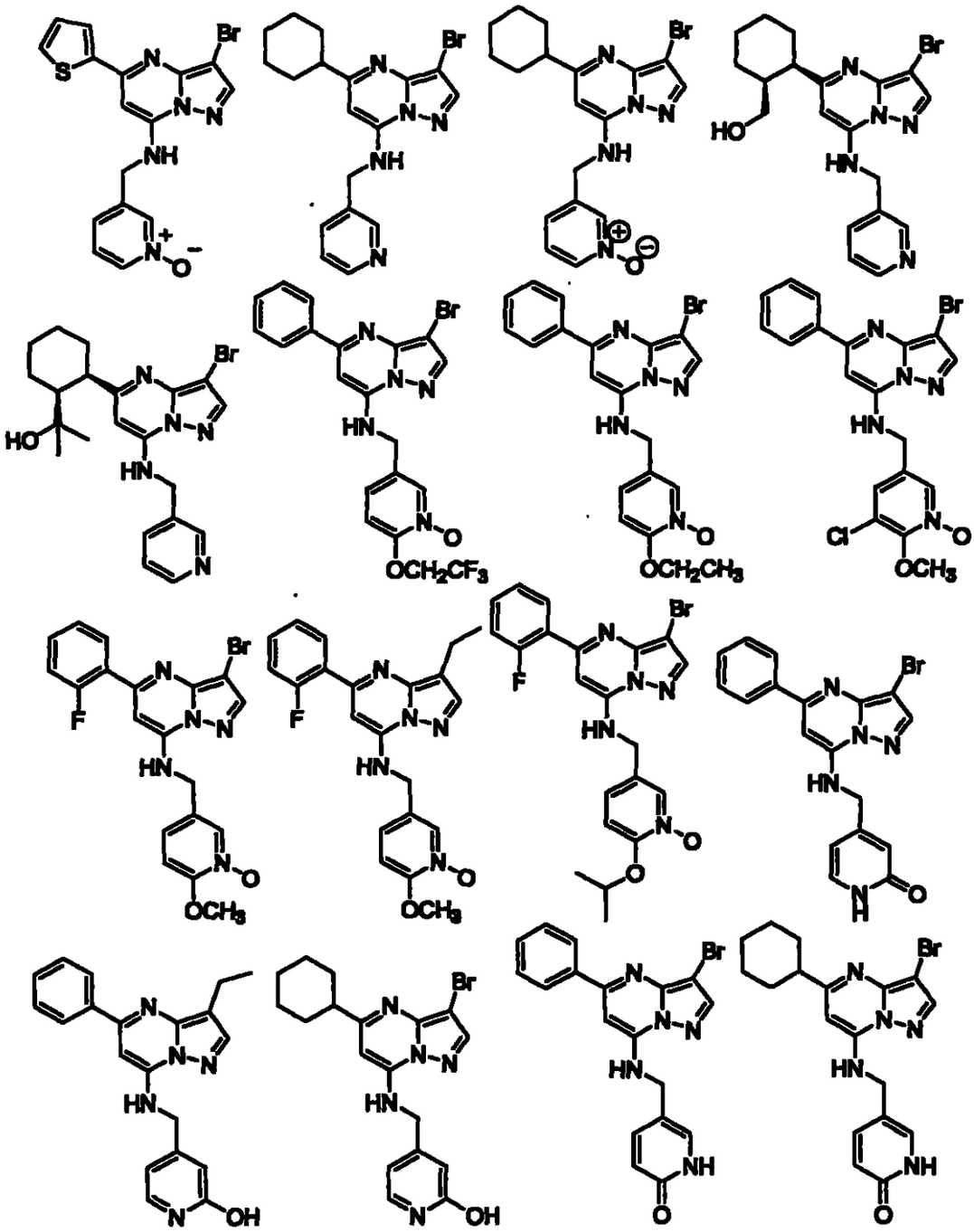
or

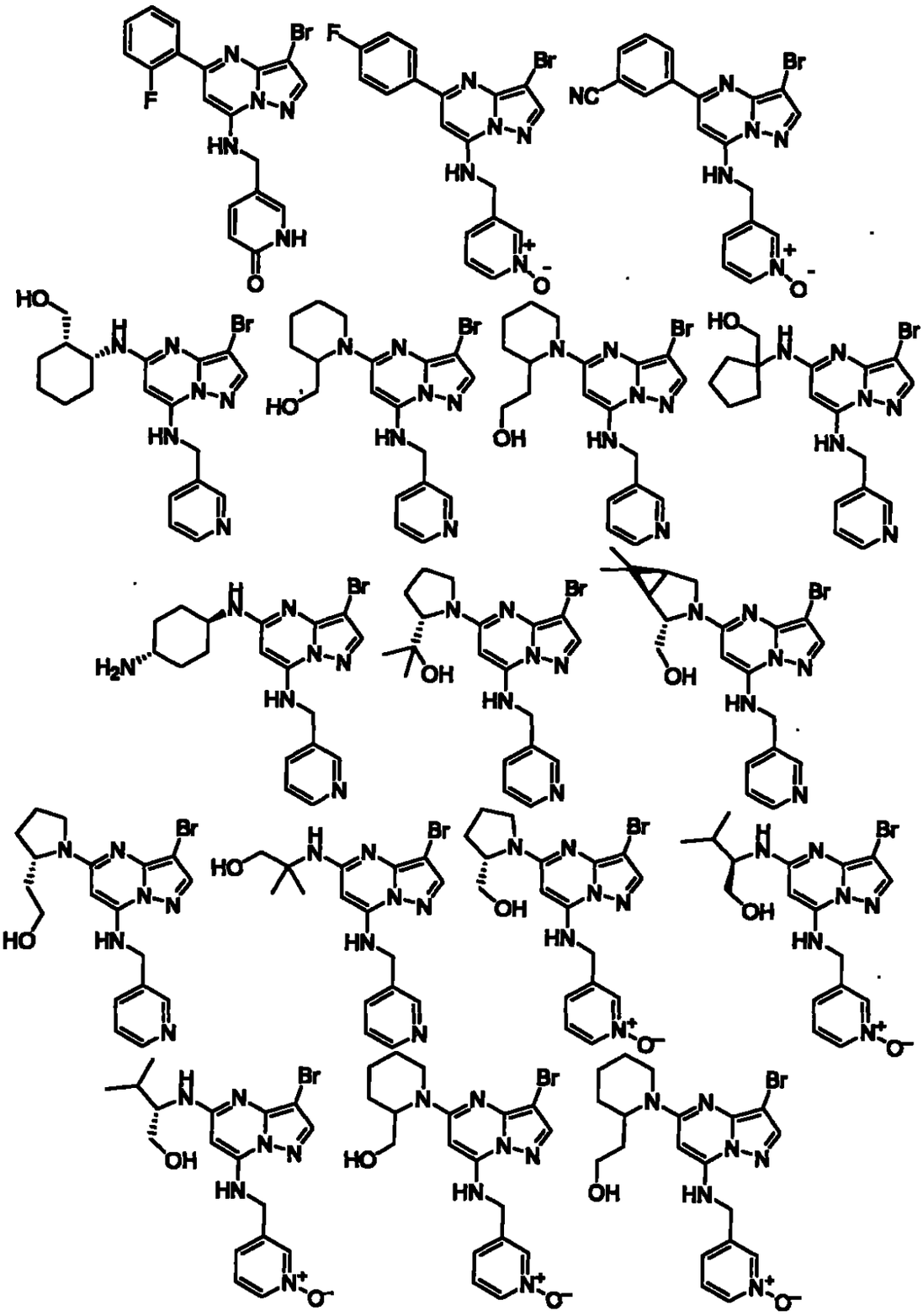
or a pharmaceutically acceptable salt or solvate thereof.

29. A compound of the formula:

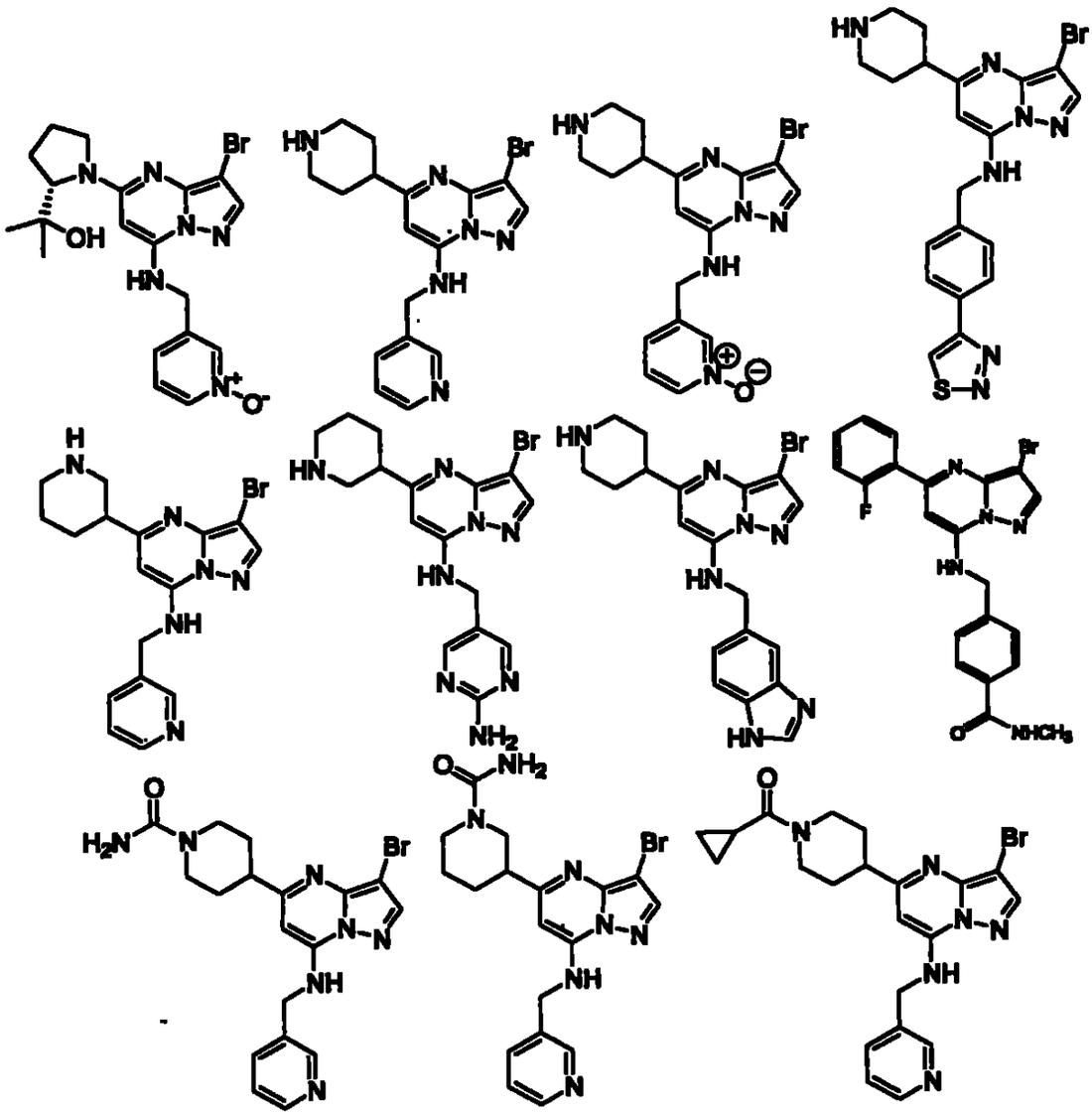


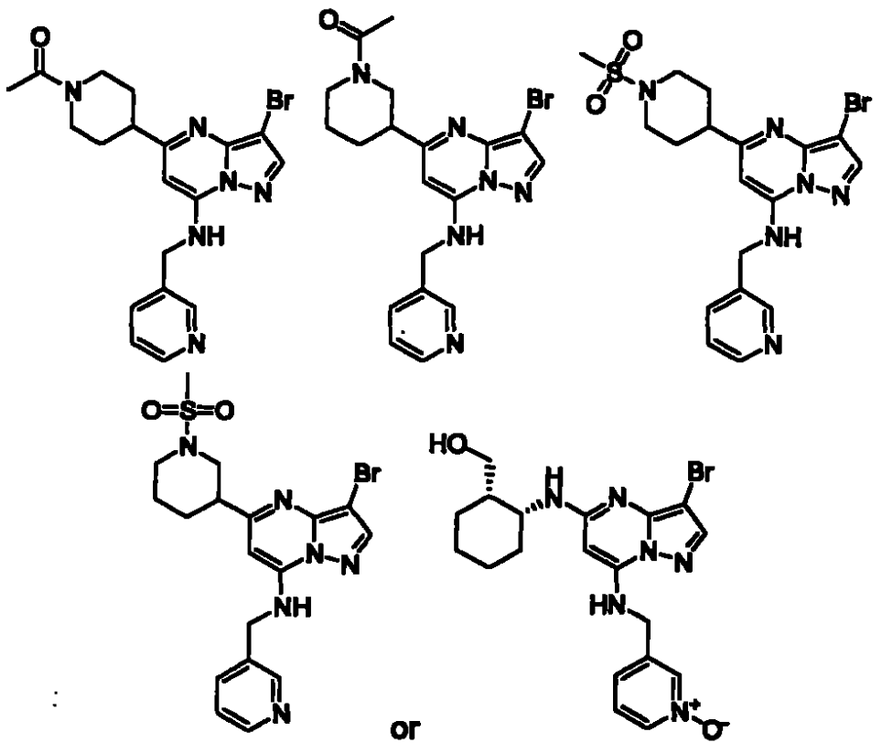
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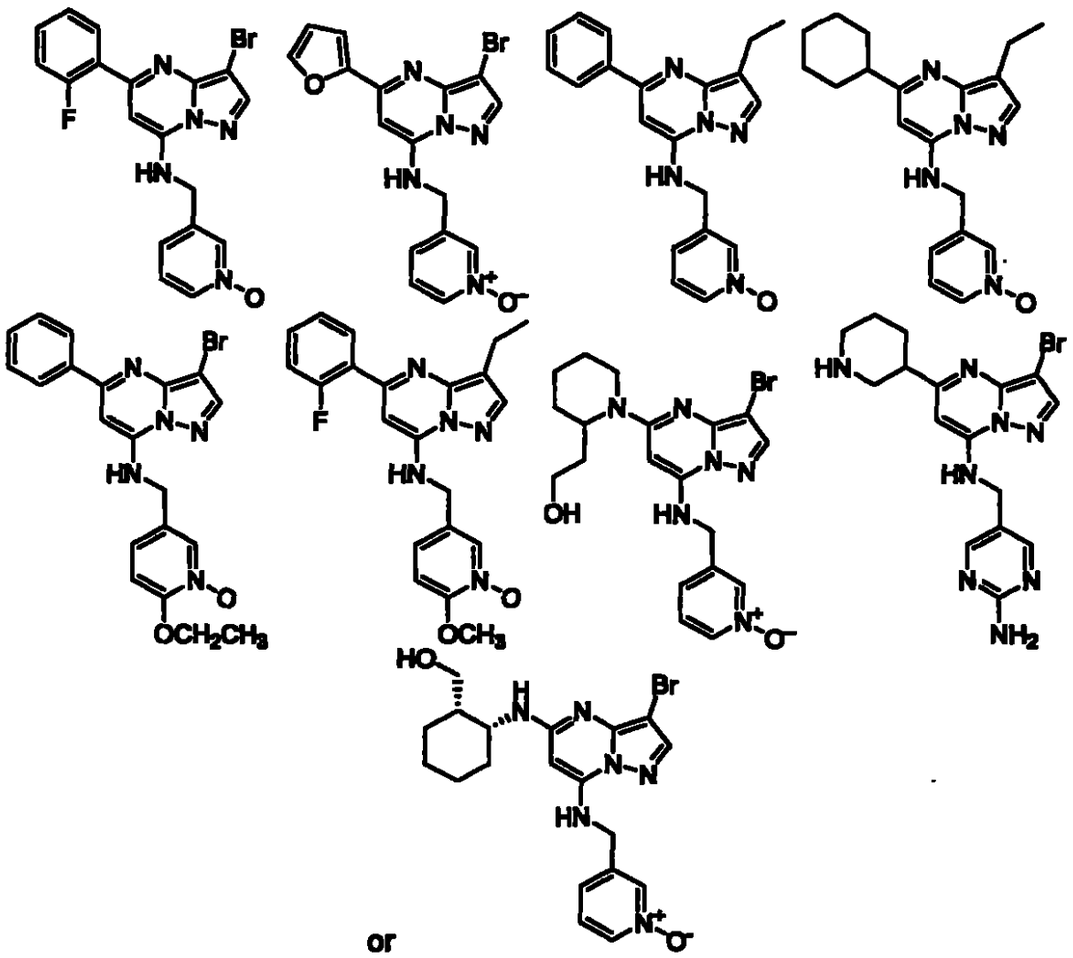




or

or a pharmaceutically acceptable salt or solvate thereof.

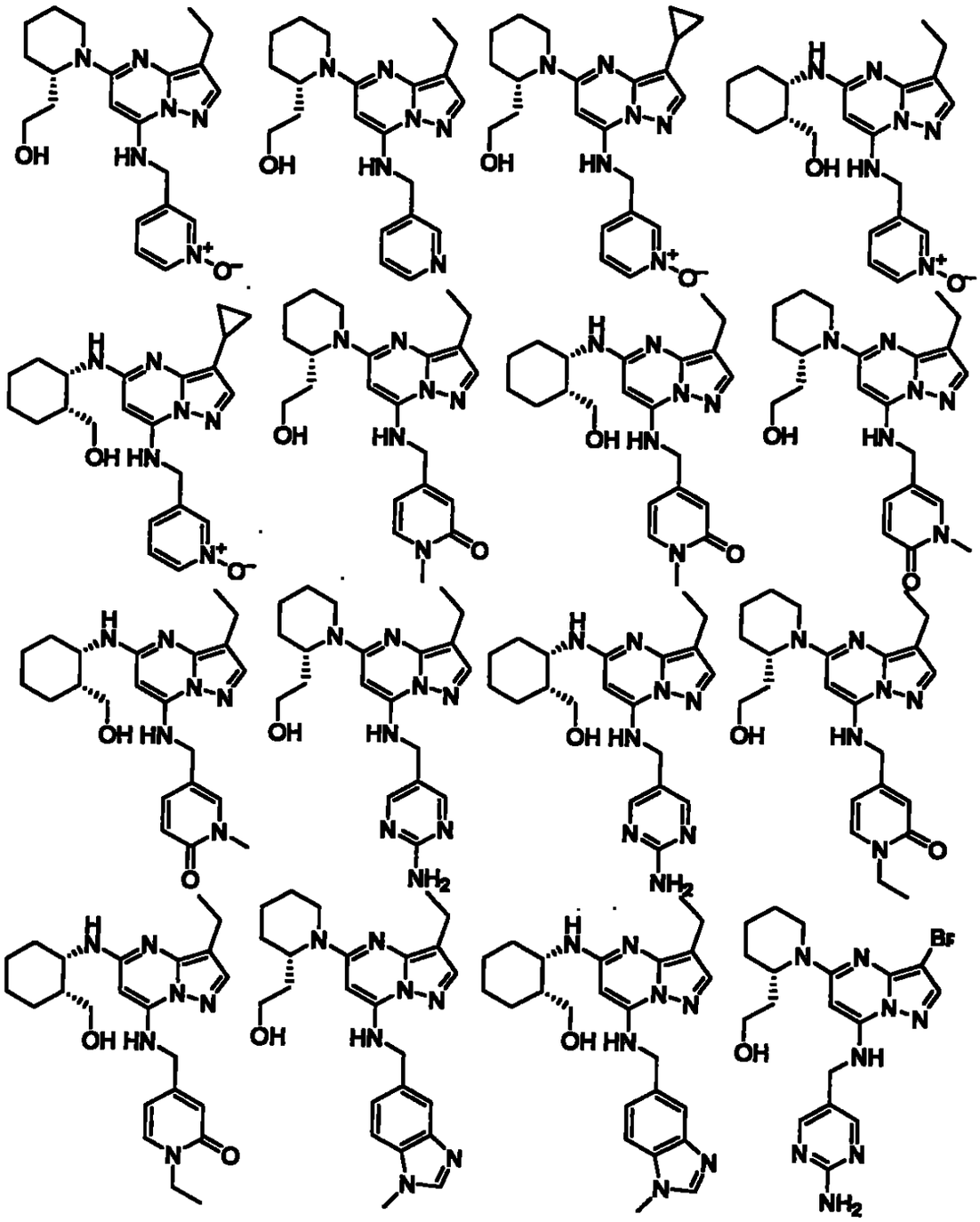
30. A compound of the formula:

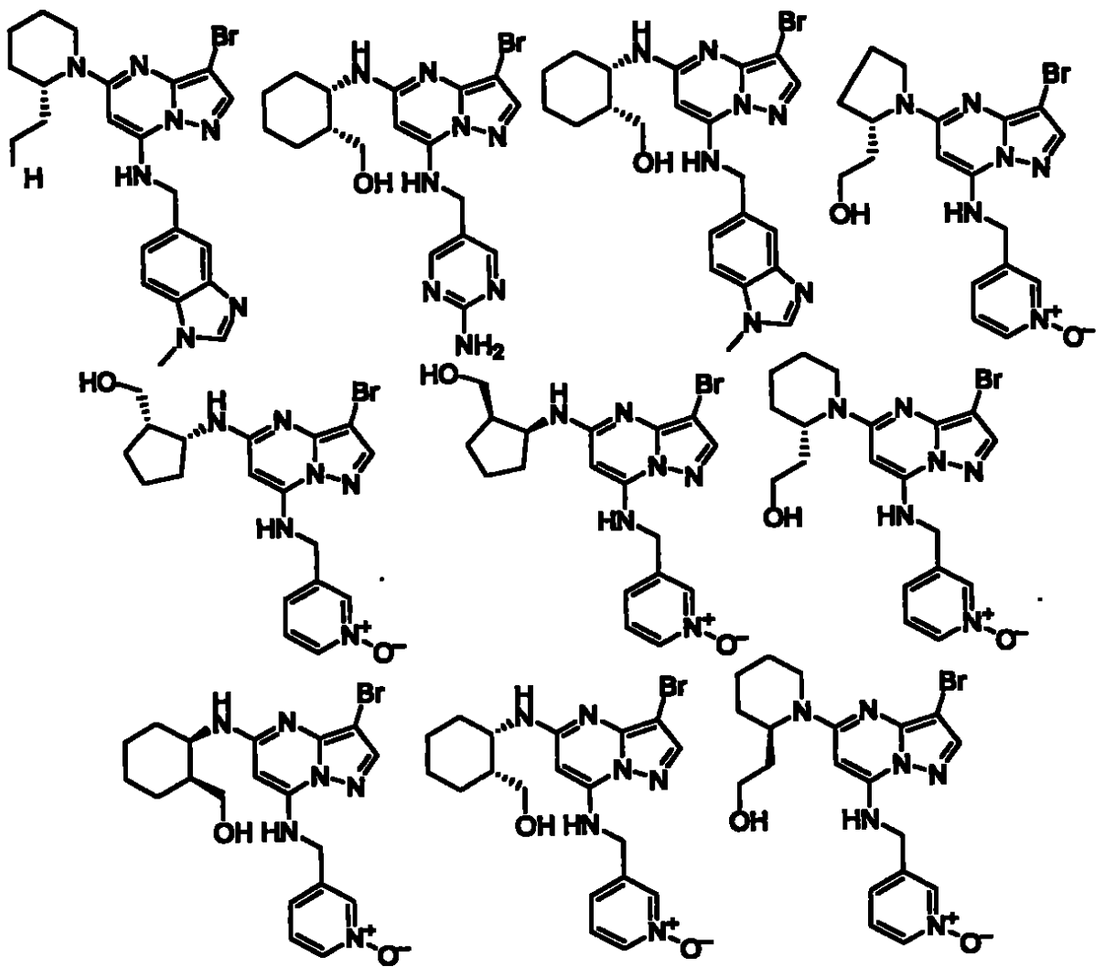


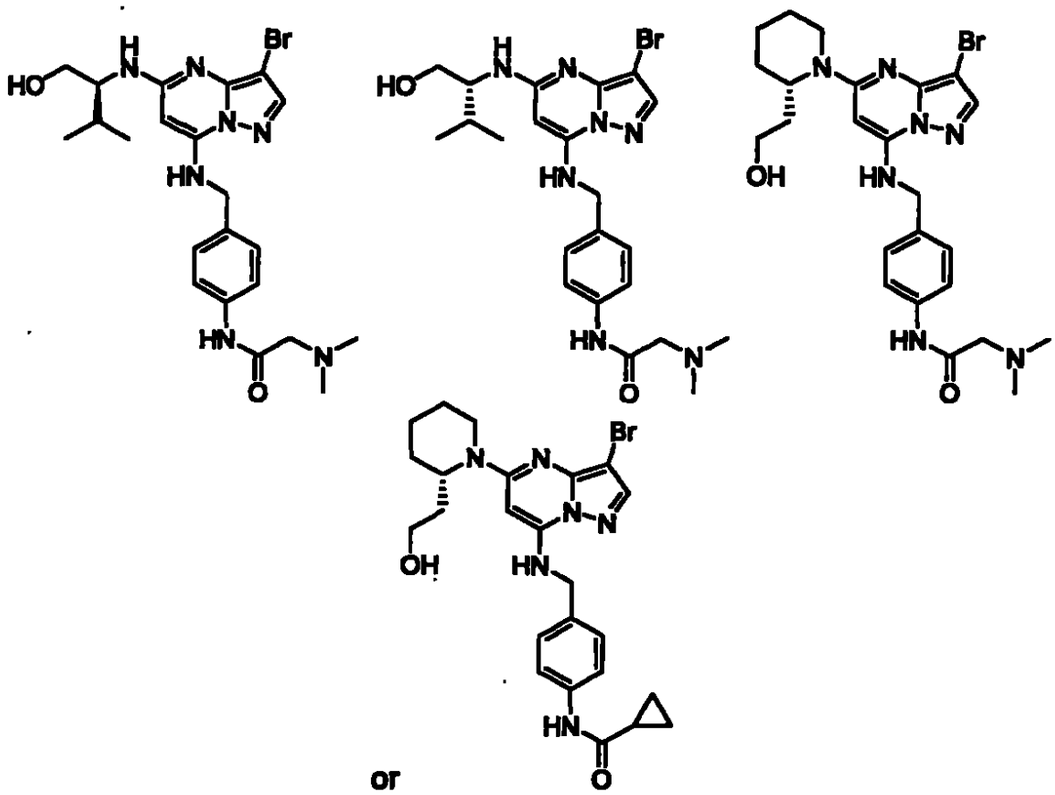
or

or a pharmaceutically acceptable salt or solvate thereof.

31. A compound of the formula:







or

or a pharmaceutically acceptable salt or solvate thereof.

32. A method of inhibiting one or more cyclin dependent kinases, comprising administering a therapeutically effective amount of at least one compound of claim 1 to a patient in need of such inhibition.

33. A method of treating one or more diseases associated with cyclin dependent kinase, comprising administering a therapeutically effective amount of at least one compound of claim 1 to a patient in need of such treatment.

34. The method of claim 33, wherein said cyclin dependent kinase is CDK2.

35. The method of claim 33, wherein said cyclin dependent kinase is mitogen activated protein kinase (MAPK/ERK).

36. The method of claim 33, wherein said cyclin dependent kinase is glycogen synthase kinase 3 (GSK3beta).

37. The method of claim 33, wherein said disease is selected from the group consisting of:

cancer of the bladder, breast, colon, kidney, liver, lung, small cell lung cancer, 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 and Burkett's lymphoma;

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

fibrosarcoma, rhabdomyosarcoma;

astrocytoma, neurobiastoma, glioma and schwannomas;

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

38. 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 or solvate 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.

39. The method of claim 38, further comprising radiation therapy.

40. The method of claim 38, wherein said anti-cancer agent is selected from the group consisting of a cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, CPT-11, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, methoxtrexate, 5FU, 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, CPT-11, Anastrazole, Letrazole, Capecitabine, Reloxafine, Droloxafine, or Hexamethylmelamine..

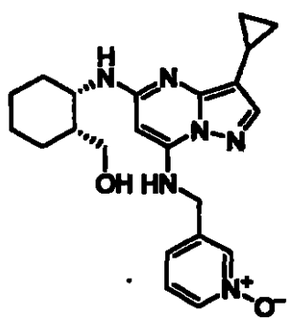
41. A pharmaceutical composition comprising a therapeutically effective amount of at least one compound of claim 1 in combination with at least one pharmaceutically acceptable carrier.

42. The pharmaceutical composition of claim 39, additionally comprising one or more anti-cancer agents selected from the group consisting of cytostatic agent, cisplatin, doxorubicin, taxotere, taxol, etoposide, CPT-11, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epothilones, tamoxifen, 5-fluorouracil, methoxtrexate, 5FU, 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, 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, CPT-11, Anastrazole, Letrazole, Capecitabine, Reloxafine, Droloxafine, or Hexamethylmelamine.

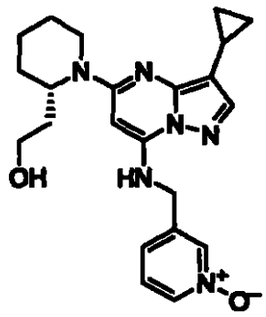
43. A compound of claim 1 in purified form.

44. A compound of the formula:



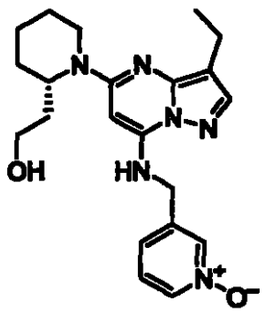
or a pharmaceutically acceptable salt or solvate thereof.

45. A compound of the formula:



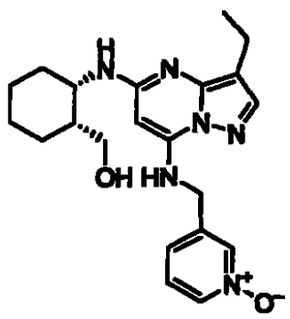
or a pharmaceutically acceptable salt or solvate thereof.

46. A compound of the formula:



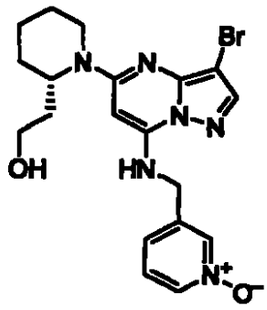
or a pharmaceutically acceptable salt or solvate thereof.

47. A compound of the formula:



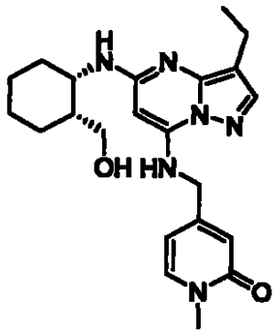
or a pharmaceutically acceptable salt or solvate thereof.

48. A compound of the formula:



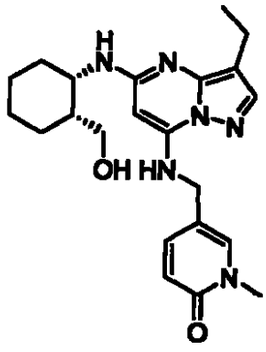
or a pharmaceutically acceptable salt or solvate thereof.

49. A compound of the formula:



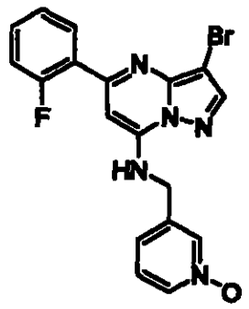
or a pharmaceutically acceptable salt or solvate thereof.

50. A compound of the formula:



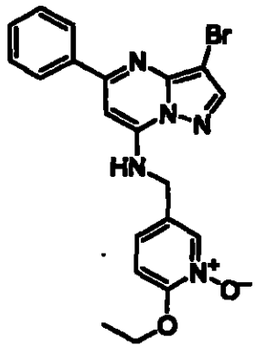
or a pharmaceutically acceptable salt or solvate thereof.

51. A compound of the formula:



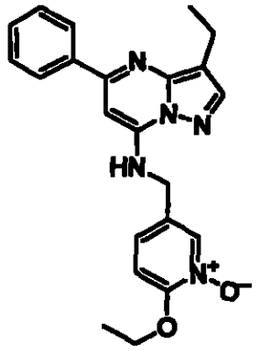
or a pharmaceutically acceptable salt or solvate thereof.

52. A compound of the formula:



or a pharmaceutically acceptable salt or solvate thereof.

53. A compound of the formula:



or a pharmaceutically acceptable salt or solvate thereof.

OC01617K1-AR. No
325 325

Memoria Descriptiva

de la

Patente de Invención

Sobre

"PIRAZOLOPIRIMIDINAS NOVEDOSAS COMO INHIBIDORES DE QUINASA CICLINA-DEPENDIENTES"

Solicitada por:

SCHERING CORPORATION * PHARMACOPEIA DRUG DISCOVERY, INC., *residentes en* ***2000 Galloping Hill Road Kenilworth, NUEVA JERSEY 07033-0530 * 3000 Eastpark Boulevard, Cranbury, NUEVA JERSEY 08512,***

E. U. DE NORTEAMERICA.

212093
US/RF

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PIRAZOLOPIRIMIDINAS NOVEDOSAS COMO INHIBIDORES DE QUINASA CICLINA-DEPENDIENTES

Referencia a Solicitudes Relacionadas

La presente solicitud es una Continuación en Parte de la Solicitud de Patente Estadounidense, Acta No. 10/654,546 presentada el 3 de Septiembre de 2003, que reivindica prioridad de las solicitudes estadounidenses de patente provisionales, Actas Nos. 60/408.027 presentada el 4 de septiembre de 2002 y 60/421,959 presentada el 29 de octubre de 2002.

Campo de la Invención

La presente invención se refiere a pirazolo[1,5-a]pirimidina compuestos útiles como inhibidores de proteína quinasa (tales como, por ejemplo, los inhibidores de las quinasas ciclina-dependientes, proteína quinasa activada por mitógenos (MAPK/ERK), quinasa de sintasa de glicogen 3(GSK3beta) y los similares), composiciones farmacéuticas que contienen los compuestos, y métodos para el tratamiento usando los compuestos y composiciones para tratar enfermedades tales como, por ejemplo, cáncer, inflamación, artritis, enfermedades virósicas, enfermedades neurodegenerativas tales como enfermedad de Alzheimer, enfermedades cardiovasculares y enfermedades fungales. La presente solicitud reivindica el beneficio de prioridad de las solicitudes de patente estadounidenses provisionales, Actas No. 60/408.027 presentada el 4 de septiembre de 2002, y Acta No. 60/421.959 presentada el 29 de octubre de 2002.

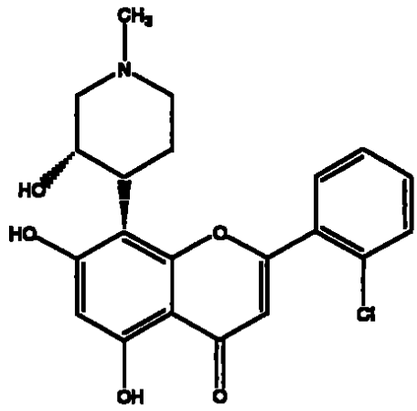
Antecedentes de la Invención

Los inhibidores de proteína quinasa incluyen quinasas tales como, por ejemplo, los inhibidores de las quinasas ciclina-dependientes las quinasas ciclina-dependientes (CDKs), proteína quinasas activas por mitógenos (MAPK/ERK), quinasa de glicogen sintasa 3 (GSK3beta), y los similares. Los inhibidores de proteína quinasa son descriptas, por ejemplo, en M. Hale *et* al en WO02/22610 A1 y por Y. Mettey *et* al en *J. Med. Chem.*, (2003) 46 222-236. Las quinasas ciclina-dependientes son quinasas de proteína de serina/treonina, que son la fuerza impulsora detrás del ciclo celular y de la proliferación celular. Las CDK individuales, tales como, CDK1, CDK2, CDK3, CDK4, CDK5, CDK6 y CDK7,

CDK8 y similares, desempeñan roles distintos en el progreso del ciclo celular y se pueden clasificar como enzimas de fase G1, S, o G2M. La proliferación sin control es una marca distintiva de las células cancerígenas y la falta de regulación de la función de la CDK se produce con mucha frecuencia en varios tumores sólidos importantes. CDK2 y CDK4 son de especial interés ya que sus actividades frecuentemente se encuentran reguladas de manera incorrecta en una amplia variedad de cánceres humanos. La actividad de CDK2 se requiere para el progreso a través de la fase G1 a la fase S del ciclo celular, y CDK2 es uno de los componentes claves del punto de verificación de G1. Los puntos de verificación sirven para mantener la secuencia adecuada de los eventos del ciclo celular y permiten que la célula responda a insultos o a señales proliferativas. mientras que la pérdida del control adecuado del punto de verificación en células cancerígenas contribuye con la tumorgénesis. La ruta CDK2 influencia la tumorgénesis en el nivel de la función supresora del tumor (por ej, p52, RB y p27) y activación oncogénica (ciclina E). Muchos informes demostraron que el activador, ciclina E, y el inhibidor, p27, de CDK2 estarán sobre o subexpresados, respectivamente, en el cáncer de mama, colon, pulmón de células no pequeñas, gástrico, de próstata, de vejiga, linfoma no Hodgkin, ovarios y otros cánceres. Se demostró que sus expresiones alteradas se correlacionan con los niveles incrementados de actividad de CDK2 y la poca supervivencia total. Esta observación hace que CDK2 y sus rutas reguladoras sean objetivos obligados para los años de desarrollo, se reportaron una cantidad de moléculas pequeñas orgánicas competitivas de 5'-trifosfato de adenosina (ATP) al igual que péptidos en la literatura como inhibidores de CDK para el tratamiento potencial de cáncerres. La patente estadounidense U.S. 6.413.974, col. 1, línea 23- col. 15, línea 10 ofrece una buena descripción de varias CDKs y su relación con varios tipos de cáncer.

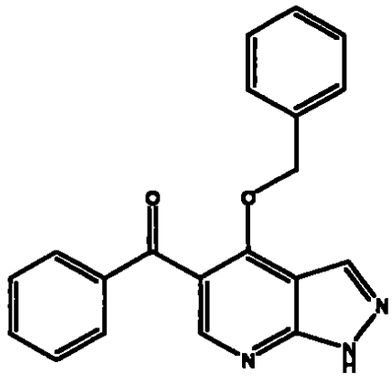
Los inhibidores de CDK son conocidos. Por ejemplo, flavopiridol (Fórmula I) es un inhibidor no selectivo de CDK que se encuentra actualmente sujeto a ensayos clínicos humanos, A. M. Sanderowicz *et al*, *J. Clin. Oncol.* (1998) 16, 2986-2999.

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Fórmula I

Otros inhibidores conocidos de las CDK 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 patente estadounidense 6.107.305 describe ciertos pirazolo[3,4-b] piridina compuestos como inhibidores CDK. Un compuesto ilustrativo de la patente '305 posee la Fórmula II:



Fórmula II

K. S. Kim *et al*, *J. Med. Chem.* 45 (2002) 3905-3927 y WO 02/10162 revelan ciertos aminotiazol compuestos como inhibidores CDK.

Se conocen las pirazolopirimidinas. Por ejemplo, WO92/18504, WO02/50079, WO95/35298, WO02/40485, EP94304104,6, EP0628559 (equivalente a Patentes Estadounidenses 5.602.136, 5.602.137 y 5.571.813), Patente Estadounidense 6,383,790, *Chem. Pharm. Bull.*, (1999) 47 928, *J. Med. Chem.*, (1977) 20, 296, *J. Med. Chem.*, (1976) 19 517 y *Chem. Pharm. Bull.*, *(1962)* 10 620 revelan varias pirazolopirimidinas. Otras publicaciones de interés son: WO 03/101993 (publicada el 11 de diciembre de 2003), WO 03/091256

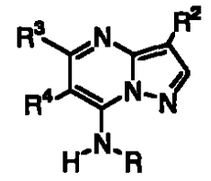
(publicada el 6 de noviembre de 2003), y DE 10223917 (publicada el 11 de diciembre de 2003).

Existe la necesidad de nuevos compuestos, formulaciones, tratamientos y terapias para tratar enfermedades y trastornos asociados con las CDK. Por consiguiente, es un objeto de la presente invención proveer compuestos útiles para el tratamiento o prevención o alivio de dichas enfermedades y trastornos.

Resumen de la Invención

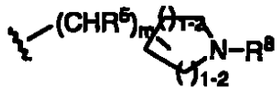
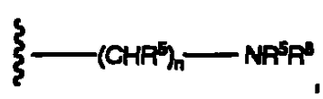
En sus varias realizaciones, la presente invención provee una clase novedosa de pirazolo[1,5-a]pirimidina compuestos como inhibidores de of quinasas ciclina-dependientes, métodos para preparar dichos compuestos, composiciones farmacéuticas que comprenden uno o más de tales compuestos, métodos para preparar formulaciones farmacéuticas que comprenden que comprenden uno o más de tales compuestos, y métodos de tratamiento, prevención, inhibición o alivio de una o más enfermedades asociadas con las CDKs usando dichos compuestos o composiciones farmacéuticas.

En un aspecto, la presente solicitud revela un compuesto, o sales aceptables para uso farmacéutico o solvatos de dicho compuesto, dicho compuesto posee la estructura general que se muestra en la Fórmula III:

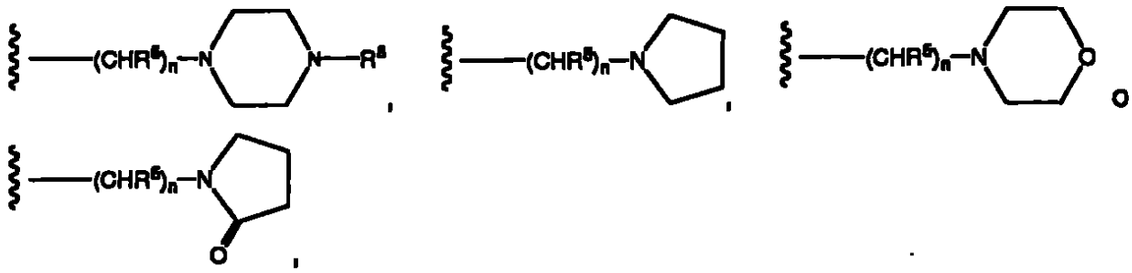


Fórmula III

en el cual:

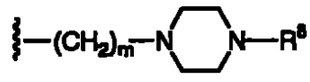
R es H, alquilo, alquenilo, alquinilo, arilalquilo, arilalquenilo, cicloalquilo, cicloalquilalquilo, alquenilalquilo, alquinilalquilo, heterociclilo, heterociclilalquilo, heteroarilalquilo (incluyendo el N-óxido de dicho heteroarilo), -$(CHR^5)_n$-arilo, -$(CHR^6)_n$-heteroarilo,  , 

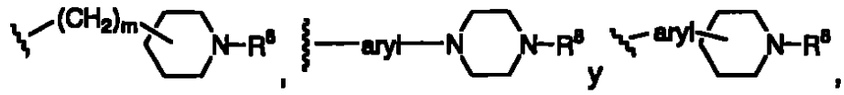
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donde cada uno de dicho alquilo, alquenilo, alquinilo, arilo, cicloalquilo, heterociclilo, y heteroarilo puede ser no sustituido o sustituido opcionalmente con uno o más restos que pueden ser iguales o diferentes, cada resto siendo seleccionado independientemente 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 se selecciona del grupo que consiste en 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 se seleccionan independientemente del listado de R^9 que se muestra adelante, arilo sustituido con 1-3 arilo o grupos heteroarilo que pueden ser iguales o diferentes y se seleccionan independientemente 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 se seleccionan independientemente de grupos fenilo, piridilo, tiofenilo, furanilo y tiazolo, heteroarilo fusionado con un grupo arilo o heteroarilo,

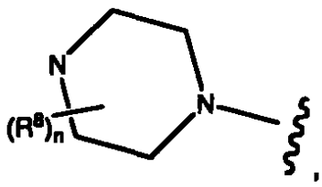


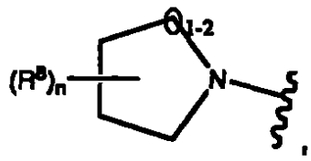


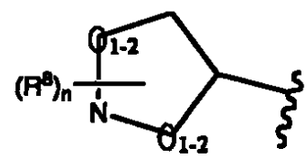
donde uno o más de los arilo y/o uno o más de los heteroarilo en las definiciones establecidas anteriormente para R^2 puede ser no sustituido o sustituido opcionalmente con uno o más restos que pueden ser iguales o diferentes, cada resto siendo seleccionado independientemente del grupo que consiste en

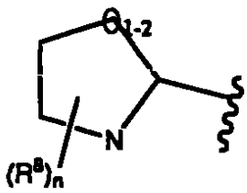
halógeno, -CN, -OR^5, -SR^5, -$S(O_2)R^6$, -$S(O_2)NR^5R^6$, -NR^5R^6, -$C(O)NR^5R^6$, CF_3, alquilo, arilo y OCF_3;

R^3 se selecciona 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,



,


,


y


donde cada uno de dicho alquilo, cicloalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heteroarilo y heteroarilalquilo para R^3 los restos heterociclilo cuyas estructuras se muestran inmediatamente arriba para R^3 pueden ser no sustituidos o sustituidos opcionalmente de manera independiente con uno o más restos que pueden ser iguales o diferentes, cada resto siendo seleccionado independientemente 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, -$S(O_2)R^6$, -$S(O_2)NR^5R^6$, -$N(R^5)S(O_2)R^7$, -$N(R^5)C(O)R^7$ y -$N(R^5)C(O)NR^5R^6$, con la salvedad que ningún carbono adyacente a un átomo de nitrógeno en un anillo heterociclilo posee un resto – OR^5;

R^4 es H, halo o alquilo;

R^5 es H, alquilo, arilo o cicloalquilo;

R^6 se selecciona del grupo que consiste en H, alquilo, alquenilo, arilo, arilalquilo, arilalquenilo, cicloalquilo, heterociclilo, heterociclilalquilo, heteroarilo, y heteroarilalquilo, donde cada uno de dicho alquilo, arilo, arilalquilo, cicloalquilo, heterociclilo, heterociclilalquilo, heteroarilo, y heteroarilalquilo puede ser no sustituido o sustituido opcionalmente con uno o más restos que pueden ser iguales o diferentes, cada resto siendo seleccionado independientemente 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} se selecciona 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 puede ser no sustituido o sustituido opcionalmente con uno o más restos que pueden ser iguales o diferentes, cada resto siendo seleccionado independientemente 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 el resto $-NR^5R^{10}$, o (ii) R^5 y R^6 en el resto $-NR^5R^6$, se pueden unir para formar un resto cicloalquilo o heterociclilo, con cada uno de dichos restos cicloalquilo o heterociclilo siendo no sustituido o siendo sustituido opcionalmente de manera independiente con uno o más grupos R^9;

R^7 se selecciona 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 ser no sustituidos o sustituidos opcionalmente de manera independiente con uno o más restos que pueden ser iguales o diferentes, cada resto siendo seleccionado independientemente 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 se selecciona del grupo que consiste en R^6, $-OR^6$, $-C(O)NR^5R^{10}$, $-S(O_2)NR^6R^{10}$, $-C(O)R^7$, $-C(=N-CN)-NH_2$, $-C(=NH)-NHR^6$, heterociclilo, y $-S(O_2)R^7$;

R^9 se selecciona del grupo que consiste en halógeno, -CN, $-NR^5R^{10}$, $-C(O_2)R^6$, $-C(O)NR^5R^{10}$, $-OR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^{10}$;

m es 0 a 4;

n es 1 a 4; y

p es 1 a 4,

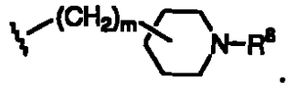
con la salvedad que cuando R^2 es fenilo, R^3 no sea alquilo, alquinilo o halógeno, y que cuando R^2 es arilo, R no sea  , y con la salvedad adicional que cuando R es arilalquilo, entonces cualquier sustituyente heteroarilo en el arilo de dicho arilalquilo contiene al menos tres heteroátomos.

Los compuestos de Fórmula III pueden ser útiles como inhibidores de quinasa proteínas y pueden ser útiles en el tratamiento y prevención de enfermedades proliferativas, por ejemplo, cáncer, inflamación y artritis. También pueden ser útiles para el tratamiento de enfermedades neurodegenerativas tales como enfermedad de Alzheimer, enfermedades cardiovasculares, enfermedades virósicas y fungales.

Descripción detallada

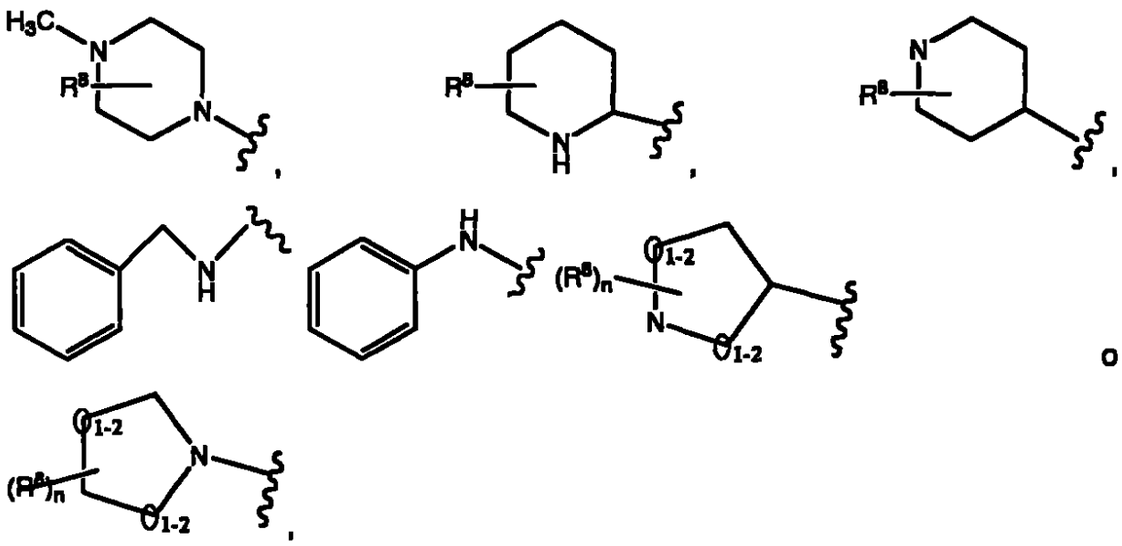
En una realización, la presente invención revela pirazolo[1,5-a]pirimidina compuestos que se representan mediante la Fórmula estructural III, o una sal aceptable para uso farmacéutico o solvato del mismo, en los cuales los diversos restos son según se describió anteriormente.

En otra realización, R es $-(CHR^5)_n$-arilo, $-(CHR^5)_n$-heteroarilo, $-(CHR^5)_n$-heteroarilo (con dicho heteroarilo siendo sustituido con un heteroarilo adicional, igual o diferente), $-(CHR^5)_n$-heterociclilo (con dicho heterociclilo siendo sustituido con un heterociclilo adicional, igual o diferente), o



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 dicho alquilo, anio, heteroarilo, cicloalquilo y las estructuras heterociclilo que se muestran inmediatamente arriba para R^3 se sustituyen opcionalmente con uno p más restos que pueden ser iguales o diferentes, cada resto siendo seleccionado independientemente 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 salvedad que ningún carbono adyacente a un átomo de nitrógeno en un anillo heterociclilo posee un resto –OR^5.

En otra realización, R^4 es H o alquilo inferior.

En otra realización, R^5 es H, alquilo inferior o cicloalquilo.

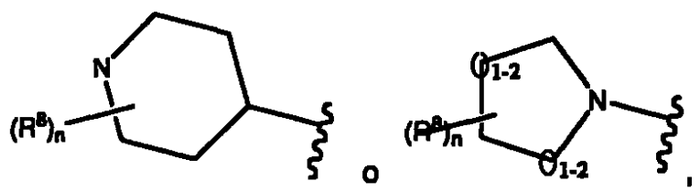
En otra realización, n es 1 a 2.

En una realización adicional, R es -(CHR^6)$_n$-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,



donde dichos alquilo, arilo y restos heterociclilo que se muestran inmediatamente arriba para R^3 se sustituyen opcionalmente con uno o más restos que pueden ser

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iguales o diferentes, cada resto siendo seleccionado independientemente 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.

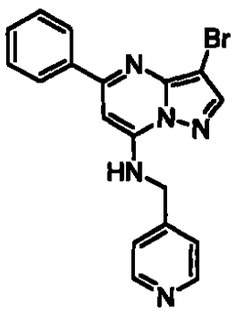
En una realización adicional, R^6 es alquilo o hidroxialquilo.

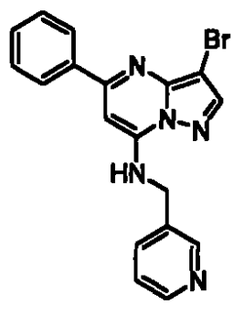
En una realización adicional, n es 1.

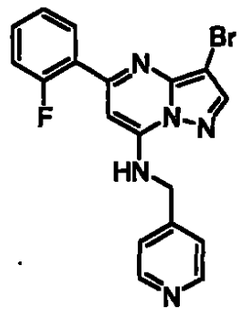
En una realización adicional, p es 1 o 2.

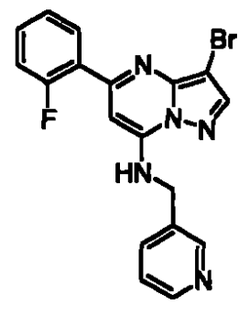
Otra realización revela los compuestos inventivos que se muestran en la Tabla 1, que exhibió actividad inhibidora de CDK2 de alrededor de 0,0001μM a > alrededor de 5 μM. Los métodos de ensayo se describen más adelante (desde la página 333 en adelante).

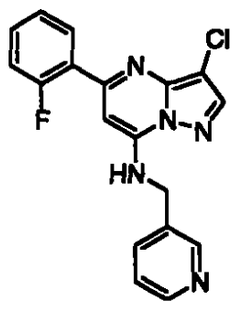
Tabla 1

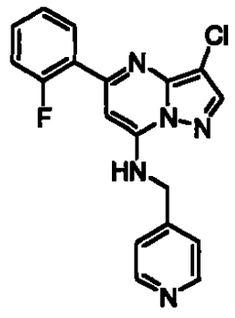


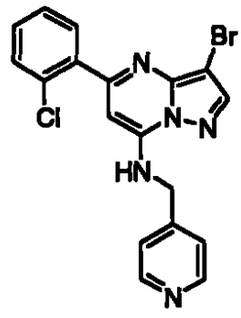


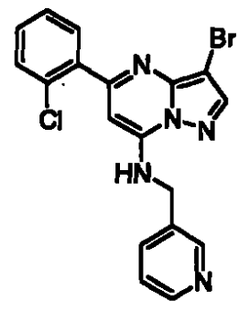


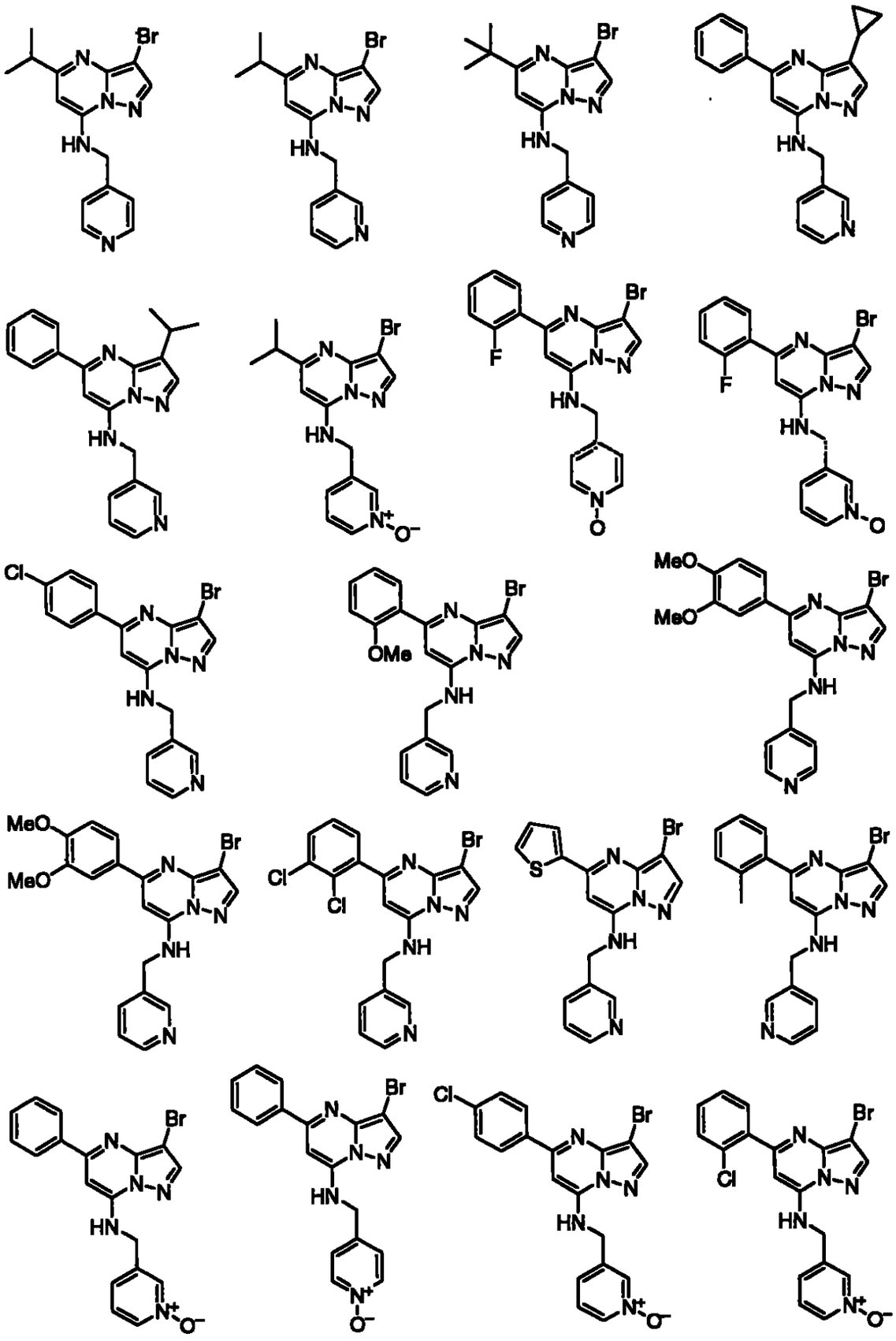


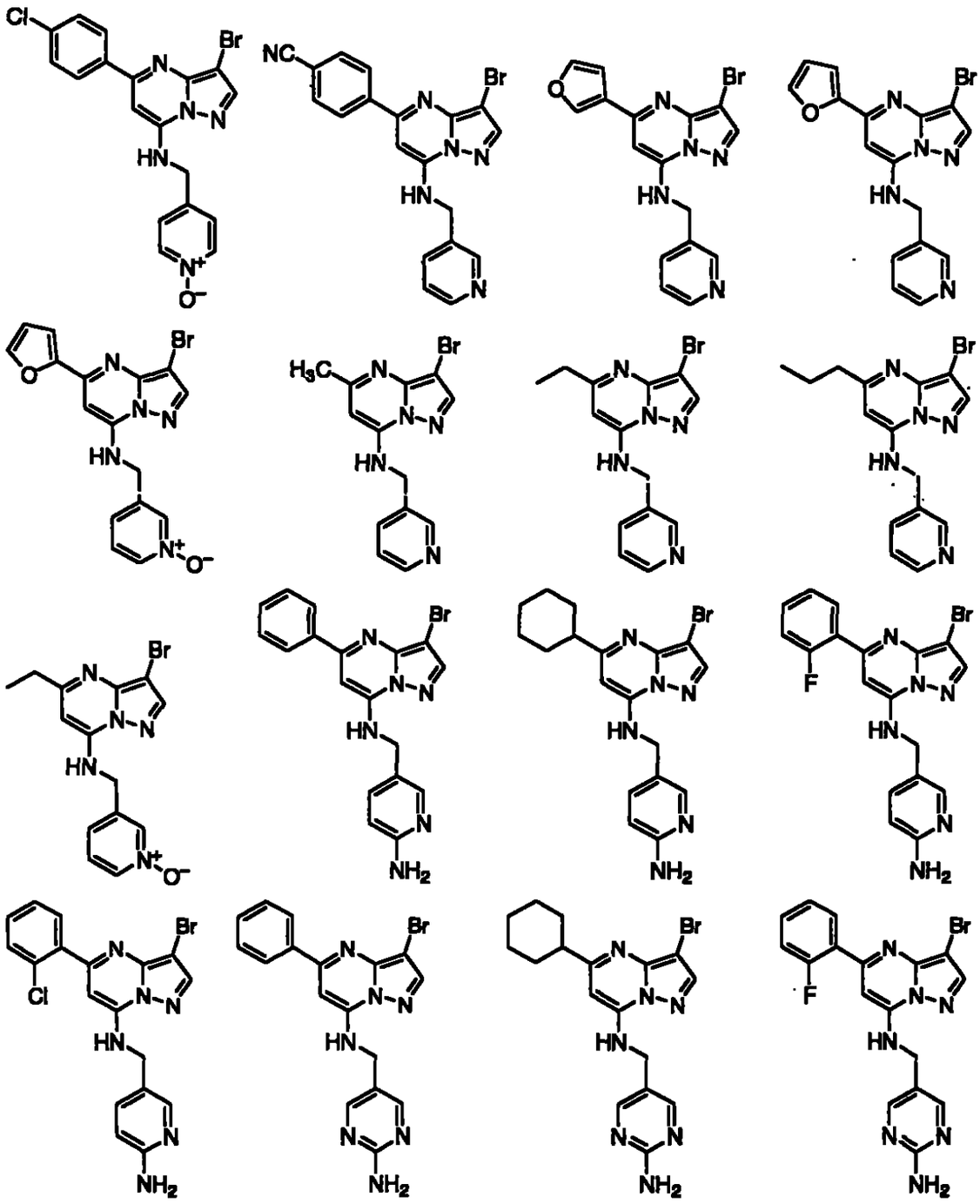


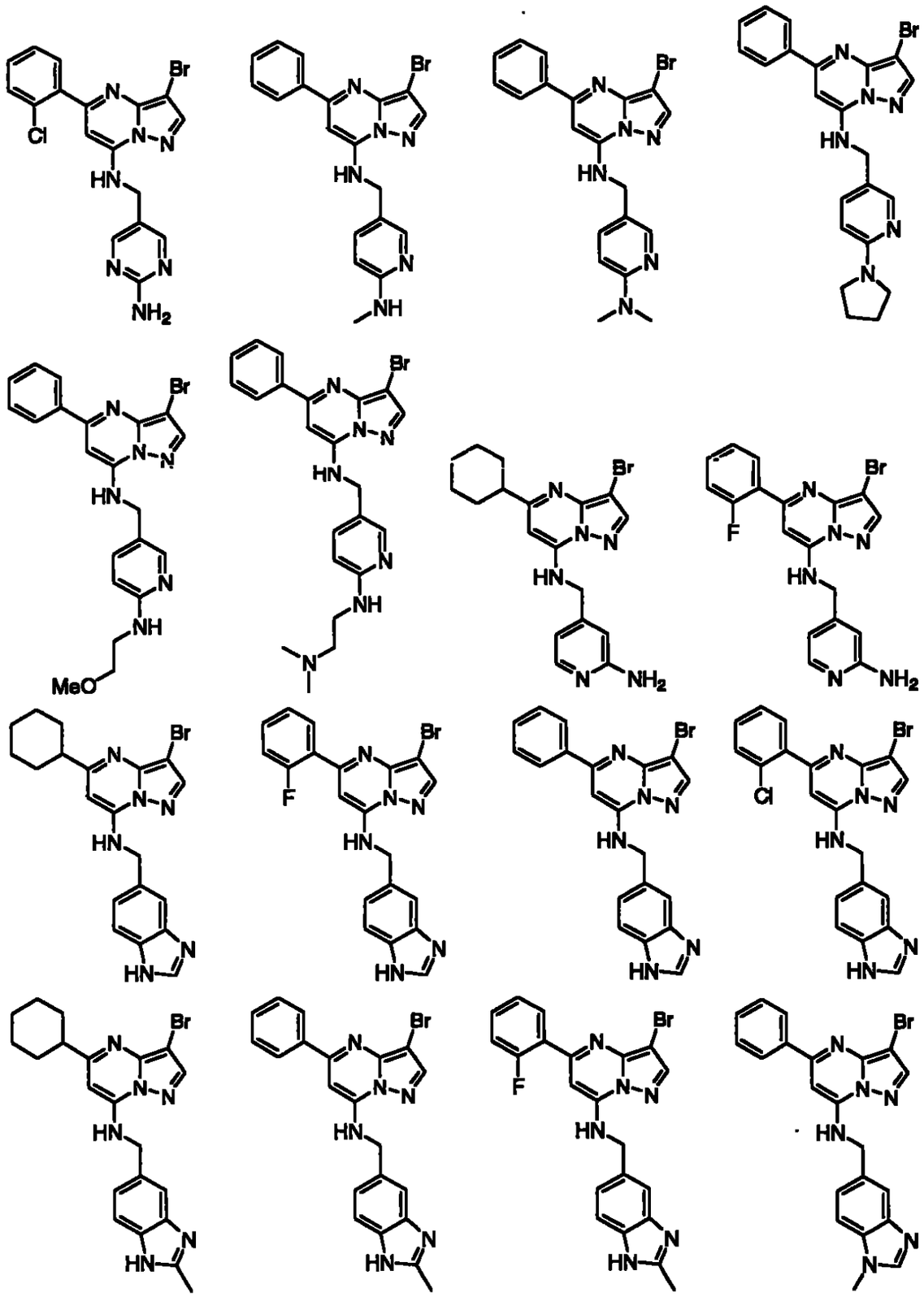


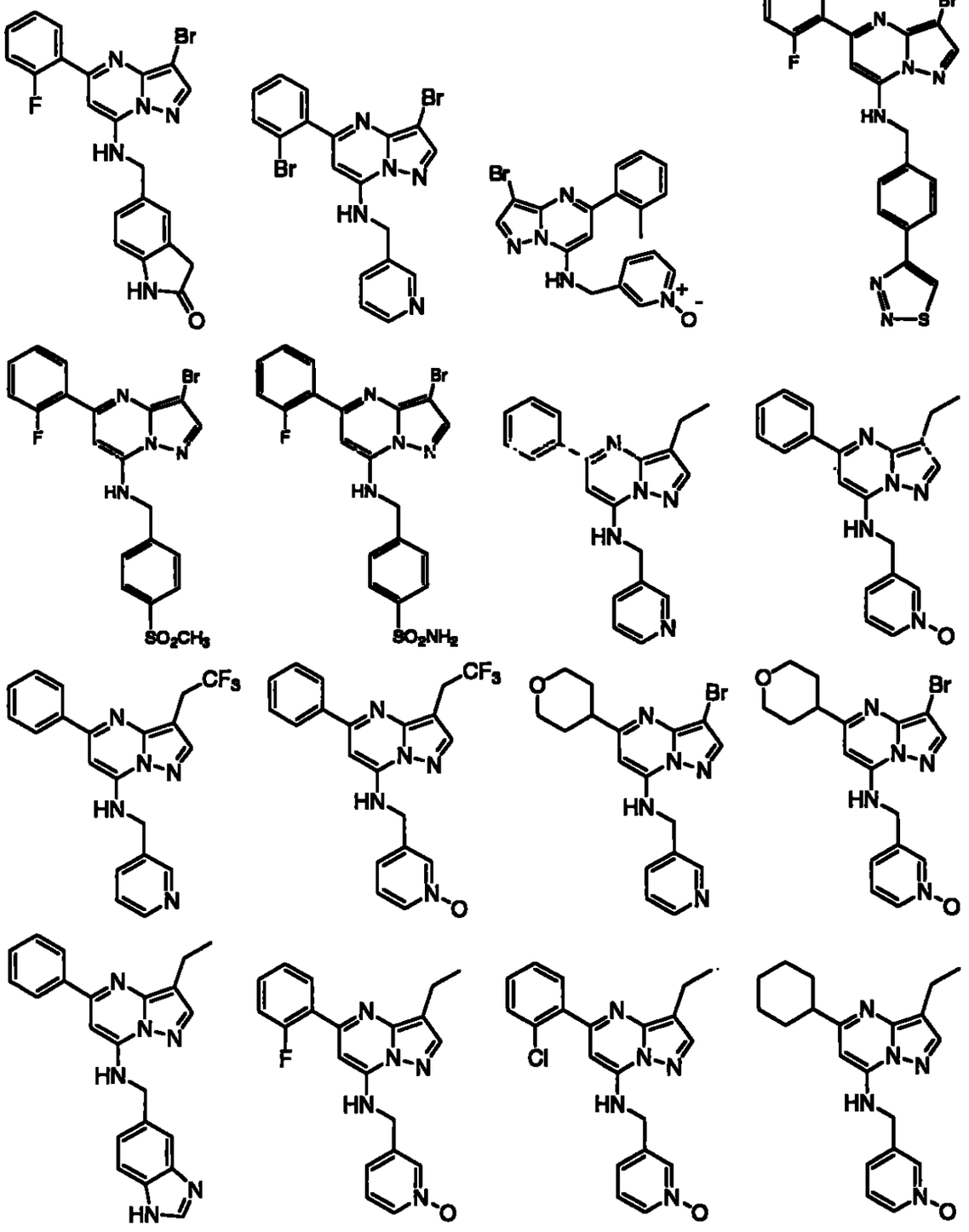


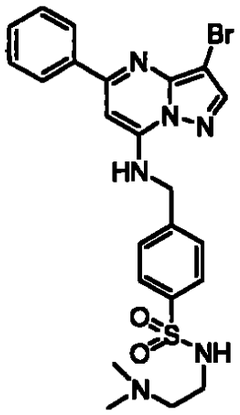
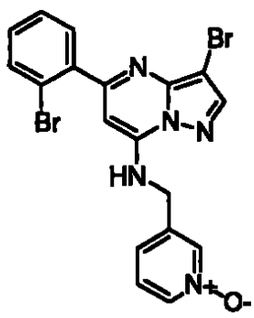
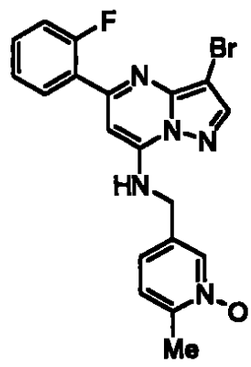
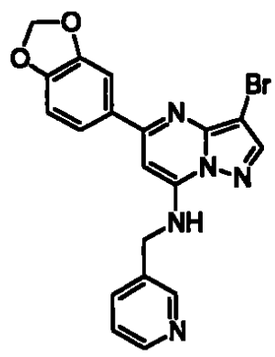
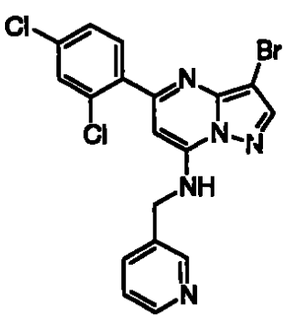
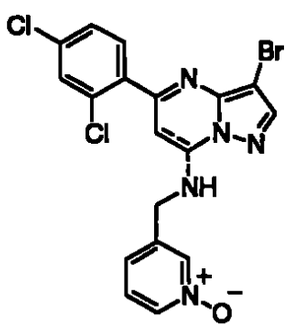
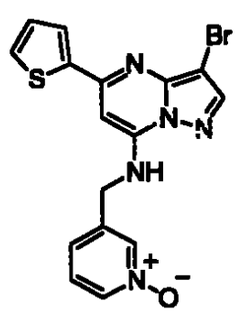
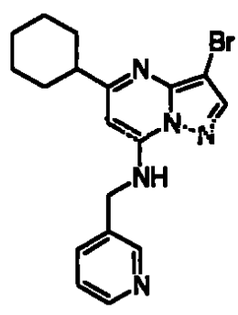
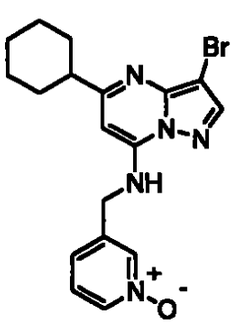
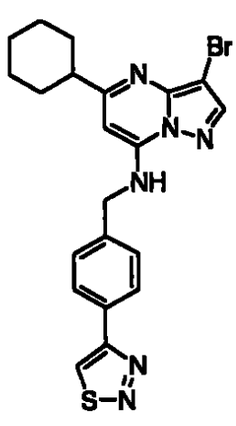
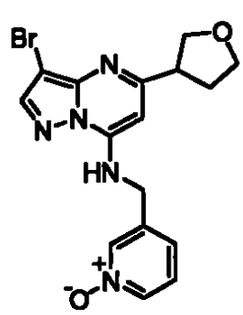
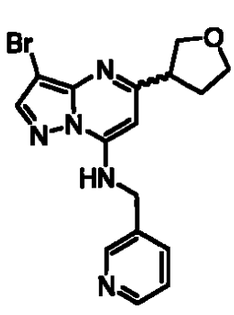
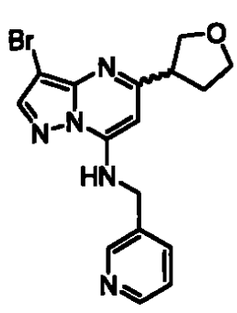
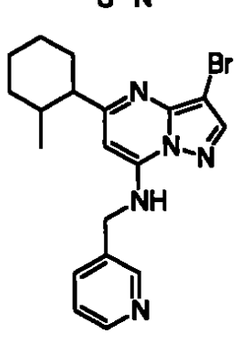
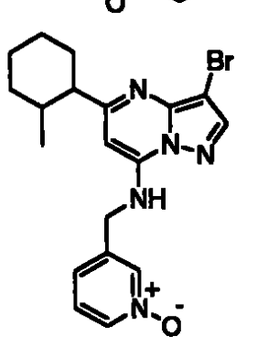
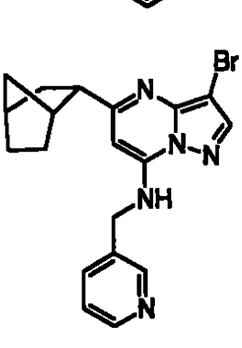


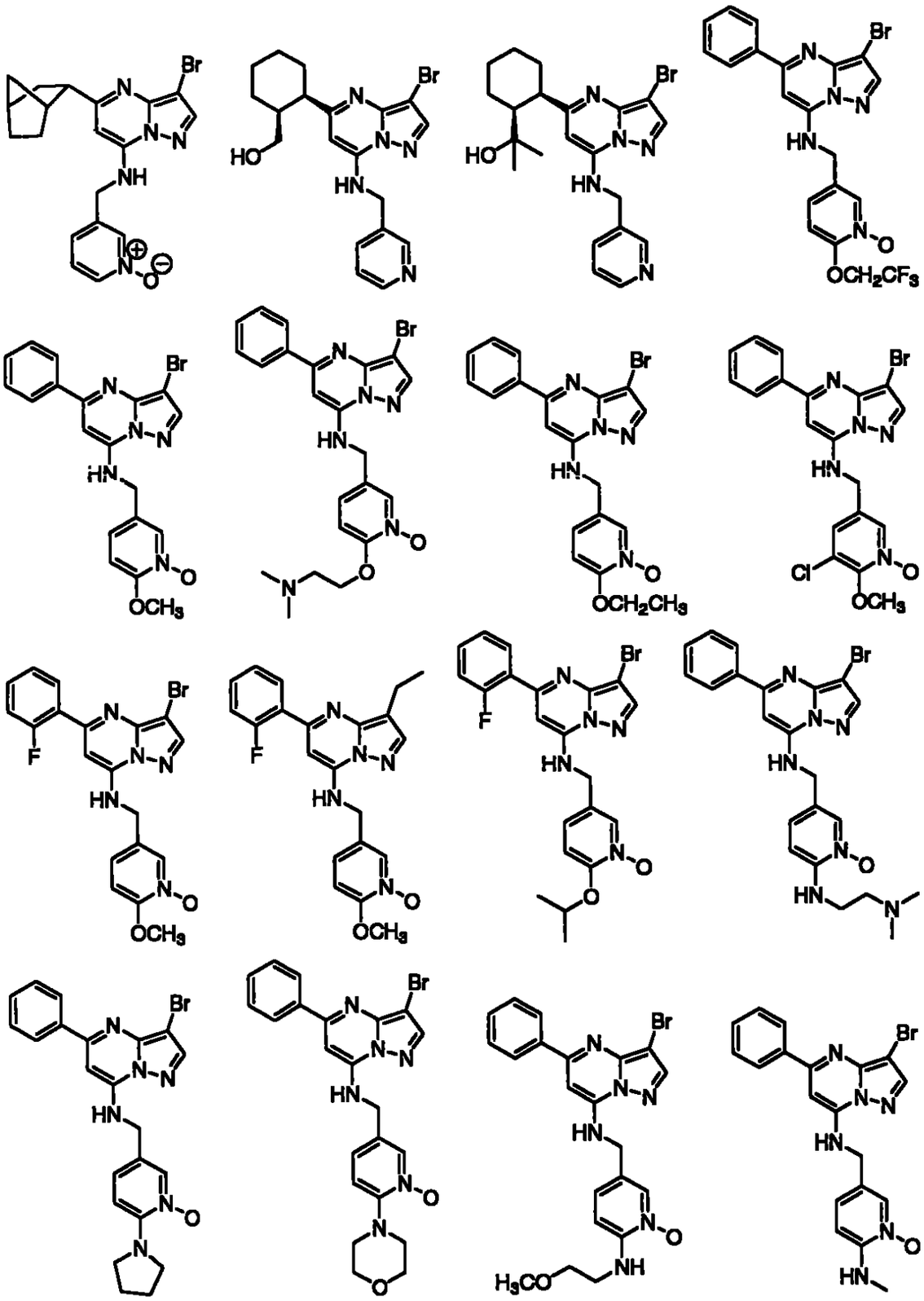


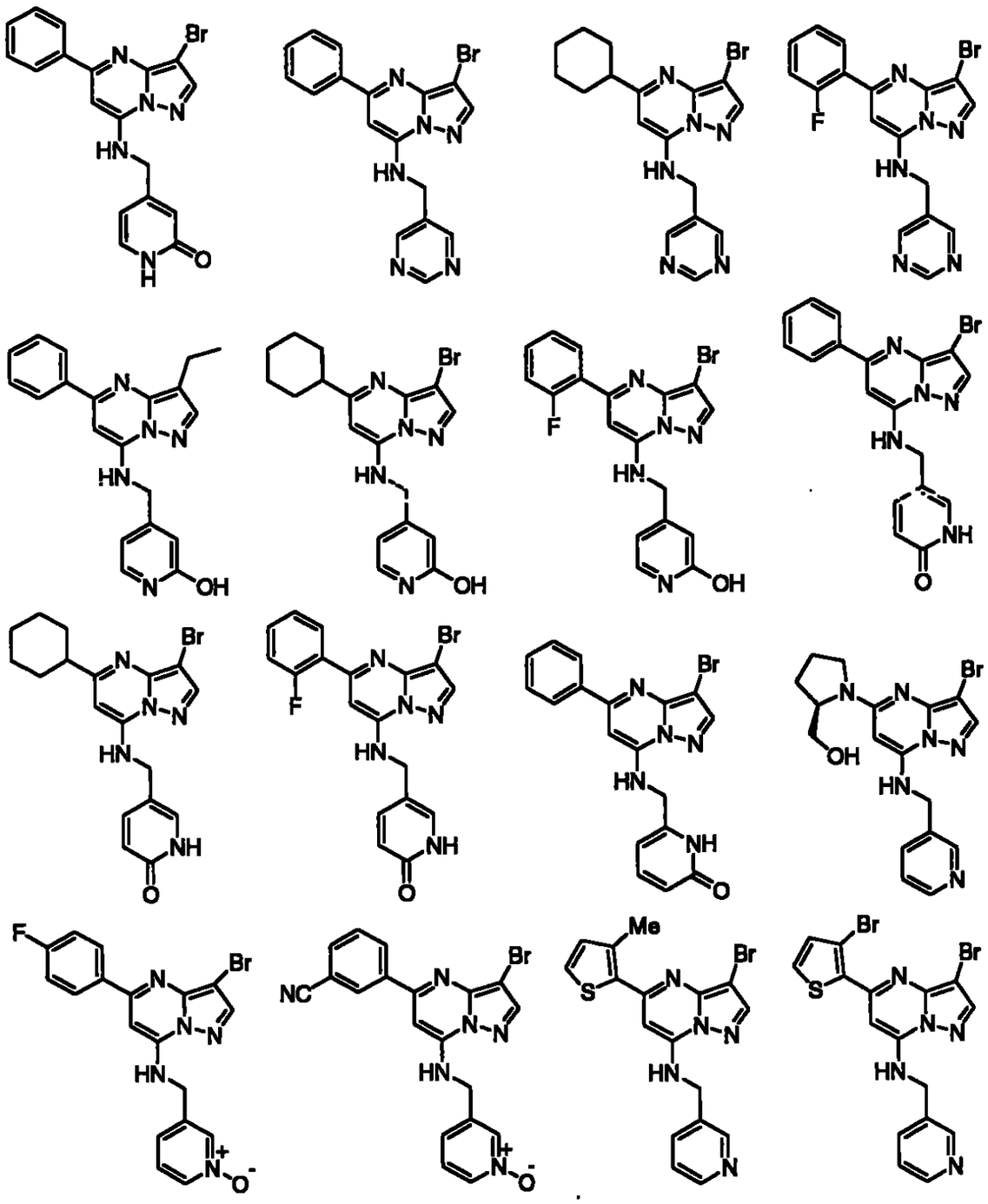


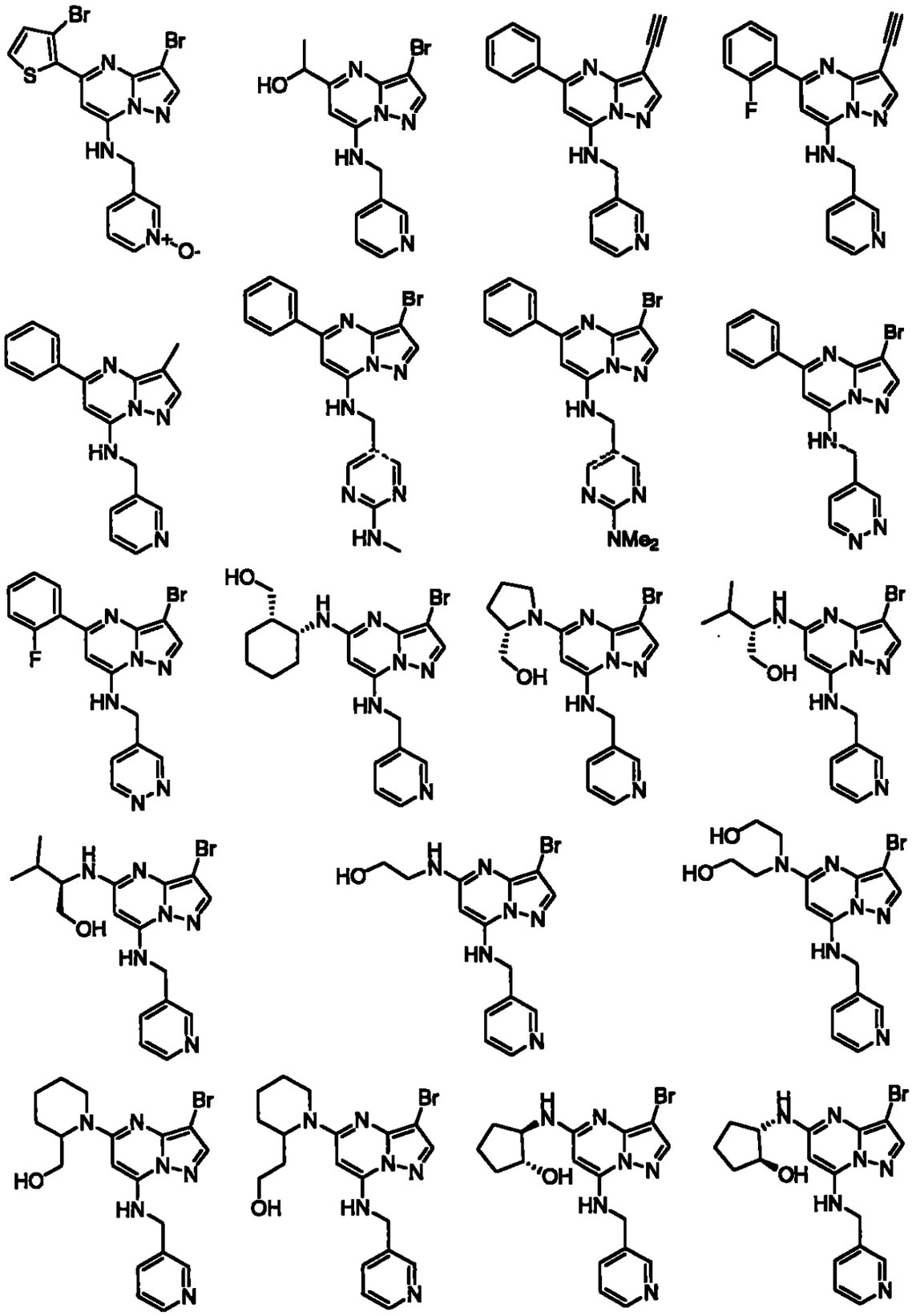


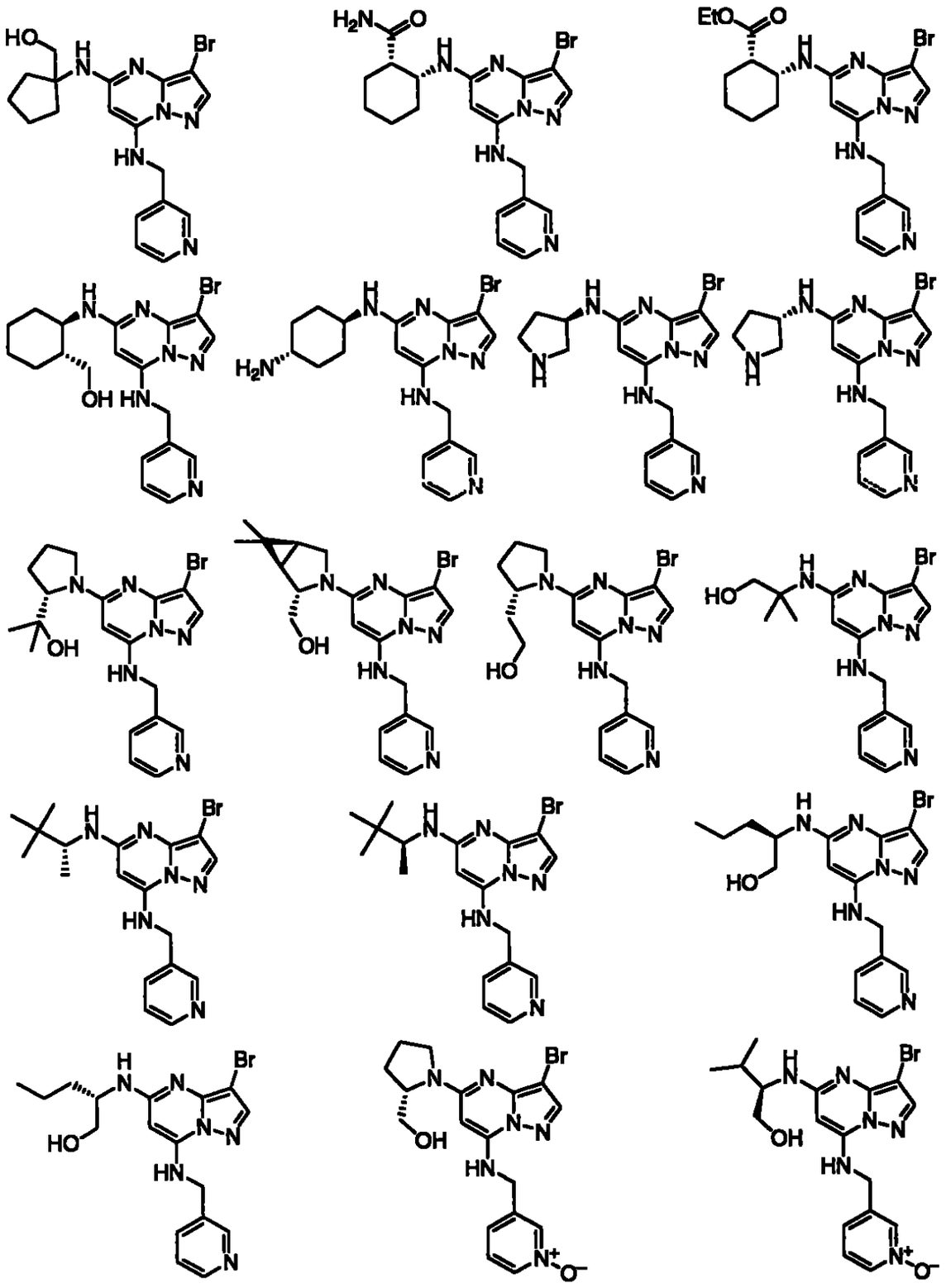


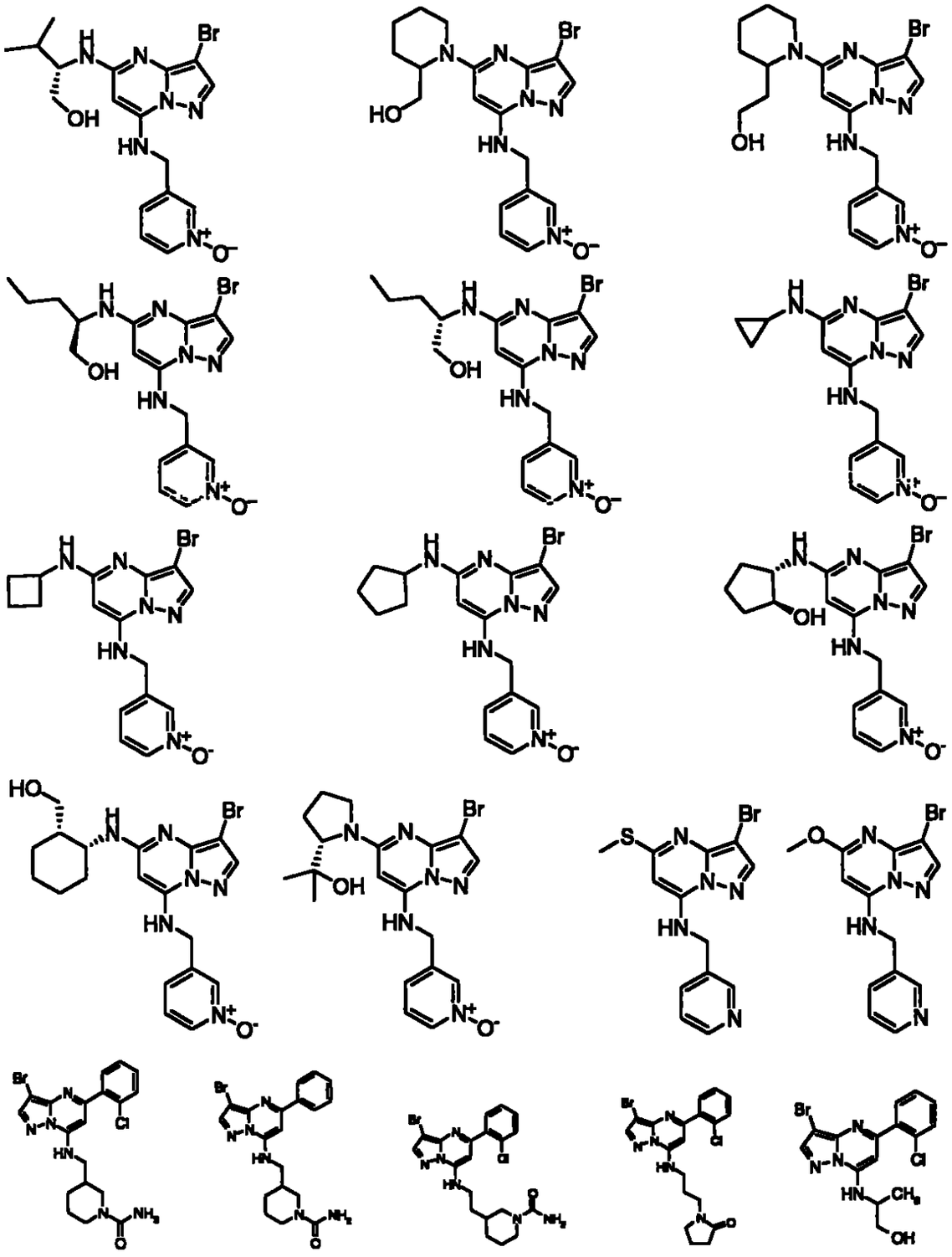



















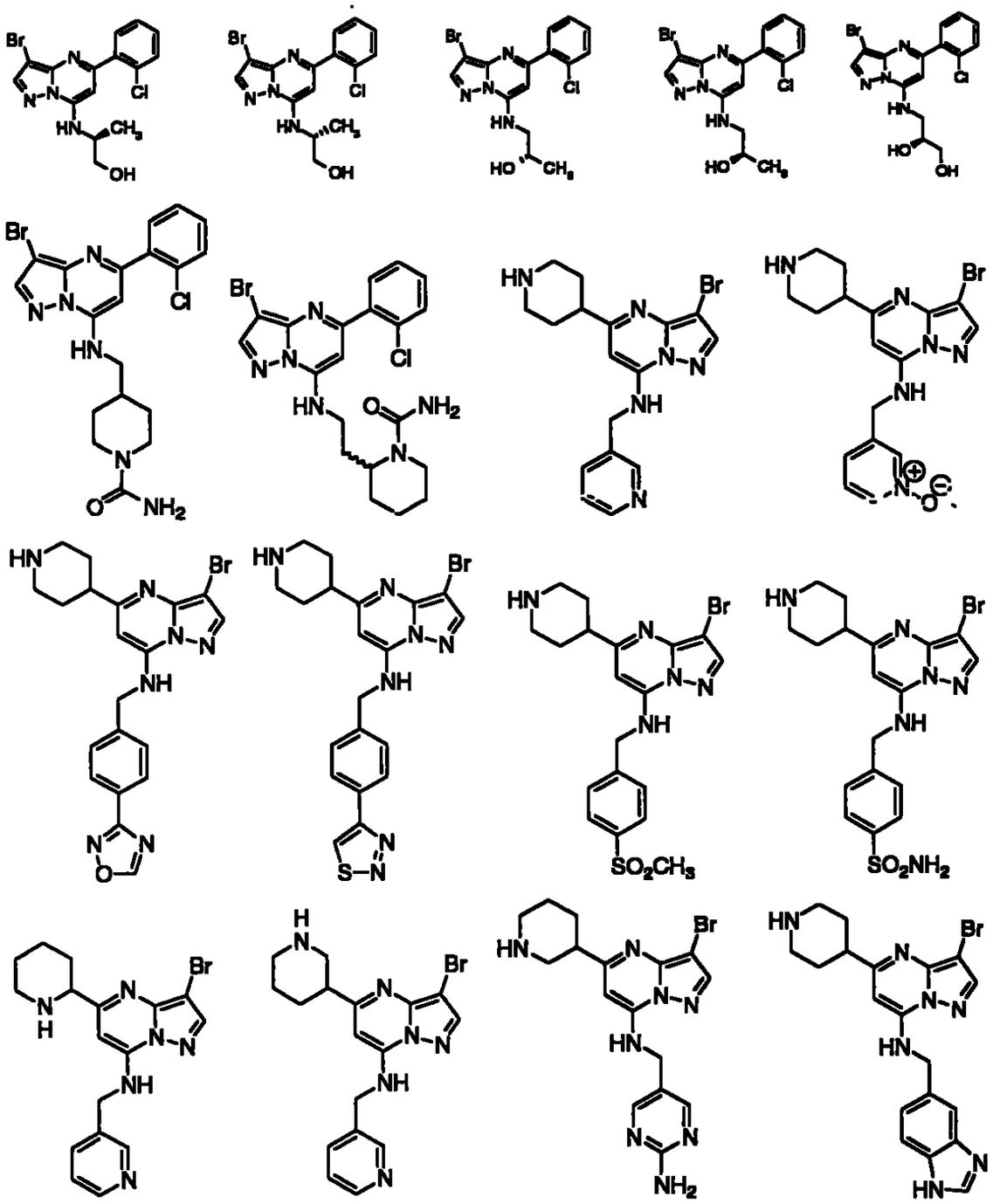


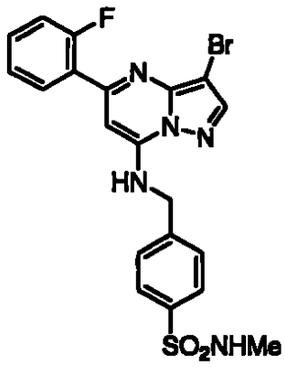


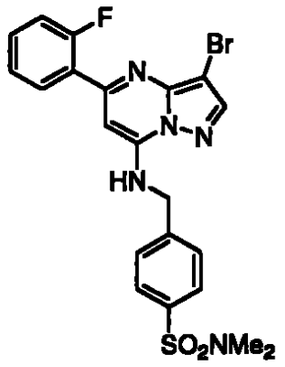


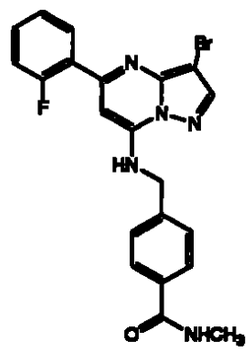


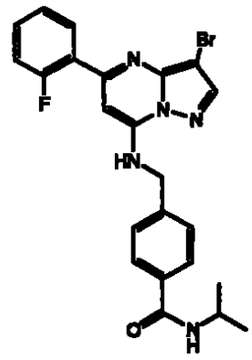
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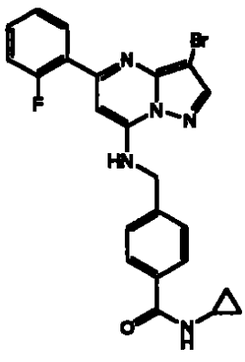


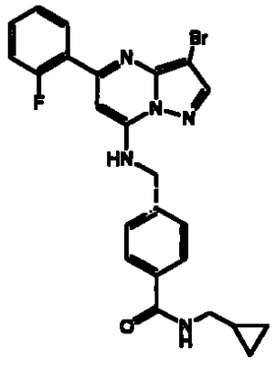

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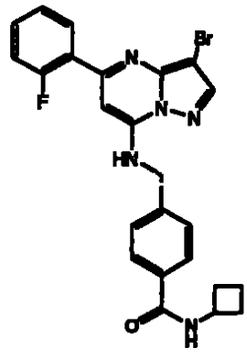

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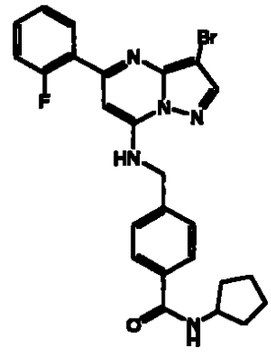

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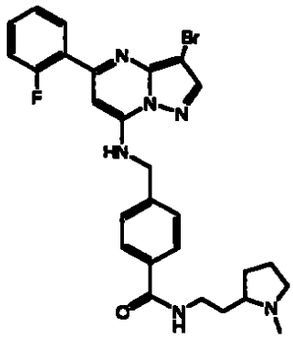

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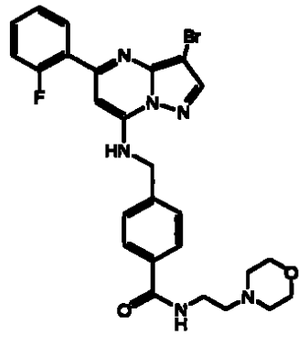

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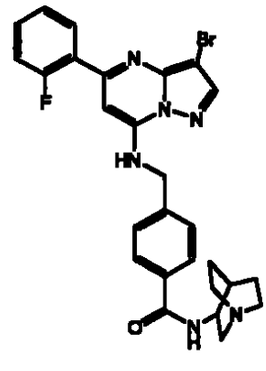

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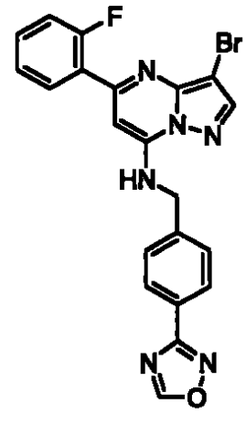

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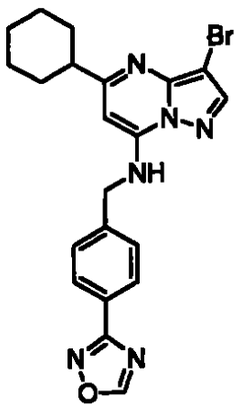

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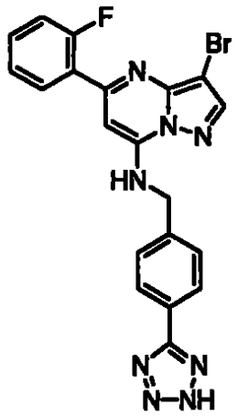

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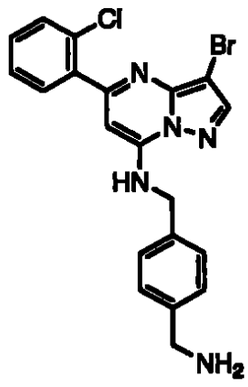

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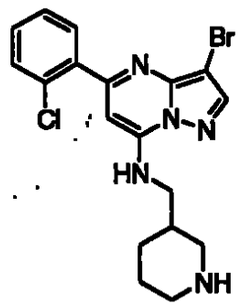

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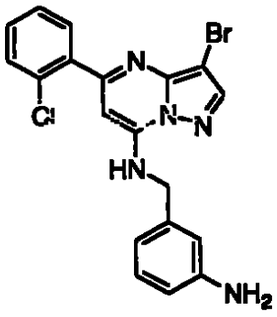

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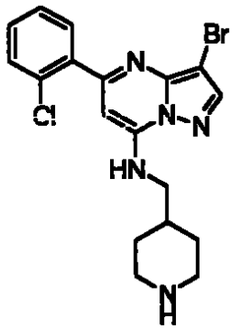


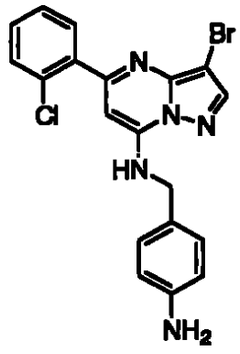


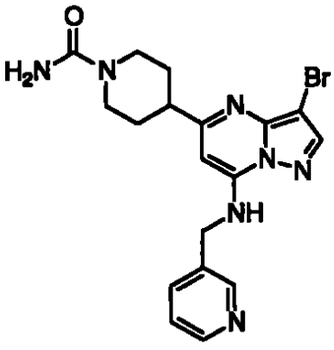


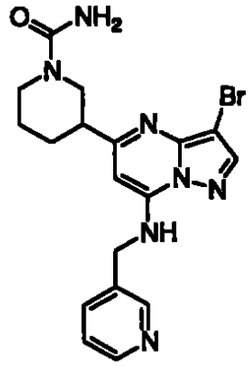


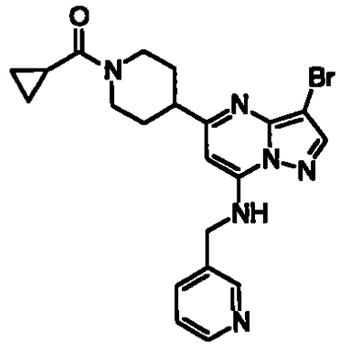


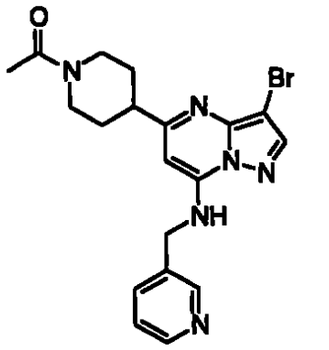


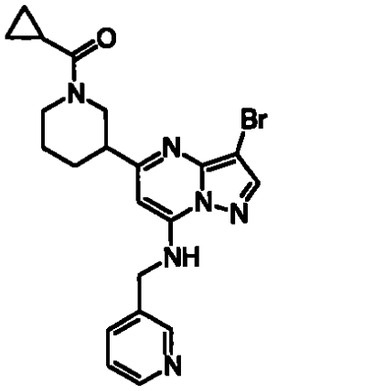


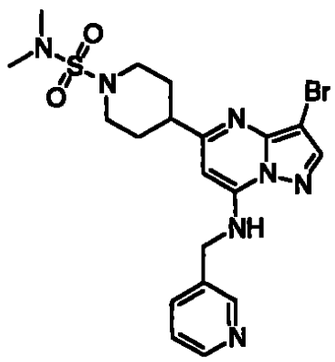


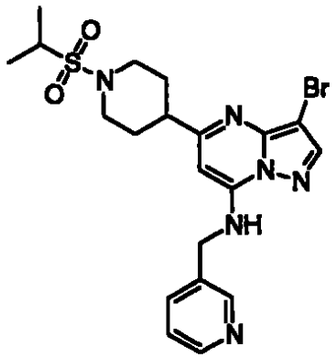


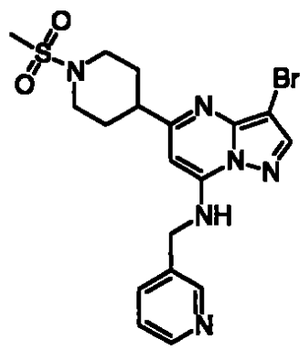


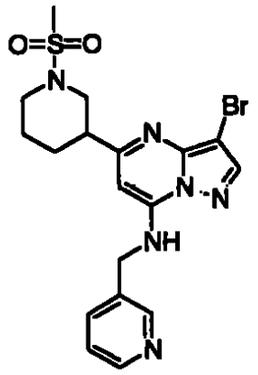


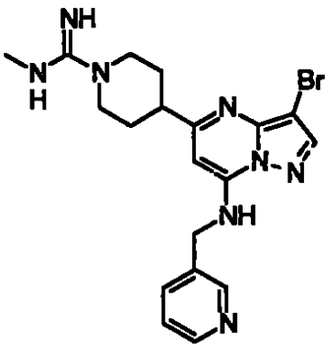


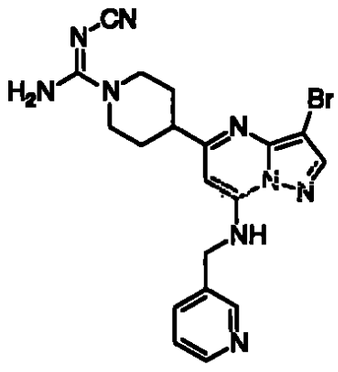


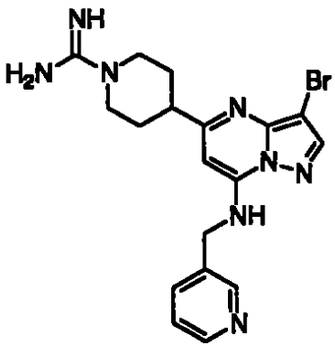


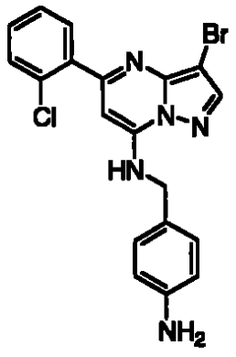


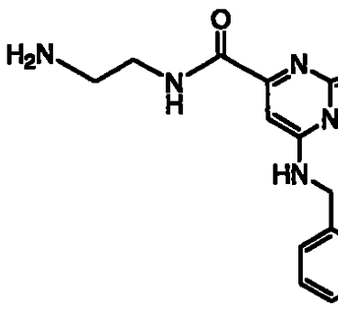






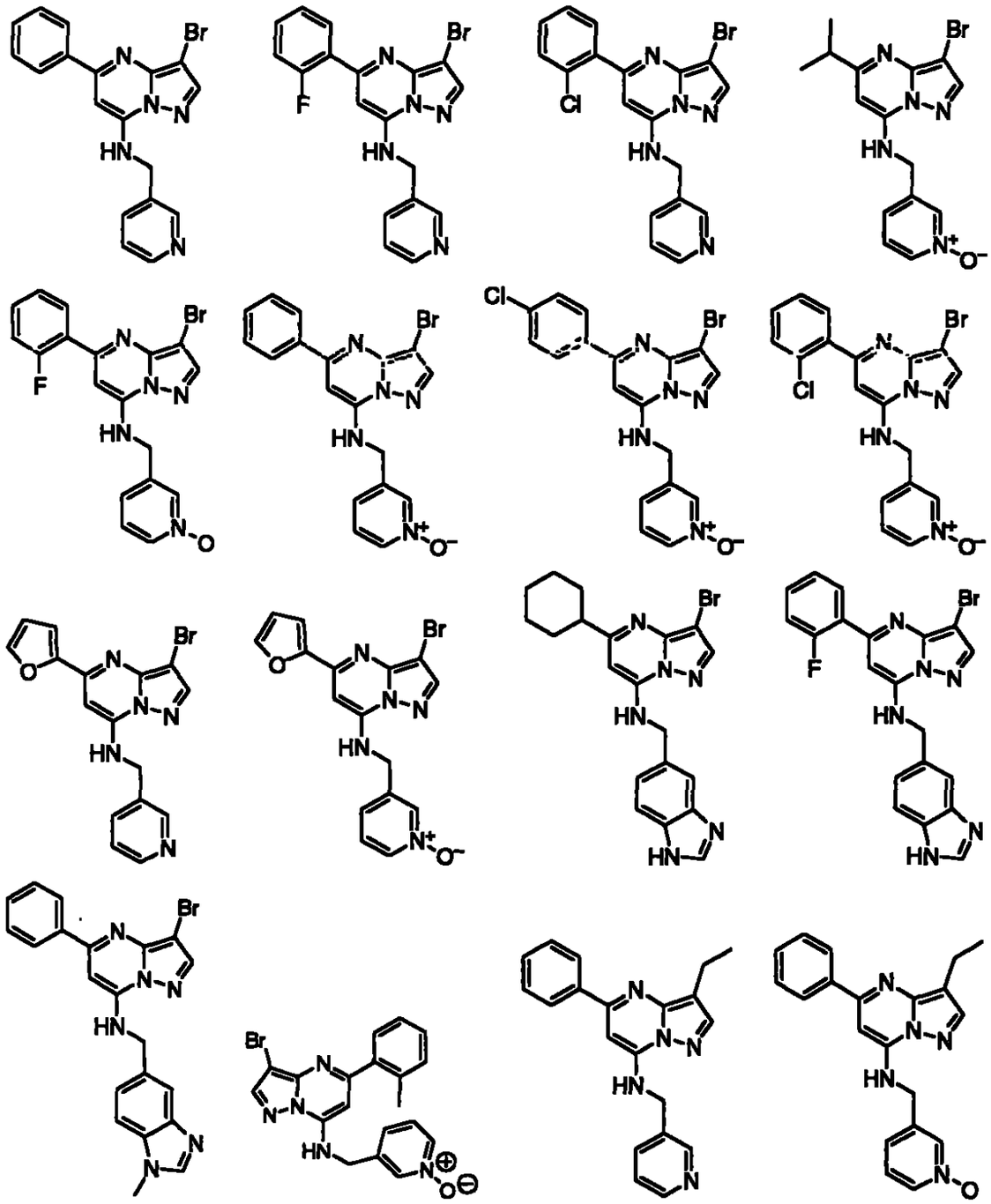


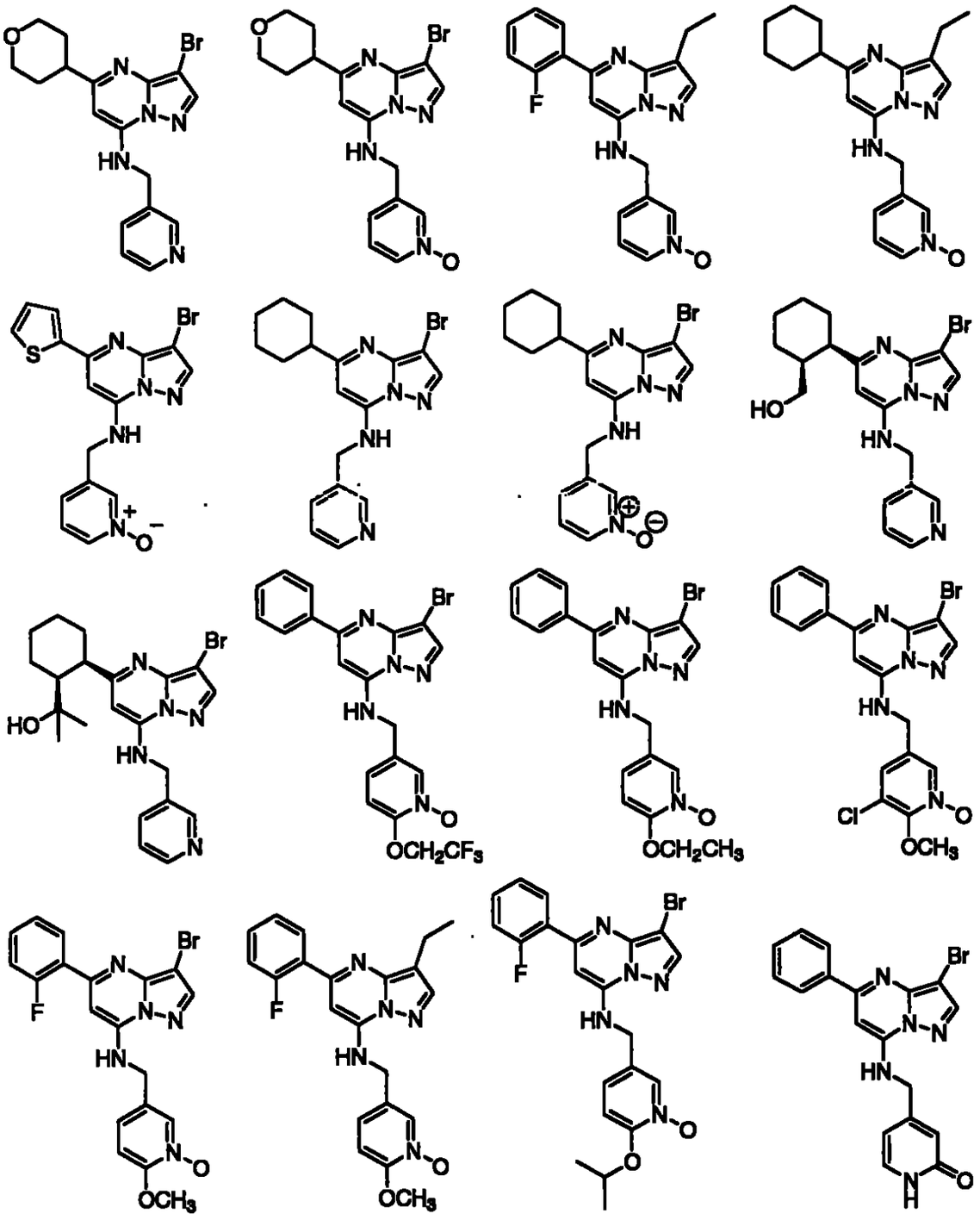


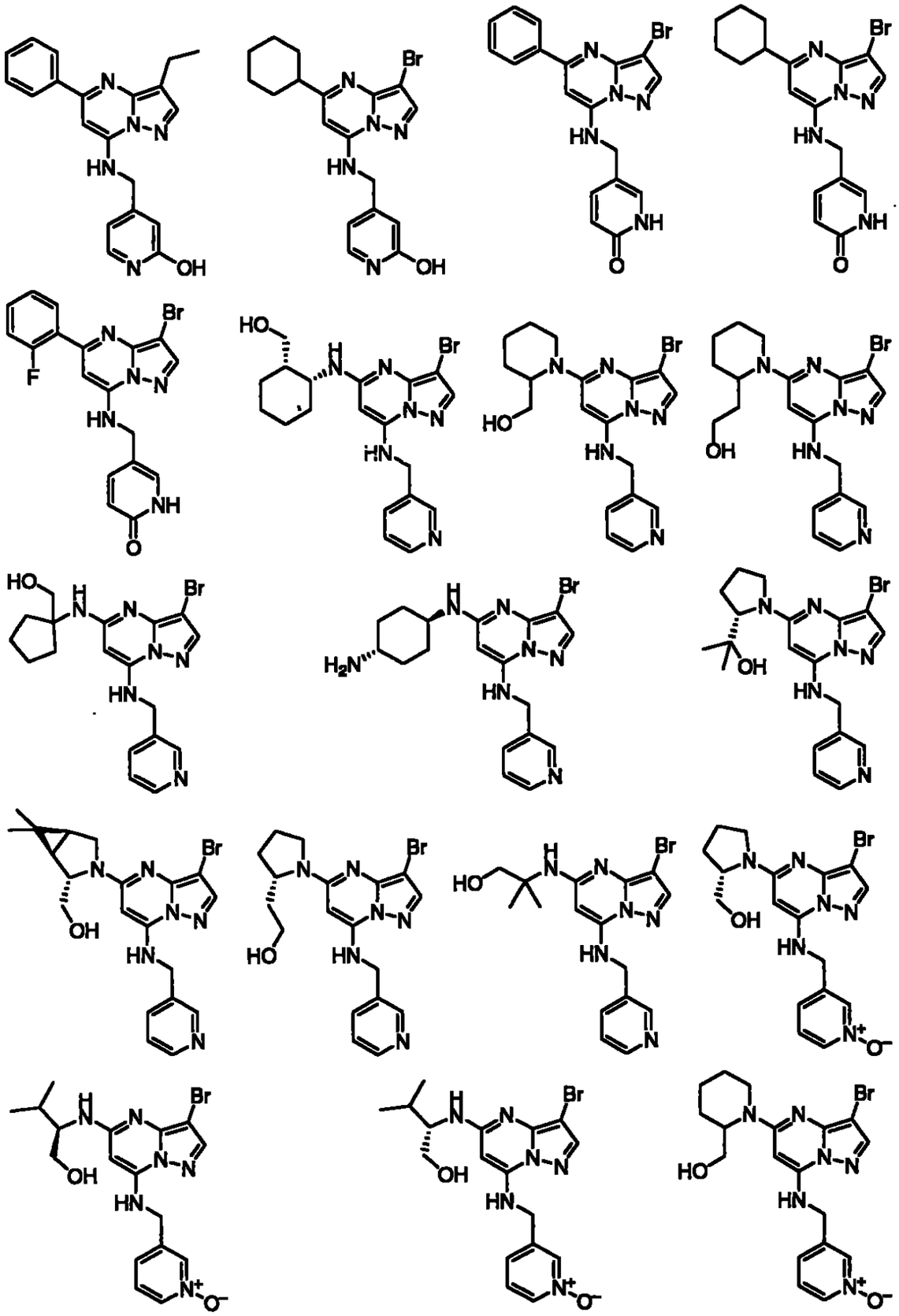


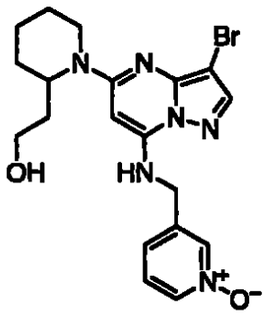
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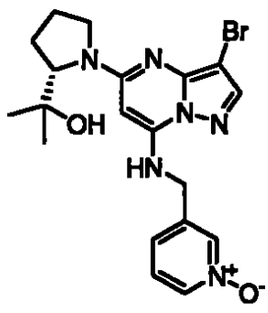
Otra realización de la invención revela los siguientes compuestos, que exhibieron actividad inhibidora de CDK2 de alrededor de 0,0001μM a alrededor de 0,5 μM:

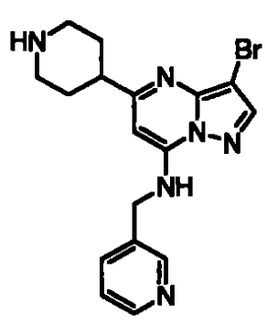


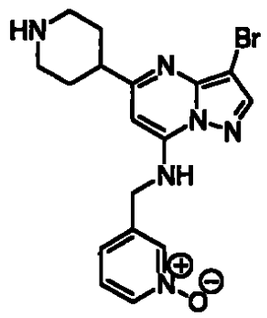


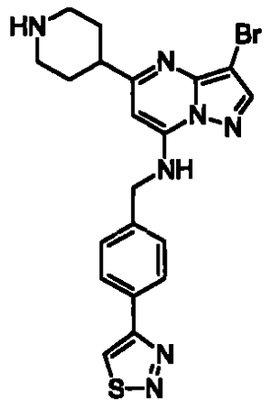


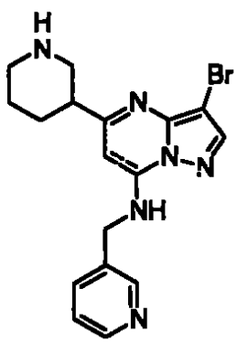


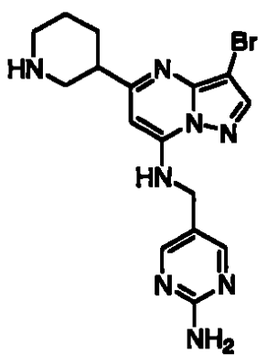


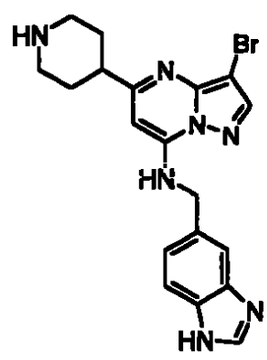


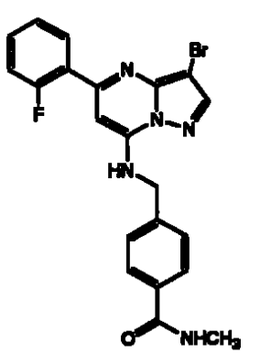


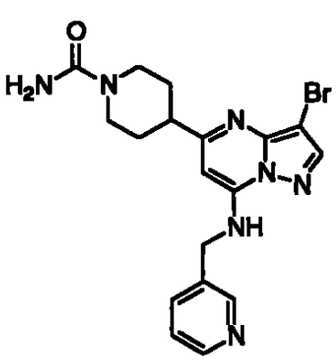


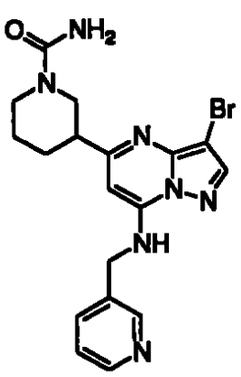


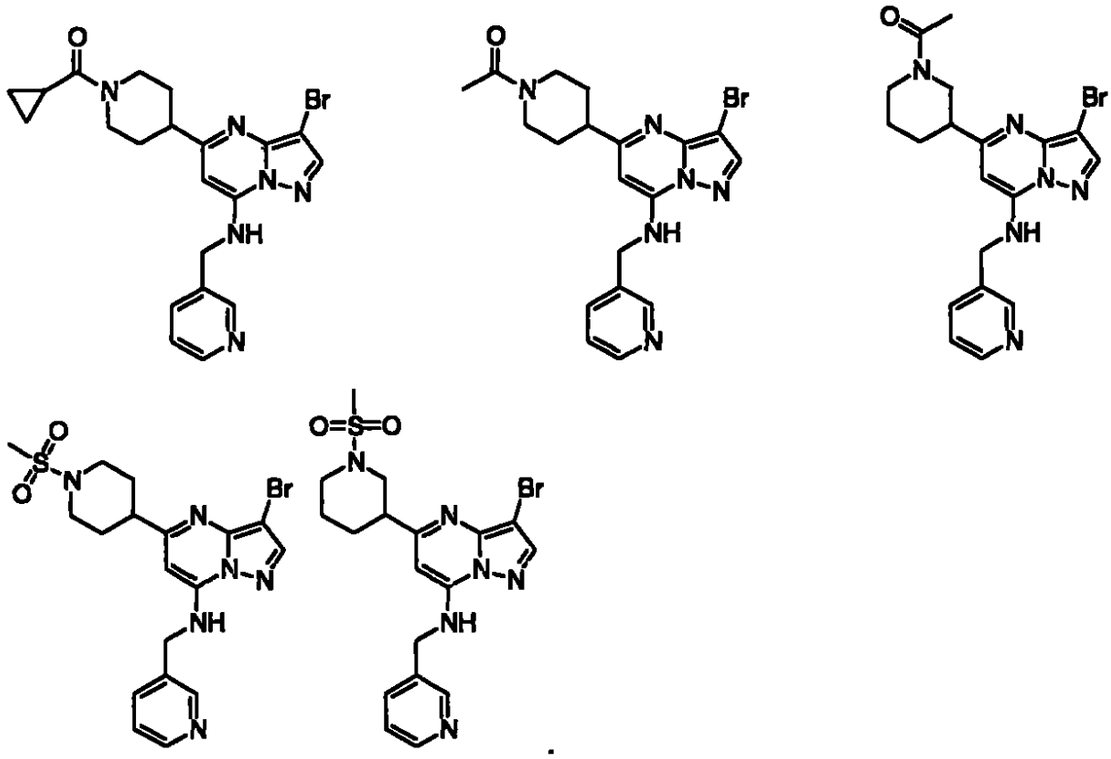




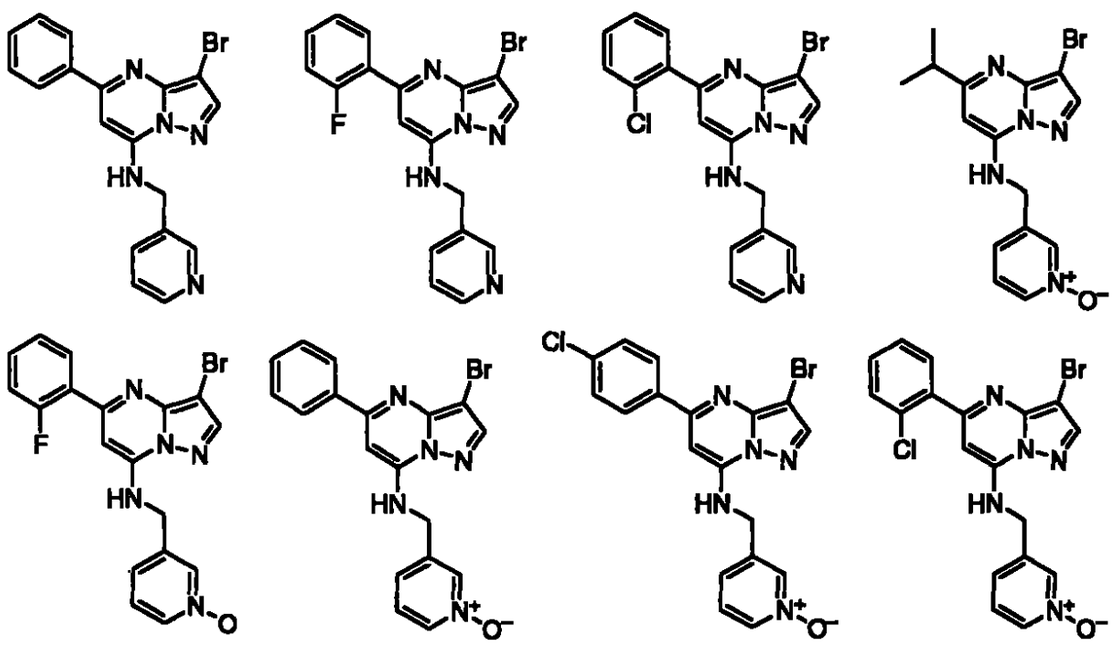


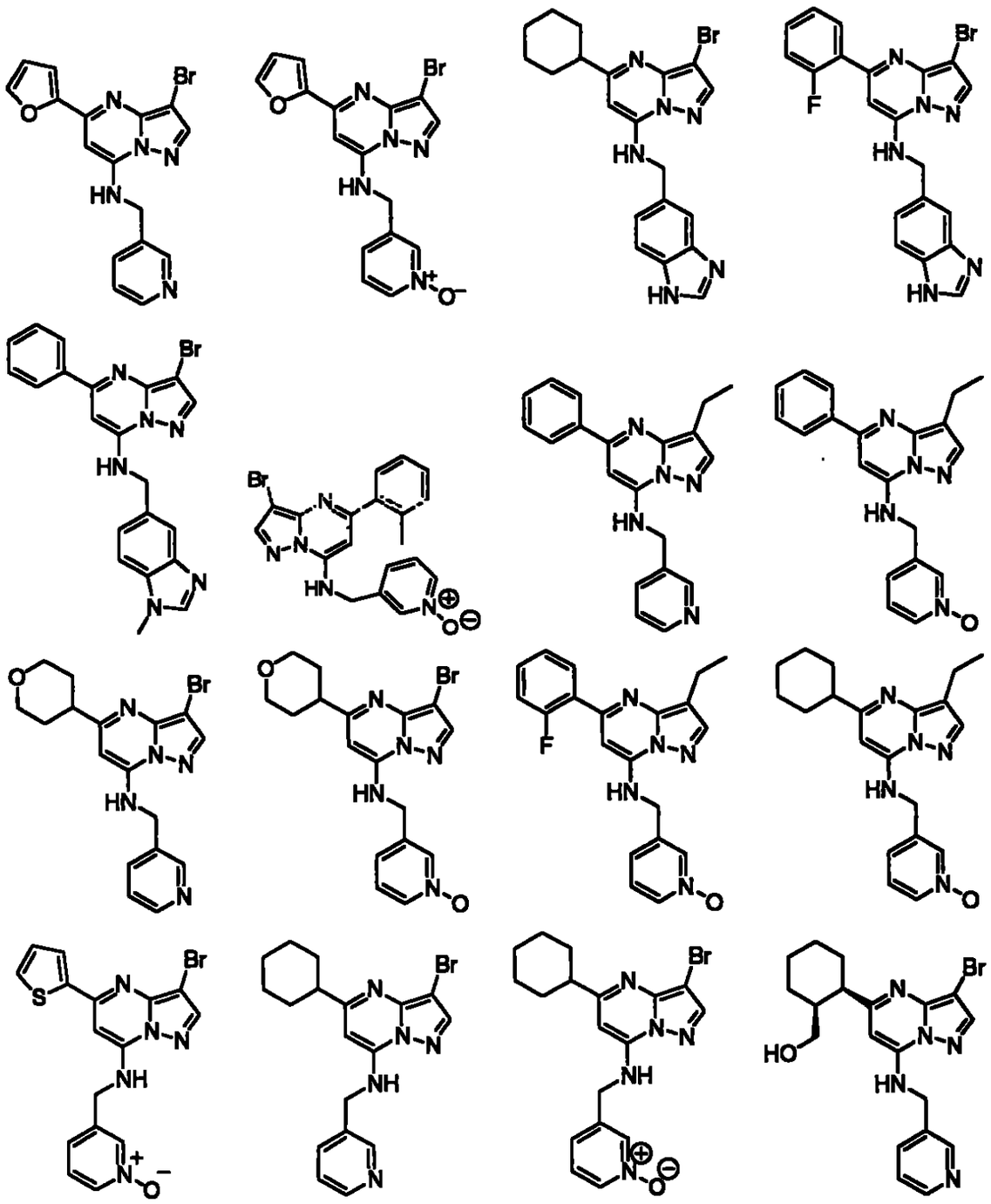


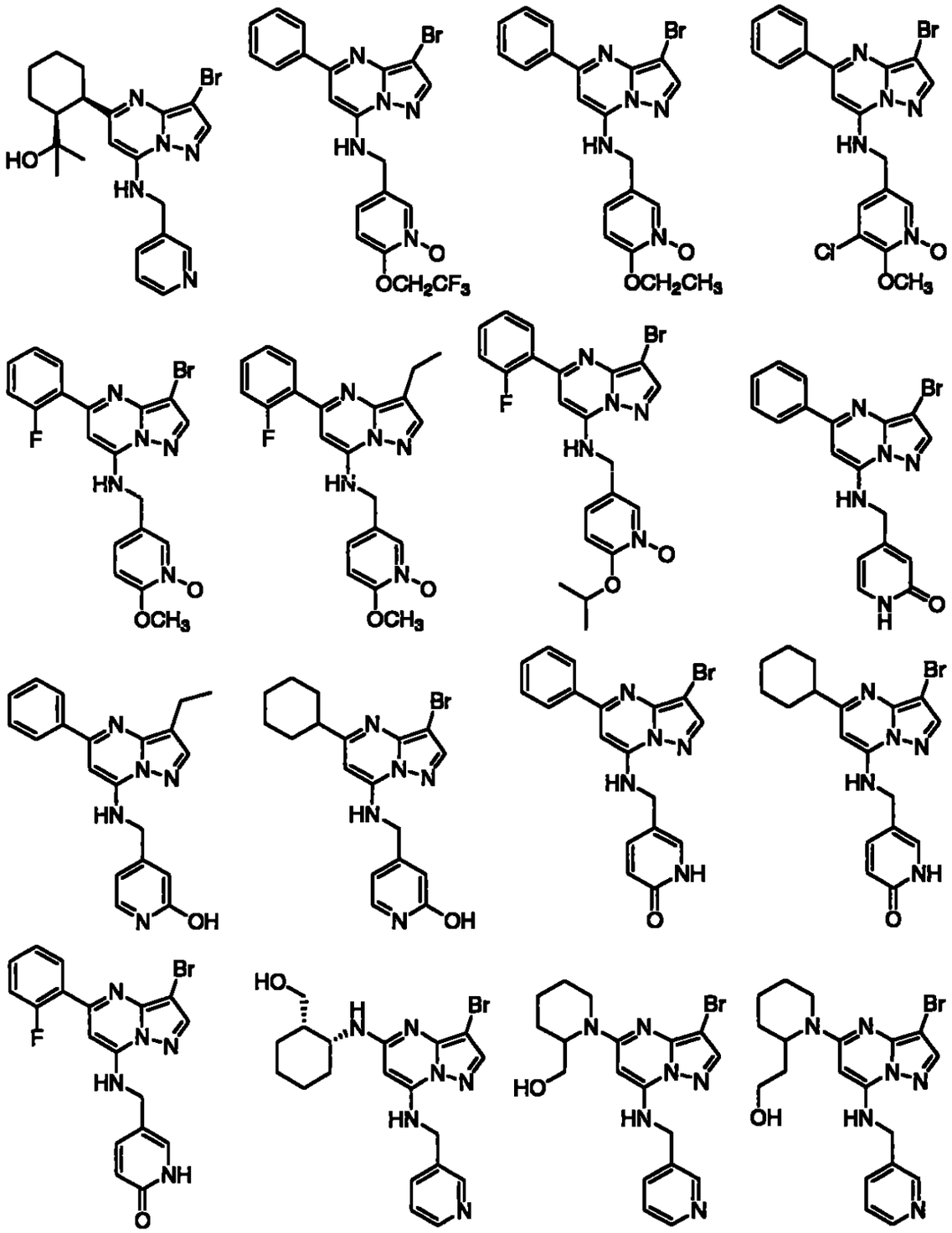


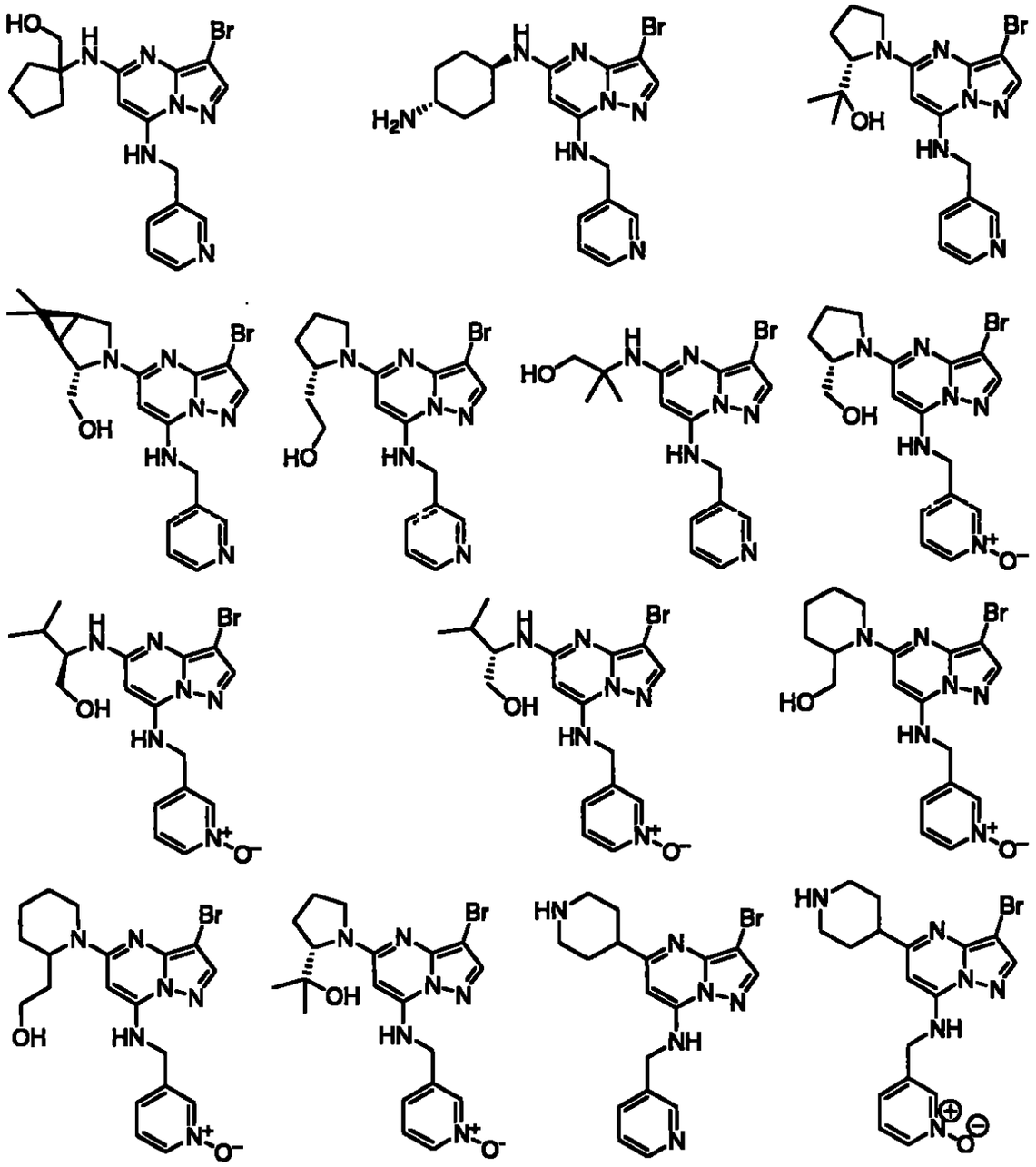


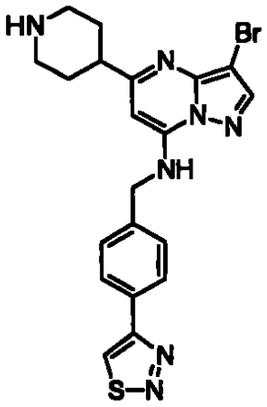
Otra realización de la invención revela los siguientes compuestos, que exhibieron actividad inhibidora de CDK2 de alrededor de 0,0001μM a alrededor de 0,1 μM:

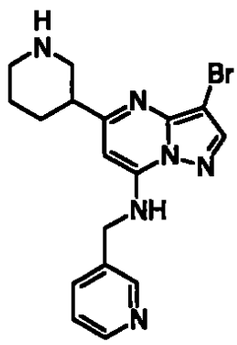


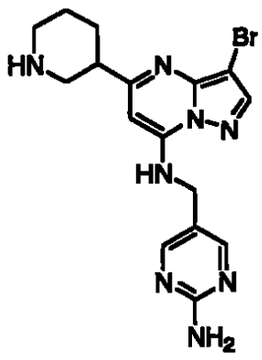


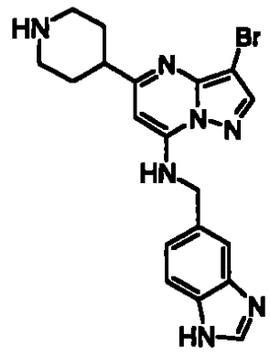


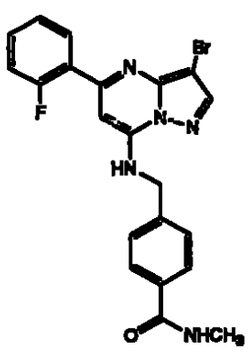


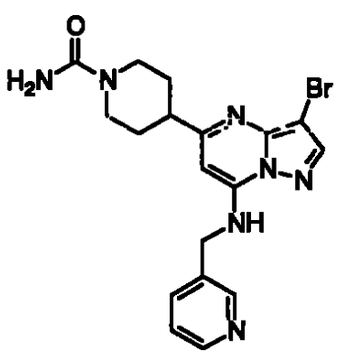


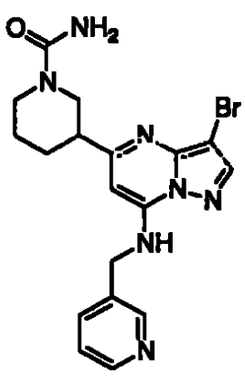


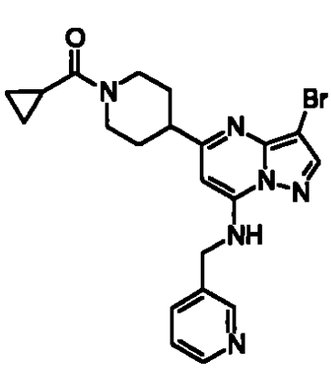


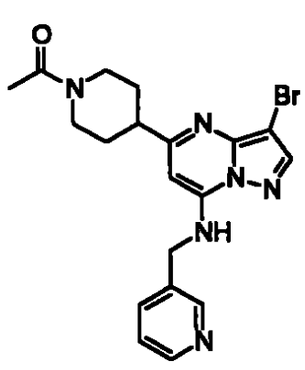


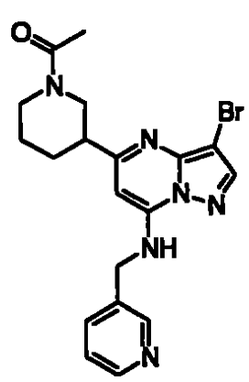


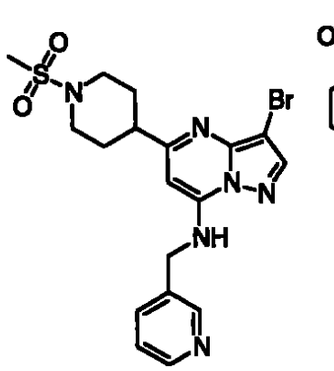


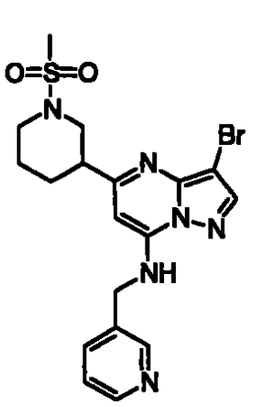












Según se usó anteriormente, y a lo largo de la presente revelación, se entenderá que los siguientes términos, salvo que se indique lo contrario, poseen los siguientes significados:

"Paciente" incluye tanto seres humanos como animales.

"Mamífero" significa seres humanos y otros animales mamíferos.

"Alquilo" significa un grupo hidrocarbonado alifático que puede ser recto o ramificado y que comprende alrededor de 1 a alrededor de 20 átomos de carbono en la cadena. Los grupos alquilo preferidos contienen alrededor de 1 a alrededor de 12 átomos de carbono en la cadena. Más grupos alquilo preferidos contienen alrededor de 1 a alrededor de 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 lineal alquilo. "Alquilo inferior" significa un grupo que posee alrededor de 1 a alrededor de 6 átomos de carbono en la cadena que puede ser recto o ramificado. El término "alquilo sustituido" significa que el grupo alquilo puede ser sustituido con uno o más sustituyentes que pueden ser iguales o diferentes, cada sustituyente siendo seleccionado independientemente 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 adecuados incluyen metilo, etilo, n-propilo, isopropilo y t-butilo.

"Alquinilo" significa un grupo hidrocarbonado alifático que contiene al menos un enlace triple carbono-carbono y que puede ser recto o ramificado y que comprende alrededor de 2 a alrededor de 15 átomos de carbono en la cadena. Los grupos alquinilo preferidos poseen alrededor de 2 a alrededor de 12 átomos de carbono en la cadena; y más preferentemente de alrededor de 2 a alrededor de 4 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 lineal alquinilo. "Alquinilo inferior " significa alrededor de 2 a alrededor de 6 átomos de carbono en la cadena que puede ser recta o ramificada. Ejemplos no limitativos de grupos alquinilo adecuados incluyen etinilo, propinilo, 2-butinilo y 3-metilbutinilo. El término "alquinilo sustituido" significa que el grupo alquinilo puede

estar sustituido con uno o más sustituyentes que pueden ser iguales o diferentes, cada sustituyente siendo seleccionado independientemente del grupo que consiste en alquilo, arilo y cicloalquilo.

"Arilo" significa un sistema de anillo aromático monocíclico o multicíclico que comprende alrededor de 6 a alrededor de 14 átomos de carbono, preferentemente alrededor de 6 a alrededor de 10 átomos de carbono. El grupo arilo se puede sustituir opcionalmente con uno o más "sustituyentes del sistema de anillo" que pueden ser iguales o diferentes, y que son según se define en la presente. Ejemplos no limitativos de grupos arilo adecuados incluyen fenilo y naftilo.

"Heteroarilo" significa un sistema de anillo aromático monocíclico o multicíclico que comprende alrededor de 5 a alrededor de 14 átomos anulares, preferentemente alrededor de 5 a alrededor de 10 átomos de anillo, en los cuales uno o más de los átomos de anillo es un elemento que no es carbono, por ejemplo nitrógeno, oxígeno o azufre, solo o en combinación. Los heteroarilo preferidos contienen alrededor de 5 a alrededor de 6 átomos de anillo. El "heteroarilo" se puede sustituir opcionalmente con uno o más "sustituyentes del sistema de anillo" que pueden ser iguales o diferentes, y son según se definió en la presente. El prefijo aza, oxa o tia antes de la denominación de la raíz del heteroarilo significa que al menos un átomo de nitrógeno, oxígeno o azufre respectivamente, se encuentra presente como un átomo anular. Un átomo de nitrógeno de un heteroarilo se puede oxidar opcionalmente al N-óxido correspondiente. Ejemplos no limitativos de heteroarilo adecuados 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 los similares. El término "heteroarilo" también se refiere a restos heteroarilo saturados tales como, por ejemplo, tetrahidroisoquinolilo, tetrahidroquinolilo y los similares.

"Aralquilo" o "arilalquilo" significa un grupo aril-alquil- en el cual el arilo y alquilo son según se describió anteriormente. Los aralquilo preferidos comprende un grupo alquilo inferior. Ejemplos no limitativos de grupos aralquilo adecuados incluyen bencilo, 2-fenetilo y naftalenilmetilo. El enlace al resto progenitor es a través del alquilo.

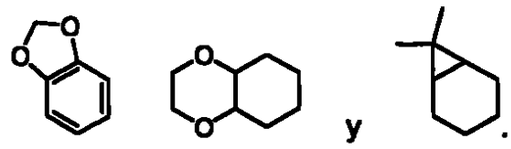
"Alquilarilo" significa un grupo alquil-aril- en el cual el alquilo y arilo son según se describió anteriormente. Los alquilarilo preferidos comprenden un grupo alquilo inferior. Un ejemplo no limitativo de un grupo alquilarilo adecuado es tolilo. El enlace al resto progenitor es a través del arilo.

"Cicloalquilo" significa un sistema de anillo no aromático mono o multicíclico que comprende alrededor de 3 a alrededor de 10 átomos de carbono, preferentemente alrededor de 5 a alrededor de 10 átomos de carbono. Los anillos cicloalquilo contienen alrededor de 5 a alrededor de 7 átomos de anillo. El cicloalquilo se puede sustituir opcionalmente con uno o más "sustituyentes del sistema de anillo" que pueden ser iguales o diferentes, y son según se definió anteriormente. Ejemplos no limitativos de cicloalquilo monocíclicos adecuados incluyen ciclopropilo, ciclopentilo, ciclohexlo, cicloheptilo y los similares. Ejemplos no limitativos de cicloalquilo multicíclicos adecuados incluyen 1-decalinilo, norbornilo, adamantilo y los similares, al igual que especies saturadas parcialmente tales como, por ejemplo, indanilo, tetrahidronaftilo y los similares.

"Halógeno" significa flúor, cloro, bromo o yodo. Se prefieren flúor, cloro y bromo.

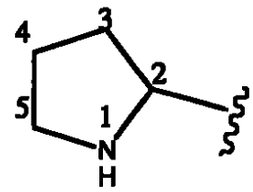
"Sustituyente del sistema anular" significa un sustituyente unido a un sistema anular aromático o no aromático que, por ejemplo, reemplaza un hidrógeno disponible en el sistema anular. Los sustituyentes del sistema de anillo pueden ser iguales o diferentes, cada uno siendo seleccionado independientemente del grupo que consiste en alquilo, alquenilo, alquinilo, arilo, heteroarilo, aralquilo, alquilarilo, heteroaralquilo, heteroarilalquenilo, heteroarilalquinilo, alquilheteroarilo, hidroxi, hidroxialquilo, alcoxi, arilioxi, 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-alquil-, $Y_1Y_2NC(O)$-, $Y_1Y_2NSO_2$- y -$SO_2NY_1Y_2$, en los cuales Y_1 y Y_2 puede ser igual o diferente y se seleccionan independientemente del grupo que consiste en hidrógeno, alquilo, arilo, cicloalquilo, y aralquilo. "Sustituyente del sistema anular" también puede significar un resto simple que reemplaza simultáneamente dos hidrógenos disponibles en dos átomos de carbono adyacentes (un H en cada carbono) en un sistema de anillo. Ejemplos de dicho resto son metilén dioxi, etilendioxi, -$C(CH_3)_2$- y los similares que forman restos tales como, por ejemplo:



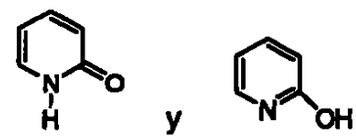
"Heterociclilo" significa un sistema anular no aromático saturado monocíclico o multicíclico que comprende alrededor de 3 a alrededor de 10 átomos de anillo, preferentemente alrededor de 5 a alrededor de 10 átomos de anillo, en el cual uno o más de los átomos en el sistema de anillo es un elemento que no es carbono, por ejemplo nitrógeno, oxígeno o azufre, solo o en combinación. No existen átomos de oxígeno y/o azufre adyacentes presentes en el sistema de anillo. Los heterociclos preferidos contienen alrededor de 5 a alrededor de 6 átomos de anillo. El prefijo aza, oxa o tia antes del nombre de la raíz del heterociclilo significa que al menos un átomo de nitrógeno, oxígeno o azufre, respectivamente, s se encuentra presente como un átomo anular. Cualquier–NH en un anillo heterociclilo puede existir protegido tal como, por ejemplo, como un grupo -N(Boc), -N(CBz), -N(Tos) y los similares; tales protecciones también son consideradas como parte de la presente invención. El heterociclilo se puede sustituir opcionalmente con uno o más "sustituyentes del sistema de anillo" que pueden ser iguales o diferentes, y son según se define en la presente. El átomo de nitrógeno o azufre del heterociclilo se puede oxidar opcionalmente al N-óxido, S-óxido o S,S-dióxido correpsondiente. Ejemplos no limitativos de anillos heterocíclicos monocíclicos adecuados incluyen piperidilo, pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, 1,4-dioxanilo, tetrahidrofuranilo, tetrahidrotiofenilo, lactama, lactona, y los similares.

Se debe observar que en sistemas anulares que contienen hetero-átomos de la presente invención, no hay grupos hidroxilo en los átomos de carbono adyacentes a un N, O o S, al igual que no hay grupos N o S en el carbono adyacente a otro heteroátomo. Por lo tanto, por ejemplo, en el anillo:



no hay -OH unido directamente a los carbonos marcados 2 y 5.

Se debe observar que formas tautoméricas tales como, por ejemplo, los restos:



son consideradas equivalentes en ciertas realizaciones de la presente invención.

"Alquinilalquilo" significa un grupo alquinil-alquil- en el cual el alquinilo y alquilo son según se describió anteriormente. Los alquinilalquilos preferidos contienen un alquinilo inferior y un grupo alquilo inferior. El enlace al resto progenitor es por medio del alquilo. Ejemplos no limitativos de grupos alquinilalquilo adecuados incluyen propargilmetilo.

"Heteroaralquilo" significa un grupo heteroaril-alquil- en el cual el heteroarilo y alquilo son según se describió anteriormente. Los heteroaralquilos preferidos contiene un grupo alquilo inferior. Ejemplos no limitativos de grupos aralquilo incluyen piridilmetilo, y quinolin-3-ilmetilo. El enlace al resto progenitor es a través del alquilo.

"Hidroxialquilo" significa un grupo HO-alquil-en el cual alquilo es según se definió anteriormente. Los hidroxialquilos preferidos contienen alquilo inferior. Ejemplos no limitativos de grupos hidroxialquilo adecuados incluyen hidroximetilo y 2-hidroxietilo.

"Acilo" significa un grupo H-C(O)-, alquil-C(O)- o cicloalquil-C(O)-, grupo en el cual los diversos grupos son según se describió anteriormente. El enlace al resto progenitor es a través del carbonilo. Los acilo preferidos contienen un alquilo

inferior. Ejemplos no limitativos de grupos acilo adecuados incluyen formilo, acetilo y propanoilo.

"Aroilo" significa un grupo aril-C(O)- en el cual el grupo arilo es según se describió anteriormente. El enlace al resto progenitor es a través del carbonilo. Ejemplos no limitativos de grupos adecuados incluyen benzoilo y 1- naftoilo.

"Alcoxi" significa un grupo alquil-O- en el cual el grupo alquilo es as previously described. Ejemplos no limitativos de grupos alcoxi adecuados incluyen metoxi, etoxi, n-propoxi, isopropoxi y n-butoxi. El enlace al resto progenitor es a través del oxígeno de éter.

"Ariloxi" significa un grupo aril-O- en el cual el grupo arilo es según se describió anteriormente. Ejemplos no limitativos de grupos ariloxi adecuados incluyen fenoxi y naftoxi. El enlace al resto progenitor es a través del oxígeno de éter.

"Aralquiloxi" significa un grupo aralquil-O- en el cual el grupo aralquilo es según se describió anteriormente. Ejemplos no limitativos de aralquiloxi adecuados incluye benciloxi y 1- o 2-naftalenemetoxi. El enlace al resto progenitor es a través del oxígeno de éter.

"Alquiltio" significa un grupo alquil-S- en el cual el grupo alquilo es según se describió anteriormente. Ejemplos no limitativos de grupos alquiltio adecuados incluyen metiltio y etiltio. El enlace al resto progenitor es a través del azufre.

"Ariltio" significa un grupo aril-S- en el cual el grupo arilo es según se describió anteriormente. Ejemplos no limitativos de grupos ariltio adecuados incluyen feniltio y naftiltio. El enlace al resto progenitor es a través del azufre.

"Aralquiltio" significa un grupo aralquil-S- en el cual el grupo aralquilo es según se describió anteriormente. Un ejemplo no limitativo de un grupo aralquiltio adecuado es benciltio. El enlace al resto progenitor es a través del azufre.

"Alcoxicarbonilo" significa un grupo alquil-O-CO-. Ejemplos no limitativos de grupos alcoxicarbonilo adecuados incluye metoxicarbonilo y etoxicarbonilo. El enlace al resto progenitor es a través del carbonilo.

"Ariloxicarbonilo" significa un grupo aril-O-C(O)-. Ejemplos no limitativos de adecuados ariloxicarbonilo grupos incluyen fenoxicarbonilo y naftoxicarbonilo. El enlace al resto progenitor es a través del carbonilo.

"Aralcoxicarbonilo" significa un grupo aralquil-O-C(O)-. Un ejemplo no limitativo de un grupo adecuado aralcoxicarbonilo es benciloxicarbonilo. El enlace al resto progenitor 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 al resto progenitor es a través del sulfonilo.

"Arilsulfonilo" significa un grupo aril-$S(O_2)$-. El enlace al resto progenitor es a través del sulfonilo.

El término "sustituido" significa que uno o más hidrógenos en el átomo designado se reemplaza con una selección del grupo indicado, siempre que no se exceda la valencia normal del átomo designado en las circunstancias existentes, y que los resultados de la sustitución ten un compuesto estable. Las combinaciones de sustituyentes y/o variables se permiten solo si tales combinaciones producen compuestos estables. Mediante "compuesto estable" o "estructura estable" se significa un compuesto que es suficientemente robusto para sobrevivir el aislamiento a un grado útil de pureza de una mezcla de reacción, y la formulación en un agente terapéutico eficaz.

El término "sustituido opcionalmente" significa sustitución opcional con los grupos, radicales o restos especificados.

El término "aislado" o "en forma aislada " para un compuesto, se refiere al estado físico de dicho compuesto después de ser aislado de un proceso sintético o fuente natural o combinación de los mismos. El término "purificado" o "en forma purificada" para un compuesto se refiere al estado físico de dicho compuesto después de que se obtiene de un proceso de purificación o procesos descriptos en la presente o conocidos para un experto, en una pureza suficiente para que se pueda caracterizar mediante técnicas analíticas estándar descriptas en la presente o conocidas para el experto.

Se debe observar que se asume que cualquier heteroátomo con valencias no cubiertas en el texto, esquemas, ejemplos y Tablas en la presente posee el(los) átomo(s) de hidrógeno para cubrir las valencias.

Cuando un grupo funcional en un compuesto se denomina "protegido", esto significa que el grupo se encuentra en forma modificada para evitar reacciones

secundarias no deseadas en el sitio protegido cuando se somete el compuesto a una reacción. Los grupos protectores adecuados serán reconocidos por aquellos con experiencia ordinaria en la técnica, al igual que en referencia a libros de texto estándar tales como, por ejemplo, T. W. Greene *et al*, *Protective Grupos in organic Synthesis* (1991), Wiley, New York.

Cuando cualquier variable (por ej, arilo, heterociclo, R^2, etc.) se presente más de una vez en cualquier constituyente o en la Fórmula III, su definición en cada ocurrencia es independiente de su definición en cualquier otra ocurrencia.

De acuerdo con su uso en la presente, el término "composición" pretende abarcar un producto que comprende los componentes especificados en las cantidades especificados, al igual que cualquier producto que resulte, directa o indirectamente, de la combinación de los componentes especificados en las cantidades especificados.

Los pro-fármacos y solvatos de los compuestos de la invención también se contemplan en la presente. El término "pro-fármaco", según se usa en la presente, denota un compuesto que es un precursor de fármaco que, al administrarlo a un sujeto, sufre una conversión química mediante procesos metabólicos o químicos para dar un compuesto de Fórmula III o una sal y/o solvato del mismo. Se provee una discusión de profármacos en T. Higuchi y V. Stella, *Pro-drugs as Novel Dehígadoy Systems* (1987) 14 de A.C.S. Symposium Series, y en *Bioreversible Carriers in Drug Design*, (1987) Edward B. Roche, ed., American Pharmaceutical Association y Pergamon Press, ambas de las cuales se incorporan a la presente a modo de referencia a la misma.

"Solvato" significa una asociación física de un compuesto de la presente invención con una o más moléculas del solvente. Esta asociación física comprende grados que varían de en unión iónica y covalente, incluyendo unión de hidrógeno. En ciertas instancias, el solvato se podrá aislar, por ejemplo, cuando se incorporan una o más moléculas de solvente en la celosía de cristal del sólido cristalino. "Solvato" abarca tanto la fase de la solución y solvatos aislables. Ejemplos no limitativos de solvatos adecuados incluyen etanolatos, metanolatos, y los similares. "Hidrato" es un solvato en el cual la molécula del solvente es H_2O.

"Cantidad efectiva " o "cantidad efectiva terapéuticamente " se usa para describir una cantidad de compuesto o u una composición de la presente invención efectiva para la inhibición de las CDK(s) y por lo tanto que produce el efecto terapéutico, de alivio, inhibidor o preventivo deseado.

Los compuestos de Fórmula III pueden formar sales que también se encuentran dentro del alcance de la presente invención. Se entiende que la referencia a un compuesto de Fórmula III en la presente incluye la referencia a las sales de los mismos, salvo que se indique lo contrario. El término "sal(es)", según se emplea en la presente, denota sales ácidas formadas con ácidos inorgánicos y/u orgánicos, al igual que sales básicas formadas con bases inorgánicas y/u orgánicas. Adicionalmente, cuando un compuesto de Fórmula III contiene un resto básico, tal como, pero sin limitarse a piridina o imidazol, y un resto ácido, tal como, pero sin limitarse a un ácido carboxílico, se pueden formar zwitteriones ("sales internas ") y se incluyen en el término "sal(es)" de acuerdo con su uso en la presente. Se prefieren las sales aceptables para uso farmacéutico (es decir, no tóxicas, aceptables fisiológicamente), aunque también son útiles otras sales. Se pueden formar sales de los compuestos de la Fórmula III, por ejemplo, por medio de hacer reaccionar un compuesto de Fórmula III con una cantidad de ácido o base, tal como una cantidad equivalente, en un medio tal como uno en el cual la sal se precipita o en un medio acuoso seguida por liofilización.

Sales ácidos de adición de ejemplo incluyen acetatos, ascorbatos, benzoatos, benzensulfonatos, bisulfatos, boratos, butiratos, citratos, alcanforatos, alcanforsulfonatos, fumaratos, clorhidratos, bromhidratos, yodohidratos, lactatos, maleatos, metansulfonatos, naftalensulfonatos, nitratos, oxalatos, fosfatos, propionatos, salicilatos, succinatos, sulfatos, tartratos, tiocianatos, toluensulfonates (también conocidos como tosilatos,) y los similares. Adicionalmente, se tratan ácidos que en general son considerados adecuados para la formación de sales útiles para uso farmacéutico de compuestos farmacéuticos básicos, por ejemplo, por S. Berge *et al, Journal of Pharmaceutical Sciences* (1977) 66(1) 1-19; P. Gould, *International J. of Pharmaceutics* (1986) 33 201-217; Anderson *et al, The Practice of Medicinal Chemistry* (1996), Academic Press, New York; y in *The Orange Book* (Food & Drug Administration,

Washington, D.C. on their website). Estas revelaciones se incorporan a la presente a modo de referencia a las mismas.

Las sales básicas de ejemplo incluyen sales de amonio, sales de metal alcalino tales como sales de sodio, litio, y potasio, sales de metal alcalino térreo tales como sales de calcio y magnesio, sales con bases orgánicas, (por ejemplo, aminas orgánicas), tales como diciclohexilaminas, t-butil aminas, y sales con amino ácidos tales como arginina, lisina y los similares. Los grupos básicos que contienen nitrógeno se pueden cuaternizar con agentes tales como haluros de alquilo inferior (por ejemplo cloruros de metilo, etilo, y butilo, bromuro y yoduro), dialquil sulfato (por ejemplo dimetil, dietil, y dibutil sulfatos, haluros de cadena extensa (por ejemplo cloruros de decilol, laurilo. y estearilo, bromuros y yoduros), haluros de aralquilo (por ejemplo bencil y fenetilo bromides), y otros.

Todas dichas sales ácidas y sales de base pretenden ser sales aceptables para uso farmacéutico dentro del alcance de la invención y todas las sales ácidos y de base son consideradas equivalentes a las formas libres de los compuestos correspondientes para los fines de la invención.

Los compuestos de Fórmula III, y sales, solvatos y profármacos de los mismos, pueden existir en su forma tautomérica (por ejemplo, como una amida o amino éter). La totalidad de tales formas tautoméricas se contemplan en la presente como parte de la presente invención.

Todos los esteroisómeros (por ejemplo, isómeros geométricos, isómeros ópticos y los similares) de los presentes compuestos (incluyendo aquellos de sales, solvatos y profármacos de compuestos al igual que las sales y solvatos de los profármacos), tales como aquellos que pueden existir debido a carbonos asimétricos en varios sustituyentes, incluyendo formas enantioméricas (que pueden existir aún en ausencia de carbonos asimétricos), formas rotaméticas, atropisómeros y formas diastereoméricas, se contemplan dentro de la alcance de la presente invención, con isómeros posicionales (tales como, por ejemplo, 4-piridilo y 3-piridilo). Los estereoisómeros individuales de los compuestos de la invención pueden, por ejemplo, estar sustancialmente libres de otros isómeros, o se pueden mezclar, por ejemplo, como racematos o con todos los otros estereoisómeros, u otros seleccionados. Los centros quirales de la presente

invención pueden poseer la configuración S o R según lo definido por las Recomendaciones *IUPAC* 1974. Se pretende que el uso de los términos "sal", "solvato" "profármaco" y los similares, se aplique de manera equivalente a la sal, solvato y profármaco de enantiómeros, estereoisómeros, rotámeros, tautómeros, isómeros posicionales, racematos o profármacos de los compuestos inventivos.

Los compuestos de acuerdo con la invención posee propiedades farmacológicas; en particular, los compuestos de Fórmula III pueden ser inhibidores de las proteínas quinasa tales como, por ejemplo, los inhibidores de las quinasas ciclina-dependientes, proteína quinasa activada por mitógenos (MAPK/ERK), glicogen sintasa quinasa 3(GSK3beta) y los similares. Las quinasas ciclina-dependientes (CDKs) incluyen, por ejemplo, CDC2 (CDK1), CDK2, CDK4, CDK5, CDK6, CDK7 y CDK8. Se espera que los compuestos novedosos de Fórmula III sean de utilidad en la terapia de enfermedades proliferativas tales como cáncer, enfermedades autoinmunes, enfermedades virósicas, enfermedades fungales, trastornos neurológicosl/neurodegenerativos, artritis, inflamación, anti-proliferativo (por ejemplo, retinopatía), enfermedad neuronal, alopecia y cardiovascular. Muchas de estas enfermedades y trastornos se enumeran en U.S. 6.413.974 citadas anteriormente, cuya revelación se incorpora a la presente.

Más específicamente, los compuestos de Fórmula III pueden ser útiles en el tratamiento de una variedad de cánceres, incluyendo (pero sin limitarse a) los siguientes:

carcinoma, incluyendo aquel de la vejiga, mama, colon, riñón, hígado, pulmón, incluyendo cáncer celular de pulmón, esófago, vesícula, ovario, páncreas, estómago, cerviz, tiroides, próstata, y piel, incluyendo carcinoma celular escamoso;

tumores hematopoyéticos de las líneas linfoides, incluyendo leucemia, leucemia linfocítica aguda, leucemia linfoblástica aguda, linfoma de célula B, linfoma de célula T, linfoma de Hodgkins, linfoma no Hodgkins, linfoma de célula pilosa y linfoma de Burkett;

tumores hematopoyéticos del linaje mieloide, incluyendo leucemias mielógenas agudas y crónicas, síndrome mielodisplásico y leucemia promielocítica;

tumores de origen mesenquimal, incluyendo fibrosarcoma y rabdomiosarcoma;

tumores del sistema nervioso central y periférico, incluyendo astrocitoma, neuroblastoma, glioma y schwannomas; y

otros tumores, incluyendo melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, keratoctantoma, cáncer folicular tiroide y sarcoma Kaposi.

Debido al rol clave de las 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 que caracteriza la proliferación celular abnormal, por ejemplo, hiperplasia benigna de próstata, poliposis adenomatosis familial, neuro-fibromatosis, aterosclerosis, fibrosis pulmonar, artritis, psoriasis, glomerulonefritis, restenosis a continuación de angioplastía o cirugía vascular, formación de cicatrices hipertróficas, enfermedad de inflamación de intestino, rechazo de transplante, shock endotóxico e infecciones fungales.

Los compuestos de Fórmula III también pueden ser útiles en el tratamiento de la enfermedad de Alzheimer, según lo sugerido por el descubrimiento reciente que la CDK5 está relacionado con la fosforilación de la proteína tau (*J. Biochem,* (1995) 117, 741-749).

Los compuestos de Fórmula III pueden inducir o inhibir la apoptosis. La respuesta apoptica es aberrante en una variedad de enfermedades humanas. Los compuestos de Fórmula III, como moduladores de apoptosis, serán útiles en el tratamiento de cáncer (incluyendo, pero sin limitarse a auqellos tipos mencionados anteriormente en la presente), infecciones virales (incluyendo pero sin limitarse a herpevirus, poxvirus, virus Epstein- Barr, Sindbis virus y adenovirus), prevención del desarrollo del SIDA en individuos infectas con VIH, enfermedadse autoinmunes (incluyendo pero sin limitarse a lupus sistémico, eritematoso, glomerulonefritis autoinmune mediada, artritis reumatoidea,

psoriasis, enfermedad de intestino inflamado y diabetes mellitus autoinmune), trastornos neurodegenerativos (incluyendo pero sin limitarse a la enfermedad de Alzheimer, demencia relacionada con SIDA, enfermedad de Parkinson', esclerosis lateral amiotrópica, retinitis pigmentosa, atrofia muscular espinal y degeneración cerebelar), síndromes mielodisplásicos, anemia aplásicas, lesión isquémica asociada con infartos al miocardio, infarto y lesión de reperfusión, arritmia, aterosclerosis, enfermedades de hígado inducidas por toxina o relacionadas con alcohol, enfermedades hematológicas (incluyendo pero sin limitarse a anemia crónica y anemia aplásica), enfermedades degenerativas del sistema musculoóseo (incluyendo pero sin limitarse a osteoporosis y artritis) rinosinusitis sensible a aspirina, fibrosis cística, esclerosis múltiple, enfermedades de riñón y dolor debido a cáncer.

Los compuestos de Fórmula III, como inhibidores de las CDKs, pueden modular el nivel celular de la síntesis de ARN y ADN. Estos agentes, por consiguiente, seróan útiles en el tratamiento de infecciones virales (incluyendo pero sin limitarse a VIH, virus papiloma humano, herpesvirus, poxvirus, virus Epstein-Barr, virus Sindbis y adenovirus).

Los compuestos de Fórmula III también pueden ser útiles en la quimioprevención del cáncer. La quimioprevención se define como inhibidora del desarrollo del cáncer invasivo ya sea mediante el bloqueo del evento mutagénico que se inicia o mediante el bloqueo del avance de las células pre-malignas que ya han sufrido una agresión o mediante la inhibición del regreso del tumor.

Los compuestos de Fórmula III también pueden ser útiles en la inhibición de la angiogénesis y metástasis del tumor.

Los compuestos de Fórmula III también pueden actuar como inhibidores de otras proteína quinasas, por ejemplo, proteína quinasa C, her2, raf 1, MEK1, quinasa MAP, receptor EGF, receptor PDGF, IGF receptor, PI3 quinasa, wee1 quinasa, Src, Abl y por lo tanto pueden ser efectivo en el tratamiento de enfermedades asociadas con otras proteína quinasas.

Otro aspecto de la presente invención es un método para el tratamiento de un mamífero (*por ejemplo*, un ser humano) que posee una enfermedad o afección asociada con las CDK por medio de administrar una cantidad efectiva

terapéuticamente de al menos un compuesto de Fórmula III, o una sal aceptable para uso farmacéutico o solvato de dicho compuesto al mamífero.

Una dosificación preferida es de alrededor de 0,001 a 500 mg/kg del peso corporal/día del compuesto de Fórmula III. Una dosificación preferida especialmente es de alrededor de 0,01 a 25 mg/kg de peso corporal/día de un compuesto de Fórmula III, o una sal aceptable para uso farmacéutico o solvato de dicho compuesto.

Los compuestos de esta invención también pueden ser útiles en combinación (administrados juntos o en secuencia) con uno o más tratamientos anti-cáncer tales como terapia de radiación, y/o uno o más agentes anticancerígenos seleccionados del grupo que consiste en agentes citostáticos, agentes citotóxicos (tales como por ejemplo, pero sin limitarse a, agentes de ADN interactivos (tales como cisplatina o doxorubicina)); taxanos (por ejemplo taxotere, taxol); inhibidores de topoisomerasa II (tales como etoposido); inhibidores topoisomerasa I (tales como irinotecan (o CPT-11), camptostar, o topotecan); agentes interactivos de tubulina (tales como paclitaxel, docetaxel o las epotilonas); agentes hormonales (tal como tamoxifen); inhibidores de timidilato sintasa (tal como 5-fluorouracilo); anti-metabolitos (tal como metoxtrexato); agentes alquilantes (tales como temozolomida (TEMODAR™ de Schering-Plough Corporation, Kenilworth, New Jersey), ciclofosfamida); inhibidores de proteína 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-piperidinecarboxamida, o SCH 66336 de Schering-Plough Corporation, Kenilworth, New Jersey), tipifarnib (Zarnestra® o R115777 de Janssen Pharmaceuticals), L778,123 (un inhibidor de proteína transferasa de farnesilo de Merck & Company, Whitehouse Station, New Jersey), BMS 214662 (un inhibidor de proteína transferasa de farnesilo de Bristol-Myers Squibb Pharmaceuticals, Princeton, New Jersey); inhibidores de transducción de señal (tal como, Iressa (de Astra Zeneca Pharmaceuticals, England), Tarceva (inhibidores de EGFR quinasa), anticuerpos para EGFR (por ejemplo, C225), GLEEVEC™ (inhibidor de C-abl quinasa de Novartis Pharmaceuticals, East Hanover, New Jersey); interferonas tal como, por ejemplo, intron (de Schering-Plough Corporation), Peg-

Intron (de Schering-Plough Corporation); combinaciones de terapias hormonales; combinaciones de aromatasa; ara-C, adriamicina, citoxan, y gemcitabina.

Otros agentes anti-cancerígenos (también conocidos como anti-neoplásicos) incluyen, pero sin limitarse a, mostaza de uracilo, clometina, Ifosfamida, Melfalan, Clorambucilo, Pipobroman, Trietilenmelamina, Trietilentiofosforamina, Busulfan, Carmustina, Lomustina, estreptozocina, Dacarbazina, Floxuridina, Citarabina, 6-Mercaptopurina, 6-Tioguanina, fosfato de Fludarabina, oxaliplatin, leucovirin, oxaliplatin (ELOXATIN™ de Sanofi-Synthelabo Pharmaeuticals, France), Pentostatina, Vinblastina, Vincristina, Vindesina, Bleomicina, Dactinomicina, Daunorubicina, Doxorubicina, Epirubicina, Idarubicina, Mitramicina, Deoxicoformicina, Mitomicin-C, L-Asparaginasa, Teniposido 17□-Etinilestradiol, Dietilstilbestrol, Testosterona, Prednisona, Fluoximesterona, Dromostanolone propionato, Testolactona, Megestrolacetato, Metilprednisolona, Metiltestosterona, Prednisolona, Triamcinolona, Clorotrianiseno, Hidroxiprogesterona, Aminoglutetimida, Estramustina, Medroxiprogesteronacetato, Leuprolida, Flutamida, Toremifeno, goserelin, Cisplatin, Carboplatin, Hidroxiurea, Amsacrina, Procarbazina, Mitotano, Mitoxantrona, Levamisol, Navelbeno, Anastrazol, Letrazol, Capecitabina, Reloxafina, Droloxafina, o Hexametilmelamina.

Si se formulan como una dosis fija, tales productos de combinación emplean los compuestos de la presente invención dentro del rango de dosificación que se describe en la presente y el otro agente o tratamiento activo farmacéuticamente dentro de su rango de dosificación. Por ejemplo, se descubrió que la olomucina del inhibidor CDC2 actúa sinergísticamente con agentes citotóxicos conocidos en la inducción de apoptosis (*J. Cell Sci.*, (1995) 108, 2897. Los compuestos de Fórmula III también se pueden administrar en secuencias con agentes anticancerígenos o citotóxicos conocidos cuando una formulación de combinación no es apropiada. La invención no está limitada en la secuencia de administración; los compuestos de Fórmula III se pueden administrar ya sea antes o después de la administración del agente anticancerígeno o citotóxico conocido. Por ejemplo, la actividad citotóxica del flavopiridol inhibidor de quinasa ciclina-dependiente está afectada por la secuencia de administración con agentes

anticancerígenos. *Cáncer Research*, (1997) 57, 3375. Tales técnicas se encuentran dentro de las capacidades de las personas con experiencia en la técnica al igual que de los médicos que asisten.

Por consiguiente, en un aspecto, la presente invención incluye combinaciones que comprenden una cantidad de al menos un compuesto de Fórmula III, o una sal aceptable para uso farmacéutico o solvato del mismo, y una cantidad de uno o más tratamientos anticancerígenos enumerados y agentes anticancerígenos anteriores en los cuales las cantidades de compuestos/ tratamientos producen el efecto terapéutico deseado.

Las propiedades farmacológicas de los compuestos de la presente invención se pueden confirmar mediante una cantidad de ensayos farmacológicos. Los ensayos farmacológicos ejemplificados que se describen más adelantes se llevaron a cabo sin los compuestos de acuerdo con la invención y sus sales.

La presente invención también está dirigida a composiciones farmacéuticas que comprenden al menos un compuesto de Fórmula III, o una sal aceptable para uso farmacéutico o solvato de dicho compuesto y al menos un vehículo aceptable para uso farmacéutico.

Para preparar composiciones farmacéuticas a partir de los compuestos descriptos por la presente invención, vehículos inertes, aceptables para uso farmacéutico pueden ser sólidos o líquidos. Las preparaciones de forma sólida incluyen, polvos, comprimidos, gránulos dispersables, cápsulas, pastillas masticables y supositorios. Los polvos y comprimidos pueden estar compuestos por alrededor de 5 a alrededor del 95 porciento de componente activo. Los vehículos sólidos adecuados son conocidos en la técnica, por ejemplo, carbonato de magnesio, estearato de magnesio, talco, azúcar o lactosa. Los comprimidos, polvos, pastillas masticables y cápsulas se pueden usar como formas de dosificación sólida adecuadas para la administración oral. Ejemplos de vehículos aceptables para uso farmacéutico y métodos de fabricación de varias composiciones se pueden encontrar en A. Gennaro (ed.), *Remington's Pharmaceutical Sciences*, 18th Edition, (1990), Mack Publishing Co., Easton, Pensilvania.

Las preparaciones en forma líquida incluyen soluciones, suspensiones y emulsiones. Como un ejemplo, se pueden mencionar agua o soluciones de agua-glicol propileno para inyección parenteral o adición de edulcorantes u opacadores para soluciones orales, suspensiones y emulsiones. Las preparaciones de forma líquida también incluyen soluciones para administración intranasal.

Las preparaciones en aerosol adecuadas para inhalación pueden incluir soluciones y sólidos en forma de polvo, que se pueden encontrar en combinación con un vehículo aceptable para uso farmacéutico, tal como un gas comprimido inerte, por ejemplo nitrógeno.

También se incluyen preparaciones en forma sólida que se pretende convertir, inmediatamente después del uso, en preparaciones en forma líquida ya sea para administración oral o parenteral. Tales formas líquidas incluyen soluciones, suspensiones y emulsiones.

Los compuestos de la invención también se pueden entregar transdérmicamente. Las composiciones transdérmicas pueden tomar la forma de cremas, lociones, aerosoles y/o emulsiones y se pueden incluir en un parche transdérmico de tipo de matriz o reservorio, como son convencionales en la técnica con este fin.

Los compuestos de la presente invención también se pueden administrar por vía subcutánea.

Preferentemente, el compuesto se administra por vía oral o intravenosa.

Preferentemente, la preparación farmacéutica se encuentra en una forma de dosificación unitaria. En dicha forma, la preparación se subdivide en dosis unitarias de tamaño adecuado que contienen cantidades apropiadas del componente activo, por ejemplo, una cantidad efectiva para lograr el efecto deseado.

La cantidad de compuesto activo en una dosis unitaria de preparación se puede variar o regular de alrededor de 1 mg a alrededor de 100 mg, preferentemente de alrededor de 1 mg a alrededor de 50 mg, más preferentemente de alrededor de 1 mg a alrededor de 25 mg, de acuerdo con la aplicación en particular.

La dosis real que se emplea puede variar que depende de los requisitos del paciente y de la gravedad de la afección que se trata. La determinación del régimen adecuado de dosificación para una situación en particular se encuentra dentro del conocimiento de la técnica. Para mayor conveniencia, la dosificación diaria total se puede dividir y administrar en porciones durante el día según se requiera.

La cantidad y frecuencia de administración de los compuestos de la invención y/o de las sales aceptables para uso farmacéutico del mismo se regularán de acuerdo con el criterio del médico que asiste considerando factores tales como la edad, estado y tamaño del paciente, al igual que gravedad de los síntomas que se someten a tratamiento. Un régimen de dosificación típico recomendado para la administración oral puede oscilar de alrededor de 1 mg/día a alrededor de 500 mg/día, preferentemente 1 mg/día a 200 mg/día, en dosis divididas en dos a cuatro.

Otro aspecto de la presente invención es un equipo que comprende una cantidad efectiva terapéuticamente de al menos un compuesto de Fórmula III, o una sal aceptable para uso farmacéutico o solvato de dicho compuesto un portador, vehículo o diluyente aceptable para uso farmacéutico.

Otro aspecto más de la presente invención es un equipo que comprende una cantidad de al menos un compuesto de Fórmula III, o una sal aceptable para uso farmacéutico o solvato de dicho compuesto y una cantidad de al menos una terapia anticáncer y/o agente anticancerígeno enumerados anteriormente, en los cuales las cantidades de los dos o más componentes producen el efecto terapéutico deseado.

La invención que se revela en la presente se ejemplifica por medio de las siguientes preparaciones y ejemplo que no se debe considerar que limitan el alcance de la invención. rutas mecanísticas y estructuras análogas alternativas serán evidentes para aquellos con experiencia en la técnica.

Cuando se presentaron los datos de las RMN, se obtuvieron los espectros de ^1H en ya sea una Varian VXR-200 (200 MHz, ^1H), Varian Gemini-300 (300 MHz) o XL-400 (400 MHz) y se reportan como ppm en campo descendentes de Me_4Si con cantidad de protones, multiplicidades, y constantes de acoplamiento en

Hertz indicadas parenteralmente. Cuando se presentaron los datos de LC/MS, los análisis se realizaron usando un espectrómetro de masa Applied Biosystems API-100 y Shimadzu SCL-10A LC columna: Altech platinum C18, 3 microns, 33mm x 7mm ID; flujo de gradiente: 0 min – 10% CH_3CN, 5 min – 95% CH_3CN, 7 min – 95% CH_3CN, 7,5 min – 10% CH_3CN, 9 min – alto. Se dan el tiempo de retención y el ión del progenitor observado.

Se puede hacer referencia a los siguientes solventes y reactivos mediante su abreviaturas entre paréntesis:

Cromatografía de capa delgada: TLC

diclorometano: CH_2Cl_2

acetato de etilo: AcOEt o EtOAc

metanol: MeOH

trifluoroacetato: TFA

trietilamina: Et_3N o TEA

butoxicarbonilo: n-Boc o Boc

espectroscopía de resonancia magnética nuclear: RMN

espectrometría de masa de cromatografía líquida: LCMS

espectrometría de masa de alta definición: HRMS

mililitros: mL

milimoles: mmol

microlitros: µl

gramos: g

miligramos: mg

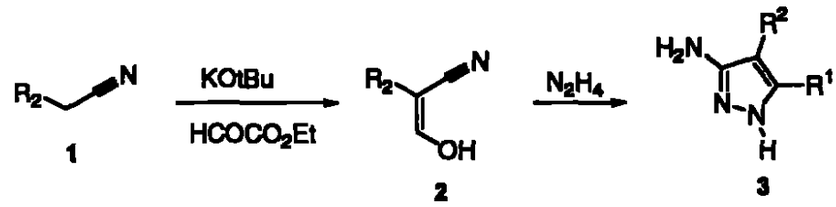
temperatura ambiente o ta (ambiente): alrededor de 25ºC.

dimetoxietano: DME

EJEMPLOS

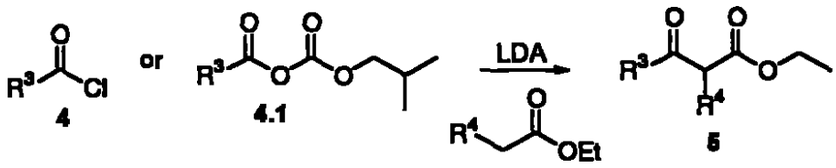
En general, los compuestos descriptos en la presente invención se pueden preparar a través de los rutas generales descriptas a continuación en el Esquema 1.

Esquema 1



El tratamiento del nitrilo de partida con t-butóxido de potasio y formato de etilo produce el intermediario enol 2 que al tratarlo con hidrazina da el 3-aminopirazol sustituido deseado. La condensación de compuestos de tipo 3 con el ceto éster con grupos funcionales de manera apropiada de tipo 5 da lugar a las piridonas 6 según se muestra en el Esquema 3. Los ceto ésteres usados en esta ruta general se encuentran disponibles comercialmente o se pueden preparar según se ilustra en el Esquema 2.

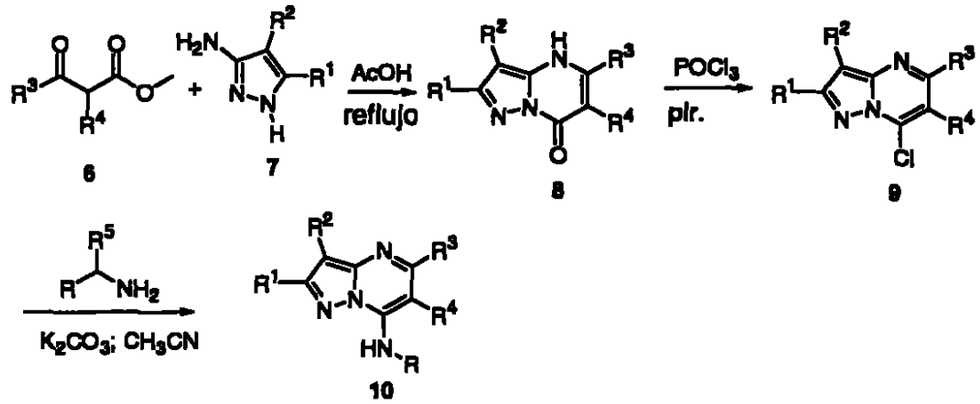
Esquema 2



Los cloruros de tipo 9 se pueden preparar mediante el tratamiento de las piridonas 8 con $POCl_3$, Cuando R^2 es igual a H, es posible la sustitución en esta posición en los compuestos de tipo 9 mediante halogenación electrofílica, acilación, y varias otras sustituciones aromáticas electrofílicas.

La introducción de los grupos funcionales del N7-amino se puede lograr mediante el desplazamiento del cloruro de los compuestos de tipo 9 mediante la reacción con la amina apropiada según se muestra en el Esquema 3.

Esquema 3

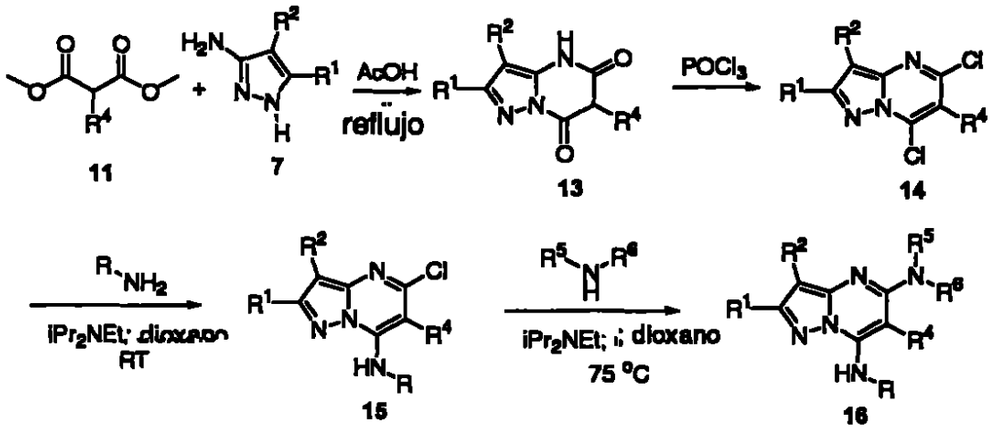


La condensación de compuestos de tipo 7 con el malonato éster con grupos funcionales de manera apropiada de tipo 11 da lugar a las piridonas 13 según se muestra en el Esquema 4.

Los cloruros de tipo 14 se pueden preparar mediante el tratamiento de las 13 con $POCl_3$. Cuando R^2 es H, la sustitución en esta posición es posible en los compuestos de tipo 9 mediante halogenación electrofílica, acilación, y varias otras sustituciones aromáticas electrofílicas.

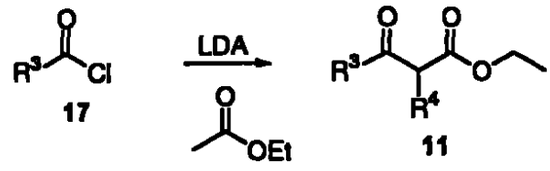
La incorporación de los grupos funcionales de N7-amino se puede lograr a través de el desplazamiento regioselectivo del cloruro de los compuestos de tipo 14. Incorporación de los grupos funcionales N5-amino mediante la adición de una amina apropiada a temperatura más elevada.

Esquema 4



De manera alternativa, las condensaciones de los aminopirazolos de tipo 7 con un ceto éster con grupos funcionales de manera apropiada según se preparó en el Esquema 5, genera los compuestos de tipo 13 según se muestra en el Esquema 4.

Esquema 5



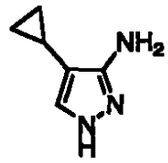
Los cloruros de tipo 14 se pueden preparar mediante el tratamiento con las piridonas 13 con $POCl_3$. Cuando R^2 es igual a H, la sustitución en esta posición

es posible en los compuestos de tipo 14 mediante halogenación electrofílica, acilación, y varias otras sustituciones aromáticas electrofílicas.

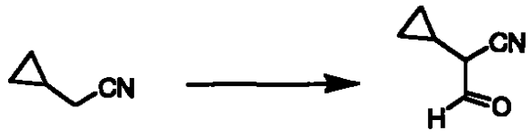
La incorporación de los grupos funcionales N7-amino se puede lograr a través del desplazamiento del cloruro de los compuestos de tipo 15.

Ejemplos preparativos:

EJEMPLO PREPARATIVO 1:

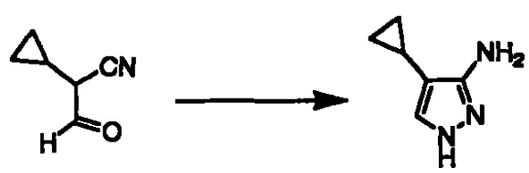


Paso A:



Se siguió Un procedimiento en la Patente Alemana DE 19834047 A1, p 19. A una solución de KOtBu (6,17 g, 0,055 mol) en THF anhídrido (40 ml) se agregó, gota a gota, una solución de ciclopropilacetonitrilo (2,0 g, 0,025 mol) y formato de etilo (4,07 g, 0,055 mol) en THF anhídrido (4 ml). Inmediatamente se formó un precipitado. Esta mezcla se agitó durante 12 hr. Se concentró en vacío y el residuo se agitó con Et_2O (50 ml). El residuo resultante se decantó y se lavó con Et_2O (2 x 50 ml) y se eliminó Et_2O del residuo en vacío. El residuo se disolvió en H_2O (20 ml) frío y el pH se reguló 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 $MgSO_4$ y se concentraron en vacío para dar el aldehído como un líquido de color tostado.

Paso B:



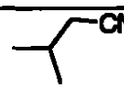
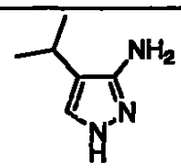
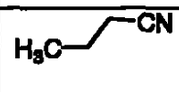
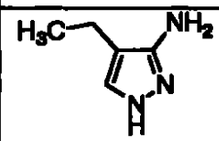
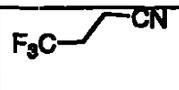
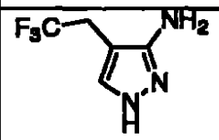
Se disolvieron el producto del Ejemplo Preparativo 1, Paso A (2,12 g, 0,0195 mol), $NH_2NH_2 \cdot H_2O$ (1,95 g, 0,039 mol) y 1,8 g (0,029 mol) de CH_3CO_2H glacial (1,8 g, 0,029 mol) en EtOH (10 ml). Se reflujó durante 6 hr. y se concentró en vacío. El residuo se suspendió en CH_2Cl_2 (150 ml) y el pH se reguló a 9 con

NaOH 1N. La capa orgánica se lavó con salmuera, se secó sobre $MgSO_4$ y se concentró en vacío para dar el producto como un sólido ceroso de color naranja.

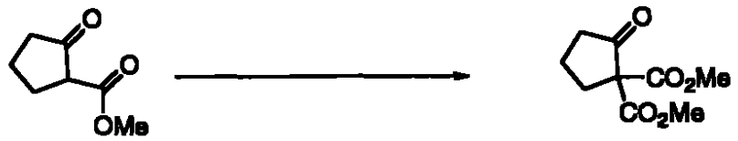
EJEMPLOS PREPARATIVOS 2-4:

Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 1, sustituyendo solamente el nitrilo que se muestran en la Columna 2 de la Tabla 2, los compuestos en la columna 3 de la Tabla 2 se prepararon:

TABLA 2

Ej. Prep.	Columna 2	Columna 3
2		
3		
3,10		

EJEMPLO PREPARATIVO 4



Se agregó 2-carbometoxiciclopentanona (6,6 ml, 0,05 mol) en THF (15 ml) gota a gota a una suspensión agitada vigorosamente de NaH (60% en aceite mineral, 4 g, 0,1 mol) en THF (100 ml) a 0 – 10 °C. Al cesar 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 monitoreó mediante TLC para la desaparición del material de partida. La mezcla de reacción se desactivó cuidadosamente con agua y se dividió entre acetato de etilo y solución saturada de cloruro de amonio en un embudo. Agitada y separada, la capa orgánica se lavó con salmuera y se secó sobre sulfato anhídrido de sodio.

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Los solventes se eliminaron, y el residuo se purificó mediante cromatografía flash, eluyó con 5% y luego 10% de acetato de etilo en hexano. Se obtuvo 9,4 g de aceite incoloro con 94% de rendimiento. ^{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 litio diisopropilamida en THF (2,0 N, 0,04 mol) a –65 °C, se agregó 2,2-dicarbometoxiciclopentanona (4 g, 0,02 mol) gota a gota en THF (60 ml). La mezcla de reacción resultante se agitó a la misma temperatura antes de agregar cloroformato de metilo (1,54 ml, 0,02 mol). La mezcla de reacción se agitó durante una hora y se vertió en solución de cloruro de amonio saturado 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 eliminaron in vacuo, y el residuo se purificó mediante cromatografía flash, eluyó con acetato de etilo incrementado del 30% a 50% en hexano. Se obtuvo 2,3 g de aceite amarillento con 58% de rendimiento. ^{1}H RMN ($CDCl_3$) δ 3,77(s, 6H), 3,32(t, 1H), 3,60-3,10(m, 4H).

EJEMPLO PREPARATIVO 6:



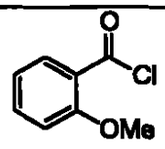
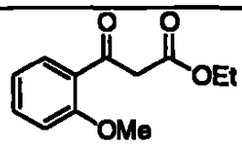
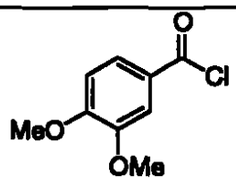
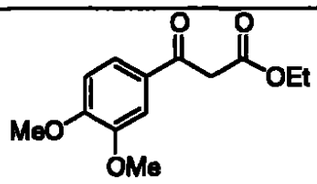
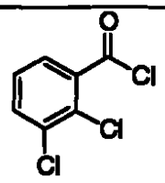
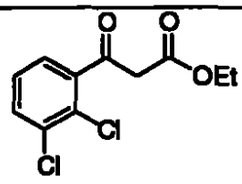
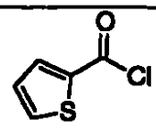
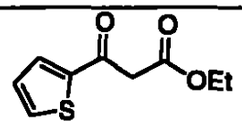
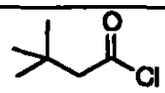
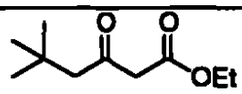
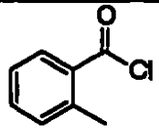
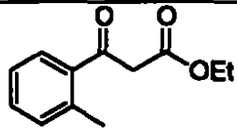
Las reacciones se llevaron a cabo según se describió en (K. O. Olsen, *J. Org. Chem.*, (1987) 52, 4531 – 4536). Por consiguiente, se agregó acetato de etilo destilado recientemente, gota a gota a una solución agitada de diisopropilamida de litio en THF de -65 a –70° C. La solución resultante se agitó durante 30 min y se agregó el clorácido como una solución en THF. La mezcla de reacción se agitó a –65 a –70° C durante 30 min y luego se finalizó mediante la adición de solución de HCl 1 N. La mezcla resultante de dos fases se dejó

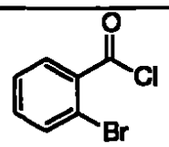
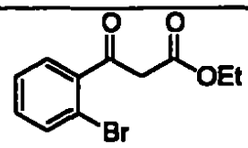
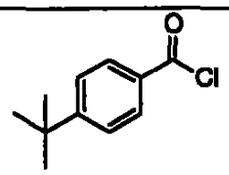
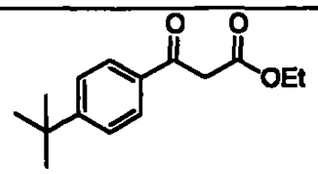
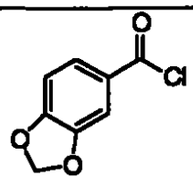
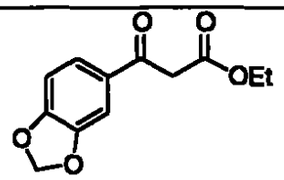
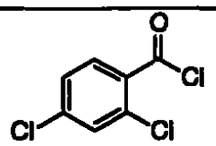
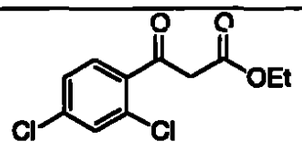
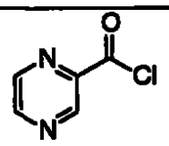
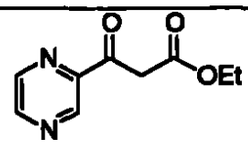
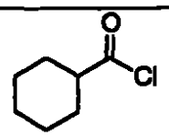
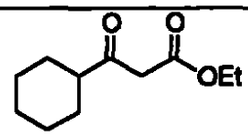
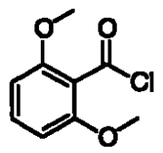
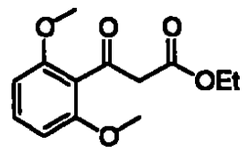
calentar a temperatura ambiente. La mezcla resultante se diluyó con EtOAc (100 ml) y se recolectó la capa orgánica. La capa acuosa se extrajo con EtOAc (100 ml). Las capas orgánicas se combinaron, se lavaron con salmuera, se secaron (Na_2SO_4), y se concentraron en *vacuo* para dar los β-ceto ésteres, que se usaron en las condensaciones posteriores.

EJEMPLOS PREPARATIVOS 7-19:

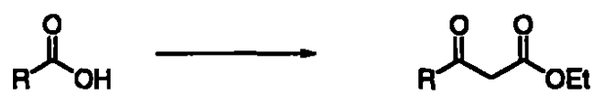
Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 6, sustituyendo solamente los cloruros ácidos que se muestran en la Columna 2 de la Tabla 3, se prepararon los β-ceto ésteres que se muestran en la Columna 3 de la Tabla 3:

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:



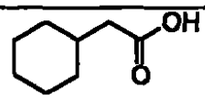
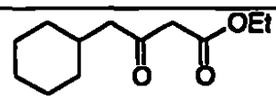
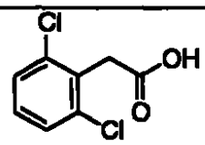
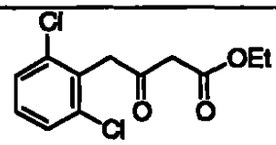
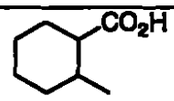
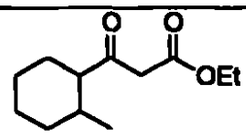
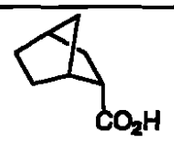
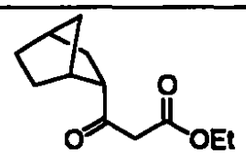
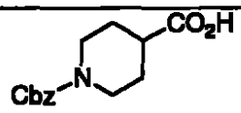
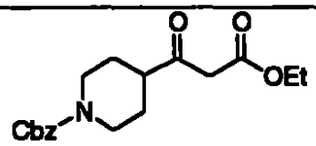
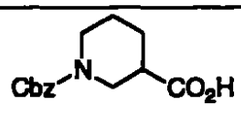
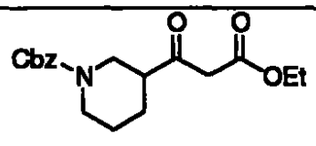
A una solución del ácido en THF se agregó Et_3N, seguido por cloroformato isobutilo de –20 s –30°C. Posteriormente, la mezcla se agitó durante 30 min de –20 a –30°C, se filtró clorhidrato de trietilamina bajo Argón, y el filtrado se agregó a la mezcla de reacción de LDA-EtOAc (preparada según se describió en el Método

A) de –65 a –70°C. Después de la adición de HCl 1 N, seguido por el procesamiento de la mezcla de reacción y la evaporación de los solventes, los β-ceto ésteres brutos se aislaron se aislaron. El material bruto se usó en las condensaciones posteriores.

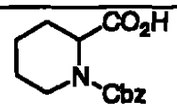
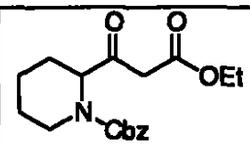
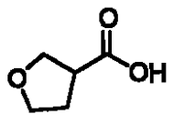
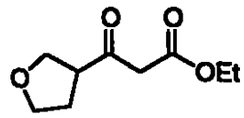
EJEMPLOS PREPARATIVOS 21 - 28:

Esencialmente mediante las mismas condiciones expuestas en el Ejemplo Preparativo 20 sustituyendo solamente 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:

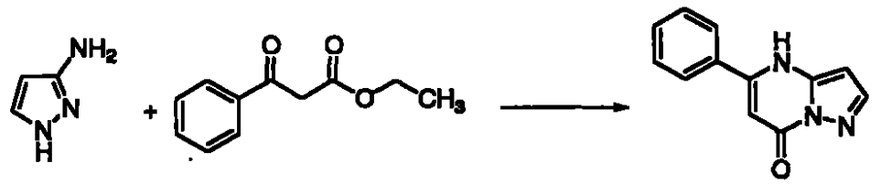
TABLA 4

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

386

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:



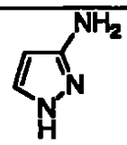
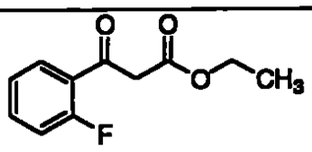
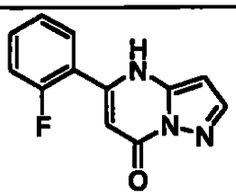
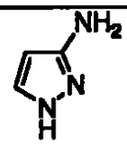
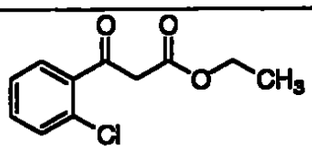
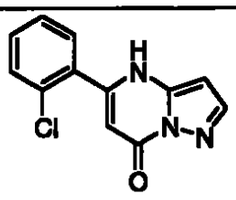
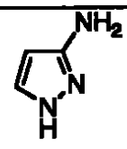
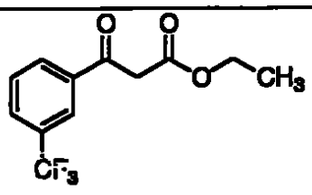
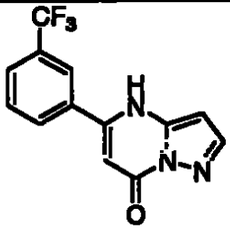
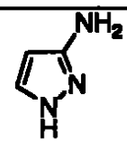
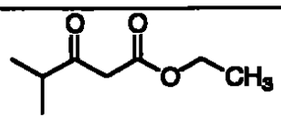
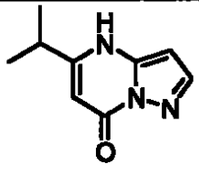
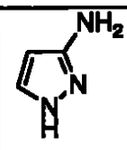
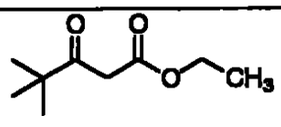
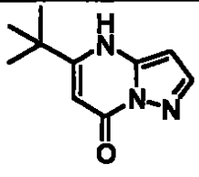
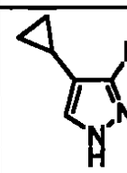
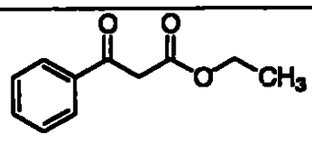
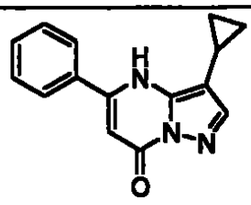
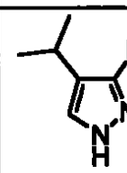
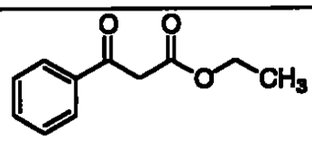
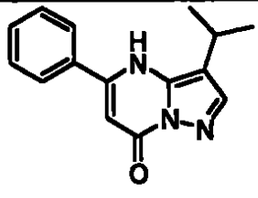
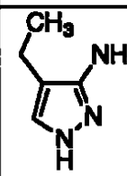
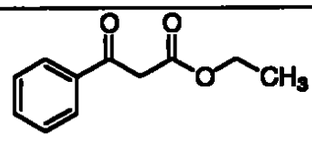
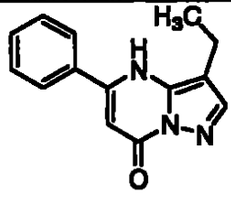
Se calentó una solución de 3-aminopirazol (2,0g, 24,07 mmol) y benzoilacetato de etilo (4,58 ml, 1,1 eq.) en AcOH (15 ml) a reflujo durante 3 horas. La mezcla de reacción se enfrió hasta temperatura ambiente y se concentró *in vacuo*. El sólido resultante se diluyó con EtOAc y se filtró para dar un sólido blanco (2,04 g, 40% de rendimiento).

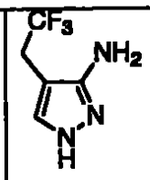
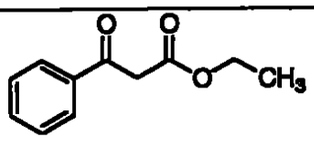
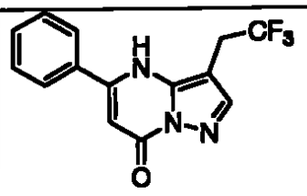
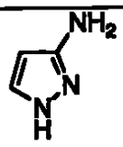
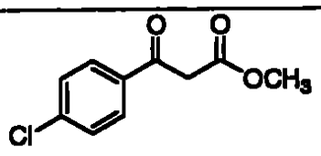
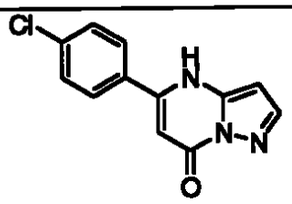
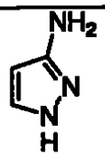
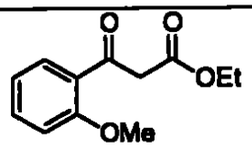
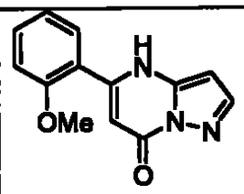
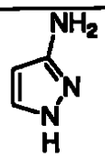
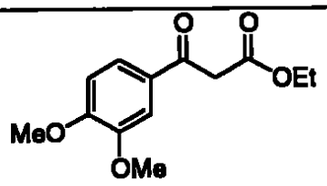
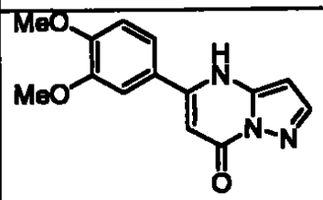
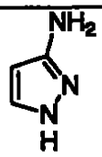
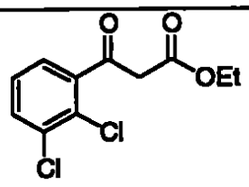
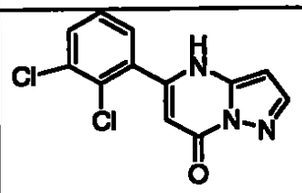
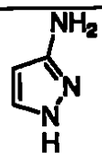
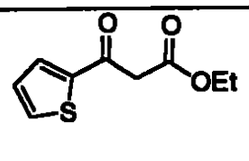
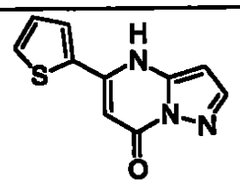
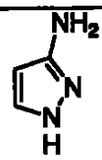
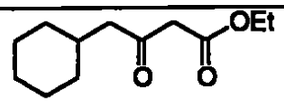
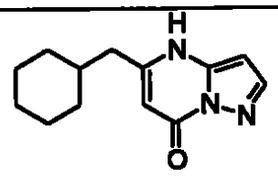
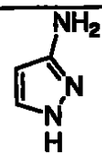
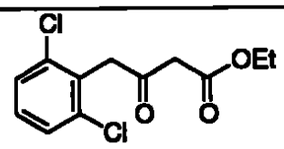
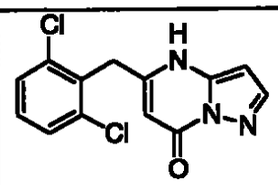
EJEMPLOS PREPARATIVOS 30-73:

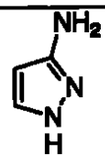
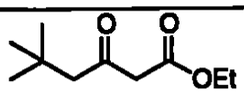
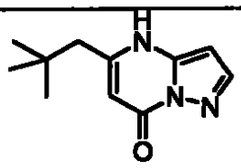
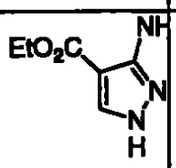
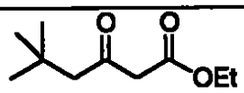
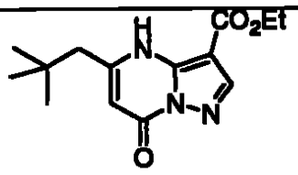
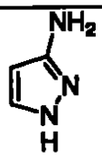
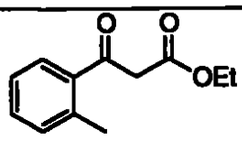
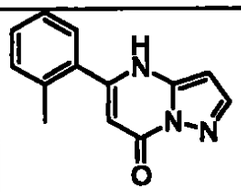
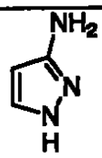
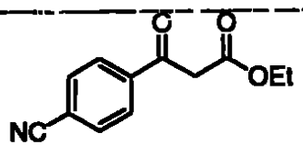
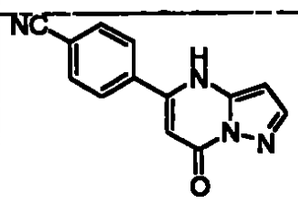
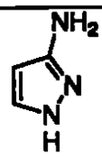
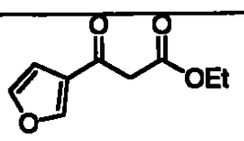
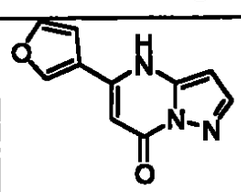
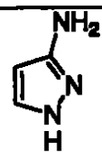
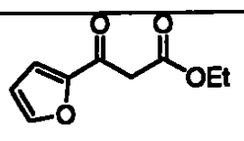
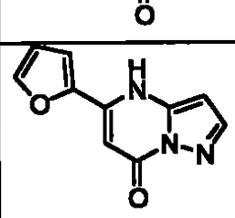
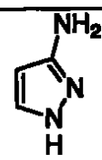
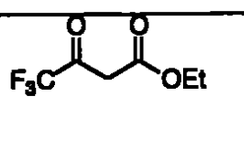
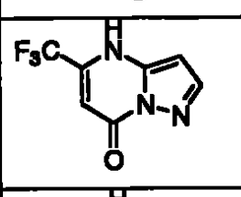
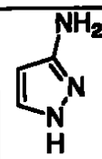
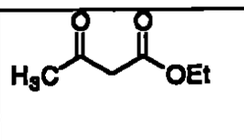
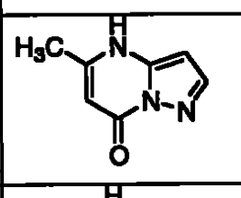
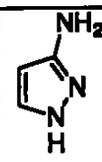
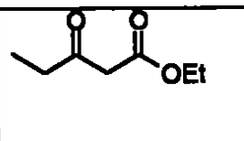
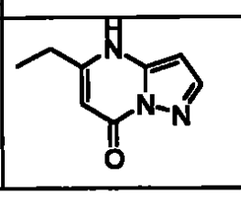
Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 29, sustituyendo solamente el aminopirazol que se muestra en la Columna 2 de la Tabla 5 y el éster que se muestra en la Columna 3 de la Tabla 5, se prepararon los compuestos que se muestran en la Columna 4 de la Tabla 5:

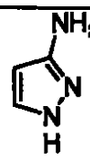
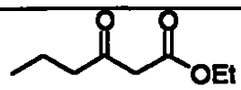
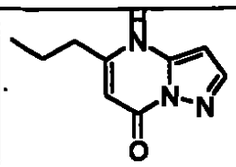
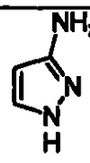
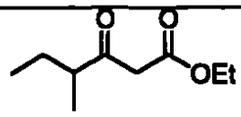
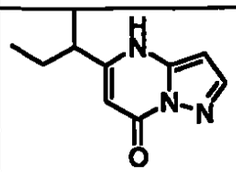
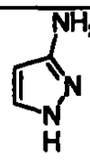
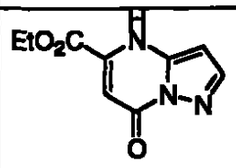
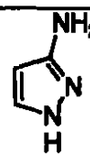
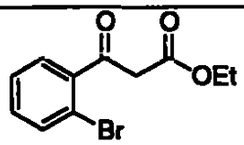
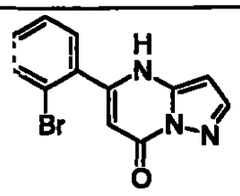
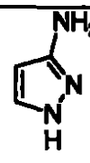
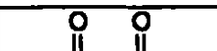
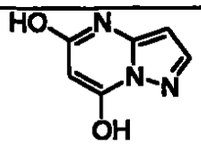
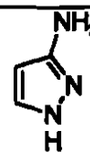
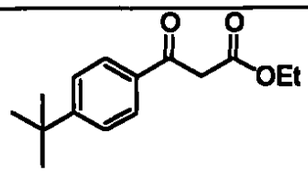
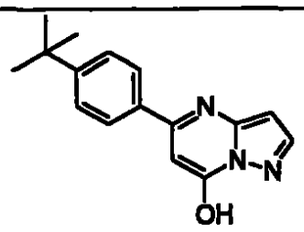
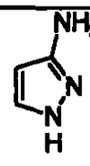
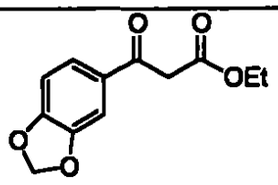
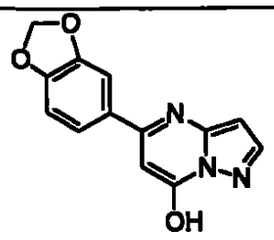
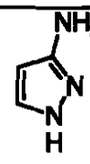
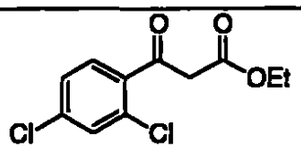
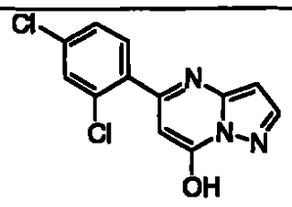
TABLA 5

Ej. Prep.	Columna 2	Columna 3	Columna 4	Columna 5

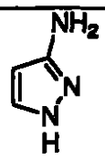
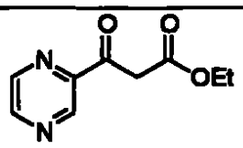
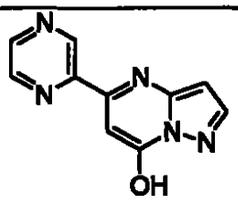
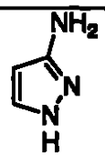
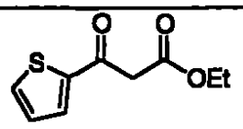
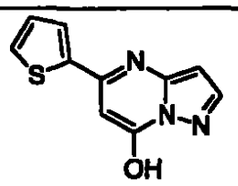
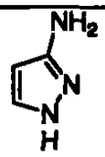
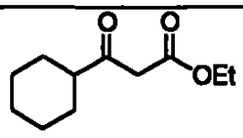
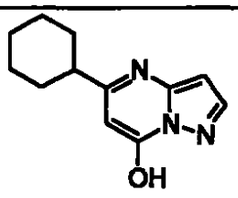
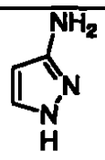
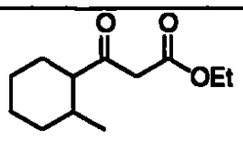
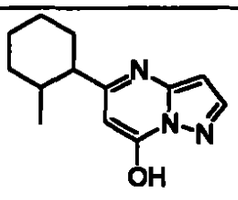
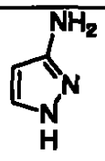
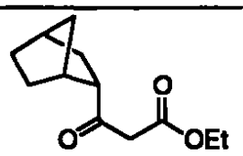
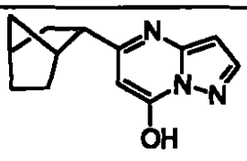
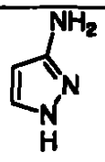
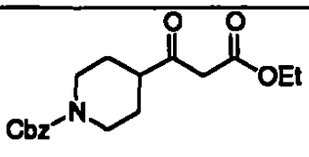
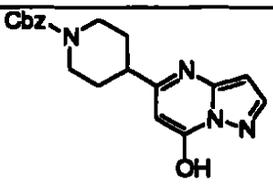
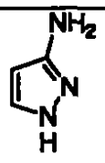
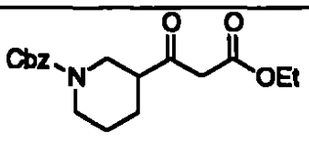
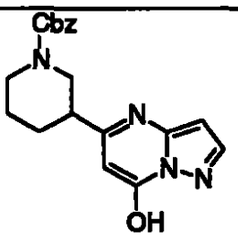
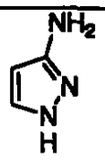
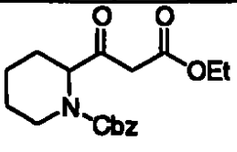
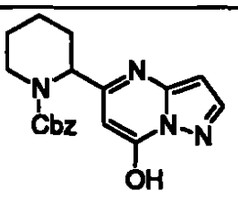
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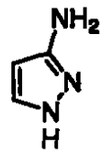
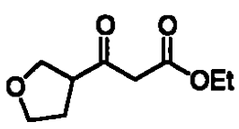
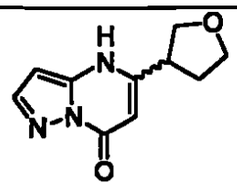
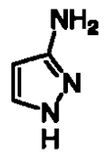
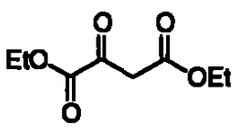
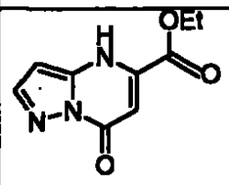
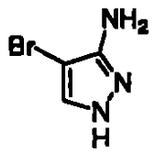
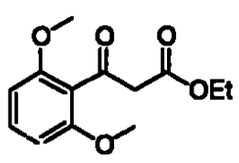
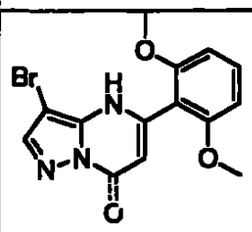
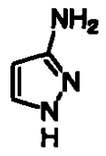
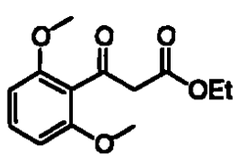
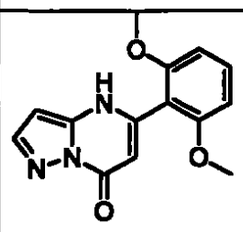
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59				Rendimiento = 46 MH^+ = 268
60				Rendimiento = 63 MH^+ = 255
61				Rendimiento = 80 MH^+ = 280

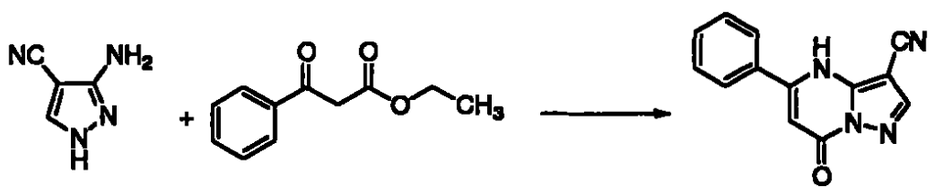
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63				Rendimiento = 51 MH^+ = 218
64				Rendimiento = 82 MH^+ =218
65				Rendimiento = 39 MH^+ =232
66				Rendimiento = 30 MH^+ =230
67				Rendimiento = 80 MH^+ =353
68				Rendimiento = 49 MH^+ =353
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392

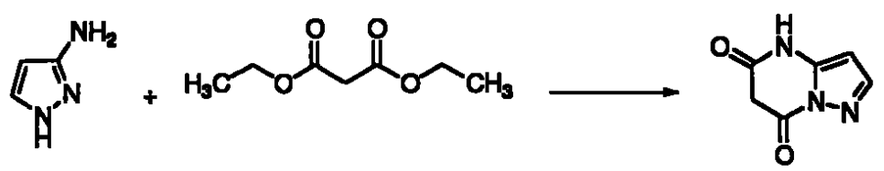
70				
71				
72				
73				

EJEMPLO PREPARATIVO 74:



Se calentaron benzoilacetato de etilo (1,76 ml, 1,1 eq.) y 3-amino-4-cianopirazol (1,0 g, 9,25 mmol) en AcOH (5,0 ml) y H_2O (10 ml) a reflujo 72 horas. La solución resultante se enfrió hasta temperatura ambiente, se concentró *in vacuo*, y se diluyó con EtOAc. El precipitado resultante se filtró, se lavó con EtOAc, y se secó *in vacuo* (0,47 g, 21% de rendimiento).

EJEMPLO PREPARATIVO 75



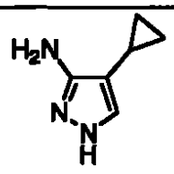
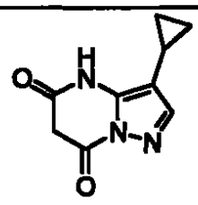
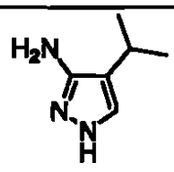
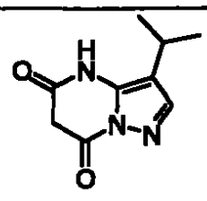
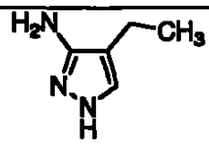
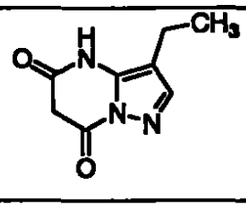
393

Se siguió el procedimiento en la patente estadounidense 3.907.799. Se agregó sodio (2,3 g, 2 eq.) a EtOH (150 ml) en porciones. Cuando el sodio se disolvió completamente, se agregaron 3-aminopirazol (4,2 g, 0,05 mol) y dietil malonato (8,7 g, 1,1 eq.) y la solución resultante se calentó a reflujo durante 3 horas. La suspensión resultante se enfrió hasta temperatura ambiente y se filtró. La torta de filtrado 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 reguló a 1-2 con HCl concentrado. La suspensión resultante se filtró, se lavó con agua (100 ml) y se secó en vacío para dar un sólido blanco (4,75 g, 63% de rendimiento).

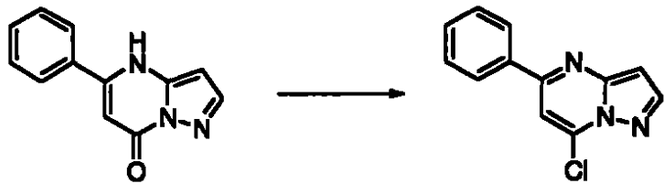
EJEMPLOS PREPARATIVOS 76-78:

Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 75, sustituyendo solamente 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:

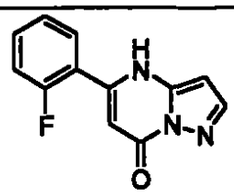
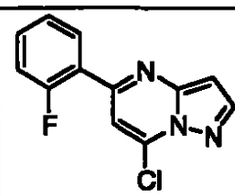
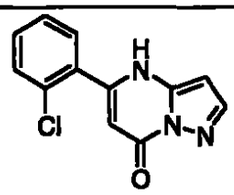
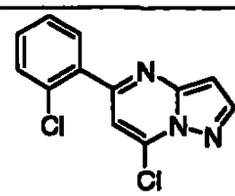


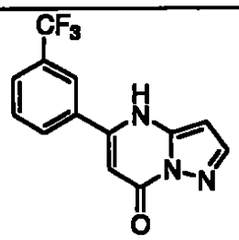
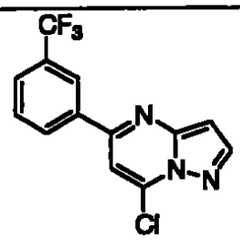
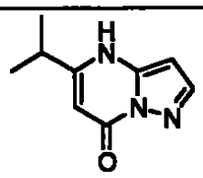
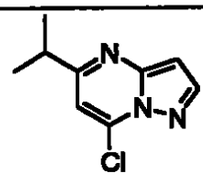
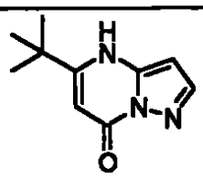
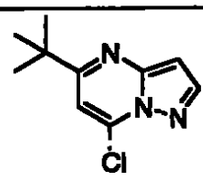
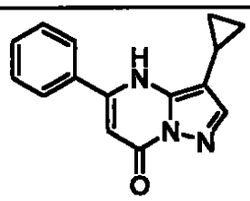
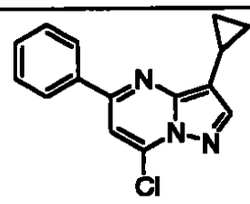
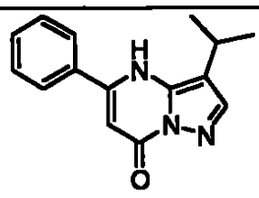
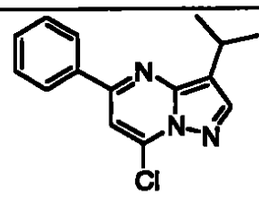
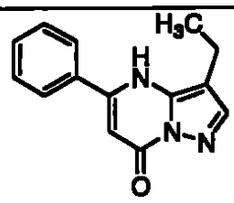
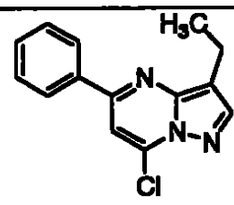
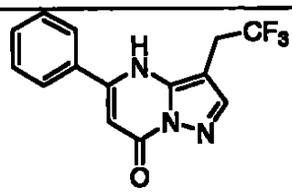
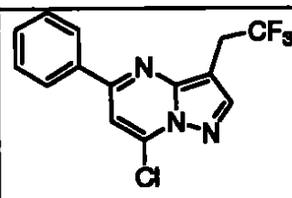
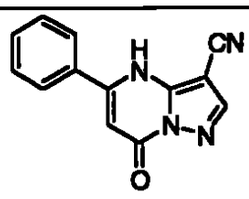
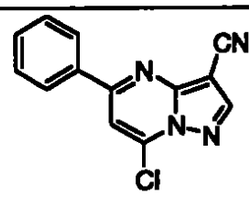
Se agitó una solución del compuesto preparado en el Ejemplo preparativo 29 (1,0 g, 4,73 mmol) en $POCl_3$ (5 ml) y piridina (0,25 ml) a temperatura ambiente 3 días. La suspensión resultante se diluyó con Et_2O, se filtró, y el residuo sólido se lavó con Et_2O. Los lavados de Et_2O combinados se enfriaron hasta 0°C y se trataron con hielo. Cuando se detuvo 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 NaCl saturado, se secaron sobre Na_2SO_4, se filtraron, y se concentraron para dar un sólido amarillo pálido (0,86 g, 79% de rendimiento). LCMS: MH^+=230.

EJEMPLO PREPARATIVO 80-122:

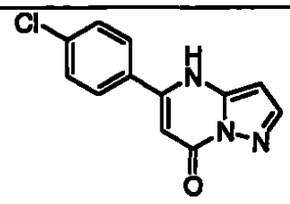
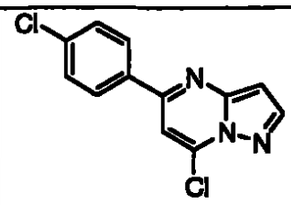
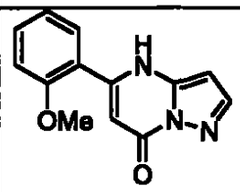
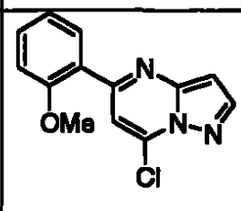
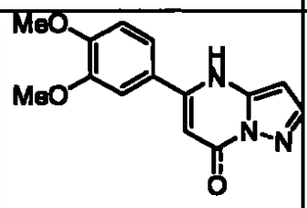
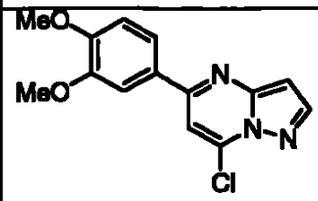
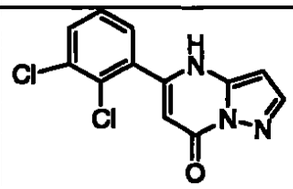
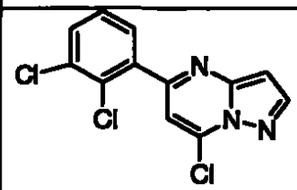
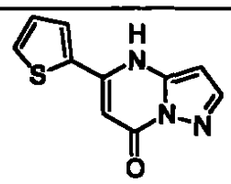
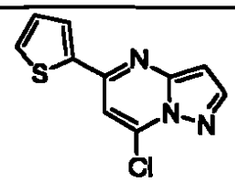
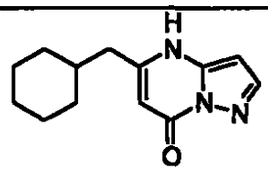
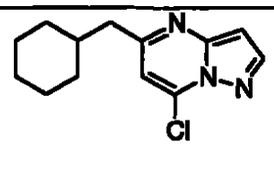
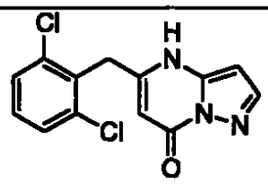
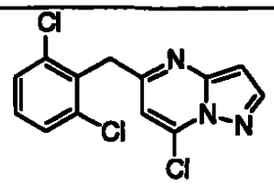
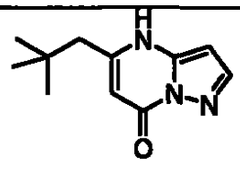
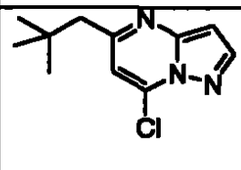
Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 79, sustituyendo solamente el compuesto que se muestra en la Columna 2 de la Tabla 7, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 7:

TABLA 7

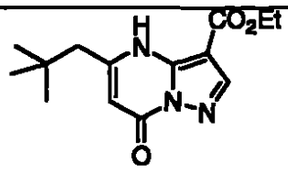
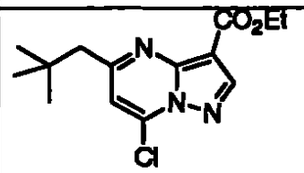
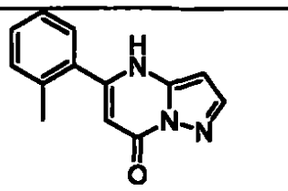
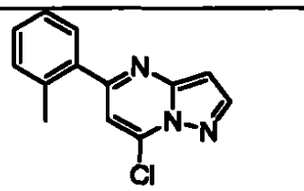
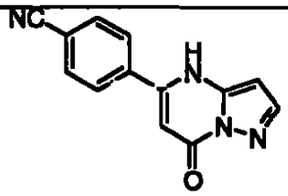
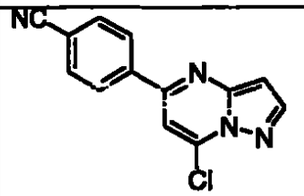
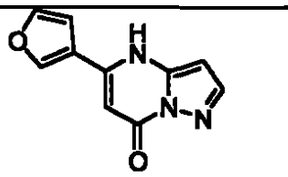
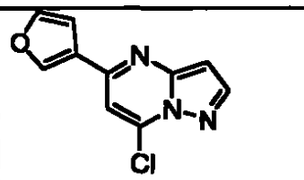
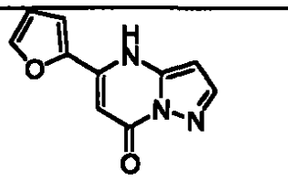
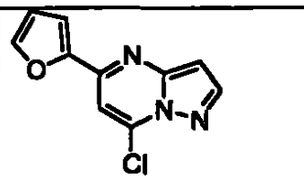
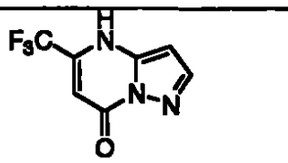
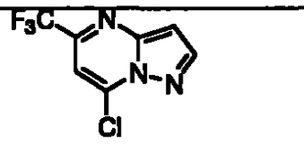
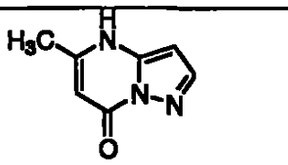
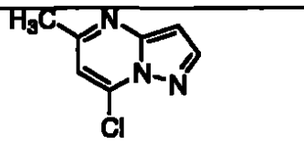
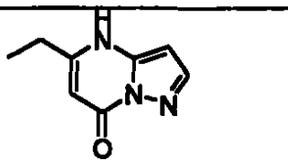
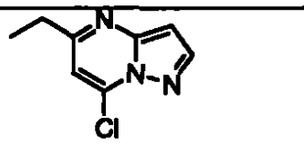
Ej. Prep.	Columna 2	Columna 3	COMPUESTO
80			MS: MH^+=248
81			

82			MS: MH^+=298
83			MS: MH^+=196
84			MS: MH^+=210
85			
86			MS: MH^+=272
87			
87,10			
88			MS: MH^+=255

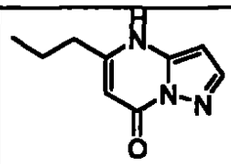
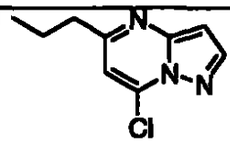
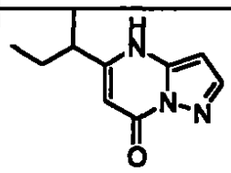
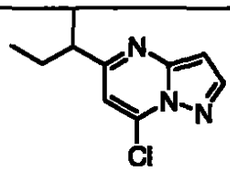
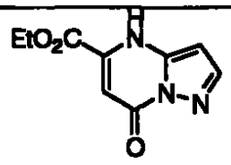
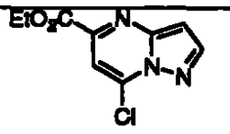
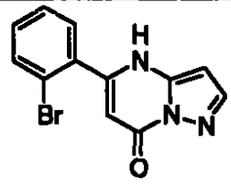
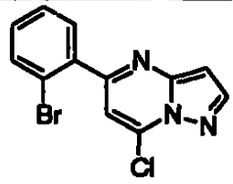
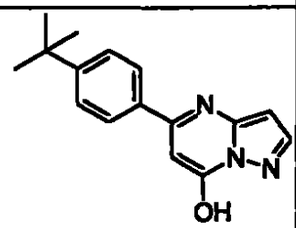
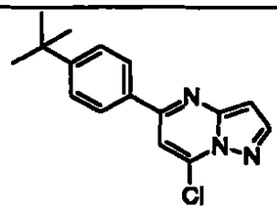
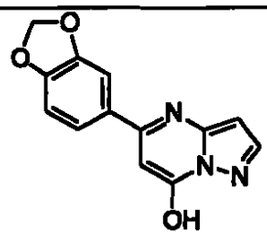
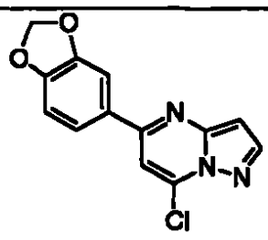
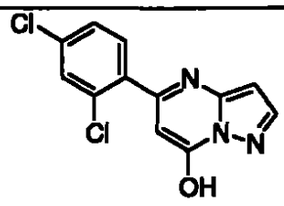
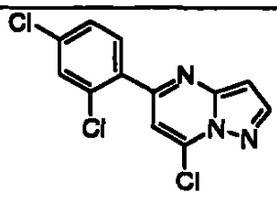
396

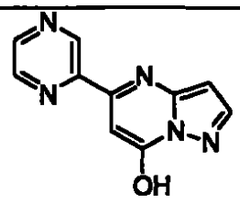
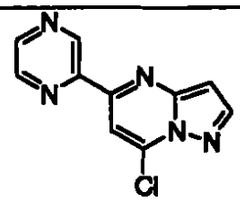
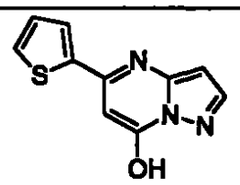
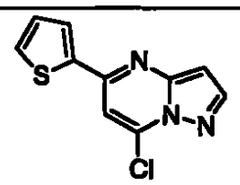
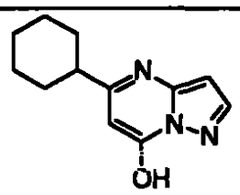
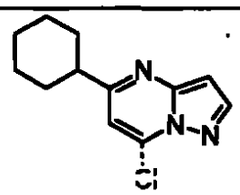
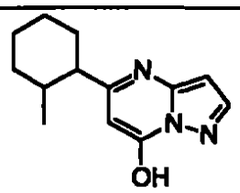
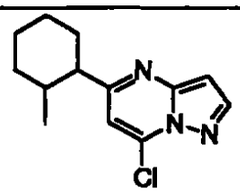
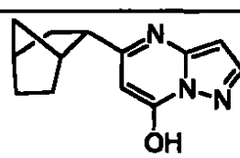
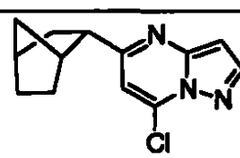
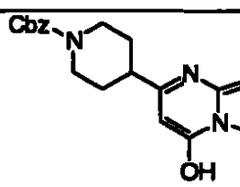
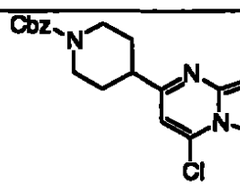
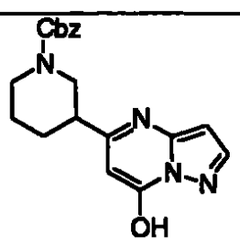
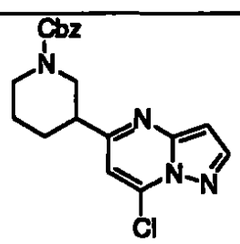
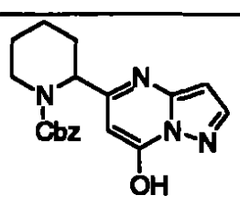
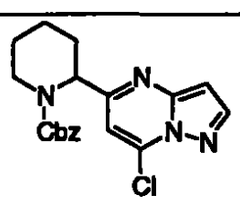
89			
90			**Rendimiento = 65%** MS: MH^+ = 260
91			**Rendimiento = 35%** MS: MH^+ = 290
92			**Rendimiento = 32%** **MS: MH^+ = 298**
93			Rendimiento = 45% **MS: MH^+ = 236**
94			Rendimiento = 100% **LCMS: MH^+ = 250**
95			Rendimiento = 88% MS: MH^+ = 314
96			**Rendimiento =43%** MS:

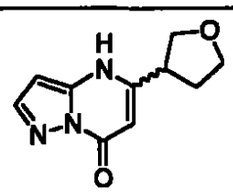
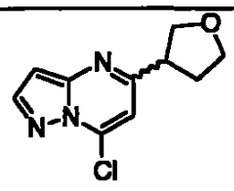
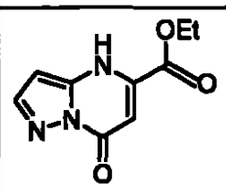
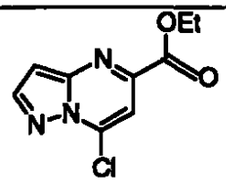
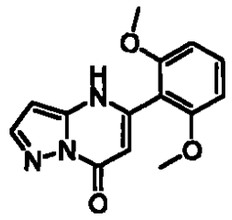
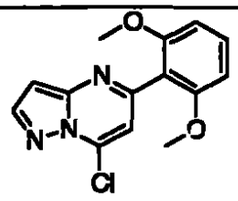
397

			MH^+=223
97			**Rendimiento =30% MS: MH^+=295**
98			**Rendimiento =98% MS: MH^+=244**
99			
100			
101			
102			
103			
104			

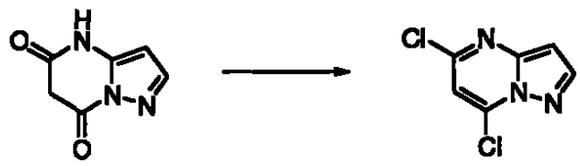
398

105			
106			
107			**45% de rendimiento; MS: MH^+=226**
108			**MS: 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% ^1H 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



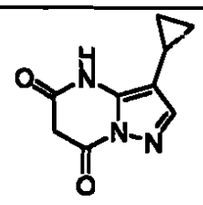
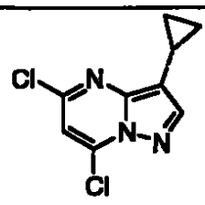
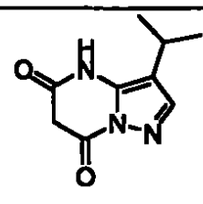
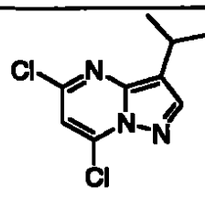
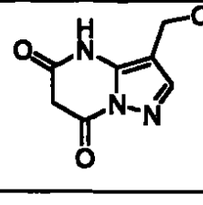
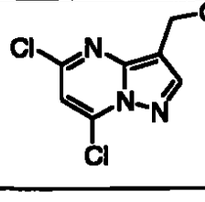
Se enfrió $POCl_3$ (62 ml) hasta 5 °C bajo nitrógeno y dimetilanilina (11,4 g, 2,8 eq.) y el compuesto preparado en el Ejemplo preparativo 75 (4,75 g, 0,032 mol). La mezcla de reacción se calentó hasta 60 °C y se agitó hasta el día siguiente. La mezcla de reacción se enfrió hasta 30 °C y se destiló el $POCl_3$ 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 reguló 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 secaron sobre $MgSO_4$, se filtraron y se concentraron. El producto bruto se purificó mediante cromatografía flash usando una solución de 50 : 50

CH_2Cl_2 : hexanos como eluyente para eluir la dimetil anilina. Luego, se cambió el eluyente a 75 : 25 CH_2Cl_2 : hexanos para eluir el producto deseado (4,58 g, 77% de rendimiento). MS: MH^+=188.

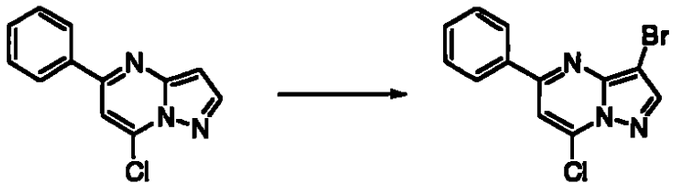
EJEMPLOS PREPARATIVOS 124-126

Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 123, sustituyendo solamente el compuesto en 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:



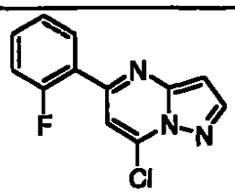
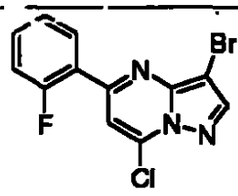
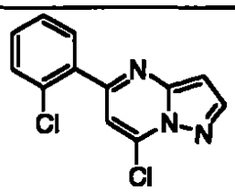
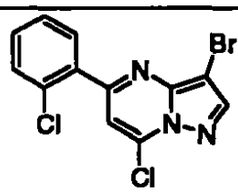
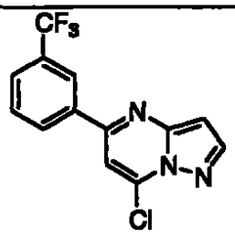
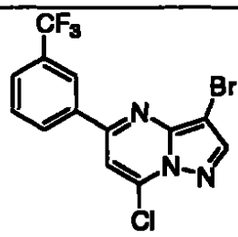
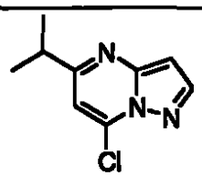
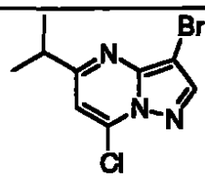
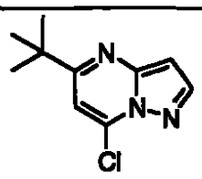
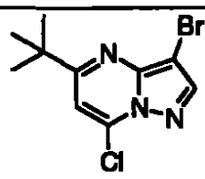
Se trató una solución del compuesto preparado en el Ejemplo preparativo 79 (0,10 g, 0,435 mmol) en CH_3CN (3 ml) con NBS (0,085 g, 1,1 eq.). La mezcla de reacción se agitó a temperatura ambiente 1 hora y se concentraron bajo presión reducida. El producto bruto se purificó mediante cromatografía flash

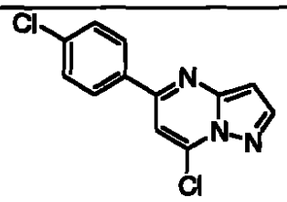
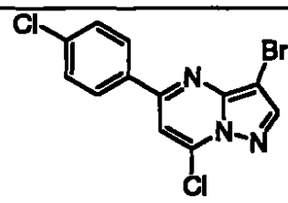
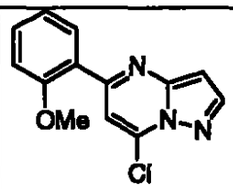
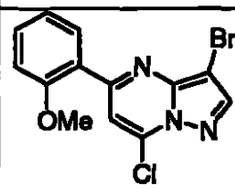
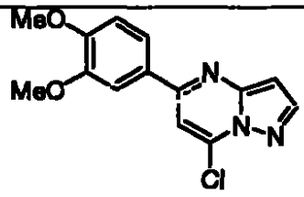
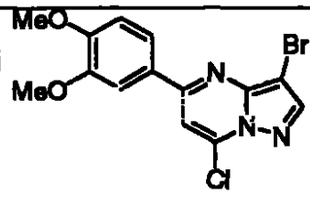
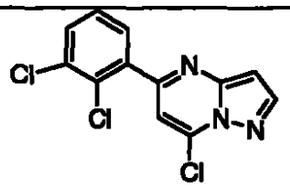
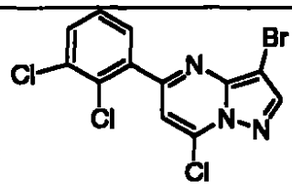
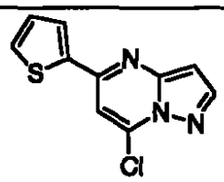
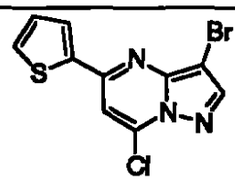
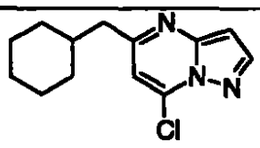
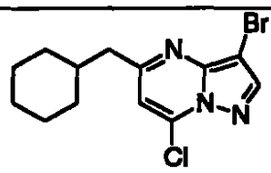
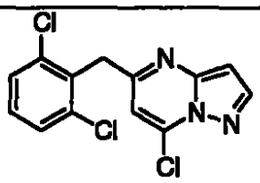
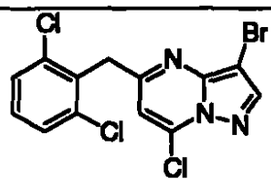
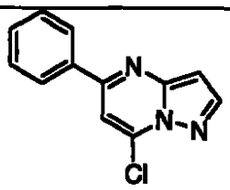
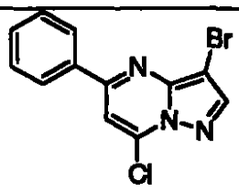
usando una solución EtOAc-en-hexanos 20% como eluyente (0,13 g, 100% de rendimiento). LCMS:MH^+=308.

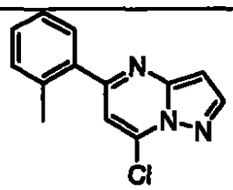
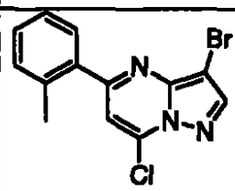
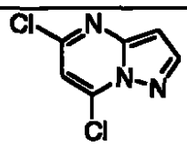
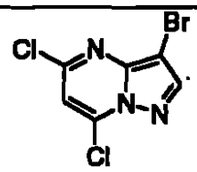
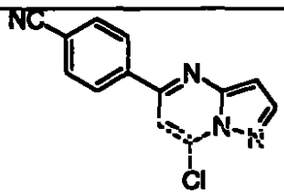
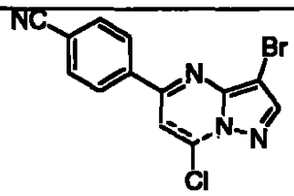
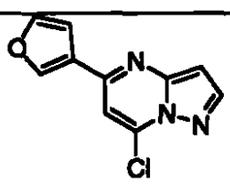
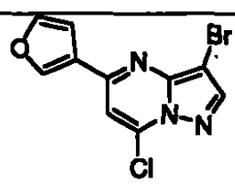
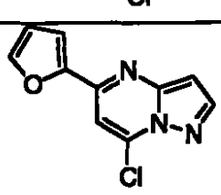
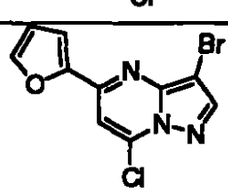
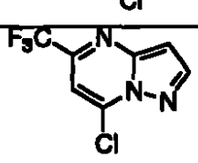
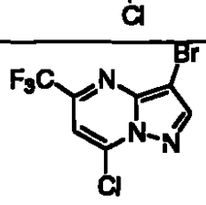
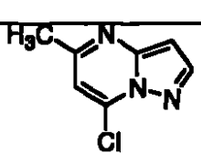
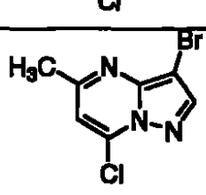
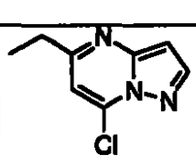
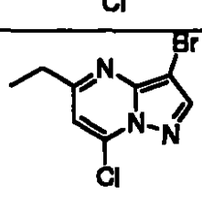
EJEMPLOS PREPARATIVOS 128-164:

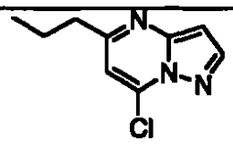
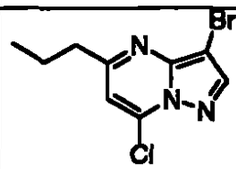
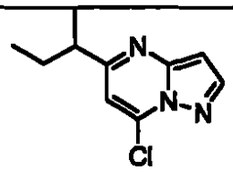
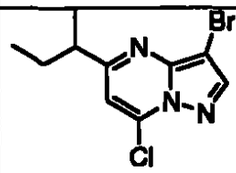
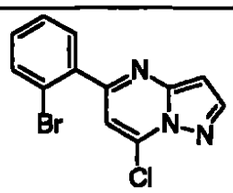
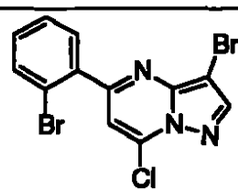
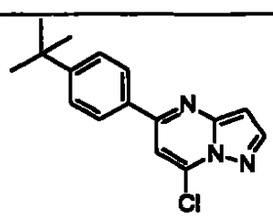
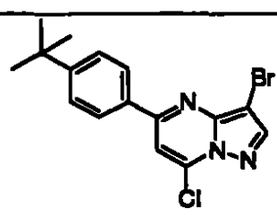
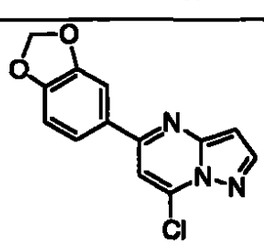
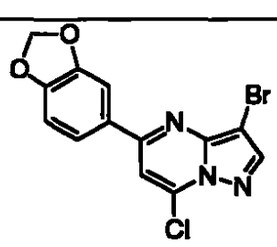
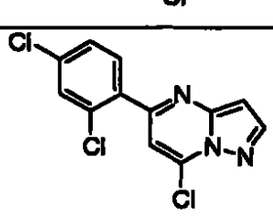
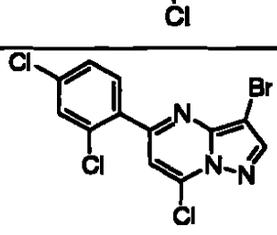
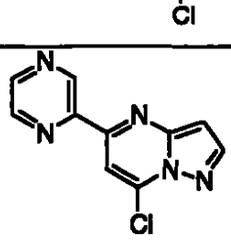
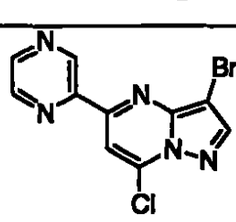
Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 127 sustituyendo solamente los compuestos que se muestran en la Columna 2 de la Tabla 9, los compuestos que se muestran en la Columna 3 de la Tabla 9 se prepararon:

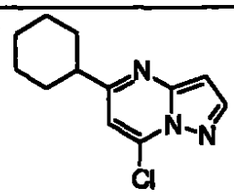
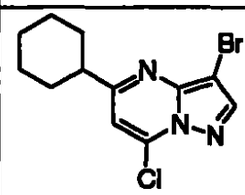
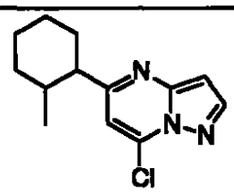
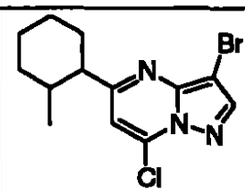
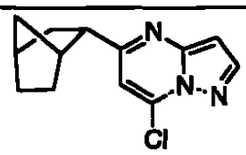
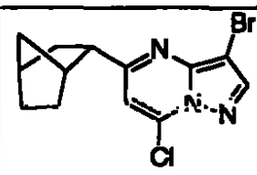
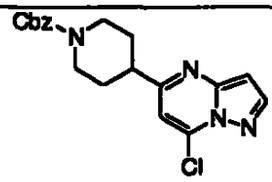
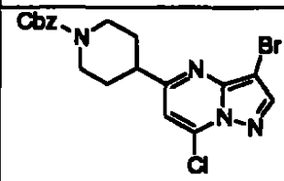
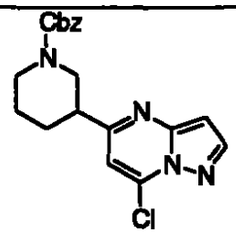
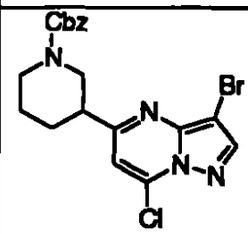
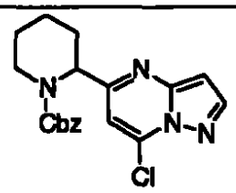
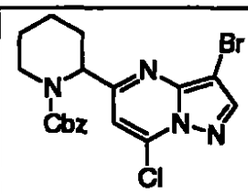
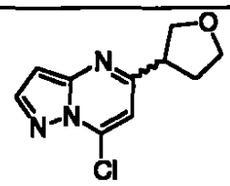
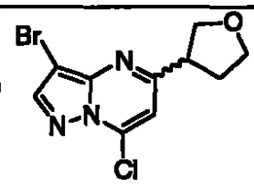
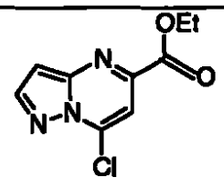
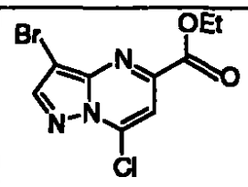
TABLA 9

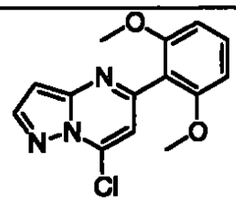
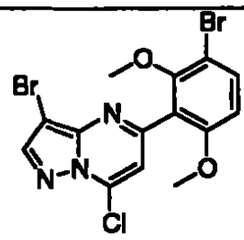
Ej. Prep.	Columna 2	Columna 3	COMPUESTO
128			MS: MH^+= 326
129			MS: MH^+= 342
130			MS: MH^+= 376
131			MS: MH^+=274
132			MS: MH^+=288

Ej. Prep.	Columna 2	Columna 3	COMPUESTO
133			
134			**Rendimiento = 75%** MS: $MH^+ = 338$
135			**Rendimiento = 52%** MS: $MH^+ = 368$
136			**Rendimiento = 87%** **MS: $MH^+ = 376$**
137			Rendimiento = 100% **MS: $MH^+ = 316$**
138			Rendimiento = 92% **MS: $MH^+ = 330$**
139			Rendimiento = 82% MS: $MH^+ = 395$
140			**Rendimiento =88%** MS: MH^+=308

Ej. Prep.	Columna 2	Columna 3	COMPUESTO
141			**Rendimiento =100%** **MS: MH^+=322**
142			**MH^+=266**
143			
144			
145			
146			
147			
148			

Ej. Prep.	Columna 2	Columna 3	COMPUESTO
149			
150			
151			**LCMS:** $MH^+ = 386$
152			Rendimiento = cuant $MH^+ = 364$
153			Rendimiento = cuant $MH^+ = 353$
154			Rendimiento = 95 $MH^+ = 378$
155			Rendimiento = 77 $MH^+ = 311$

Ej. Prep.	Columna 2	Columna 3	COMPUESTO
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**

Ej. Prep.	Columna 2	Columna 3	COMPUESTO
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:

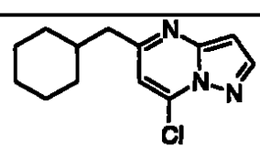
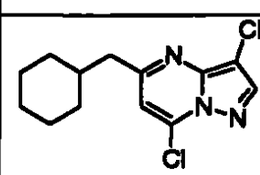


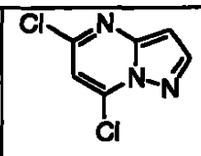
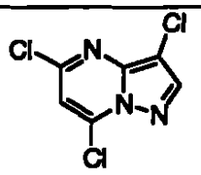
Se trató una solución del compuesto preparado en el Ejemplo preparativo 80 (0,3 g, 1,2 mmol) en CH_3CN (15 ml) con NCS (0,18 g, 1,1 eq.) y la solución resultante se calentó a reflujo 4 horas. Se agregó NCS (0,032 g, 0,2 eq.) adicional y la solución resultante se agitó a reflujo hasta el día siguiente. La mezcla de reacción se enfrió hasta temperatura ambiente, se concentró *in vacuo* y el residuo se purificó mediante cromatografía flash usando una solución de EtOAc 20% en hexanos como eluyente (0,28 g, 83% de rendimiento). LCMS: MH^+= 282.

EJEMPLO PREPARATIVO 166-167:

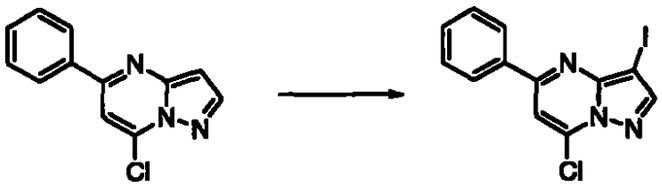
Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 165, sustituyendo solamente el compuesto que se muestra en la Columna 2 de la Tabla 10, se preparó el compuesto que se muestra en la Columna 3 de la Tabla 10:

TABLA 10

Ej. Prep.	Columna 2	Columna 3	COMPUESTO
166			Rendimiento = 82% LCMS: MH^+ = 286

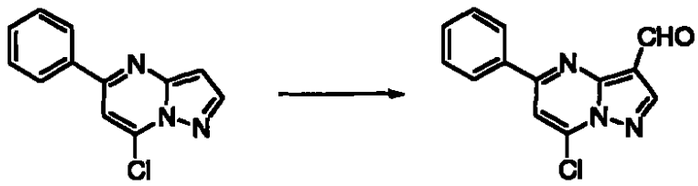
167			

EJEMPLO PREPARATIVO 167.10:



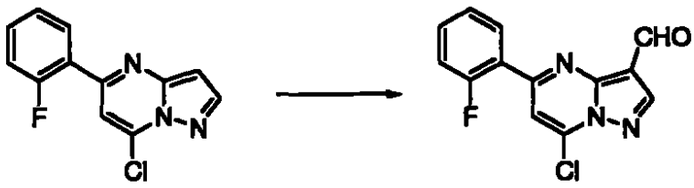
Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 165, sustituyendo solamente N-yodosuccinimida, se preparó el compuesto anterior.

EJEMPLO PREPARATIVO 168:



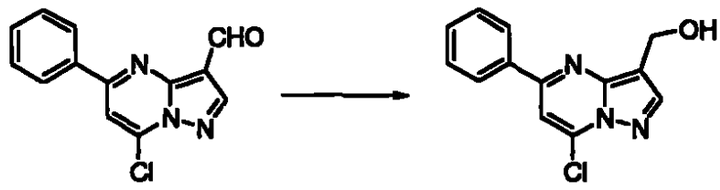
A una solución del compuesto del Ejemplo Preparativo 79 (1,0 g, 4,35 mmol) en DMF (6 ml) se agregó $POCl_3$ (1,24 ml, 3,05 eq.) y la mezcla resultante se agitó a temperatura ambiente hasta el día siguiente. La mezcla de reacción se enfrió hasta 0°C y el $POCl_3$ en exceso se desactivó mediante la adición 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 in vacuo. El producto bruto se purificó mediante cromatografía flash usando una solución de MeOH 5% en CH_2Cl_2 como eluyente (0,95 g, 85% de rendimiento). LCMS: MH^+=258.

EJEMPLO PREPARATIVO 169:



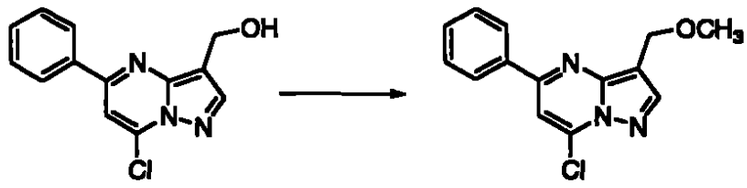
Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 168, sustituyendo solamente el compuesto preparado en el Ejemplo Preparativo 80, se preparó el compuesto anterior (0,45 g, 40% de rendimiento).

EJEMPLO PREPARATIVO 170:



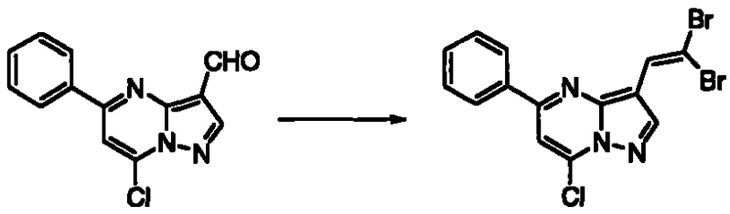
A una solución del producto del Ejemplo Preparativo 169 (0,25 g, 0,97 mmol) en THF se agregó $NaBH_4$ (0,041 g, 1,1 eq.) y la solución resultante se agitó a temperatura ambiente hasta el día siguiente. La mezcla de reacción se desactivó mediante la adición de H_2O y se extrajo con CH_2Cl_2. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron y se concentraron bajo presión reducida. El producto bruto se purificó mediante cromatografía flash usando una mezcla 60: 40 hexanos : EtOAc como eluyente (0,17 g, 69% de rendimiento). MS: MH^+=260.

EJEMPLO PREPARATIVO 171:



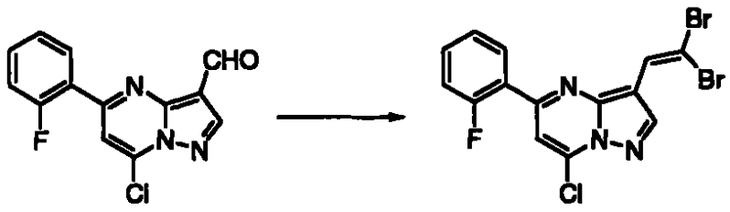
Una solución del compuesto preparado en el Ejemplo Preparativo 170 (0,12 g, 0,462 mmol), dimetil sulfate (0,088 ml, 2,0 eq), 50% NaOH (0,26 ml) y Bu_4NBr catalítico en CH_2Cl_2 (4 ml) se agitó a temperatura ambiente hasta el día siguiente. La mezcla de reacción se diluyó con H_2O y se extrajo con CH_2Cl_2. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron y se concentraron bajo presión reducida. El producto bruto se purificó mediante cromatografía flash usando una solución de 30% 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 mmol). La solución resultante se agitó a 0 °C durante 1 hora y se concentraron bajo presión reducida. El residuo se purificó mediante cromatografía flash usando una solución de 20% EtOAc en hexanos como eluyente (1,07 g, 67% de rendimiento).

EJEMPLO PREPARATIVO 173:



Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 172, sustituyendo solamente el compuesto preparado en el Ejemplo Preparativo 169, se preparó el compuesto anterior (0,5 g, 70% de rendimiento).

EJEMPLO PREPARATIVO 174:



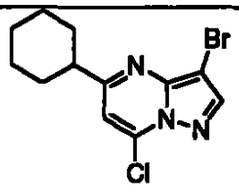
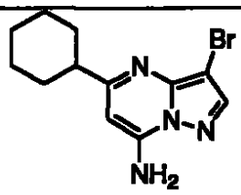
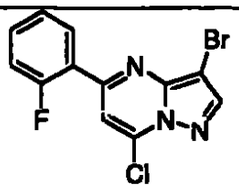
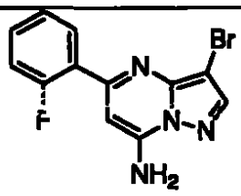
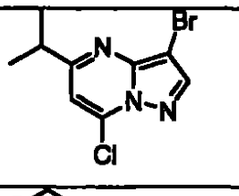
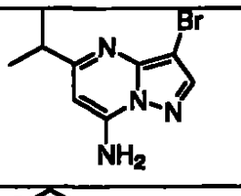
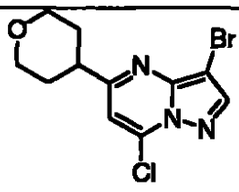
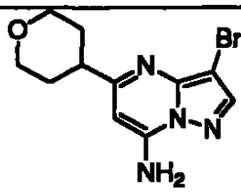
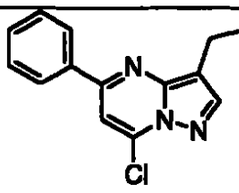
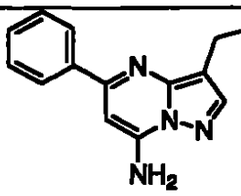
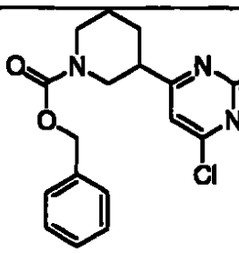
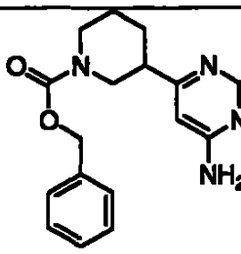
Se agitaron el compuesto preparado en el Ejemplo Preparativo 127 (3,08 g, 10,0 mmol), NH_3 2,0 M en 2-propanol (50 ml, 100,0 mmol), y NH_3 acuoso 37 % (10,0 ml) en un recipiente de presión cerrado a 50°C durante 1 día. El solvente se evaporó y el producto bruto se purificó mediante cromatografía flash 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:

Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 174, sustituyendo solamente el compuesto que se muestra en la

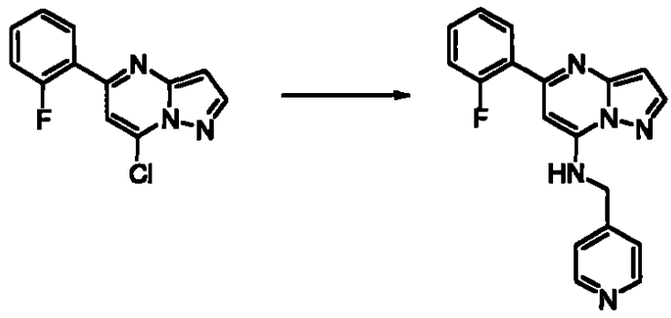
Columna 2 de la Tabla 11, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 11.

TABLA 11

Ej. Prep.	Columna 2	Columna 3
175		
176		
177		
178		
179		
180		

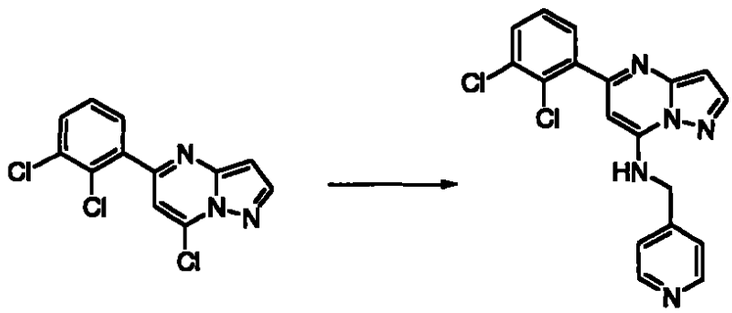
EJEMPLO PREPARATIVO 181:

412



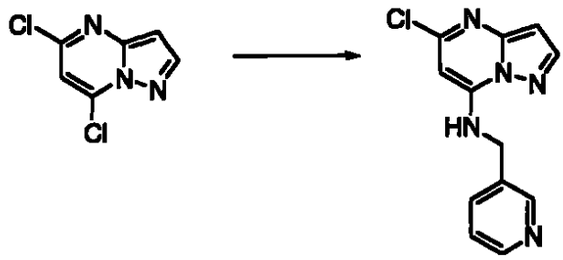
Se calentó el compuesto preparado en el Ejemplo Preparativo 80 (0,3 g, 1,2 mmol), K_2CO_3 (0,33 g, 2 eq.), y 4-aminometilpiridina (0,13 ml, 1,1 eq.) hasta reflujo hasta el día siguiente. La mezcla de reacción se enfrió hasta temperatura ambiente y se concentraron bajo presión reducida. El residuo se 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 bruto se purificó mediante cromatografía flash usando una solución de 5% (10% NH_4OH en MeOH) en CH_2Cl_2 como eluyente (0,051 g, 40% de rendimiento). LCMS: MH^+=320.

EJEMPLO PREPARATIVO 182:



Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 181, sustituyendo solamente el compuesto descripto en el Ejemplo Preparativo 92, se preparó el compuesto anterior. LCMS: MH^+=370.

EJEMPLO PREPARATIVO 183:

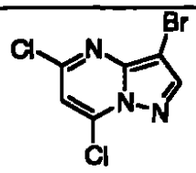
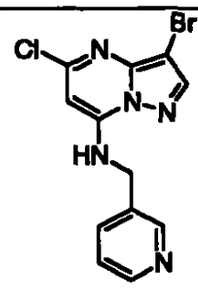
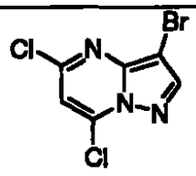
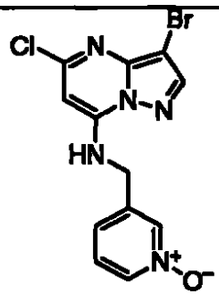


Se agregó iPr_2NEt (0,47 ml, 2,0 eq.) y 3-aminometilpiridina (0,15 ml, 1,1 eq.) a una solución del compuesto preparado en el Ejemplo Preparativo 123 (0,25 g, 1,3 mmol) en dioxano (5 ml). La solución resultante se agitó a temperatura ambiente 72 horas. La mezcla de reacción se diluyó con H_2O y se extrajo con EtOAc. Los orgánicos combinados se lavaron con H_2O y NaCl saturado, se secaron sobre Na_2SO_4, se filtraron, y se concentraron in vacuo. El producto bruto se purificó mediante cromatografía flash usando una solución de MeOH 5 % en CH_2Cl_2 como eluyente (0,29 g, 83% de rendimiento). MS: MH^+=260.

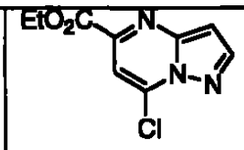
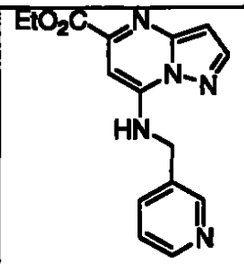
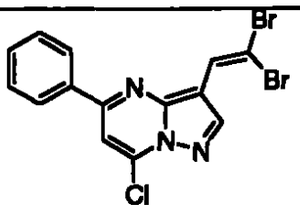
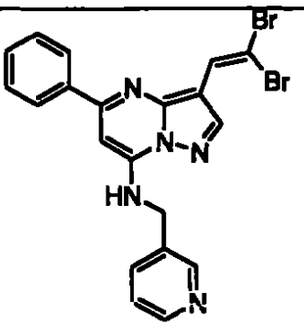
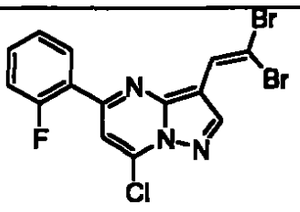
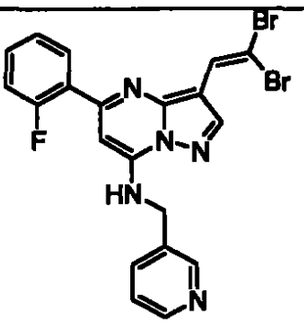
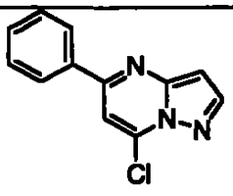
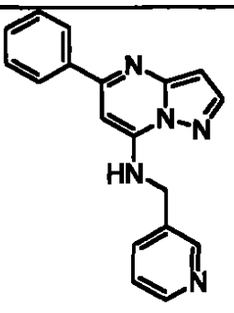
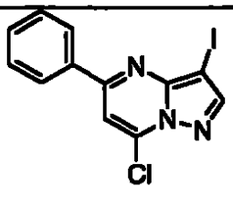
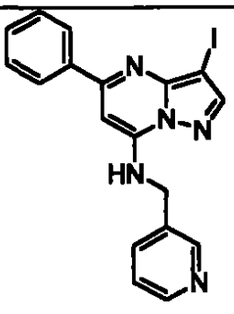
EJEMPLOS PREPARATIVOS 184-187:

Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 183, sustituyendo solamente 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

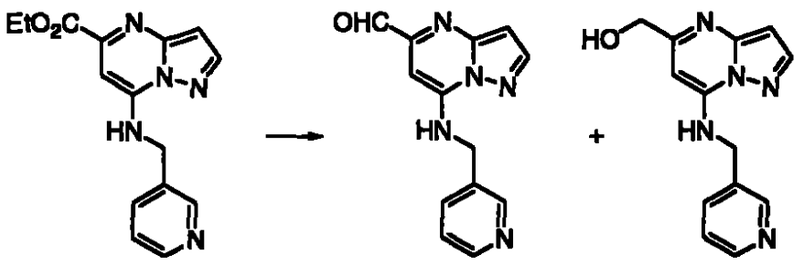
Ej. Prep.	Columna 2	Columna 3
184		
184,1		

414

185		
186		
187		
187,1		
187,11		

EJEMPLO PREPARATIVO 188 y EJEMPLO PREPARATIVO 189:

415

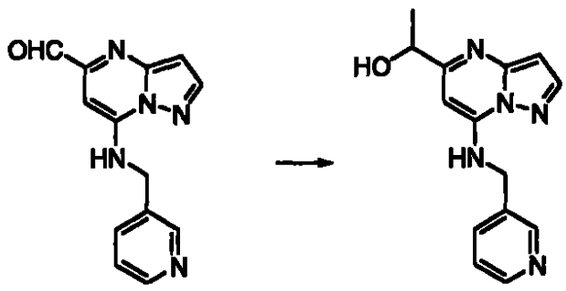


Se agregó gota a gota LAH (4,78 ml, 1M en Et_2O, 1,0 eq.) a una solución del compuesto preparado en el Ejemplo Preparativo 185 (1,18 g, 3,98 mmol) en THF (35 ml) a -78 °C. La mezcla de reacción se agitó a -78 °C durante 3 horas en dicho momento se agregó gota a gota LAH adicional (2,0 ml, 1M en Et_2O, 0,42 eq.). La mezcla de reacción se agitó 1,25 horas adicionales y se desactivó mediante la 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 suspensión 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 mediante cromatografía flash usando una solución de CH_2Cl_2 : CH_3OH (93 : 7) como eluyente para dar aldehído como el primer producto eluyente y alcohol como el segundo producto eluyente .

Ejemplo Preparativo 188: (aldehído): 0,4 g, 39% de rendimiento. MS: MH^+ = 254.

Ejemplo Preparativo 189: (alcohol): 0,25 g, 24% de rendimiento. MS: MH^+ = 256.

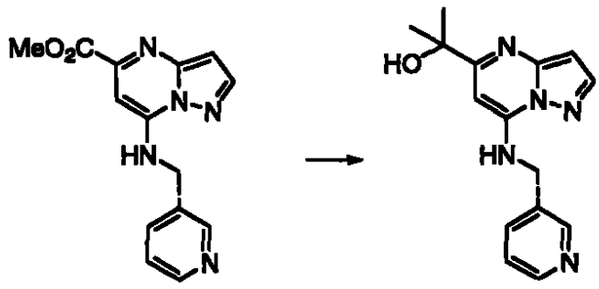
EJEMPLO PREPARATIVO 190:



A una solución del compuesto preparado en el Ejemplo Preparativo 188 (0,075 g, 0,30 mmol) en THF (2,0 ml) a 0°C se agregó CH_3MgBr (solución 0,3 ml, 3,0M en Et_2O, 3,0 eq.) gota a gota. La solución resultante se agitó a 0 °C un adicional de 1,5 horas, se calentó hasta temperatura ambiente, y se agitó hasta el día siguiente. Se agregó CH_3MgBr adicional (0,15 ml, 3,0M en Et_2O, 1, eq.) y la solución resultante se agitó 1,5 horas adicionales. La mezcla de reacción se

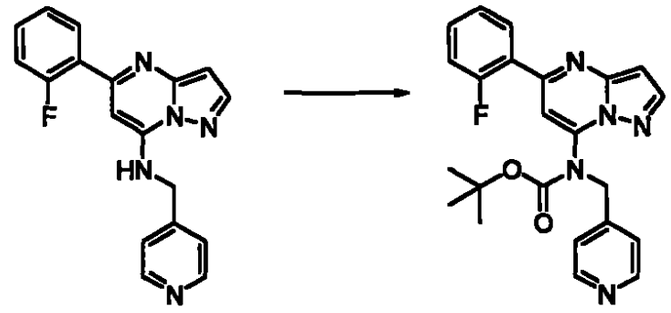
enfrió hasta 0 °C y se desactivó mediante la adición de NH_4Cl saturado. La solución resultante se diluyó con CH_2Cl_2 y H_2O y se extrajo con CH_2Cl_2. Los orgánicos combinados se lavaron con NaCl saturado y se secaron sobre Na_2SO_4, se filtraron y se concentraron. El producto bruto se purificó mediante cromatografía flash usando una solución de CH_2Cl_2 : CH_3OH (90 : 10) como eluyente (0,048 g, 60% de rendimiento). MS: $MH^+ = 270$.

EJEMPLO PREPARATIVO 191:



Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 190, sustituyendo solamente el compuesto preparado en el Ejemplo Preparativo 185 y usando MeMgBr (5 eq.) en exceso, se preparó el compuesto anterior.

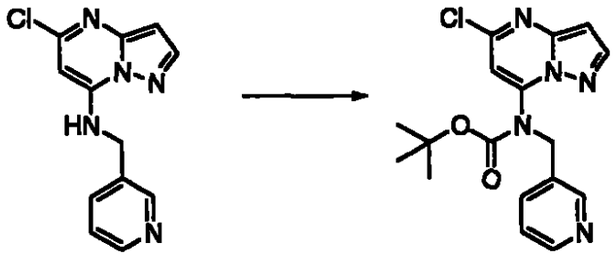
EJEMPLO PREPARATIVO 192:



El compuesto preparado en el Ejemplo Preparativo 181 (0,29 g, 0,91 mmol), 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 3 días. Se agregó BOC_2O adicional (0,10g, 0,5 eq.) y la mezcla de reacción se agitó 4 horas. La mezcla de reacción se concentró en vacuo, 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 bruto se purificó mediante

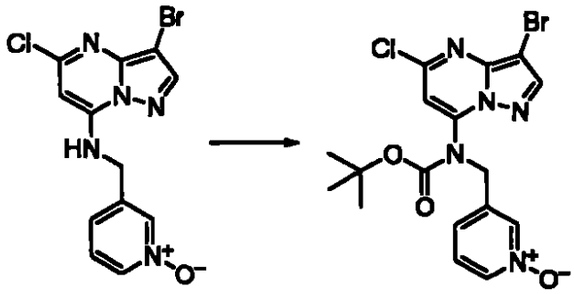
cromatografía flash usando una solución de 5% (10% NH_4OH en MeOH) en CH_2Cl_2 como eluyente (0,35 g, 91% de rendimiento). LCMS: MH^+= 420.

EJEMPLO PREPARATIVO 193:



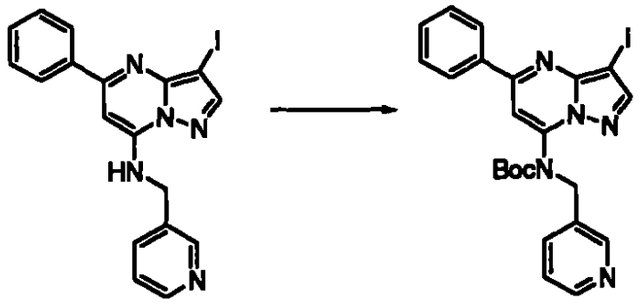
Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 192, sustituyendo solamente el compuesto preparado en el Ejemplo Preparativo 183, se preparó el compuesto anterior. MS: MH^+ = 360.

EJEMPLO PREPARATIVO 193,10:



Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 192, sustituyendo solamente el compuesto preparado en el Ejemplo Preparativo 184,1, se preparó el compuesto anterior. MS: MH^+ = 454.

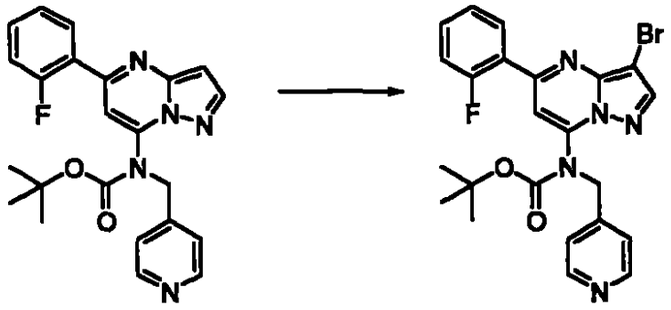
EJEMPLO PREPARATIVO 194:



Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 192, sustituyendo solamente el compuesto anterior preparado en el

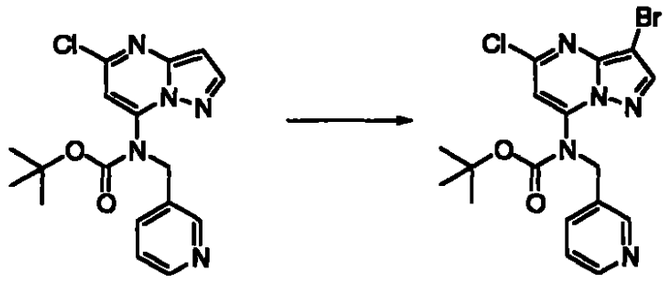
Ejemplo Preparativo 187,11, se preparó el compuesto anterior (0,223 g, 88% de rendimiento). MS: MH^+ = 528.

EJEMPLO PREPARATIVO 195:



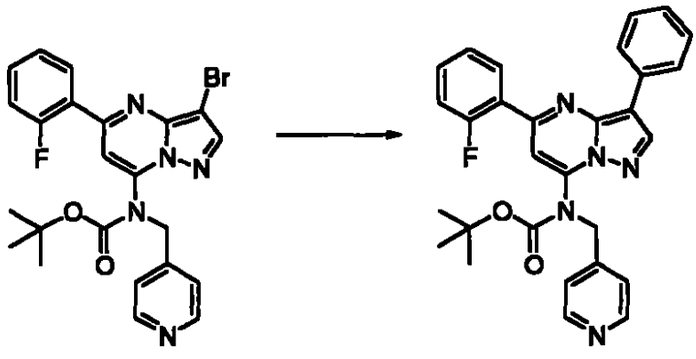
Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 127, sustituyendo solamente el compuesto preparado en el Ejemplo Preparativo 192, se preparó el compuesto anterior (0,38 g, 95% de rendimiento). LCMS: MH^+= 498.

EJEMPLO PREPARATIVO 196:



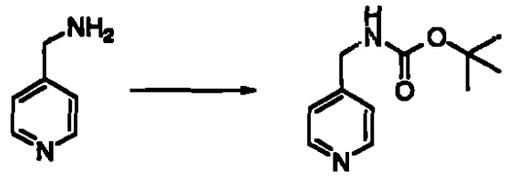
Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 195, sustituyendo solamente el compuesto preparado en el Ejemplo Preparativo 193, se preparó el compuesto anterior (0,3 g, 83% de rendimiento). MS: MH^+ = 438.

EJEMPLO PREPARATIVO 197:



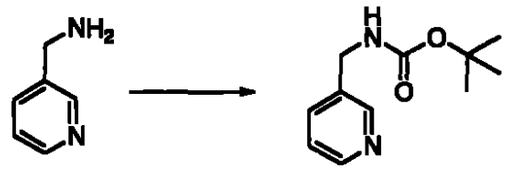
Se calentó una solución del compuesto preparada en el Ejemplo Preparativo 195 (0,15 g, 0,3 mmol), ácido fenilborónico (0,073 g, 2,0 eq.), K_3PO_4 (0,19 g, 3,0 eq.), y $Pd(PPh_3)_4$ (0,017 g, 5 mol %) a reflujo en DME (16 ml) y H_2O (4 ml) 7 horas. La solución resultante se enfrió hasta temperatura ambiente, 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 bruto se purificó mediante cromatografía flash usando una solución de 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 mmol) 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 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 filtró y se concentraron bajo presión reducida. El producto bruto se purificó mediante cromatografía flash usando una solución de 5% (10% NH_4OH en MeOH) en CH_2Cl_2 como eluyente para dar un sólido amarillo (2,62 g, 91% de rendimiento). LCMS: MH^+= 209.

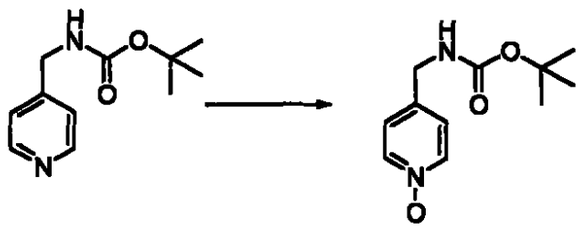
EJEMPLO PREPARATIVO 199:



Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 198, sustituyendo solamente 3-aminometilpiridina, se preparó el compuesto anterior como un aceite amarillo (2,66 g, 92% de rendimiento). LCMS: MH^+= 209,

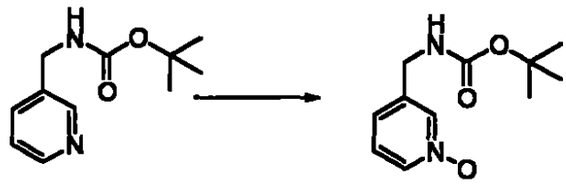
EJEMPLO PREPARATIVO 200:

420



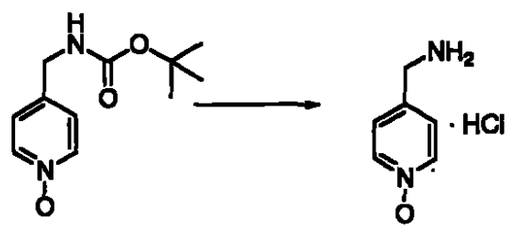
A una solución del compuesto preparado en el Ejemplo Preparativo 198 (0,20 g, 0,96 mmol) en CH_2Cl_2 (5 ml) a 0°C se agregó *m*-CPBA (0,17 g, 1,0 eq) y la solución resultante stirred a 0°C 2 horas y stored at 4°C hasta el día siguiente, en dicho momento, la mezcla de reacción se calentó hasta temperatura 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 bruto se purificó mediante cromatografía flash usando una solución de 10% (10% NH_4OH en MeOH) como eluyente: LCMS: MH^+= 255.

EJEMPLO PREPARATIVO 201:



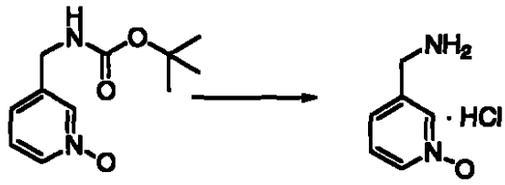
Se agregó una solución de oxona (58,6 g) en H_2O (250 ml) gota a gota al compuesto preparado en el Ejemplo Preparativo 199 (27 g, 0,13 mol) y $NaHCO_3$ (21,8 g, 2,0 eq.) en MeOH (200 ml) y H_2O (250 ml). La solución resultante se agitó a temperatura ambiente hasta el día siguiente. La mezcla de reacción 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 dar un sólido blanco (21,0 g, 72% de rendimiento). MS: MH^+= 255.

EJEMPLO PREPARATIVO 202:



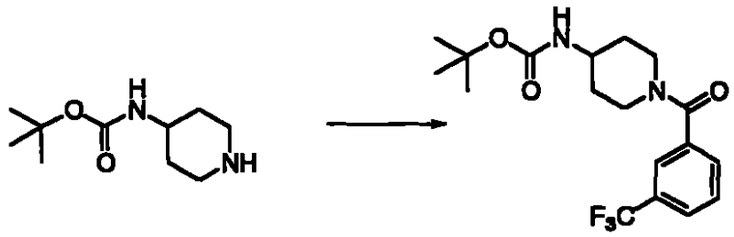
Se agitó el compuesto preparado en el Ejemplo Preparativo 200 (0,29 g, 1,29 mmol) a temperatura ambiente en HCl 4M en dioxano (0,97 ml) 2 horas. La mezcla de reacción se concentró en vacuo y se usó sin purificación adicional. LCMS: MH^+= 125.

EJEMPLO PREPARATIVO 203:



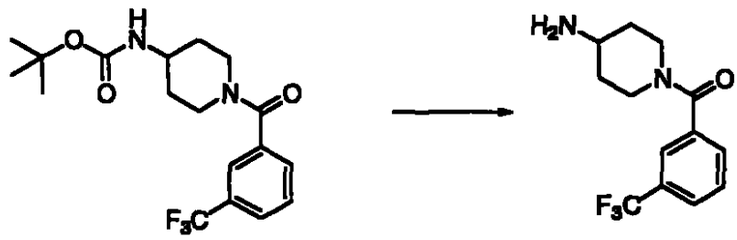
Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 202, sustituyendo solamente el compuesto preparado en el Ejemplo Preparativo 201, se preparó el compuesto que se mostró anteriormente. LCMS: MH^+= 125.

EJEMPLO PREPARATIVO 204:



Se agregó TEA (1,40 ml, 2,5 eq.) y cloruro 3-trifluorometil benzoilo (1,05 g, 1,25 eq.) a 4-N-t-Butoxicarbonilaminopiperidina (0,8 g, 4,0 mmol) en CH_2Cl_2 (10 ml) a 0°C. La solución resultante se agitó 15 minutos y se calentó hasta temperatura ambiente y se agitó 3 horas. La mezcla de reacción se diluyó con CH_2Cl_2 y se lavó con Na_2CO_3 5% (2 x 100 ml). La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentraron para dar un sólido amarillo pálido (rendimiento bruto cuantitativo).

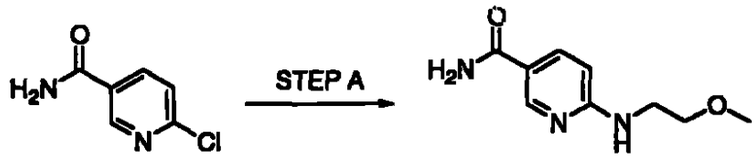
EJEMPLO PREPARATIVO 205:

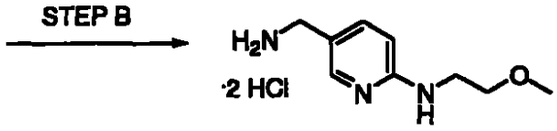


422

Se agregó TFA (8 ml) a una solución del compuesto preparado en el Ejemplo Preparativo 204 (1,0 g, 2,76 mmol) en CH_2Cl_2 (15 ml) a 0°C y la solución resultante se agitó a 0°C durante 30 minutos y temperatura ambiente 1 hora. La mezcla de reacción se vertió en 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 bruto se purificó mediante cromatografía flash usando una solución de 20% (7N NH_3 en MeOH) en CH_2Cl_2 como eluyente (0,6 g, 82% de rendimiento).

EJEMPLOS PREPARATIVOS 206:





PASO A:

Se agregó Na_2CO_3 (0,81g, 7,67 mmol) a una solución de 6-cloronicotinamida (1g, 6,39 mmol) en alcohol isoamilo (15 ml) a temperatura ambiente seguido por metoxietilamina (0,67 ml, 7,67 mmol). La mezcla se calentó a 130 °C durante 16h, se enfrió a ta, y se filtró a través de un filtro de vidrio medio. el filtrado resultante se concentró bajo presión reducida y el sólido resultante se trituró con Et_2O (2 x 10 ml). el sólido bruto se colocó bajo alto vacío para dar 1,2 g (96%) de un sólido amarillo claro. M+H = 196.

PASO B:

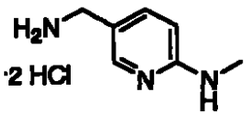
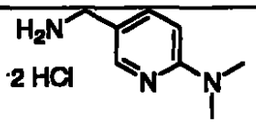
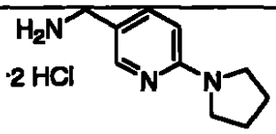
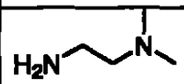
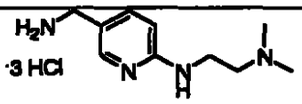
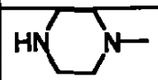
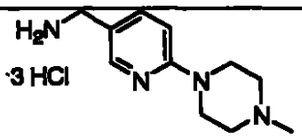
A una solución de amida (1,2 g, 6,12 mmol) del Ejemplo Preparativo 206, Paso A en THF (5 ml) a 0°C se agregó una solución de BH_3-THF (43 ml; 43 mmol) gota a gota durante 10 min. La solución resultante se calentó hasta ta y se agitó. durante 14 h. La mezcla se enfrió hasta 0 °C y se trató en secuencias con HCl 6M (35 ml), agua (30 ml), y MeOH (150 ml). La mezcla se agitó durante 8 h y se

concentró bajo presión reducida. El residuo bruto se trituró con MeOH, se concentró bajo presión reducida, y se colocó bajo alto vacío para dar 1,6 g (82%) de un sólido blanco como la sal del diclorhidrato. M+H (base libre) = 182,0. Este material se usó bruto en el acoplamiento con aductos 7-Cl.

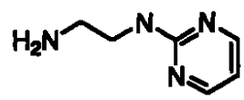
EJEMPLOS PREPARATIVOS 207-211:

Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 206, usando solamente las aminas que se muestran en la Columna 2 de la Tabla 13, se prepararon las aminas que se muestran en la Columna 3 de la Tabla 13:

TABLA 13

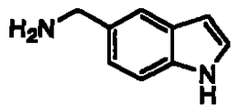
Ej. Prep.	Columna 2 (Amina)	Columna 3 (Amina)	COMPUESTO M+H (base libre)
207			M+H = 138
208			M+H = 152
209			M+H = 178
210			M+H = 195
211			M+H = 207

EJEMPLO PREPARATIVO 212:



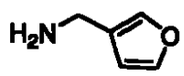
Se preparó el compuesto anterior de acuerdo con los métodos descriptos en WO 91/18904.

EJEMPLO PREPARATIVO 213:



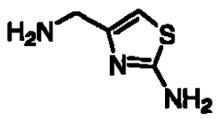
Se preparó el compuesto anterior de acuerdo con los métodos descriptos en US 6,180,627 B1.

EJEMPLO PREPARATIVO 214:



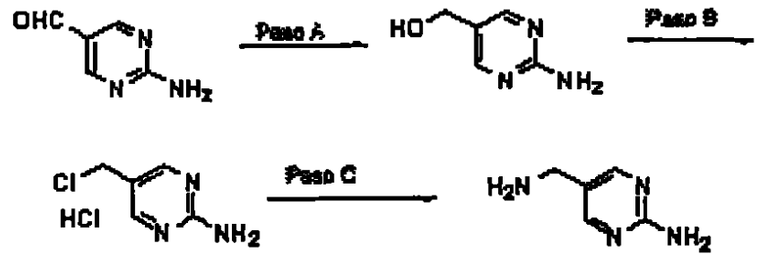
La amina conocida se preparó según se describió en *J. Med. Chem.* (2001), *44*, 4505-4508.

EJEMPLO PREPARATIVO 215:



La amina conocida se preparó según se describió en *J. Med. Chem.* (1997), *40*, 3726-3733.

EJEMPLO PREPARATIVO 216:



PASO A:

Se enfrió una solución de aldehído (50 g, 0,41 mol) [WO 0232893] en MeOH (300 ml) hasta 0 °C y se trató cuidadosamente con $NaBH_4$ (20g, 0,53 mol en 6 lotes) durante 20 minutos. Luego se permitió que la reacción se caliente hasta 20 °C y se agitó durante 4 horas. La mezcla se enfrió nuevamente hasta 0 °C, se desactivó cuidadosamente con NH_4Cl acuoso saturado, y se concentró. La cromatografía flash (5–10% 7N NH_3-MeOH/CH_2Cl_2) dio el alcohol primario (31g, 62%) como un sólido amarillo claro.

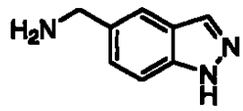
PASO B:

Una suspensión de alcohol (31 g, 0,25 mol) del Ejemplo Preparativo 216, Paso A en CH_2Cl_2 (500 ml) se enfrió hasta 0 °C y se trató lentamente con $SOCl_2$ (55ml, 0,74 mol durante 30 minutos). Luego, la reacción se agitó hasta el día siguiente a 20 °C. El material se concentró, se suspendió en acetona, y luego se filtró. El sólido beige resultante se secó hasta el día siguiente en vacuo (38,4g, 52%, sal de HCl).

PASO C:

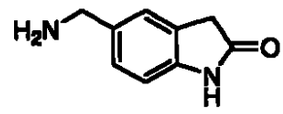
A un tubo de presión de 15 ml cargado con una barra para agitar se agregó cloruro (150 mg, 0,83 mmol) del Ejemplo Preparativo 216, Paso B seguido por 7 M NH_3/MeOH (10 ml). La solución resultante se agitó durante 48 h a temperatura ambiente en cuyo momento la mezcla se concentró bajo presión reducida para dar un sólido amarillo claro(0,146 g, 83%). M+H (base libre) = 140.

EJEMPLO PREPARATIVO 217:



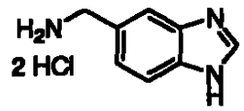
Se preparó el compuesto anterior de acuerdo con los métodos descriptos en WO 00/26210.

EJEMPLO PREPARATIVO 218:



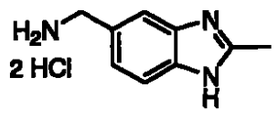
Se preparó el compuesto anterior de acuerdo con los métodos descriptos en WO 99/10325.

EJEMPLO PREPARATIVO 219:



El diclorhidrato de amina conocida se preparó de acuerdo con métodos descriptos en WO 02/64211.

EJEMPLO PREPARATIVO 220:



Se preparó el compuesto anterior de acuerdo con métodos descriptos en WO 02/64211.

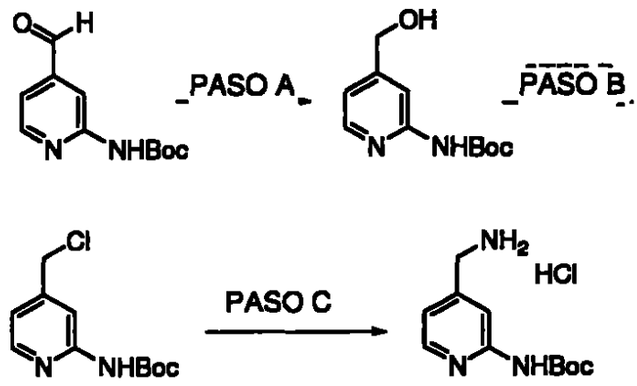
EJEMPLO PREPARATIVO 221:



El alcohol primario conocido se preparó de acuerdo con WO 00/37473 y se convirtió en el diclorhidrato de amina deseado en diseño análogo al Ejemplo Preparativo 220 de acuerdo con WO 02/064211.

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EJEMPLO PREPARATIVO 222:



PASO A:

A una solución de aldehído (WO 02/32893) (0,46 g, 2,07 mmol) en MeOH/THF (2 ml/2 ml) a 0°C se agregó $NaBH_4$ (94 mg, 2,48 mmol) en una porción. La mezcla resultante se agitó durante 12 h a temperatura ambiente y se diluyó con acuoso sat. NH_4Cl (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 dar 417 mg (90% de rendimiento) de un sólido blanco. M+H = 225.

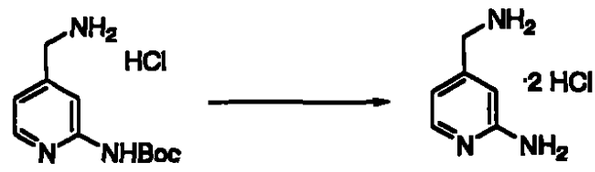
PASO B:

Al alcohol bruto del Ejemplo Preparativo 222, paso A (0,4 g, 1,78 mmol) en CH_2Cl_2 (4 ml) se agregó $SOCl_2$ (0,65 ml, 8,91 mmol) y la mezcla se agitó durante 2 h a temperatura ambiente. La mezcla se concentró bajo presión reducida para dar 407 mg (94%) de un sólido amarillo claro. M+H = 243. El producto bruto se capturó sin purificación adicional.

PASO C:

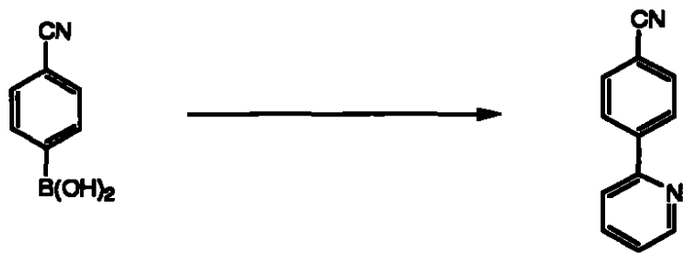
A una solución de cloruro bruto del Ejemplo Preparativo 222, Paso B (0,33 g, 1,36 mmol) en un tubo de presión cargado con NH_3 7M /MeOH (35 ml) y la mezcla se agitó durante 72 h. La mezcla se concentró bajo presión reducida para dar 257 mg (85%) de un semisólido amarillo. M+H (base libre) = 224.

EJEMPLO PREPARATIVO 223:



A una matraz cargada con amina clorhidrato (0,24 g, 1,1 mmol) del Ejemplo Preparativo 222 y una barra para agitar se agregó HCl4N /dioxano (10 ml). La solución resultante se agitó durante 12h a temperatura ambiente, se concentró bajo presión reducida, y se trituró con CH_2Cl_2 (3 x 5 ml). El producto bruto se filtró, se lavó con Et2O (2 x 5ml), y se secó en alto vacío para dar 0,19g (91%) como la sal del diclorhidrato. M+H (base libre) = 124.

EJEMPLO PREPARATIVO 224:

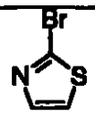
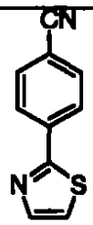
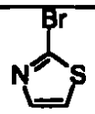
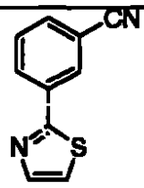
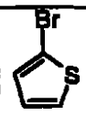
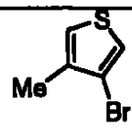
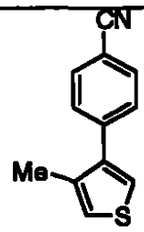


Se agregó $Pd(PPh_3)_4$ (0,404 gm, 0,35 mmol) a una solución degasada de ácido 4-cianobenceno borónico (1,029 g, 7 mmol) y 2-bromopiridina (1,11 g, 7 mmol) en 75 ml acetonitrilo. Se agregó solución de carbonato de sodio 0,4 M (35 ml) a la mezcla de reacción y la solución resultante se refluió a 90°C bajo Ar durante 24 horas (el avance de la reacción se monitoreó mediante TLC). La mezcla de reacción se enfrió y se separó la capa acuosa. La capa orgánica que contiene el producto y catalizador gastado se mezcló con gel de sílice (15 g) y se concentró hasta que se secó. El 4-(2-piridil)-benzonitrilo se aisló mediante cromatografía en la 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).

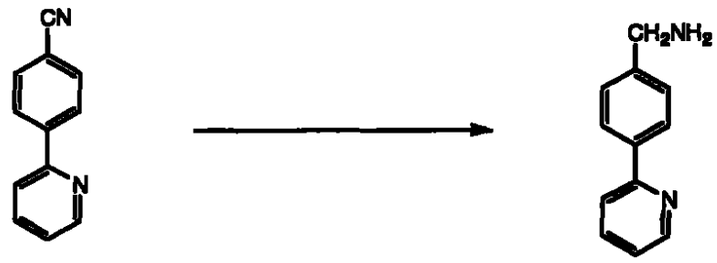
EJEMPLOS PREPARATIVOS 225-228:

Por medio de seguir esencialmente el mismo procedimiento descripto en el Ejemplo Preparativo 224, sustituyendo solamente los bromuros en la Columna 2 de la Tabla 14, se prepararon los compuestos en 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:



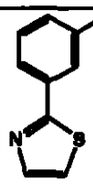
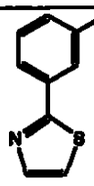
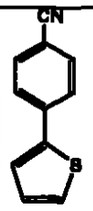
Se agregó lentamente la solución BH_3-THF (1 M, 24 ml, 5 eq) a una solución en agitación de 4-(2-piridil)-benzonitrilo (0,85 g, 4,72 mmol) en THF anhídrido (25 ml) bajo Ar, y la solución resultante se reflujó durante alrededor de 12 hr. La solución se enfrió hasta 0°C usando agua congelada. Se agregó gota a gota metanol (15 ml) a la mezcla de reacción fría y se agitó durante 1 h para

destruir el exceso BH_3. Se agregó lentamente HCl – metanol (1M, 10 ml) a la mezcla de reacción y se reflujó durante 5 h. La solución se concentró hasta que se secó y el residuo se disolvió en 25 ml agua y se extrajo con éter para eliminar cualquier material que no se hizo reaccionar. La solución acuosa se neutralizó con carbonato de potasio sólido a pH 10-11. La amina libre, que se formó de esa manera 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).

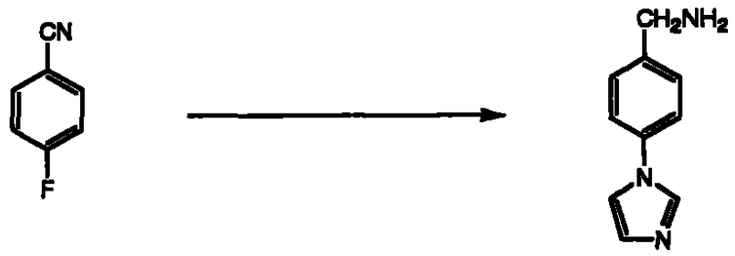
EJEMPLOS PREPARATIVOS 230-233:

Por medio de seguir esencialmente el mismo procedimiento expuesto en el Ejemplo Preparativo 229, se prepararon los compuestos en 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:



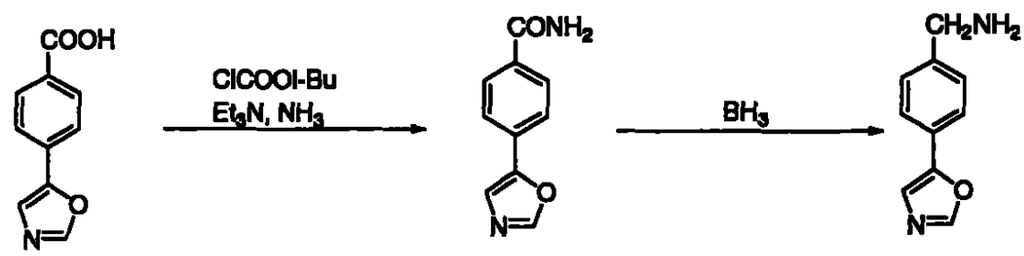
Paso A:

Se agitó una mezcla de 4-fluorobenzonitrilo (3 g, 25 mmol) y sodio imidazolilo (2,48 g, 27,5 mmol) en DMF (50 ml) a 80°C bajo Ar durante 12 h. El progreso de la reacción se monitoreó mediante TLC. La mezcla de reacción se concentró en vacuo y el residuo se diluyó con 50 ml agua y se agitó. La mezcla acuosa se extrajo con EtOAc (2 x 50 ml). Los extractos combinados de EtOAc se secaron sobre MgSO4 anhídrido, se concentraron, y el 4-(1-imidazolil)-benzonitrilo se aisló mediante cromatografía en la 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).

Paso B:

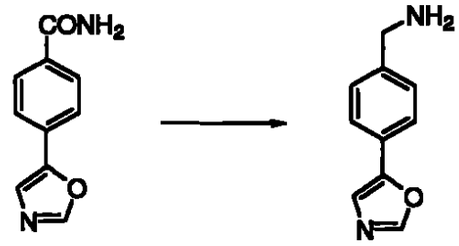
Se disolvió 4-(1-imidazolil)-benzonitrilo (1g, 5,92 mmol) en THF anhídrido (10 ml) y se agregó gota a gota a una solución en agitación de LAH –THF (1 M en THF, 18 ml) a temperatura ambiente. La mezcla de reacción se reflujó bajo Ar durante 2 h y el progreso se monitoreó mediante TLC. La mezcla se enfrió hasta 0°C y se desactivó mediante la adición gota a gota de una solución de Na_2SO_4 – H_2O saturada. La mezcla se agitó durante 1 h y se filtró para remover las sales de litio. El filtrado se secó sobre MgSO4 anhídrido y se concentraron para obtener 4-(1-imidazolil)-bencilamina (0,8 g, 80%). LCMS: MH^+ = 174.

EJEMPLO PREPARATIVO 235:



Se enfrió una mezcla de ácido 4-(5-oxazolil)benzóico (1,0 g, 5,46 mmol) y Et_3N (552 mg, 5,46 mmol) en 25 ml de THF hasta 0 °C y se agregó ClCOO*i*-Bu (745 mg, 5,46 mmol) gota a gota. Una vez finalizada la adición, la mezcla de reacción se agitó durante adicional 5 min y luego se agregó NH_4OH ac. (0,63 ml de solución 28%, 10,46 mmol). Después de la agitar hasta el día siguiente, el solvente se evaporó, el residuo se capturó en agua y se basificó a pH 9. El sólido precipitado se filtró, se lavó con agua y se secaron sobre P_2O_5 en un desecador de vacío para dar 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:



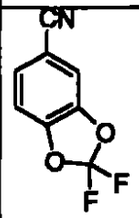
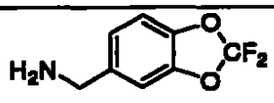
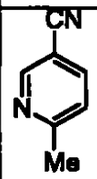
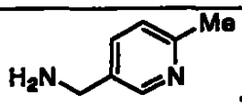
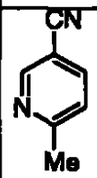
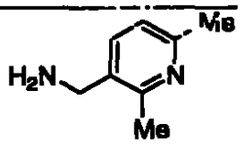
Una suspensión de 4-(5-oxazolil) benzamida (500 mg, 2,657 mmol) en 10 ml de THF seco se enfrió hasta 0 °C y 10 ml de BH_3 1 M. Se agregó THF (10,00 mmol). Los contenidos se reflujaron hasta el día siguiente y se destruyó el exceso de boro mediante la adición gota a gota de metanol. El solvente se evaporó y el residuo se trató con HCl metanólico para descomponer el complejo amina-boro. Después de la evaporación del metanol, el residuo se capturó en agua, se basificó a pH 10 y el producto se extrajo para DCM. La capa de DCM se secó (K_2CO_3) y se eliminó el solvente para dar 150 mg (32%) de 4-(5-oxazolil)bencilamina: ^1H 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:

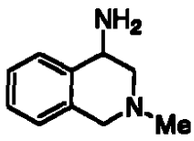
Esencialmente, por medio de los mismos procedimientos expuestos anteriormente, se redujeron los compuestos en la columna 2 de la Tabla 16 usando el método indicado en la Columna 3 de la Tabla 16 para dar la amina indicada en la Columna 4 de la Tabla 16.

Tabla 16

Ej.	Columna 2	Columna 3	Columna 4	COMPUESTO

Prep.				
237		BH_3		^1H RMN ($CDCl_3$) δ 7,15-6,90 (m, 3H), 3,85 (s, 2H), 1,45 (s, 2H)
238		H_2		^1H 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		

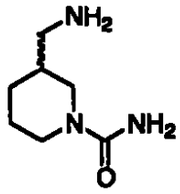
EJEMPLO PREPARATIVO 240



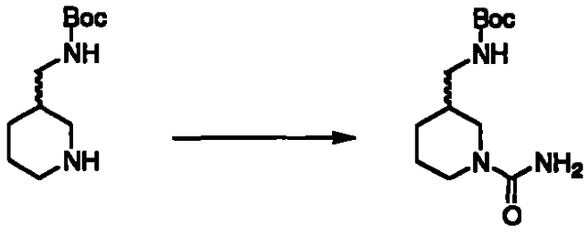
Preparado mediante el procedimiento de la literatura (PCT Int. Appl, WO 0105783): ^1H RMN ($CDCl_3$) δ 7,35 (d, 1H), 7,24-7,10 (m, 2 H), 7,02 (d, 1H), 3,95 (t, 1H), 3,70 (d, 1H), 3,37 (d, 1H), 2,65 (m, 2H), 2,45 (s, 3H), 1,90 (bs, 2H).

EJEMPLO PREPARATIVO 241:

3-(AMINOMETIL)PIPERIDIN-1-CARBOXAMIDA

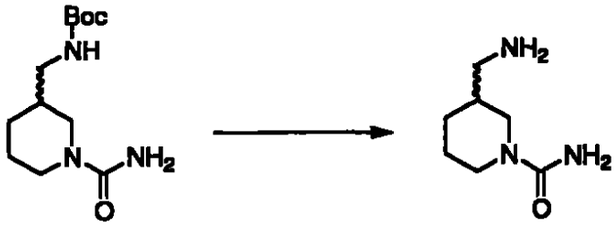


A. 3-(*ter*-BUTOXICARBONILAMINOMETIL)PIPERIDIN-1-CARBOXAMIDA



Se disolvió 3(R/S)-(*ter*-Butoxicarbonilaminometil)piperidina (3g, 14,0mmoles) en diclorometano anhídrido (50ml) y se agregó trimetilsililisocianato (9,68g, 11,4ml, 84,0mmoles). La mezcla se agitó bajo Argón a 25°C durante 68h. Se agregó trimetilsililisocianato adicional (4,84g, 5,7ml, 42,0 mmoles) y la mezcla se agitó a 25°C durante un total de 90h. La mezcla se evaporó hasta que se secó y se sometió a cromatografía en columna de gel de sílice (30x5cm) usando 2% de (10% conc. hidróxido de amonio en metanol)-diclorometano como el eluyente para dar 3-(*ter*-butoxicarbonilaminometil)piperidin-1-carboxamida (3,05g, 85%): FABMS: m/z 258,1 (MH^+); HRFABMS: m/z 258,1816 (MH^+). Calculado 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_20 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



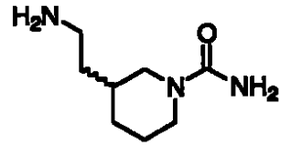
Se disolvió 3-(*ter*-Butoxicarbonilaminometil)piperidin-1-carboxamida (150mg, 0,583mmoles) (preparado según se describió en el Ejemplo Preparativo 241, Paso A anterior) en metanol (3ml). Se agregó ácido sulfúrico conc. 10% en 1,4-dioxano (7,9 ml) y la mezcla se agitó a 25°C durante 1h. La mezcla se diluyó con metanol y se agregó BioRad AG1-X8 resina (forma OH^-) hasta que se basificó el pH. La resina se filtró, se lavó con metanol, se evaporó hasta la sequedad y se sometió a cromatografía en columna de gel de sílice (15x2cm) usando diclorometano seguido por 15% (hidróxido de amonio 10% conc. en metanol)-diclorometano como el eluyente para dar la 3-(aminometil)piperidin-1-carboxamida (80mg, 87%): FABMS: m/z 158,1 (MH^+); HRFABMS: m/z 158,1294 (MH^+). Calculado para $C_7H_{16}N_3O$: m/z 158,1293; δ_H ($CDCl_3$ + gota de 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,

435

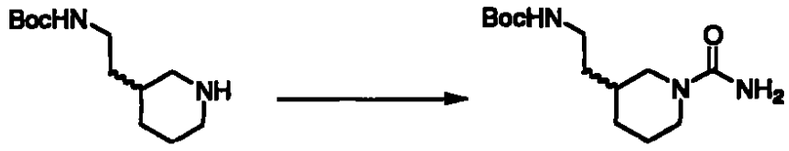
CH_2), 3,70 (1H, m, -C<u>H</u>$_2$NH$_2$), 3,78 (1H, m, -C<u>H</u>$_2$NH$_2$) y 5,24 ppm (1H, bs, NH); δ c ($CDCl_3$ + gota CD_3OD) CH_2: 24,1, 28,6, 44,0, 44,8, 47,9; CH: 38,3; C: 159,0.

<u>EJEMPLO PREPARATIVO 242:</u>

3-(2-AMINOETIL)PIPERIDIN-1-CARBOXAMIDA



A. 3-(2-ter-BUTOXICARBONILAMINOETIL)PIPERIDIN-1-CARBOXAMIDA



Se disolvió 3-(2-*ter*-Butoxicarbonilaminoetil)piperidina (500mg, 2,19mmoles) en anhídrido diclorometano (10 ml) y se agregó trimetilsililisocianato (2,96ml, 21,9 mmoles). La mezcla se agitó bajo Argón a 25°C durante 3,35 h. 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 la sequedad y se sometió a cromatografía en columna de gel de sílice (15x5cm) usando 5% (hidróxido de amonio conc. 10% en metanol)-diclorometano como el eluyente para dar 3-(2-*ter*-butoxicarbonilaminoetil)piperidin-1-carboxamida (417,7mg, 70%): FABMS: m/z 272,0 (MH^+); HRFABMS: m/z 272,1979 (MH^+). Calculado 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<u>H</u>$_3$)$_3$), 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



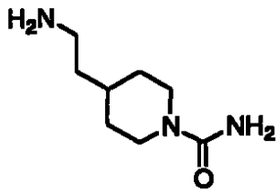
Se disolvió 3-(2-*ter*-Butoxicarbonilaminoetil)piperidin-1-carboxamida (392,7mg, 1,45mmoles) (preparado según se describió en el Ejemplo Preparativo

436

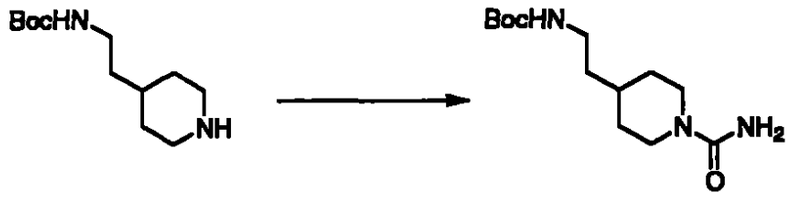
242, Paso A anterior) en metanol (7,5ml) y se agregó ácido sulfúrico conc. 10% en 1,4-dioxano (19,5ml). La mezcla se agitó a 25°C durante 1,25h. La mezcla se diluyó con metanol y se agregó BioRad AG1-X8 resina (forma OH^-) hasta que el pH fue básico. La resina se filtró, se lavó con metanol, se evaporó hasta la sequedad y se sometió a cromatografía en columna de gel de sílice (30x2,5cm) usando 15% (hidróxido de amonio conc. 10% en metanol)-diclorometano como el eluyente para dar 3-(2-aminoetil)piperidin-1-carboxamida (233mg, 94%): FABMS: m/z 172,1 (MH^+); HRFABMS: m/z 172,1444(MH^+). Calculado 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

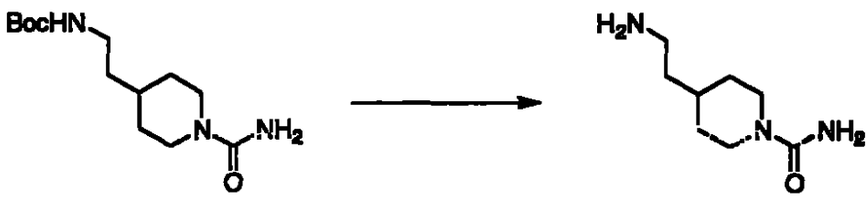


Se disolvió 4-(2-*ter*-Butoxicarbonilaminoetil)piperidina (500 mg, 2,19 mmoles) en anhídrido diclorometano (10ml) y se agregó trimetilsililisocianato (2,96ml, 21,9mmoles). La mezcla se agitó bajo Argón a 25°C durante 3,25 h. La mezcla se diluyó con diclorometano y se lavó con bicarbonato de sodio acuoso saturado. La capa orgánica se secó ($MgSO_4$), se filtró, se evaporó hasta la sequedad y se sometió a cromatografía en columna de gel de sílice (15x5cm) usando 5% (hidróxido de amonio conc. 10% en metanol)-diclorometano como el eluyente para dar 4-(2-*ter*-butoxicarbonilaminoetil)piperidin-1-carboxamida

437

(308,2mg, 52%): FABMS: m/z 272,0 (MH^+); HRFABMS: m/z 272,1965 (MH^+). Calculado para $C_{13}H_{25}O_3N_3$: 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) 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.

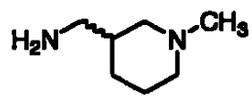
A. 3-(2-AMINOETIL)PIPERIDIN-1-CARBOXAMIDA



Se disolvió 4-(2-*ter*-Butoxicarbonilaminoetil)piperidin-1-carboxamida (283,3mg, 1,04mmoles) (preparado según se describió en el Ejemplo Preparativo 243, Paso A anterior) en metanol (5,4 ml) y se agregó ácido sulfúrico conc. 10% en 1,4-dioxano (14,2ml) y la mezcla se agitó a 25°C durante 1,25h. La mezcla se diluyó con metanol y BioRad AG1-X8 resin (forma OH^-) se agregó hasta que el pH fue básico. La resina se filtró, se lavó con metanol, se evaporó hasta la sequedad y se sometió a cromatografía en columna de gel de sílice (30x2,5 cm) usando 15% (hidróxido de amonio conc. 10% en metanol)-diclorometano como el eluyente para dar the 3-(2-aminoetil)piperidin-1-carboxamida (170mg, 95%): FABMS: m/z 172,1 (MH^+); HRFABMS: m/z 172,1442. Calculado 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

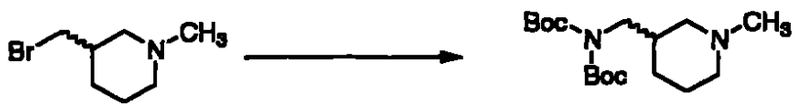


A. 3-(BROMOMETIL)-1-METILPIPERIDINA



Se disolvió 3-(hidroximetil)-1-metilpiperidina (2g, 15,5mmoles) en anhídrido acetonitrilo (32 ml) y se agregó anhídrido piridina (2,02ml, 24,8 mmoles) y la solución se enfrió hasta 0°C. Se agregó dibromotrifenilfosforano (8,49g, 20,2mmoles) a 0°C y se dejó que la mezcla se caliente hasta 25°C y se agitó durante 94h. La mezcla se evaporó hasta la sequedad y el residuo se sometió a cromatografía sobre una columna de gel de sílice (30x5cm) usando elución de gradiente con diclorometano, dietiléter 35% en diclorometano y 5-10% metanol en diclorometano como el eluyente para dar 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.

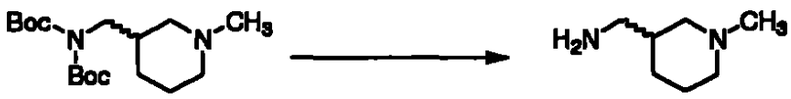
A. 3-(Di-ter-BUTOXICARBONILAMINOMETIL)-1-METILPIPERIDINA



Se disolvieron 3-(Bromometil)-1-metilpiperidina (1,5g, 7,81mmoles) (del Ejemplo Preparativo 244, Paso A anterior) y di-*ter*-butiliminodicarboxilato (1,697g, 7,81 mmoles) en acetonitrilo anhídrido (25ml). Se agregaron carbonato de cesio (5,1g, 15,6 mmoles) y yoduro de litio (52mg, 0,391 mmoles) y la mezcla se agitó a 70°C durante 20h. La mezcla se evaporó hasta que se secó 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 que se secó. el residuo se sometió a cromatografía sobre una columna de gel de sílice (30x5cm) usando 3% metanol en diclorometano como el eluyente para dar 3-(di-*ter*-butoxicarbonilamino)-1-metilpiperidina (1,331g, 52%): FABMS: m/z 329,2 (MH^+); HRFABMS: m/z 329,2438 (MH^+). Calculado 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,

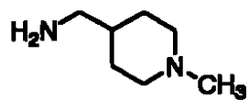
A. 3-(AMINOMETIL)-1-METILPIPERIDINA



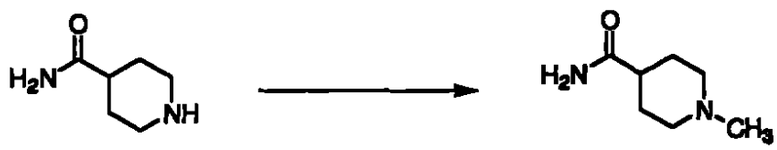
Se disolvió 3-(Di-*ter*-butoxicarbonilamino)-1-metilpiperidina (500mg, 1,52mmoles) (del Ejemplo Preparativo 244, Paso B anterior) en metanol (7,5ml) y se agregó 10% (v/v) ácido sulfúrico conc. en 1,4-dioxano (19,75ml). La solución se agitó a 25°C durante 0,5h. Se agregó metanol (300ml), seguido por BioRad AG1-X8 resina (*forma* OH^-) hasta que el pH fue ~10. La resina se filtró y se lavó con metanol (2x200ml). Los eluatos combinados se evaporaron hasta que se secaron y el residuo se sometió a cromatografía sobre una columna de gel de sílice (30x2,5cm) usando 10% (hidróxido de amonio conc. 10% en metanol)-diclorometano como el eluyente para dar 3-(aminometil)-1-metilpiperidina (69,2mg, 35%): FABMS: *m/z* 129,1 (MH^+); HRFABMS: *m/z* 129,1392 (MH^+). Calculado 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, -$C\underline{H_2}NH_2$) y 2,92 ppm (1H, m, -$C\underline{H_2}NH_2$); δ_C ($CDCl_3$) CH_3: 46,7; CH_2: 25,2, 28,0, 46,3, 56,4, 60,3; CH: 39,9.

<u>EJEMPLO PREPARATIVO 245:</u>

4-(AMINOMETIL)-1-METILPIPERIDINA



A. 1-METILISONIPECOTAMIDA



Se disolvió Isonipecotamida (10g, 78,0mmoles) en agua destilada (100ml) y se agregó formaldehído acuoso 37% (7,6ml, equivalente a 2,81g HCHO, 93,6 mmoles). Se agregó Pd-C 10% húmedo (8 espátulas de cuchara) bajo Argon y la mezcla se hidrogenó a 25°C y 50psi durante 43h. El catalizador se filtró a través de Celite y este último se lavó con agua y metanol. Los filtrados combinados se evaporaron hasta que se secaron y el residuo se sometió a cromatografía sobre una columna de gel de sílice (60x5cm) usando 8%-10%-20% (hidróxido de amonio conc. 10% en metanol)-diclorometano como el eluyente para dar 1-metilisonipecotamida (7,15g, 64%): FABMS: m/z 143,1 (MH^+); HRFABMS: m/z 143,1184 (MH^+). Calculado 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

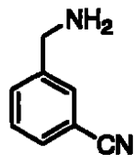


Se disolvió 1-Metilisonipecotamida (6,75g, 47,5mmoles) (preparado según se describió en el Ejemplo Preparativo 245, Paso A anterior) en THF anhídrido (350ml) y la mezcla resultante se agregó en porciones a una suspensión agitada de hidróxido de litio aluminio (1,8g, 47,5mmoles) en THF anhídrido (100ml) a 0°C bajo nitrógeno. La mezcla se agitó a 0°C durante 30 min y luego se calentó a 66°C durante 25h bajo nitrógeno. Se agregó agua destilada (1,88ml) gota a gota a la mezcla agitada a 0°C, seguido por hidróxido de sodio acuoso 20% (1,42ml) y luego agua destilada (6,75ml) y la mezcla se agitó durante 15 min. La mezcla se filtró y los sólidos se lavaron con THF y diclorometano. Los filtrados combinados se evaporaron hasta que se secaron y se sometieron a cromatografía en una columna de gel de sílice (30x5cm) usando 15%-20% (hidróxido de amonio conc. 10% en metanol)-diclorometano como el eluyente para dar 4-(aminometil)-1-

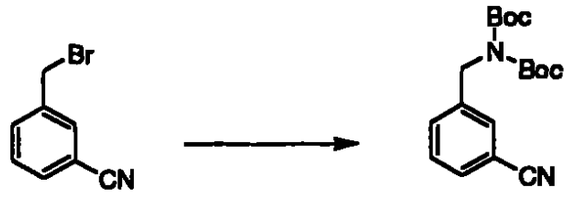
metilpiperidina (0,678g, 11%): FABMS: m/z 129,1 (MH^+); HRFABMS: m/z 129,1389 (MH^+). Calculado para $C_7H_{17}N_2$: m/z 129,1392; δ_H (d_6-DMSO): 2,08ppm (3H, s, $-NCH_3$); δ_C (d_6-DMSO): CH_3: bajo picos de DMSO; CH_2: 29,6, 29,6, 46,7, 55,2, 55,2; CH: 46,2.

EJEMPLO PREPARATIVO 246:

3-(AMINOMETIL)BENZONITRILO

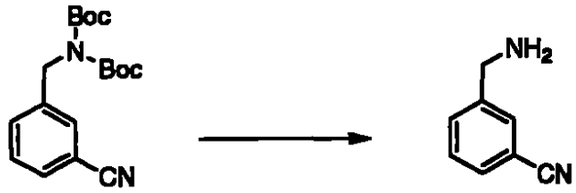


A. 3-(Di-*ter*-BUTOXICARBONILAMINO)BENZONITRILO



Se disolvieron 3-(Bromometil)benzonitrilo (5g, 25,5mmoles) y di-ter-butiliminodicarboxilato (5,54g, 25,5mmoles) en THF anhídrido (50ml) y se agregaron carbonato de cesio (16,62g, 25,5mmoles) y yoduro de litio (170,5mg, 1,275 mmoles). La mezcla se agitó a 70°C durante 22h y la reacción se procesó según se describió en el Ejemplo Preparativo 89, Paso B anterior. El residuo se sometió a cromatografía sobre una columna de gel de sílice (60x5cm) usando 5% acetato de etilo en hexano como el eluyente para dar 3-(di-*ter*-butoxicarbonilamino)benzonitrilo (7,39g, 87%): FABMS: m/z 333,2 (MH^+); HRFABMS: m/z 333,1815 (MH^+); Calculado 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.

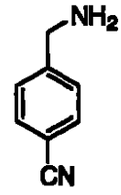
B. 3-(AMINOMETIL)BENZONITRILO



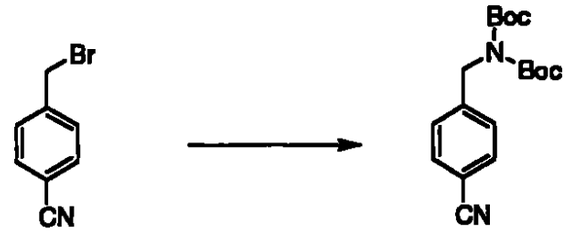
Se disolvió 3-(Di-*ter*-butoxicarbonilamino)benzonitrilo (2g, 6,0mmoles) (preparado según se describió en el Ejemplo Preparativo 246, Paso A anterior) en metanol (30ml) y se agregó 10%(v/v) (10% ácido sulfúrico conc. en 1,4-dioxano) (79ml). La solución se agitó a 25°C durante 0,25h y se procesó según se describió en el Ejemplo Preparativo 89, Paso C anterior). El residuo se sometió a cromatografía sobre una columna de gel de sílice (15x5cm) usando 3% (hidróxido de amonio conc. 10% en metanol)-diclorometano como el eluyente para dar el compuesto de título (651,4 mg, 82%): FABMS: m/z 133,1 (MH^+); HRFABMS: m/z 133,0762 (MH^+). Calculado para $C_8H_8N_2$: m/z 133,0766 ; δ_H ($CDCl_3$) 2,57 (2H, s, $-CH_2\underline{NH_2}$), 3,92 (2H, s, $-C\underline{H_2}NH_2$), 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



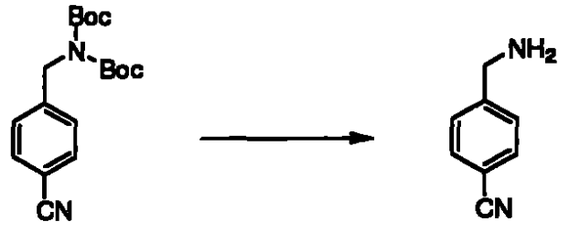
A. 3-(Di-*ter*-BUTOXICARBONILAMINOMETIL)BENZONITRILO



Se disolvieron 4-(Bromometil)benzonitrilo (5g, 25,5mmoles) y di-ter-butiliminodicarboxilato (5,54g, 25,5mmoles) en THF anhídrido (50ml) y se

agregaron carbonato de cesio (16,62g, 25,5mmoles) y yoduro de litio (170,5mg, 1,275mmoles). La mezcla se agitó a 70°C durante 23h y la reacción se procesó según se describió en el Ejemplo Preparativo 244, Paso B anterior. El residuo se sometió a cromatografía sobre una columna de gel de sílice (50x5cm) usando 5% acetato de etilo en hexano como el eluyente para dar 4-(di-*ter*-butoxicarbonilaminometil)benzonitrilo (7,07g, 83%): FABMS: m/z 333,2 (MH^+); HRFABMS: m/z 333,1816 (MH^+). Calculado 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; 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



Se disolvió 4-(Di-*ter*-butoxicarbonilaminometil)benzonitrilo (2g, 6,0mmoles) (preparado según se describió en el Ejemplo Preparativo 247, Paso A anterior) en TFA (4ml) y la solución se agitó a 25°C durante 0,25h. 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 que se secó. El residuo se sometió a cromatografía sobre una columna de gel de sílice (15x5cm) usando 3% (hidróxido de amonio conc. 10% en metanol)-diclorometano como el eluyente para dar 4-(aminometil)benzonitrilo (108mg, 68%): FABMS: m/z 133,1 (MH^+); HRFABMS: m/z133,0764 (MH^+). Calculado para $C_8H_9N_2$: 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) 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

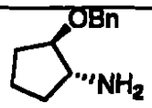
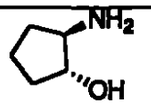
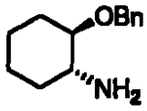
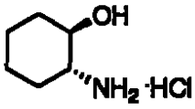
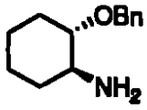
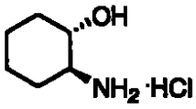


A una solución de (1*S*,2*S*)-2-benciloxiciclopentil amina (1,5 g, 7,84 mmol) en MeOH (50 ml) a temperatura ambiente se agregó Pd/C 10 % (50% húmedo, 1,0 g) seguido por la adición gota a gota de HCl conc. (0,7 ml). La mezcla se agitó bajo un globo de H_2 durante 14 h y el catalizador se filtró a través de un lecho de Celite. El lecho de Celite se lavó con MeOH (2 x 10 ml) y el filtrado resultante se concentró bajo presión reducida para dar 0,97 g (90%) de un semisólido amarillo; M+H (base libre) = 102.

EJEMPLOS PREPARATIVOS 249-251

De un modo análogo al Ejemplo preparativo 248, las cicloalquil aminas protegidas por bencilo (Columna 2) se convirtieron en los derivados de aminocicloalkanol clorhidrato deseados (Columna 3) según se enumeró en la Tabla 17.

TABLA 17

Ej.	Columna 2 (Amina)	Columna 3 (Método de escisión)	COMPUESTO M+H
249			M+H = 102 (base libre)
250			M+H = 116 (base libre)
251			M+H = 116 (base libre)

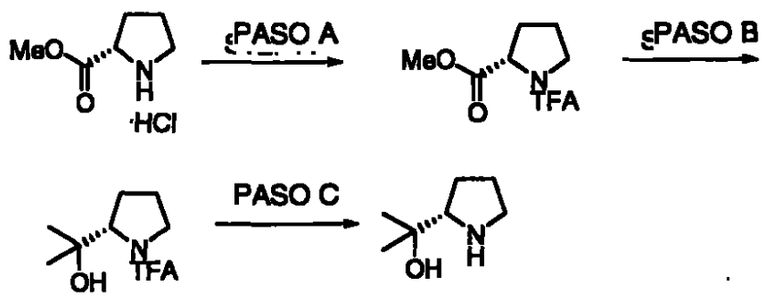
945

EJEMPLO PREPARATIVO 252



A una solución de éster (que se preparó de acuerdo con *J. Org. Chem.* (1999), *64*, 330) (0,5 g, 2,43 mmol) en THF (8 ml) a 0°C se agregó $LiAlH_4$ (0,37 g, 9,74 mmol) en una porción. La mezcla resultante se calentó a reflujo durante 12h y se enfrió hasta 0 °C. La mezcla se trató en secuencias con H_2O (1 ml), NaOH 1 M (1 ml), y H_2O (3 ml). CH_2Cl_2 (10 ml) se agregó a la mezcla que se agitó vigorosamente durante 30 min. La mezcla se filtró a través de un lecho de Celite which se lavó generosamente con CH_2Cl_2 (3 x 5 ml). El filtrado resultante se concentró bajo presión reducida para dar 0,41 g (85%) de un sólido amarillo/anaranjado. M+H = 142.

EJEMPLO PREPARATIVO 253



PASO A:

A una solución de clorhidrato de *L*-prolina metil éster (0,50 g, 3,0 mmol) en CH_2Cl_2 (15 ml) a 0°C se agregó Et_3N (1,1 ml, 7,55 mmol) seguido por TFAA (0,56 ml, 3,92 mmol). La mezcla se agitó durante 12 h a temperatura ambiente y 1N HCl (25 ml) se agregó. Las capas se separaron y la capa orgánica se lavó secuencialmente con $NaHCO_3$ acuoso sat. (1 x 25 ml), y salmuera (1 x 25 ml). La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida para dar 0,72 g (100%) de un aceite amarillo. M+H = 226. El material bruto se tomó sobre el Paso B sin purificación adicional.

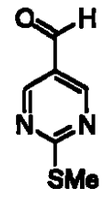
PASO B:

A una solución del compuesto preparado en el Ejemplo preparativo 253, Paso A (0,68 g, 3,0 mmol) en THF (20 ml) a 0°C se agregó MeMgI (5,1 ml, 3,0M en Et_2O) gota a gota durante 10 min. La solución resultante se agitó durante 16 h a temperatura ambiente en dicho momento la mezcla se desactivó mediante la adición de NH_4Cl acuoso sat.. La mezcla se concentró hasta que se secó y el residuo resultante se agitó con EtOAc (100 ml) durante 45 min y se filtró. El filtrado se concentró bajo presión reducida para dar 0,68g (100%) de un aceite amarillo/anaranjado. M+H = 226. El material bruto se tomó sobre el Paso C sin purificación adicional.

PASO C:

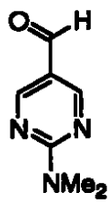
A una solución del compuesto preparado en el Ejemplo preparativo 253, Paso B (0,68 g, 3,0 mmol) en MeOH (5 ml) se agregó una solución de KOH (0,68 g, 12,1 mmol) en MeOH (5 ml). La mezcla se agitó a reflujo durante 12h y a temperatura ambiente durante 72h en dicho momento la mezcla se concentró hasta que se secó. El residuo bruto se suspendió en EtOAc (50 ml) y se agitó vigorosamente durante 30 min y se filtró. Este procedimiento se repitió dos veces más y el filtrado resultante se concentró bajo presión reducida para dar 128 mg (33%) de un aceite marrón/ naranja. M+H = 130. Este material se usó sin purificación adicional en el paso de acoplamiento siguiente.

EJEMPLO PREPARATIVO 254:



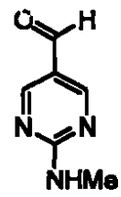
El aldehído se preparó de acuerdo con el procedimiento de Gupton (*J. Heterocyclic Chem.* (1991), *28*, 1281).

EJEMPLO PREPARATIVO 255



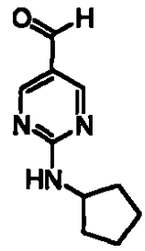
Usando el aldehído del Ejemplo Preparativo 254, el procedimiento de Gupton (*J. Heterocyclic Chem.* (1991), *28*, 1281) se usó para preparar el aldehído de título.

EJEMPLO PREPARATIVO 256



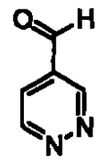
El aldehído de título se preparó de acuerdo con el procedimiento de Ragan et. al *Synlett* (2000), *8*, 1172-1174.

EJEMPLO PREPARATIVO 257



La reacción del clorhidrato de ciclopentil guanidina (*Org. Lett.* (2003), *5*, 1369-1372) bajo las condiciones de Ragan (*Synlett* (2000), *8*, 1172-1174) dio el aldehído de título.

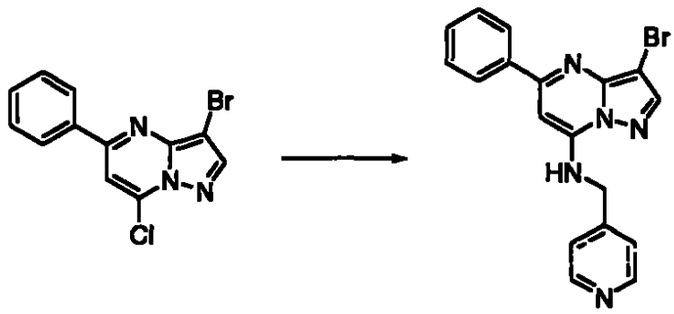
EJEMPLO PREPARATIVO 258



El compuesto de título se preparó de acuerdo con la literatura conocida *Monatshefte fur Chemie* (1973), *104*, 1372-1382.

EJEMPLOS

EJEMPLO 1:



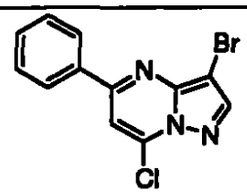
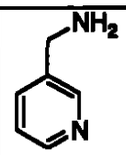
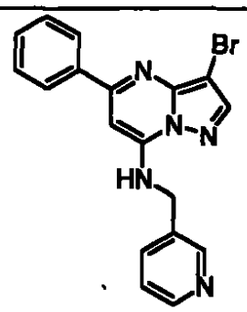
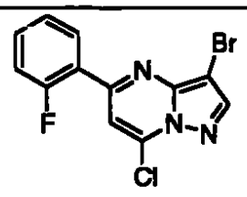
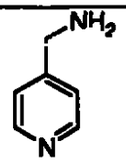
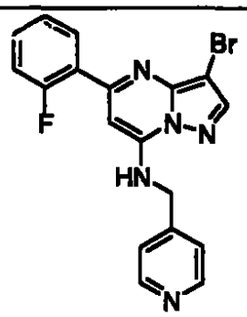
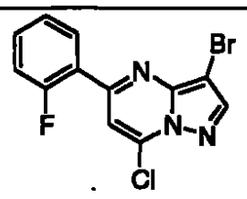
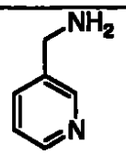
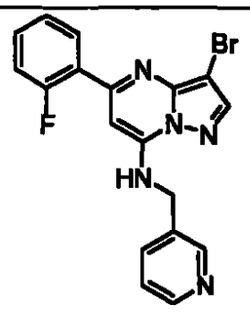
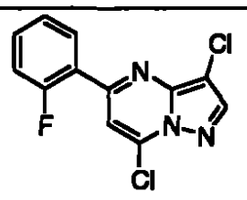
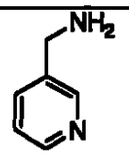
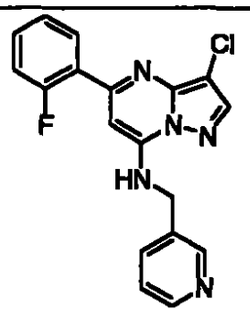
Se agitó una solución de el producto del Ejemplo Preparativo 127 (0,27 g, 0,875 mmol), 4-aminometilpiridina (0,12 g, 1,3 eq.), y K_2CO_3 (0,24 g, 2 eq.) en CH_3CN (5 ml) a temperatura ambiente 48 horas. La mezcla de reacción se diluyó con H_2O y se extrajo con CH_2Cl_2. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron y se concentraron. El producto bruto se purificó mediante cromatografía flash usando una solución MeOH 4% en CH_2Cl_2 como eluyente (0,28 g, 93% de rendimiento). LCMS: MH^+=380; mp= >205°C (dec).

EJEMPLOS 2-210:

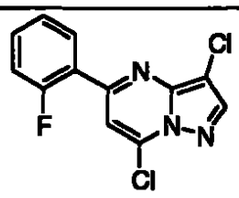
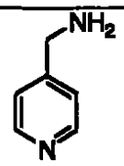
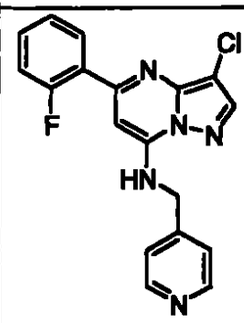
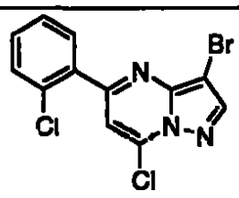
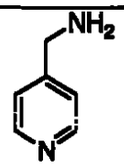
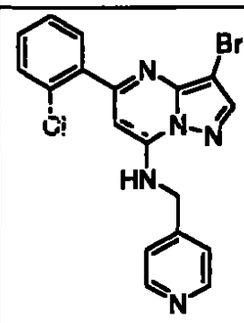
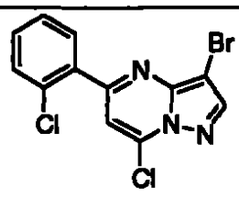
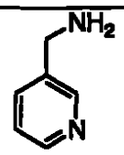
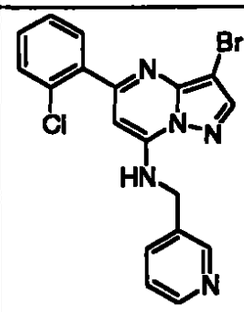
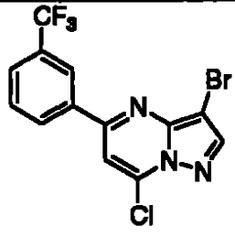
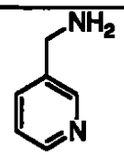
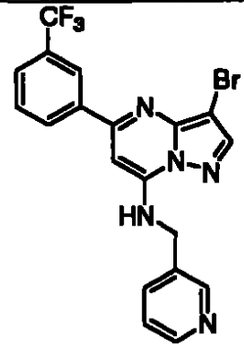
Por medio de seguir esencialmente el mismo procedimiento expuesto en el Ejemplo 1, sustituyendo solamente los cloruros que se muestran en la Columna 2 de la Tabla 18 y las aminas que se muestran en la Columna 3 de la Tabla 18, se prepararon los compuestos en la columna 4 de la Tabla 18:

450
449

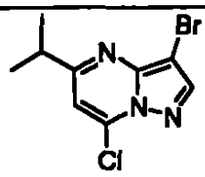
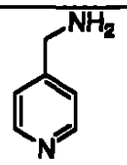
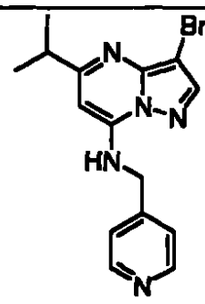
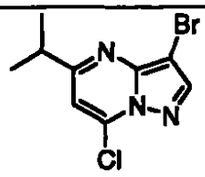
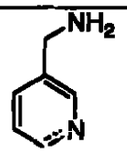
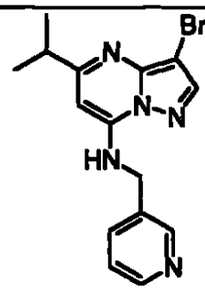
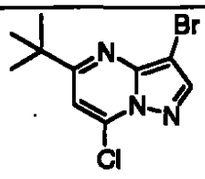
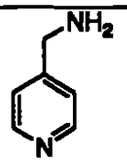
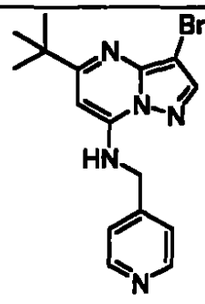
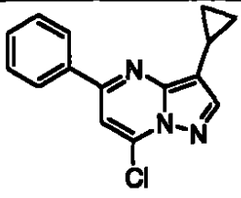
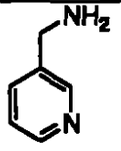
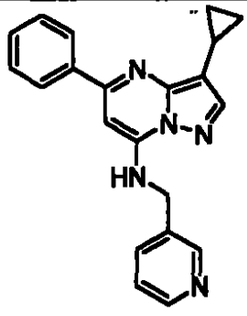
TABLA 18

Ej.	Columna 2	Columna 3	Columna 4	Datos
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

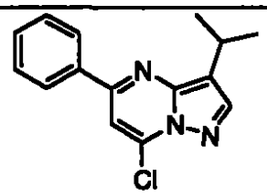
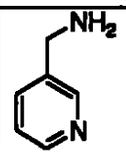
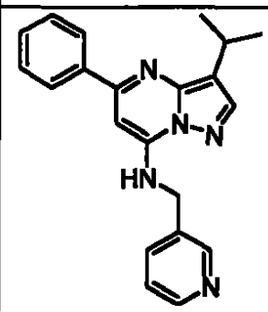
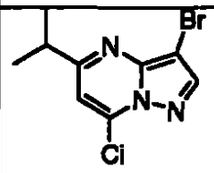
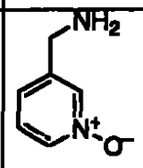
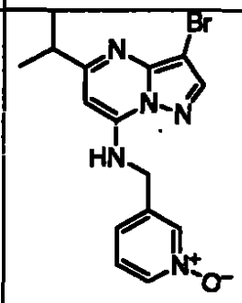
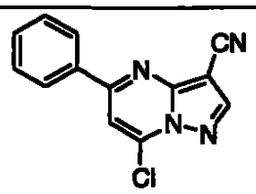
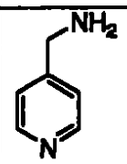
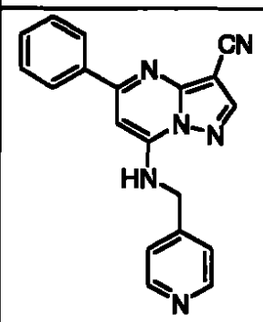
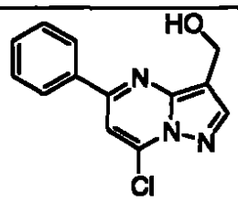
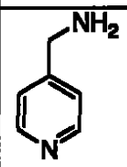
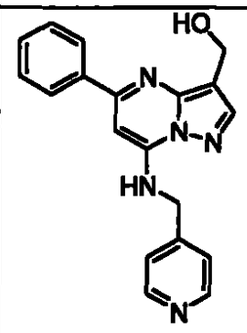
~~451~~
450

Ej.	Columna 2	Columna 3	Columna 4	Datos
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

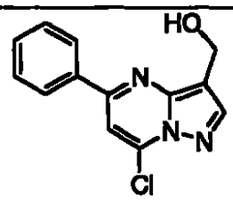
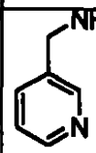
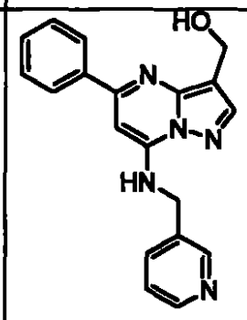
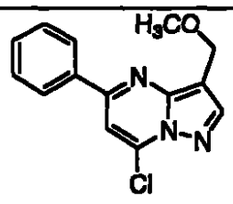
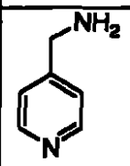
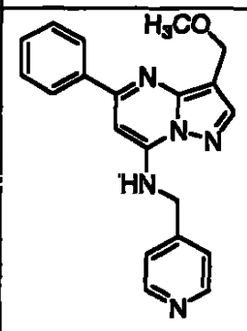
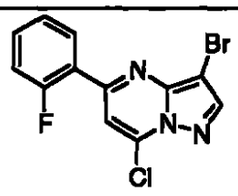
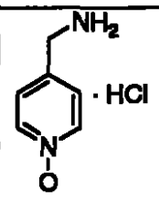
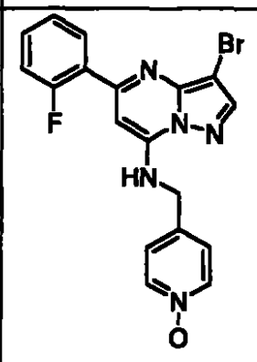
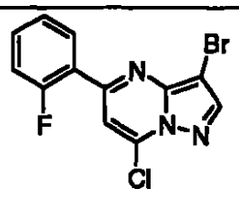
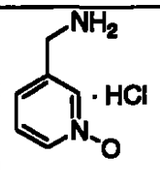
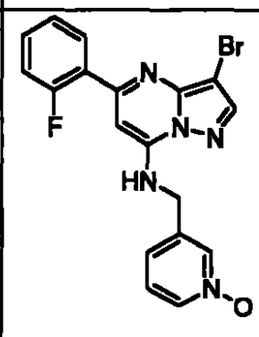
~~452~~
451

Ej.	Columna 2	Columna 3	Columna 4	Datos
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

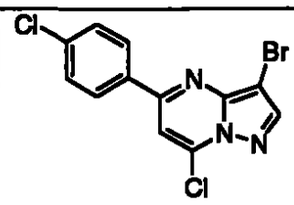
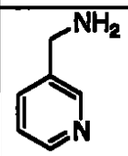
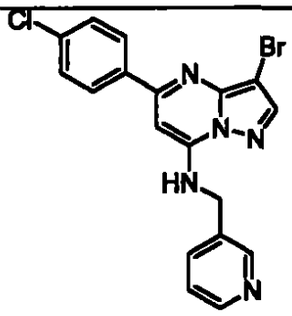
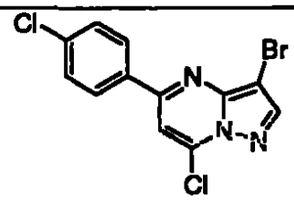
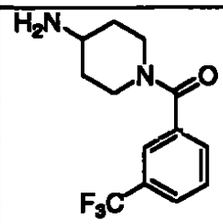
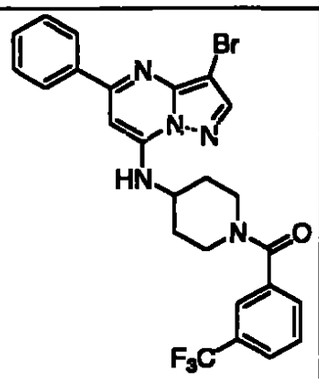
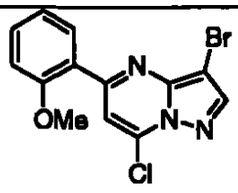
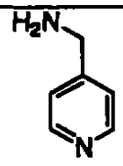
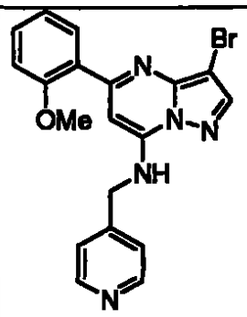
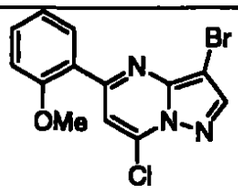
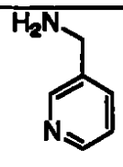
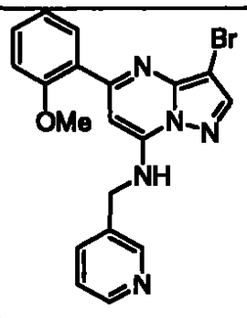
~~453~~
452

Ej.	Columna 2	Columna 3	Columna 4	Datos
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

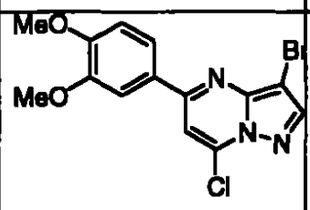
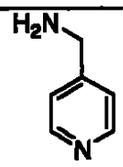
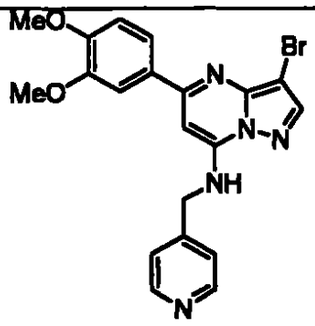
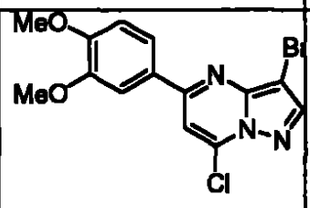
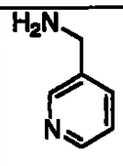
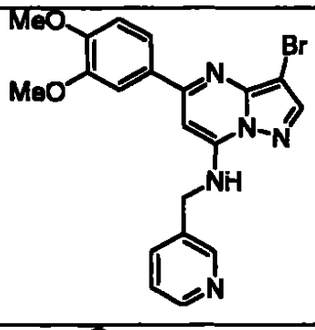
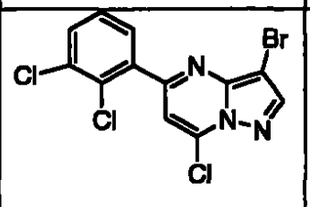
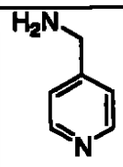
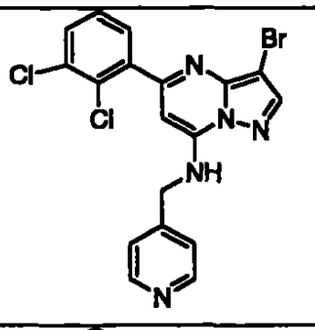
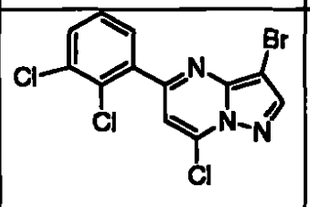
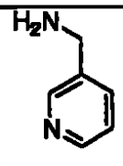
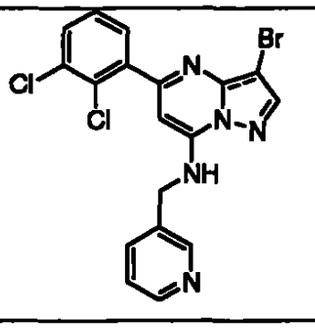
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Ej.	Columna 2	Columna 3	Columna 4	Datos
17, 1				MS: MH^+ = 332,
18				LCMS: MH^+= 346; mp= 58-65°C
19				LCMS: MH^+= 414; mp= 211-213°C
20				LCMS: MH^+= 414; mp= 194-197°C

~~415~~
454

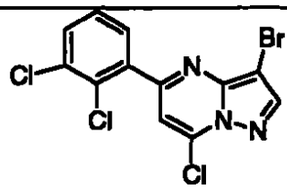
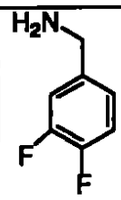
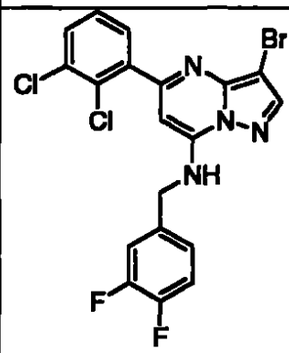
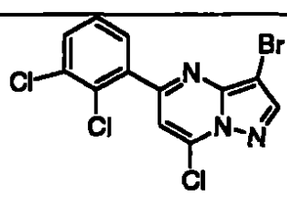
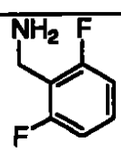
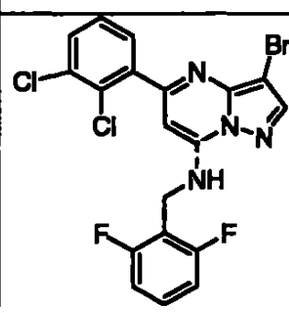
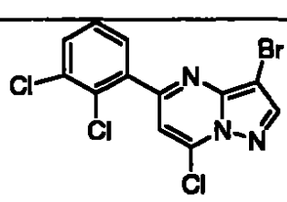
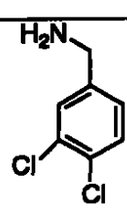
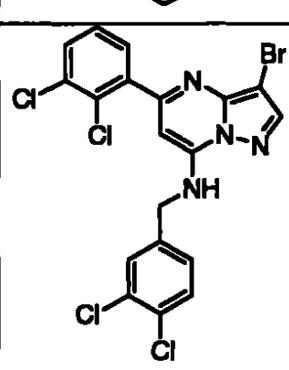
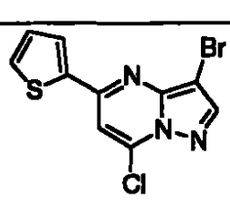
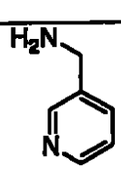
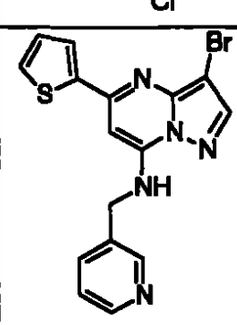
Ej.	Columna 2	Columna 3	Columna 4	Datos
21				MS: MH^+ = 414 m.p. 211 – 216°C
22				LCMS: MH^+= 544; mp= 104-107°C
23				Rendimiento = 83% LCMS: MH^+ = 410,
24				Rendimiento = 84% LCMS: MH^+ = 410,

~~456~~
455

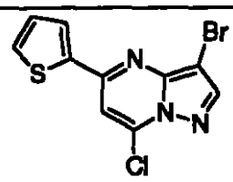
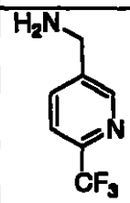
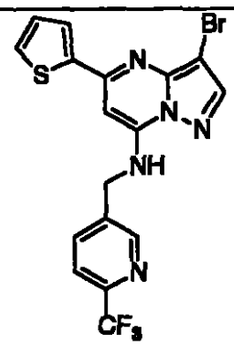
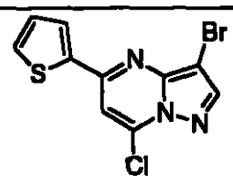
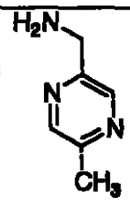
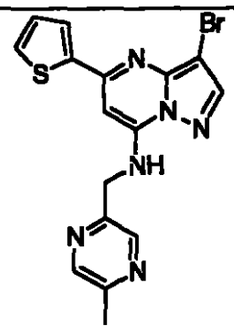
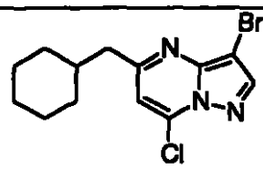
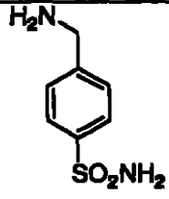
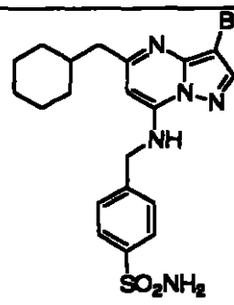
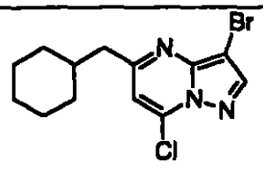
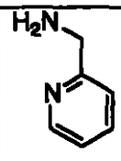
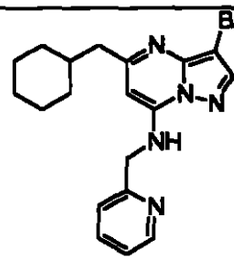
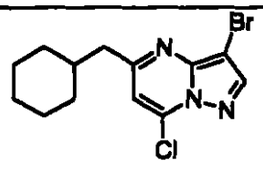
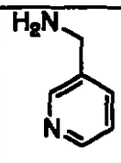
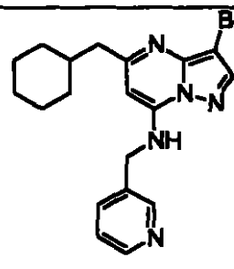
Ej.	Columna 2	Columna 3	Columna 4	Datos
25				Rendimiento = 96% LCMS: MH^+ = 440,
26				Rendimiento = 99% LCMS: MH^+ = 440,
27				Rendimiento = 89% LCMS: MH^+ = 448,
28				Rendimiento = 78% LCMS: MH^+ = 448,

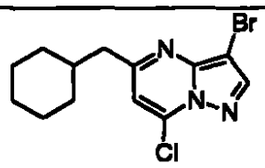
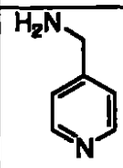
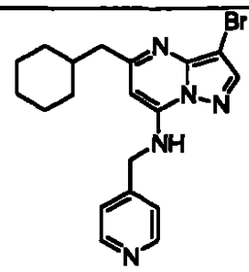
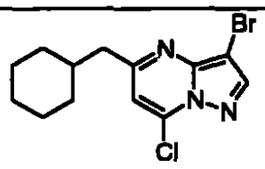
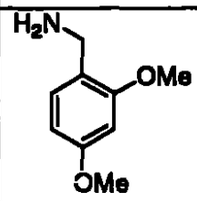
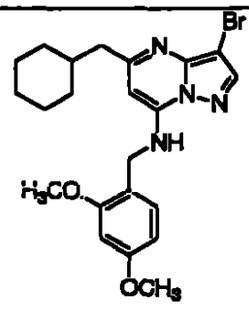
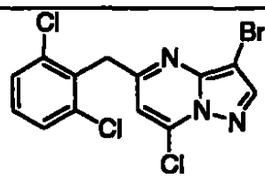
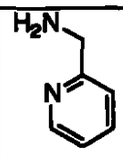
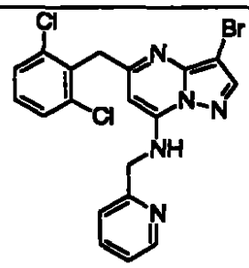
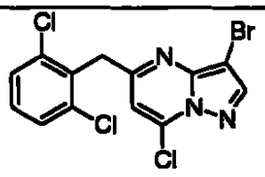
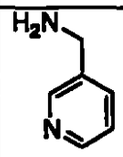
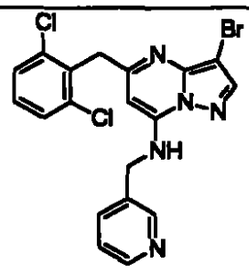
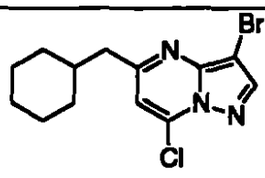
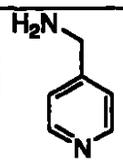
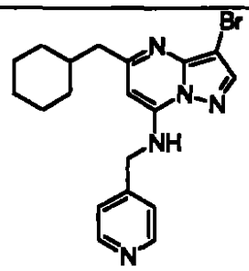
457

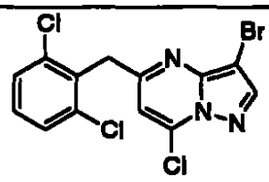
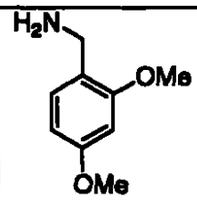
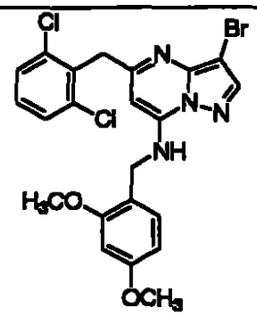
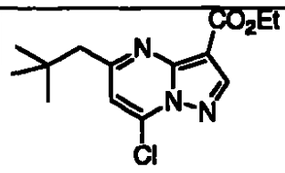
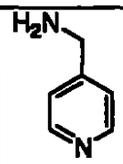
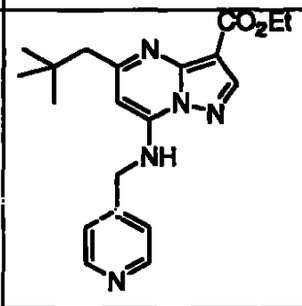
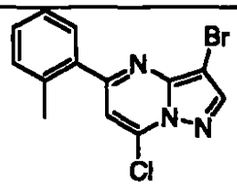
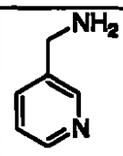
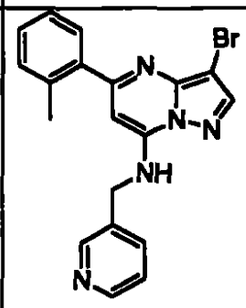
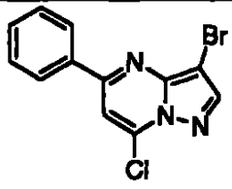
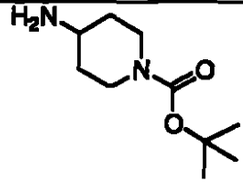
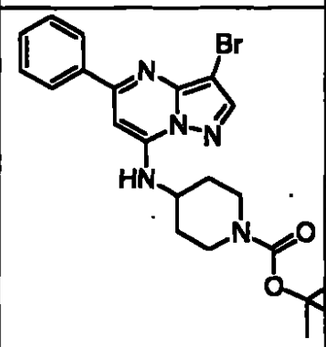
456

Ej.	Columna 2	Columna 3	Columna 4	Datos
30				Rendimiento = 96% LCMS: MH^+ = 483,
31				Rendimiento = 35% LCMS: MH^+ = 483,
32				Rendimiento = 77% LCMS: MH^+ = 515,
33				Rendimiento = 100% m.p. 179°C LCMS: MH^+ = 388

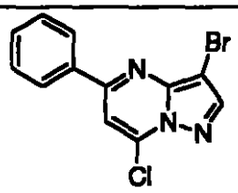
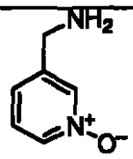
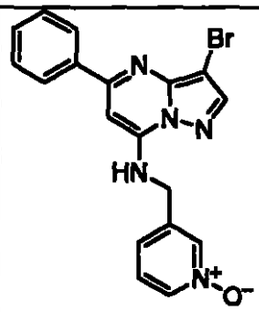
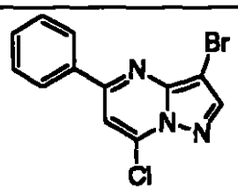
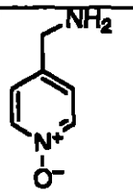
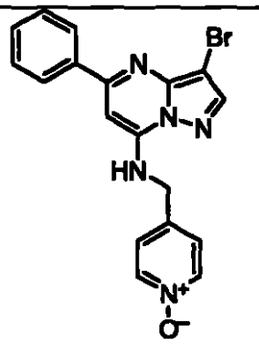
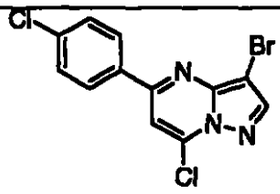
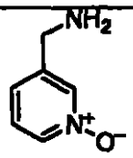
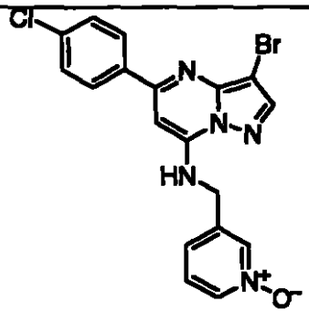
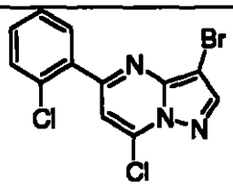
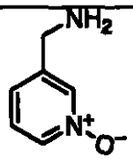
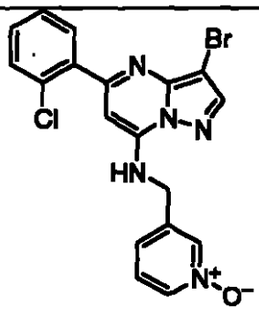
YDB
457

Ej.	Columna 2	Columna 3	Columna 4	Datos
34				Rendimiento = 99% m.p. 186°C LCMS: MH^+ = 456
35				Rendimiento = 98% m.p. 181°C LCMS: MH^+ = 401
36				Rendimiento = 63% m.p. 192°C LCMS: MH^+ = 480
37				Rendimiento = 75% m.p. 126 – 127°C LCMS: MH^+ = 400
38				Rendimiento = 94% *m.p. 132 - 133°C* LCMS: MH^+ =

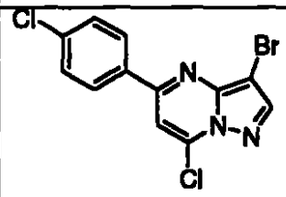
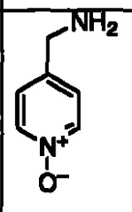
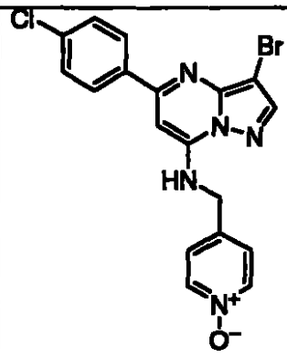
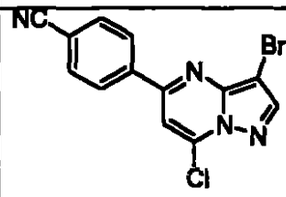
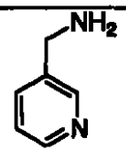
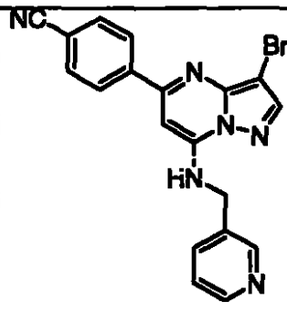
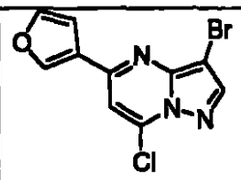
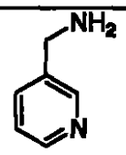
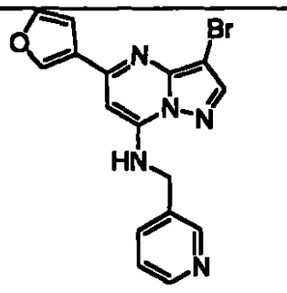
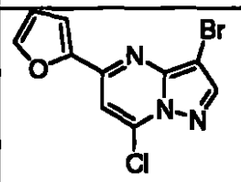
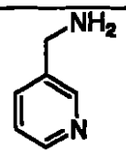
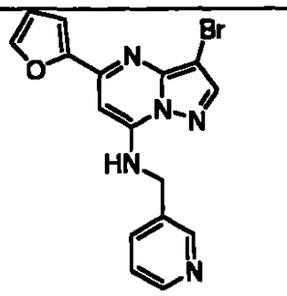
Ej.	Columna 2	Columna 3	Columna 4	Datos
				400
39				Rendimiento = 95% m.p. 121 – 122°C LCMS: MH^+ = 400
40				Rendimiento = 98% LCMS: MH^+ = 460
41				Rendimiento = 87% m.p. 170 - 171°C LCMS: MH^+ = 464
42				Rendimiento = 84% m.p. 216 - 217°C LCMS: MH^+ = 464
43				Rendimiento = 96% m.p. 214°C LCMS: MH^+ = 464

Ej.	Columna 2	Columna 3	Columna 4	Datos
44				Rendimiento = 95% m.p. 158°C LCMS: MH^+ = 522
45				Rendimiento =90% LCMS: MH^+= 278
46				Rendimiento =100% ; LCMS: MH^+=394
47				LCMS: MH+ = 473 m.p. 84 - 87°C

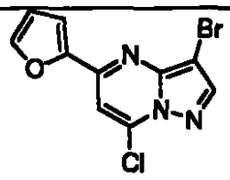
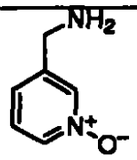
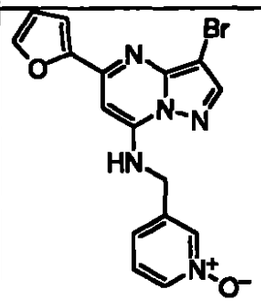
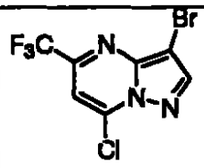
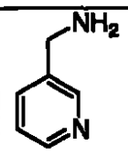
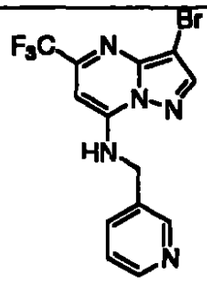
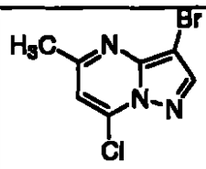
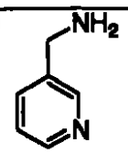
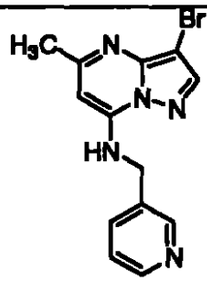
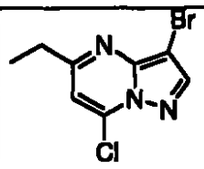
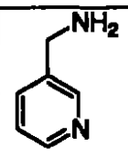
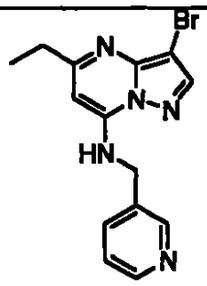
~~461~~
460

Ej.	Columna 2	Columna 3	Columna 4	Datos
48				MS: MH^+ = 396 m.p. 91,5 – 93,3°C
49				MS: MH^+ = 396 m.p. 198 – 199°C
50				MS: MH^+ = 430 m.p. 242 – 244°C
51				MS: MH^+ = 430 m.p. 218°C

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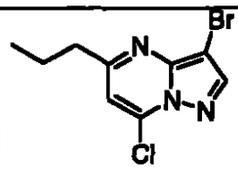
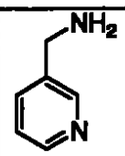
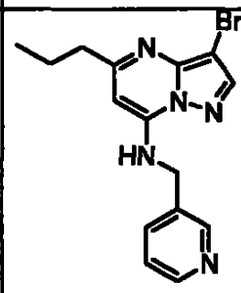
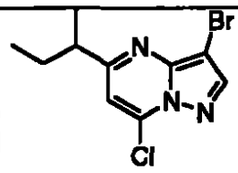
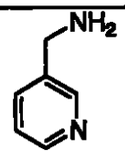
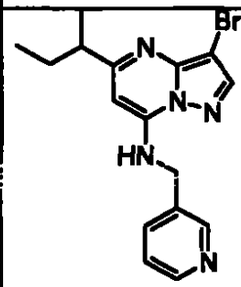
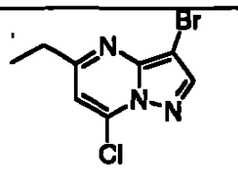
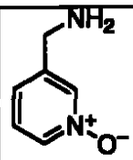
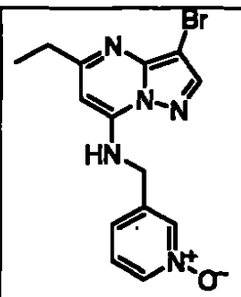
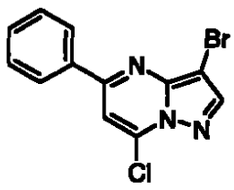
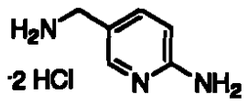
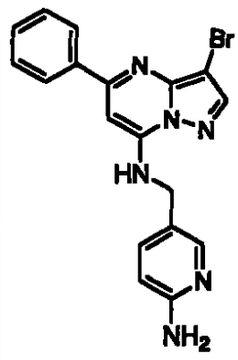
Ej.	Columna 2	Columna 3	Columna 4	Datos
52				MS: MH^+ = 430 m.p. 230 – 233°C
54				MS: MH^+ = 405 m.p. 185 – 188°C
55				MS: MH^+ = 370 m.p. 229 – 232°C
56				MS: MH^+ = 370 m.p. 85 – 90°C

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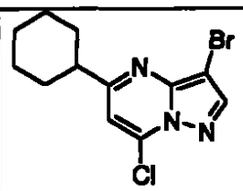
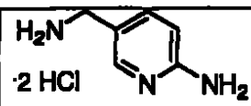
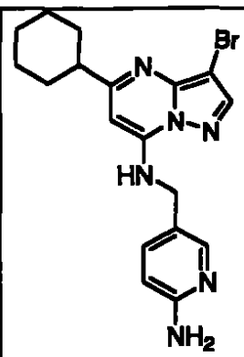
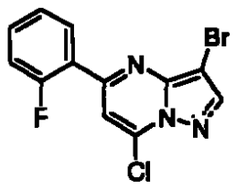
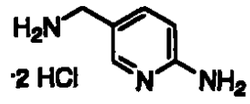
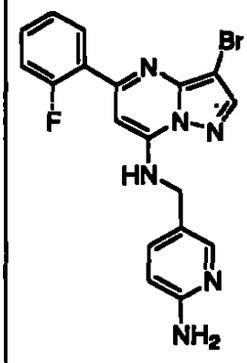
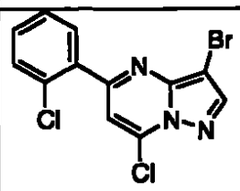
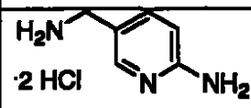
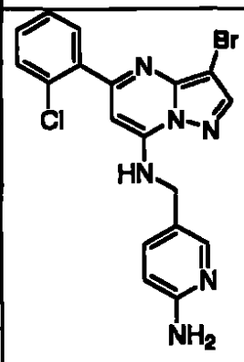
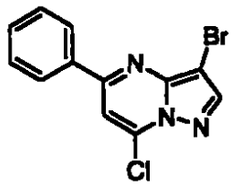
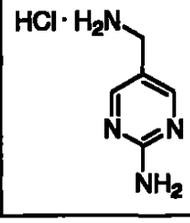
Ej.	Columna 2	Columna 3	Columna 4	Datos
57				MS: MH^+ = 386 m.p. 227 – 230°C
58				MS: MH^+ = 372 m.p. 212 – 215°C
59				MS: MH^+ = 318 m.p. 169 – 171°C
60				MS: MH^+ = 332 m.p. 170 – 173°C

~~464~~

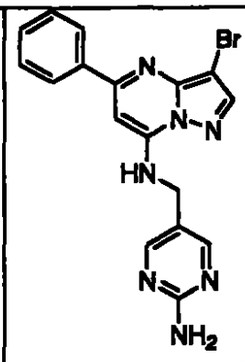
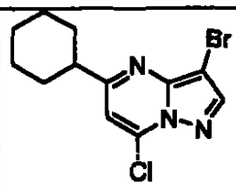
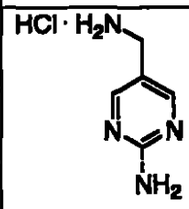
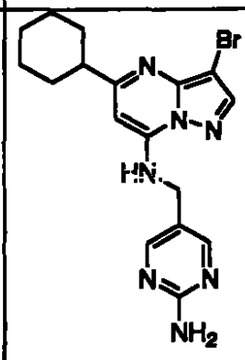
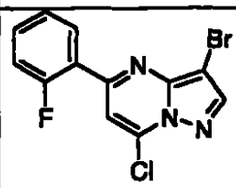
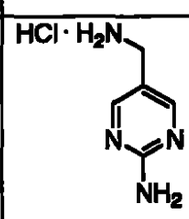
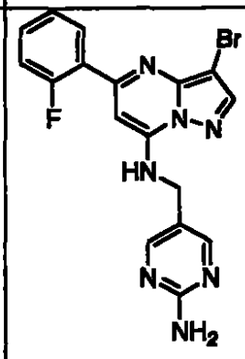
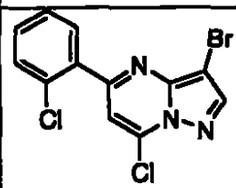
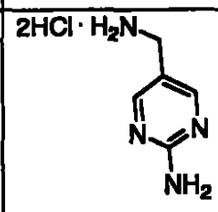
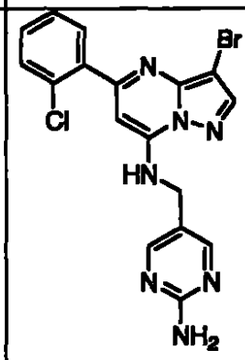
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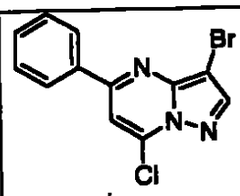
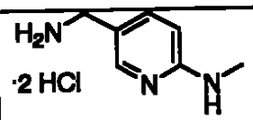
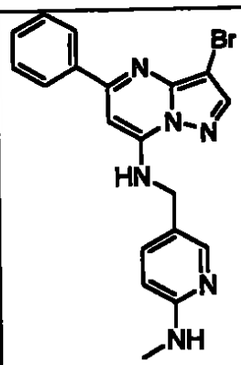
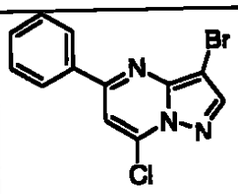
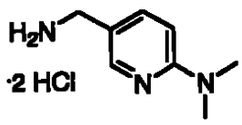
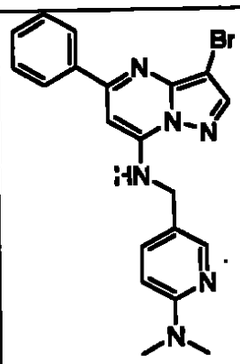
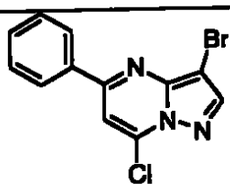
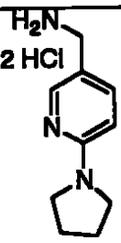
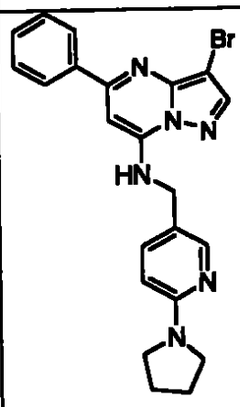
Ej.	Columna 2	Columna 3	Columna 4	Datos
61				MS: MH^+ = 346 m.p. 156 – 159°C
62				MS: MH^+ = 360 m.p. 114 – 116°C
63				MS: MH^+ = 348 m.p. 197 – 200°C
64				1. mp = 230-232 2. M+H = 396

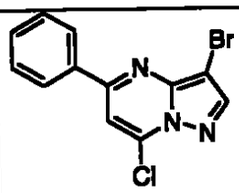
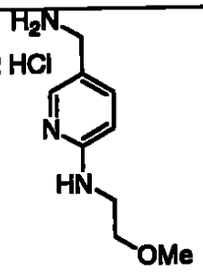
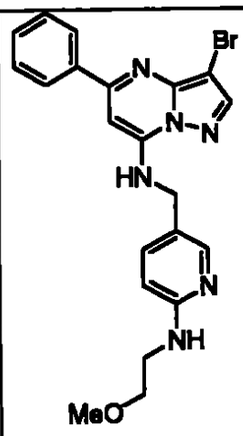
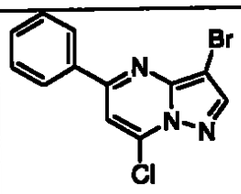
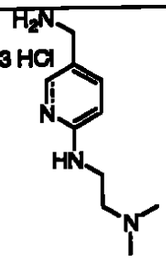
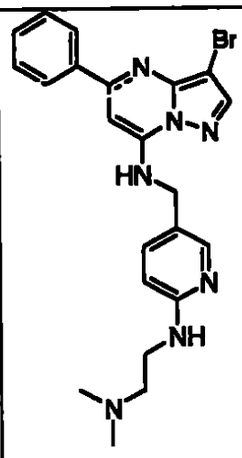
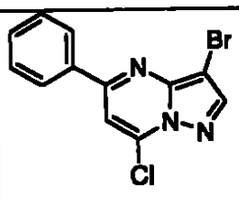
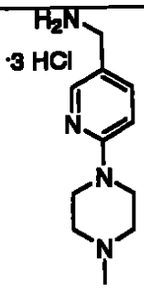
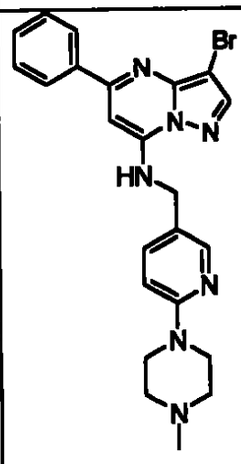
~~465~~
464

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

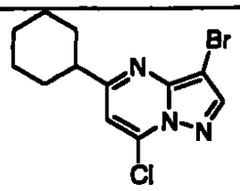
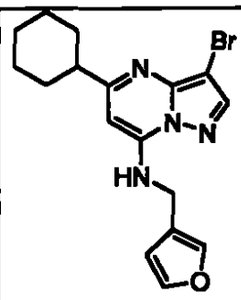
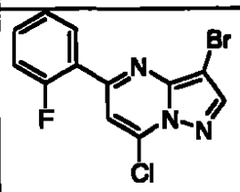
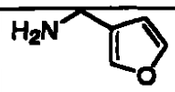
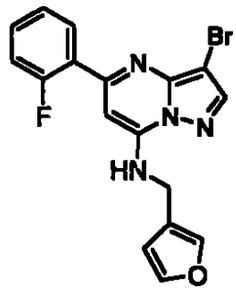
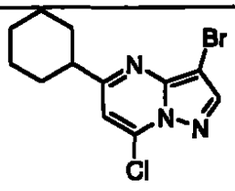
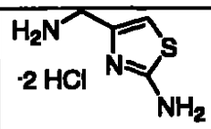
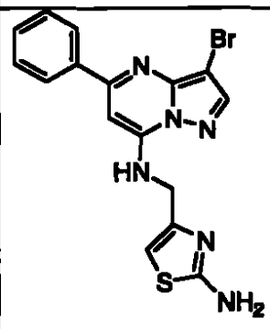
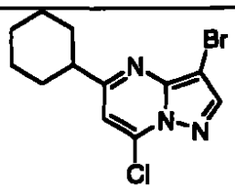
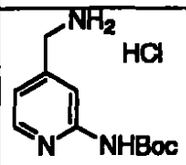
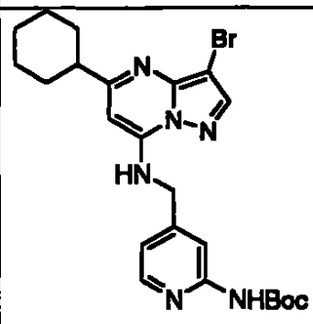
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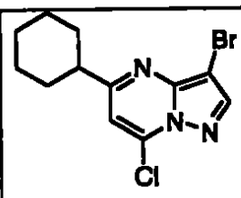
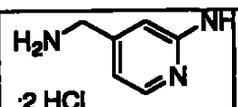
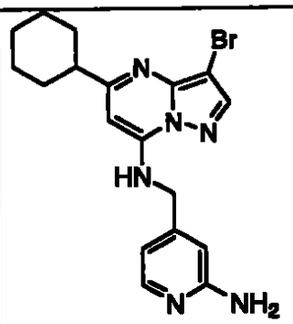
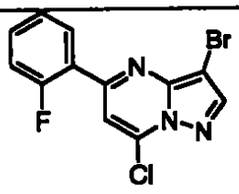
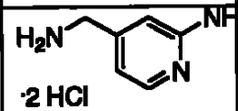
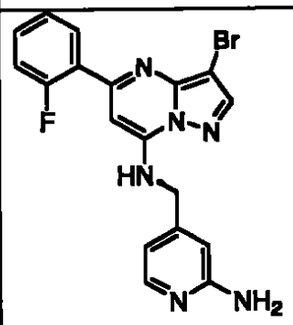
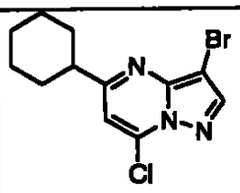
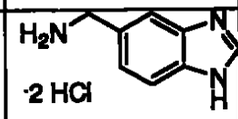
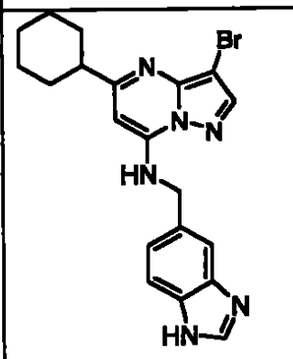
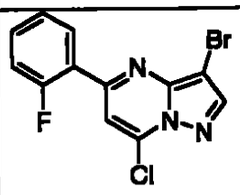
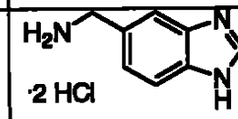
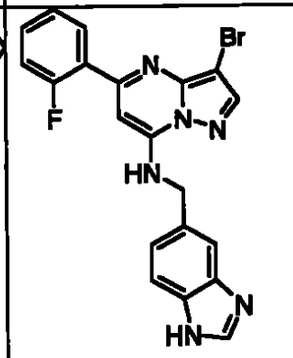
				
69				1. mp = >250 2. M+H = 403
70				1. mp = 230-232 2. M+H = 415
71				1. mp = 235-238 2. M+H = 431

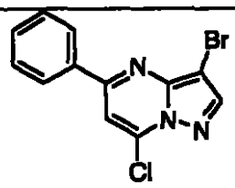
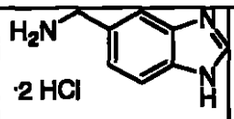
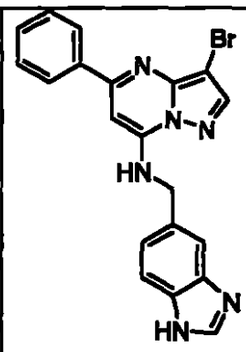
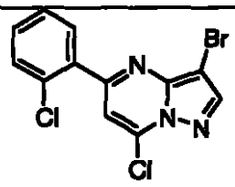
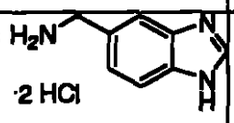
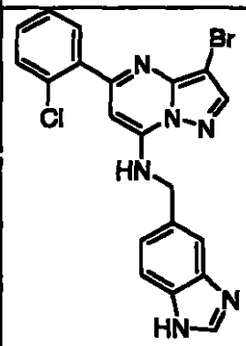
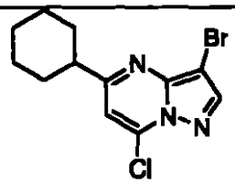
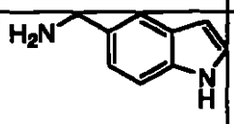
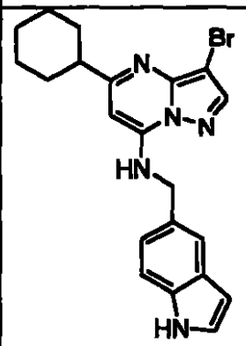
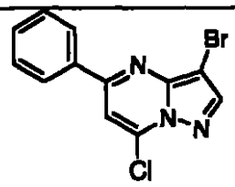
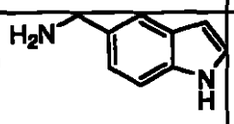
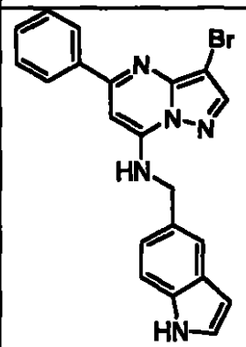
72				1. mp = 186-188 2. M+H = 410
73				1. mp = 136-138 2. M+H = 424
74				1. mp = 192-195 2. M+H = 450

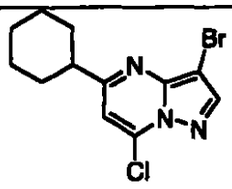
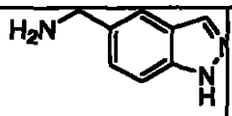
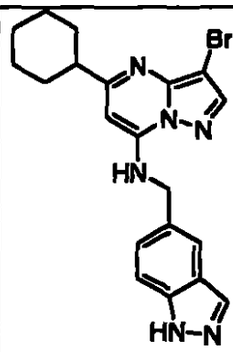
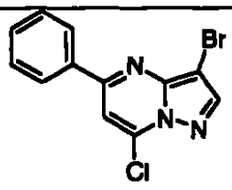
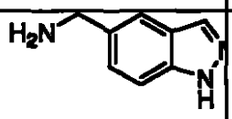
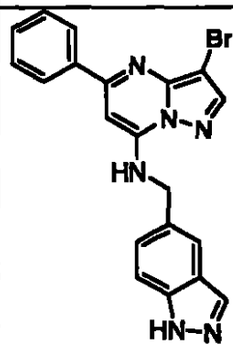
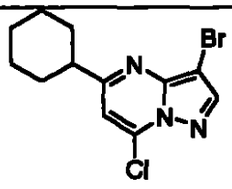
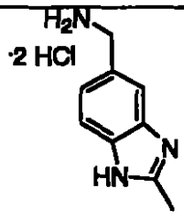
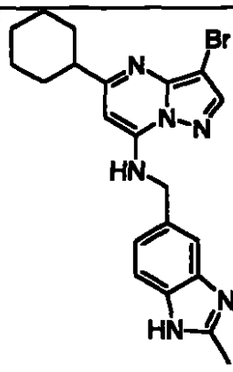
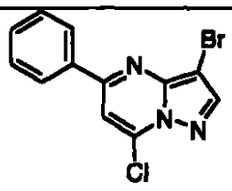
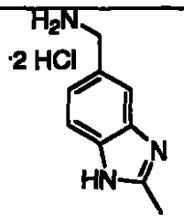
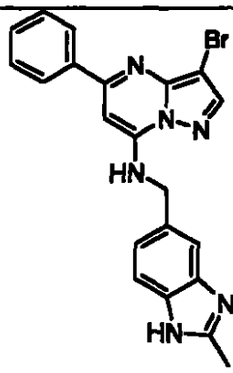
75				1. mp = 88-90 2. M+H = 454
76				1. mp = 230-232 2. M+H = 467
77				1. mp = 131-133 2. M+H = 479

~~469~~
468

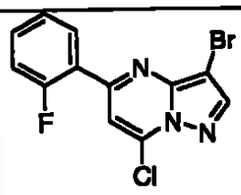
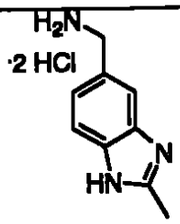
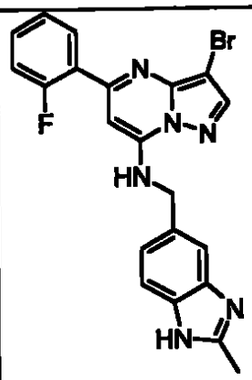
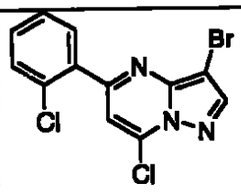
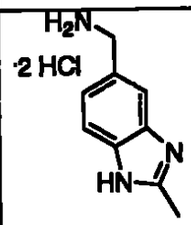
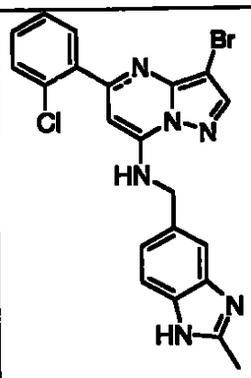
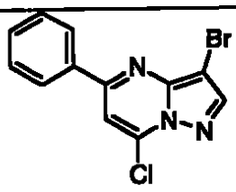
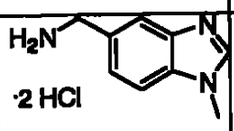
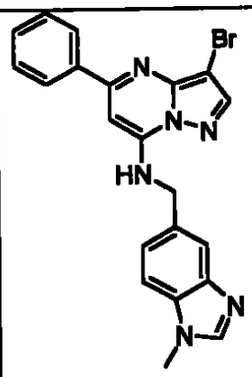
78				1. mp = 85-88 2. M+H = 376
79				1. mp = 131-133 2. M+H = 388
80				1. mp = 206-208 2. M+H = 408
81				1. mp = 108-110 2. M+H = 502

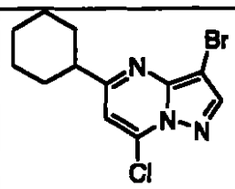
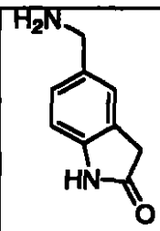
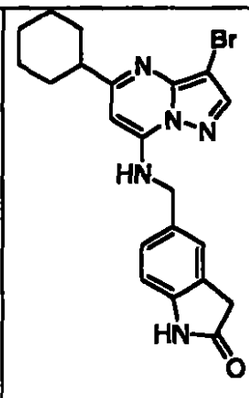
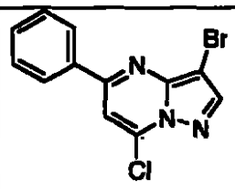
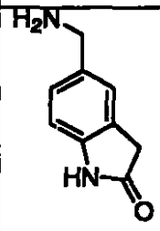
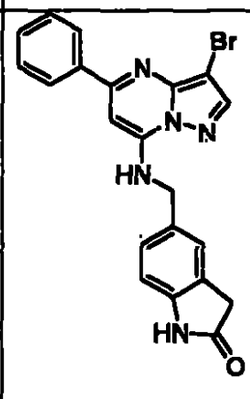
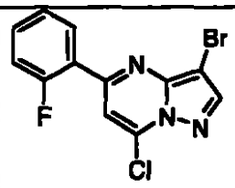
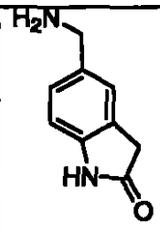
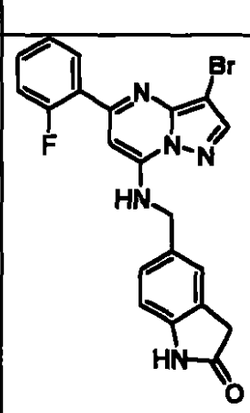
82		 ·2 HCl		1. mp = 83-85 2. M+H = 402
83		 ·2 HCl		1. mp = 220 2. M+H = 414
84		 ·2 HCl		1. mp = 154-156 2. M+H = 426
85		 ·2 HCl		1. mp = 152-153 2. M+H = 438

86		 ·2 HCl		1. mp = 159-161 2. M+H = 420
87		 ·2 HCl		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

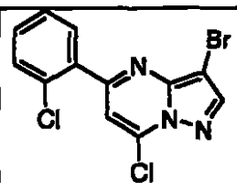
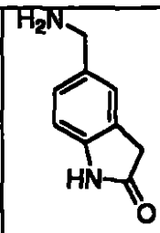
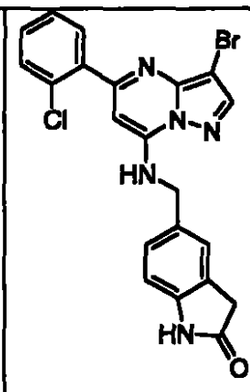
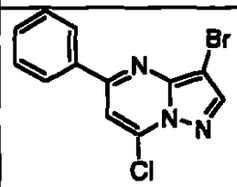
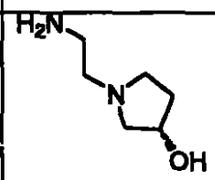
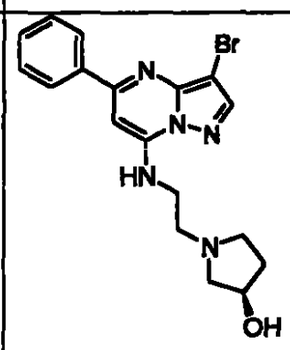
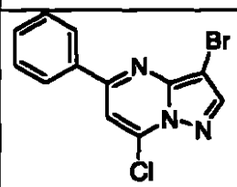
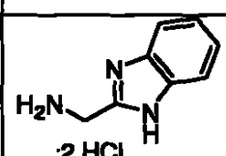
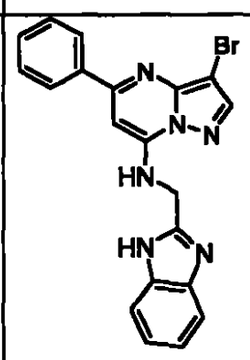
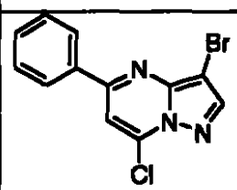
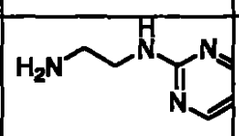
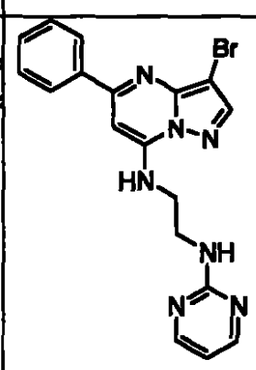
~~473~~
472

94				1. mp = 173-175 2. M+H = 452
95				1. mp = 174-176 2. M+H = 469
96				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

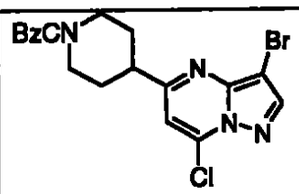
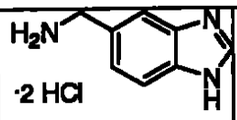
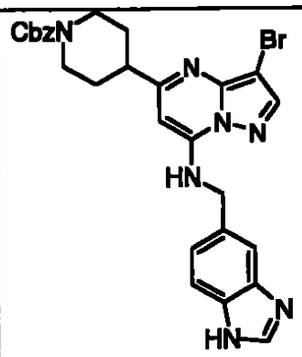
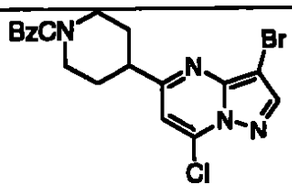
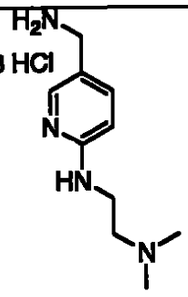
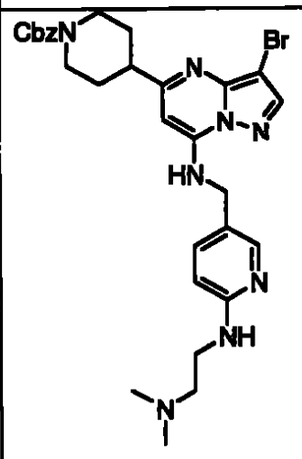
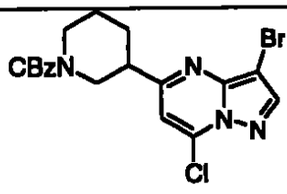
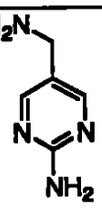
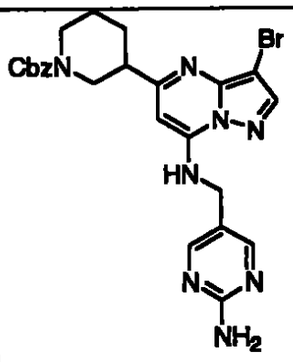
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474

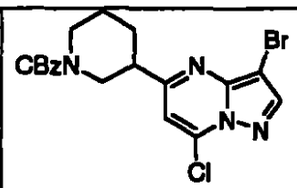
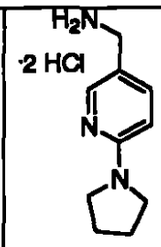
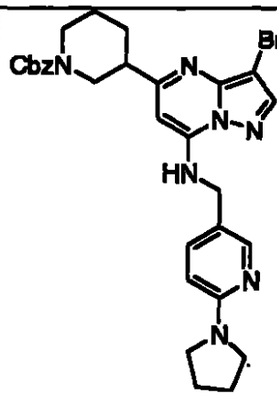
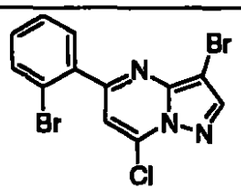
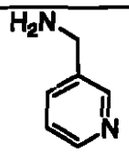
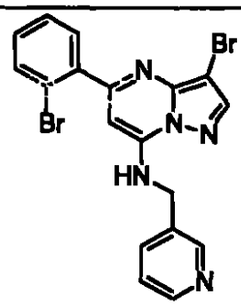
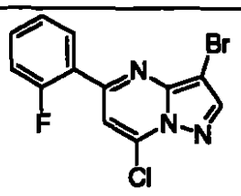
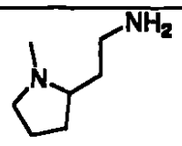
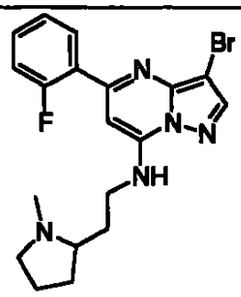
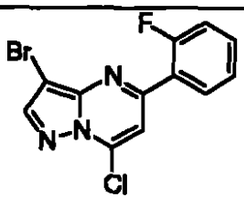
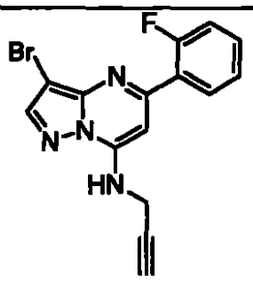
100				1. mp = 219-221 2. M+H = 469
101				1. mp = 64-66 2. M+H = 403
102				1. mp = 168-170 2. M+H = 420
103				1. mp = 213-216 2. M+H = 411

476

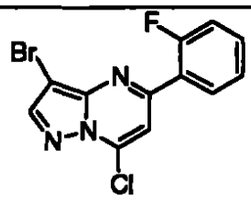
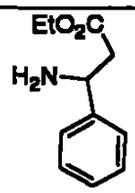
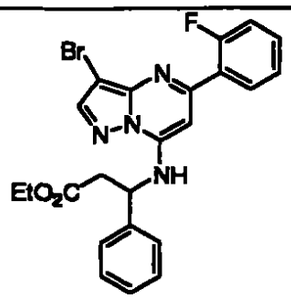
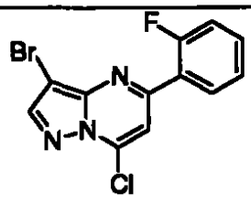
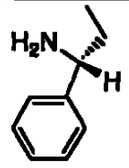
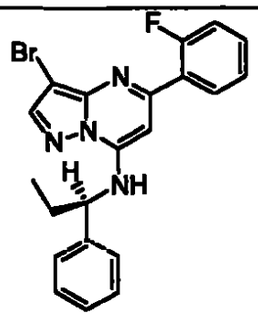
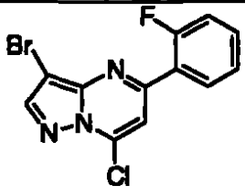
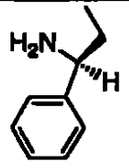
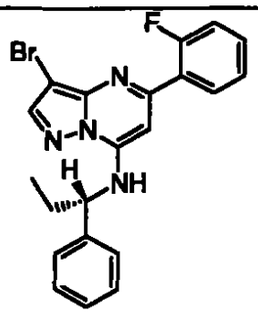
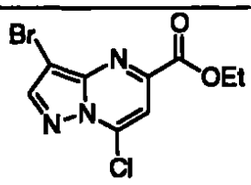
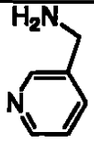
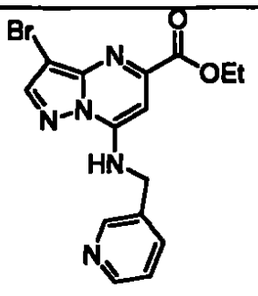
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104				1. mp = 98-100 2. M+H = 561
105				1. mp 70-72 2. M+H = 608
106				1. mp 168-170 2. M+H = 538

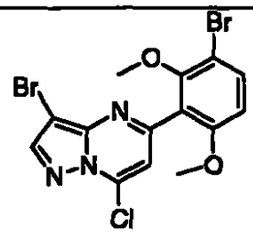
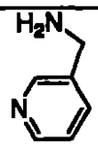
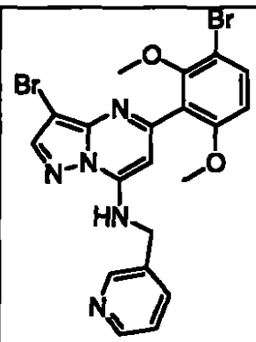
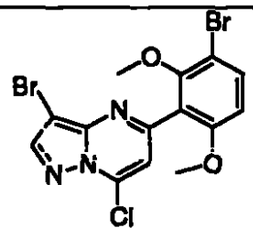
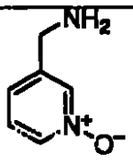
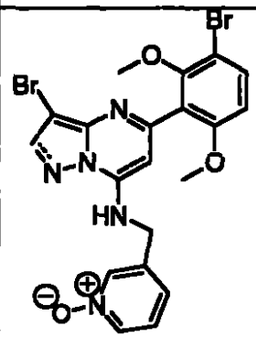
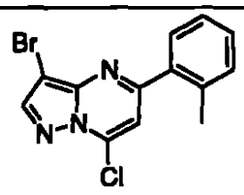
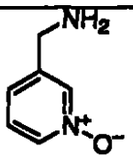
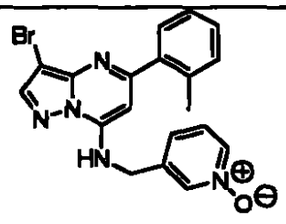
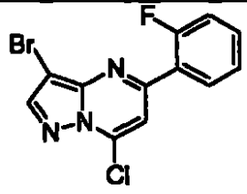
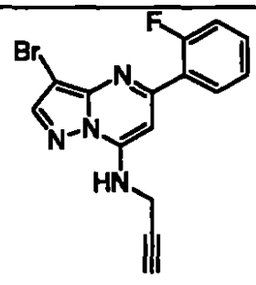
~~477~~
476

107				1. mp 189-191 2. M+H = 592
108				**LCMS: MH^+ = 458;**
109				Rendimiento = 89 LCMS: MH^+ = 418 m. p. = 131-132 °C
110				**Rendimiento =95%** **LCMS: MH^+= 347**

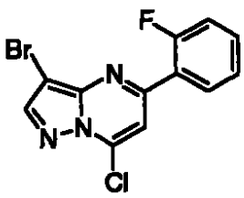
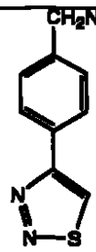
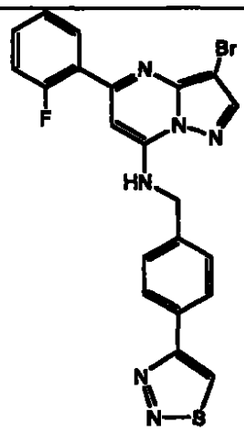
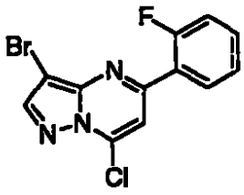
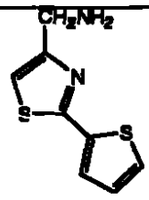
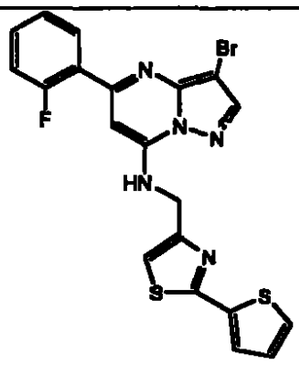
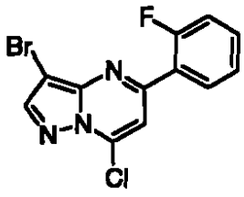
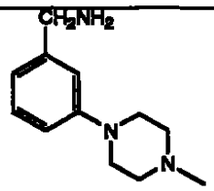
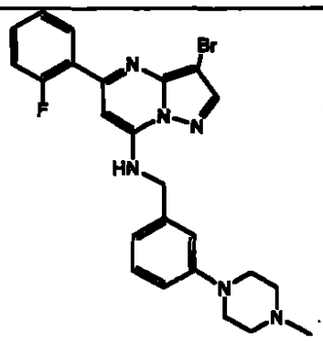
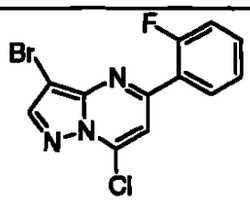
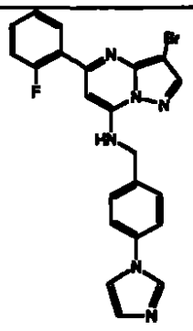
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111				**Rendimiento =91%** 3H); LCMS: MH^+= 484
112				**Rendimiento =87%** LCMS: MH^+= 427
113				**Rendimiento =80%** LCMS: MH^+= 427
114				**Rendimiento =91%** LCMS: MH^+= 378

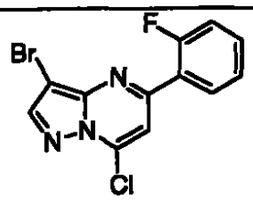
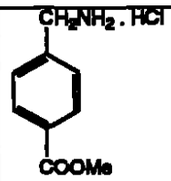
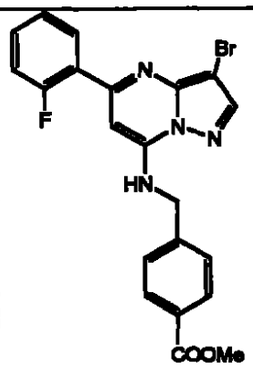
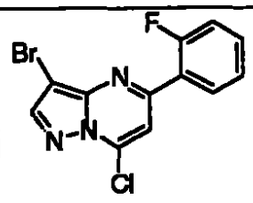
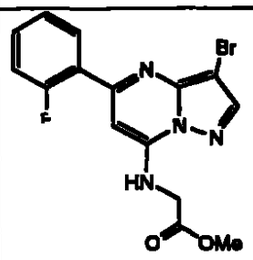
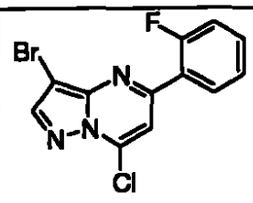
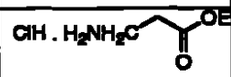
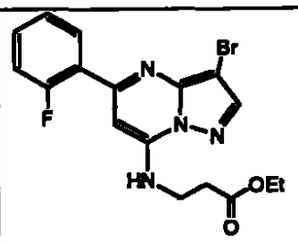
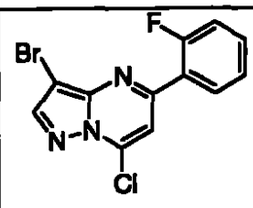
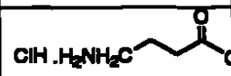
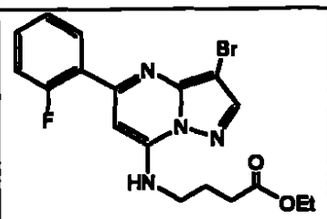
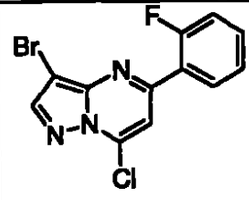
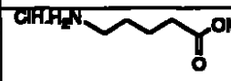
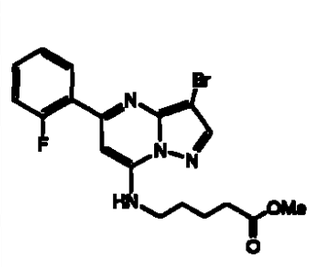
478 479

115				**Rendimiento =92%** **, 3H); LCMS: MH^+=520**
116				**Rendimient =98%** **LCMS:** **MH^+=536**
117				**Rendimiento =82%** **LCMS:** **MH^+=410**
118				**Rendimiento =95%** **LCMS: MH^+= 347**

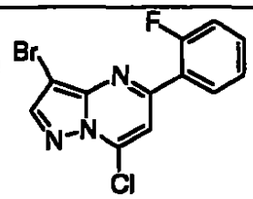
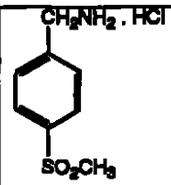
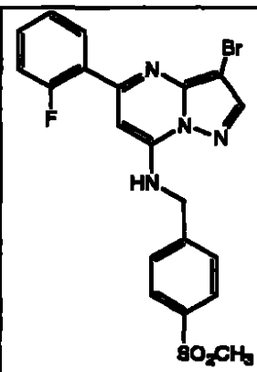
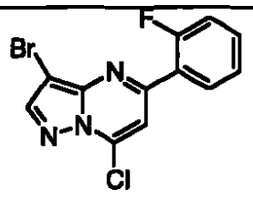
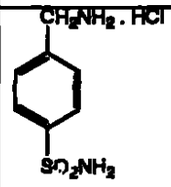
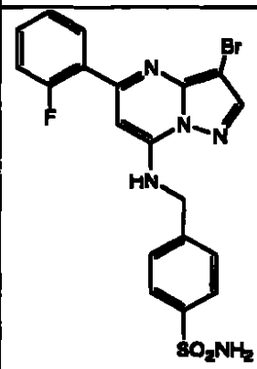
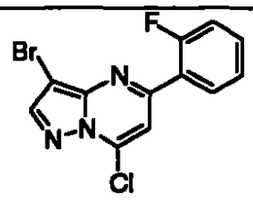
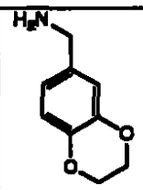
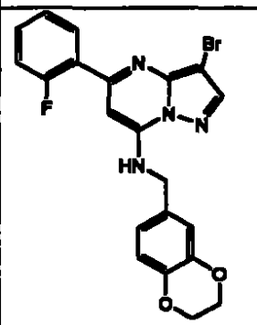
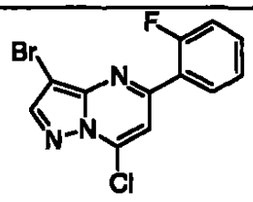
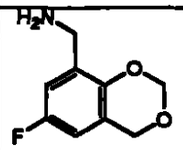
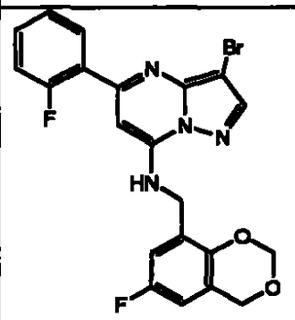
479 480

121				**Rendimiento = 65%** **LCMS: MH^+ = 481,02**
126				**Rendimient =71%** **MH^+ = 486**
127				**Rendimiento =71%** **MH^+ = 495,1**
128				**Rendimiento =55%** **MH^+ = 463**

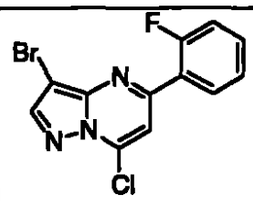
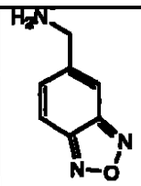
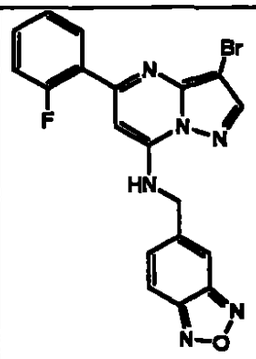
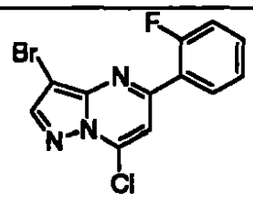
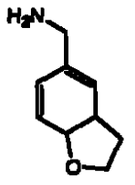
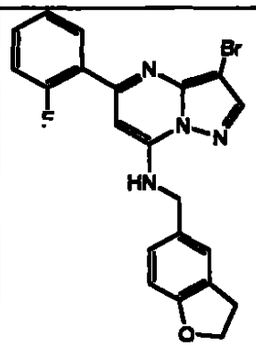
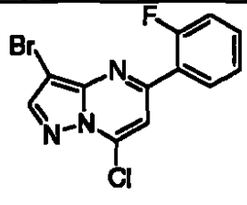
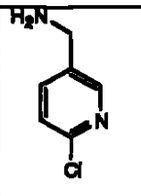
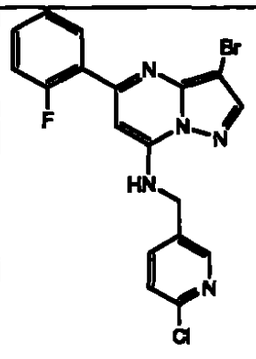
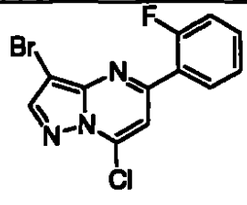
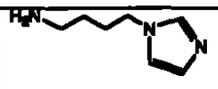
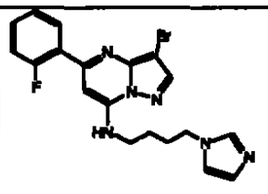
480

129				**Rendimiento = 77%** LCMS: MH^+ = 455
130				^1H RMN (Rendimiento = 75% LCMS: MH^+ = 379
131				**Rendimiento = 75%** LCMS: MH^+ = 407
132				**Rendimiento = 75%** LCMS: MH^+ = 421
133				**Rendimiento = 70%** LCMS: MH^+ = 421

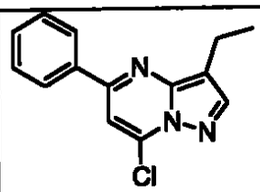
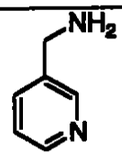
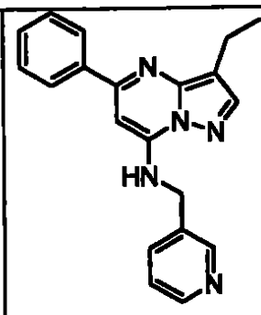
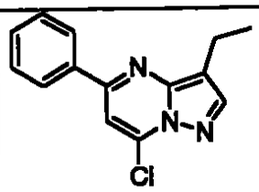
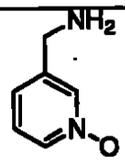
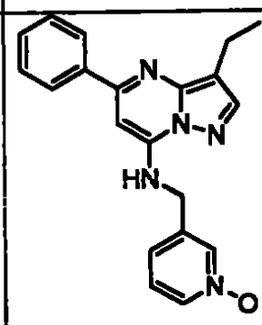
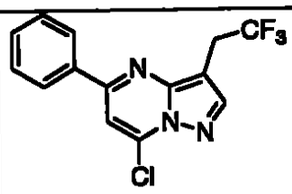
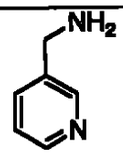
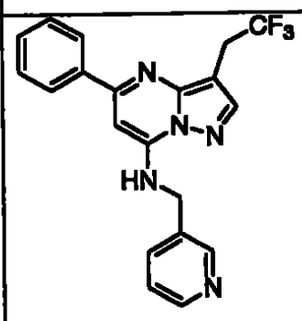
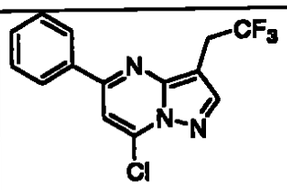
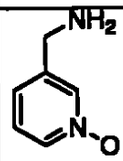
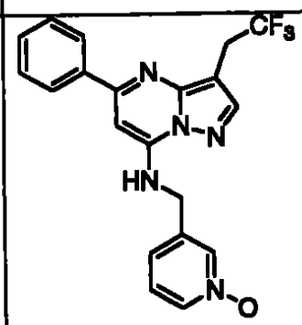
481

134				**Rendimiento = 78%** LCMS: MH^+ = 475
135				**Rendimiento = 75%** LCMS: MH^+ = 476
136				**Rendimient = 65%** LCMS: MH^+ = 455
137				**Rendimiento = 55%** LCMS: MH^+ = 473)

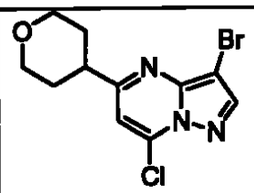
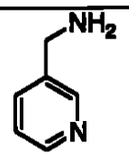
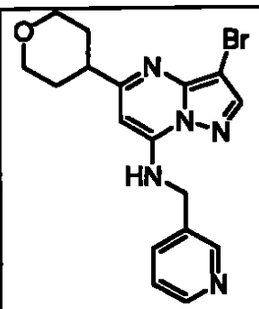
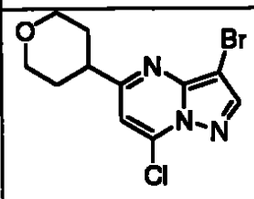
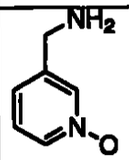
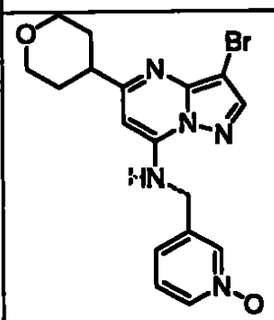
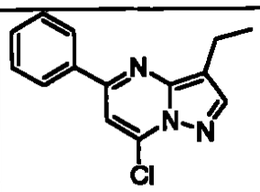
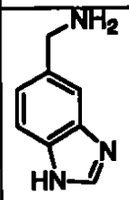
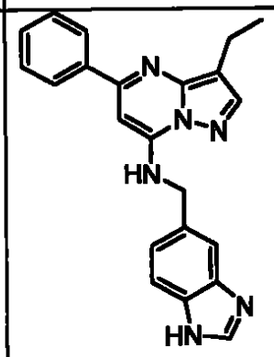
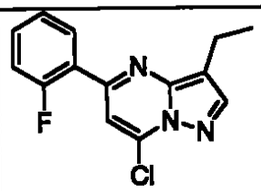
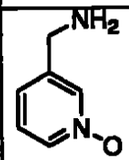
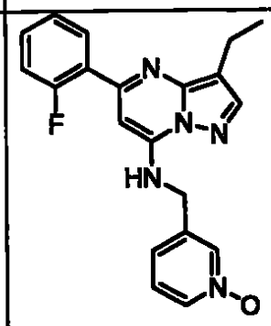
482

138				**Rendimiento = 60%** LCMS: MH^+ = 439
139				**Rendimiento = 65%** LCMS: MH^+ = 441
140				**Rendimiento = 80%** LCMS: MH^+ = 432
141				**Rendimiento = 60%** LCMS: MH^+ = 429

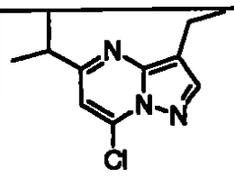
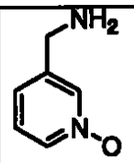
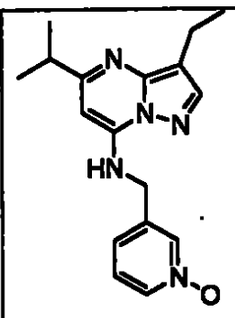
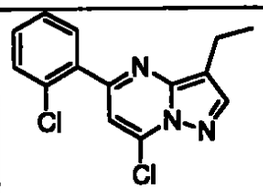
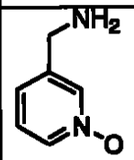
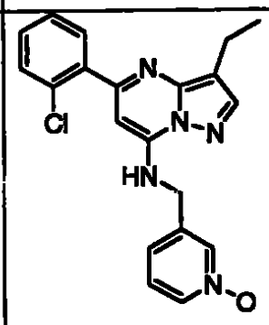
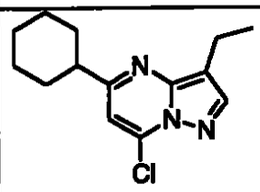
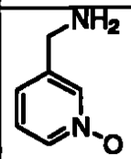
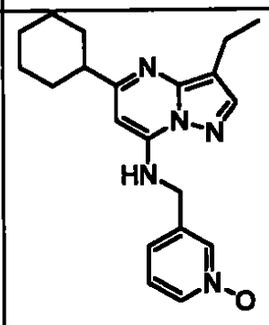
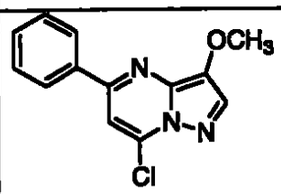
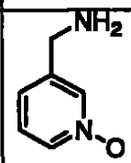
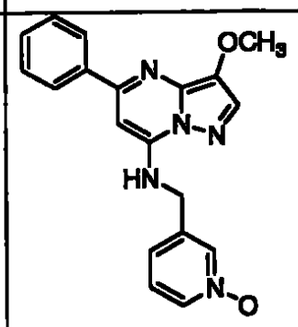
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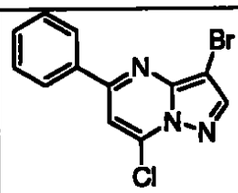
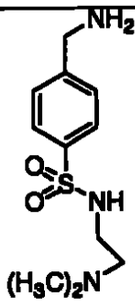
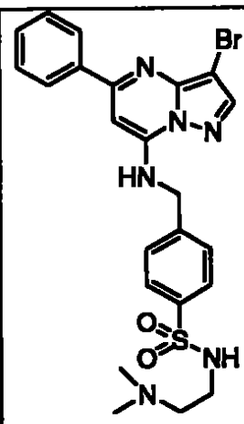
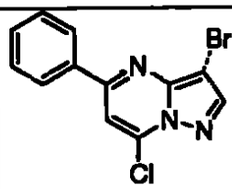
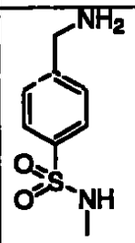
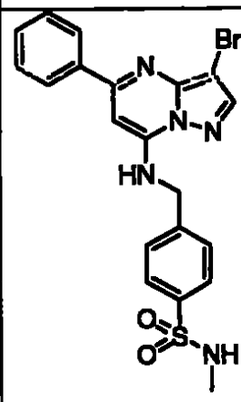
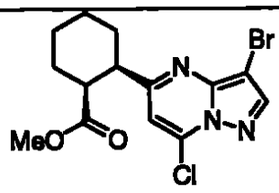
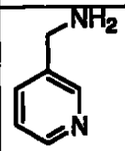
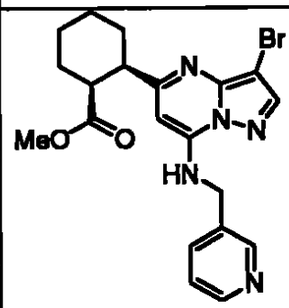
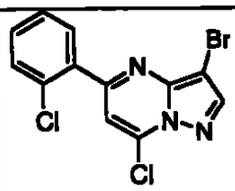
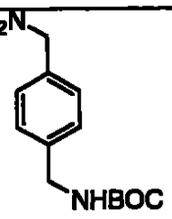
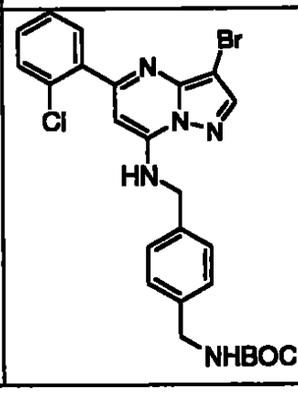
142				LCMS: MH^+=330; mp=109-111°C
143				LCMS: MH^+=346; mp=186-188°C
144				LCMS: MH^+=384; mp=148-150°C
145				LCMS: MH^+=400; mp=186-188°C

484

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

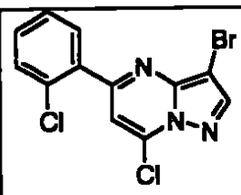
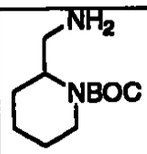
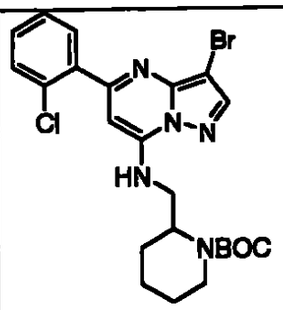
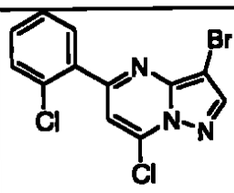
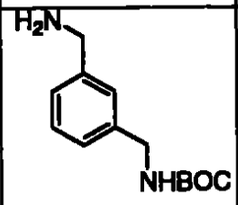
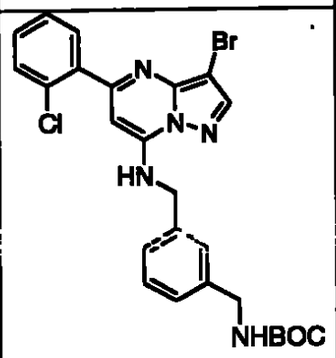
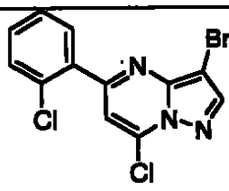
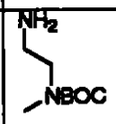
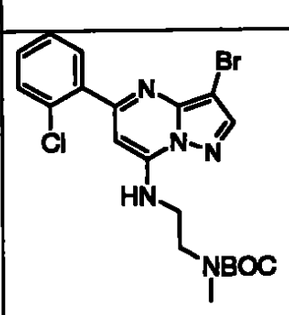
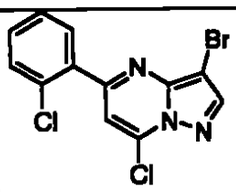
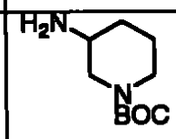
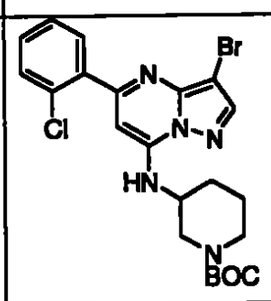
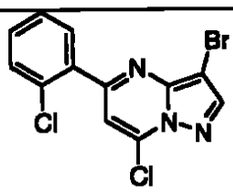
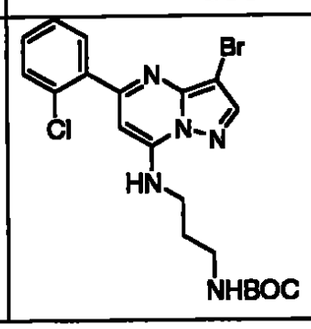
485

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

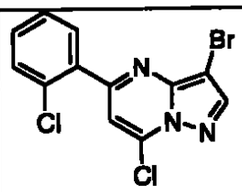
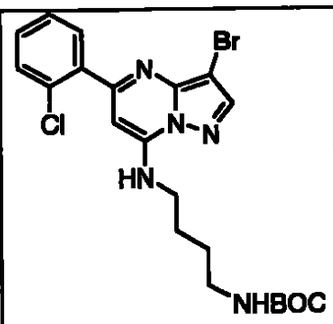
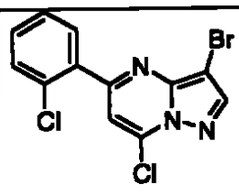
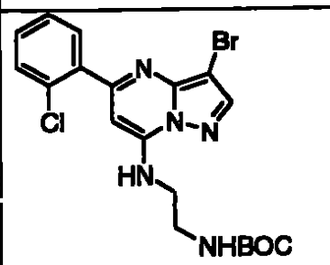
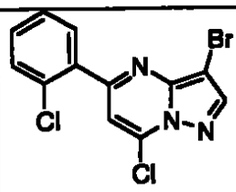
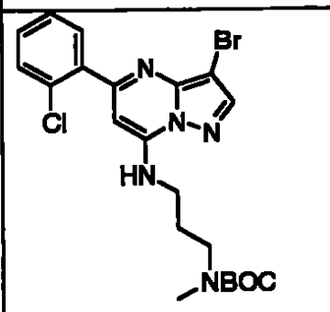
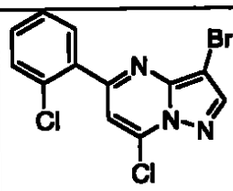
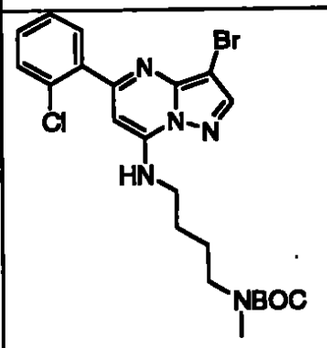
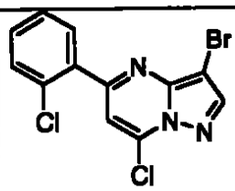
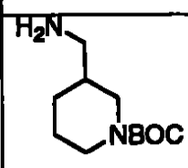
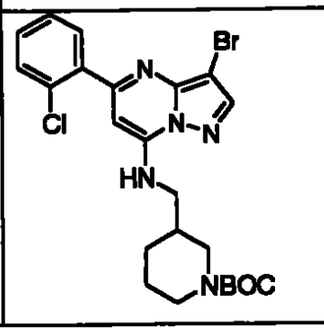
154				LCMS: M2H$^+$=531; mp=78-80°C
155				LCMS: M2H$^+$=474; mp=161-163°C
156				LCMS: M$^+$=444; mp=48-51°C
157				MH$^+$ = 542,1

06-783305

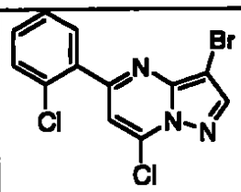
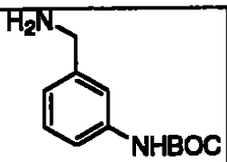
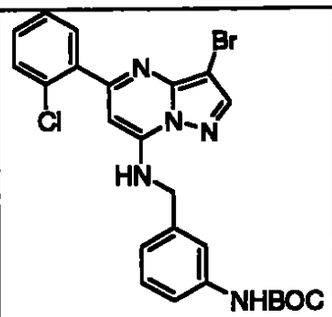
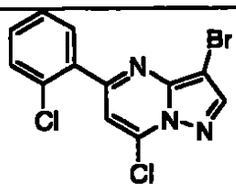
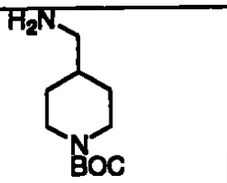
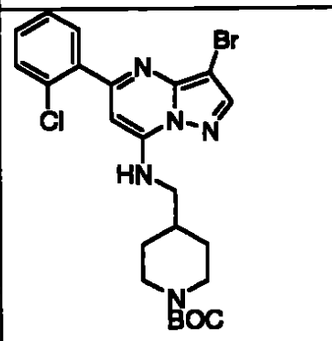
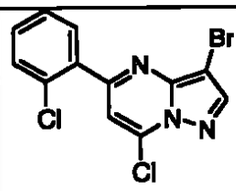
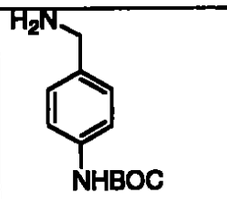
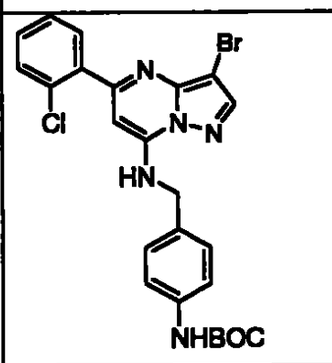
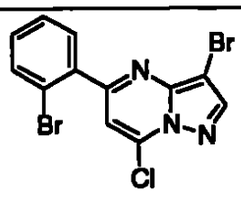
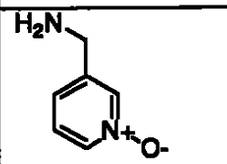
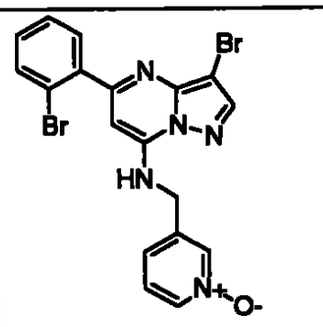
487

158				$MH^+ = 520,1$
159				$MH^+ = 542,1$
160				$MH^+ = 480,1$
161				$MH^+ = 506,1$
162				$MH^+ = 480,1$

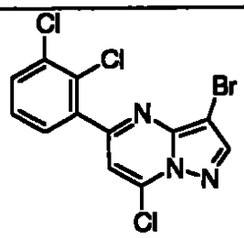
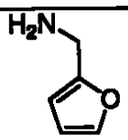
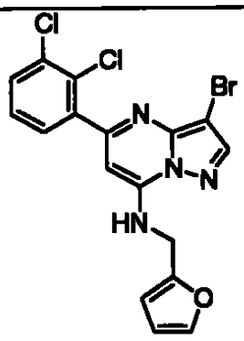
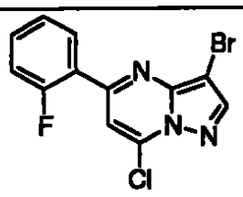
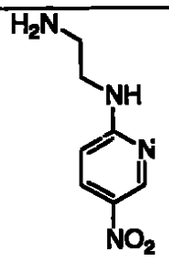
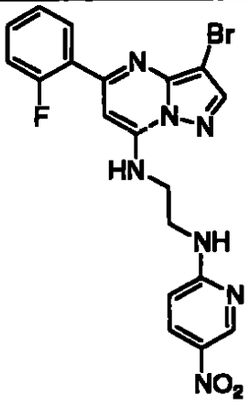
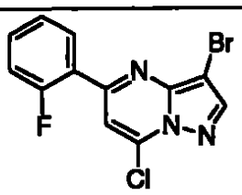
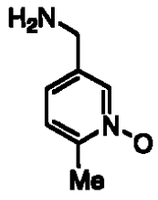
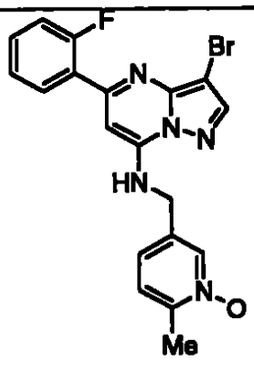
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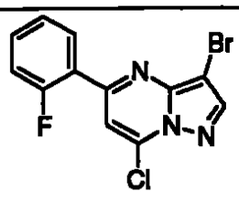
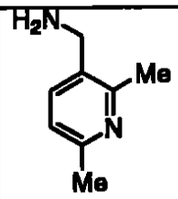
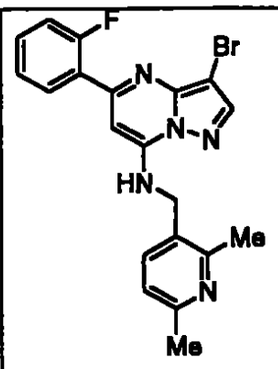
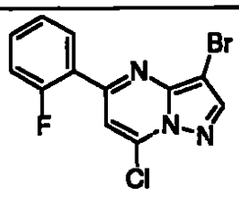
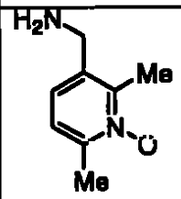
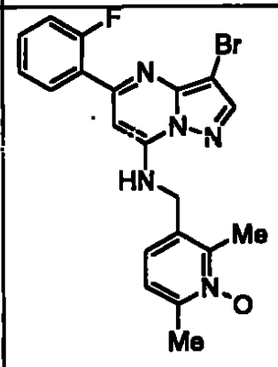
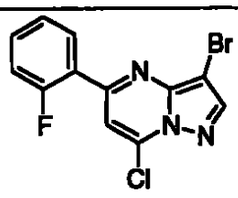
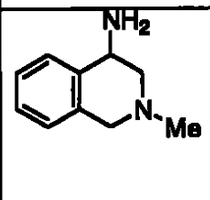
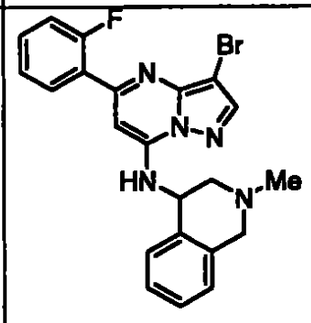
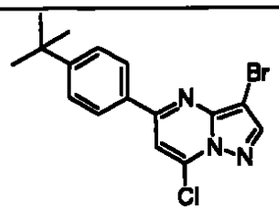
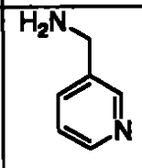
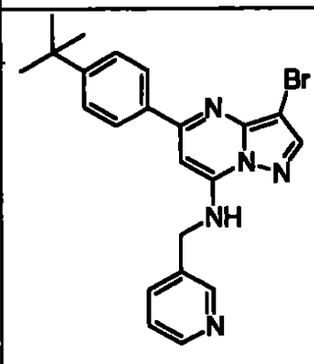
163				$MH^+ = 494,1$
164				$MH^+ = 466,1$
165				$MH^+ = 494,1$
166				$MH^+ = 508,1$
167				$MH^+ = 520,1$

489

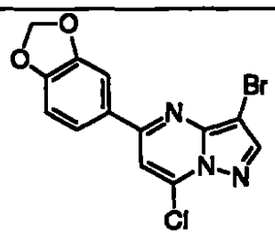
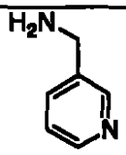
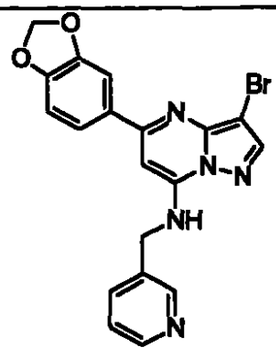
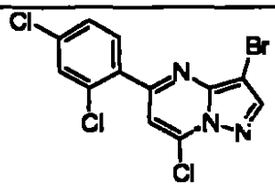
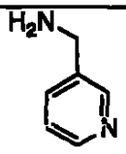
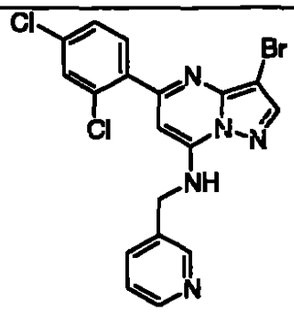
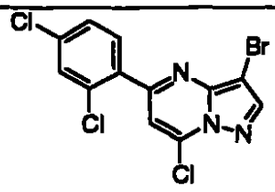
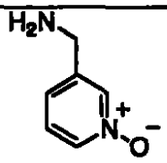
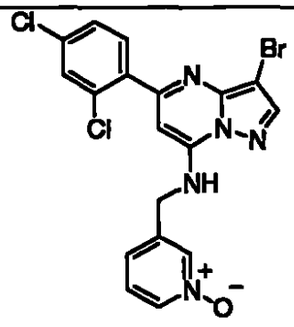
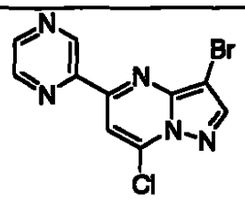
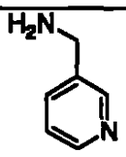
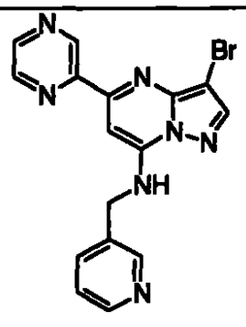
168				$MH^+ = 528,1$
169				$MH^+ = 520,1$
170				$MH^+ = 528,1$
171				LCMS: $MH^+ = 474$;

490

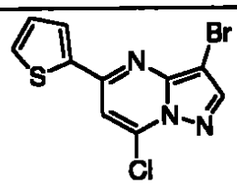
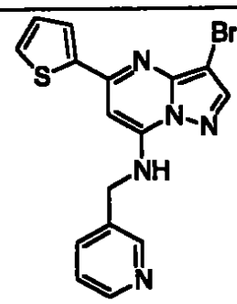
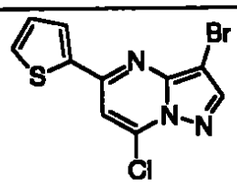
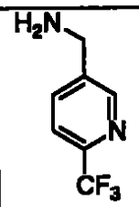
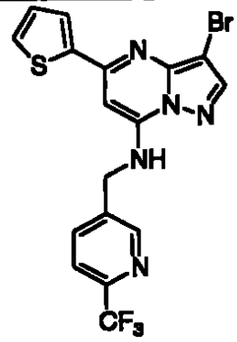
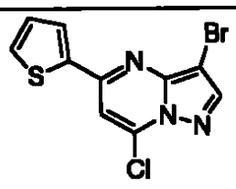
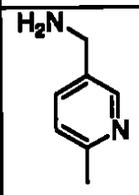
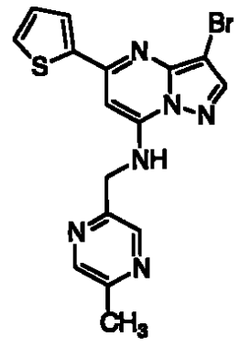
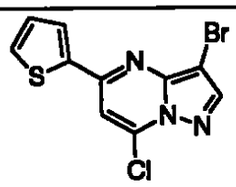
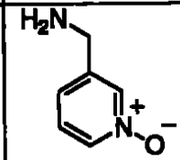
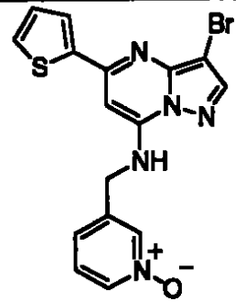
172				**LCMS: MH^+ = 437;**
173				**LCMS: MH^+ = 472;**
174				**LCMS: MH^+ = 428,1**

175				LCMS: MH^+ = 426,2
176				LCMS: MH^+ = 442,0
177				LCMS: MH^+ = 452,0
178				Rendimiento = 90 MH^+ =436 m. pt. = 89,1 °C

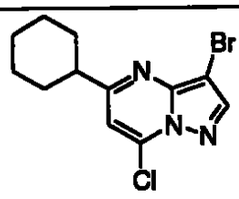
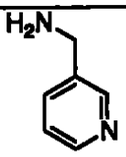
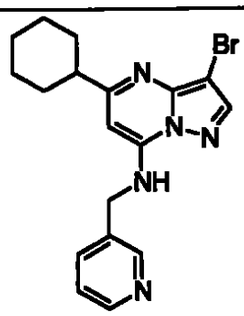
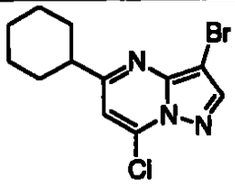
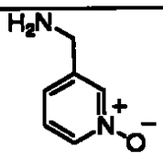
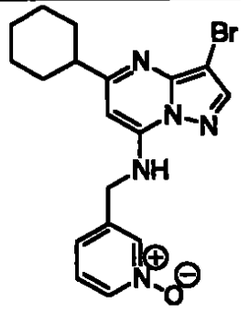
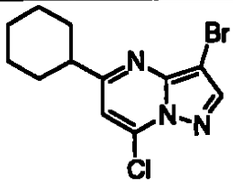
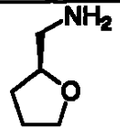
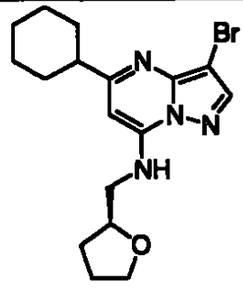
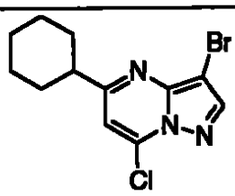
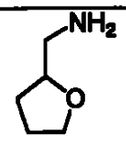
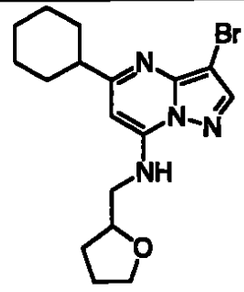
492

179				MH^+ =424 m. pt. = 188,2 °C
180				MH^+ =448 m. pt. = 211,3 °C
181				Rendimiento = cuant. MH^+ = 464
182				MH^+ = 382 m. pt. = 185,8 °C

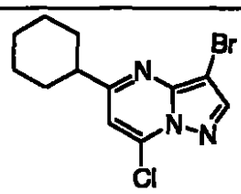
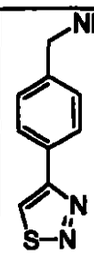
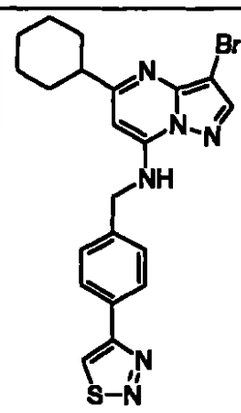
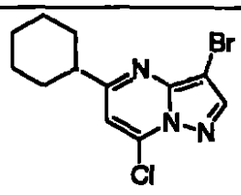
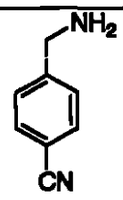
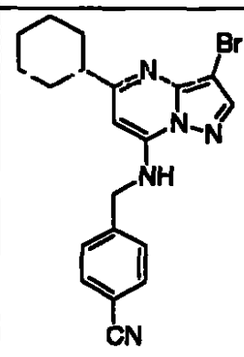
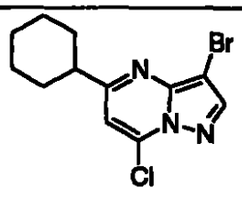
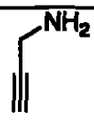
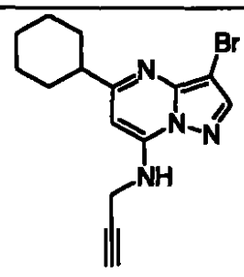
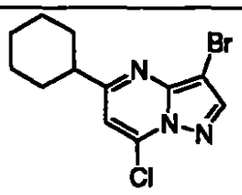
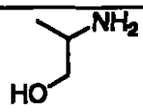
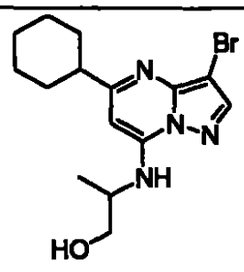
493

183				$MH^+ = 387$ m. pt. = 181 – 182 °C
184				$MH^+ = 453$
185				$MH^+ = 401$ m. pt. = 178,3 °C
186				$MH^+ = 402$

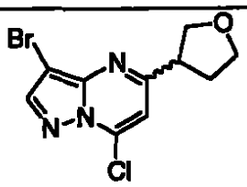
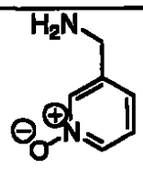
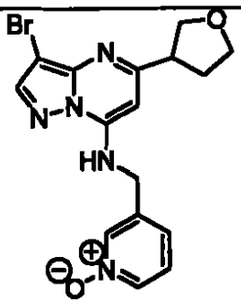
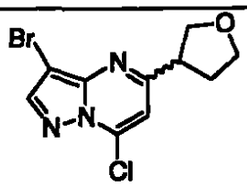
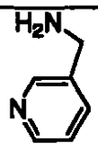
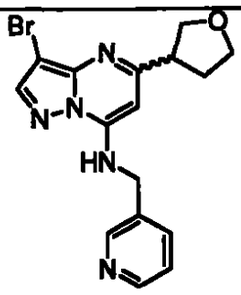
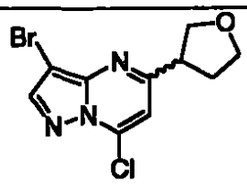
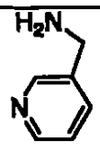
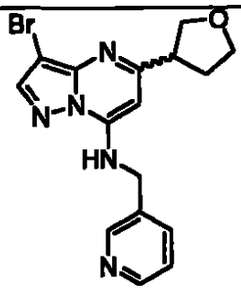
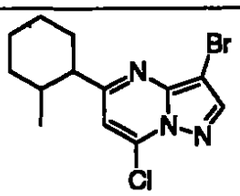
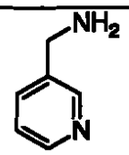
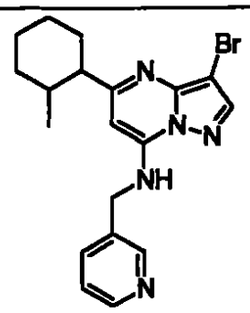
494

187				Rendimiento = 91 $MH^+ = 386$ m. pt. = 148,3 °C
188				Rendimiento = 65 $MH^+ = 402$ m. pt. = 174,5 °C
189				$MH^+ = 379$ m. pt. = 82 – 83 °C
190				$MH^+ = 379$ m. pt. = 50,7 °C

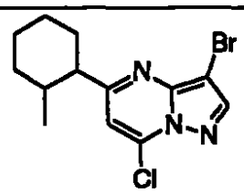
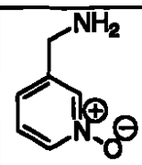
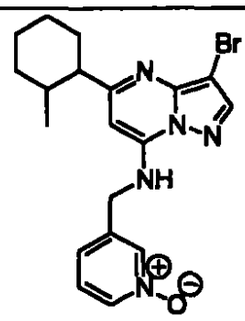
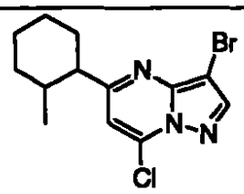
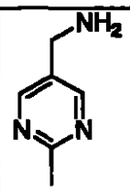
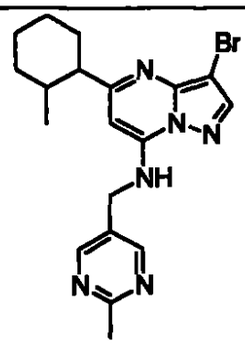
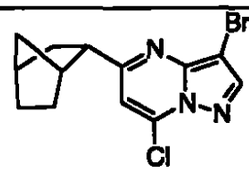
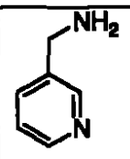
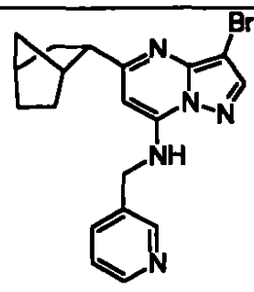
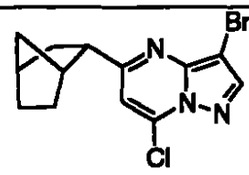
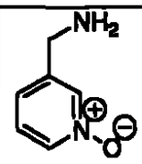
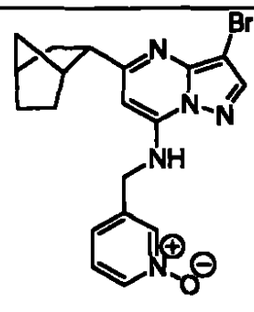
495

191				Rendimiento = 89 MH^+ = 469 m. pt. = 186,7°C
192				Rendimiento = 93 MH^+ = 410 m. pt. = 86,7°C
193				Rendimiento = 76 MH^+ = 333 m. pt. = 120,3°C
194				Rendimiento = 86 MH^+ = 353 m. pt. = 188,9 °C

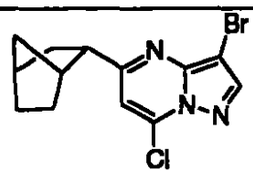
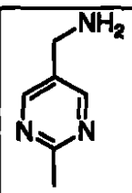
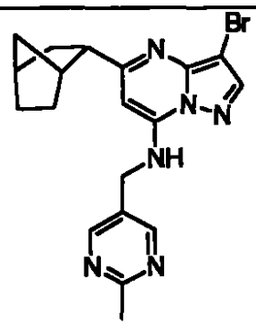
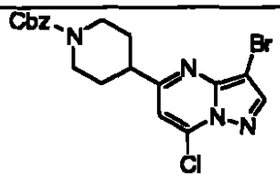
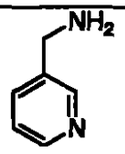
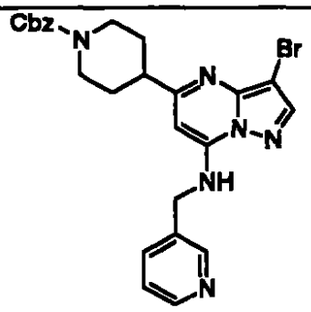
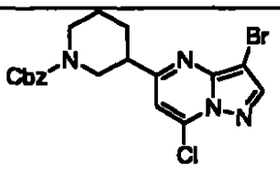
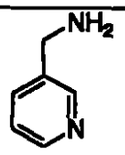
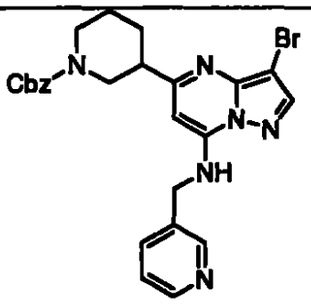
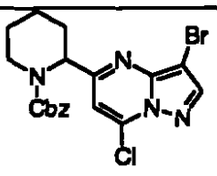
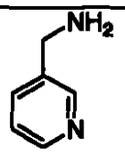
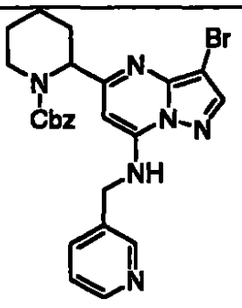
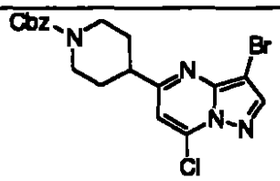
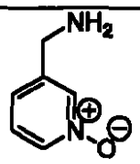
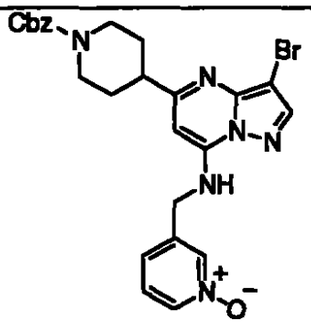
496

195				**Rendimiento =11%** **LCMS:374** **MH^+= 390**
196				**Rendimiento =88%** **LCMS:374** **MH^+= 346**
197				**Rendimiento =88%** **LCMS:374** **MH^+= 346**
198				Rendimiento = MH^+ = 400 m. pt. = 111,5 – 112,2 °C

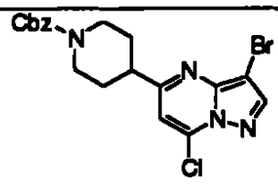
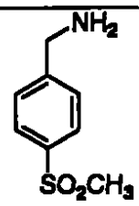
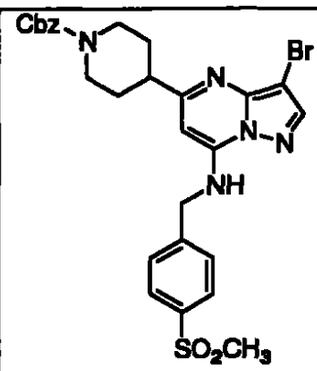
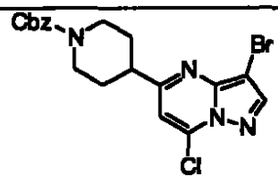
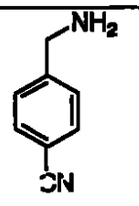
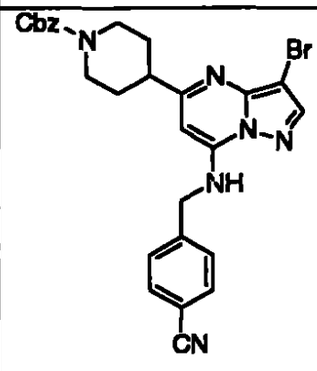
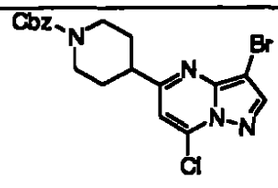
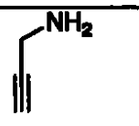
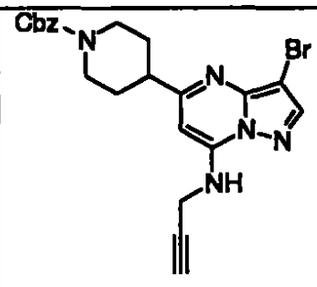
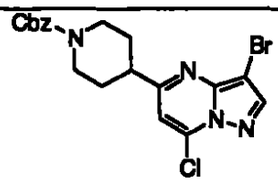
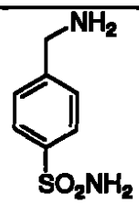
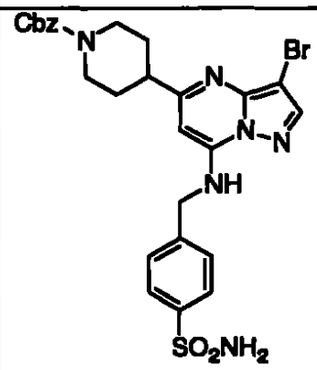
497, 498

199				$MH^+ = 416$
200				$MH^+ = 415$
201				$MH^+ = 398$ m.p. = 156,5°C
202				$MH^+ = 414$ m.p. = 89,5 °C

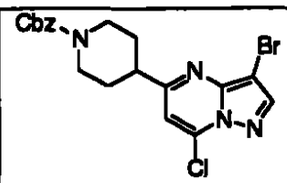
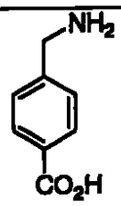
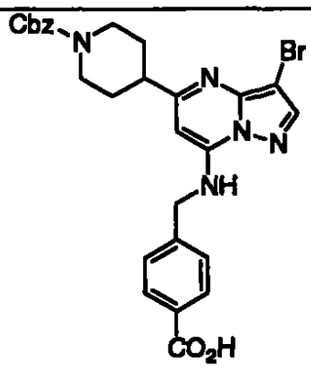
498

203				$MH^+ = 413$
204				Rendimiento = 86 $MH^+ = 521$ m.p. = 79,9 °C
204 ,10				
204 ,11				Rendimiento = 87 $MH^+ = 521$ m.p. = 128,6 °C
205				Rendimiento = 99 $MH^+ = 537$ m.p. = 83,5 °C

499 500

206				Rendimiento = 94 MH^+ = 598 m.p. = 110,8 °C
207				Rendimiento = cuant. MH^+ = 545
208				Rendimiento = 96 MH^+ = 468 m.p. = 69,2 °C
209				MH^+ = 498 m.p. = 226,5 °C

500

210				$MH^+ = 564$ m.p. = 174,2 °C

Datos adicionales para ejemplos selectos dados 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)

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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)

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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)

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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).

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).

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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).

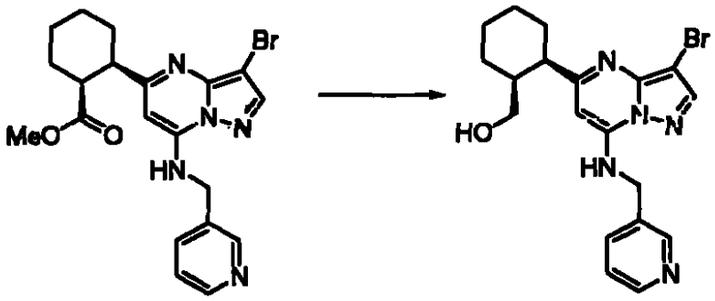
Ejemplo 199: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,29 (s, 1H), 8,15 (br s, 1H), 7,95 (s, 1H), 7,28 (d, 1H), 7,05 - 6,95 (appt t, 1H), 5,70 (s, 1H), 4,62 (d, 2H), 2,90 (m, 1H), 2,30 (m, 1H), 1,9 – 1,2 (m, 8H), 0,65 (d, 3H).

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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).

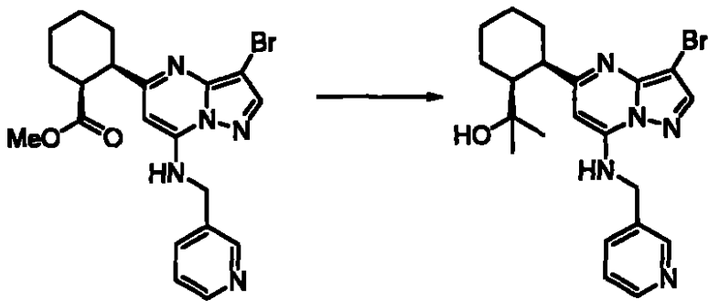
Ejemplo 203: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,10 (s, 1H), 8,08 (s, 1H), 6,27 (s, 2H), 4,95 (s, 2H), 3,00 – 2,90 (dd, 2H), 2,60 (m, 2H), 2,48 (br s, 1H), 2,39 (s, 3h), 2,25 m, 1H), 1,95 – 1,70 (m, 3H).

EJEMPLO 211:



A una solución del compuesto preparado en el Ejemplo 156 (100 mg, 0,23 mmol) en THF seco (4 ml) se agregó $LiAlH_4$ (1,0 M en THF, 0,110 ml, 0,110 mmol) a °C bajo N_2. La mezcla se agitó a 0°C durante 1hr, 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 min y luego se desactivó con MeOH (2,0 ml). El solvente se evaporó y el producto bruto se purificó mediante cromatografía flash usando 10:1 CH_2Cl_2:MeOH como eluyente. Se obtuvo sólido blanco (46 mg, 49%). LCMS: M^+= 416, Mp=71-72 °C.

EJEMPLO 212:

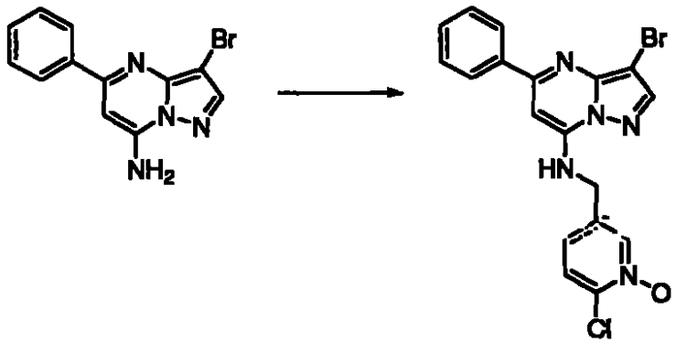


A una solución del compuesto preparado en el Ejemplo 156 (70 mg, 0,16 mmol) en THF seco (3 ml) se agregó MeMgBr (3,0 M en Et_2O, 1,10 ml, 3,20 mmol) bajo N_2. La mezcla se agitó a 25°C durante 45 min y luego se desactivó

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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 filtró. El solvente se evaporó y el producto bruto se purificó mediante cromatografía flash usando 20:1 CH_2Cl_2:MeOH como eluyente. Se obtuvo sólido blanco (25 mg, 36%). LCMS: M^+= 444. Mp=76-80 °C.

EJEMPLO 213:



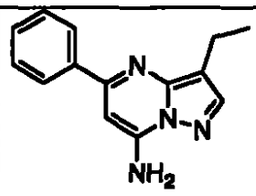
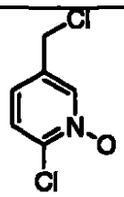
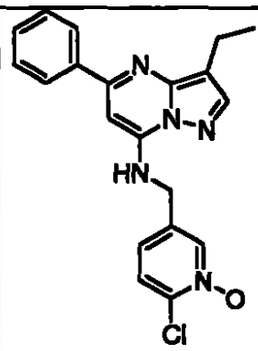
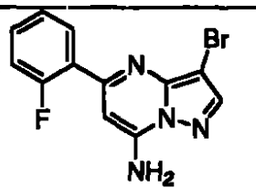
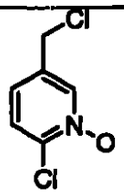
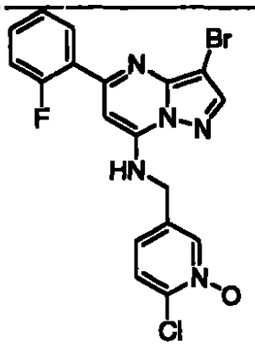
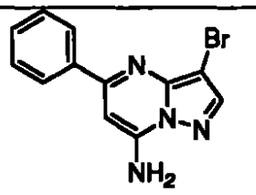
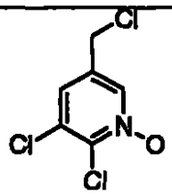
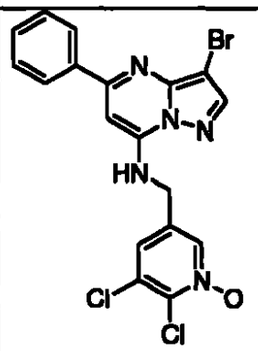
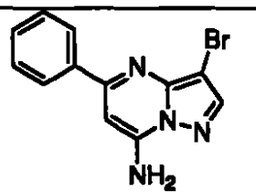
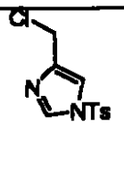
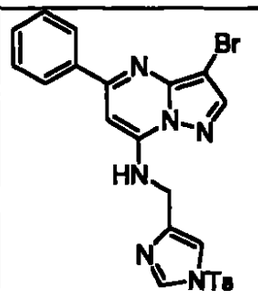
Se agregó DMF anhídrido (40 ml) bajo N_2 al compuesto preparado en el Ejemplo Preparativo 174 (2,50 g, 8,65 mmol) y 60 % NaH en aceite mineral (346 mg, 8,65 mmol). La mezcla se agitó a 25°C durante 1 hr, luego se agregó lentamente N-óxido de 2-cloro-5-clorometilpiridina (1,54 g, 8,65 mmol) en DMF anhídrido (20 ml). La mezcla se agitó a 25°C durante 18 hr, el solvente se evaporó y el producto bruto se purificó mediante cromatografía flash usando 30:1 CH_2Cl_2:MeOH como eluyente. El sólido que se obtuvo de esta manera se trituró mediante 50 ml de 1:1 EtOAc: hexano. Se obtuvo un sólido amarillo pálido (1,25 g, 34%). LCMS: MH^+=432. Mp=224-226 °C.

EJEMPLOS 214-217:

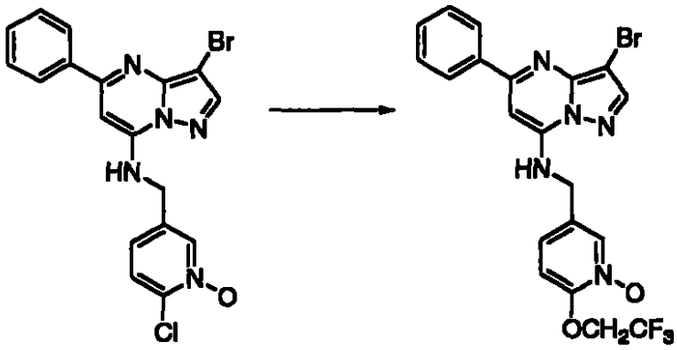
Mediante esencialmente el mismo procedimiento expuesto en el Ejemplo 213, combinando los compuestos que se muestran en la Columna 2 de la Tabla 19 con los compuestos en la columna 3 de la Tabla 19, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 19.

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TABLA 19

Ej.	Columna 2	Columna 3	Columna 4	COM-PUESTO
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

EJEMPLO 218:



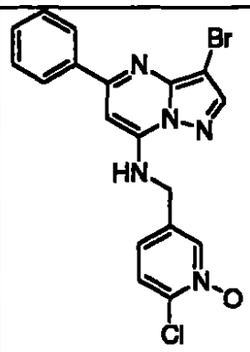
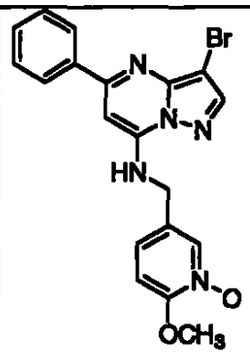
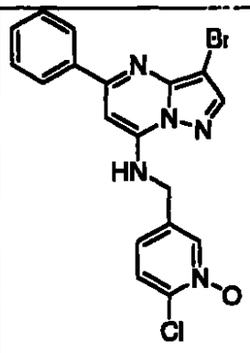
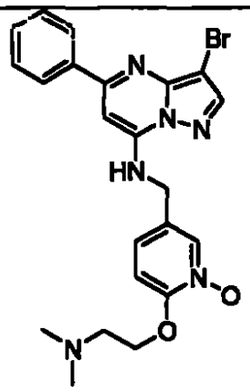
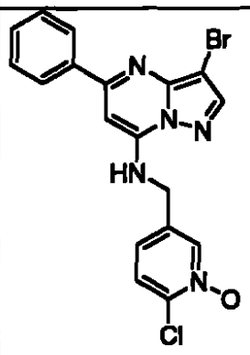
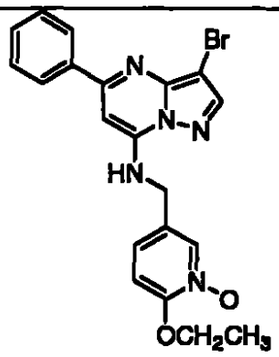
Se agregó CF_3CH_2OH (3,0 ml) bajo N_2 a NaH 60% en aceite mineral (40 mg, 1,0 mmol), la mezcla se agitó durante 20 min, luego el producto preparado en el Ejemplo 213 (50 mg, 0,12 mmol) se agregó. La mezcla se refluió durante 20 hr, el solvente se evaporó, y el residuo se purificó mediante cromatografía flash usando 20:1 CH_2Cl_2:MeOH como eluyente para dar un sólido amarillo pálido (35 mg, 61%). LCMS: $M2H^+$=496, Mp=208-210 °C.

EJEMPLOS 219-225:

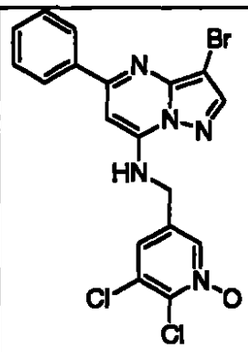
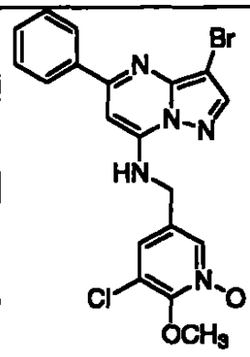
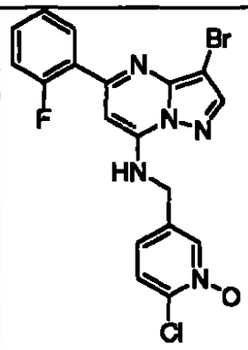
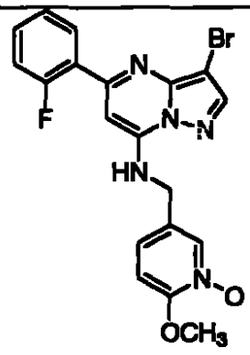
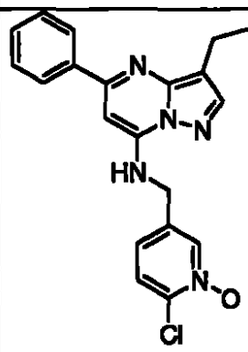
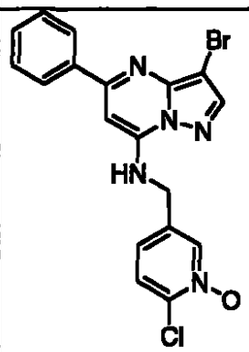
Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 218, combinando los compuestos que se muestran en la Columna 1 de la Tabla 20 con el alcohol apropiado, se prepararon los compuestos que se muestran en la Columna 2 de la Tabla 20.

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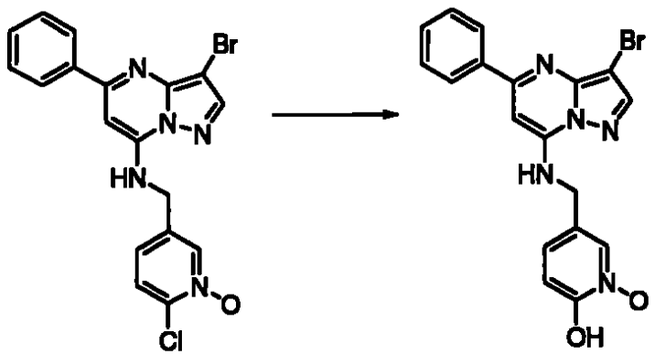
TABLA 20

Ej.	Columna 1	Columna 2	Datos
219			LCMS: M^+=426; mp=126-128°C
220			LCMS: M^+=433; mp=89-91°C
221			LCMS: $M2H^+$=442; mp=112-114°C

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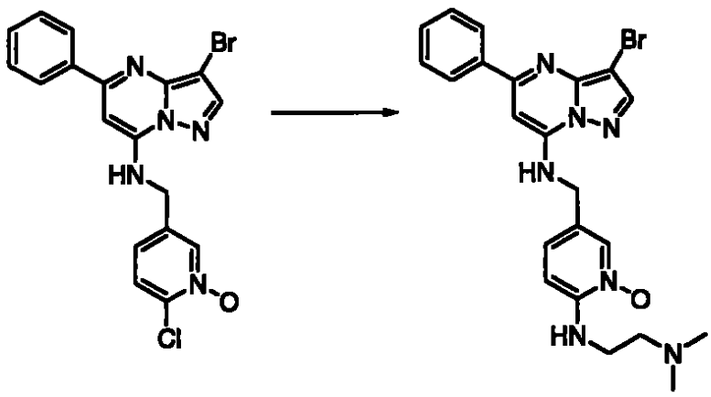
222			LCMS: MH^+=462; mp=121-123°C
223			LCMS: MH^+=444; mp=112-114°C
224			LCMS: M^+=376; mp=°C
225			LCMS: MH^+=; mp=°C

EJEMPLO 226:



Una mezcla del producto preparado en el Ejemplo 213 (100 mg, 0,23 mmol) y KOH (95 mg, 1,70 mmol) en 1,2-dimetoxietano (3ml) y H_2O (1,5 ml) se reflujó bajo N_2 durante 20 hr, se desactivó con (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 Et_2O (5 ml) al filtrado y se dejó que la mezcla repose hasta el día siguiente. El sólido se eliminó mediante 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 sólido blancuzco (5 mg, 5%). LCMS: M^+=412. Mp= 206-208°C.

EJEMPLO 227:



Se agitó una mezcla del producto preparado en el Ejemplo 213 (129 mg, 0,30 mmol), N,N-dimetiletilendiamina (0,165 ml, 1,50 mmol), y diisopropiletilamina (0,10 ml) en N-metilpirrolidinona anhidro (1,0 ml) a 100°C durante 24 hr. El solvente se evaporó, y el residuo se purificó mediante cromatografía flash usando

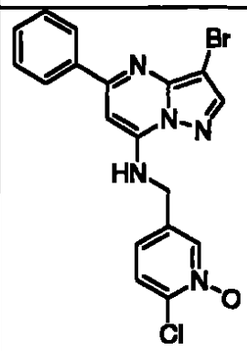
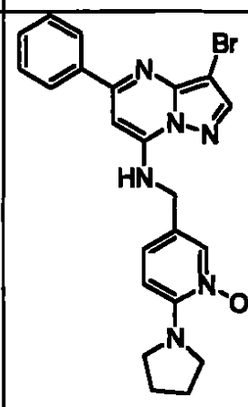
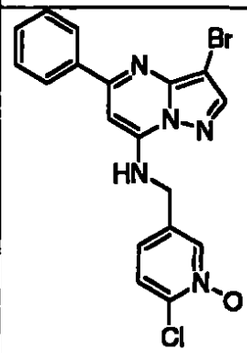
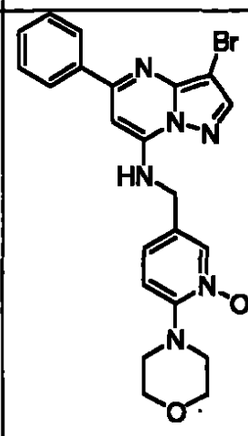
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20:1 CH_2Cl_2: 7N NH_3 en MeOH como eluyente para dar sólido amarillo pálido (110 mg, 76%). LCMS: M^+=482. Mp=76-78 °C.

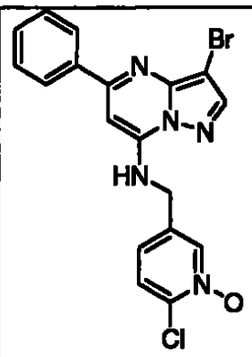
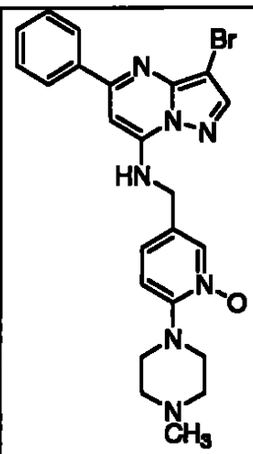
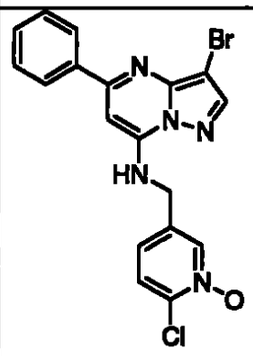
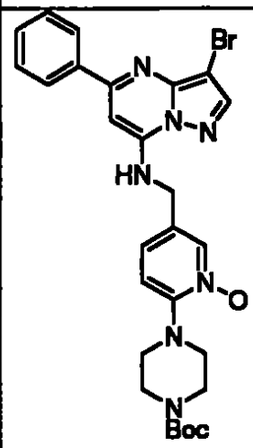
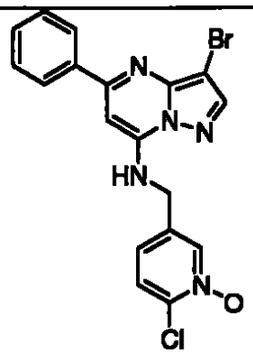
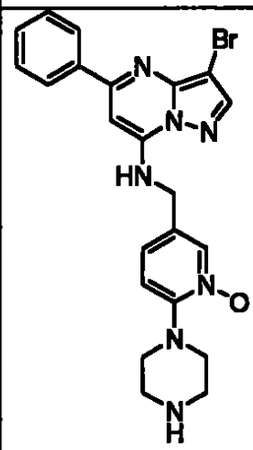
EJEMPLOS 228-233:

Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 227, combinando los compuestos que se muestran en la Columna 1 de la Tabla 21 con la amina apropiada, los compuestos que se muestran en la Columna 2 de la Tabla 21 se prepararon.

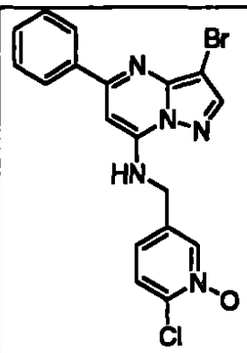
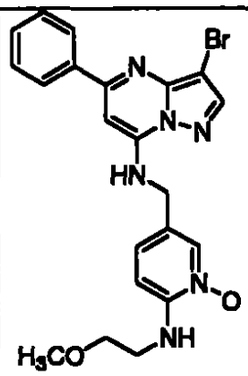
TABLA 21

Ej.	Columna 1	Columna 2	Datos
228			LCMS: M2H$^+$=467; mp126-128=°C
229			LCMS: M^+=481; mp=128-130°C

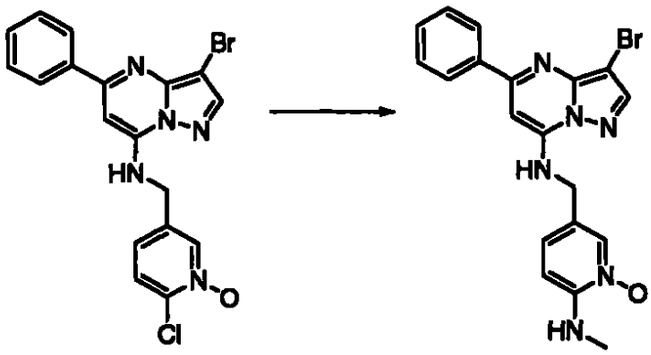
513 514

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

514

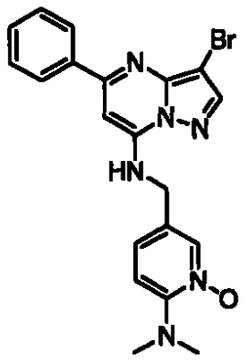
233			LCMS: $M2H^+$=471; mp=88-90°C

EJEMPLO 234:



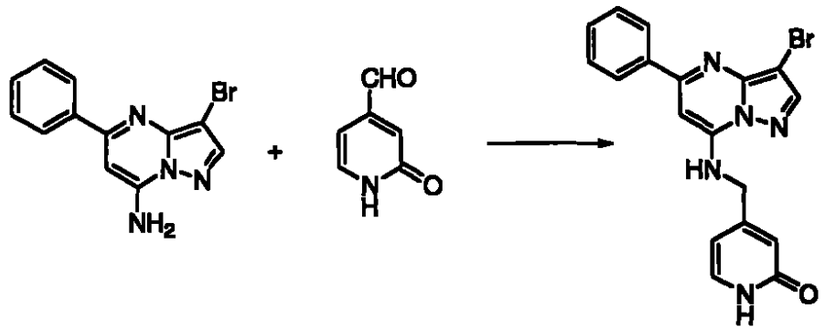
Se agitó una mezcla del producto preparado en el Ejemplo 213 (80 mg, 0,19 mmol) y metilamina 2,0 M en THF en un recipiente de presión cerrado a 50°C durante 72 hr. El solvente se evaporó, y el residuo se purificó mediante cromatografía flash usando 10:1 CH_2Cl_2: MeOH como eluyente para dar sólido amarillo pálido (40 mg, 51%). LCMS: $M2H^+$=427, Mp=217-219°C.

EJEMPLO 235:



Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 234, el compuesto que se mostró anteriormente se preparó. LCMS: $M2H^+$=441. Mp=98-101 °C.

EJEMPLO 236:



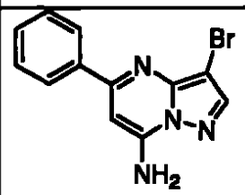
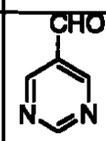
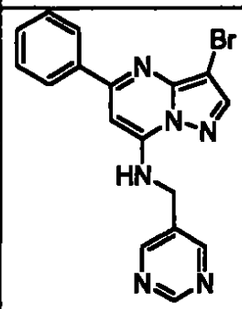
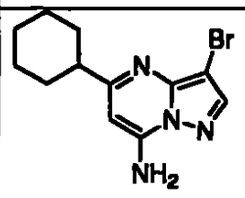
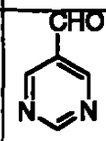
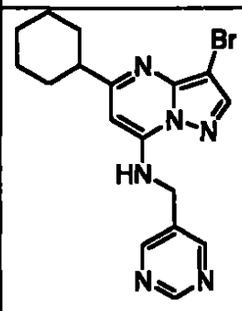
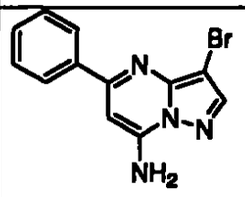
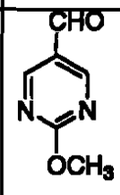
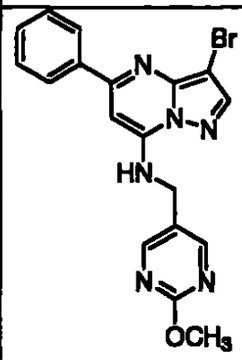
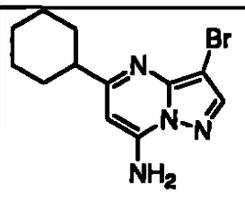
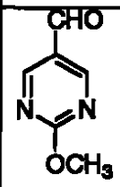
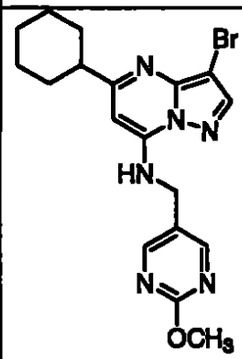
Se agitaron el compuesto preparado en el Ejemplo Preparativo 174 (140 mg, 0,48 mmol) y el aldehído (71 mg, 0,58 mmol) en THF anhídrido (4 ml) a 50°C bajo N_2. Se agregó $Ti(OiPr)_4$ (0,574 ml, 1,92 mmol), la mezcla se agitó a 50°C 3 hr, y se enfrió a 25°C. Se agregó $NaBH_3CN$ (181 mg, 2,88 mmol), la mezcla se agitó durante 2 horas más, luego se vertió en Na_2CO_3 10 % acuoso (100 ml), y se extrajo con CH_2Cl_2 (3 x 50 ml). Los extractos combinados se secaron sobre Na_2SO_4, se filtró, y el solvente se evaporó. El residuo se purificó mediante cromatografía flash usando 15:1 CH_2Cl_2:MeOH como eluyente para dar sólido amarillo pálido (40 mg, 21%). LCMS: MH^+=398. Mp>230 °C.

EJEMPLOS 237-256:

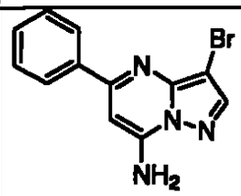
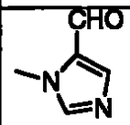
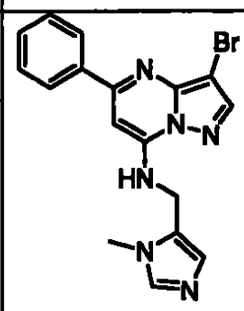
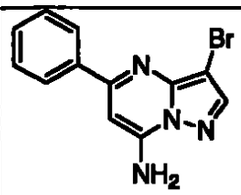
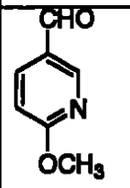
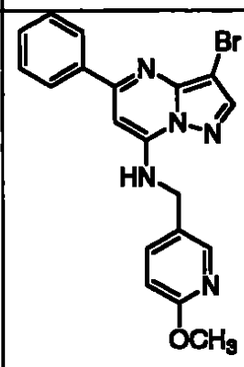
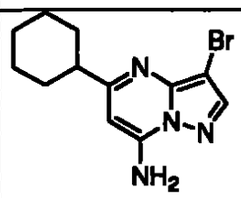
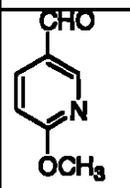
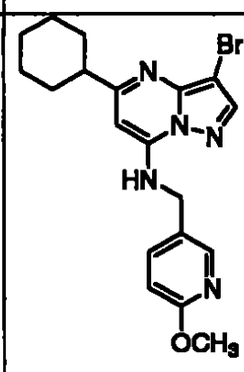
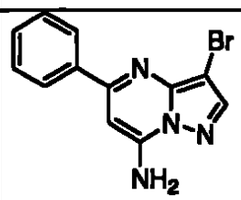
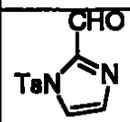
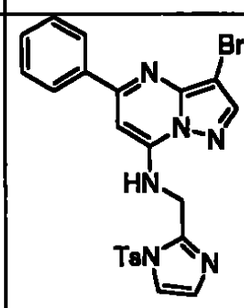
Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 236, combinando los compuestos que se muestran en la Columna 2 y 3 de la Tabla 22, se prepararon los compuestos que se muestran en la Columna 4 de la Tabla 22.

516

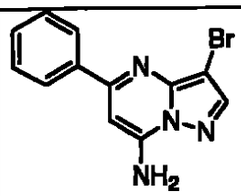
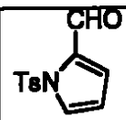
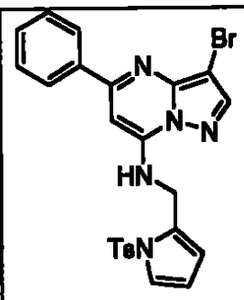
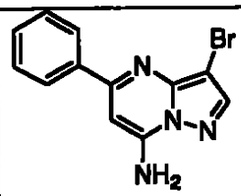
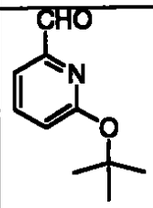
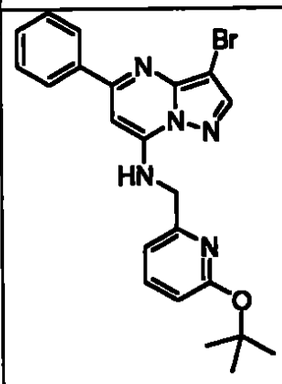
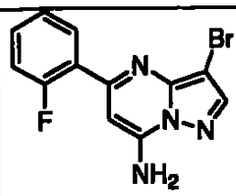
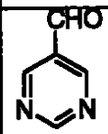
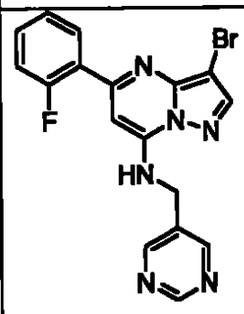
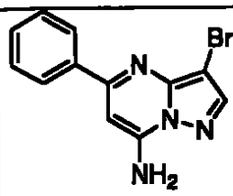
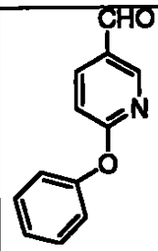
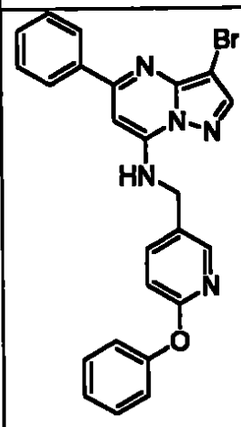
TABLA 22

Ej.	Columna 2	Columna 3	Columna 4	Datos
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

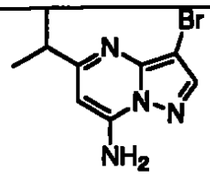
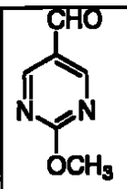
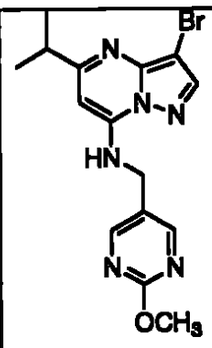
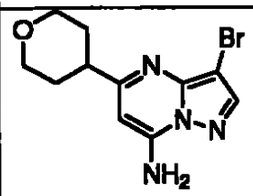
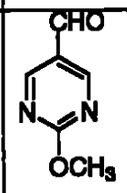
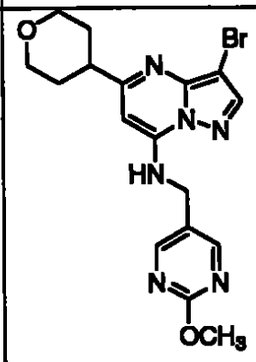
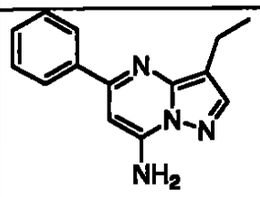
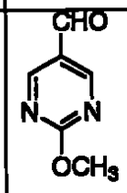
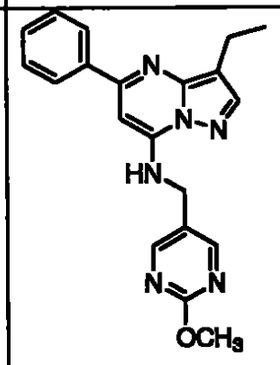
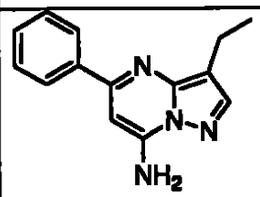
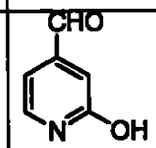
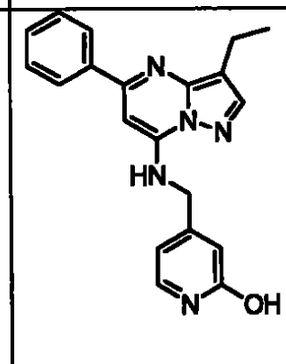
517

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

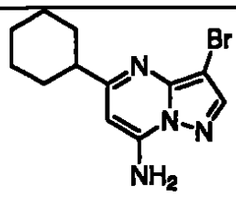
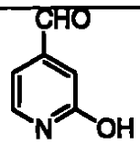
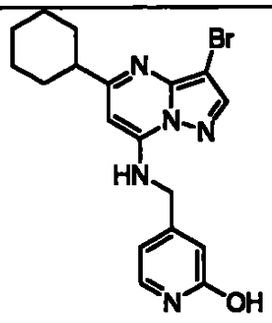
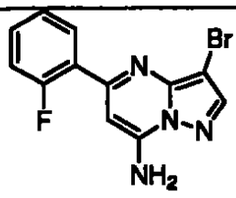
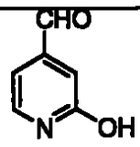
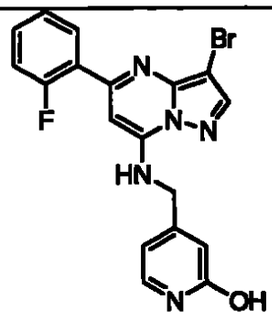
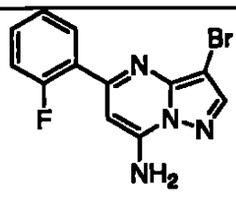
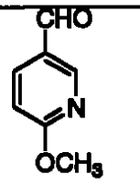
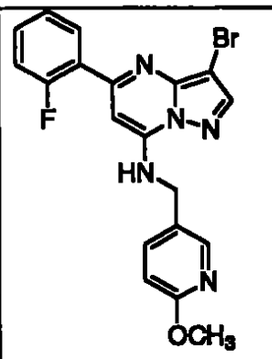
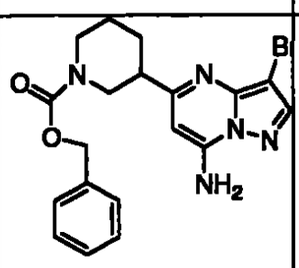
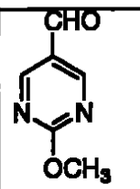
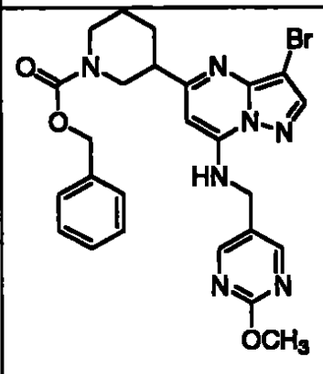
518

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.

519 ~~520~~

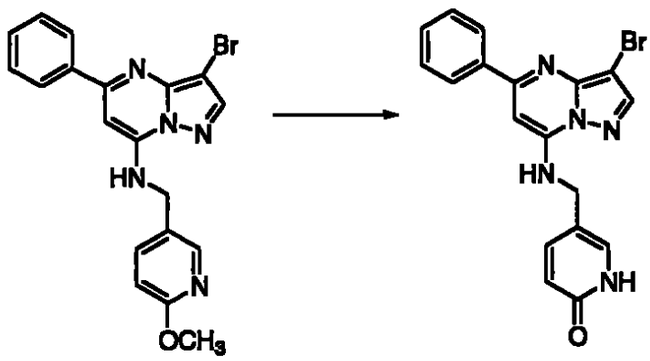
249				LCMS: MH^+= 377; mp= 65-67°C
250				LCMS: $M2H^+$=421; mp=87-93°C
251				LCMS: MH^+=361; mp>225°C
252				LCMS: MH^+=346; mp=270-271°C

520

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

521

EJEMPLO 257:

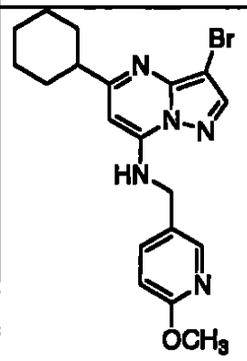
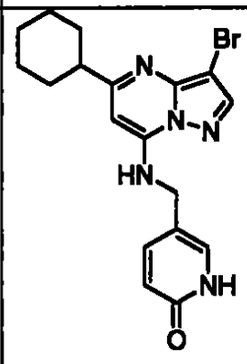


Se agitaron una mezcla del compuesto preparado en el Ejemplo 242 (100 mg, 0,24 mmol), HCl acuoso conc. (1,0 ml) y ácido acético (2,0 ml) a 100°C bajo N_2 durante 2 hr, luego se vertieron en Na_2CO_3 (15 g), y se extrajeron con 1:1 acetona:CH_2Cl_2 (3 x 30 ml). Los extractos combinados se filtraron, y el solvente se evaporó. El residuo se purificó mediante cromatografía flash usando 10:1 CH_2Cl_2:MeOH como eluyente para dar sólido amarillo pálido (36 mg, 37%). LCMS: $M2H^+$=398,

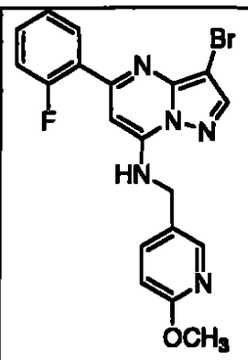
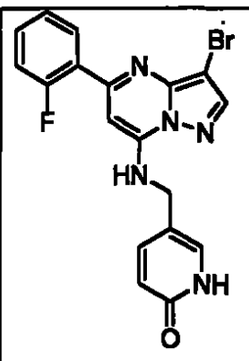
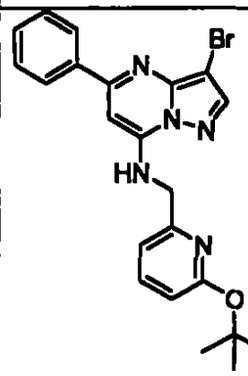
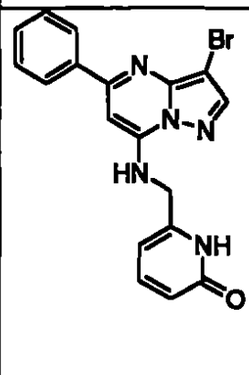
EJEMPLOS 258-260:

Esencialmente mediante el mismo procedimiento expuesto 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.

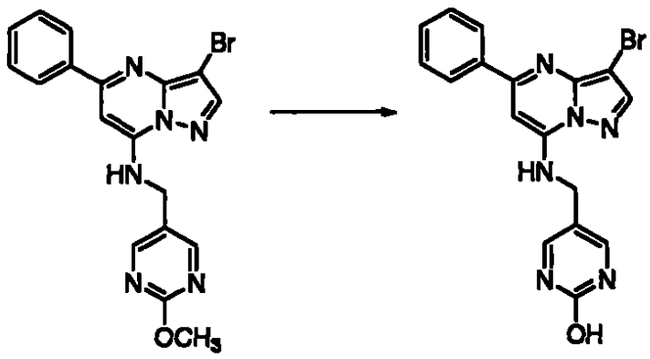
TABLA 23

Ej.	Columna 1	Columna 2	Datos
258			LCMS: M^+=402; mp=229-231°C

522

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

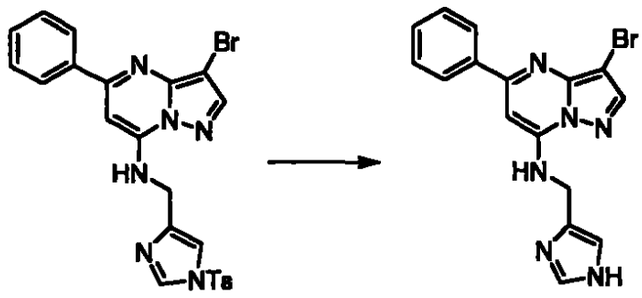
EJEMPLO 261:



A una solución agitada del compuesto preparado en el Ejemplo 239 (41 mg, 0,10 mmol) en CH_2Cl_2 se agregó BBr_3 1,0 M (0,30 ml, 0,30 mmol) en CH_2Cl_2 a -78°C. La mezcla se agitó a -78°C durante 5 min, luego a 24°C durante 3 hr, luego se agregó MeOH (2,0 ml) y la mezcla se agitó durante 10 min. El solvente se evaporó y el residuo se purificó mediante cromatografía flash usando 5:1:0,1 CH_2Cl_2:MeOH:conc. NH_4OH como eluyente para dar sólido blanco (39 mg, 99%). LCMS: M^+=397, Mp>230 °C.

EJEMPLO 262:

523

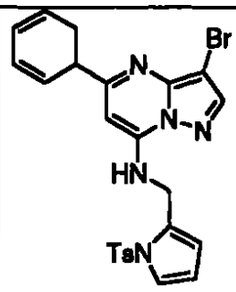
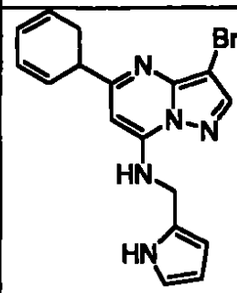
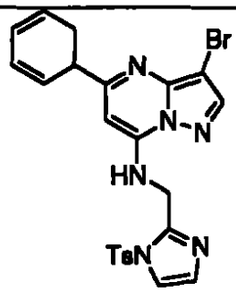
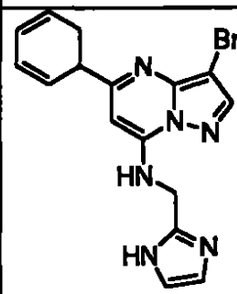


Una mezcla del producto preparado en el Ejemplo 217 (40 mg, 0,077 mmol) y 5,0 M acuoso NaOH (0,8 ml) en MeOH (3,0 ml) se reflujó bajo N_2 durante 1 hr. Se agregó $NaHCO_3$ (700 mg), el solvente se evaporó, y el residuo se purificó mediante cromatografía flash usando 10:1:0,1 CH_2Cl_2: MeOH: NH_4OH conc. como eluyente para dar sólido blanco (10 mg, 35%). LCMS: $M2H^+$=371. Mp=237-239 °C.

EJEMPLOS 263-264:

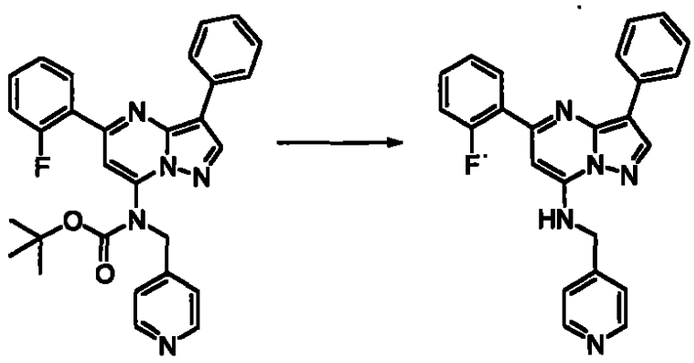
Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 262, a partir de los compuestos que se muestran en la Columna 1 de la Tabla 24, se prepararon los compuestos que se muestran en la Columna 2 de la Tabla 24.

TABLA 24

Ej.	Columna 1	Columna 2	Datos
263			LCMS: $M2H^+$=370; mp=166-168°C
264			LCMS: $M2H^+$=371; mp=180-182°C

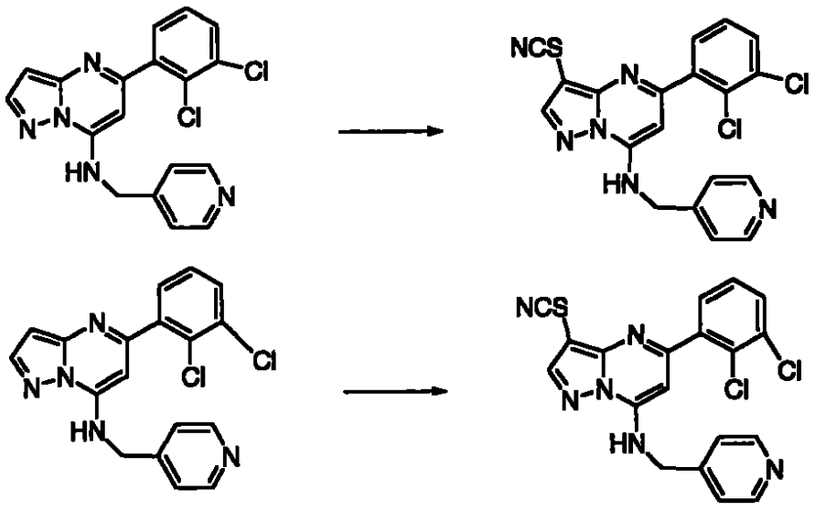
524

EJEMPLO 265:



Se agregó TFA (0,5 ml) a una solución del compuesto preparado en el Ejemplo Preparativo 197 (0,08 g, 0,16 mmol) en CH_2Cl_2 (2,0 ml) a 0°C y la solución resultante se agitó 2,5 horas y se almacenó a 4°C hasta el día siguiente en dicho momento se agregó TFA (0,5 ml). La solución resultante se agitó 4 horas y se concentraron in vacuo. El residuo se neutralizó con NaOH 1N y se extrajo con CH_2Cl_2. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtró, y se concentraron bajo presión reducida. El producto bruto se purificó mediante cromatografía flash usando una solución de 2,5% (10% NH_4OH en MeOH) en CH_2Cl_2 como eluyente (0,009 g, 15% de rendimiento). LCMS: MH^+=396; mp= 53-54°C.

EJEMPLO 266:

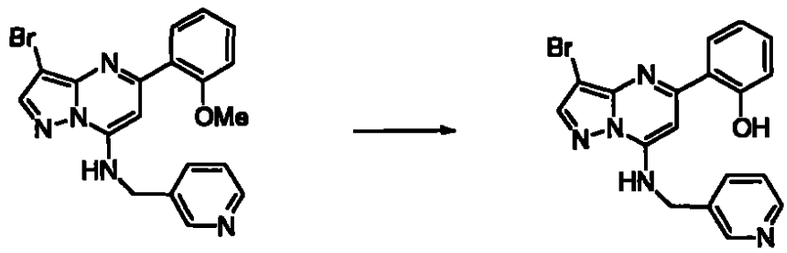


Se enfrió una solución del compuesto preparado en el Ejemplo Preparativo 182 (26 mg, 0,070 mmol) y tiocianato de potasio (13 mg, 0,14 mmol) en MeOH (1

525

ml) en un baño de agua fría. A la misma , se agregó gota a gota una solución de bromo (22 mg, 0,14mmol) en MeOH (0,7 ml). La mezcla de reacción resultante se agitó durante 4 h a temperatura ambiente y los volátiles se eliminaron bajo presión reducida. El residuo obtenido se suspendió en una pequeña cantidad de CH_2Cl_2, el bromuro de potasio se filtró y se reguló el pH del filtrado a alrededor de 7 mediante la adición de amoníaco acuoso. Este se concentró bajo presión reducida y el aceite residual se purificó mediante cromatografía de capa delgada preparativa usando MeOH 15% en CH_2Cl_2 como eluyente (26 mg, 87% de rendimiento). ^{1}H 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.

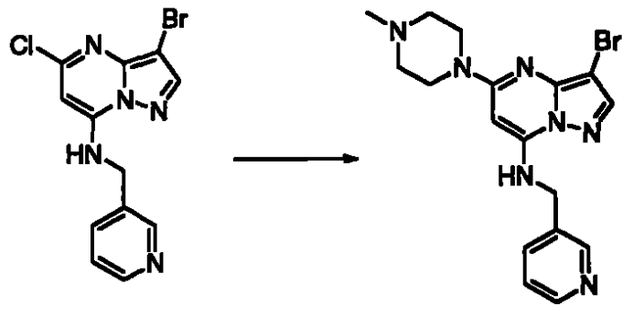
EJEMPLO 267:



Se agregó gota a gota tribromuro de boro (1 M en CH_2Cl_2, 0,60 ml, 0,60 mmol) a una solución congelada agitada del compuesto preparado en el Ejemplo 24 (50 mg, 0,12 mmol) en CH_2Cl_2 (1,5 ml) bajo una atmósfera de argón. La mezcla de reacción resultante se agitó a 0°C durante 30 minutos, se dejó que se caliente hasta temperatura ambiente, y se agitó hasta el día siguiente. La mezcla se desactivó mediante la 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 in vacuo (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:

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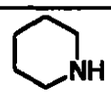
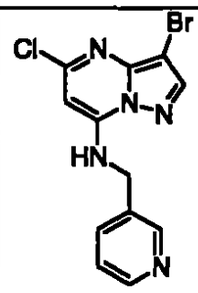
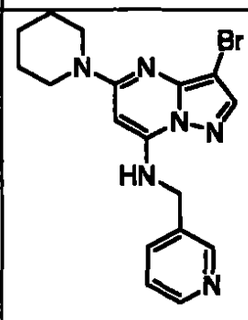


Se calentó una solución del compuesto del Ejemplo Preparativo 184 (0,05 g, 0,15 mmol), N-metilpiperazina (20 µl, 1,2 eq.) y iPr_2Et (52 µl, 2,0 eq.) en dioxano(1 ml) a 70 °C hasta el día siguiente. La mezcla de reacción se enfrió hasta temperatura ambiente y se diluyó con H_2O y $NaHCO_3$ saturado. La 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 bruto se purificó mediante TLC preparativa usando una solución de 5% (NH_4OH 10% en MeOH) en CH_2Cl_2 como eluyente (0,028 g, 47% de rendimiento). MS: MH^+= 402, mp = 210 °C (dec.)

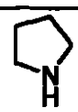
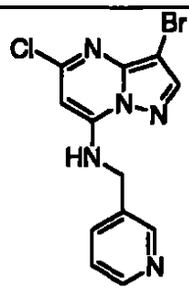
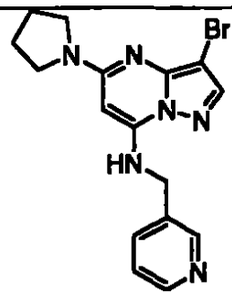
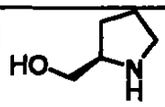
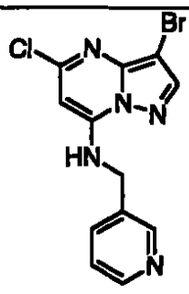
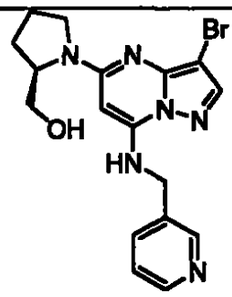
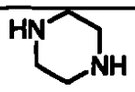
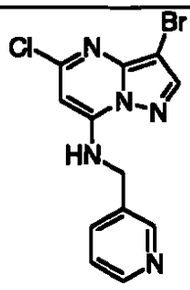
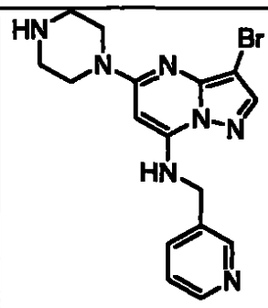
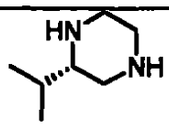
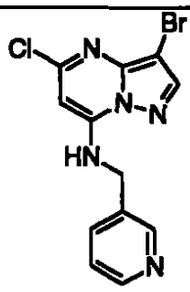
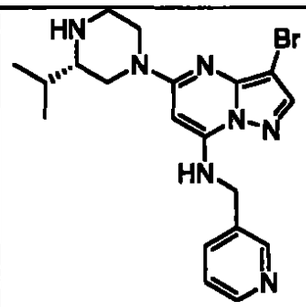
EJEMPLOS 269-275:

Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 268, sustituyendo solamente la amina en la Columna 2 de la Tabla 25 y los cloruros en la Columna 3 de la Tabla 25, se prepararon los compuestos que se muestran en la Columna 4 de la Tabla 25:

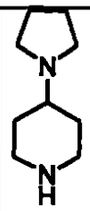
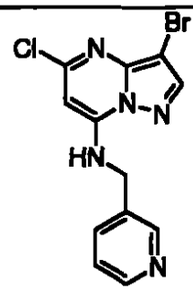
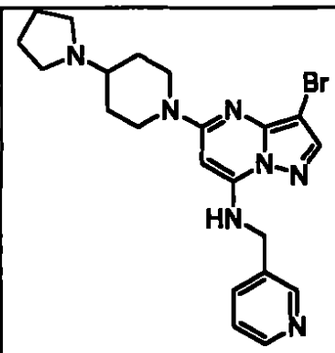
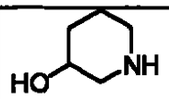
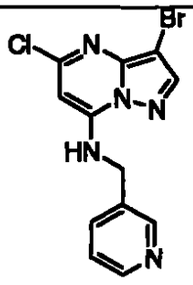
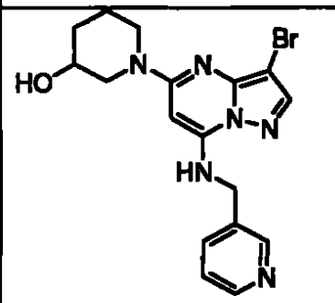
TABLA 25

Ej.	Columna 2	Columna 3	Columna 4	COMPUESTO
269				MS: MH^+ = 387 m.p. 182 – 183°C

527

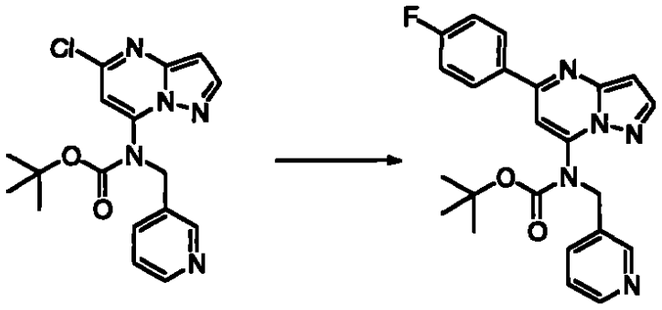
270				MS: MH^+ = 373 m.p. 190 – 191 °C
271				MS: MH^+ = 403 m.p. 227 – 230 °C
272				MS: MH^+ = 388 m.p. 198 – 201 °C
273				MS: MH^+ = 430 m.p. 100-103 °C

528

274				MS: MH^+ = 456 m.p. 175 – 178 °C
275				MS: MH^+ = 403 m.p. 218 °C

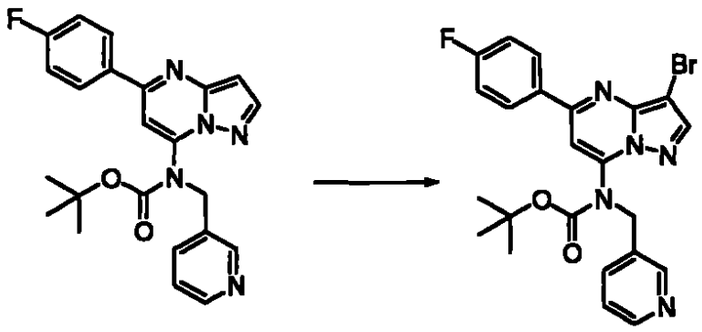
EJEMPLO 276:

Paso A:



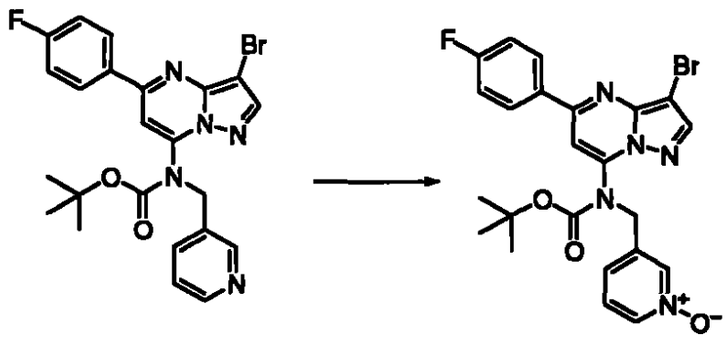
Se agregó bromuro de 4-fluorofenil magnesio (0,68 ml, 1,2 eq.) al compuesto preparado en el Ejemplo Preparativo 193 (0,20 g, 0,55 mmol) y $PdCl_2(dppf)_2$ (0,037 g, 10 mol%) en THF y la solución resultante se agitó a temperatura ambiente 72 horas. La mezcla de reacción se diluyó con NH_4Cl saturado y 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 bruto se purificó mediante cromatografía flash usando EtOAc puro como eluyente (0,15 g, 65% de rendimiento). MS: MH^+ = 420.

Paso B:



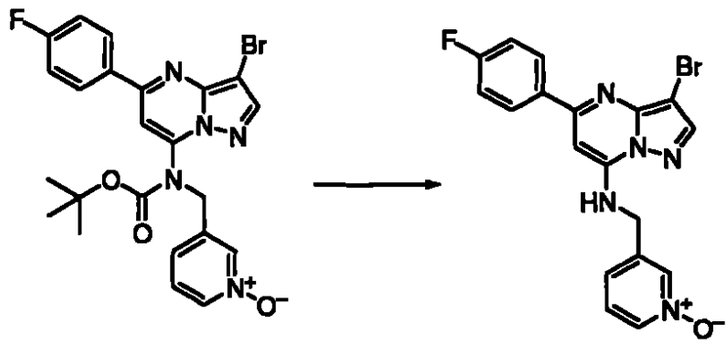
Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 127, sustituyendo solamente el compuesto preparado en el Ejemplo 276, Paso A, se preparó el compuesto anterior (0,17 g, 94% de rendimiento).

Paso C:



Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 200 sustituyendo solamente el compuesto preparado en el Ejemplo 276, Paso B, el compuesto anterior se preparó (0,1g, 100% de rendimiento).

Paso D:



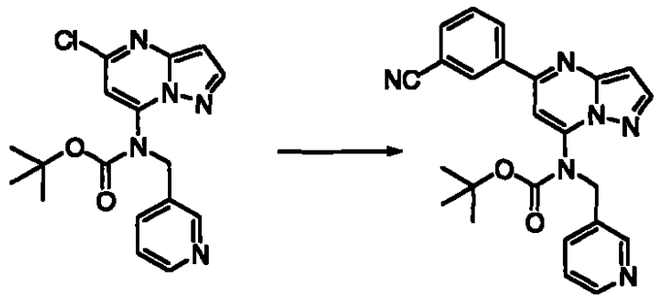
Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 265, sustituyendo solamente el compuesto preparado en el Ejemplo 276, Paso C,

530

se preparó el compuesto anterior (0,049 g, 62% de rendimiento). MS: MH^+ = 414; mp = 110-115 °C.

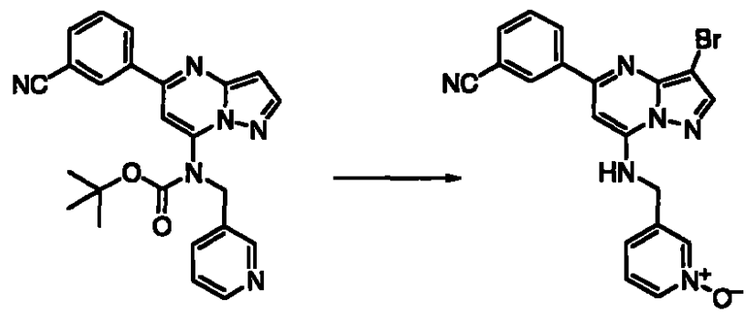
EJEMPLO 277:

Paso 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 mmol) en DMF (2,0 ml) y la solución resultante se calentó a 80 °C g durante 144 horas. La mezcla de reacción se enfrió hasta 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 bruto se purificó mediante cromatografía flash usando una solución pura de EtOAC como eluyente (0,07 g, 29% de rendimiento). MS: MH^+ = 427.

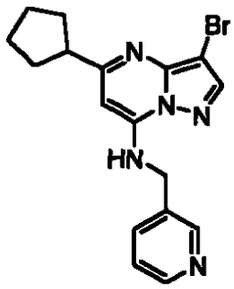
Paso B a Paso D:



esencialmente mediante los mismos procedimientos expuestos en el Ejemplo 276, Paso B a Paso D, se preparó el compuesto anterior (0,023 g, 53% de rendimiento). MS: MH^+ = 421; mp = 230 °C (dec.)

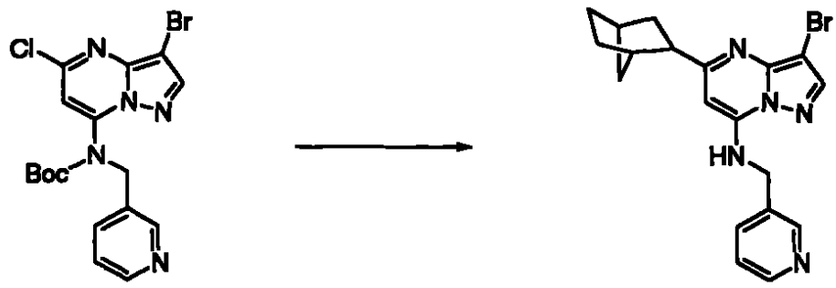
EJEMPLO 278:

531



Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 276, sustituyendo solamente el bromuro de ciclopropilmagnesio adecuado en el Paso A, se preparó el compuesto. MS: MH^+ = 372; m. p. = 96-98 °C.

EJEMPLO 279:



La reacción de acoplamiento cruzado de zinc catalizada con paladio se llevó a cabo de manera similar al procedimiento descripto en *J. Org. Chem.* (1999), 453. Se reflujó una solución de la cloropirazolopirimidina (200 mg, 0,458 mmol), $Pd(PPh_3)_4$ (53 mg, 0,046 mmol), y bromuro *exo*-2-norbonilzinc (0,5 M en THF, 0,95 ml, 0,47 mmol) en DMF (2 ml) a 100°C (temperatura del baño de aceite) hasta el día siguiente. La mezcla de reacción se desactivó con NH_4Cl saturado a medias 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 mediante cromatografía flash usando una solución de EtOAc 50% en hexanos como eluyente. Una solución del producto obtenido protegido por *N*-Boc (121 mg, 53% de rendimiento, LCMS: MH^+ = 498) y se agitó TFA (1 ml) en CH_2Cl_2 (2 ml) a temperatura ambiente durante 2 hr. Los volátiles se eliminaron 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 in *vacuo* (96 mg, 99% de rendimiento). LCMS: MH^+ = 398; ^1H RMN ($CDCl_3$) δ 8,78

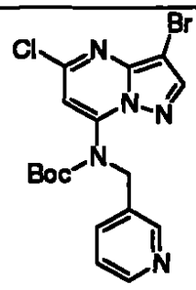
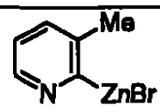
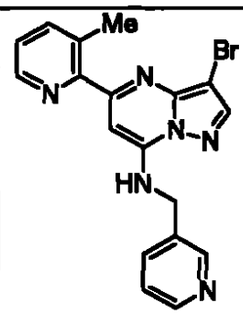
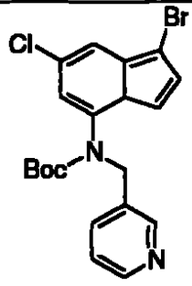
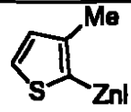
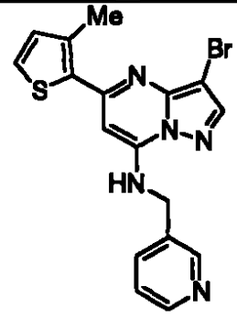
532

(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).

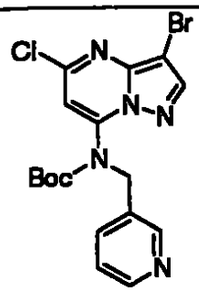
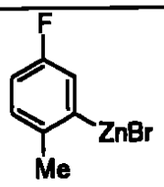
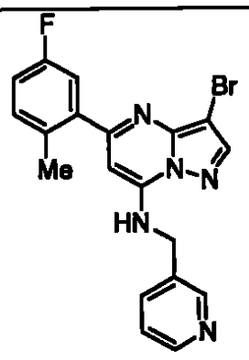
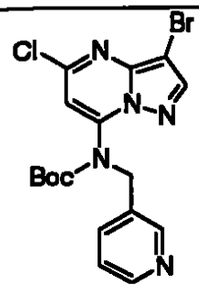
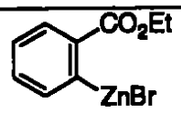
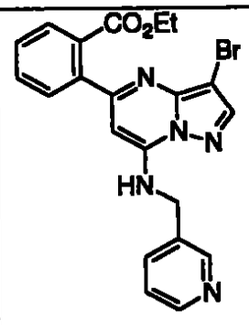
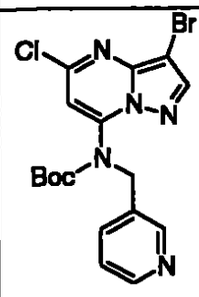
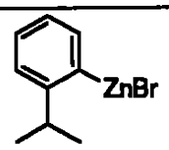
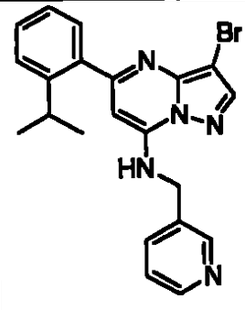
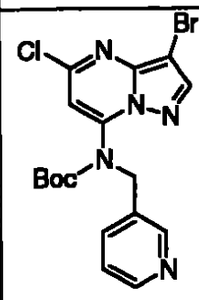
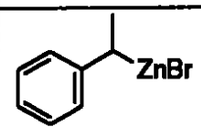
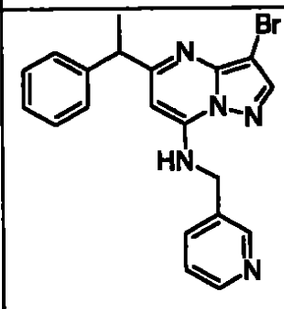
EJEMPLOS 280-294:

Por medio de seguir esencialmente el mismo procedimiento expuesto en el Ejemplo 279, sustituyendo solamente los cloruros que se muestran en la Columna 2 de la Tabla 26 y los reactivos de órgano zinc que se muestran en la Columna 3 de la Tabla 26, se prepararon los compuestos en la columna 4 de la Tabla 26:

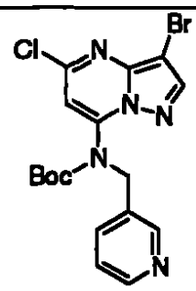
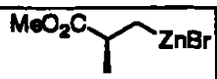
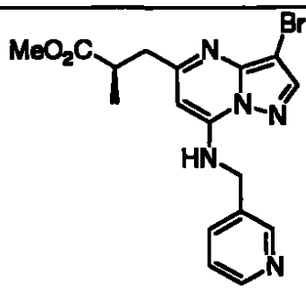
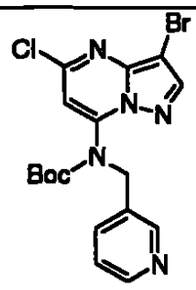
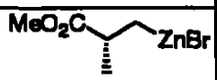
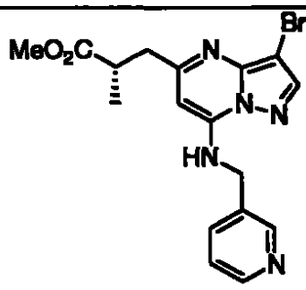
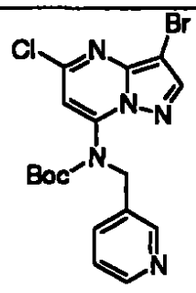
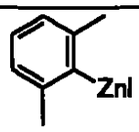
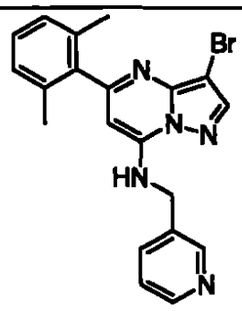
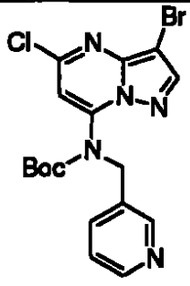
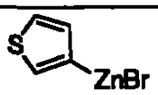
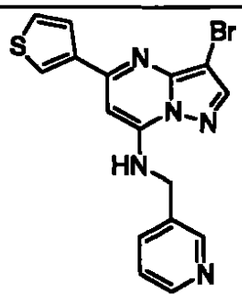
Tabla 26

Ej.	Columna 2	*Columna 3*	Columna 4	Datos
280				LCMS: MH^+ = 395
281				LCMS: MH^+ = 400

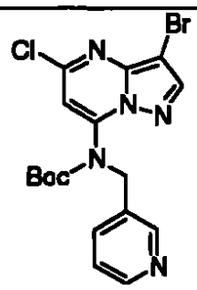
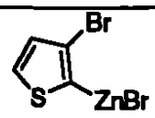
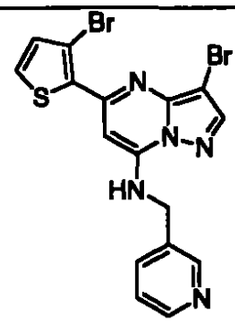
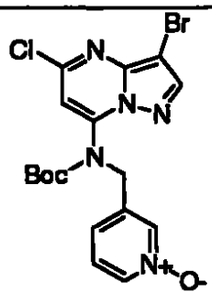
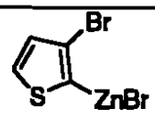
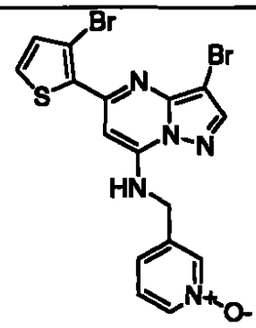
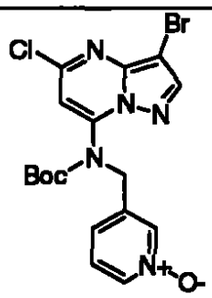
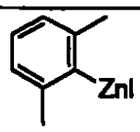
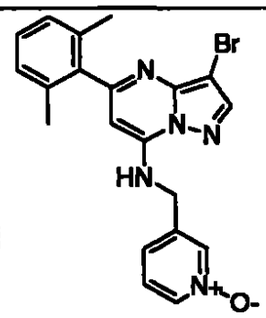
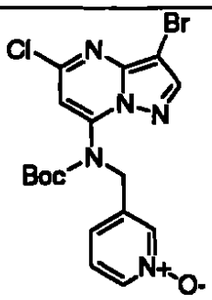
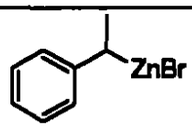
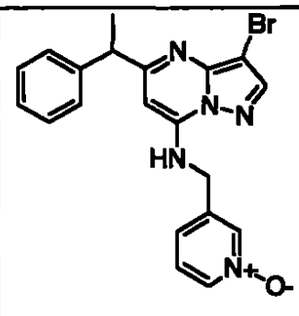
533

282				LCMS: MH^+ = 412
283				LCMS: MH^+ = 452
284				LCMS: MH^+ = 422
285				LCMS: MH^+ = 408

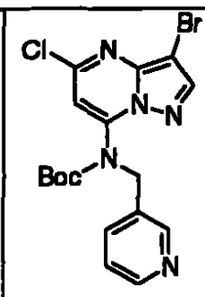
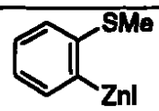
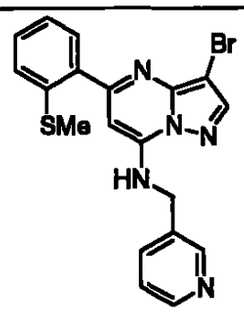
534

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

535

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

536

294				LCMS: MH^+ = 426

A Continuación se muestran datos adicionales para compuestos selectos.

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).

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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).

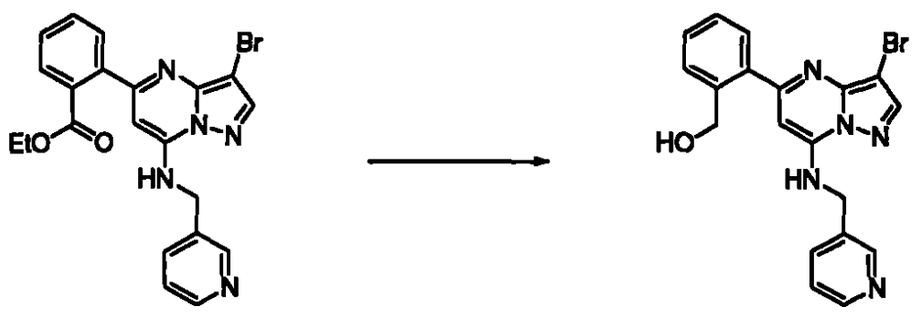
EJEMPLO 291: ^{1}H RMN (DMSO-d_6) δ 9,12 (s, 1H), 8,40 (s, 1H), 8,33 (s, 1H), 8,13 (m, 1H), 7,82 (d, J = 5,1 Hz, 1H), 7,40-7,39 (m, 2H), 7,22 (d, J = 5,1 Hz, 1H), 6,86 (s, 1H), 4,86 (s, 2H).

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).

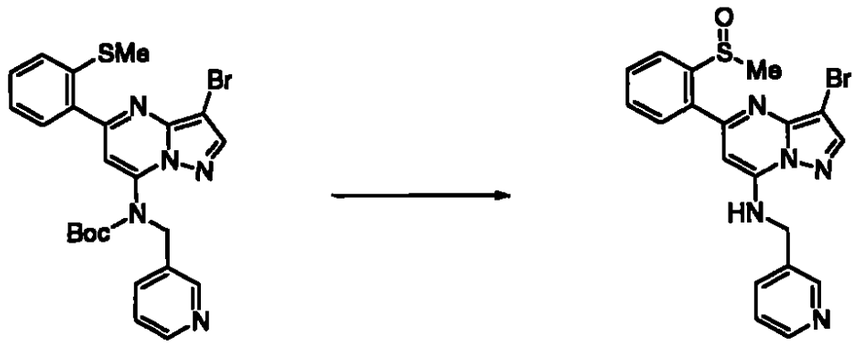
EJEMPLO 295:



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A una suspensión de hidruro de litio aluminio (10 mg, 0,26 mmol) en THF anhídrido (2 ml) a 0°C se agregó, gota a gota, una solución del compuesto preparado en el Ejemplo 283 (20 mg, 0,044 mmol) en THF anhídrido (2 ml). La mezcla resultante se reflujó durante 1 hr y se agitó a temperatura ambiente hasta el día siguiente, 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 bruto se purificó mediante cromatografía de capa delgada preparativa usando un MeOH 5% en solución de EtOAc como eluyente (15 mg, 83% de rendimiento). LCMS: $MH^+ = 410$; ^1H 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:

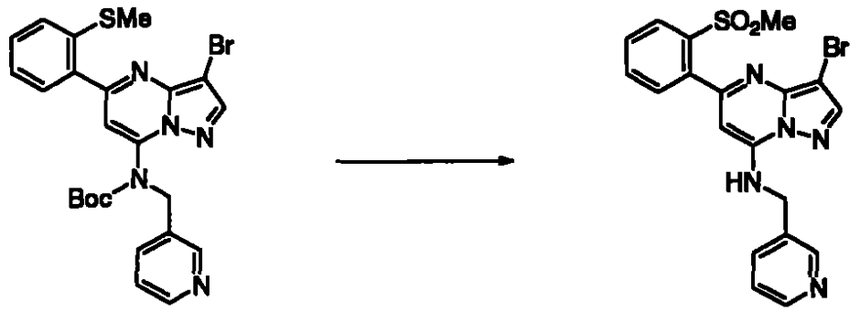


Se agregó *m*-CPBA (18 mg, 0,10 mmol) A una solución del compuesto protegido por N-Boc preparado en el Ejemplo 294 (45 mg, 0,085 mmol) en CH_2Cl_2 (4 ml) a –50°C. Después de agitar durante 1 hr a –50°C more *m*-CPBA (4 mg, 0,02 mmol) se agregó. La mezcla se agitó durante 2 hr adicionales, se diluyó con CH_2Cl_2 (20 ml), y se lavó con saturado $NaHCO_3$ (20 ml). La fase orgánica se secó sobre $MgSO_4$ y se concentraron bajo presión reducida. El residuo se purificó mediante cromatografía de capa delgada preparativa usando una solución de MeOH 2,5% en CH_2Cl_2 como eluyente. Se agitó una solución del producto protegido por N-Boc obtenido (37 mg, 80% de rendimiento, LCMS: $MH^+ = 542$) y TFA (1 ml) en CH_2Cl_2 (2 ml) a temperatura ambiente durante 2 hr. Los volátiles se eliminaron bajo presión reducida. El residuo se disolvió en CH_2Cl_2, se neutralizó

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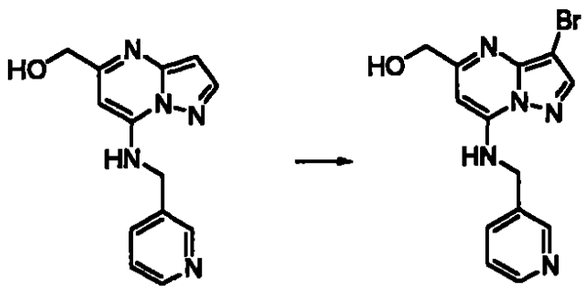
con $NaHCO_3$ saturado, y se extrajo con CH_2Cl_2. La fase orgánica se secó sobre $MgSO_4$ y se concentraron bajo presión reducida. El producto bruto se purificó mediante cromatografía de capa delgada preparativa usando una solución de MeOH 5% en EtOAc como eluyente (26 mg, 89% de rendimiento). LCMS: 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 protegido por N-Boc preparado en el Ejemplo 294 (56 mg, 0,11 mmol) en CH_2Cl_2 (4 ml) a 0°C se agregó *m*-CPBA (42 mg, 0,24 mmol). Después de agitar durante 2 hr a temperatura ambiente se agregó más *m*-CPBA (13 mg, 0,075 mmol). La mezcla se agitó a temperatura ambiente hasta el día siguiente, 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 concentraron bajo presión reducida. El residuo se purificó mediante cromatografía de capa delgada preparativa usando una solución de MeOH 2,5% en EtOAc como eluyente. Se agitó una solución del producto obtenido protegido por N-Boc (29 mg, 49% de rendimiento, LCMS: MH^+ = 558) y TFA (1 ml) en CH_2Cl_2 (2 ml) a temperatura ambiente durante 2 hr. Los volátiles se eliminaron 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 bruto se purificó mediante cromatografía de capa delgada preparativa usando una solución de MeOH 2,5% 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

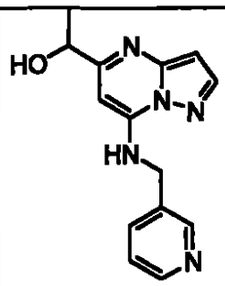
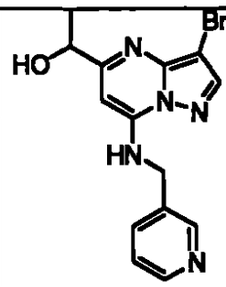
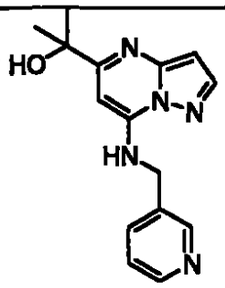
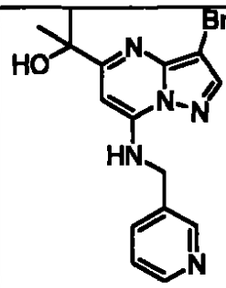


Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 127, sustituyendo solamente el compuesto preparado en el Ejemplo Preparativo 189, se preparó el compuesto anterior. MS: MH^+ = 334; mp = 170-173 °C.

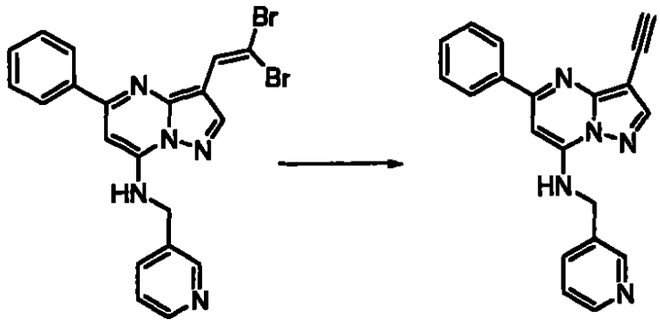
Ejemplos 299-300:

Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 298, sustituyendo solamente el compuesto que se muestra en la Tabla 27, Columna 2, se prepararon los compuestos que se muestran en Tabla 27, Columna 3:

Tabla 27

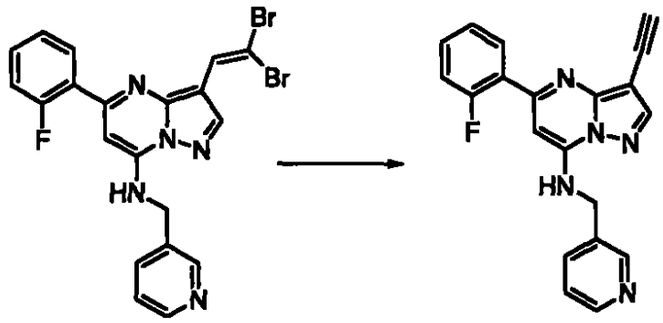
Ej.	Columna 2	Columna 3	COMPUESTO
299			MS: MH^+ = 348 m.p. = 73 – 83 °C
300			MS: MH^+ = 362 m.p. = 165 – 175 °C

EJEMPLO 301:



A una solución del compuesto preparado en el Ejemplo Preparativo 186 (0,1 g, 0,21 mmol) 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 2 horas a -78 °C, se desactivó con H_2O, se calentó hasta 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 bruto se purificó mediante TLC preparativa usando una solución de 2,5% (NH_4OH 10% en CH_3OH) en CH_2Cl_2 como eluyente (0,013 g, 20% de rendimiento). MS: MH^+ = 326; mp = 71-72 °C.

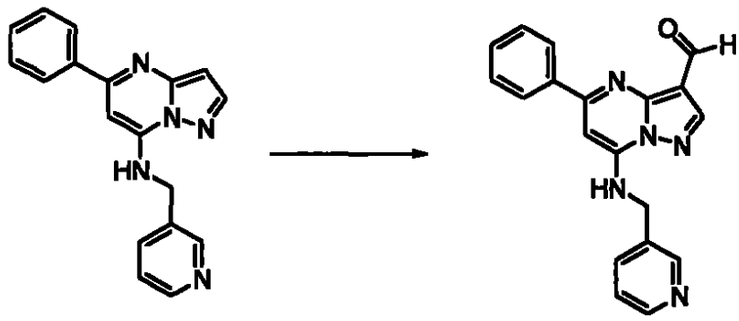
EJEMPLO 302:



Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 301, sustituyendo solamente el compuesto del Ejemplo Preparativo 187, se preparó el compuesto anterior (0,049 g, 68% de rendimiento).MS: MH^+ = 344; mp = 69-71 °C.

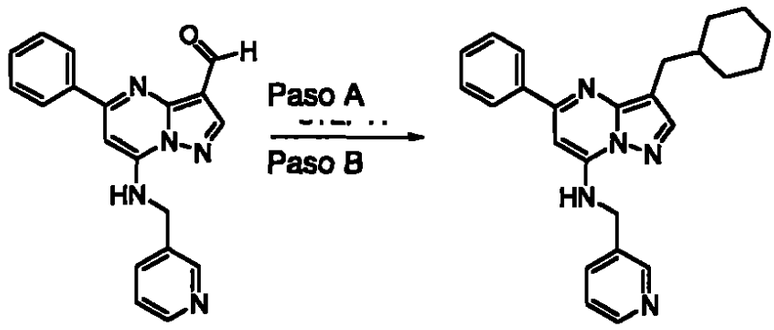
EJEMPLO 303:

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A una solución del aducto 3-H del Ejemplo Preparativo 187,1 (0,70 g, 2,32 mmol) en DMF (4,2 ml) a 0°C se agregó $POCl_3$ (0,67 ml, 7,2 mmol) gota a gota. La mezcla se agitó durante 14h a temperatura ambiente, e enfrió a 0 °C, y se desactivó mediante la adición de hielo. Se agregó NaOH 1N cuidadosamente para regular 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 bruto se recristalizó a partir de EtOAc para dar 0,43 g (56%) de un sólido amarillo. mp 181-183 °C; M+H = 330.

EJEMPLO 304:



PASO A:

A una solución del aldehído (100 mg, 0,30 mmol) del Ejemplo 303 en THF (1 ml) a 0°C se agregó bromuro de ciclohexil magnesio (0,46 ml, 2,0M en Et_2O) gota a gota durante 5 min. La mezcla resultante se agitó a 0 °C durante 2h y a temperatura ambiente durante 12h. La mezcla se enfrió hasta 0 °C y se trató con NH_4Cl acuoso sat. (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

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lavaron con salmuera (1 x 5 ml), se secaron (Na_2SO4), se filtraron y se concentraron bajo presión reducida para dar 110 mg (89%) de un semisólido amarillo pálido. M+H = 414. Este material se llevó a cabo en bruto hasta el Paso B sin purificación adicional.

PASO B:

A una solución de alcohol (53 mg, 0,13 mmol) en CH_2Cl_2 (0,5 ml) a 0°C se agregó Et_3SiH (24 µl, 0,15 mmol) seguido por TFA (24 µl, 0,30 mmol). La mezcla se agitó durante 2 h a 0°C y a temperatura ambiente durante 2 h en dicho momento se agregaron porciones adicionales de Et_3SiH (24 µl, 0,15 mmol) y TFA (24 µl, 0,30 mmol) y la mezcla se agitó durante 3 h a temperatura ambiente (hasta que se completaron mediante TLC). La mezcla se concentró bajo presión reducida y el residuo bruto se dividió entre CH_2Cl_2 (5 ml) y $NaHCO_3$ acuoso sat. (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 filtró y se concentraron bajo presión reducida. El producto bruto se purificó mediante TLC preparativa (8 x 1000 mM) eluyendo con CH_2Cl_2/MeOH (22:1) para dar 29 mg (56%) de un semisólido amarillo. M+H = 398.

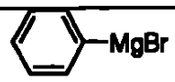
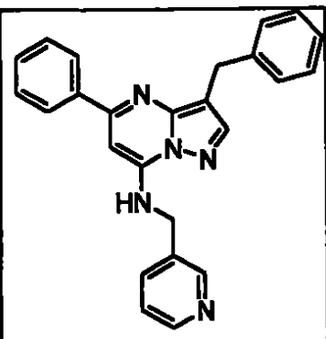
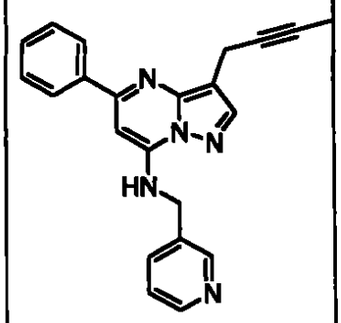
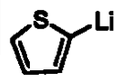
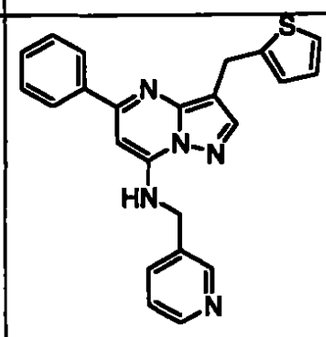
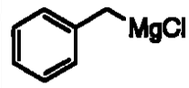
EJEMPLOS 305-312:

Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 304, usando el aldehído del Ejemplo 303 y sustituyendo los reactivos Grignard o de organolito que se muestran en la Columna 2 de la Tabla 28, se prepararon los compuestos en la columna 3 de la Tabla 28:

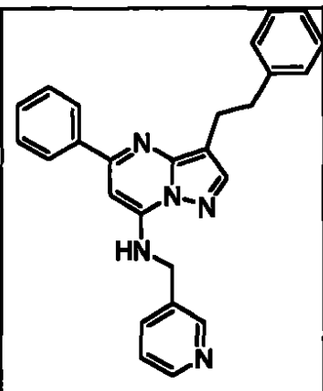
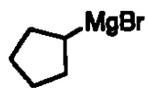
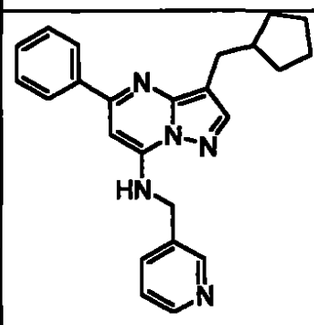
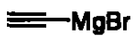
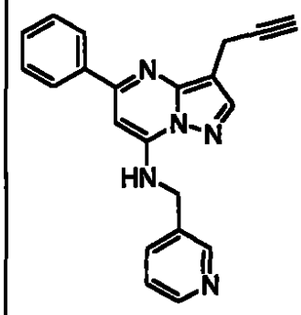
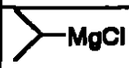
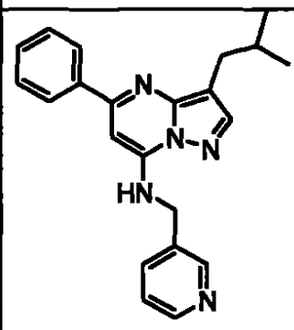
TABLA 28

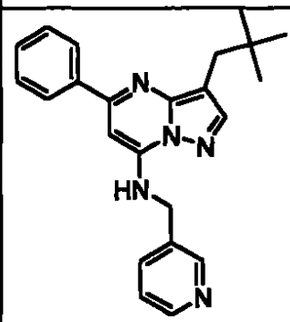
Ej.	Columna 2 (Organometálico)	Columna 3 (Estructura final)	COMPUESTO 1, mp (°C) 2, M+H
305			1, aceite amarillo

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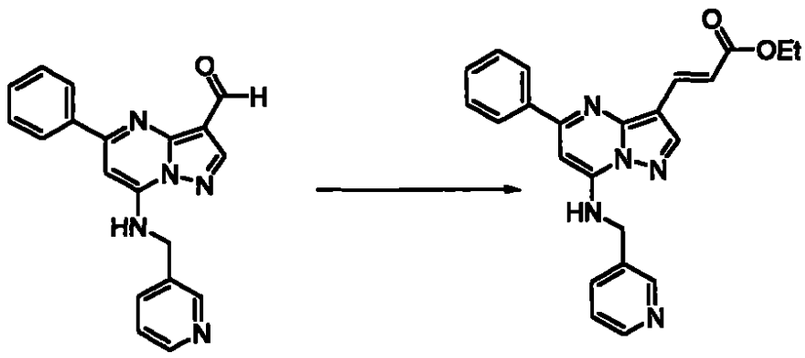
			2, M+H = 392
306			1, aceite rojo 2, M+H = 353
307			1, aceite rojo 2, M+H = 398
308			1, aceite amarillo 2, M+H = 406

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309			1,semisólido amarillo 2, M+H = 384
310			1, semisólido 2, M+H = 340
311			1, mp = 141-143 2, M+H = 358

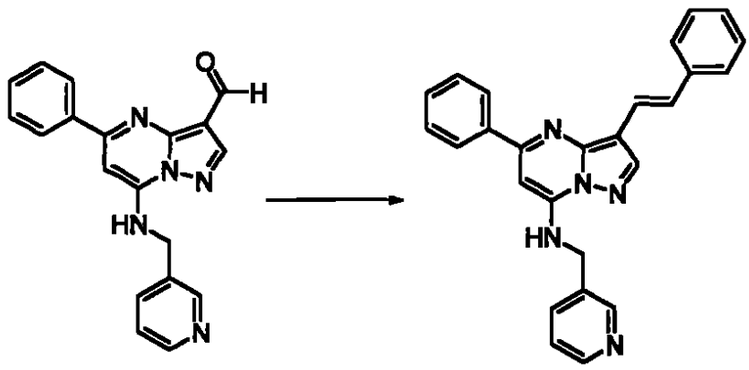
312			1, mp = 148-150 2, M+H = 372

EJEMPLO 313:



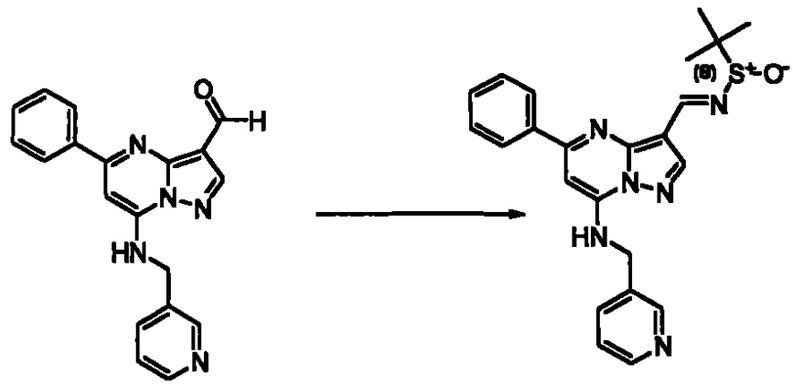
A una solución del aldehído (81 mg, 0,25 mmol) del Ejemplo 303 en benceno (2,5 ml) se agregó carboetoximetilen trifenil fosforano (0,12 g, 0,33 mmol) en una porción. La mezcla se calentó a reflujo durante 24h, se enfrió hasta ta, y se concentró bajo presión reducida. La mezcla se diluyó CH_2Cl_2 (5 ml), 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 bruto se purificó mediante TLC preparativa (8 x 1000 µM) eluyendo con CH_2Cl_2/MeOH (20:1) para dar 98 mg (100%) de sólido blanco. mp 151-153 °C; M+H = 400.

EJEMPLO 314:



A una mezcla de bromuro de benciltrifenilfosfonio (0,59 g, 1,37 mmol) en THF (3 ml) se agregó NaH (55 mg, 1,37 mmol) y la mezcla se agitó durante 30 min. Se agregó el aldehído (0,15 g, 0,46 mmol) del Ejemplo 303 en una porción simple y la mezcla se calentó a reflujo durante 36h. La mezcla se enfrió hasta temperatura ambiente y se concentró bajo presión reducida. La mezcla se diluyó CH_2Cl_2 (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 bruto se purificó mediante TLC preparativa (8 x 1000 µM) eluyendo con CH_2Cl_2/MeOH (20:1) para dar 58 mg (32%) de un sólido amarillo. mp 138-141 °C; M+H = 404.

EJEMPLO 315:

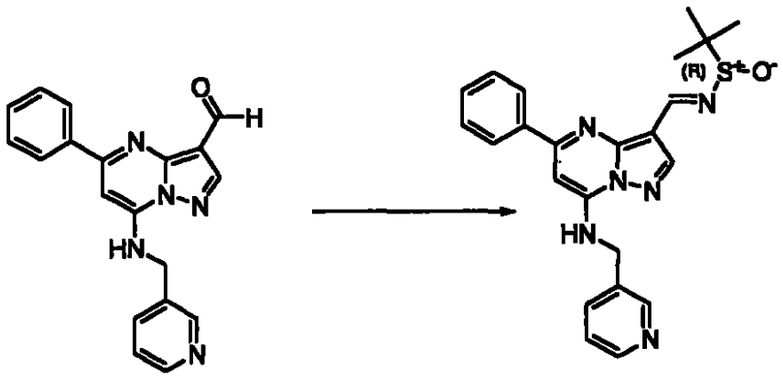


A una solución del aldehído (0,20 g, 0,60 mmol) del Ejemplo 303 en THF (3 ml) se agregó Ti (i-OPr)$_4$ (0,36 ml, 1,21 mmol) gota a gota seguido por la adición de (*S*)-(-)-2-metil-2-propanesulfinamida (74 mg, 0,61 mmol). La mezcla resultante se agitó durante 18h a reflujo, se enfrió hasta ta, y se desactivó con salmuera (2

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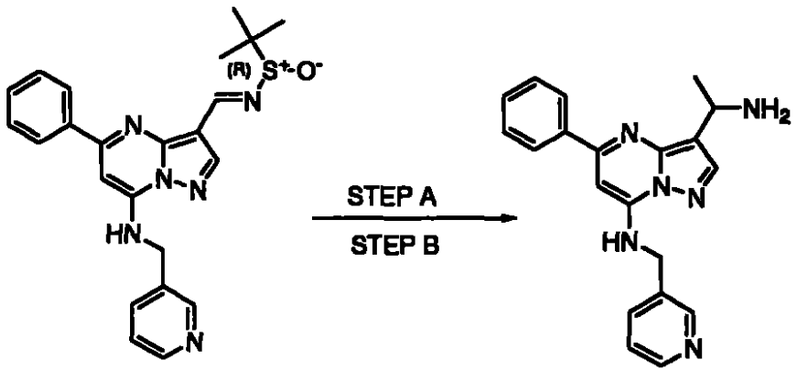
ml). La mezcla se filtró a través de un taco de Celite que se lavó con EtOAc (2 x 2 ml). Las capas se separaron y la capa acuosa se extrajo con EtOAc (2 x 4 ml). Las capas orgánicas se combinaron, se secaron (Na_2SO_4), se filtraron y se concentraron bajo presión reducida. El producto bruto se purificó mediante TLC preparativa (8 x 1000 µM) eluyendo con CH_2Cl_2/MeOH (20:1) para dar 0,21 g (80%) de sólido amarillo. mp 108-110 °C; M+H = 433.

EJEMPLO 316:



Preparado de la misma manera que el Ejemplo 315 con la salvedad que se sustituye (*R*)-(-)-2-metil-2-propanesulfinamida para dar 0,25 g (94%) como un sólido amarillo. mp 107-109 °C; M+H = 433.

EJEMPLO 317:



PASO A:

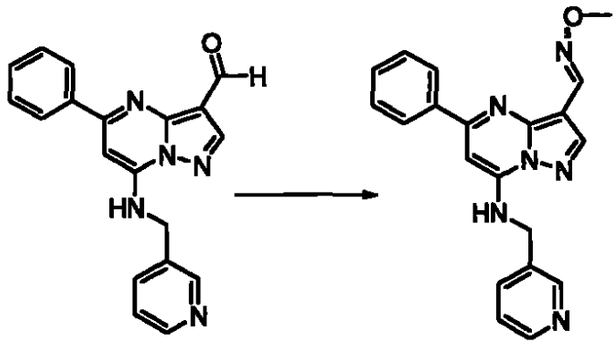
549

A una solución de sulfinimina (50 mg, 0,12 mmol) del Ejemplo 316 en CH_2Cl_2 (2,5 ml) a -40 °C se agregó MeMgBr (96 ml, 0,29 mmol) gota a gota. La mezcla se agitó durante 5h a -40 °C y se agitó a temperatura ambiente durante 12h. Una porción adicional de MeMgBr (96 ml, 0,29 mmol) y la mezcla se agitó durante 12 h. Se agregó NH_4Cl acuoso sat. (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 dar 30 mg (58%) de residuo bruto. Este material se capturó en el paso siguiente sin purificación.

PASO B:

Al material bruto del Paso A (30 mg, 0,067 mmol) en MeOH (2 ml) se agregó HCl conc. (2 ml). La mezcla se agitó a temperatura ambiente durante 12h y la mezcla se concentró hasta que se secó. El material bruto se dividió entre CH_2Cl_2 (3 ml) y $NaHCO_3$ acuoso sat. (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 dar 6 mg (24%) del compuesto de título as un sólido amarillo claro. mp 100-102 °C; M + H = 345.

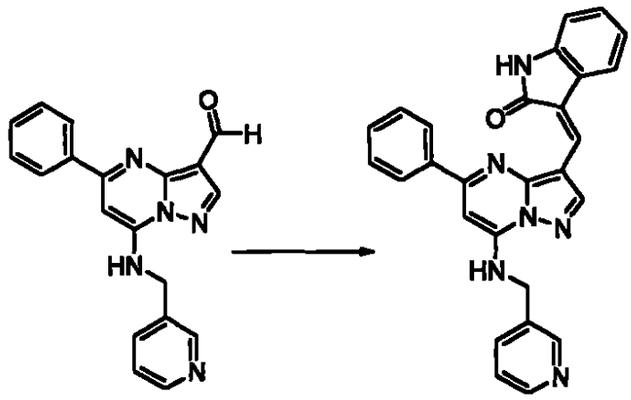
EJEMPLO 318:



A una solución del aldehído (75 mg, 0,23 mmol) del Ejemplo 300 en THF/CH_2Cl_2 (5 ml/1ml) a temperatura ambiente se agregó $MeONH_2HCl$ (38 mg, 0,46 mmol) seguido por la adición gota a gota fr piridina (46 µl, 0,57 mmol). La mezcla se agitó durante 72h a temperatura ambiente n ese momento la mezcla se concentró hasta que se secó. El material bruto se dividió entre CH_2Cl_2 (3 ml) y $NaHCO_3$ acuoso sat. (2 ml) y las capas se separaron. La capa acuosa se extrajo

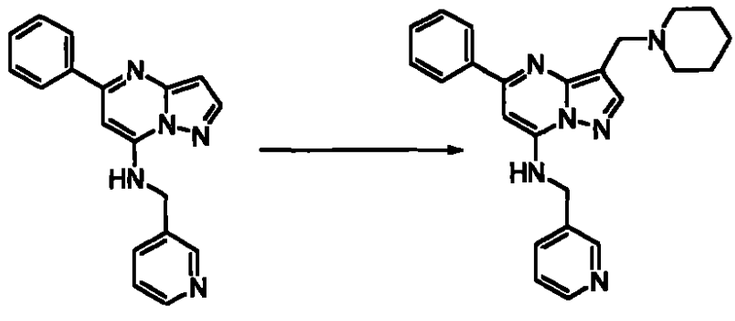
con CH_2Cl_2 (2 x 3 ml) y las capas orgánicas se combinaron. La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida. El producto bruto se purificó mediante TLC preparativa (3 x 1000 µM) eluyendo con CH_2Cl_2/MeOH (22:1) para dar 90 mg (100%) de un sólido amarillo claro. mp 173-175 °C ; M + H = 359.

EJEMPLO 319:



A solución del aldehído (60 mg, 0,18 mmol) del Ejemplo 303 para EtOH (2,5 ml) se agregó oxindol (48 mg, 0,37 mmol) seguido por piperidina (3 gotas). La mezcla se calentó a reflujo durante 14h y la mezcla se enfrió hasta temperatura ambiente. El precipitado resultante se filtró y se lavó con EtOH frío (2 x 2 ml). El producto se secó bajo alto vacío para dar 81 mg (100%) del compuesto de título como un sólido naranja/marrón. mp 182-185 °C; M+H = 445.

EJEMPLO 320:



A una solución del análogo 3-H (106 mg, 0,35 mmol) del Ejemplo Preparativo 187,10 en AcOH (2 ml) se agregó acuoso formaldehído 37% (1,5 ml; 1,40 mmol) seguido por piperidina (100 µl; 0,37 mmol). La mezcla resultante se

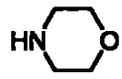
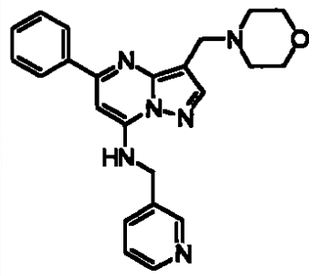
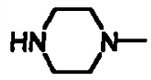
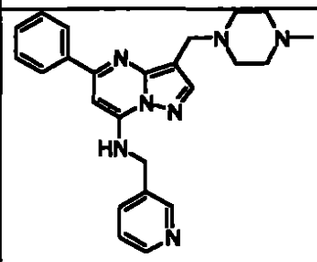
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agitó a temperatura ambiente durante 24h y el AcOH se eliminó bajo presión reducida. La mezcla se diluyó con agua (2 ml) y se neutralizó con NaOH 2M hasta pH = 8. La capa acuosa se extrajo con CH_2Cl_2 (3 x 7 ml) y las capas orgánicas se combinaron. La capa orgánica se lavó con salmuera (1 x 4 ml), se secó (Na_2SO_4), se filtró, y se concentraron bajo presión reducida para dar 96 mg (69%) de un sólido blancuzco. mp 88-90 °C; M+H 399.

EJEMPLOS 321-322:

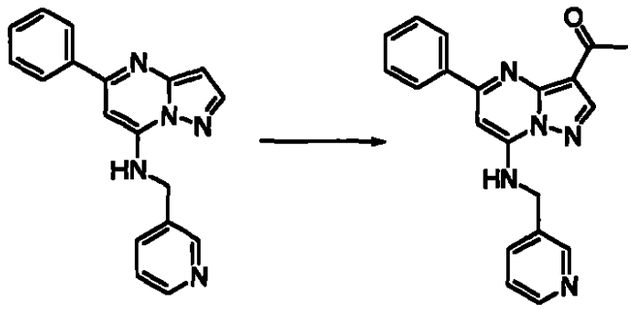
Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 320, sustituyendo solamente las aminas en la Columna 2 de la Tabla 29 y usando el aducto 3-H del Ejemplo Preparativo 187,10, se prepararon los compuestos en la columna 3 de la Tabla 29:

TABLA 29

Ej.	Columna 2 (Amina)	Columna 3 (Estructura final)	COMPUESTO 1, mp (°C) 2, M+H
321			1, mp = 178-180 2, M+H = 401
322			1. mp = 102-104 2. M+H = 414

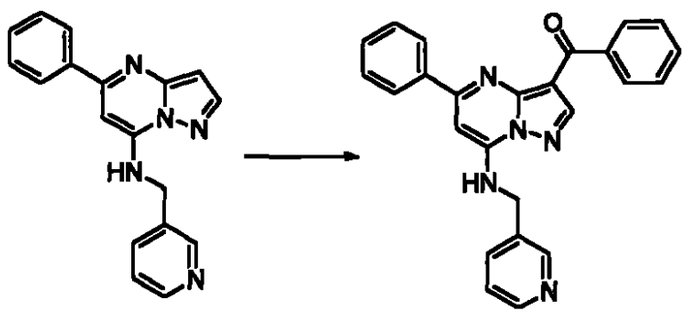
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EJEMPLO 323:



A una solución de análogo 3-H (113 mg, 0,38 mmol) del Ejemplo Preparativo 187,10 en CH_2Cl_2 (5 ml) a temperatura ambiente se agregó $AlCl_3$ (215 mg, 1,61 mmol) seguido por AcCl (100 ml, 1,40 mmol). La mezcla se calentó a reflujo durante 12h y se enfrió hasta temperatura ambiente. La mezcla se trató secuencialmente con HCl 3M (3 ml) seguido por $NaHCO_3$ acuoso sat. (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 bruto se purificó mediante TLC preparativa (8 x 1000 mM) eluyendo con CH_2Cl_2/MeOH (20:1) para dar 68 mg (52%) de sólido blanco. mp 220-221 °C; M+H = 344.

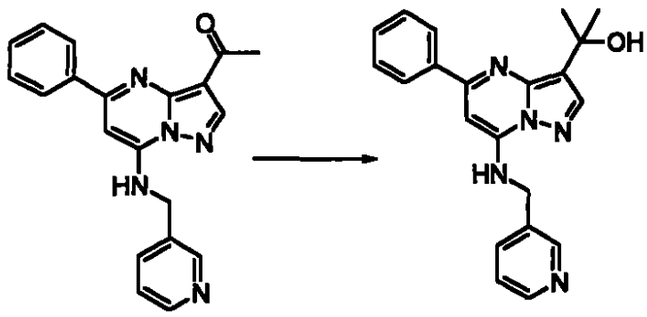
EJEMPLO 324:



Usando el método descripto en el Ejemplo 323, con la salvedad del uso del cloruro de benzoilo, se preparó el compuesto de título en 61% de rendimiento como un sólido blanco. mp 172-175 °C; M+H = 406.

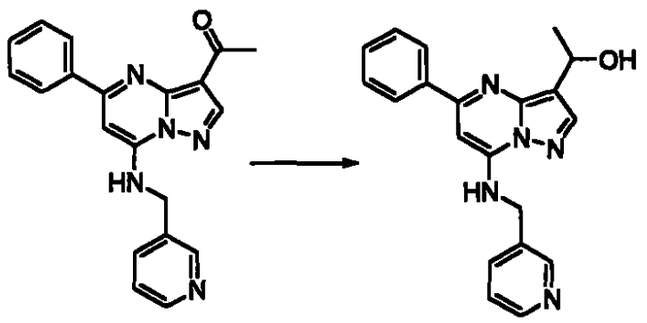
EJEMPLO 325:

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A una solución de cetona (100 mg, 0,29 mmol) del Ejemplo 323 en CH_2Cl_2 (2,5 ml) a 0°C se agregó MeMgBr (0,35 ml, 3,0M en Et_2O) gota a gota. La mezcla resultante se agitó durante 18h a temperatura ambiente y se desactivó cuidadosamente mediante la adición de NH_4Cl acuoso sat. (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 filtró y se concentraron bajo presión reducida. El producto bruto se purificó mediante TLC preparativa (8 x 1000 µM) eluyendo con CH_2Cl_2/MeOH (10:1) para dar 68 mg (52%) de un sólido amarillo. mp 160-162 °C; M+H = 360.

EJEMPLO 326:

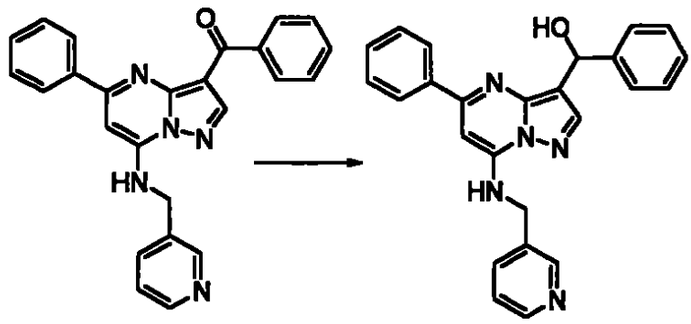


A una solución de cetona (84 mg, 0,24 mmol) del Ejemplo 323 en MeOH/THF (1:1; 2 ml total) a 0°C se agregó $NaBH_4$ (12 mg, 0,30 mmol) en una porción. La mezcla resultante se agitó durante 18h a temperatura ambiente y se agregó una poción adicional de $NaBH_4$ (12 mg, 0,30 mmol). La mezcla se agitó durante 12h, en dicho momento la mezcla se desactivó con hielo seguido por la adición de NaOH 1M para regular 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

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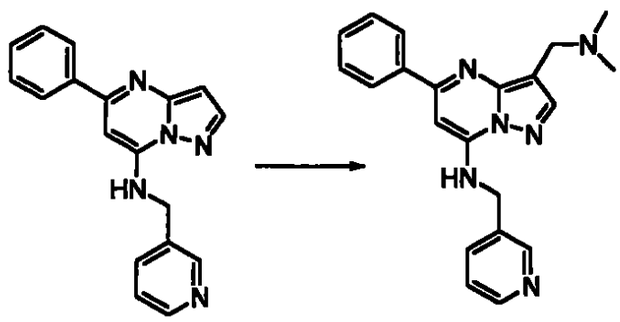
concentraron bajo presión reducida. El producto bruto se purificó mediante TLC preparativa (8 x 1000 µM) eluyendo con CH_2Cl_2/MeOH (10:1) para dar 25 mg (30%) de un sólido amarillo. mp 148-150 °C; M+H = 346.

EJEMPLO 327:



Usando el mismo procedimiento que el descripto en el Ejemplo 326, la cetona (84 mg, 0,21 mmol) se convirtió en 53 mg (62%) como un sólido amarillo claro. mp 78-80 °C; M+H = 408.

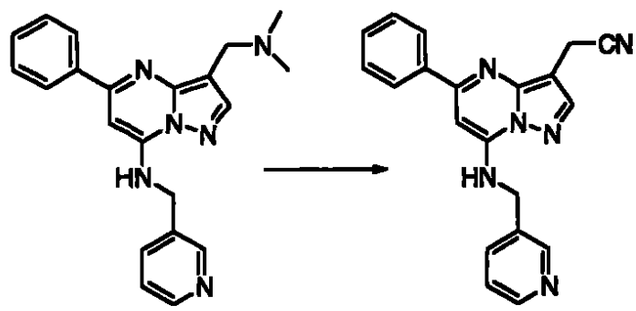
EJEMPLO 328:



A una solución de aducto 3-H (1,3 g, 4,31 mmol) del Ejemplo Preparativo 187,10 en CH_2Cl_2 (50 ml) se agregó sal de Eschenmoser (0,79 g, 4,31 mmol) seguido por la adición gota a gota de TFA (0,56 ml, 7,33 mmol). La mezcla se agitó a temperatura ambiente durante 48 h y se diluyó con CH_2Cl_2 (250 ml). La capa orgánica se lavó con $NaHCO_3$ acuoso sat. (2 x 125 ml) para dar 1,41 h (92%) de un sólido amarillo. mp 231-233 °C; M+H = 359.

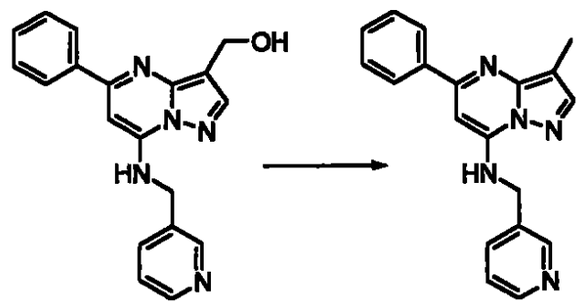
EJEMPLO 329:

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A una solución del aducto de amina terciaria (100 mg, 0,28 mmol) del Ejemplo 328 en DMF acuoso 50% (5 ml) en un tubo de presión se agregó KCN (0,15 g, 2,32 mmol). El tubo se tapó y se calentó a 100 °C durante 96h. La mezcla se enfrió hasta 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 bruto se purificó mediante TLC preparativa (4 x 1000 µM) eluyendo con EtOAc para dar 21 mg (30%) de sólido marrón. mp 152-155 °C; M+H = 341.

EJEMPLO 330:

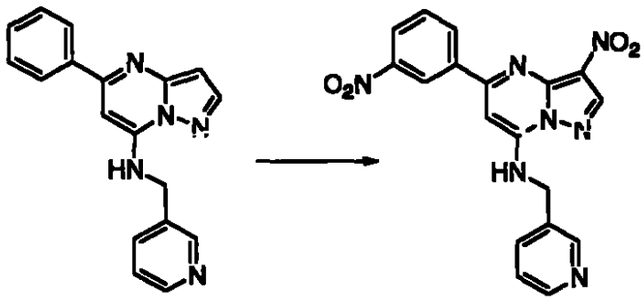


A una solución de alcohol (45 mg, 0,14 mmol) del Ejemplo 17,10 en CH_2Cl_2 (0,7 ml) a 0°C se agregó Et_3SiH (26 µl, 0,16 mmol) seguido por TFA (25 µl, 0,33 mmol). La mezcla se agitó durante 2 h a 0°C y a temperatura ambiente durante 2 h en ese momento se agregaron porciones adicionales de Et_3SiH (26 µl, 0,16 mmol) y TFA (25 µl, 0,33 mmol) y la mezcla se agitó durante 4 h a temperatura ambiente (hasta que se completó por TLC). La mezcla se concentró bajo presión reducida y el residuo bruto se dividió entre CH_2Cl_2 (3 ml) y $NaHCO_3$ acuoso sat.

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(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 lavó con salmuera (1 x 5 ml), se secaron (Na_2SO_4), se filtraron y se concentraron bajo presión reducida. El producto bruto se purificó mediante TLC preparativa (4 x 1000 mM) eluyendo con CH_2Cl_2/MeOH (20:1) para dar 21 mg (48%) de un sólido amarillo. mp 146-148 °C; M+H = 316.

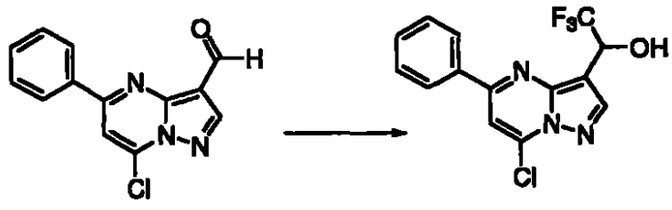
EJEMPLO 331:



A una solución del aducto 3-H (90 mg, 0,30 mmol) del Ejemplo Preparativo 187,10 en H_2SO_4 conc. (2 ml) a 0°C se agregó HNO_3 humeante (30 µl, 0,72 mmol) gota a gota. La mezcla resultante se agitó durante 1 h a 0°C en ese momento se agregó hielo (~1g) a la mezcla. Se recolectó el precipitado resultante y se lavó con agua (2 x 2 ml) y CH_2Cl_2 (2 x 2 ml). El producto bruto se secó bajo alto vacío para dar 67 mg (60%) de la sal del monosulfato como un sólido amarillo/naranja. mp 250 °C; M+H (free base) = 392.

EJEMPLO 332:

Paso A:

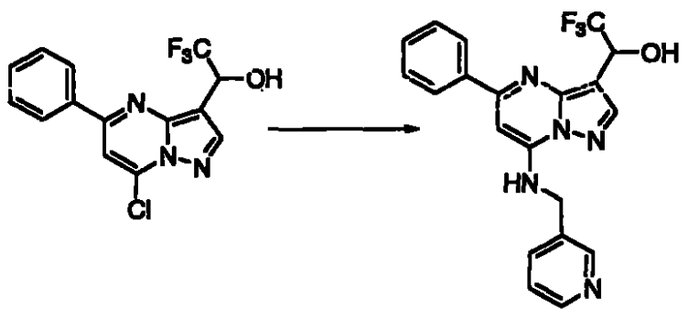


A una solución del aldehído (0,10 g, 0,39 mmol) del Ejemplo Preparativo 168 en THF (2,5 ml) a 0°C se agregó CF_3TMS (64 ml, 0,43 mmol) seguido por

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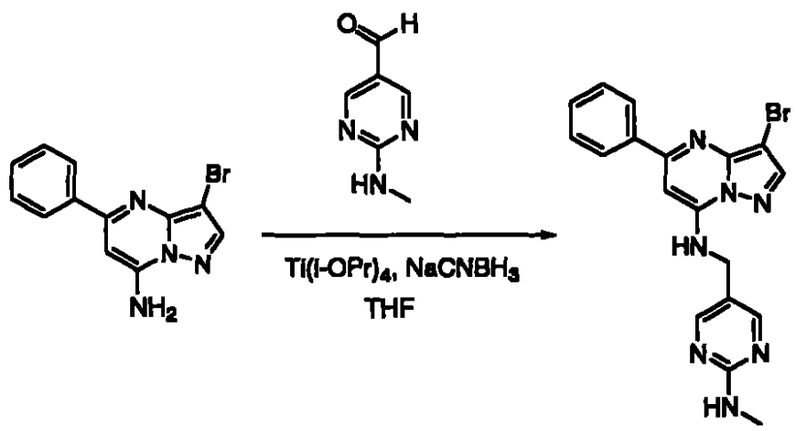
CsF (10 mg). La mezcla resultante se agitó durante 2 h a 0°C y 2h a temperatura ambiente. Se agregó HCl 1M (5 ml) y la mezcla se diluyó con CH_2Cl_2 (10 ml). Las capas se separaron, la capa acuosa se extrajo con CH_2Cl_2 (2 x 10 ml), y las capas orgánicas se combinaron. La capa orgánica se lavó con salmuera (1 x 10 ml), se secó (Na_2SO_4), se filtró, y se concentraron bajo presión reducida para dar 127 mg (99%) de un semisólido amarillo. M+H =328. El producto bruto se continuó sin purificación adicional.

Paso B:



Mediante el uso del procedimiento general expuesto en el Ejemplo 1, el aducto 7-Cl (127 mg, 0,39 mmol) del Ejemplo 332, Paso A se hizo reaccionar con 3-(aminometil)piridina (73 µl, 0,43 mmol) para dar 80 mg (51%) del compuesto de título como un sólido amarillo claro. mp 68-72 °C; M+H = 400.

EJEMPLO 333:



A una solución de anilina (200 mg, 0,69 mmol) del Ejemplo Preparativo 174 en THF (6 ml) a temperatura ambiente se agregó aldehído (114 mg, 0,83 mmol)

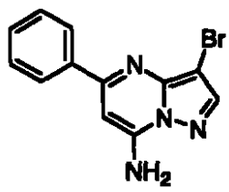
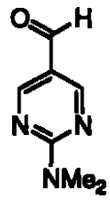
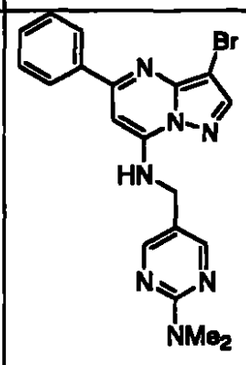
558

del Ejemplo Preparativo 256 seguido por la adición gota a gota de Ti(*i*-OPr)$_4$ (0,82 ml, 2,77 mmol). La mezcla se agitó a reflujo durante 4 h y se enfrió hasta temperatura ambiente. Se agregó $NaCNBH_3$ (347 mg, 5,53 mmol) y la mezcla se agitó durante 2 h a temperatura ambiente. La mezcla se enfrió hasta 0 °C, se trató con NaOH 1M (4 ml) y salmuera (1 ml) y se agitó durante 30 min. 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 secaron (Na_2SO_4), se filtraron y se concentraron bajo presión reducida. El producto bruto se purificó mediante cromatografía preparativa de capa delgada (8 x placas de 1000 µM) eluyendo con CH_2Cl_2/MeOH (25:1) para dar 89 mg (31%) del compuesto de título como un sólido amarillo. mp 210-213 °C ; M+H = 411.

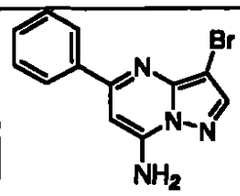
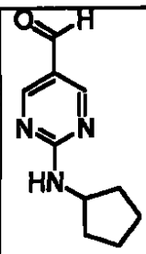
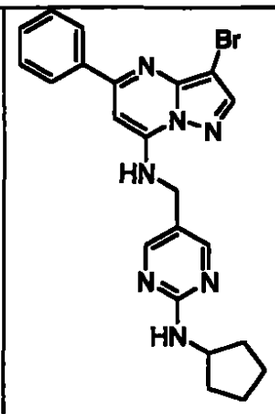
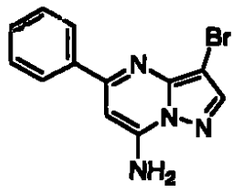
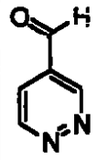
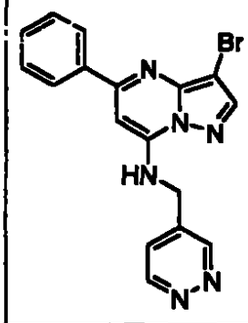
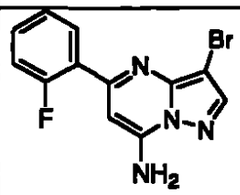
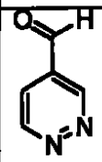
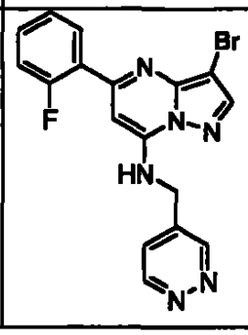
EJEMPLOS 334-337:

Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 333, usando solamente las anilinas que se muestran en la Columna 2 de la Tabla 30 y el aldehídos que se muestran en la Columna 3 de la Tabla 30, se prepararon los compuestos en la columna 4 de la Tabla 30:

TABLA 30

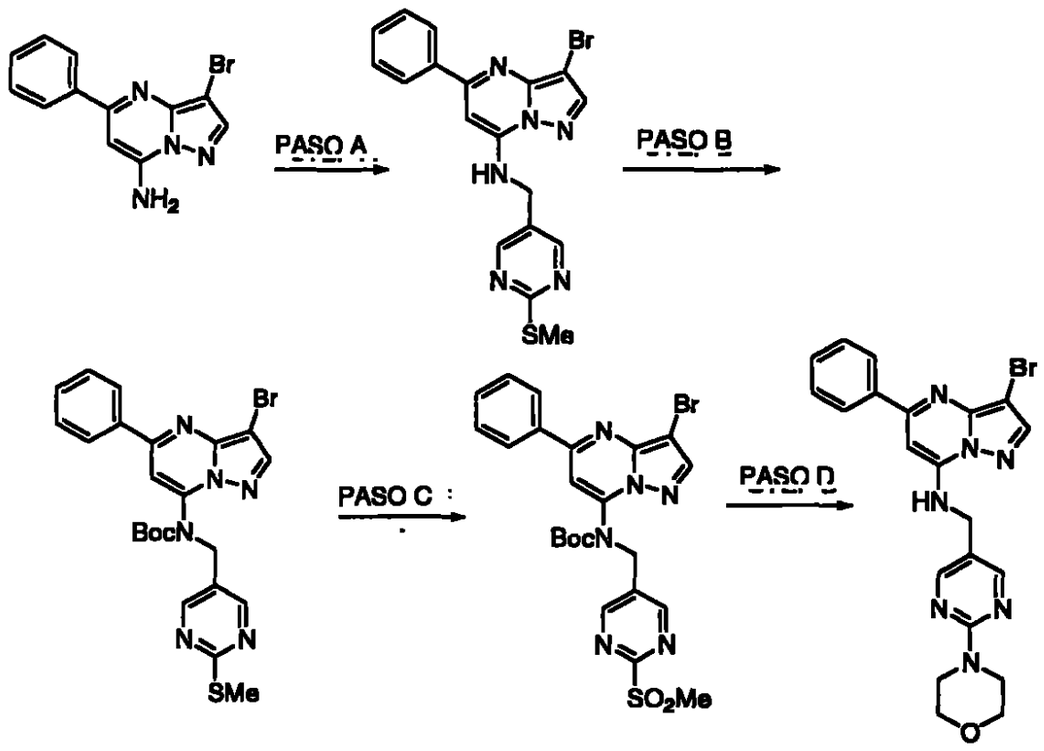
Ej.	Columna 2 (Anilina)	Columna 3 (Aldehído)	Columna 4 (Estructura final)	COMPUESTO 1. mp (°C) 2. M+H
334				1. mp = 85-87 2. M+H = 425

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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

EJEMPLO 338:

560



PASO A:

La reacción de anilina (0,20 g, 0,69 mmol) con aldehído (0,13 g, 0,83 mmol) en las condiciones de reacción descriptas en el Ejemplo 333 dio 70 mg (23%) del derivado tiometilo como un sólido amarillo. M+H = 428.

PASO B:

A una solución del derivado tiometilo (60 mg, 0,14 mmol) del Ejemplo 338, Paso A en dioxano(2 ml) se agregó Boc_2O (61 mg, 0,28 mmol) seguido por DMAP (21 mg, 0,17 mmol). La mezcla se agitó durante 14h a temperatura ambiente y se concentró bajo presión reducida. El producto bruto se purificó mediante cromatografía preparativa de capa delgada (6 x placas de 1000 µM) eluyendo con hexanos/EtOAc (4:1) para dar 61 mg (83%) del compuesto de título as un sólido amarillo. M+H = 528.

PASO C:

A una solución del derivado tiometilo del Ejemplo 338, Paso B (41 mg, 0,078 mmol) en CH_2Cl_2 (2 ml) se agregó MCPBA (33 mg, 0,19 mmol) en una porción. La mezcla resultante se agitó durante 3h a temperatura ambiente y la mezcla se diluyó con CH_2Cl_2 (5 ml) y $NaHCO_3$ acuoso sat. (2,5 ml). Las capas se

561 562

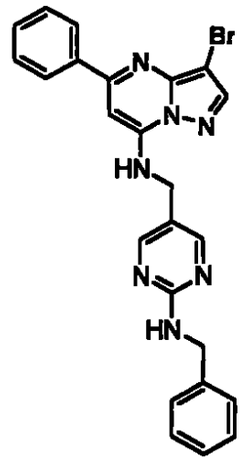
separaron, la capa acuosa se extrajo con CH_2Cl_2 (2 x 5 ml), y las capas orgánicas se combinaron. La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida para dar 40 mg (92%) del aducto de sulfota como un sólido amarillo claro. M+H = 560.

PASO D:

A una matraz cargada con sulfota del Ejemplo 338, Paso C (75 mg, 0,13 mmol) y una barra para agitar se agregó morfolina (2 ml; 22 mmol). La mezcla se calentó a reflujo durante 12h, se enfrió a ta, y se concentró hasta que se secó bajo alto vacío. El producto bruto se purificó mediante cromatografía preparativa de capa delgada (6 x placas de1000 µM) eluyendo con CH_2Cl_2/MeOH (40:1) para dar 41 mg (68%) del compuesto de título as un sólido amarillo. mp 209-210 °C; M+H = 466.

EJEMPLO 339:

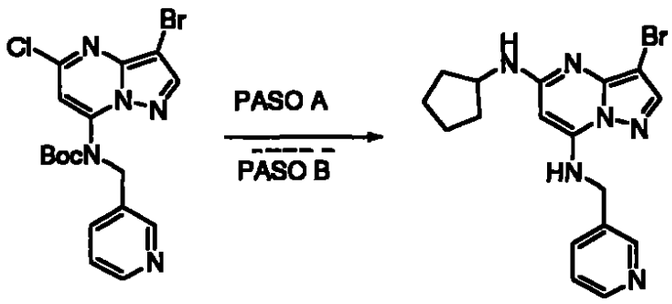
PASO A



El compuesto de título se preparó de acuerdo con el procedimiento descripto en el Ejemplo 338, con la salvedad que se usa bencil amina para dar 12 mg (70%) de un sólido blanco. mp 194-196; M+H = 487.

EJEMPLO 340:

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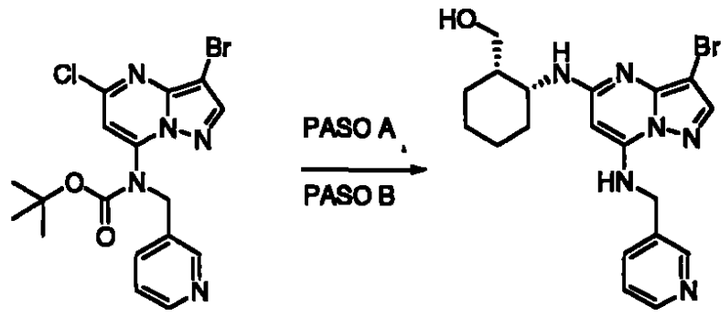
PASO A:

A una solución de aducto de 5-cloro (0,15 g, 0,34 mmol) en dioxano/DIPEA (2,5ml/1,0ml) a temperatura ambiente se agregó ciclopentilamina (0,041 µl, 0,41 mmol) gota a gota. La solución resultante se agitó a reflujo durante 16h, se enfrió a ta, y se concentró bajo presión reducida.. El material bruto se purificó mediante cromatografía preparativa de capa delgada (8 x 1000 µM) eluyendo con CH_2Cl_2/MeOH (25:1) para dar 148 mg (89%) de un aceite amarillo. M+H = 489.

PASO B: Remoción del grupo protector de t-butoxicarbonilo con TFA

A una solución del compuesto preparado en el Ejemplo 340, Paso A (135 mg, 0,28 mmol) en CH_2Cl_2 (2 ml) a temperatura ambiente se agregó TFA (0,54 ml, 7,0 mmol) gota a gota. La solución resultante se agitó durante 18 h a temperatura ambiente y se concentró bajo presión reducida. El material bruto se disolvió en CH_2Cl_2 (5 ml) y la capa orgánica se lavó secuencialmente con $NaHCO_3$ acuoso sat. (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 bruto se purificó mediante cromatografía preparativa de capa delgada (8 x 1000 µM) eluyendo con CH_2Cl_2/MeOH (20:1) para dar 105 mg (97%) de sólido blanco. mp 120-122 °C; M+H = 389.

EJEMPLO 341:

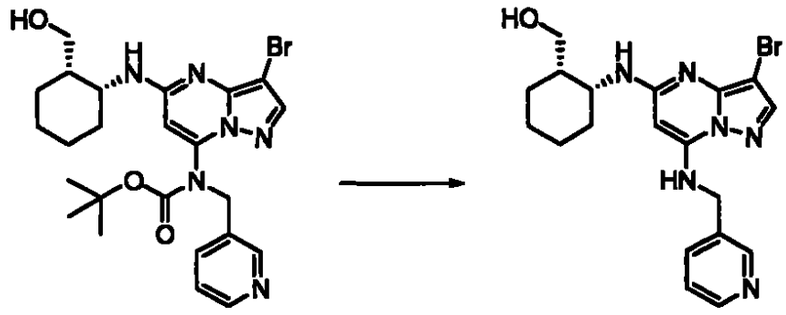


Paso A:

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Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 340, sustituyendo solamente la amina apropiada, se preparó el compuesto anterior. MS: MH^+= 431.

Paso B: remoción del grupo protector del t-butoxicarbonilo con KOH.



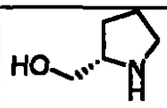
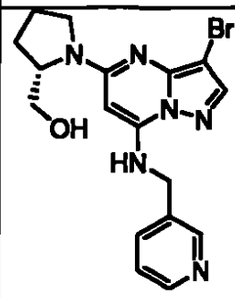
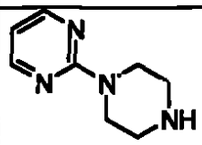
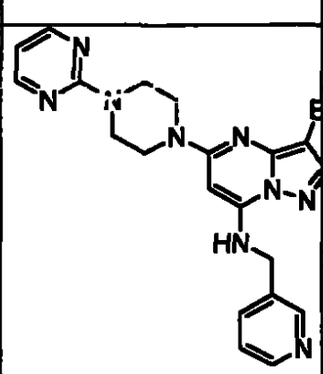
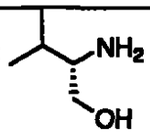
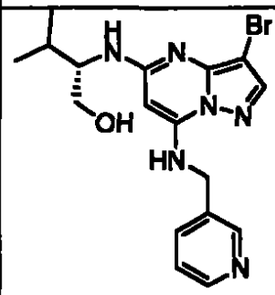
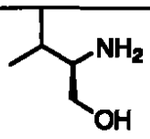
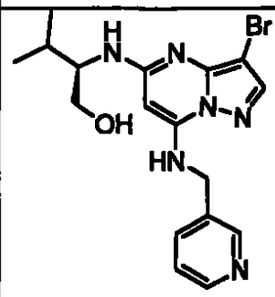
A una mezcla del compuesto preparado en el Ejemplo 341, Paso A (0,14 g, 0,26 mmol) en EtOH : H_2O (3 ml, 2 : 1) se agregó KOH (0,29 g, 20 eq.) en una porción. La solución resultante se agitó a reflujo 14 horas, se enfrió hasta temperatura ambiente, y se concentró bajo presión reducida. El residuo se capturó 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 bruto se purificó mediante TLC preparativa (8 x 1000 µM) eluyendo con solución de MeOH 5% en CH_2Cl_2 (0,066 g, 59% de rendimiento). MS: MH^+ = 432; mp = 219-221°C.

EJEMPLOS 342-397:

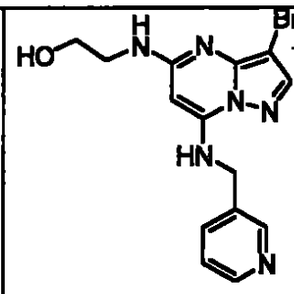
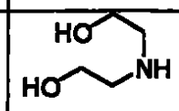
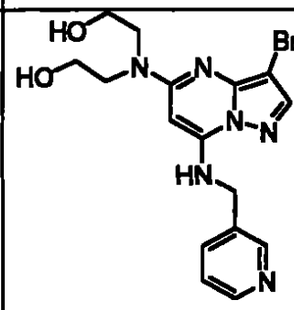
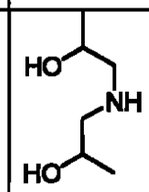
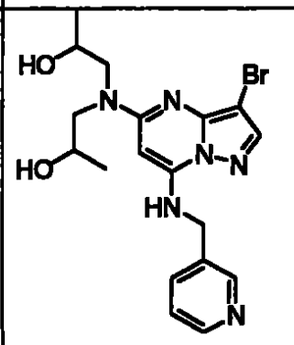
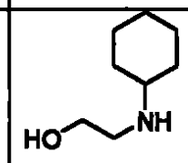
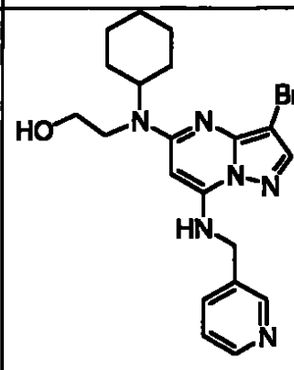
Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 340, sustituyendo solamente los cloruros en la Columna 2 de la Tabla 31 y removiendo el grupo protector del t-butoxicarbonilo mediante el método que se muestra en la Columna 3 de la Tabla 31, se prepararon los compuestos que se muestran en la Columna 4 de la Tabla 31.

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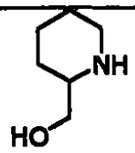
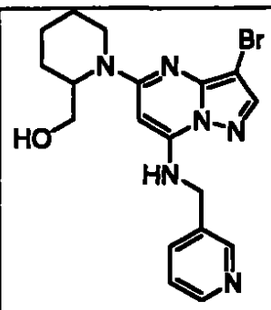
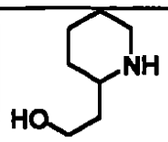
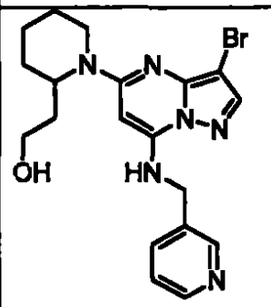
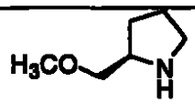
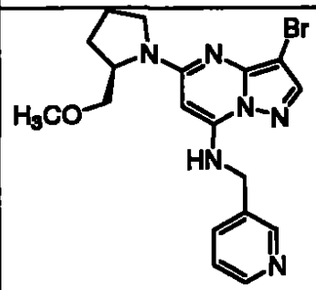
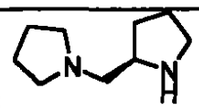
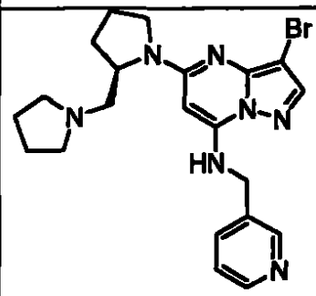
Tabla 31

Ej.	Columna 2	Columna 3	Columna 4	COMPUESTO
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

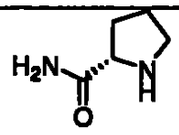
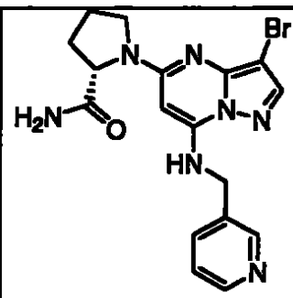
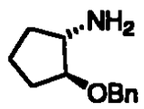
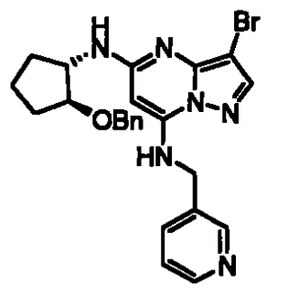
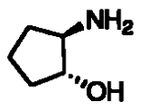
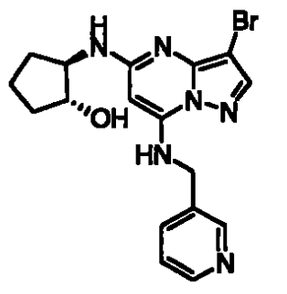
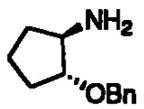
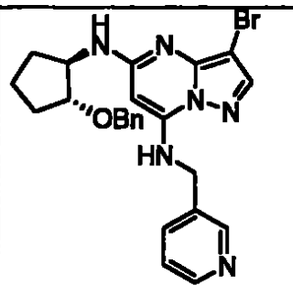
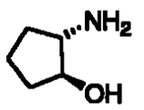
565

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

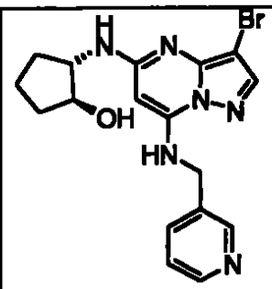
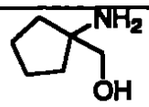
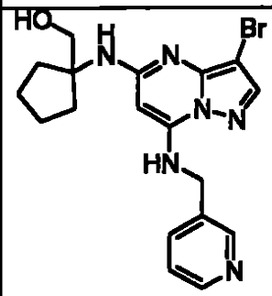
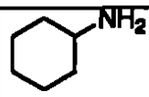
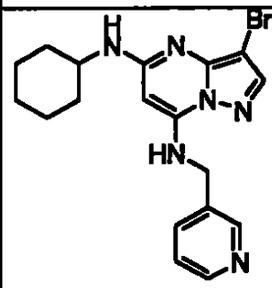
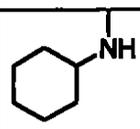
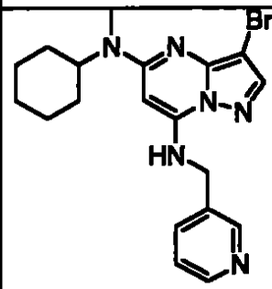
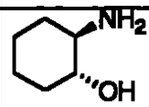
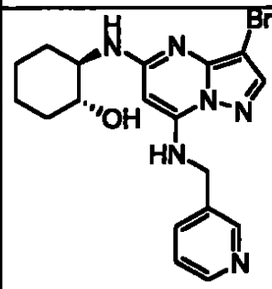
566

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

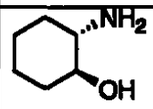
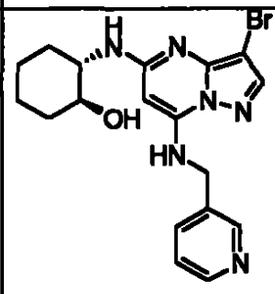
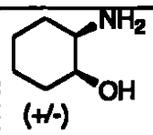
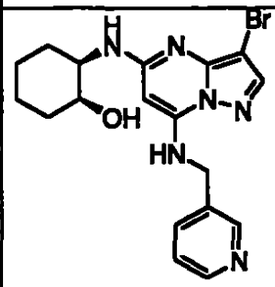
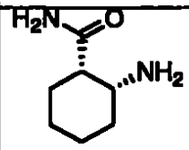
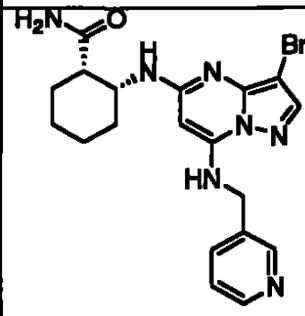
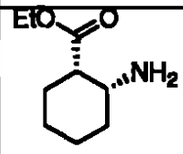
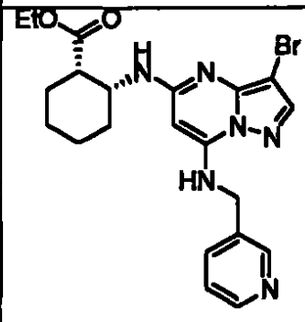
567 568

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

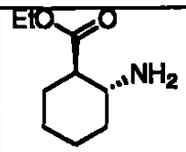
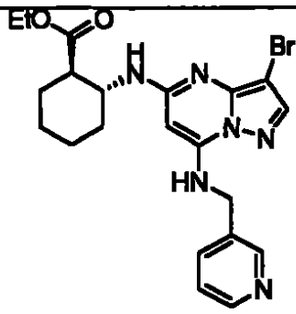
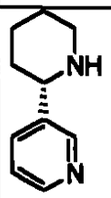
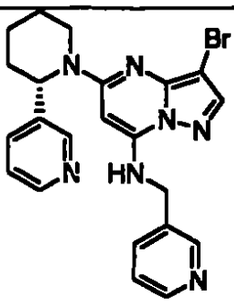
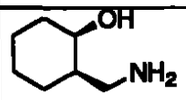
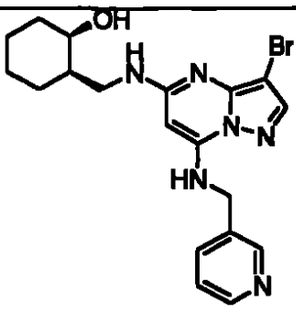
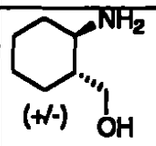
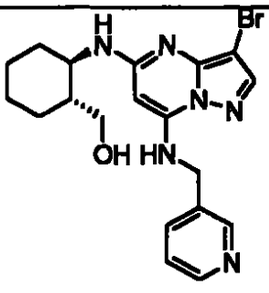
568

				
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

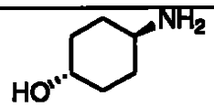
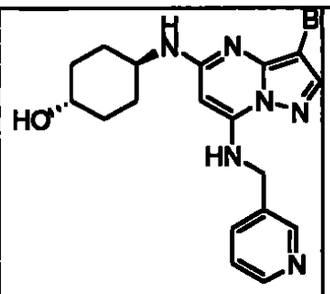
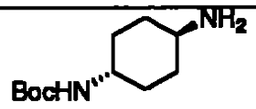
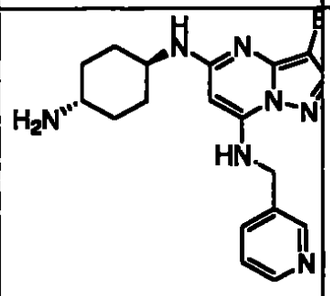
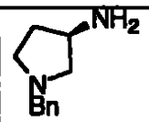
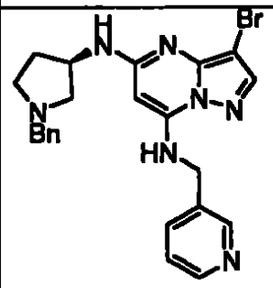
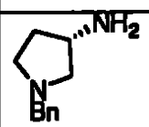
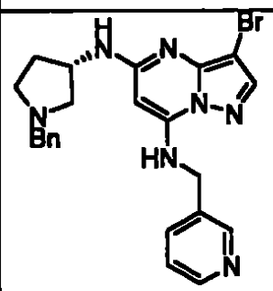
569

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

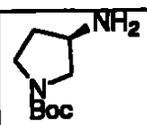
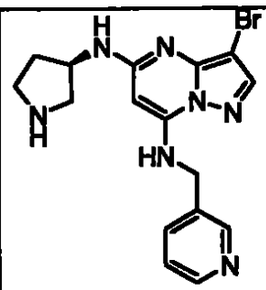
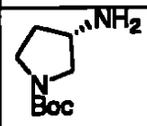
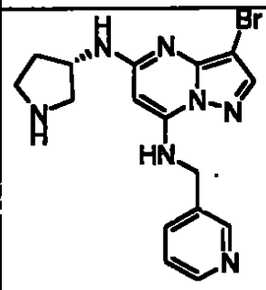
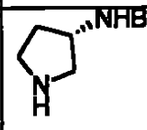
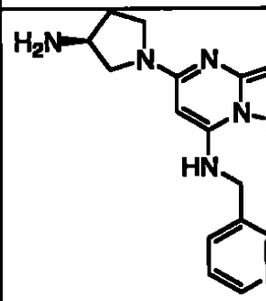
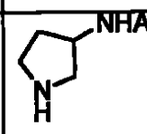
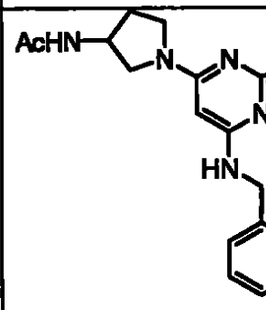
570

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

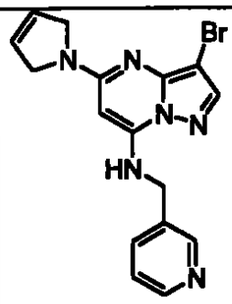
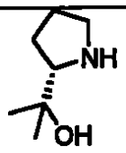
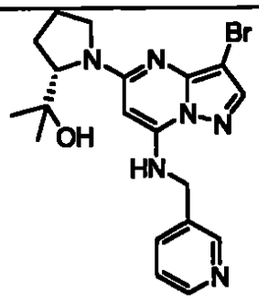
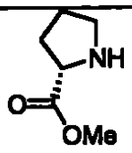
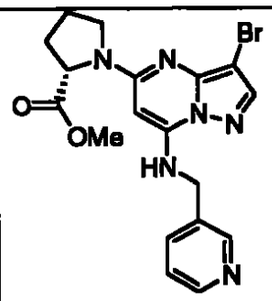
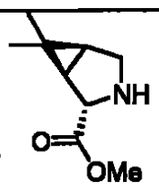
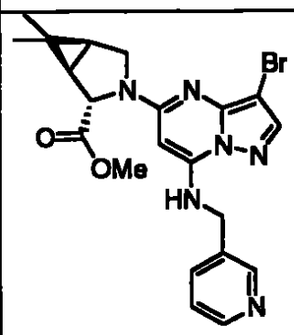
571

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

592 593

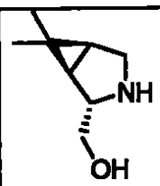
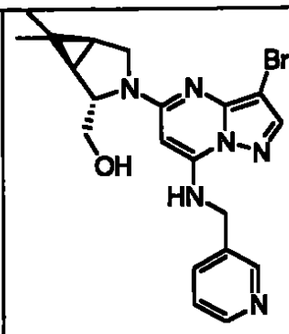
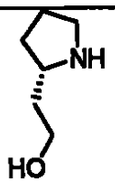
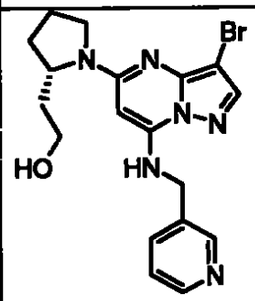
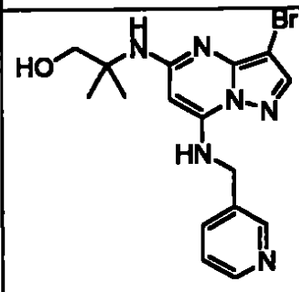
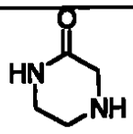
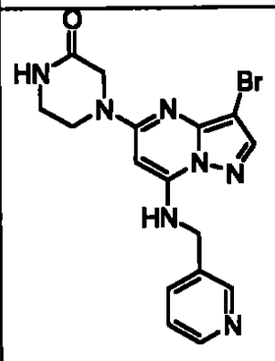
376		TFA		1. mp = 105-107 2, M+H = 389
377		TFA		1. mp = 105-107 2, M+H = 389
378		TFA		1. mp = 130-133 2, M+H = 389
379		TFA		1. mp = 132-135 2, M+H = 431

573

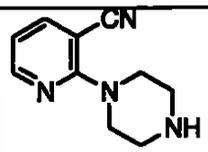
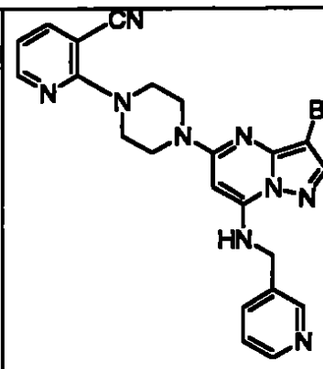
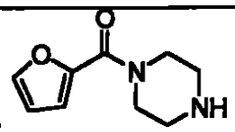
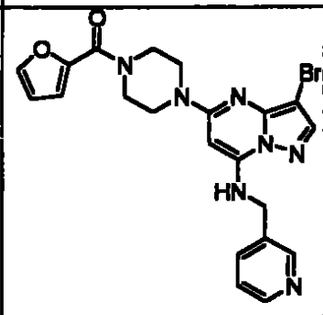
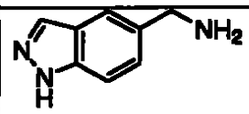
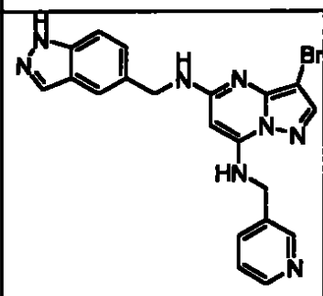
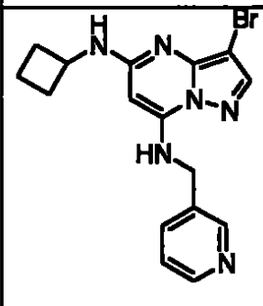
380		TFA		1. mp = 135-137 2, M+H = 372
381		KOH		1. mp =.78-82 2, M+H = 432
382		TFA		1. mp = 101-103 2, M+H = 432
383		TFA		1. mp = 92-95 2, M+H = 472

574

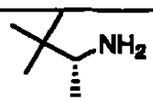
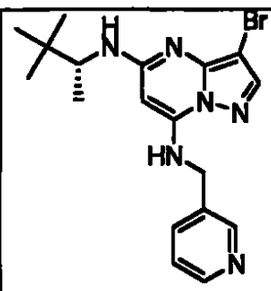
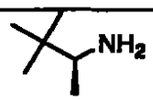
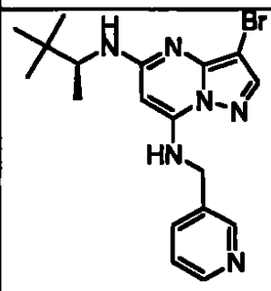
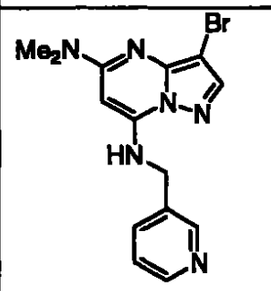
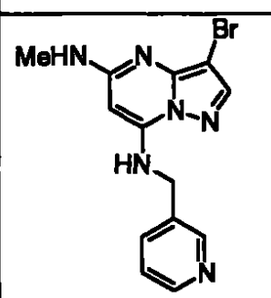
575

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

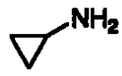
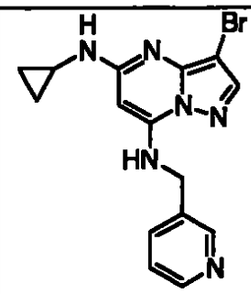
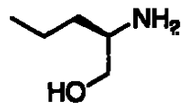
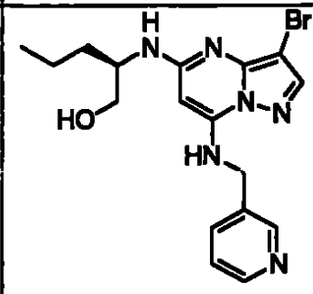
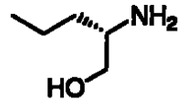
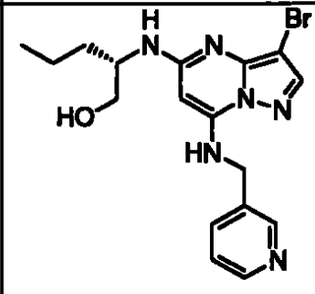
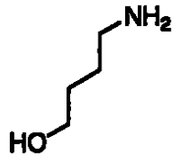
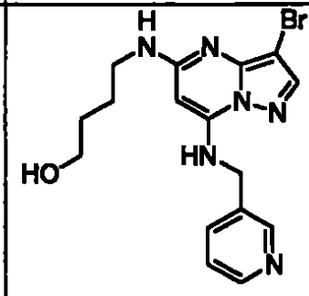
575

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

576

390		TFA		1. mp = 113-115 2. M+H = 404
391		TFA		1. mp = 114-116 2. M+H = 404
392	$HNMe_2$	TFA		LCMS: MH^+ = 347;
393	H_2NMe	TFA		LCMS: MH^+ = 333;

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

Datos adicionales para ejemplos selectos que se muestran a cotninuación:

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).

578

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).

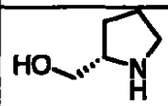
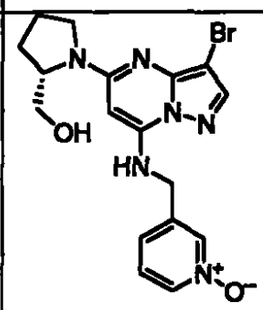
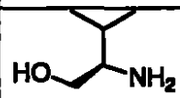
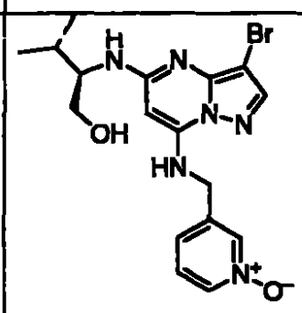
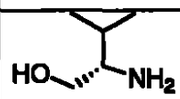
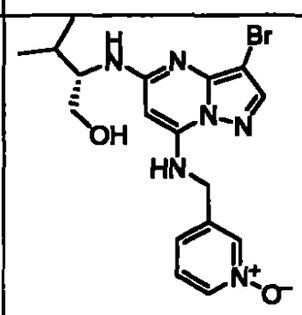
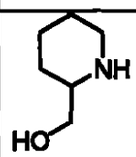
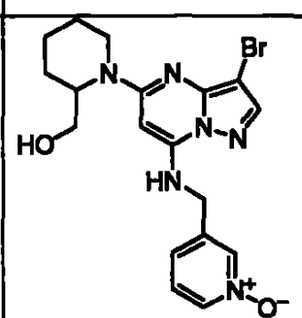
Ejemplo 397: ^{1}H RMN ($CDCl_3$) δ 8,65 (s, 1H), 8,59 (d, J = 4,5 Hz, 1H), 7,75 (s, 1H), 7,69 (m, 1H), 7,31 (m, 1H), 6,43 (t, J = 6,0 Hz, 1H), 5,06 (s, 1H), 4,88 (m, 1H), 4,55 (d, J = 6,0 Hz, 2H), 3,70 (m, 2H), 3,38 (m, 2H), 1,79-1,61 (m, 4H).

EJEMPLOS 398-416:

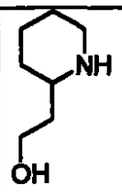
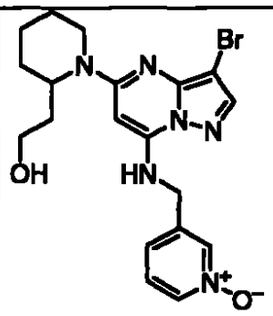
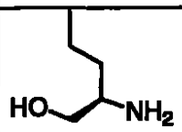
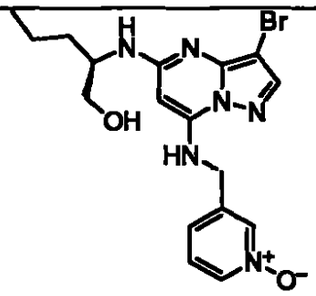
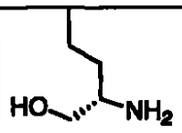
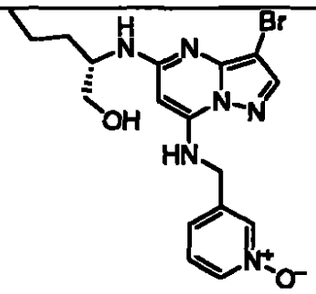
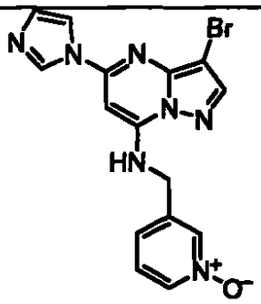
Esencialmente mediante las mismas condiciones expuestas en el Ejemplo 341, Pasos A y B sustituyendo solamente el compuesto preparado en el Ejemplo Preparativo 193,10, se prepararon los compuestos en la columna 4 de la Tabla 32.

579 580

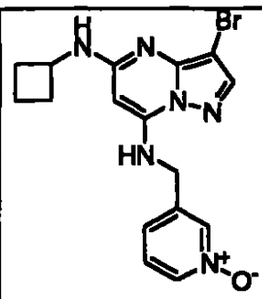
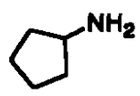
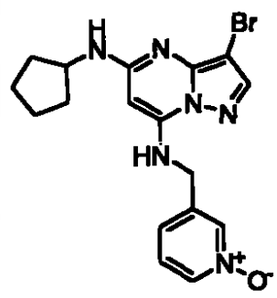
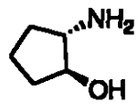
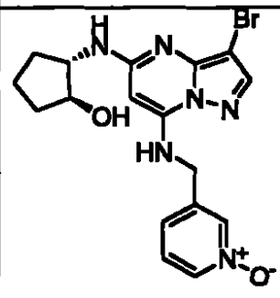
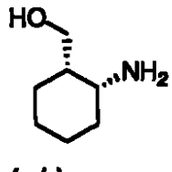
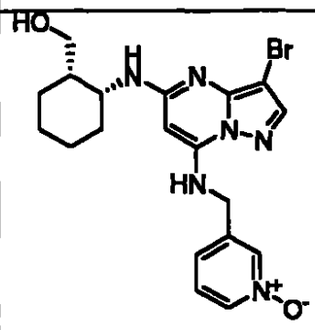
Tabla 32

Ej.	Columna 2	Columna 3	Columna 4	COMPUESTO
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

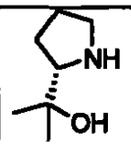
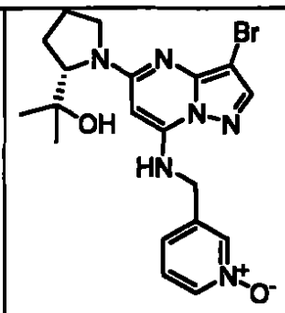
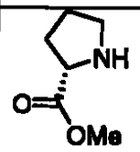
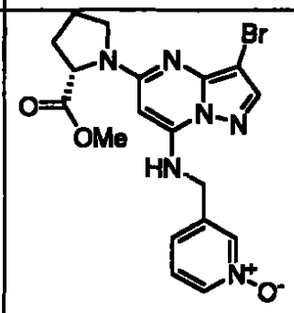
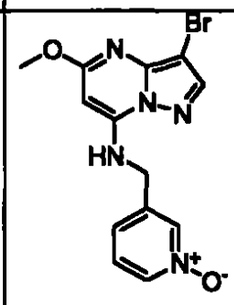
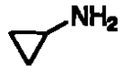
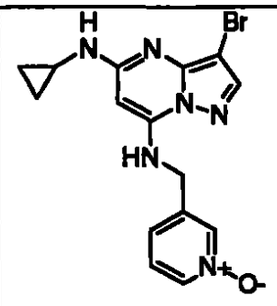
580

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

581

407		KOH		1. mp = 98-100 2. M+H = 390
408		TFA		1. mp = 170-173 2, M+H = 404
409		KOH		1. mp = 219-221 2, M+H = 420
410	 (+/-)	KOH		1. mp = 110-112 2, M+H = 448

582

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;

Datos adicionales para ejemplos selectos que se muestran a continuación:

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).

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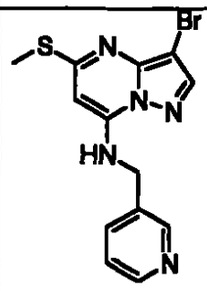
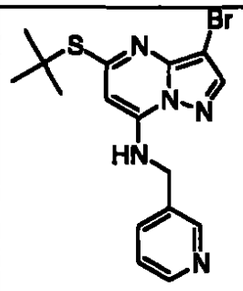
Ejemplo 403: ^{1}H RMN (DMSO-d_6+$CDCl_3$) δ 8,08 (s, 1H), 7,90 (d, J = 6,3 Hz, 1H), 7,49 (s, 1H), 7,34 (t, J = 6,3 Hz, 1H), 7,16-7,09 (m, 2H), 5,65 (d, J = 6,6 Hz, 1H), 4,97 (s, 1H), 4,90 (s, 1H), 4,29 (d, J = 6,3 Hz, 2H), 3,70 (m, 1H), 3,46 (m, 1H), 3,34 (m, 1H), 1,35-1,17 (m, 4H), 0,71 (t, J = 7,2 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).

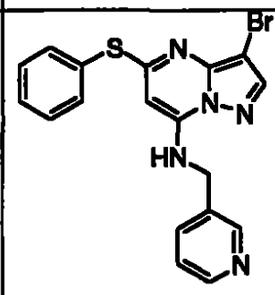
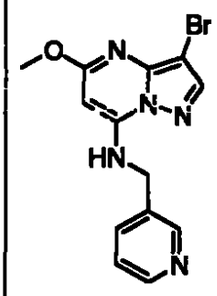
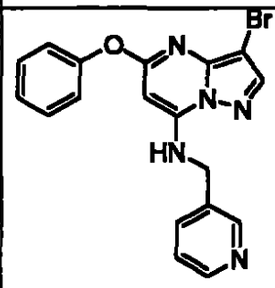
EJEMPLOS 417—421:

Mediante el procedimiento expuesto en *Chem. Pharm. Bull.* 1999, *47*, 928-938, usando los nucleófilos de oxígeno o azufre que se muestran en la Columna 2 según se describe en la Tabla 33 y por medio del uso del método de escisión enumerado en la Columna 3 de la Tabla 33, se prepararon los compuestos en la columna 4 de la Tabla 33:

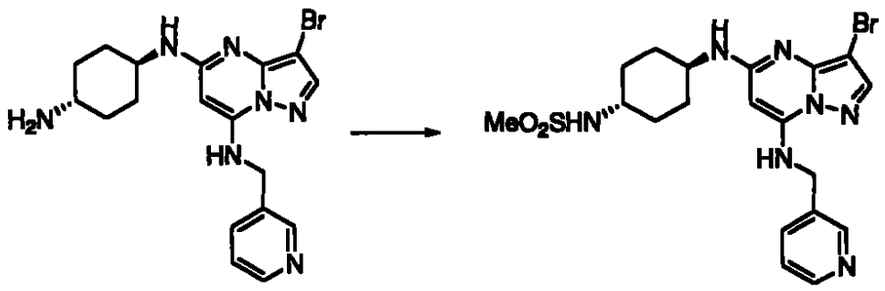
TABLA 33

Ej.	Columna 2 (Nucleófilo)	Columna 3 (Método de escisión)	Columna 4 (Estructura final)	COMPUESTO 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

584 585

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

EJEMPLO 422:



A una solución de amino compuesto (18 mg, 0,043 mmol) del Ejemplo 373 en CH_2Cl_2 (1 ml) a temperatura ambiente se agregó DIPEA (10 µL, 0,056 mmol) seguido por $MeSO_2Cl$ (4 ml, 0,052 mmol). La mezcla se agitó a temperatura

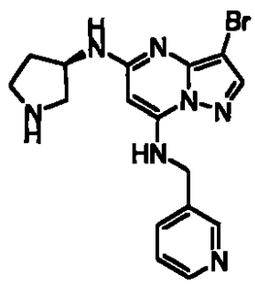
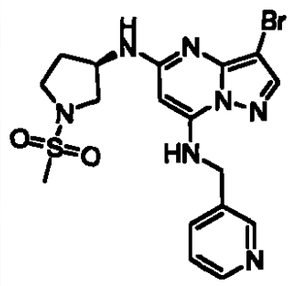
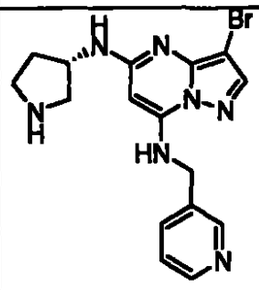
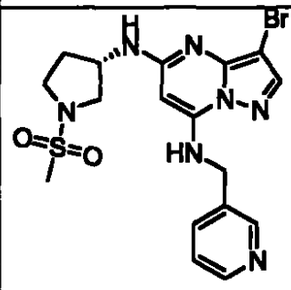
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ambiente durante 12 h y se diluyó con CH_2Cl_2 (2 ml) y $NaHCO_3$ acuoso sat. (2 ml). Las capas se separaron y la capa orgánica se extrajo con salmuera (1 x 2 ml). La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida. El material bruto se purificó mediante cromatografía preparativa de capa delgada (4 x 1000 µM) eluyendo con CH_2Cl_2/MeOH (20:1) para dar 16 mg (75%) de sólido blanco. mp 152-154 °C; M+H = 495.

EJEMPLOS 423-424:

Mediante el uso del procedimiento descripto en el Ejemplo 422, los amino compuestos (Columna 2) se transformaron en las metilsulfonamidas correspondientes (Columna 3) en la Tabla 34.

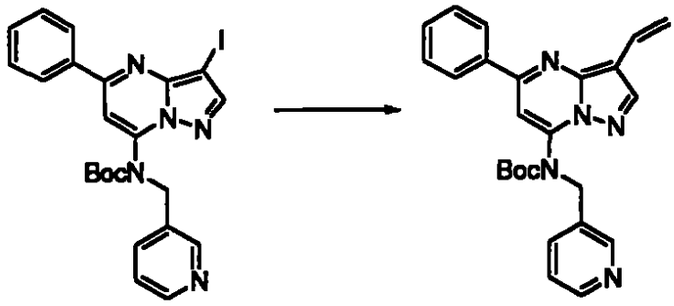
TABLA 34

Ej.	Columna 2 (Amina)	Columna 3 (Estructura final)	COMPUESTO 1. mp. 2, M+H
423			1. mp = 166-168 2, M+H = 467
424			1. mp = 165-168 2. M+H = 467

EJEMPLO 425:

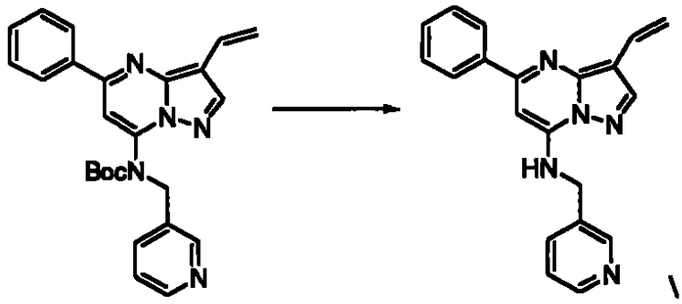
PASO A:

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Una mezcla del compuesto preparado en el Ejemplo preparativo 194 (132 mg, 0,25 mmol), tributilviniltina (95 mg, 0,30 mmol) y tetrakis(trifenilfosfina) paladio (29 mg, 0,025 mmol) en dioxano anhídrido (5 ml) se reflujó bajo N_2 durante 24 hr. El solvente se evaporó y el residuo se purificó mediante cromatografía flash usando 2:1 CH_2Cl_2:EtOAc como eluyente para dar un sólido ceroso amarillo (53 mg, 50%). LCMS: MH^+=428.

PASO B:

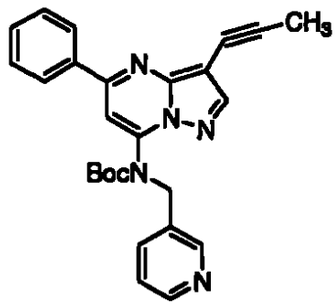


Una mezcla del compuesto preparado en el Ejemplo 425, Paso A (50 mg, 0,12 mmol) y KOH (100 mg, 1,80 mmol) en etanol (3 ml) y H_2O (0,6 ml) se agitó a 70°C bajo N_2 for 24 hr. Se agregaron $NaHCO_3$ (1,0 g), Na_2SO_4 (2,0g), y CH_2Cl_2 (20 ml), la mezcla se agitó y luego se filtró. El solvente se evaporó y el residuo se purificó mediante cromatografía flash usando 20:1:0,1 CH_2Cl_2:MeOH:conc.NH_4OH como eluyente para dar sòlido ceroso amarillo (17 mg, 45%). LCMS: MH^+=328. Mp=48-51 °C.

EJEMPLO 426:

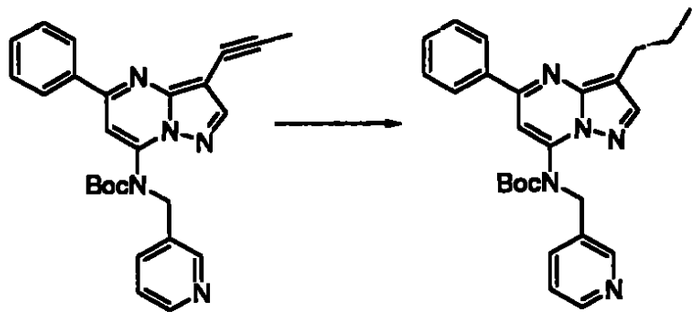
PASO A:

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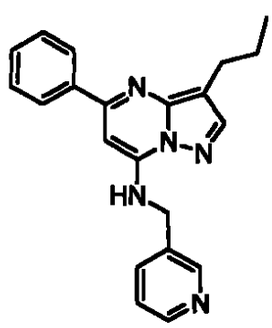
Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 425, Paso A, usando solamente tributilmetiletiniltina, se preparó el compuesto que se mostró anteriormente.

PASO B:



Se agitó una mezcla del compuesto preparado en el Ejemplo 426, Paso A (150 mg, 0,34 mmol) y PtO2 (30 mg, 0,13 mmol) en ácido acético glacial (5 ml) bajo 1 atmósfera de H_2 durante 20 hr. La mezcla se filtró, se agregó PtO2 fresco (30 mg, 0,13 mmol) y la mezcla se agitó bajo 1 atmósfera de H_2 durante 2,5 hr. La mezcla se vertió en Na_2CO_3 (20 g) y H_2O (200 ml) y esta se extrajo con CH_2Cl_2 (4x20 ml). Los extractos combinados se secaron sobre Na_2SO_4 y se filtró. El solvente se evaporó y el residuo se purificó mediante cromatografía flash usando 1:1 CH_2Cl_2:EtOAc como eluyente para dar sólido ceroso amarillo (68 mg, 45%).

PASO C:

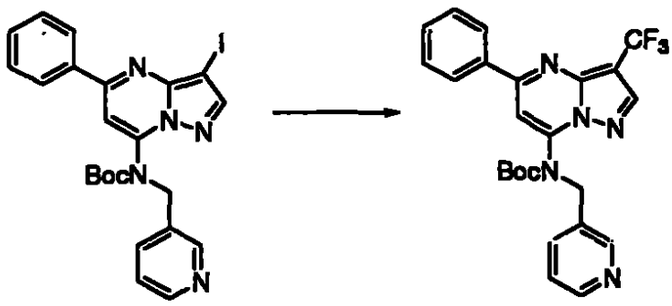


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Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 425, Paso B, sustituyendo solamente el compuesto preparado en el Ejemplo 426, Paso B, se preparó el compuesto que se mostró anteriormente, MS: MH^+=344, Mp=110-112 °C.

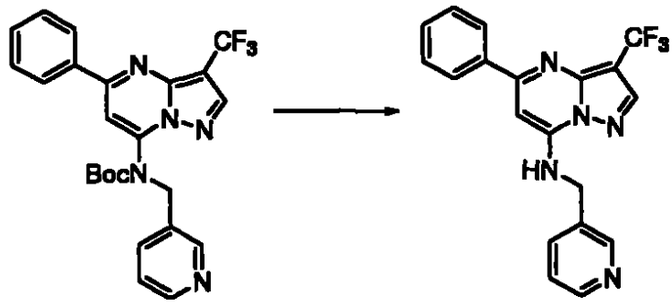
EJEMPLO 427:

PASO A:



Se agitó una mezcla del compuesto preparado en el Ejemplo preparativo 194 (527 mg, 1,00 mmol), trietil(trifluorometil)silano (666 mg, 3,60 mmol), fluoruro de potasio (210 mg, 3,60 mmol), y CuI (850 mg, 4,46 mmol) en DMF anhídrido (4 ml) en un recipiente a presión cerrado a 80°C durante 72 hr. Se agregó CH2Cl2 (80 ml) y la mezcla se filtró a través de Celite. El solvente se evaporó y el residuo se purificó mediante cromatografía flash usando 2:1 CH_2Cl_2: EtOAc como eluyente para dar sólido ceroso naranja pálido (70 mg, 15%). LCMS: M^+=470.

PASO B:



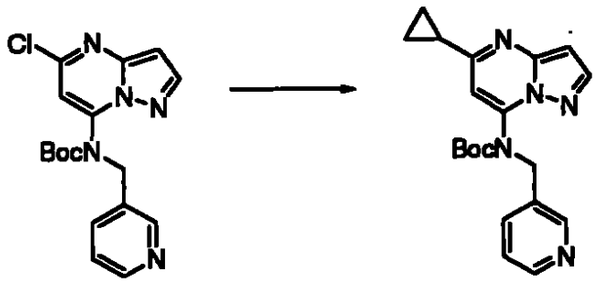
Se agregó TFA (0,70 ml) a 0°C bajo N_2 a una solución agitada del compuesto preparado en el Ejemplo 427, Paso A (70 mg, 0,15 mmol), en CH_2Cl_2 anhídrido (3 ml). La mezcla se agitó a 0°C durante 10 min, luego a 25°C durante 2 hr. Esta se vertió en Na_2CO_3 acuoso 10 % (50 ml), se extrajo con CH_2Cl_2 (3x15 ml), se secó sobre Na_2SO_4, y se filtró. El solvente se evaporó y el residuo se

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purificó mediante cromatografía flash usando EtOAc como eluyente para dar sólido blancuzco (40 mg, 73%). LCMS: M^+=370, Mp=156-158°C.

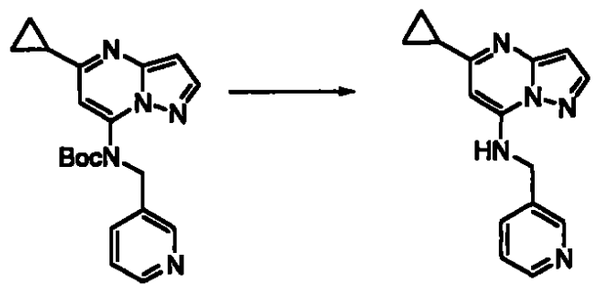
EJEMPLO 428:

PASO A:



Una mezcla del compuesto preparado en el Ejemplo preparativo 193 (100 mg, 0,28 mmol), tetraciclopropiltin (91 mg, 0,32 mmol), Pd_2dba_3 (8,0 mg, 0,009 mmol) y $Pd(Pt\text{-}Bu_3)_2$ (9,0 mg, 0,017 mmol) en dioxano anhídrido (3 ml) s reflujó bajo N_2 durante 27 hr. El solvente se evaporó y el residuo se purificó mediante cromatografía flash usando 1:1 CH_2Cl_2:EtOAc como eluyente para dar sólido ceroso incoloro (38 mg, 38%). LCMS: MH^+=366.

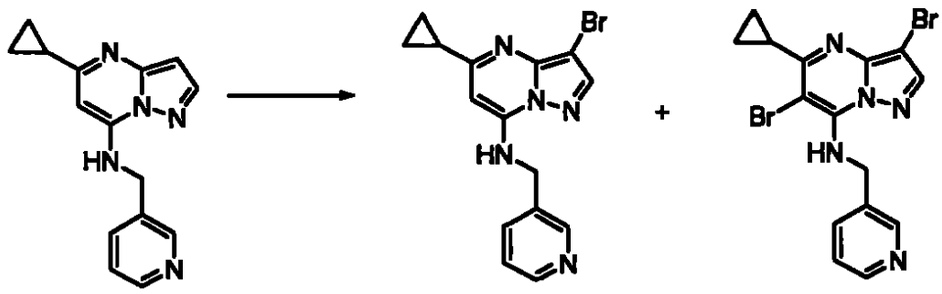
PASO B:



Se reflujó una mezcla del compuesto preparado en el Ejemplo 428, Paso A (36 mg, 0,10 mmol) y KOH (300 mg, 5,40 mmol) en etanol (3 ml), 1,2-dimetoxietano (3,0 ml0 y H_2O (0,8 ml) bajo N_2 durante 4 hr. Esta 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 mediante cromatografía flash usando 30:1 EtOAc:MeOH como eluyente para dar cera incolora (18 mg, 69%). LCMS: MH^+=266.

PASO C:

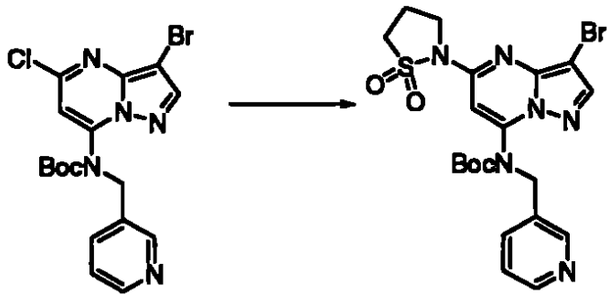
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Se agregó N-bromosuccinimida (12 mg, 0,068 mmol) en anhídrido CH_3CN (2 ml) bajo N_2 a una solución agitada del compuesto preparado en el Ejemplo 428, Paso B (18 mg, 0,068 mmol), en anhídrido CH_3CN (2 ml). La mezcla se agitó a 25°C durante 2 hr. El solvente se evaporó y el residuo se purificó mediante cromatografía flash usando EtOAc como eluyente para dar 5 mg (17%) del compuesto de dibromo (sólido blanco, LCMS: MH^+=370, mp= 150-152°C) y 8 mg (34%) del compuesto de monobromo (sólido incoloro, LCMS: M^+=344, mp= 196-198°C).

EJEMPLO 429:

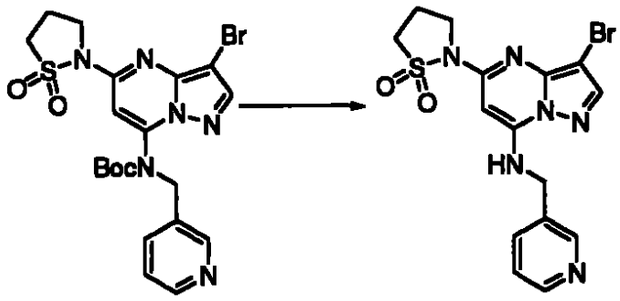
PASO A:



Se agregó 1,3-propansultama (72 mg, 0,60 mmol) en DMF anhídrido (3 ml) bajo N_2 para NaH 60 % en aceite mineral (36 mg, 0,90 mmol). La mezcla se agitó durante 20 min, luego el compuesto preparado en el Ejemplo preparativo 196 (200 mg, 0,46 mmol) se agregó. La mezcla se agitó a 100°C durante 30 min, el solvente se evaporó y el residuo se purificó mediante cromatografía flash usando EtOAc como eluyente para dar sólido incoloro (150 mg, 63%). LCMS: M^+=523.

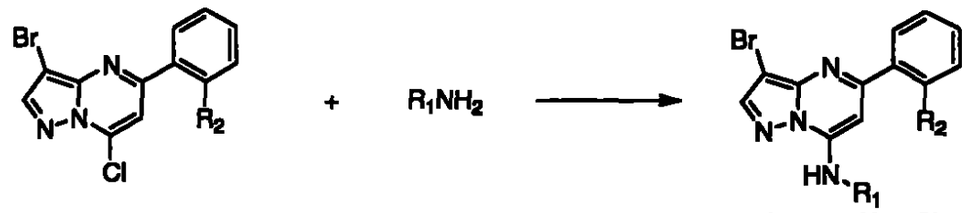
PASO B:

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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 mmol), en CH_2Cl_2 anhídrido (5 ml). La mezcla se agitó a 0°C durante 10 min, luego a 25°C durante 2 hr. Ésta se vertió en 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 mediante cromatografía flash usando 40:1 EtOAc:MeOH como eluyente para dar sólido blanco (32 mg, 28%). LCMS: M^+=423. Mp=218-220°C.

EJEMPLO 430:



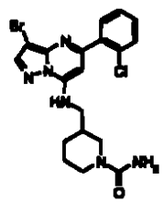
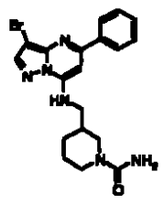
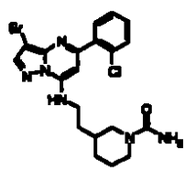
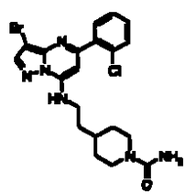
Donde: R_2 = H, o Cl

Se disolvieron 3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (1 equivalente) (preparada según se describió en el Ejemplo Preparativo 129), o 3-Bromo-7-cloro-5-fenilpirazolo[1,5-a]pirimidina (1 equivalente) (preparada según se describió en el Ejemplo Preparativo 127), R_1NH_2 (1,2 equivalentes) y diisopropil etilamina (2 equivalentes) en 1,4-dioxano anhídrido y la mezcla se calentó a 75°C durante el tiempo establecido en la Tabla 97. La solución se evaporó hasta que se secó y el residuo se sometió a cromatografía sobre una columna de gel de sílice según se describió en la Tabla 97, para dar el compuesto de título.

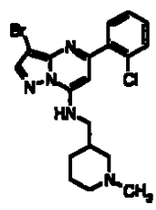
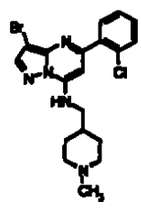
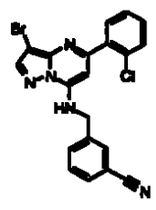
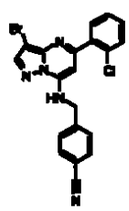
Usando los reactivos apropiados y esencialmente el mismo procedimiento según se describió anteriormente, se prepararon los productos de los Ejemplos 431 a 438. Las variaciones en las condiciones de la reacción se enuncian en la Tabla 35.

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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 conc. en metanol)-diclorometano
432		429,3	429,2	75°C / 26h 25°C / 39h	53%	15x5cm Diclorometano; 1,5% (10% Hidróxido de amonio conc. en metanol)-diclorometano
433		477,8	477,1	75°C / 26h	48%	15x5cm Diclorometano; 3,5-15% (10% Hidróxido de amonio conc. en metanol)-diclorometano
434		477,8	477,0	75°C / 26h	50%	15x5cm Diclorometano; 3,5-15% (10% Hidróxido de amonio conc. en metanol)-diclorometano

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435		434,8	434,1	75°C / 24h 25°C / 65h	53%	15x2,5cm 3% (10% Hidróxido de amonio conc. en metanol)-diclorometano
436		434,8	434,2	75°C / 27h	31%	15x2,5cm 3% (10% Hidróxido de amonio conc. en metanol)-diclorometano
437		438,7	438,1	75°C / 21h 25°C / 46h	97%	15x2,5cm 0,25% (10% Hidróxido de amonio conc. en metanol)-diclorometano
438		438,7	438,1	75°C / 28h -20°C / 72h	95%	60x2,5cm 20% Acetato de etilo in hexano

A continuación se proveen datos físicos adicionales para los compuestos:

EJEMPLO 431: Reactivos: 3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (110mg, 0,318mmoles) (preparado según se describió en el Ejemplo Preparativo 129); 3-(aminometil)piperidin-1-carboxamida (60mg, 0,382mmoles) (preparado según se describió en el Ejemplo Preparativo 241 anterior); diisopropil etilamina (0,111ml, 0,636mmoles); 1,4-dioxano anhídrido (2,5ml). Propiedades

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físicas: HRFABMS: m/z 463,0628 (MH^+). Calculado 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 (500mg, 1,62mmoles) (preparado según se describió en el Ejemplo Preparativo 127); 3-(aminometil)piperidin-1-carboxamida (306mg, 1,944mmoles) (preparado según se describió en el Ejemplo Preparativo 241 anterior); diisopropil etilamina (0,566ml, 3,24mmoles); 1,4-dioxano anhídrido (13ml). Propiedades físicas: HRFABMS: m/z 429,1031 (MH^+). Calculado 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 (347mg, 1,01mmoles) (preparado según se describió en el Ejemplo Preparativo 129); 3-(aminoetil)piperidin-1-carboxamida (208mg, 1,21mmoles) (preparado según se describió en el Ejemplo Preparativo 242 anterior); diisopropil etilamina (0,393ml, 2,02mmoles); 1,4-dioxano anhídrido (9ml). 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.

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EJEMPLO 434: Reactivos: 3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (275mg, 0,803mmoles) (preparado según se describió en el Ejemplo Preparativo 129); 4-(aminoetil)piperidin-1-carboxamida (165mg, 0,963mmoles) (preparado según se describió en el Ejemplo Preparativo 243 anterior); diisopropil etilamina (0,311ml, 0,963mmoles); 1,4-dioxano anhídrido (7,2ml). 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 (174mg, 0,507mmoles) (preparado según se describió en el Ejemplo Preparativo 129) y 3-(aminometil)-1-metilpiperidina (65mg, 0,507mmoles) (preparado según se describió en el Ejemplo Preparativo 244 anterior); diisopropil etilamina (0,178ml, 1,014mmoles); 1,4-dioxano anhídrido (2,5ml). Propiedades físicas: HRFABMS: m/z 434,0742 (MH^+). Calculado para $C_{18}H_{22}N_6BrCl$: 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 (111,4mg, 0,325mmoles) (preparado según se describió en el Ejemplo Preparativo 129); 4-(aminometil)-1-metilpiperidina (50mg, 0,39mmoles) (preparado según se describió en el Ejemplo Preparativo 245 anterior); diisopropil etilamina (0,1135ml, 0,65mmoles); 1,4-dioxano anhídrido (1,5ml). Datos físicos: HRFABMS: m/z 434,0735 (MH^+). Calculado para $C_{18}H_{22}N_6BrCl$: 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-

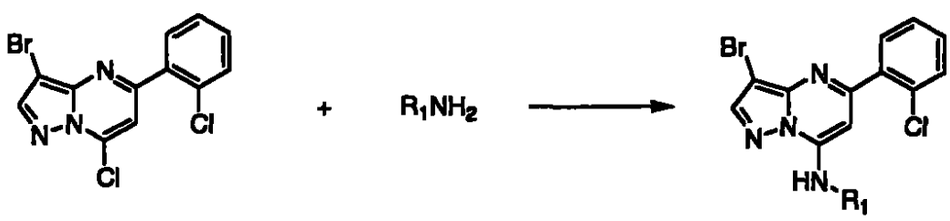
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H) y 8,00 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 46,4; CH_2: 30,2, 30,2, 48,0, 55,3, 55,3; CH: 35,4, 87,5, 127,2, 130,2, 130,2, 131,6, 143,8; C: 83,3, 132,2, 138,9, 145,7, 146,4, 158,1.

EJEMPLO 437: Reactivos: 3-Bromo-7-cloro-5-fenilpirazolo[1,5-a]pirimidina (191mg, 0,557mmoles) (preparado según se describió en el Ejemplo Preparativo 129); 3-(aminometil)benzonitrilo (88,3mg, 0,668mmoles) (preparado según se describió en el Ejemplo Preparativo 246 anterior); diisopropil etilamina (0,192ml, 1,114mmoles); 1,4-dioxano anhídrido (4,5ml). Datos físicos: HRFABMS: m/z 438,0125 (MH^+). Calculado para $C_{19}H_{12}N_5BrCl$: 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) 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 (233,5mg, 0,681mmoles) (preparado según se describió en el Ejemplo Preparativo 129); 4-(aminometil)benzonitrilo (108mg, 0,817mmoles) (preparado según se describió en el Ejemplo Preparativo 247 anterior); diisopropil etilamina (0,235ml, 1,362mmoles); 1,4-dioxano anhídrido (5,3ml). Datos físicos: HRFABMS: m/z 438,0117 (MH^+) Calculado 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:

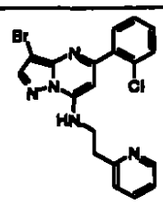
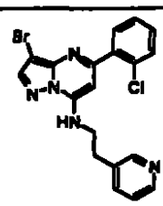


Se disolvió 3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (50mg, 0,146mmoles) (preparado según se describió en el Ejemplo Preparativo 129) en

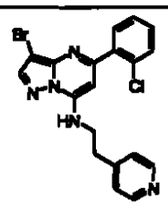
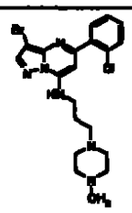
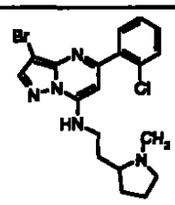
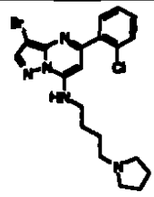
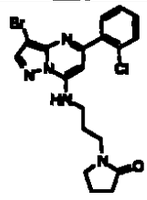
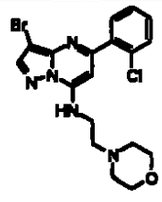
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1,4-dioxano anhídrido (5mlen un tubo de reacción en carrusel GeneVac Technologies. Se agregó resina de PS-diisopropil etilamina (161mg, 0,5828mmoles) a cada tubo. Se agregó una solución 1M preparada recientemente de la amina R_1NH_2 apropiada en 1,4-dioxano anhídrido (0,2185ml, 0,2185mmoles) a cada tubo y los tubos se sellaron y se calentaron a 70°C durante 78h con agitación magnética en el bloque de reacción. Cada tubo se filtró y la resina se lavó con 1,4-dioxano anhídrido y luego con diclorometano. Los filtrados individuales combinados de cada tubo se evaporaron hasta que se secaron y cada uno de los residuos se re- disolvió en 1,4-dioxano anhídrido (5ml) y se colocó en tubos de reacción GeneVac. A cada tubo se agregó resina de PS-isocianato (594mg, 0,8742mmoles) y resina de PS-trisamina (129mg, 0,4371mmoles) y los tubos se agitaron a 25°C durante 20h en el bloque de reacción. Las resinas se filtraron y se lavaron con 1,4-dioxano anhídrido y diclorometano. El filtrados de cada tubo se evaporaron hasta que se secaron y cada uno de los residuos se sometió a cromatografía en columna de gel de sílice usando el tamaño de columna y el eluyente que se muestra en la Tabla 36, para dar el compuesto de títulos.

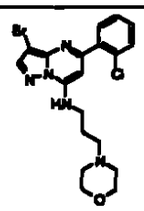
TABLA 36

Ej.	Estructura	MW	FABMS MH^+	Rendimiento	Datos cromatográficos
440		428,7	428,0	81%	15x2,5cm Diclorometano; 0,5% Metanol en diclorometano
441		428,7	428,0	48%	20x2cm Diclorometano; 1,5% Metanol en diclorometano

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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% Metanol en diclorometano
447		436,7	436,1	72%	15x2,5cm 0,5% Metanol en diclorometano

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448		450,8	450,0	53%	20x2cm Diclorometano; 0,5% Metanol en diclorometano
449		381,7	381,0	44%	20x2cm 1,5% Metanol en diclorometano

A continuación se proveen datos físicos adicionales para los compuestos:

EJEMPLO 440: Propiedades físicas: HRFABMS: m/z 428,0272 (MH^+). Calculado para $C_{19}H_{18}N_5BrCl$: 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^+). Calculado para $C_{19}H_{18}N_5BrCl$: 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^+). Calculado para $C_{19}H_{18}N_5BrCl$: 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,

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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^+). Calculado para $C_{20}H_{25}N_8BrCl$: 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, piperazina 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^+). Calculado 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^+). Calculado 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^+). Calculado 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^+). Calculado para $C_{18}H_{20}N_5OBrCl$: m/z 436,0540; δ_H ($CDCl_3$) 2,60 (4H, bm, $-N(C\underline{H}_2CH_2)_2O$),

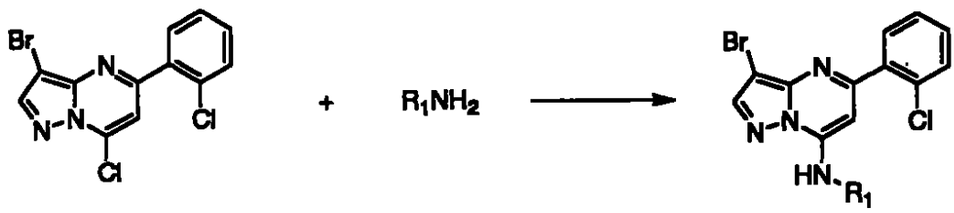
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2,83 (2H, m, =NC<u>H</u>$_2$CH$_2$NH-), 3,57 (2H, m, =NCH$_2$C<u>H</u>$_2$NH-), 3,83 (4H, m, -N(CH$_2$C<u>H</u>$_2$)$_2$O), 6,37 (1H, s, H$_6$), 6,99 (1H, bm, NH), 7,38-7,45 (2H, m, Ar-H), 7,51 (1H, m, Ar-H), 7,75 (1H, m, Ar-H) y 8,09 ppm (1H, s, H$_2$); 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^+). Calculado para $C_{19}H_{22}N_5OBrCl$: m/z 450,0696; δ_H ($CDCl_3$) 1,98 (2H, m, =NCH$_2$C<u>H</u>$_2$CH$_2$NH-), 2,58 (4H, m, -N(C<u>H</u>$_2$CH$_2$)$_2$O), 2,67 (2H,m, =NC<u>H</u>$_2$CH$_2$CH$_2$NH-), 3,59 (2H, m, =NCH$_2$CH$_2$C<u>H</u>$_2$NH-), 3,94 (4H, m, -N(CH$_2$C<u>H</u>$_2$)$_2$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^+). Calculado para $C_{15}H_{15}N_4OBrCl$: m/z 381,0118; δ_H ($CDCl_3$) 1,39 (3H, d, CHC<u>H</u>$_3$), 2,76 (1H, bm, -OH), 3,71 (1H, m, =CHC<u>H</u>$_2$OH), 3,81 (1H, m, =CHC<u>H</u>$_2$OH), 3,88 (1H, m, =C<u>H</u>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:

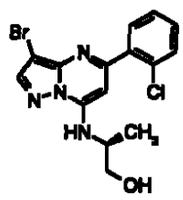
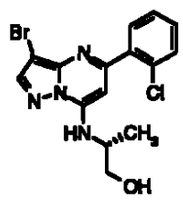


Se disolvió 3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (50mg, 0,146mmoles) (preparado según se describió en el Ejemplo Preparativo 129) en 1,4-dioxano anhídrido (5ml) en un tubo de reacción en carrusel de GeneVac Technologies. Se agregó resina de PS-diisopropil etilamina (161mg, 0,5828mmoles) a cada tubo. Se agregó una solución preparada recientemente de la amina apropiada R_1NH_2 (0,219mmoles) en 1,4-dioxano anhídrido (0,3ml) a cada tubo, con la excepción del Ejemplo 99-5 en el cual la amina se disolvió en MeOH 10% en 1,4-dioxano (0,3ml), y los tubos se sellaron y se calentaron a 70°C

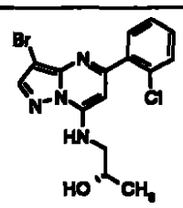
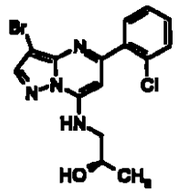
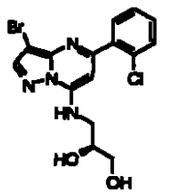
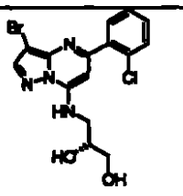
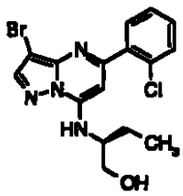
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durante 74h con agitación magnética en el bloque de reacción. Cada tubo se filtró y la resina se lavó con 1,4-dioxano anhídrido y luego con diclorometano. Los filtados individuales combinados de cada tubo se evaporaron hasta que se secaron y cada uno de los residuos se re- disolvió en 1,4-dioxano anhídrido (5ml) y se colocó en tubos de reacción GeneVac. A cada tubo se agregó resina de PS-isocianato (594mg, 0,8742mmoles) y resina de PS-trisamina (129mg, 0,4371mmoles) y los tubos se agitaron a 25°C durante 20h en el bloque de reacción. Las resinas se filtraron y se lavaron con 1,4-dioxano anhídrido y diclorometano. El filtrados de cada tubo se evaporaron hasta que se secaron y cada unos de los residuos se sometió a cromatografía en columna de gel de sílice usando el tamaño de columna y el eluyente que se muestra en la Tabla 37, para dar los compuestos de título.

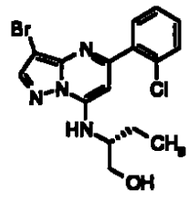
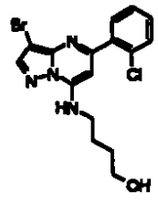
TABLA 37

Ej.	Estructura	MW	FABMS MH^+	Rendimiento	Datos cromatográficos
451		381,7	380,9	66%	15x2,5cm; 0,5% Metanol en diclorometano
452		381,7	380,9	60%	20x2cm; 0,5% Metanol en diclorometano
453		381,7	380,9	69%	15x2,5cm; 0,35% Metanol en diclorometano

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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

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459		395,7	396,0	76%	15x2,5cm; 0,35% Metanol en diclorometano

A continuación se proveen datos físicos adicionales para los compuestos:

EJEMPLO 451: Propiedades físicas: HRFABMS: m/z 381,0115 (MH^+). Calculado 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^+). Calculado 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^+). Calculado 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:

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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^+). Calculado 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^+). Calculado para $C_{15}H_{16}N_4O_2BrCl$: m/z 397,0067; $[\alpha]_D^{25°C}$ -9,5° (c= 0,28, MeOH); □H (CDCl3) 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) y 8,01 ppm (1H, s, H_2); □C (CDCl3) 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 se puede preparar esencialmente de la misma manera que se describió anteriormente.

EJEMPLO 457: Propiedades físicas: HRFABMS: m/z 395,0260 (MH^+). Calculado para $C_{16}H_{17}N_4OBrCl$: m/z 395,0274; $[\alpha]_D^{25°C}$ -34,3° (c= 0,28, MeOH); □H (CDCl3) 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) 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.

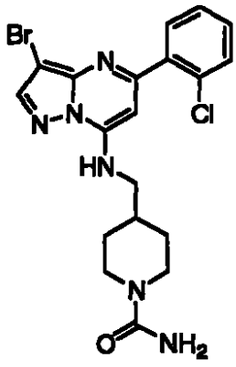
EJEMPLO 458: Propiedades físicas: HRFABMS: m/z 395,0274 (MH^+). Calculado para $C_{16}H_{17}N_4OBrCl$: m/z 395,0274; $[\alpha]_D^{25°C}$ +27,5° (c= 0,25, MeOH); □H (CDCl3) 1,05 (3H, dd, CH_3), 1,76 (1H, m, CH_2), 1,85 (1H, m, CH_2), 2,28 (1H, bs, CH_2O<u>H</u>), 3,67 (1H, m, C<u>H</u>NH), 3,77 (1H, dd, C<u>H</u>$_2$OH), 3,84 (1H, dd, C<u>H</u>$_2$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.

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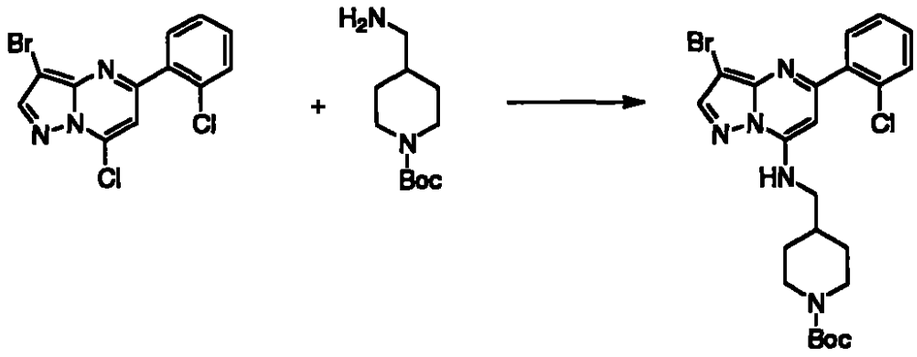
EJEMPLO 459: Propiedades físicas: HRFABMS: m/z 395,0264 (MH^+). Calculado para $C_{16}H_{17}N_4OBrCl$: m/z 395,0274; δ_H ($CDCl_3$) 1,77 (2H, m, -$NHCH_2CH_2C\underline{H}_2CH_2OH$), 1,90 (1H, bm, -$NHCH_2CH_2CH_2CH_2O\underline{H}$), 1,93 (2H, m, -$NHCH_2C\underline{H}_2CH_2CH_2OH$), 3,54 (2H, m, -$NHC\underline{H}_2CH_2CH_2CH_2OH$), 3,77 (2H, m, -$NHCH_2CH_2CH_2C\underline{H}_2OH$), 6,37 (1H, s, H_6), 6,72 (1H, m, -$N\underline{H}CH_2CH_2CH_2CH_2OH$), 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. DEL ÁCIDO 4-{[3-BROMO-5-(2-CLOROFENIL)PIRAZOLO[1,5-a] PIRIMIDIN-7-ILAMINO]METIL}PIPERIDIN-1-CARBOXÍLICO:



A. TER-BUTIL ESTER DEL ÁCIDO 4-{[3-BROMO-5-(2-CLOROFENIL) PIRAZOLO[1,5-a]PIRIMIDIN-7-ILAMINO]METIL}PIPERIDIN-1-CARBOXÍLICO:

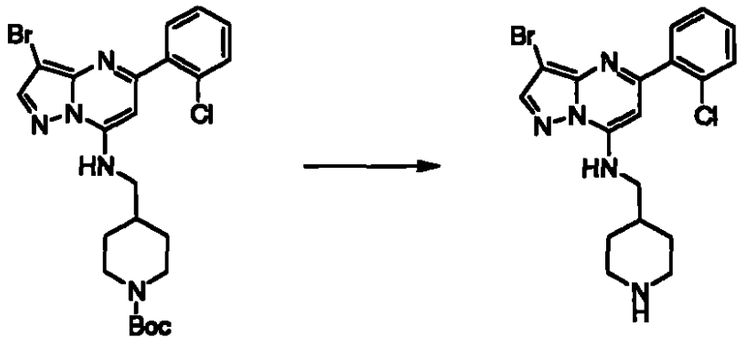


Se disolvió 3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (300mg, 0,875mmoles) (preparado según se describió en el Ejemplo Preparativo 129) en 1,4-dioxano anhídrido (6,8ml). Se agregaron 4-(aminometil)piperidin-1-carboxílico ter-butil éster del ácido (225mg, 1,05mmoles) y diisopropil etilamina

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(0,3055ml, 1,75mmoles) y la mezcla se calentó a 75°C durante 24h. La solución se evaporó hasta que se secó y el residuo se sometió a cromatografía sobre una columna de gel de sílice (15x5cm) usando diclorometano como el eluyente para dar ter-butil éster del ácido 4-{[3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-ilamino]metil}piperidin-1-carboxílico (461,2mg, 100%): FABMS: m/z 520,1 (MH^+); HRFABMS: m/z 520,1111 (MH^+). Calculado 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, 67,5, 127,2, 130,2, 130,3, 131,5, 143,9; C: 79,7, 83,3, 132,1, 138,6, 145,4, 146,3, 154,7, 158,1.

B. [3-BROMO-5-(2-CLOROFENIL)PIRAZOLO[1,5-a]PIRIMIDIN-7-il]PIPERIDIN-4-ILMETILAMINA:

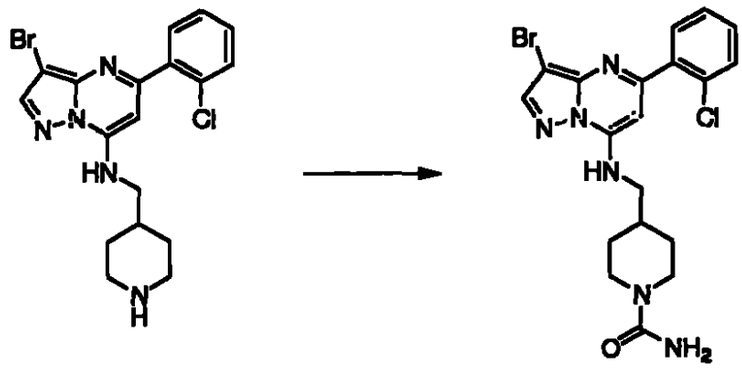


Se disolvió 4-{[3-Bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-ilamino] metil}piperidin-1-carboxílico ter-butil éster del ácido (441mg, 0,847mmoles) (preparado según se describió en el Ejemplo 460, Paso A anterior) en metanol (4,5ml) y se agregó ácido sulfúrico conc. 10% (v/v) en 1,4-dioxano (11,46ml). La mezcla se agitó a 25°C durante 0,5h. El producto el producto se procesó según se describió en el Ejemplo preparativo 241, paso B y se sometió a cromatografía en columna de gel de sílice (15x5cm) usando 8% (hidróxido de amonio conc. 10% en metanol)-diclorometano como el eluyente para dar [3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-il]piperidin-4-ilmetilamina (314,4mg, 88%): FABMS: m/z 420,0 (MH^+); HRFABMS: m/z 420,0585 (MH^+). Calculado para

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$C_{18}H_{20}N_5BrCl$: 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 DEL ÁCIDO 4-{[3-BROMO-5-(2-CLOROFENIL)PIRAZOLO[1,5-a]PIRIMIDIN-7-ILAMINO]METIL}PIPERIDIN-1-CARBOXÍLICO:

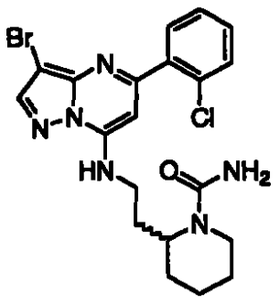


Se disolvió [3-Bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-il]piperidin-4-ilmetilamina (57mg, 0,136mmoles) (preparado según se describió en el Ejemplo 460, Paso B anterior) en diclorometano anhídrido (1,2ml) y se agregó trimetilsililisocianato (0,091ml, 0,679mmoles). La mezcla se agitó a 25°C durante 2,5h. 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 que se secó. El residuo se sometió a cromatografía en una columna de gel de sílice (30x2,5cm) usando 3% (10% hidróxido de amonio conc. en metanol)-diclorometano como el eluyente para dar amida del ácido 4-{[3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-ilamino]metil}piperidin-1-carboxílico (53,7mg, 86%): FABMS: m/z 463,1 (MH^+); HRFABMS: m/z 463,0647 (MH^+). Calculado 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.

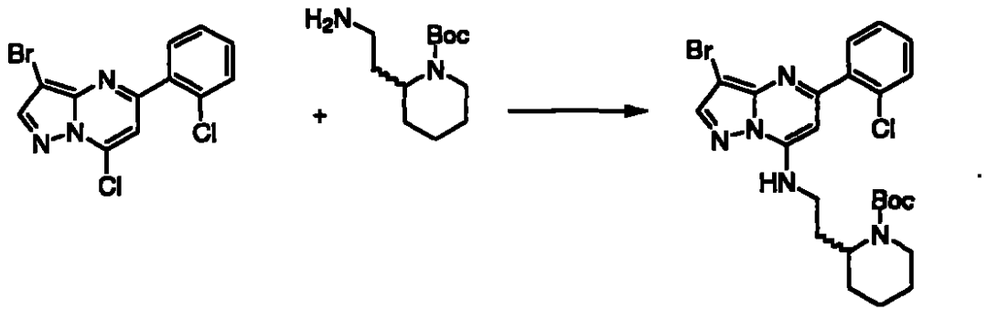
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EJEMPLO 461:

AMIDA DEL ÁCIDO 2 -{2-[3-BROMO-5-(2-CLOROFENIL)PIRAZOLO[1,5-a] PIRIMIDIN-7-ILAMINO]ETIL}PIPERIDIN-1-CARBOXÍLICO:



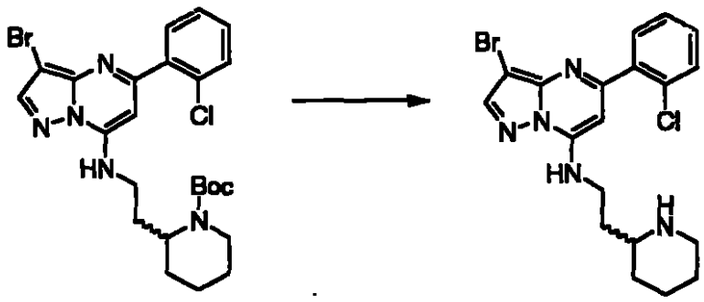
A. TER-BUTIL ESTER DEL ÁCIDO 2-{2-[3-BROMO-5-(2-CLOROFENIL) PIRAZOLO[1,5-a]PIRIMIDIN-7-ILAMINO]ETIL}PIPERIDIN-1-CARBOXÍLICO:



Se disolvió 3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (400mg, 1,166mmoles) (preparado según se describió en el Ejemplo Preparativo 129) en 1,4-dioxano anhídrido (5,7ml). Se agregaron ter-butil éster del ácido 2-aminoetilpiperidin-1-carboxílico (266mg, 1,166mmoles) y diisopropil etilamina (0,409ml, 2,33mmoles) y la mezcla se calentó a 75°C durante 48h. Se agregó diisopropil etilamina adicional (0,204ml, 1,166mmoles) y se continuó calentando durante un total de 58h. La solución se evaporó hasta que se secó y el residuo se sometió a cromatografía sobre una columna de gel de sílice (15x5cm) usando diclorometano seguido por 0,3% (hidróxido de amonio conc. 10% en metanol)-diclorometano como el eluyente para dar ter-butil éster del ácido 2-{[3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-ilamino]etil}piperidin-1-carboxílico (491,1mg,

79%): FABMS: m/z 534,1 (MH^+); HRESIMS: m/z 534,12797 (MH^+). Calculado 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:

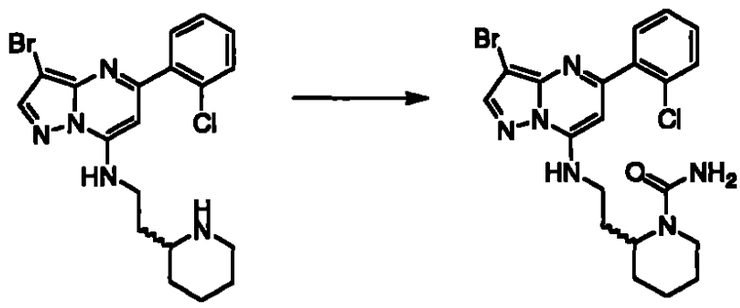


Se disolvió ter-butil éster del ácido 2-{[3-Bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-ilamino]etil}piperidin-1-carboxílico (465mg, 0,869mmoles) (preparado según se describió en el Ejemplo 461, Paso A anterior) en metanol (4,5ml) y se agregó ácido sulfúrico conc. 10% (v/v) en 1,4-dioxano (11,76ml). La mezcla se agitó a 25°C durante 1,5h. El producto el producto se procesó según se describió en el Ejemplopreparativo 241, paso B y se sometió a cromatografía en una columna de gel de sílice (15x5cm) usando 3,5% (hidróxido de amonio conc. 10% en metanol)-diclorometano como el eluyente para dar [3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-il]piperidin-2-iletil)amina (365,6mg, 97%): FABMS: m/z 434,1 (MH^+); HRFABMS: m/z 434,0726 (MH^+). Calculado 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,

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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.

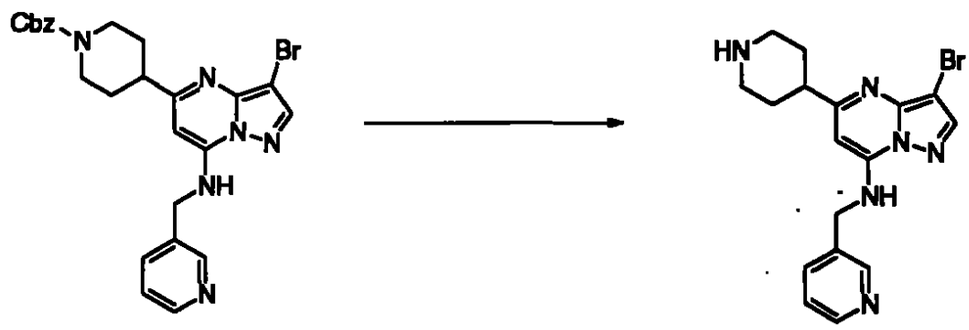
C. AMIDA DEL ÁCIDO 2-{2-[3-BROMO-5-(2-CLOROFENIL)PIRAZOLO[1,5-a]PIRIMIDIN-7-ILAMINO]ETIL}PIPERIDIN-1-CARBOXÍLICO:



Se disolvió [3-Bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-il]piperidin-2-iletil)amina (200mg, 0,46mmoles) (preparado según se describió en el Ejemplo 461, Paso B anterior) en anhídrido diclorometano (2ml) y se agregó trimetilsililisocianato (0,31ml, 2,3mmoles). La mezcla se agitó a 25°C durante 1,25h. Se agregó trimetilsililisocianato adicional (0,155ml, 1,15mmoles) y se continuó agitando durante un total de 3h. 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 que se secó. El residuo se sometió a cromatografía sobre una columna de gel de sílice (30x2,5cm) usando 2% (hidróxido de amonio conc. 10% en metanol)-diclorometano como el eluyente para dar amida del ácido 2-{2-[3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-ilamino]etil}piperidin-1-carboxílico (106,3mg, 48%): FABMS: m/z 477,0 (MH^+); HRFABMS: m/z 477,0804 (MH^+). Calculado 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:

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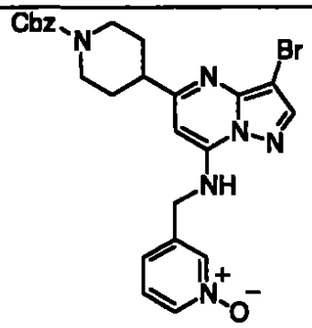
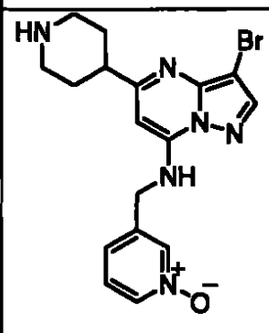


A una solución del compuesto preparado en el Ejemplo 204 (1,11 g, 2,12 mmol) en acetonitrilo anhídrido (20 ml) se agregó TMSI (1,70 g, 8,52 mmol), gota a gota a temperatura ambiente. Después de 10 minutos se removió el acetonitrilo *in vacuo*. La espuma amarilla resultante se trató con solución de HCl 2 N (7 ml) y luego se lavó inmediatamente con Et_2O (5X). El pH de la solución acuosa se reguló a 10 con NaOH 50 % (aq) y el producto se aisló mediante saturation of la solución with NaCl (s) seguido por extraction with CH_2Cl_2 (5X) para dar el producto cristalino (733 mg, 89% de rendimiento). MH^+ = 387; m. p. = 207,5 °C.

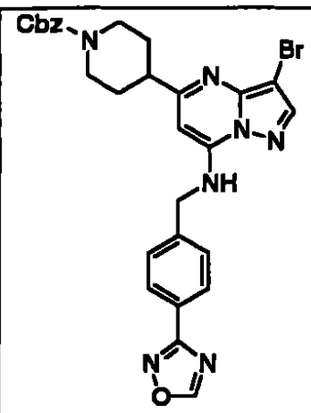
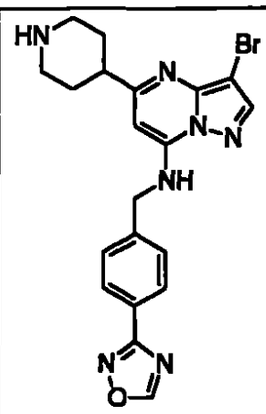
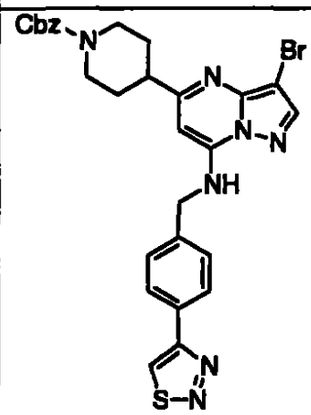
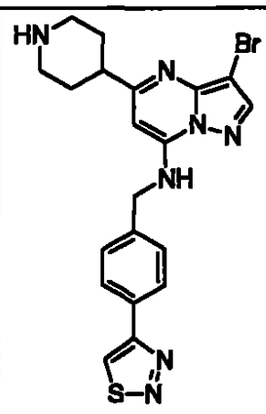
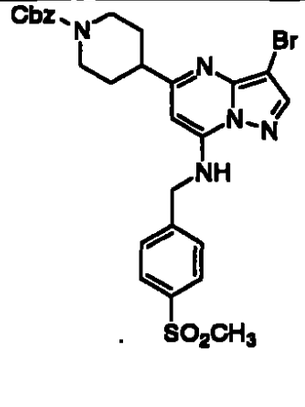
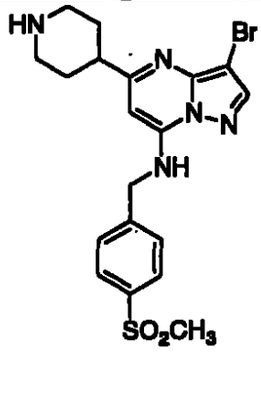
EJEMPLOS 463-472:

Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 462, sustituyendo solamente 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 la Tabla 38.

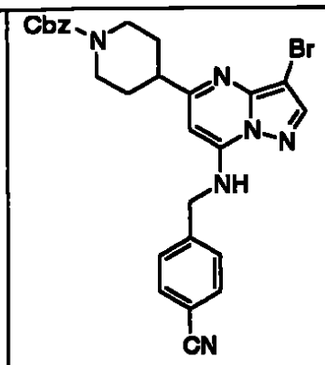
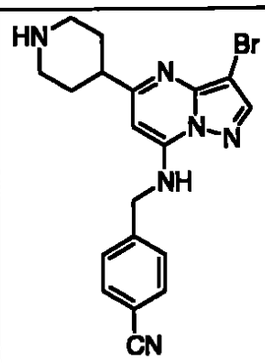
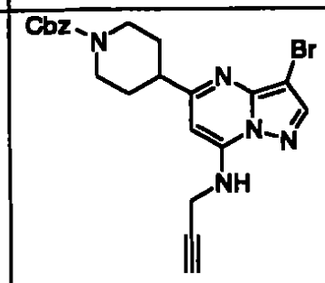
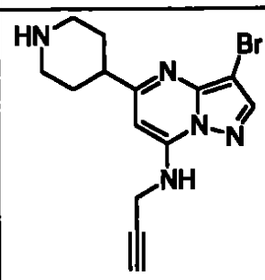
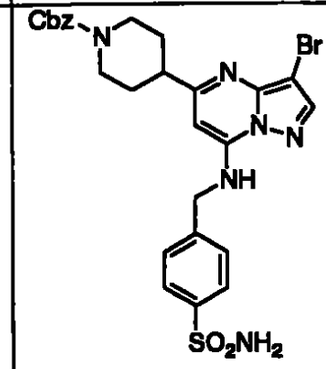
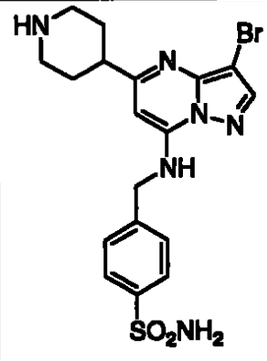
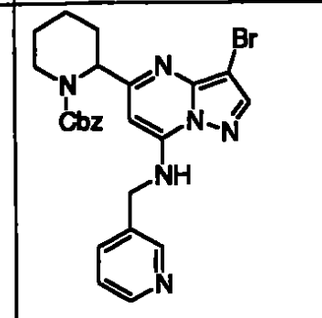
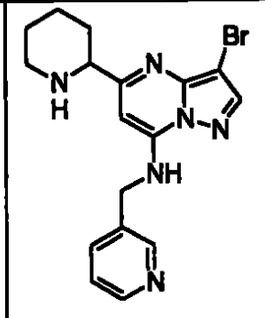
TABLA 38

Ej.	Columna 2	Columna 3	COMPUESTO
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).

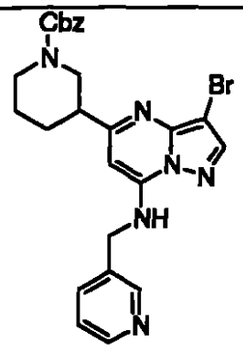
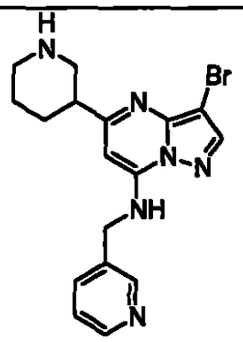
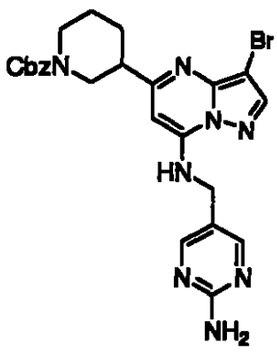
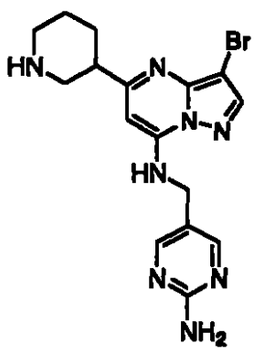
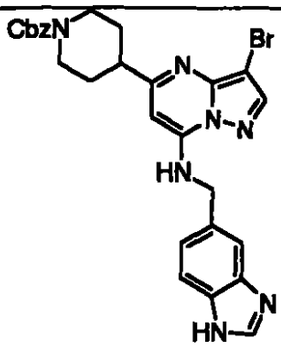
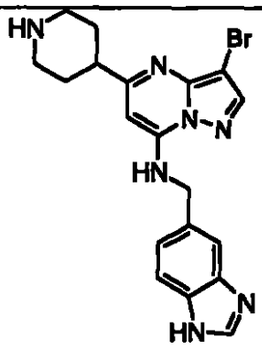
613

464			$MH^+ = 454$ m. p. = 175,4 °C
465			Rendimiento = 87 $MH^+ = 470$ m. p. = 220 °C m. pt (sal del clorhidrato) = 164,3 °C
466			$MH^+ = 464$ m. p. = 206 °C

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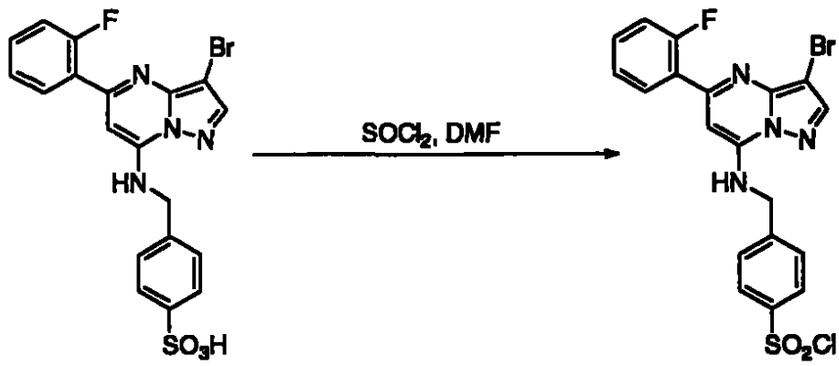
467			$MH^+ = 411$ m. p. = 169,5 °C
468			$MH^+ = 334$ m. p. = 176,2 °C
469			$MH^+ = 465$ m. p. = 250,4 °C
470			$MH^+ = 387$ m. p. = 68,5 °C

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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

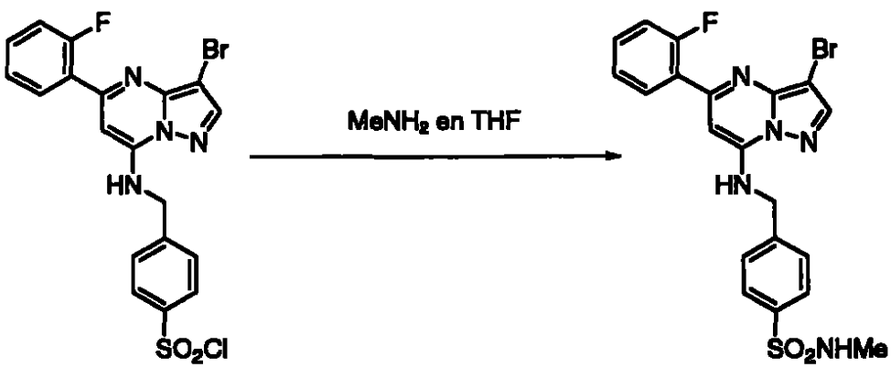
EJEMPLO 473:

Paso A:



Una solución del àcido sulfónico (560 mg, 1,17 mmol) en 5 ml de DMF seco se enfrió hasta 0 °C y se agregó $SOCl_2$ (278 mg, 2,34 mmol). La mezcla de reacción se llevó hasta TA y se agitó hasta el día siguiente. El día siguiente los contenidos se vertieron en hielo y se reguló cuidadosamente el pH a 8. El producto se extrajo para EtOAc y se eliminó el solvente después de secar (Na_2SO_4) para dar 240 mg (41%) del cloruro sulfonilo bruto que se usó para el siguiente paso sin purificación adicional. ^1H 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).

Paso B:



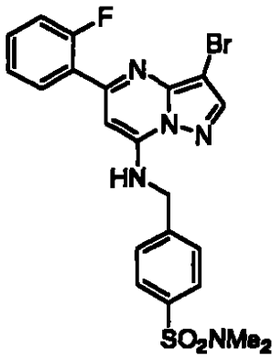
Se trató una solución del compuesto preparado en el Ejemplo 473, Paso A (120 mg, 0,24 mmol) en 10 ml de THF con 2 ml de $MeNH_2$ 1 M (2,00 mmol) en THF a temperatura ambiente hasta el día siguiente. Se eliminó el solvente y el

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residuo se purificó mediante cromatografía (sílice, hexano:EtOAc (4:1→1:1)) para dar 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.

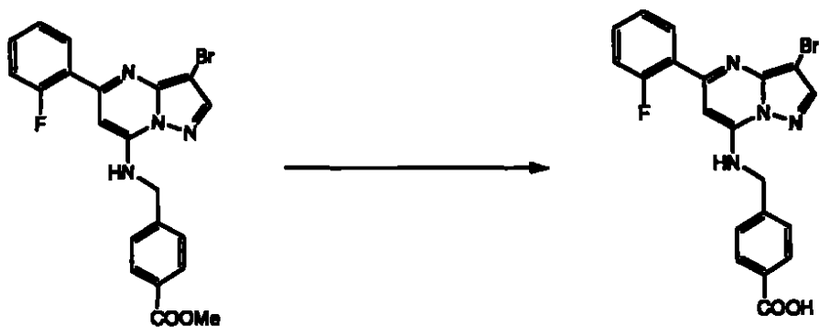
EJEMPLO 474:



Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 473, sustituyendo solamente 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:



Se agitó una mezcla del compuesto preparado en el Ejemplo 129 (300 mg, 0,66 mmol), NaOH (5 g), CH_3OH –H_2O (100 ml, 90:10) a 25 °C durante alrededor de 15 h. El progreso de la hidrólisis se verificó mediante TLC. La mezcla de reacción se concentró para eliminar el metanol. El concentrado se diluyó con 50

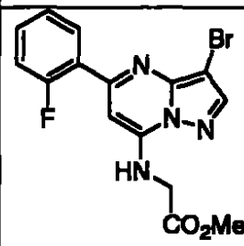
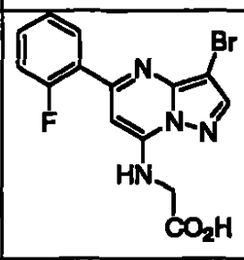
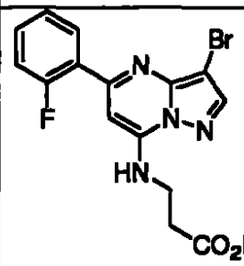
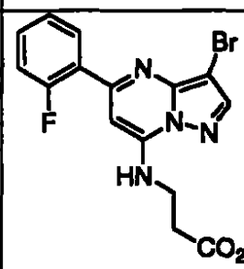
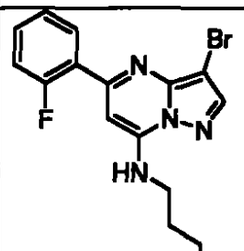
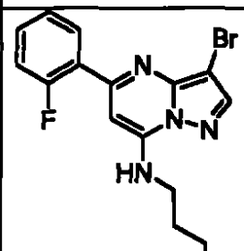
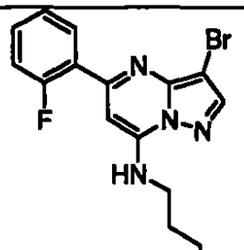
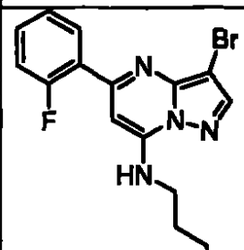
618

ml agua, y se extrajo con éter para remover cualquier éster sin reaccionar. La solución acuosa que se obtuvo de esa manera, se neutralizó con HCl 3 N para pH 4 para obtener ácido libre, se filtró y se lavó repetidas veces con agua. El ácido se secó en vacío (270 mg, 93%) y se usó sin purificación adicional.

Ejemplo 476-479:

Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 475, sustituyendo solamente los compuestos en 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	COMPUESTO
476			Rendimiento = 82% LCMS: MH^+ = 365
477			Rendimiento = 82% LCMS: MH^+ = 379
478			Rendimiento = 72% LCMS: MH^+ = 393
479			Rendimiento = 70% LCMS: MH^+ = 407

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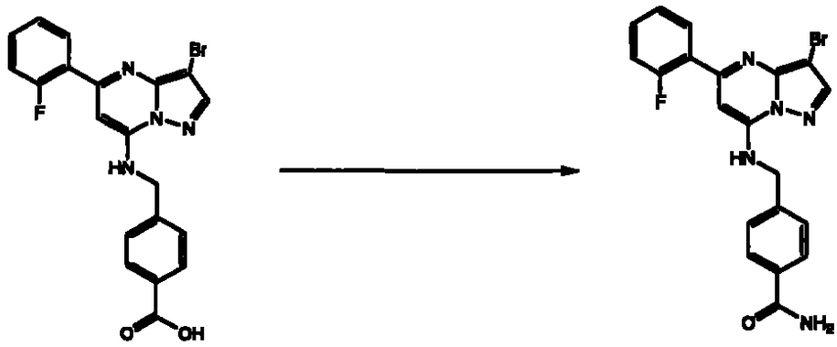
Datos adicionales para ejemplos selectos que se muestran a continuación:

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).

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:



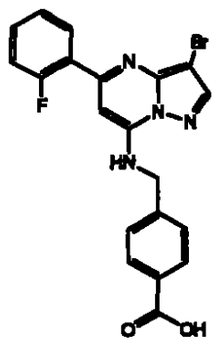
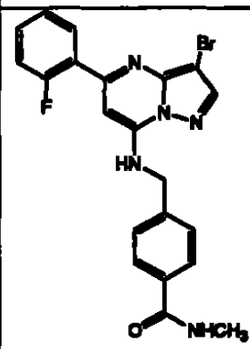
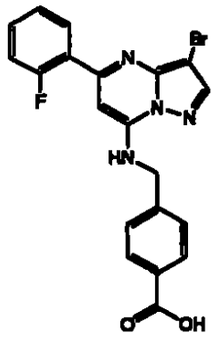
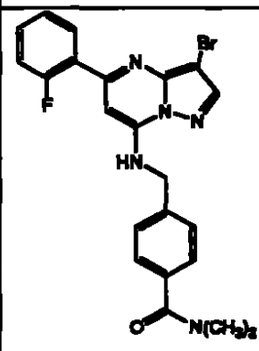
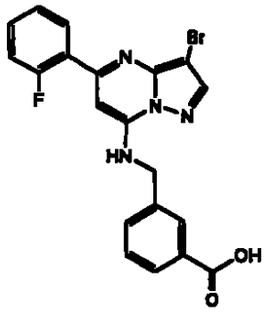
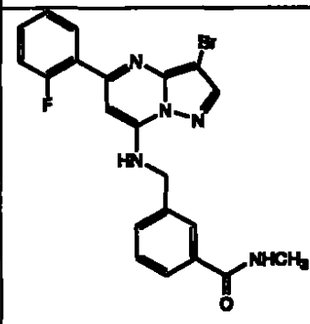
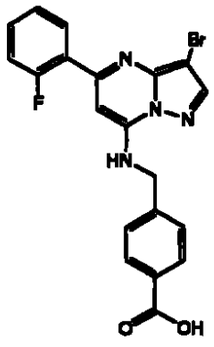
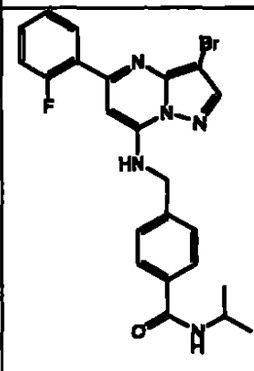
Se agitó una mezcla del ácido del Ejemplo 475 (85mg, 0,193 mmol) y Et_3N (20 mg, 0,193 mmol) en THF (20 ml) a 25 °C durante 15 min. Se agregó cloroformato de isobutirilo (28mg, 0,205 mmol) a la mezcla de reacción y se agitó durante 10 min seguido por la adición de solución de NH4OH (0,5 ml). La mezcla de reacción se agitó durante 1 hr y se concentraron hasta que se secaron. La masa seca se purificó mediante cromatografía en columna.

EJEMPLOS 481-509:

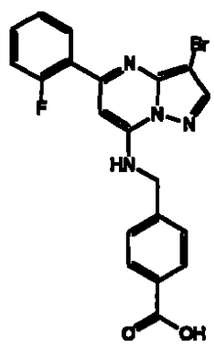
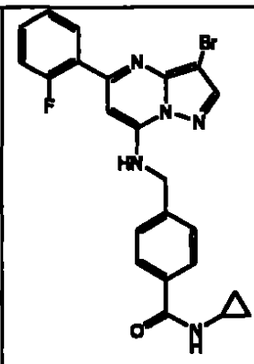
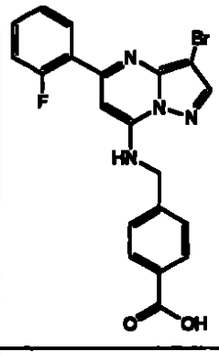
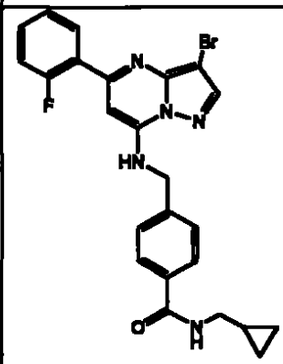
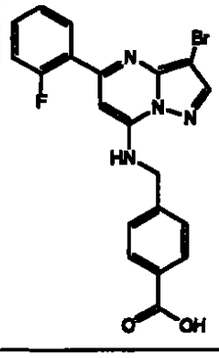
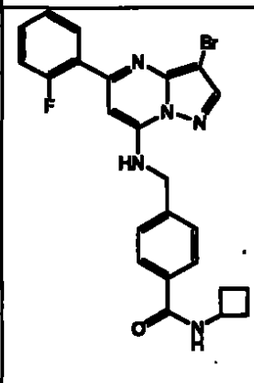
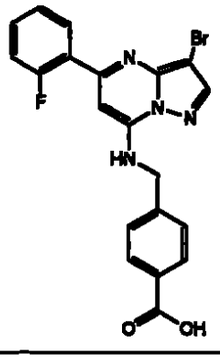
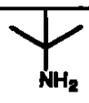
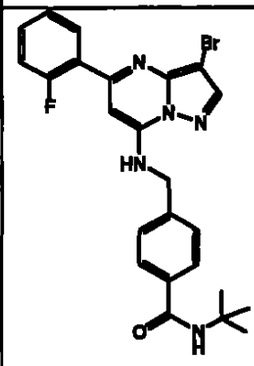
Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 480, sustituyendo solamente el ácido carboxílico que se muestra en la Columna 2 de la Tabla 40 y la amina que se muestra en la Columna 3 de la Tabla 40, se prepararon los compuestos que se muestran en la Columna 4 de la Tabla 40.

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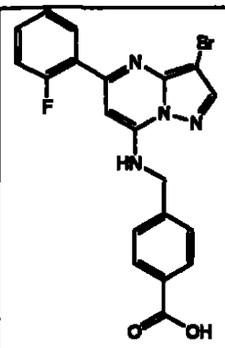
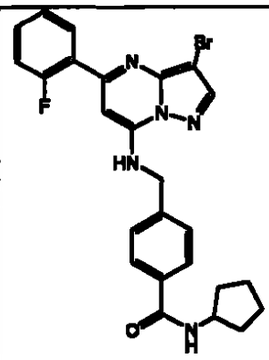
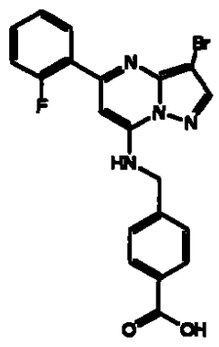
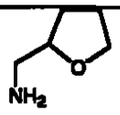
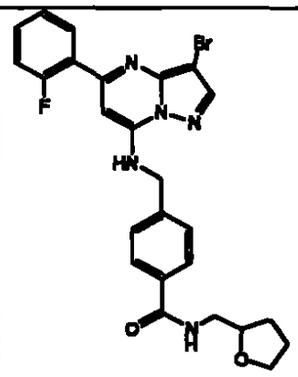
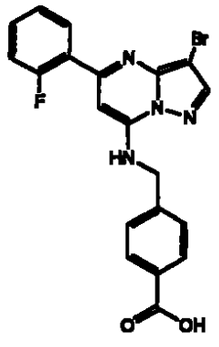
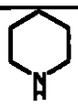
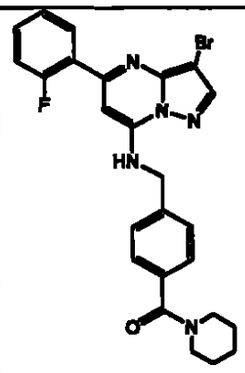
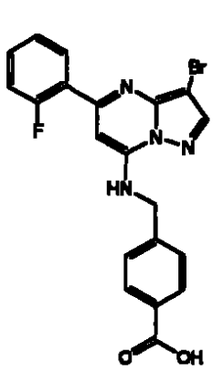
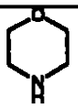
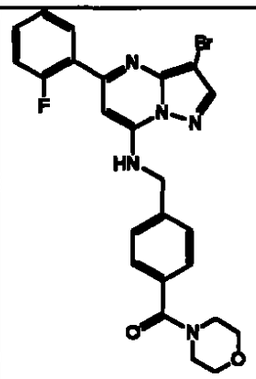
Tabla 40

Ej.	Columna 2	Columna 3	Columna 4	COMPUESTO
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

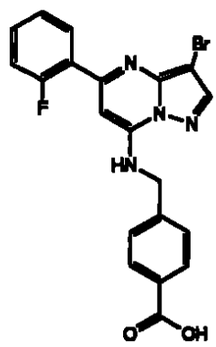
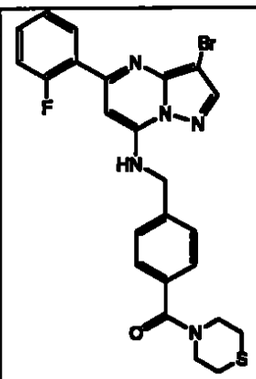
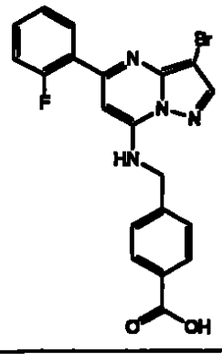
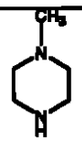
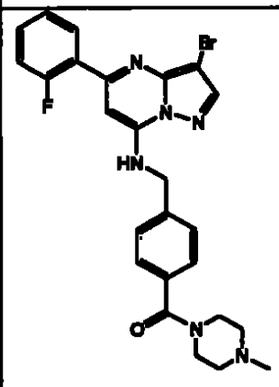
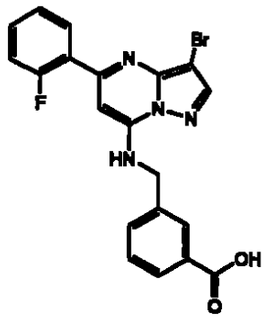
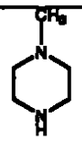
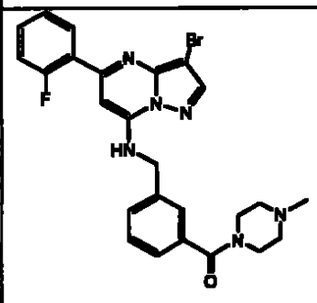
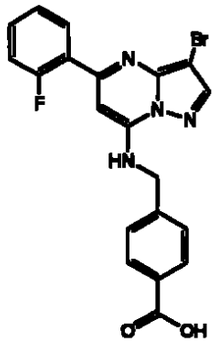
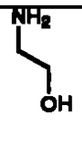
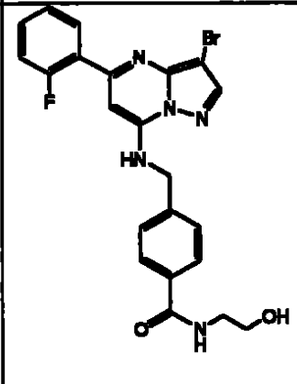
621

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

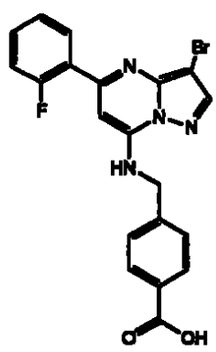
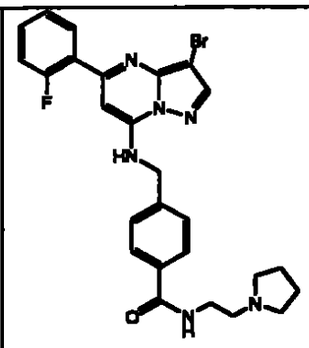
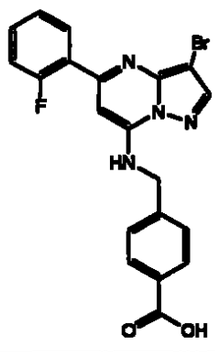
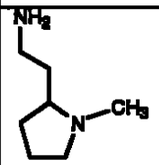
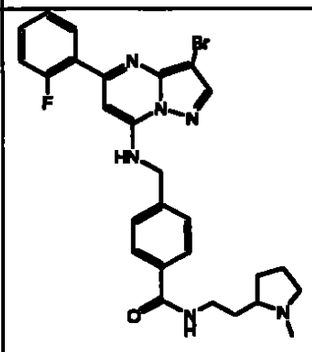
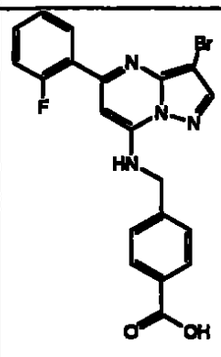
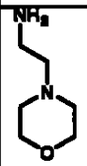
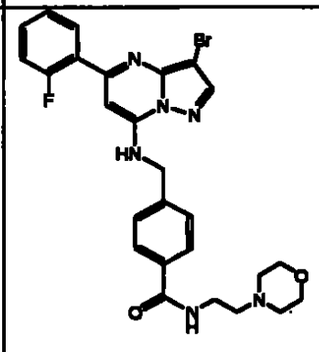
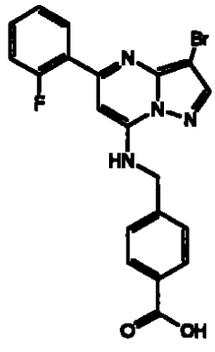
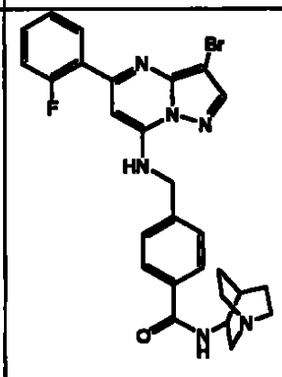
622

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

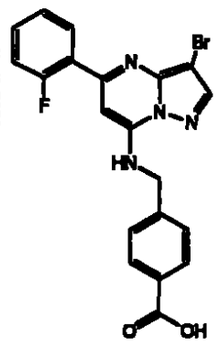
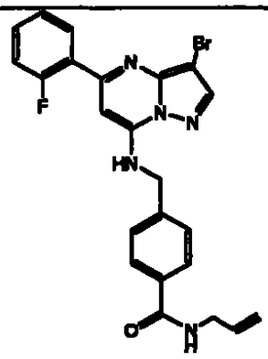
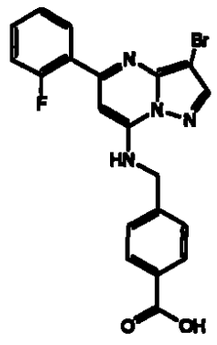
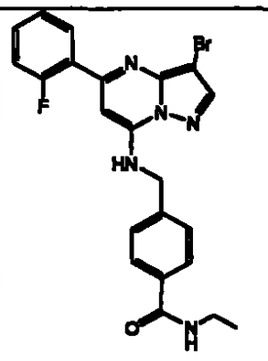
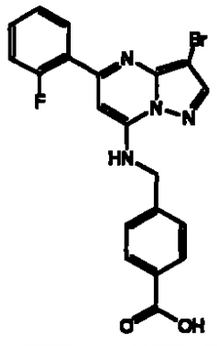
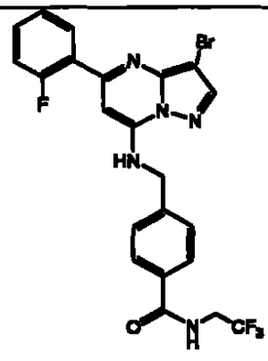
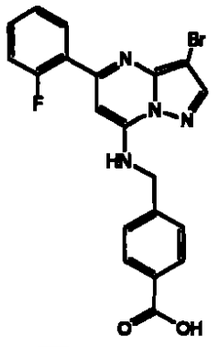
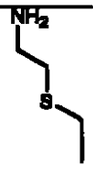
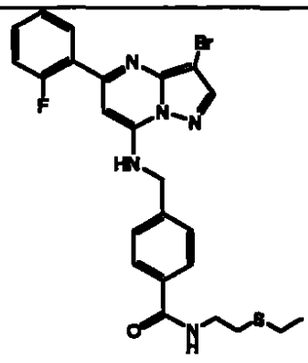
623

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

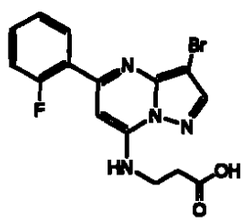
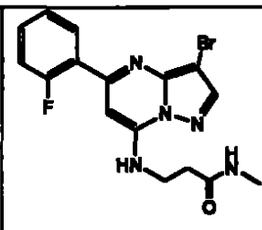
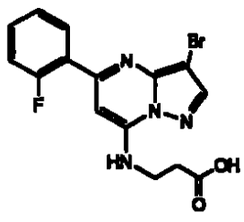
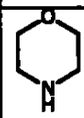
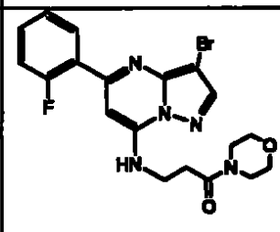
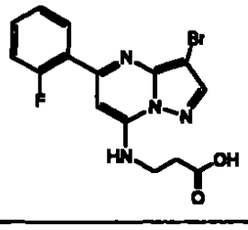
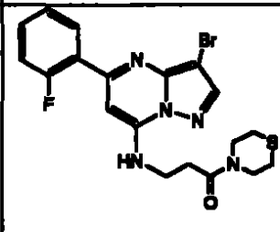
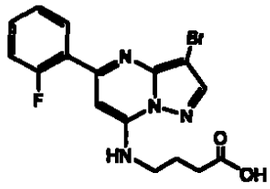
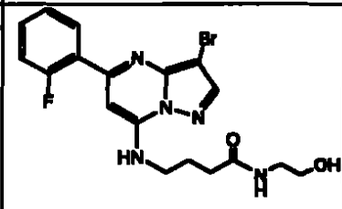
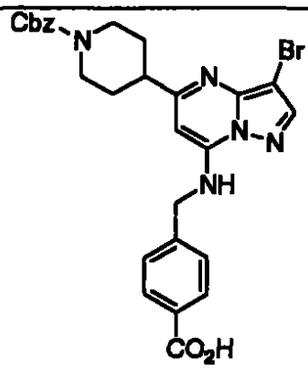
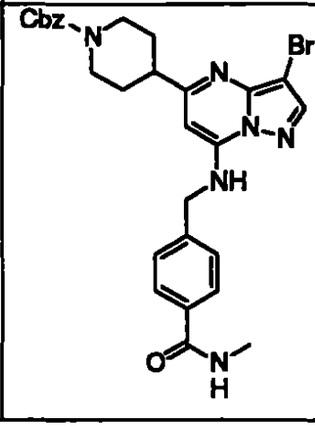
624

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

625

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

626

505		CH_3NH_2		Rendimiento =60% MH^+ = 392
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

Datos adicionales para ejemplos selectos dados a continuación:

627

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).

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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).

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Ejemplo 501: ^{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).

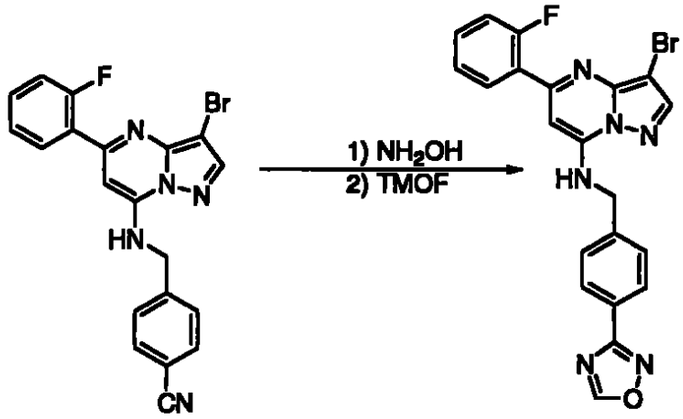
Ejemplo 505: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,4 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 7,0 (t, 1H), 6,5 (s, 1H), 3,8 (m, 2H), 2,7 (t, 2H), 3,0 (d, 3H).

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:

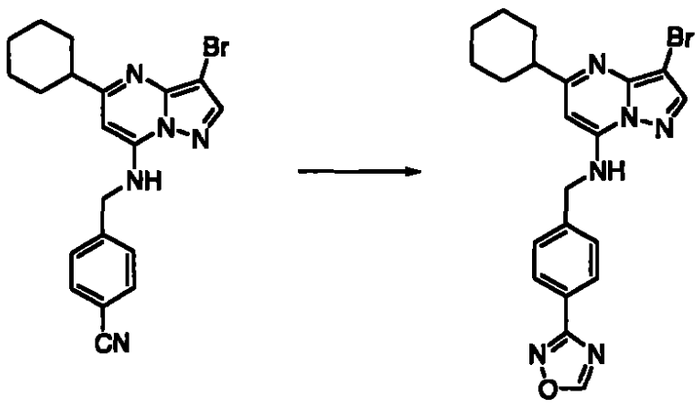


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Se agregó una solución de NaOH (59 mg, 1,47 mmol) en 1 ml de agua a una suspensión de $NH_2OH.HCl$ (102 mg, 1,47 mmol) en 10 ml de metanol a 0 °C. Después de 5 min, se agregó el compuesto preparado en el Ejemplo 210,10 (208 mg, 0,49 mmol) y la mezcla de reacción se reflujó hasta el día siguiente. Se eliminó el solvente *in vacuo* 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 bruta resultante se suspendió en ortoformato trimetilo que contiene la cantidad catalítica del ácido PTS y se reflujó hasta el día siguiente. Se eliminó el solvente y el residuo se capturó en EtOAc. La capa de EtOAc se lavó con aq $NaHCO_3$ seguido por agua y salmuera. El solvente se evaporó y el residuo se purificó mediante cromatografía (sílice, hexano:EtOAc (1:1)) para dar 80 mg (35%) del oxadiazol. ^1H RMN ($CDCl_3$) 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.

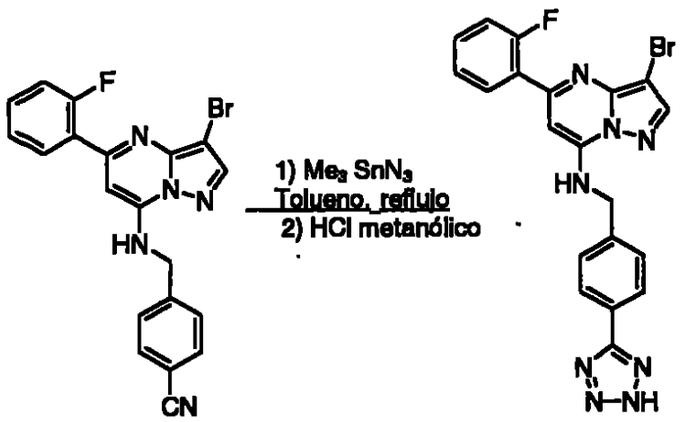
Ejemplo 510:



Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 509, sustituyendo solamente el compuesto preparado en el Ejemplo Preparativo 192, se preparó el compuesto anterior. rendimiento = 75; MH^+ = 453; m. p. = 79,3°C.

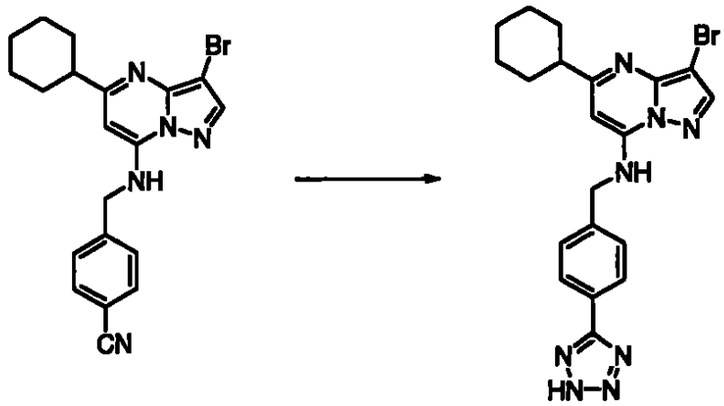
EJEMPLO 511:

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Se reflujó una mezcla del nitrilo (235 mg, 0,56 mmol) y Me_3SnN_3 (343 mg, 1,67 mmol) en 20 ml de tolueno seco durante 2 días bajo Ar. Se eliminó el solvente *in vacuo* y el residuo se disolvió en metanol seco. El HCl gaseoso se burbujeó a través de la solución durante 15 min y se dejó que la mezcla de reacción repose hasta el día siguiente a temperatura ambiente. Al día siguiente, el solvente se eliminó, el residuo se capturó en agua y el pH se reguló a 5. El producto precipitado se extrajo en EtOAc. La evaporación de la capa de EtOAc después del secado (Na_2SO_4) dio el residuo que se purificó mediante cromatografía (sílice, DCM:MeOH (98:2→95:5)) para dar 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.

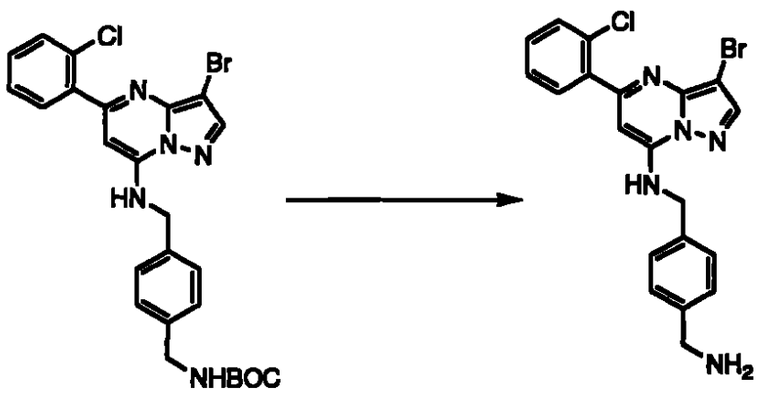
EJEMPLO 512:



Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 511, sustituyendo solamente el compuesto preparado en el Ejemplo 192, se preparó el compuesto anterior. Rendimiento = 64; MH^+ = 453; m. p. = 238,9°C.

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EJEMPLO 513:

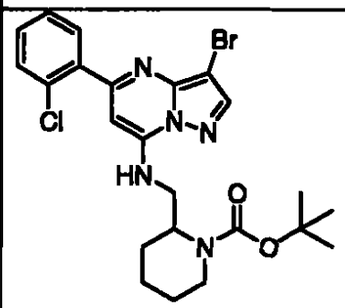
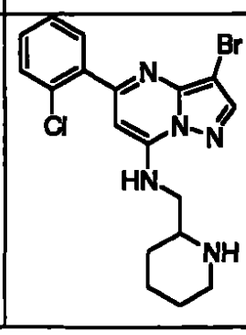


El compuesto preparado en el Ejemplo 157 se disolvió en dioxano (30 ml) y se agregó una solución de HCl-dioxano (4 M, 30 ml). La mezcla de reacción se agitó a temperatura ambiente durante 4 h. La mezcla de reacción se evaporó bajo presión reducida y se agregó acetato de etilo (200 ml). La solución orgánica se lavó con hidruro de sodio 1 N seguido por salmuera saturada. La capa orgánica se secó sobre sulfato de sodio anhídrido y se evaporó bajo presión reducida. $MH^+ = 442,1$.

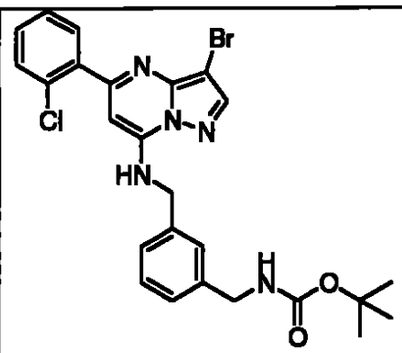
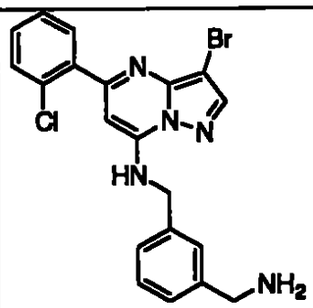
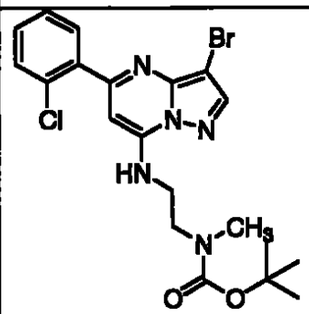
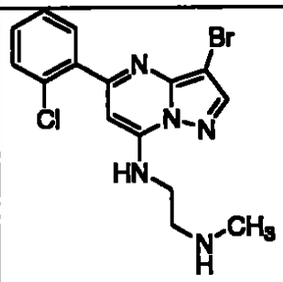
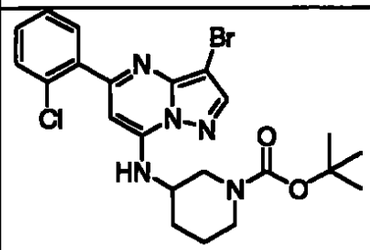
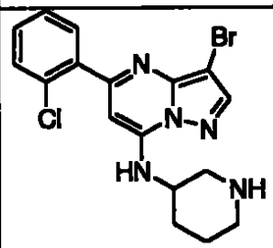
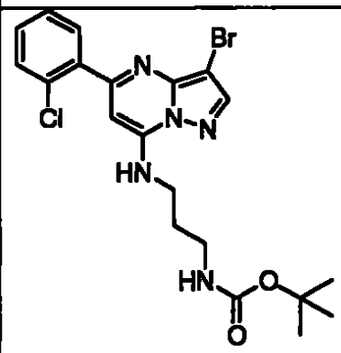
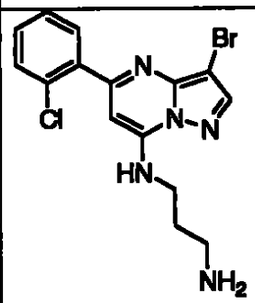
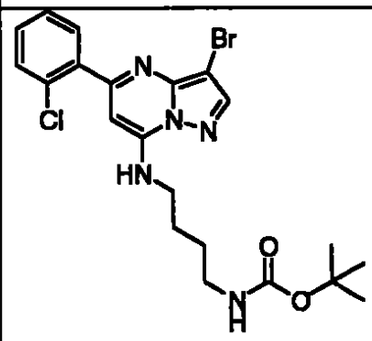
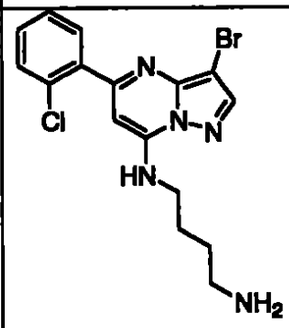
EJEMPLO 514-526:

Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 513, sustituyendo solamente 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.

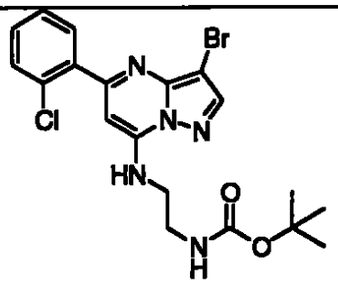
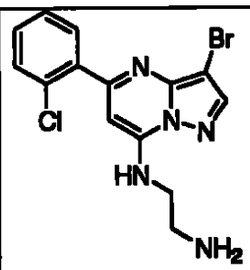
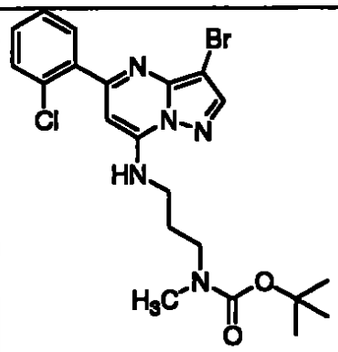
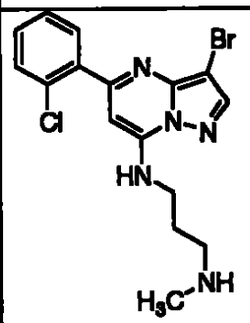
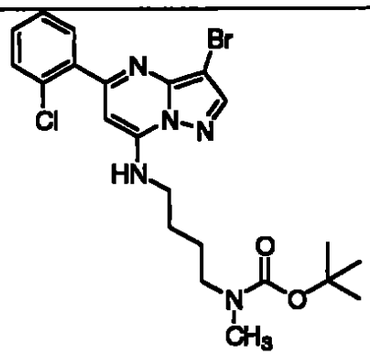
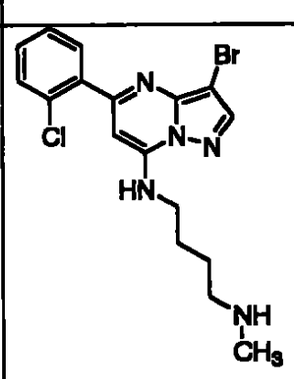
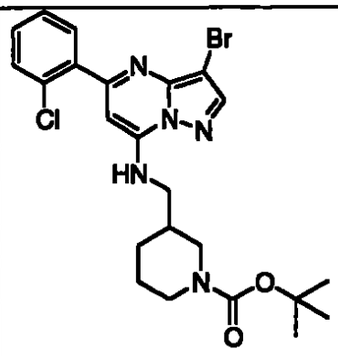
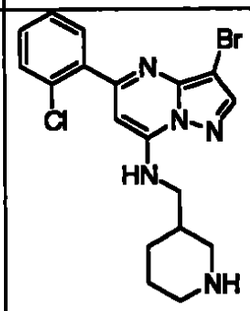
TABLA 41

Ej.	Columna 2	Columna 3	COMPUESTO
514			$MH^+ = 420,1$

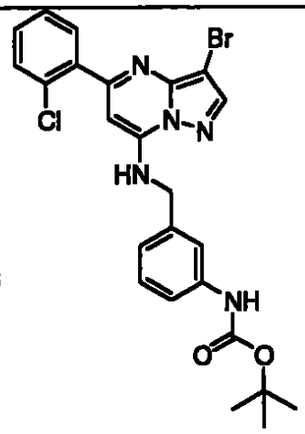
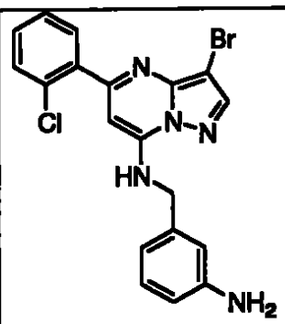
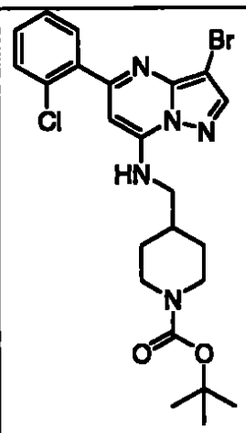
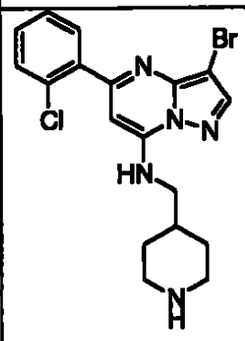
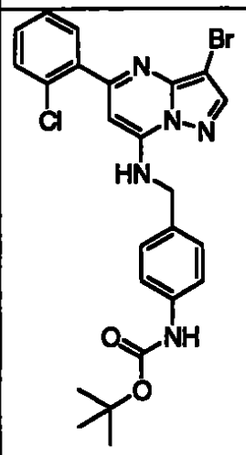
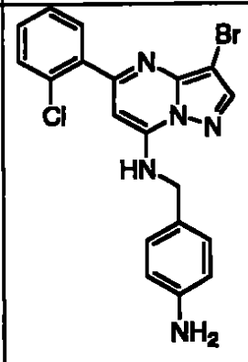
633

515			$MH^+ = 442,1$
516			$MH^+ = 380,1$
517			$MH^+ = 406,1$
518			$MH^+ = 380,1$
519			$MH^+ = 394,1$

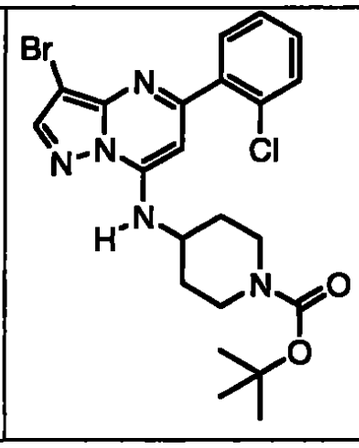
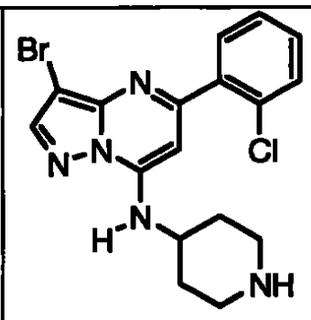
634 655

520			$MH^+ = 366$
521			$MH^+ = 394$
522			$MH^+ = 408,1$
523			$MH^+ = 420,1$

635

524			
525			$MH^+ = 420,1$
526			$MH^+ = 428,1$

636

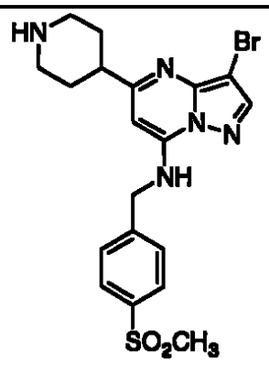
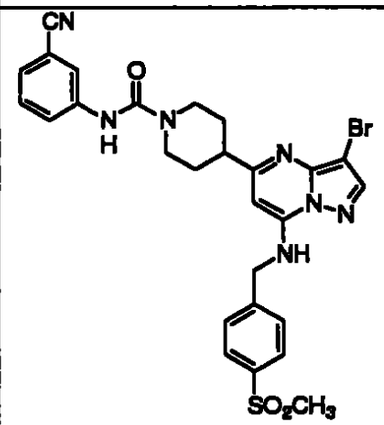
526,10			

EJEMPLOS 528-564:

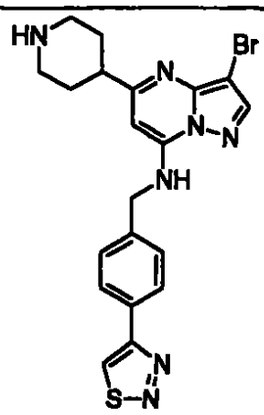
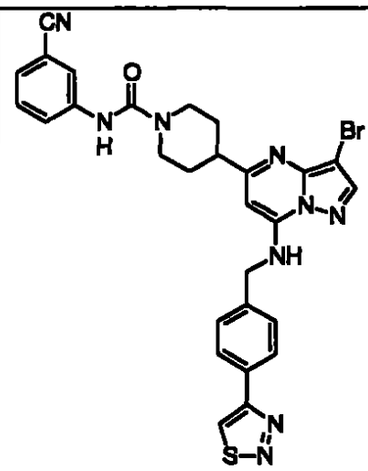
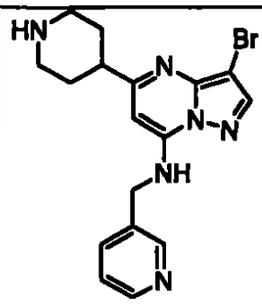
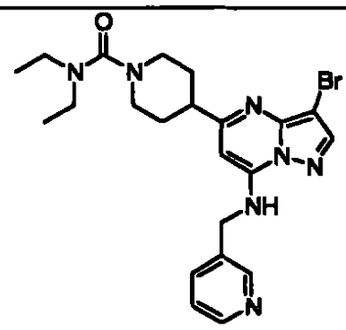
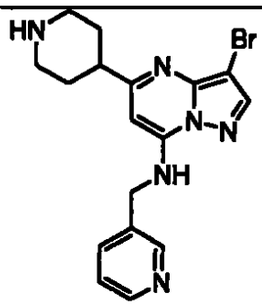
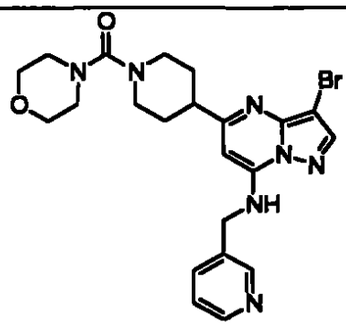
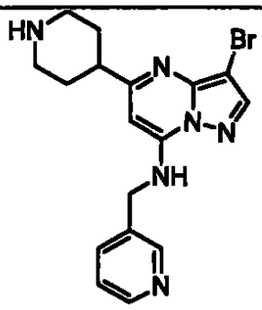
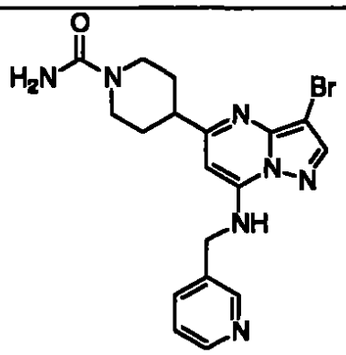
Procedimiento general para la formación de la biblioteca paralela de 5-piperidinilo:

A una mezcla del material de partida (80 mg, 0,21 mmol) que se muestra en la Columna 2 de la Tabla 42 en CH_2Cl_2 anhídrido (1,5 ml) se agregó DIPEA (75 µl, 0,42 mmol) y el reactivo de extremo apropiado (1,1 equiv., 0,23 mmol). Después de 1 a 2 h, la mezcla de reacción se aplicó a una placa de 1000 micrones de TLC preparativa y posteriormente se desarrolló usando a EtOH – CH_2Cl_2 8 – 10 % como eluyente para dar los compuestos que se muestran en la Columna 3 de la Tabla 42.

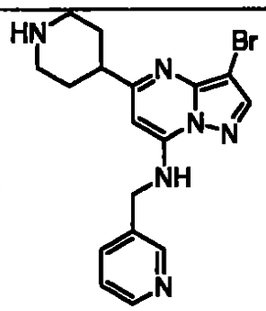
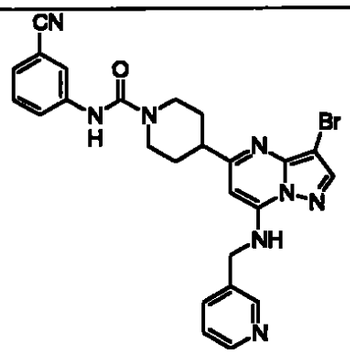
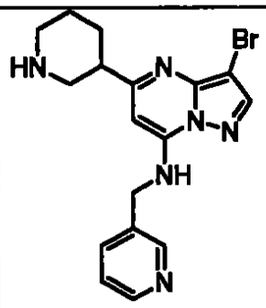
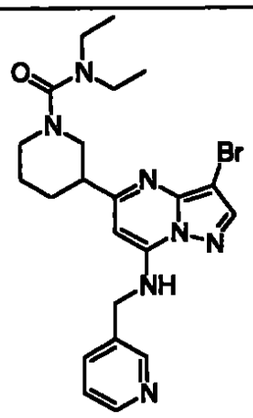
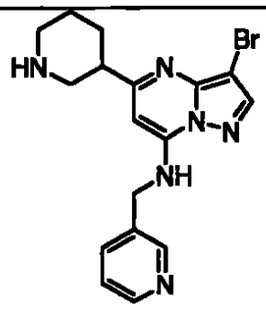
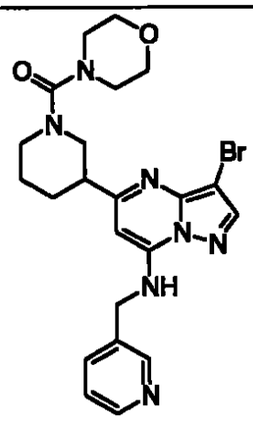
TABLA 42

Ej.	Columna 2	Columna 3	COMPUESTO
528			MH^+ = 608 m. p. = 230,1 °C

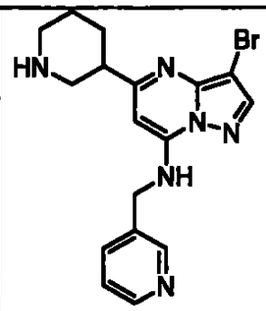
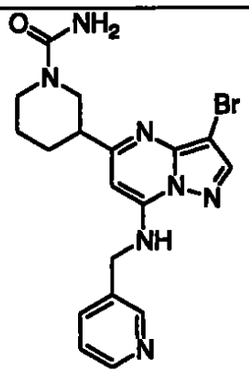
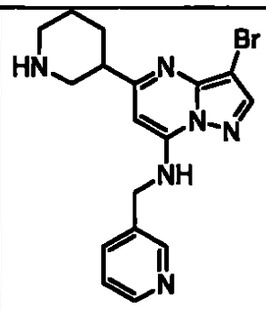
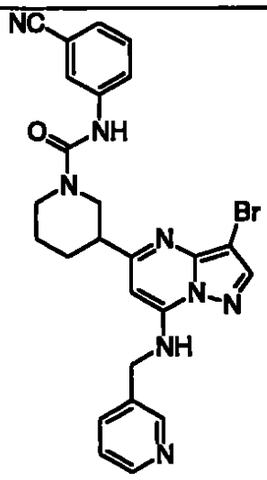
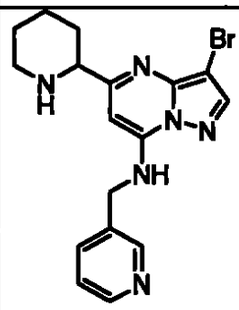
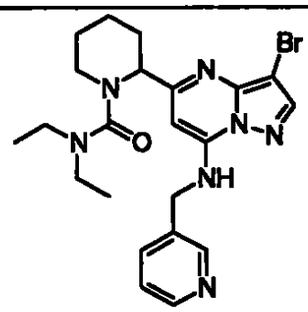
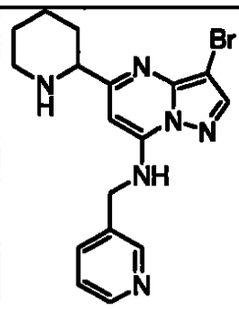
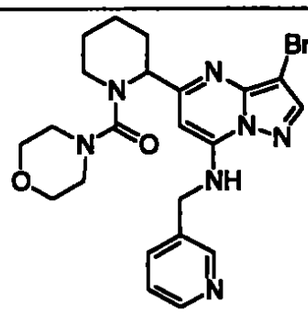
637

529			Rendimiento = 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

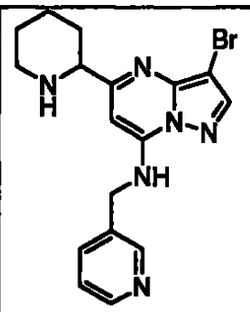
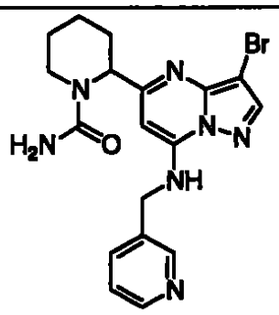
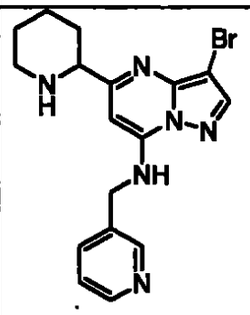
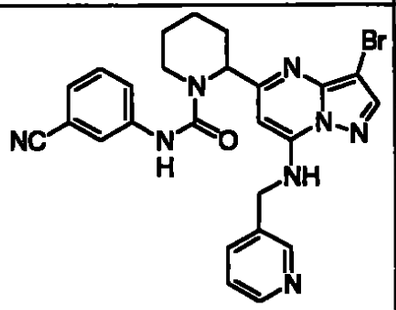
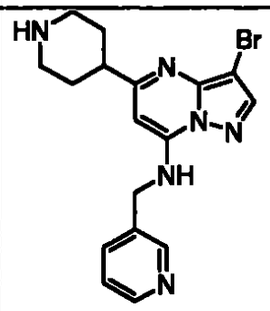
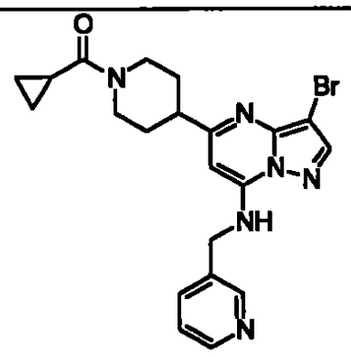
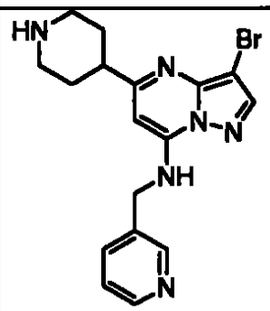
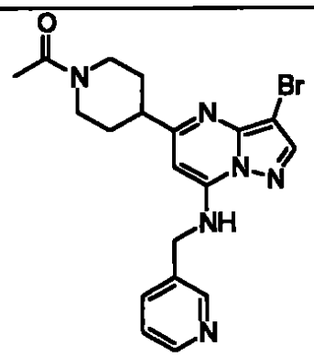
638

533			$MH^+ = 531$ m. p. =105,9 °C
534			$MH^+ = 486$
535			$MH^+ = 500$

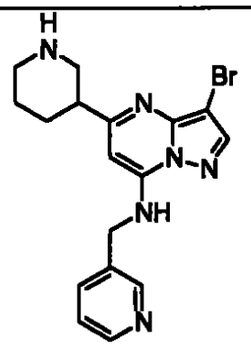
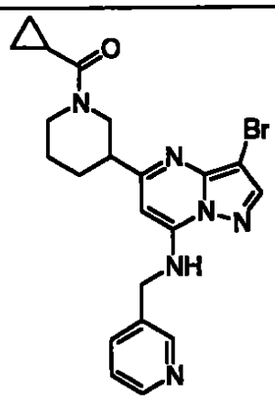
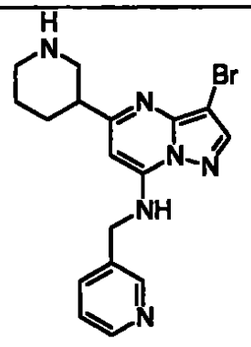
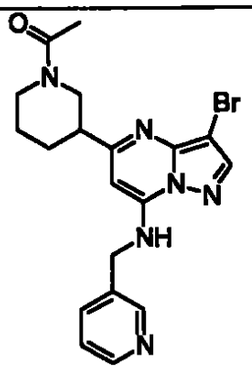
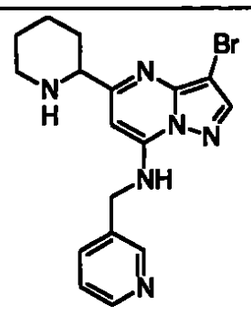
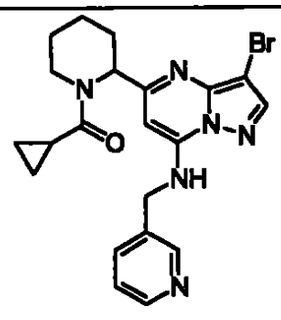
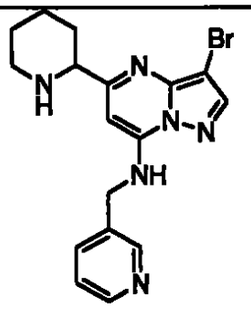
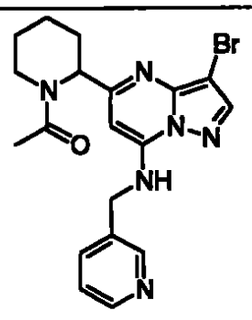
639

536			$MH^+ = 430$
537			$MH^+ = 531$
538			$MH^+ = 486$ m. p. = 69,6 °C
539			$MH^+ = 500$ m. p. = 82,3 °C

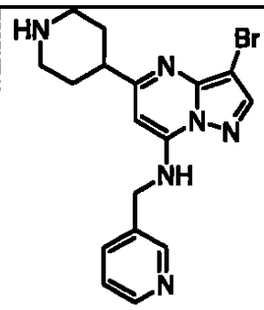
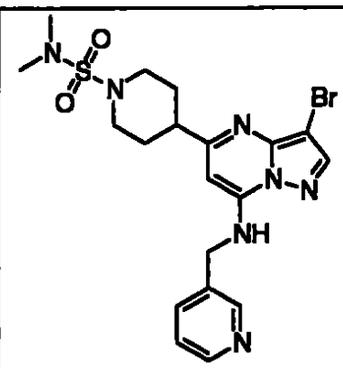
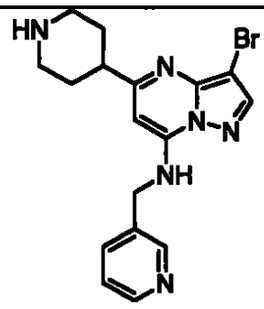
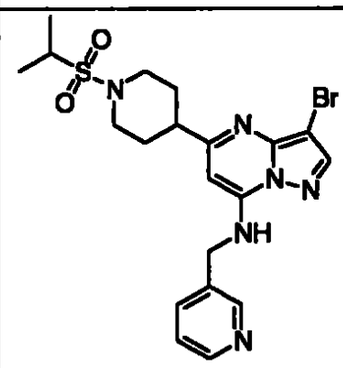
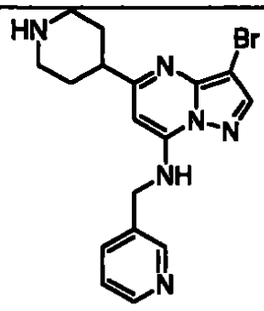
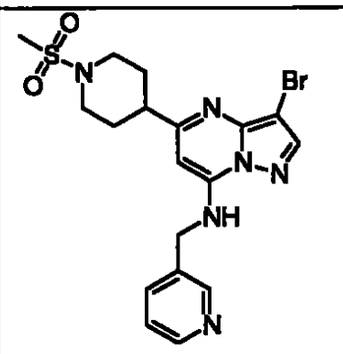
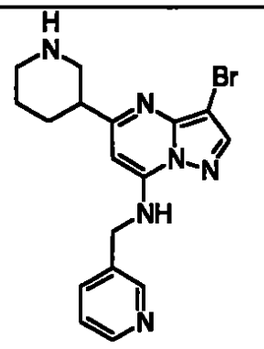
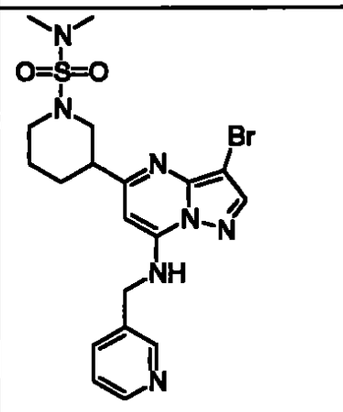
640

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

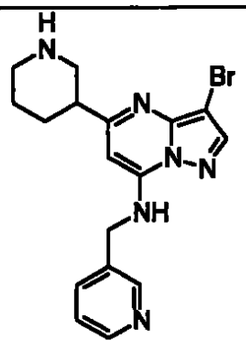
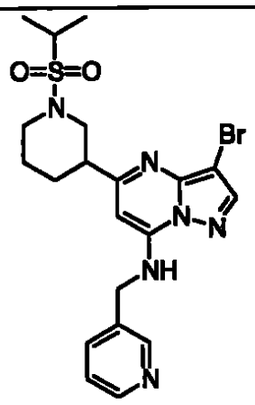
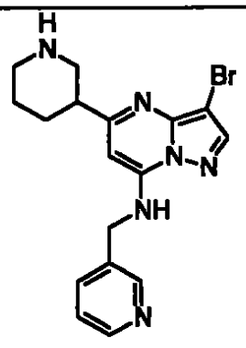
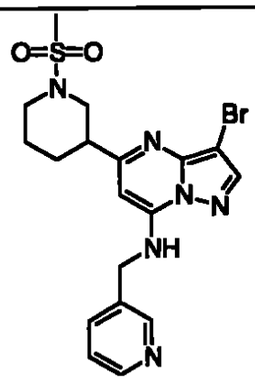
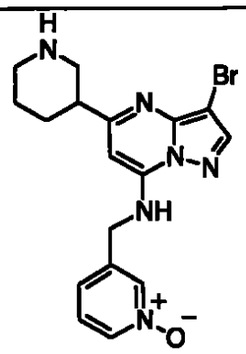
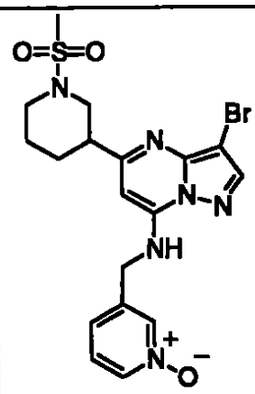
641

544			$MH^+ = 455$
545			$MH^+ = 429$
546			$MH^+ = 455$ m. p. =80,1 °C
547			$MH^+ = 429$ m. p. = 64,7 °C

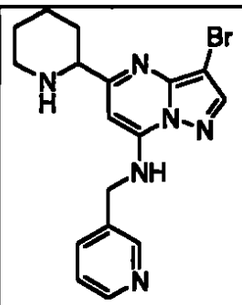
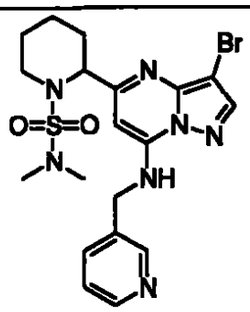
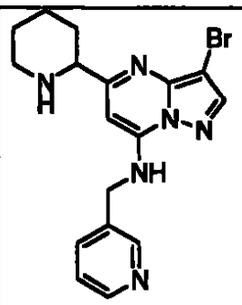
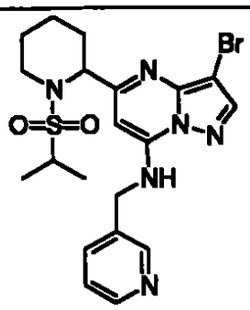
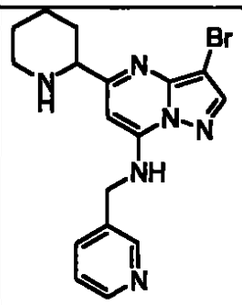
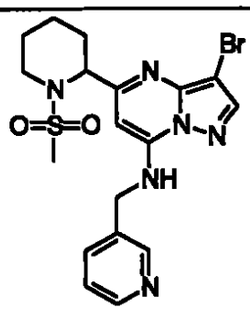
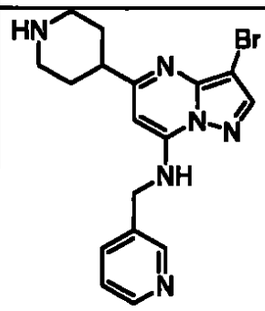
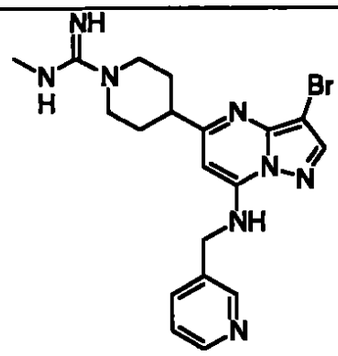
642

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			$MH^+ = 494$

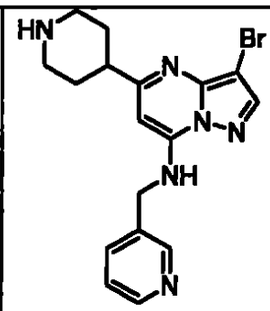
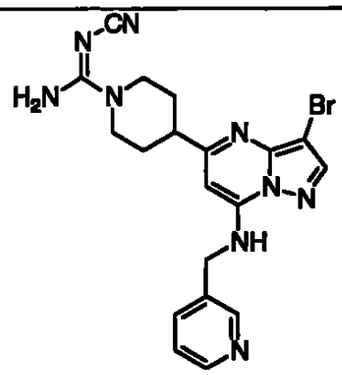
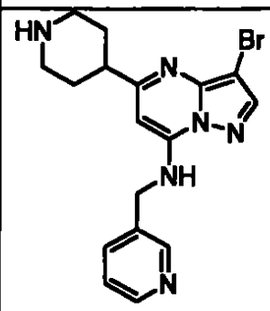
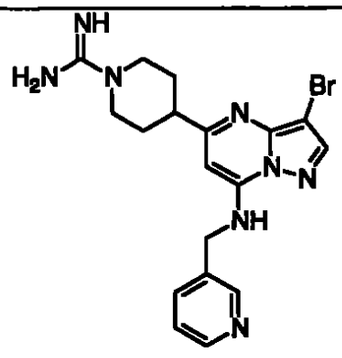
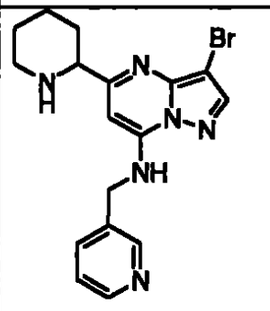
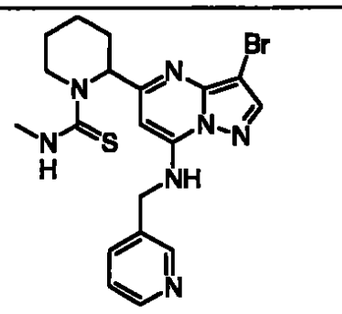
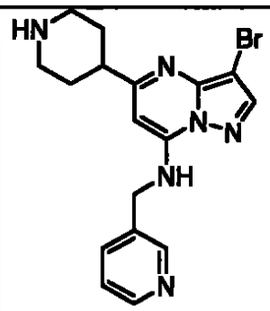
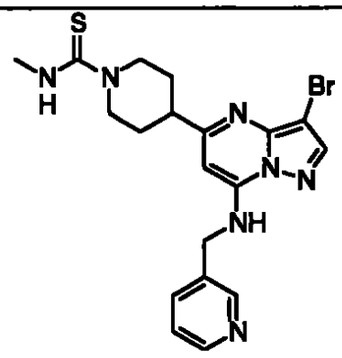
643

552			$MH^+ = 493$
553			$MH^+ = 465$
554			$MH^+ = 481$ m. p. = 102,7 °C

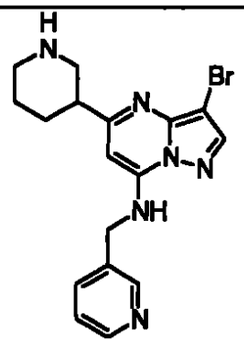
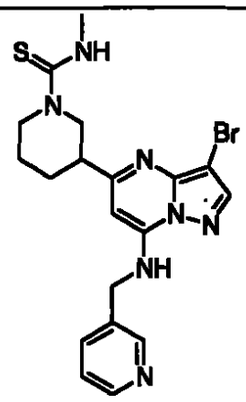
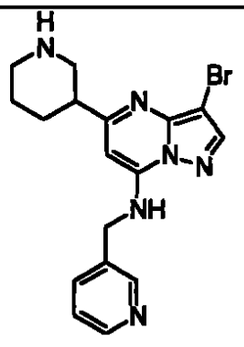
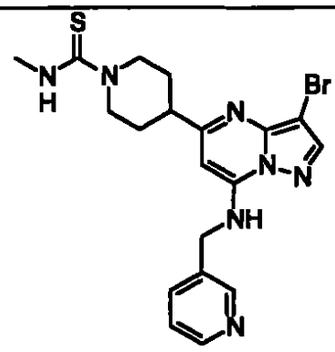
699

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			Rendimiento = cuant. MH^+ = 443 m. p. = 98,3 °C (HCl salt)

695

559			$MH^+ = 454$
560			Rendimiento = cuant. $MH^+ = 429$ m. p. = 111,5 – 112, 6 °C
561			$MH^+ = 460$ m. p. = 122,7 °C
562			$MH^+ = 460$ m. p. = 95,4 °C

696

563			$MH^+ = 460$
564			$MH^+ = 460$ m. p. = 95,4 °C

Datos adicionales para ejemplos selectos dados 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).

647

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).

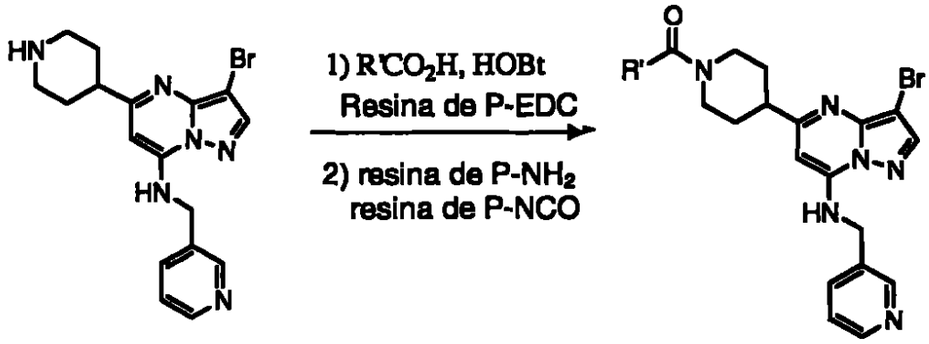
Ejemplo 553: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,67 (s, 1H), 8,62 (br s, 1H), 7,96 (s, 1H), 7,74 – 7,69 (d, 1H), 7,36 – 7,31 (dd, 1H), 6,70 – 6,66 (t, 1H), 5,98 (s, 1H), 4,67 – 4,63 (d, 2H), 3,88 – 3,81 (m, 1H), 3,71 – 3,65 (m, 1H), 3,20 – 3,11 (dd, 1H), 3,02 – 2,91 (m, 1H), 2,90 – 2,80 (m, 4H), 2,01 – 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,

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).

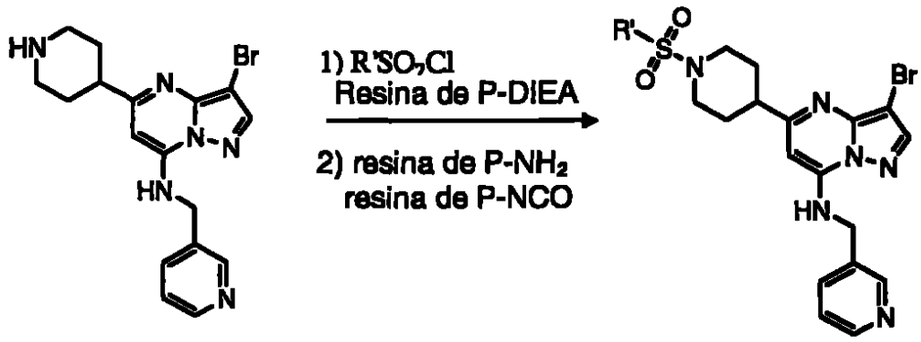
PROCEDIMIENTO GENERAL 1: Procedimiento para de síntesis paralela de formación de la amida:



La síntesis paralela se llevó a cabo en bloques de reacción de 96 pocillos de polipropileno con una tapa superior extraíble y una tapa inferior fija. Cada pocillo de reacción se preparó con una frita inferior de polipropileno de 20 micrones y el volumen máximo fue 3 ml. El bloque de recolección no se equipó con una frita inferior. A cada pocillo de reacción se agregó una solución de una amina (0,021 mmol) disuelta en una mezcla de DMF-THF-MeCN (4:3:3 v/v, 0,95 ml), resina de EDC (P-EDC, Polymer Laboratories Ltd., 43 mg, 0,063 mmol), 1-hidroxibenzotriazol (HOBt, 5,67 mg, 0,042 mmol) y una solución de un ácido carboxílico en dimetilformamida (1 M, 0,0315 ml, 0,0315 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 h. La solución del producto bruto se filtró en un pocillo de reacción cargado con resina de trisamina (P-NH2, Argonaut Tech. Inc., 30 mg, 0,126 mmol) y reina de isocianato (P-NCO, Argonaut Tech. Inc., 35 mg, 0,063 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 h y se filtró en el bloque de recolección. La solución del producto se evaporó bajo presión reducida para dar el producto de amida deseado.

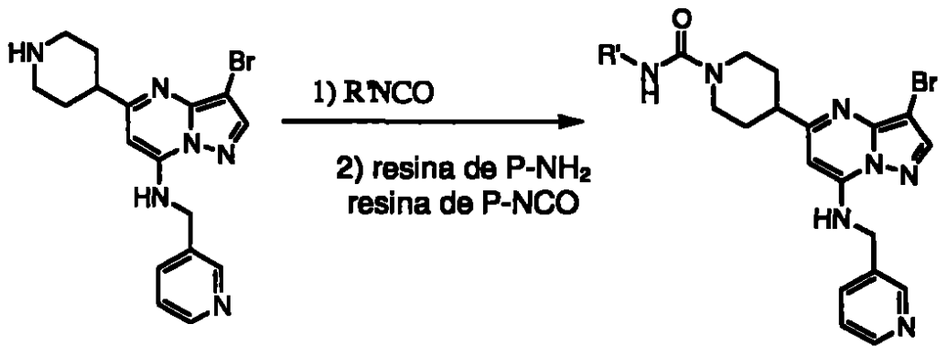
PROCEDIMIENTO GENERAL 2: Procedimiento para síntesis paralela de formación de sulfonamida

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La síntesis paralela se llevó a cabo en bloques de reacción de 96 pocillos de polipropileno con una tapa superior extraíble y una tapa inferior fija. Cada pocillo de reacción se preparó con una frita inferior de polipropileno de 20 micrones y el volumen máximo fue 3 ml. El bloque de recolección no se equipó con una frita inferior. A cada pocillo de reacción se agregó una solución de una amina (0,021 mmol) 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 mmol) y una solución de un cloruro sulfonilo en dimetilformamida (1 M, 0,0315 ml, 0,0315 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 h. La solución del producto bruto se filtró en un pocillo de reacción cargado con resina de trisamina (P-NH2, Argonaut Tech. Inc., 30 mg, 0,126 mmol) y reina de isocianato (P-NCO, Argonaut Tech. Inc., 35 mg, 0,063 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 h y se filtró en el bloque de recolección. La solución del producto se evaporó bajo presión reducida para dar el producto de sulfonamida deseado.

PROCEDIMIENTO GENERAL 3: Procedimiento para la síntesis paralela de formación de urea

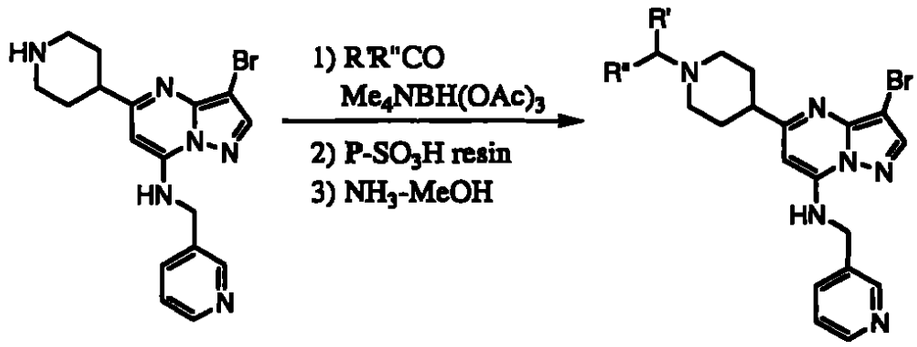


La síntesis paralela se llevó a cabo en bloques de reacción de 96 pocillos de polipropileno con una tapa superior extraíble y una tapa inferior fija. Cada

650

pocillo de reacción se preparó con una frita inferior de polipropileno de 20 micrones y el volumen máximo fue 3 ml. El bloque de recolección no se equipó con una frita inferior. A cada pocillo de reacción se agregó una solución de una amina (0,021 mmol) disuelta 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 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 h. La solución del producto bruto se filtró en un pocillo de reacción cargado con resina de trisamina (P-NH2, Argonaut Tech. Inc., 30 mg, 0,126 mmol) y reina de isocianato (P-NCO, Argonaut Tech. Inc., 35 mg, 0,063 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 h y se filtró en el bloque de recolección. La solución del producto se evaporó bajo presión reducida para dar el producto de urea deseado.

PROCEDIMIENTO GENERAL 4: Procedimiento para la síntesis paralela de alquilación reductora

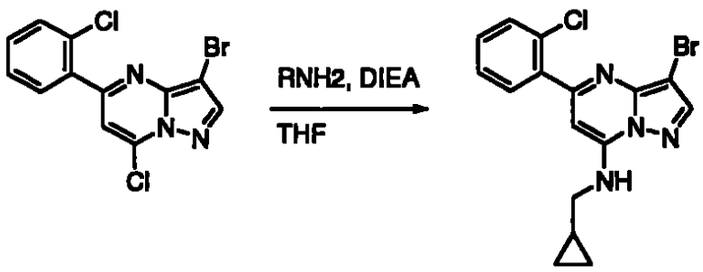


La síntesis paralela se llevó a cabo en bloques de reacción de 96 pocillos de polipropileno con una tapa superior extraíble y una tapa inferior fija. Cada pocillo de reacción se preparó con una frita inferior de polipropileno de 20 micrones y el volumen máximo fue 3 ml. El bloque de recolección no se equipó con una frita inferior. A cada pocillo de reacción se agregó una solución de una amina (0,021 mmol) 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 mmol), y una solución de triacetoxiborohidruro de tetrametilamonio (11 mg, 0,042 mmol) disuelta en AcOH-DCE mixture 1:99 v/v, 0,5 ml). La mezcla de reacción se agitó

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a temperatura ambiente durante 3 días. La solución del producto bruto se filtró en un pocillo de reacción cargado con resina de ácido sulfónico Lanterns (P-SO_3H, MimotopesPty Ltd., 0,3 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 2 h y se decantó. La resina del producto 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 min. y se filtró en el bloque de recolección. La solución del producto se evaporó bajo presión reducida para dar 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 mmol) en tetrahidrofurano se agregaron di-*iso*-propiletilamina (12 µl, 0,07), seguida por ciclopropilmetilamina (70 µl, .07 mmol; solución 1M en DMF). La mezcla de reacción se calentó to 70 °C durante 36 h y luego se enfrió a TA. La mezcla se trató con (P-NCO, Argonaut Tech. Inc 70 mg, 0,12 mmol), y P-CO_3^- (Argonaut Tech. Inc 70 mg, 0,24 mmol) y se agitó a temperatura ambiente durante 12-18 h. La solución se filtró y se evaporó hasta que se secó para dar el producto observado m/z 375,21.

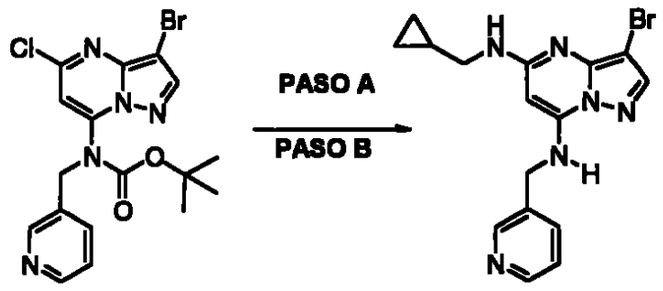
PROCEDIMIENTO GENERAL 6: Procedimiento para la síntesis paralela de pirazolo[1,5a]pirimidinas 5,N-sustituidas

Protocolos Generales:

La síntesis paralela se llevó a cabo en bloques de polipropileno de 96 pocillos, según se describe en otro lugar de la presente. En el caso que se requirió calentamiento, las reacciones se realizaron en tubos de vidrio de 2,5 ml

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sellados individualmente con una estera de polipropileno y el calentamiento se logró mediante un bloque de transferencia de calor de 96 pocillos.



PASO A:

A 3-bromo-5-cloro-7-N-Boc-alquilamino-pirazolo[1,5-a]pirimidina (17 mg, 0,04 mmol) en *p*-dioxano se agregaron DIEA (9 µl, 0,05), seguido por ciclopropil-metilamina (80 µl, .08 mmol; solución 1M en isopropanol). La mezcla de reacción se calentó a 90 °C durante 36 h y luego se enfrió a temperatura ambiente. La mezcla se trató con P-NCO (Argonaut Tech. Inc. 70 mg, 0,12 mmol) y P-CO_3^- (Argonaut Tech. Inc. 70 mg, 0,24 mmol) y se agitó a temperatura ambiente durante 12-18 h. La solución se filtró y se evaporó hasta que se secó para dar el producto.

PASO B(ácido):

El producto del PASO A se capturó en TFA35% /DCM y se agitó durante 4 h seguido por una concentración en alto vacío. El residuo se trató con HCl(aq) 10% en MeOH agitado durante 2 h y luego concentrado para dar el producto deseado. Se observó m/z 375,21.

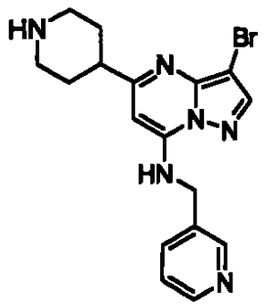
PASO B(básico):

El producto del paso A se capturó en EtOH y se trató con resina de intercambio de ión Ambersep® 900-OH (Acros, 100mg), se calentó a reflujo durante 48 h con agitación leve. La mezcla de reacción se enfrió hasta temperatura ambiente, se filtró y se concentró para dar el producto deseado.

EJEMPLO 565:

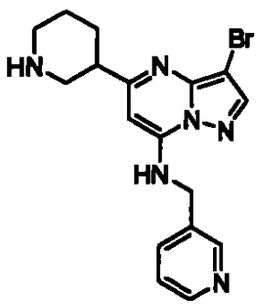
653

Por medio del uso del procedimiento expuesto en el Procedimiento General 1 y el compuesto del Ejemplo 462 que se mostró anteriormente, se prepararon los compuestos con el m/z observado que se muestra en la Tabla 43.



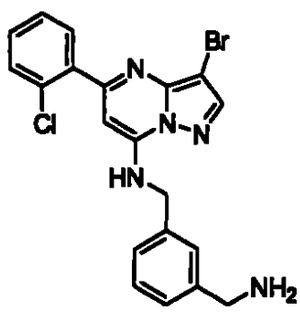
EJEMPLO 566:

Por medio del uso del procedimiento expuesto en el Procedimiento General 1 y el compuesto del Ejemplo 471 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 44 con el m/z observado.



EJEMPLO 567:

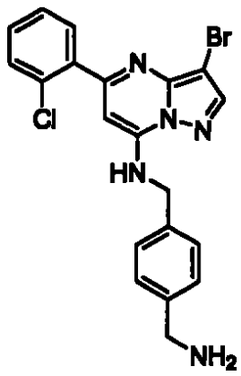
Por medio del uso del procedimiento expuesto en el Procedimiento General 1 y el compuesto del Ejemplo 515 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 45 con el m/z observado.



EJEMPLO 568:

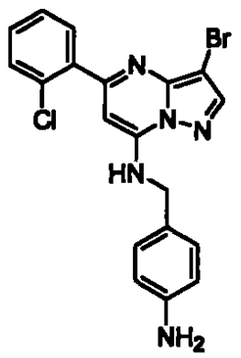
654 655

Por medio del uso del procedimiento expuesto en el Procedimiento General 1 y el compuesto del Ejemplo 513 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 46 con el m/z observado.



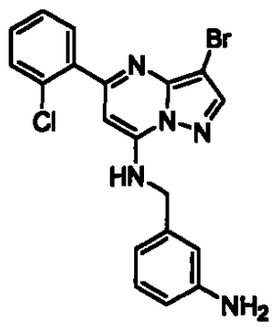
EJEMPLO 569:

Por medio del uso del procedimiento expuesto en el Procedimiento General 1 y el compuesto del Ejemplo 526 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 47 con el m/z observado.



EJEMPLO 570:

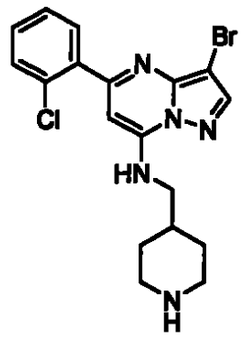
Por medio del uso del procedimiento expuesto en el Procedimiento General 1 y el compuesto del Ejemplo 524 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 48 con el m/z observado.



EJEMPLO 571:

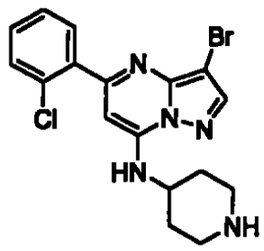
655

Por medio del uso del procedimiento expuesto en el Procedimiento General 1 y el compuesto del Ejemplo 525 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 49 con el m/z observado.



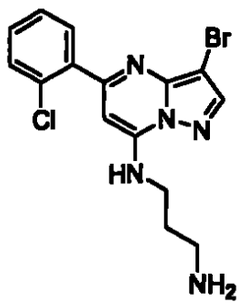
EJEMPLO 572:

Por medio del uso del procedimiento expuesto en el Procedimiento General 1 y el compuesto del Ejemplo 526,10 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 50 con el m/z observado.



EJEMPLO 573:

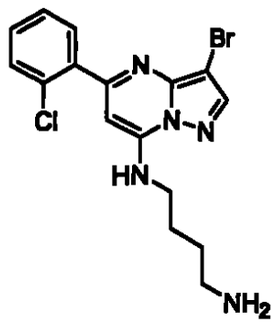
Por medio del uso del procedimiento expuesto en el Procedimiento General 1 y el compuesto del Ejemplo 518 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 51 con el m/z observado.



EJEMPLO 574:

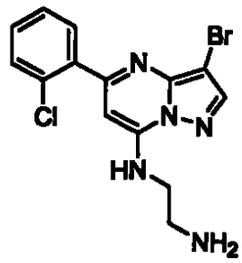
Por medio del uso del procedimiento expuesto en el Procedimiento General 1 y el compuesto del Ejemplo 519 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 52 con el m/z observado.

656



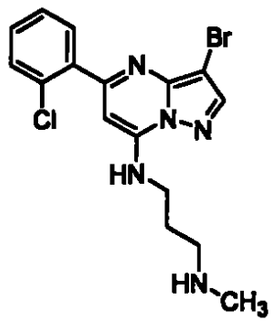
EJEMPLO 575:

Por medio del uso del procedimiento expuesto en el Procedimiento General 1 y el compuesto del Ejemplo 520 que se mostró anteriormente, se prepararon se prepararon los compuestos que se muestran en la Tabla 53 con el m/z observado.



EJEMPLO 576:

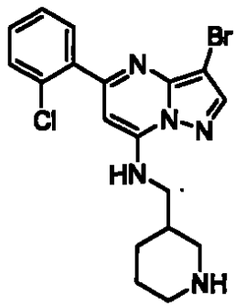
Por medio del uso del procedimiento expuesto en el Procedimiento General 1 y el compuesto del Ejemplo 522 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 54 con el m/z observado.



EJEMPLO 577:

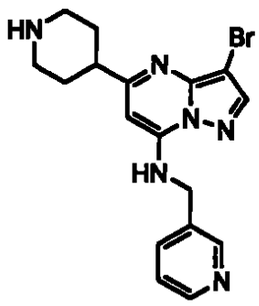
Por medio del uso del procedimiento expuesto en el Procedimiento General 1 y el compuesto del Ejemplo 523 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 55 con el m/z observado.

657 656



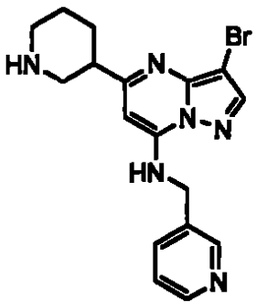
EJEMPLO 578:

Por medio del uso del procedimiento expuesto en el Procedimiento General 2 y el compuesto del Ejemplo 462 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 56 con el m/z observado.



EJEMPLO 579:

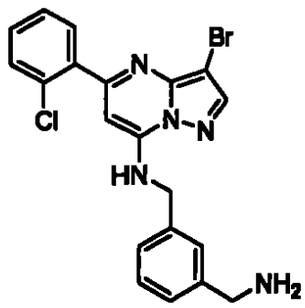
Por medio del uso del procedimiento expuesto en el Procedimiento General 2 y el compuesto del Ejemplo 471 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 57 con el m/z observado.



EJEMPLO 580:

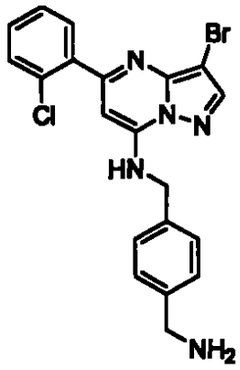
Por medio del uso del procedimiento expuesto en el Procedimiento General 2 y el compuesto del Ejemplo 515 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 58 con el m/z observado.

658 659



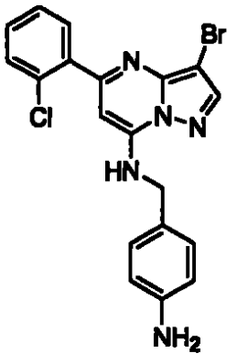
EJEMPLO 581:

Por medio del uso del procedimiento expuesto en el Procedimiento General 2 y el compuesto del Ejemplo 513 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 59 con el m/z observado.



EJEMPLO 582:

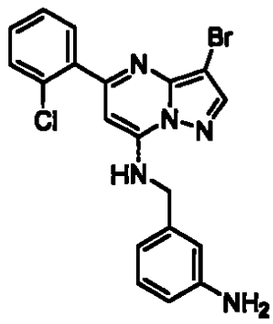
Por medio del uso del procedimiento expuesto en el Procedimiento General 2 y el compuesto del Ejemplo 513 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 60 con el m/z observado.



EJEMPLO 583:

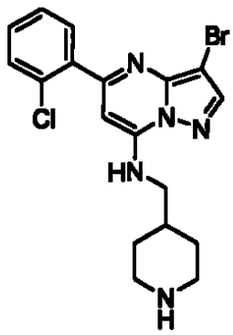
Por medio del uso del procedimiento expuesto en el Procedimiento General 2 y el compuesto del Ejemplo 524 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 61 con el m/z observado.

659 660



EJEMPLO 584:

Por medio del uso del procedimiento expuesto en el Procedimiento General 2 y el compuesto del Ejemplo 525 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 62 con el m/z observado.



EJEMPLO 585:

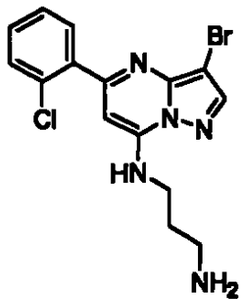
Por medio del uso del procedimiento expuesto en el Procedimiento General 2 y el compuesto del Ejemplo 526,10 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 63 con el m/z observado.



EJEMPLO 586:

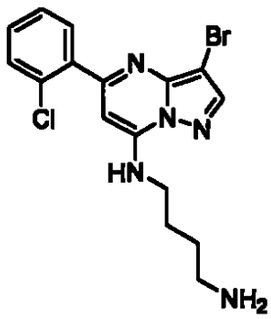
Por medio del uso del procedimiento expuesto en el Procedimiento General 2 y el compuesto del Ejemplo 518 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 64 con el m/z observado.

660



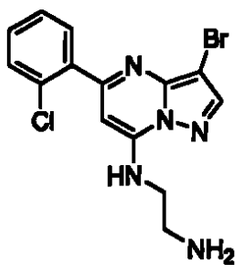
EJEMPLO 587:

Por medio del uso del procedimiento expuesto en el Procedimiento General 2 y el compuesto del Ejemplo 519 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 65 con el m/z observado.



EJEMPLO 588:

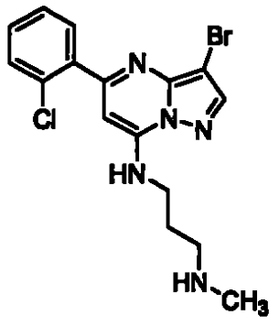
Por medio del uso del procedimiento expuesto en el Procedimiento General 2 y el compuesto del Ejemplo 520 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 67 con el m/z observado.



661 662

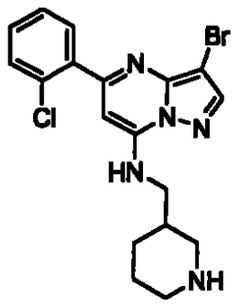
EJEMPLO 589:

Por medio del uso del procedimiento expuesto en el Procedimiento General 2 y el compuesto del Ejemplo 521 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 68 con el m/z observado.



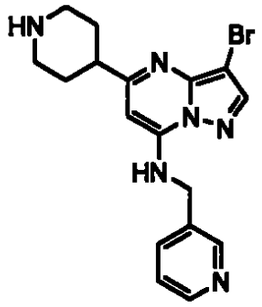
EJEMPLO 590:

Por medio del uso del procedimiento expuesto en el Procedimiento General 2 y el compuesto del Ejemplo 523 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 69 con el m/z observado.



EJEMPLO 591:

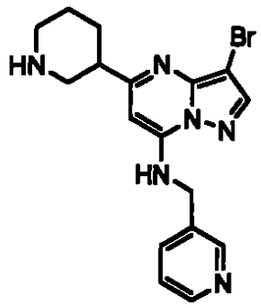
Por medio del uso del procedimiento expuesto en el Procedimiento General 3 y el compuesto del Ejemplo 462 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 70 con el m/z observado.



EJEMPLO 592:

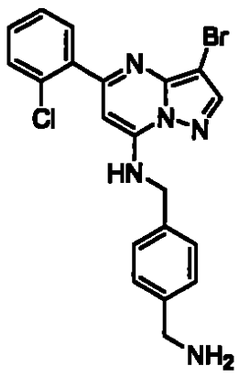
662 663

Por medio del uso del procedimiento expuesto en el Procedimiento General 3 y el compuesto del Ejemplo 471 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 71 con el m/z observado.



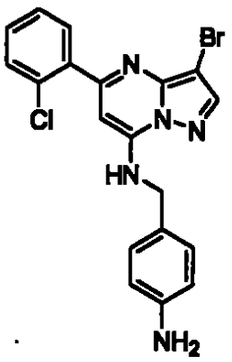
EJEMPLO 593:

Por medio del uso del procedimiento expuesto en el Procedimiento General 3 y el compuesto del Ejemplo 513 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 72 con el m/z observado.



EJEMPLO 594:

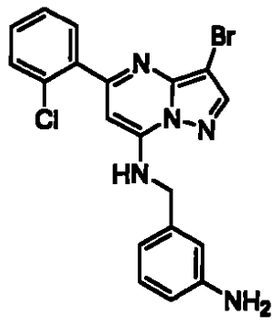
Por medio del uso del procedimiento expuesto en el Procedimiento General 3 y el compuesto del Ejemplo 524 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 73 con el m/z observado.



EJEMPLO 595:

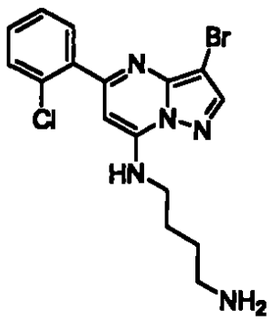
663

Por medio del uso del procedimiento expuesto en el Procedimiento General 3 y el compuesto del Ejemplo 524 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 74 con el m/z observado.



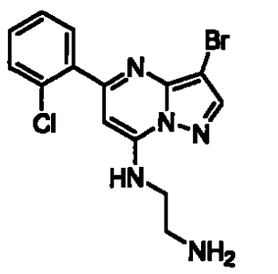
EJEMPLO 596:

Por medio del uso del procedimiento expuesto en el Procedimiento General 3 y el compuesto del Ejemplo 519 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 75 con el m/z observado.



EJEMPLO 597:

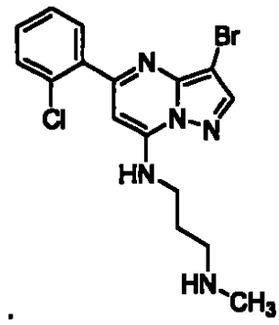
Por medio del uso del procedimiento expuesto en el Procedimiento General 3 y el compuesto del Ejemplo 520 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 76 con el m/z observado.



EJEMPLO 598:

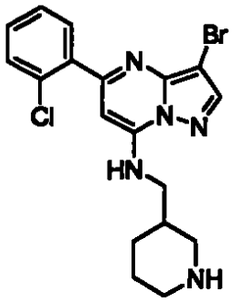
Por medio del uso del procedimiento expuesto en el Procedimiento General 3 y el compuesto del Ejemplo 521 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 77 con el m/z observado.

664 665



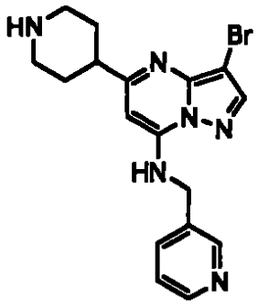
EJEMPLO 599:

Por medio del uso del procedimiento expuesto en el Procedimiento General 3 y el compuesto del Ejemplo 523 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 78 con el m/z observado.



EJEMPLO 600:

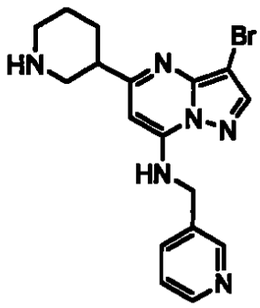
Por medio del uso del procedimiento expuesto en el Procedimiento General 4 y el compuesto del Ejemplo 462 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 79 con el m/z observado.



EJEMPLO 601:

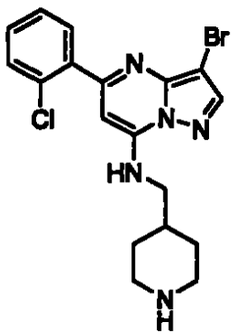
Por medio del uso del procedimiento expuesto en el Procedimiento General 4 y el compuesto del Ejemplo 471 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 80 con el m/z observado.

665



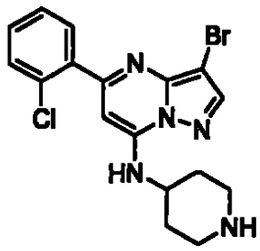
EJEMPLO 602:

Por medio del uso del procedimiento expuesto en el Procedimiento General 4 y el compuesto del Ejemplo 525 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 81 con el m/z observado.



EJEMPLO 603:

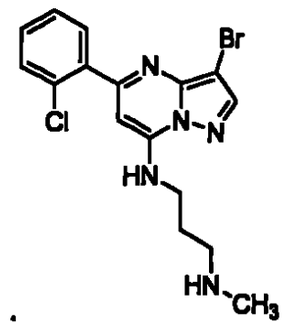
Por medio del uso del procedimiento expuesto en el Procedimiento General 4 y el compuesto del Ejemplo 526,10 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 82 con el m/z observado.



EJEMPLO 604:

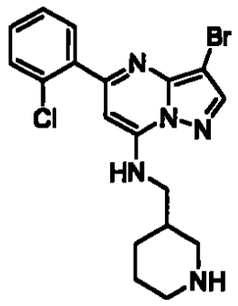
Por medio del uso del procedimiento expuesto en el Procedimiento General 4 y el compuesto del Ejemplo 521 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 83 con el m/z observado.

666



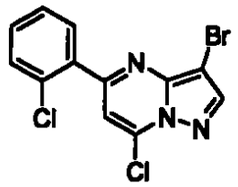
EJEMPLO 605:

Por medio del uso del procedimiento expuesto en el Procedimiento General 4 y el compuesto del Ejemplo 523 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 84 con el m/z observado.



EJEMPLO 606:

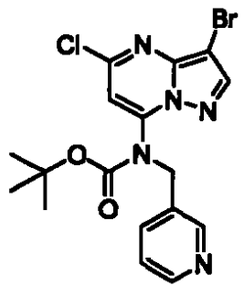
Por medio del uso del procedimiento expuesto en el Procedimiento General 5 y el compuesto del Ejemplo Preparativo 81 que se mostró anteriormente, se prepararon los compuestos que se muestran en la Tabla 85 con el m/z observado.



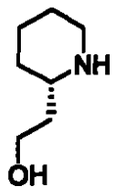
EJEMPLO 607:

Por medio del uso del procedimiento expuesto en el Procedimiento General 6 y el compuesto del Ejemplo Preparativo 196, se prepararon los compuestos que se muestran en la Tabla 86 con el m/z observado.

667

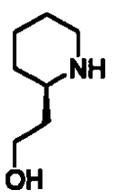


EJEMPLO PREPARATIVO 500



Se agregó piperidin-2-etanol (127 g, 980 mmol) en EtOH 95% (260 ml) a ácido *(S)*-(+)-alcanforsulfónico (228,7 g, 1,0 eq.) en EtOH 95% (150 ml) y la solución resultante se calentó hasta reflujo. A la solución caliente se agregó Et_2O (600 ml) y la solución se enfrió hasta temperatura ambiente y se dejó reposar durante 3 días. Los cristales resultantes se filtraron y se secaron *in vacuo* (25 g): mp 173-173 °C (lit. 168 °C). Luego, la sal se disolvió en NaOH (3M, 100 ml) y se agitó 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, y se concentraron bajo presión reducida para dar *(S)*-piperidin-2-etanol (7,8 g) una porción de la cual se recristalizó a partir de Et_2O: mp= 69-70 °C (lit. 68-69 °C); $[\alpha]_D$ = 14,09° ($CHCl_3$, c=0,2).

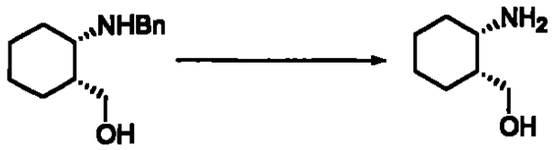
EJEMPLO PREPARATIVO 501



Esencialmente por medio del mismo procedimiento expuesto en el Ejemplo Preparativo 500 sustituyendo solamente ácido *(R)*-(-)-alcanforsulfónico, se preparó *(R)*-piperidin-2-etanol. (1,27 g): $[\alpha]_D$ = 11,3° ($CHCl_3$, c=0,2).

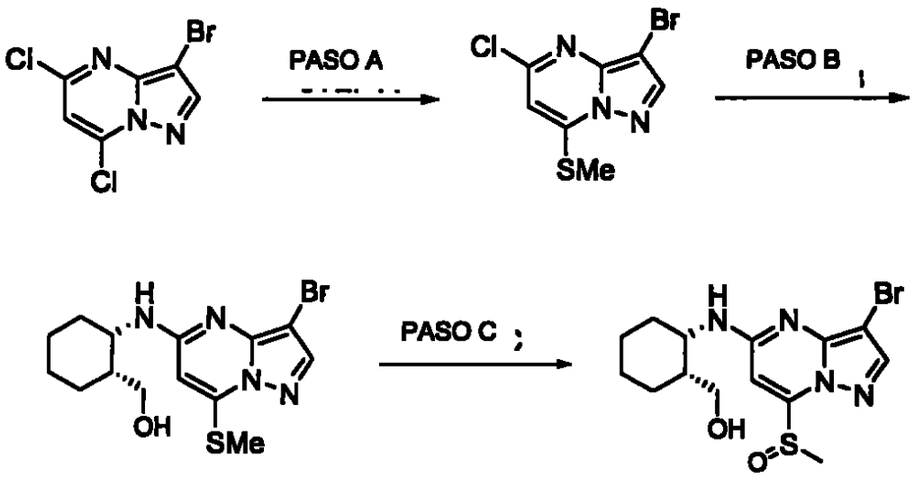
668

EJEMPLO PREPARATIVO 502



A un frasco de presión cargado con una solución de *cis*-(1*R*,2*S*)-(+)-2-(bencilamino) ciclohexanometanol (1g, 4,57 mmol) en MeOH (35 ml) se agregó 20% en peso de $Pd(OH)_2$ (0,3g, >50% húmedo) en una porción. La mezcla se agitó bajo 50 psi de H_2 en un aparato de hidrogenación Parr durante 12 h. La mezcla se purgó a N_2 y se filtró a través de un taco de Celite. El taco se lavó generosamente con MeOH (2 x 25 ml) y el filtrado resultante se concentró bajo presión reducida para dar 0,57g (97%) de un sólido blanco. M+H = 130.

EJEMPLO PREPARATIVO 503



Paso A:

A una solución de aducto 3-Br (1,1 g, 4,1 mmol) del Ejemplo Preparativo 142 en THF (40 ml) a 0°C se agregó CH_3SNa (0,32 g, 4,53 mmol) en una porción. La mezcla heterogénea se agitó durante 72 h a temperatura ambiente y la mezcla se concentró bajo presión reducida. El producto bruto 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 secaron (Na_2SO_4). La capa orgánica se filtró y se concentraron bajo presión reducida para dar 1,0 g (88%) de un sólido amarillo. mp 150-152 °C; M+H = 280. Este material se tomó sobre el Paso B sin purificación adicional.

669

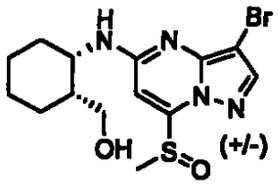
Paso B:

A una solución de derivado tiometilo (1,5 g, 5,37 mmol) del Paso A en dioxano/DIPEA (15 ml/4 ml) a temperatura ambiente se agregó amino alcohol (1,3 g, 8,06 mmol) del Ejemplo Preparativo 10. La mezcla se calentó a reflujo durante 48 h, se enfrió a ta, y se concentró bajo presión reducida. El producto bruto se purificó mediante cromatografía flash usando CH_2Cl_2/MeOH (30:1) como eluyente para dar 1,8 g del producto (90%) como un sólido amarillo cristalino. mp 167-169 °C; M+H = 373.

Paso C:

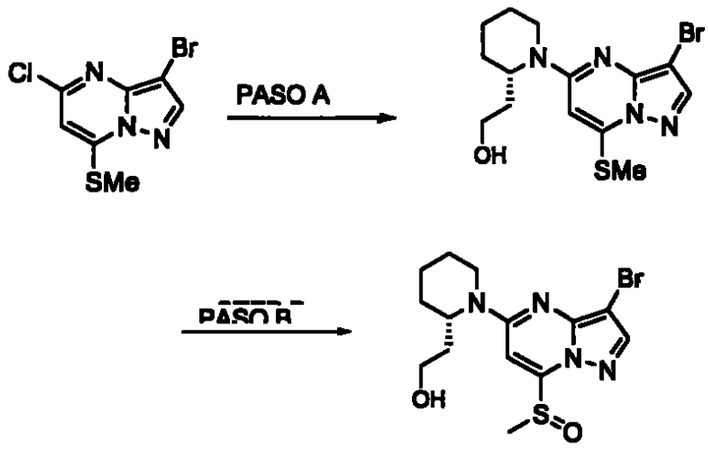
A una solución de derivado tiometilo (2,2 g, 5,92 mmol) del Paso B in CH_2Cl_2 (20 ml) a 0°C se agregó MCPBA (1,53 g, 8,9 mmol) en una porción. La mezcla resultante se agitó durante 2h a 0°C momento en el cual la mezcla se diluyó con CH_2Cl_2 (20 ml) y $NaHCO_3$ acuoso sat. (15 ml). Las capas se separaron y la capa orgánica se lavó con $NaHCO_3$ acuoso sat. (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 dar 2,0 g de un sólido marrón (87%). mp 181-183 °C; M+H = 388.

EJEMPLO PREPARATIVO 504



El compuesto de título (racémico) se preparó de acuerdo con el procedimiento expuesto en el Ejemplo Preparativo 503, con la salvedad que se sustituyó el clorhidrato de *cis*-hidroximetil-1-ciclohexilamina disponible comercialmente en el Paso B.

EJEMPLO PREPARATIVO 505



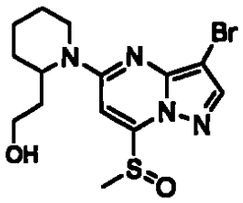
Paso A:

El tratamiento del derivado tiometilo (2,0 g, 7,2 mmol) del Paso A del Ejemplo Preparativo 503 con (*S*)-piperidin-2-etanol (1,2 g, 9,3 mmol) del Ejemplo Preparativo 500 en condiciones idénticas a las descriptas en el Paso B del Ejemplo Preparativo 503, se preparó 0,90 g (34%) del compuesto semisólido de título. mp 173-175 °C. M+H = 372.

Paso B:

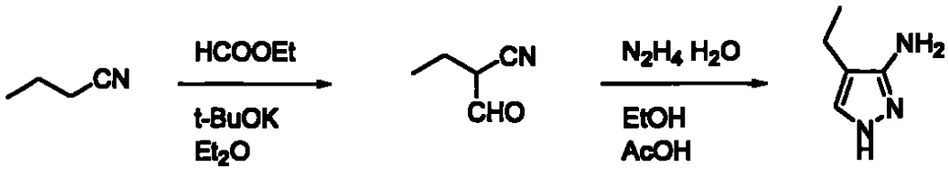
Siguiendo el procedimiento del Paso C en el Ejemplo Preparativo 503, el derivado tiometilo (0,30 g, 0,81 mmol) se trató con MCPBA (0,21 g, 1,2 mmol) para dar 0,31 g (99%) el compuesto de título como un aceite amarillo viscoso. M+H = 388.

EJEMPLO PREPARATIVO 506



El compuesto de título (racémico) se preparó de acuerdo con el procedimiento expuesto en el Ejemplo Preparativo 505, con la salvedad que se sustituyó el piperidin-2-etanol disponible comercialmente. M+H = 388.

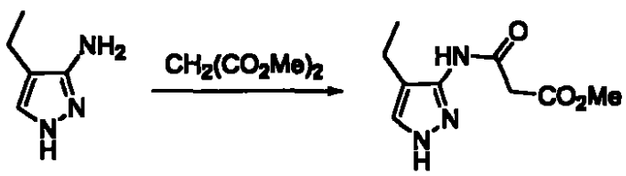
EJEMPLO PREPARATIVO 507



671

Se agitó t-BuOK (112,0g, 1,00 mol) bajo N_2 en Et_2O seco(3,0 L) n una matraz de 5 L equipada con un embudo de adición. Se agregó una mezcla de butironitrilo (69,0 g, 1,00 mol) y etilformato (77,7 g, 1,05 mol) gota a gota durante 3 hrs, luego la mezcla de reacción se agitó hasta el día siguiente a temperatura ambiente. La mezcla se enfrió hasta 0°C, se agregó AcOH (57 ml), la mezcla se filtró, y el sólido se lavó con Et_2O (500 ml). Los filtrados combinados se evaporaron a temperatura ambiente en un rotovap para dar aceite amarillo pálido (95,1g). El aceite se disolvió en EtOH seco (100 ml), se agregó 99% de monohidrato de hidrazina (48 ml), luego se agregó AcOH (14 ml), y la mezcla se reflujó bajo N_2 hasta el día siguiente. Los solventes se evaporaron y el aceite resultante se sometió a cromatografía sobre gel de sílice con CH_2Cl_2:7N NH_3 en MeOH. Se obtuvo 22,4 g (20%) de 3-amino-4-etilpirazol como aceite claro que se solidificó al dejarlo reposar.

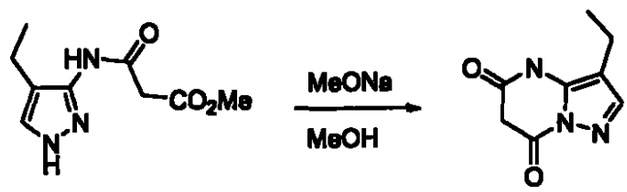
EJEMPLO PREPARATIVO 508



Paso A:

El pirazol del Ejemplo Preparativo 507 (9,80g) y dimetilmalonato (45 ml) se agitaron y se reflujaron bajo N_2 durante 3 hrs. El exceso de dimetilmalonato se evaporó en vacío y el residuo se sometió a cromatografía con 15:1 CH_2Cl_2:MeOH para dar sólido amarillo pálido (10,6 g, 57%). LCMS: MH^+ = 212.

Paso B:

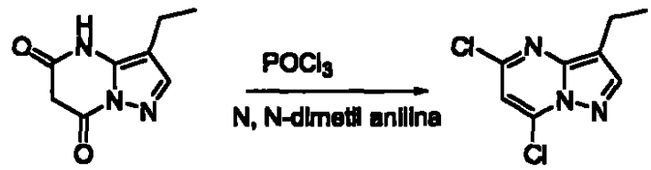


Se agregó MeOH seco (200 ml) bajo N_2 a una mezcla de la amida del Paso A (11,9g, 56,4 mmol) y metóxido de sodio (4,57g, 84,6 mmol). La mezcla se agitó y se reflujó bajo N_2 durante 5 hrs, se enfrió a ta, y se agregó HCl conc. (20 ml). Los solventes se evaporaron y el residuo se suspendió en H_2O (300 ml). el sólido

692

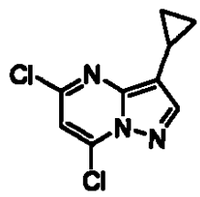
se filtró, se lavó en un filtro con 2x300 ml de H_2O, y se secó en vacío a 100°C. Se obtuvo 7,40g (73%) de sólido de color crema. LCMS: MH^+ = 180.

Paso C:



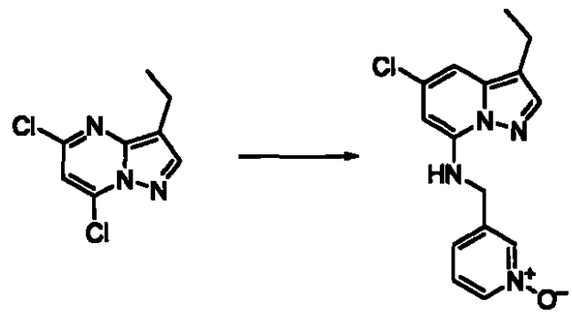
Se agregaron $POCl_3$ (100 ml) y N, N-dimetilanilina (20 ml) bajo N_2 a la dicetona del Paso B (7,70 g), y la mezcla se agitó y se reflujó durante 20 hrs bajo N_2. Luego, ésta se enfrió hasta temperatura ambiente, se vertió cuidadosamente en 1 L de hielo triturado. y se extrajo con EtOAc (2x500 ml). 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 sometió a cromatografía con CH_2Cl_2 para dar sólido amarillo pálido (8,20 g, 90%). LCMS: MH^+ = 216.

EJEMPLO PREPARATIVO 508.10



Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 508, sustituyendo solamente el compuesto del Ejemplo Preparativo 1, se preparó el compuesto anterior. LCMS: MH^+ = 228.

EJEMPLO PREPARATIVO 509



Se agitó una mezcla del dicloruro del Ejemplo Preparativo 508 (3,13g, 14,5 mmol), la amina.HCl del Ejemplo Preparativo (3,00g, 18,9 mmol), DIPEA (7,5 ml), y NMP seco (40 ml) más dioxano seco (40 ml) a 60°C durante 4 días bajo N_2. Luego, los solventes se destilaron en vacío y el residuo se sometió a

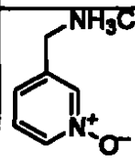
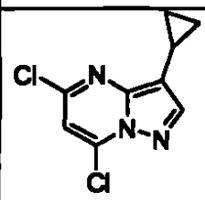
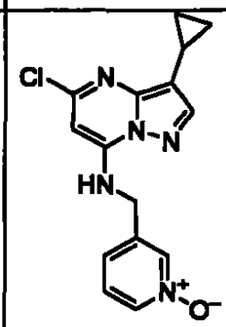
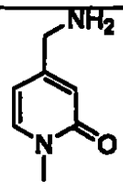
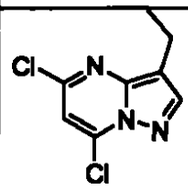
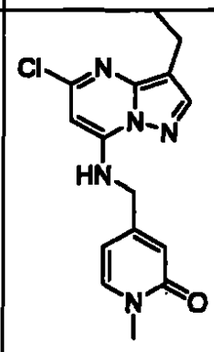
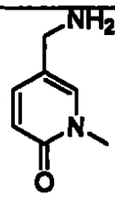
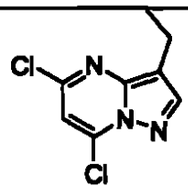
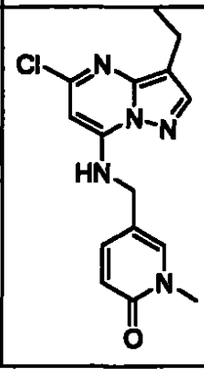
673

cromatografía con 6:1 EtOAc: MeOH y luego se sometió a cromatografía 12:1 CH_2Cl_2:MeOH. El sólido que se obtuvo de esta manera se suspendió en H_2O (100 ml), se filtró, se lavó en filtro con H_2O (2x100 ml), y se secaron en vacío. Se obtuvo sólido rosado pálido (2,37g, 54%). M+H = 304.

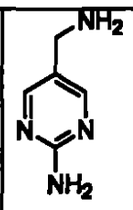
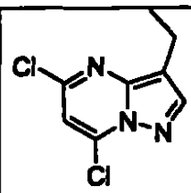
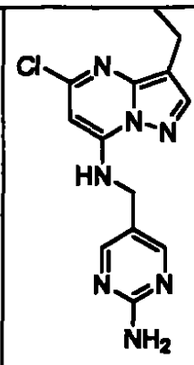
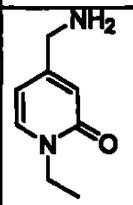
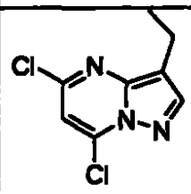
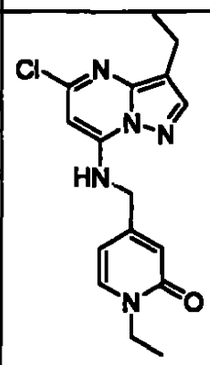
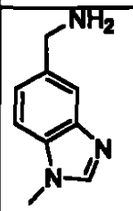
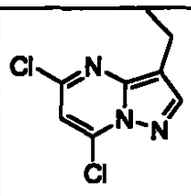
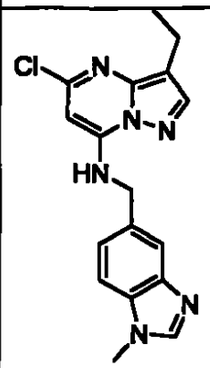
Ejemplos preparativos 510-516

Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 509, sustituyendo solamente 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	COMPUESTO
510				M+H = 316
512				M+H = 318
513				M+H = 318

674

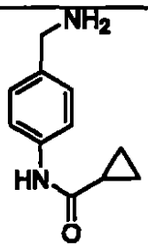
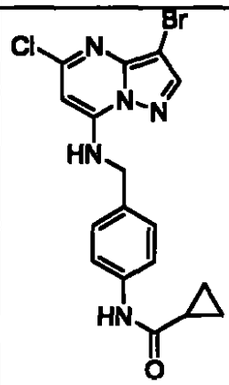
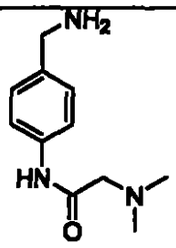
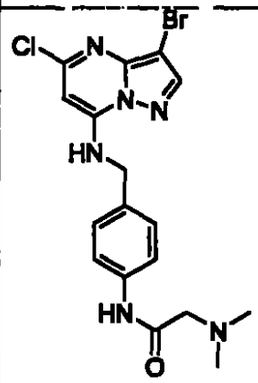
514				
515				M+H = 332
516				

EJEMPLO PREPARATIVO 517:

Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 184, sustituyendo solamente las aminas en la Columna 2 de la Tabla 501, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 501.

675

TABLA 501

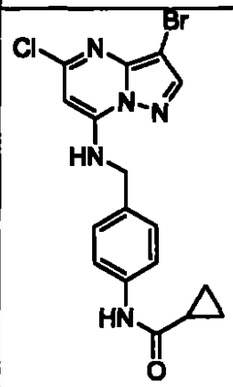
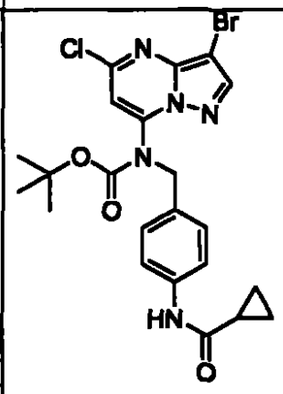
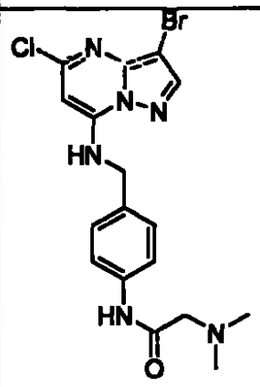
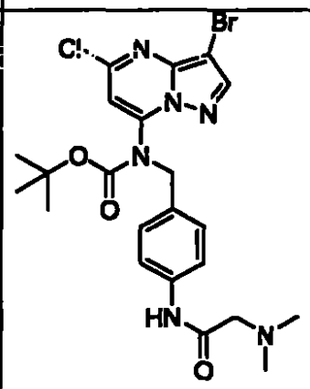
Ej. Prep.	Columna 2	Columna 3	COMPUESTO
518			M+H= 422,1
519			

EJEMPLO PREPARATIVO 520-521:

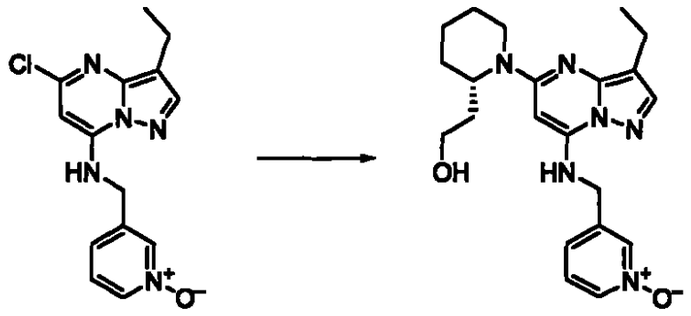
Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo Preparativo 192, sustituyendo solamente los compuestos en la columna 2 de la Tabla 502, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 502.

676

TABLA 502

Ej. Prep.	Columna 2	Columna 3	COMPUESTO
520			M+H= 522,1
521			M+H= 539,1

EJEMPLO 1000:

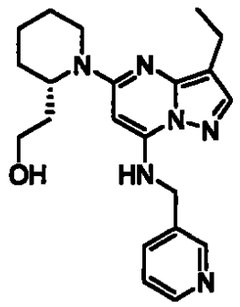


Una mezcla del compuesto preparado en el Ejemplo Preparativo 509 (1,50 g, 4,94 mmol) con el aminoalcohol del Ejemplo Preparativo 500 (1,91 g, 14,8 mmol) en NMP seco (3 ml) se agitó bajo N_2 a 160°C durante 48 hr. El NMP se destiló en vacío y el residuo se sometió a cromatografía primero con 5:1 EtOAc:MeOH, luego el producto bruto se volvió a someter a cromatografía con 10:1 CH_2Cl_2:MeOH. Se obtuvo sólido blanco (460 mg, 24%). LCSM: MH^+ = 397; mp = 113-115 °C.

677

EJEMPLO 1001:

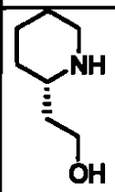
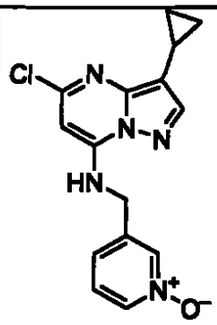
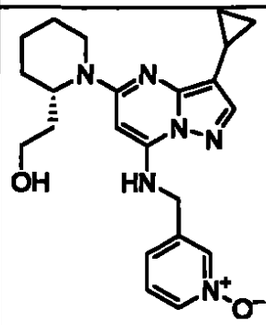
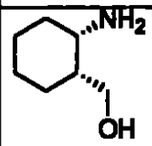
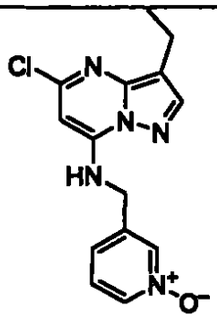
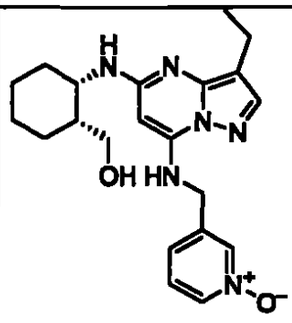
EL principal producto secundario aislado (540 mg, 29%) fue el producto desoxigenado. (LCMS: MH^+ = 381; mp = 49-52 °C):



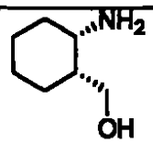
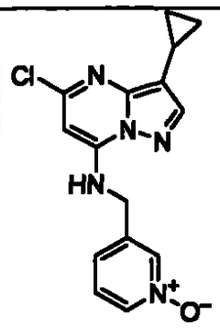
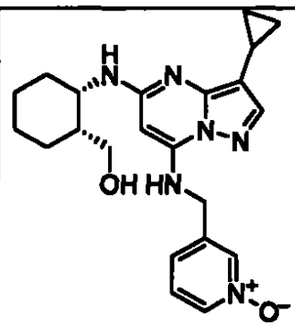
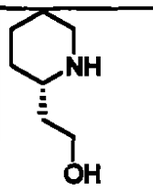
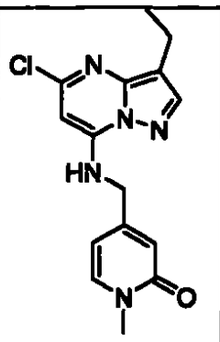
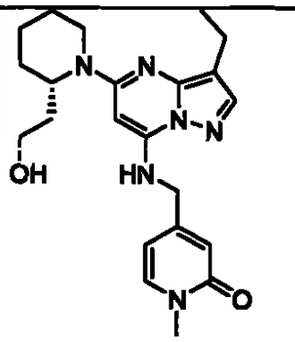
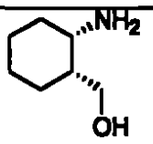
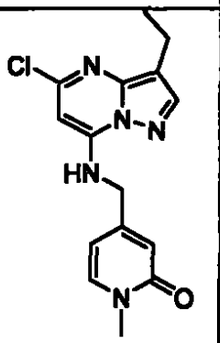
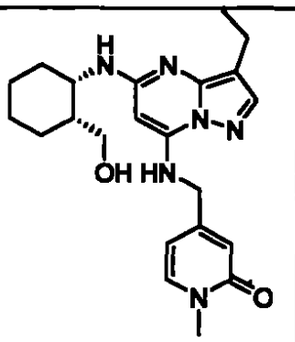
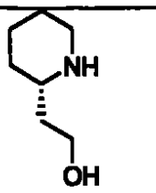
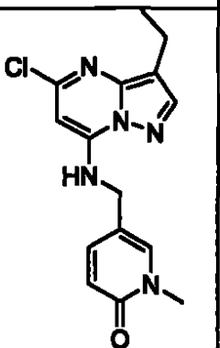
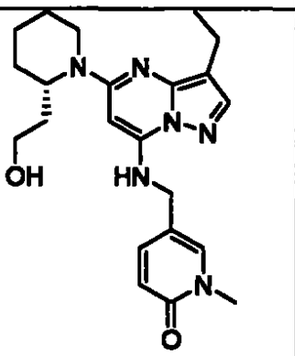
EJEMPLOS 1002 – 1014:

Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 1000, sustituyendo solamente las aminas en la Columna 2 de la Tabla 1000 y los cloruros en la Columna 3 de la Tabla 1000, se prepararon los compuestos en la columna 4 de la Tabla 1000.

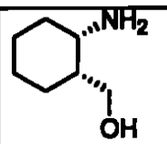
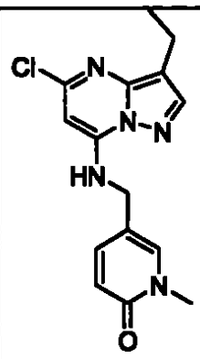
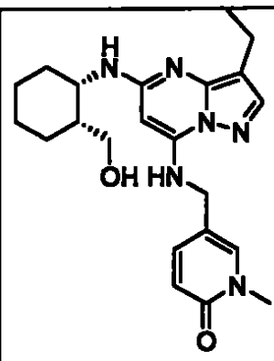
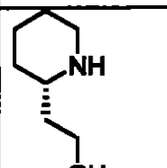
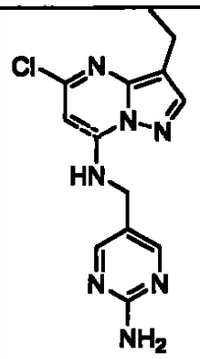
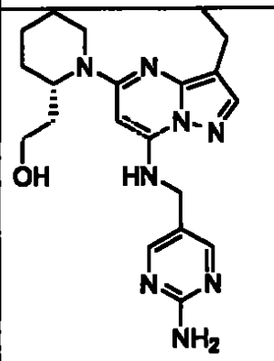
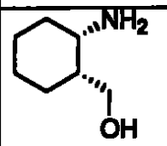
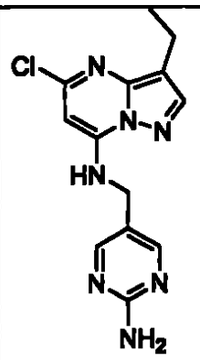
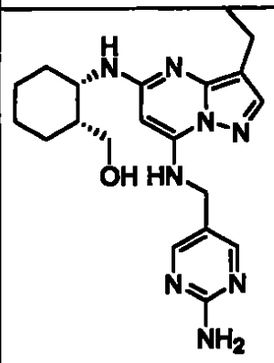
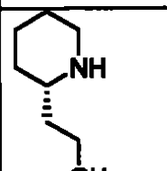
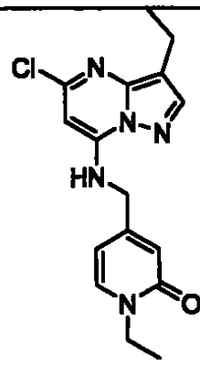
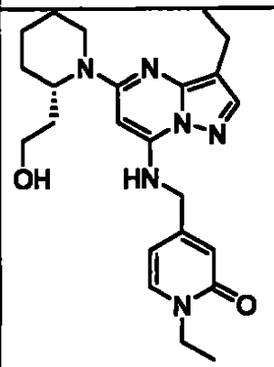
TABLA 1000

Ej.	Columna 2	Columna 3	Columna 4	COMPUESTO
1002				MH^+ = 409; mp = 165-171 °C
1003				MH^+ = 397; mp = 219-221 °C

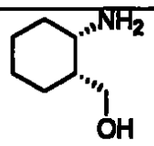
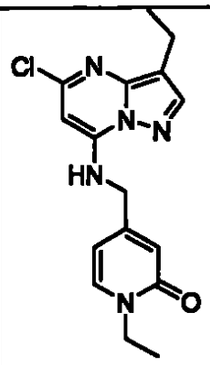
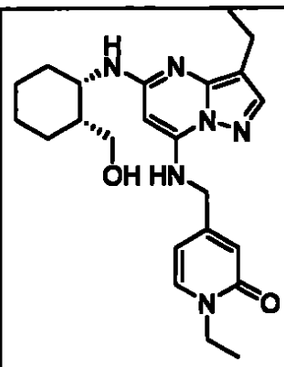
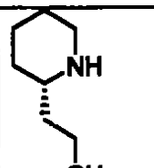
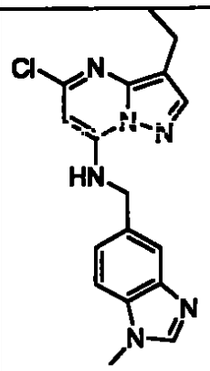
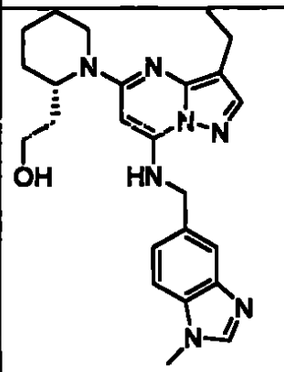
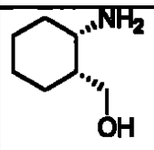
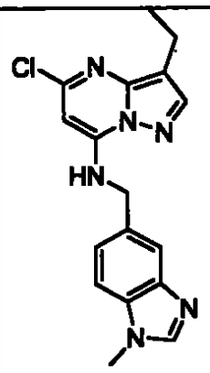
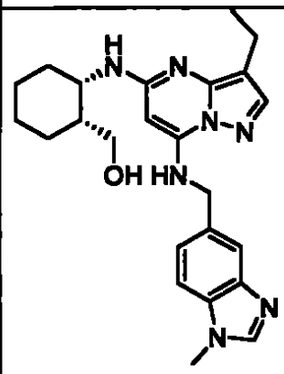
678

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

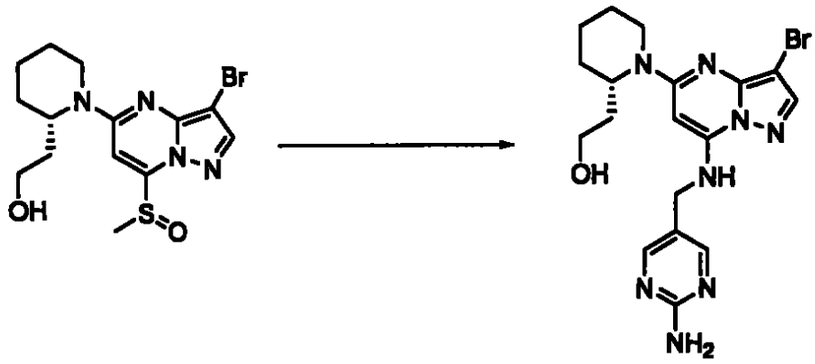
679

1008				MH^+ = 411; mp = 105-108 °C
1009				MH^+ = 397; mp = 173-177 °C
1010				MH^+ = 397; mp = 169-173 °C
1011				MH^+ = 425

680

1012				MH^+ = 425; mp = 232-234 °C
1013				
1014				

EJEMPLO 1015:



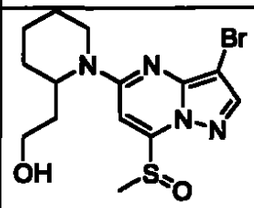
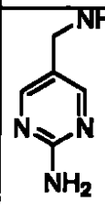
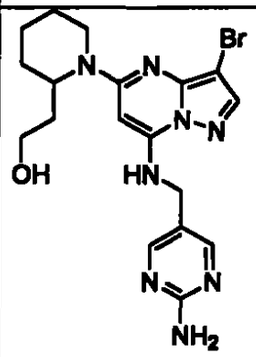
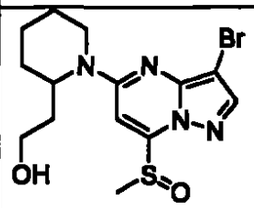
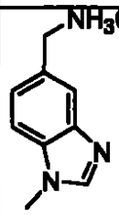
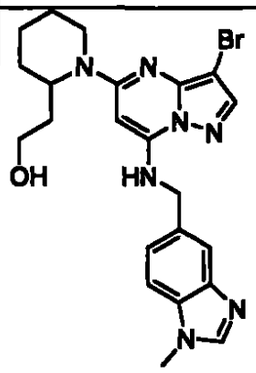
681

A una solución del sulfóxido del Ejemplo Preparativo 505 (0,10 g, 0,28 mmol) en *n*-BuOH en un tubo sellado se agregó Et_3N (0,13 ml, 1,0 mmol) s guido por el diclorhidrato de amina (0,13 g, 0,65 mmol) del Ejemplo Preparativo 216. El tubo se selló y se calentó a 100 °C, se enfrió hasta temperatura ambiente, y se concentró bajo presión reducida. El residuo bruto se purificó mediante TLC preparativa (6 x 1000 µM) eluyendo con CH_2Cl_2/MeOH (20:1) para dar 50 mg (40 %) de un sólido blanco pálido. mp 182-185 °C; M+H = 446.

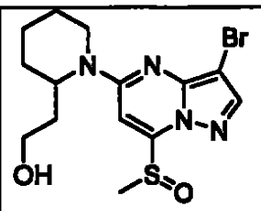
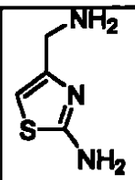
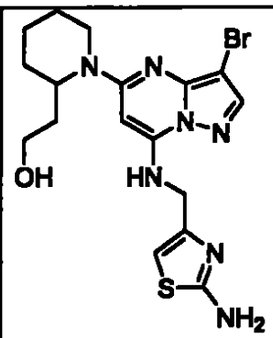
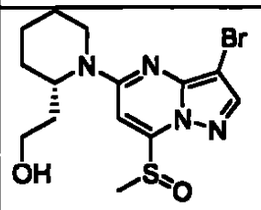
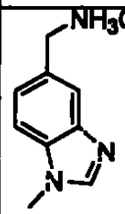
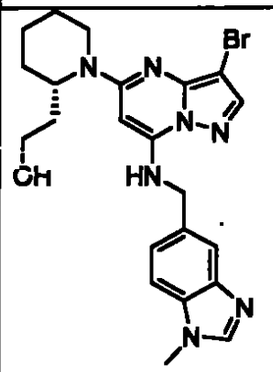
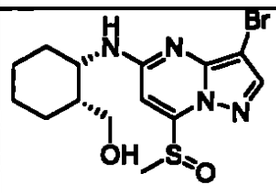
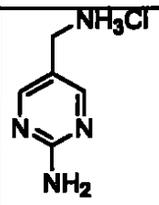
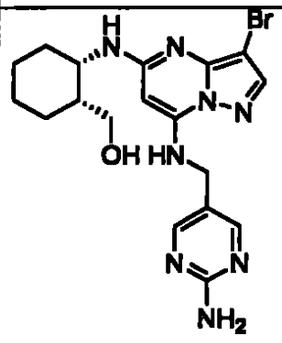
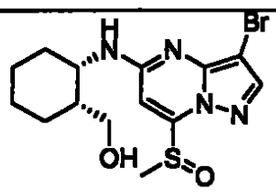
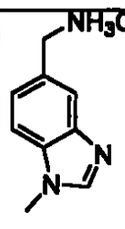
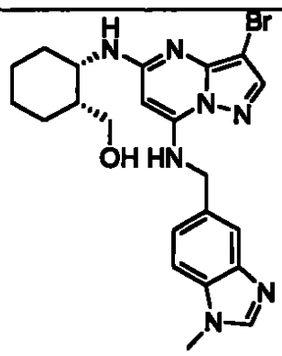
EJEMPLOS 1016-1026:

Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 1015, sustituyendo solamente el sulfóxido que se muestran 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.

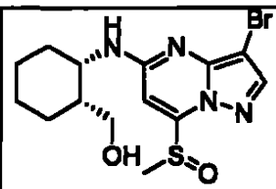
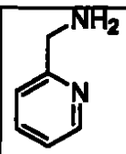
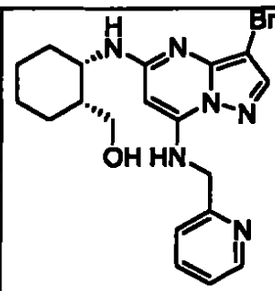
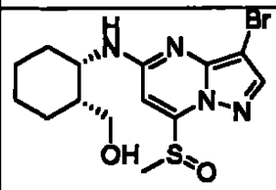
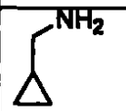
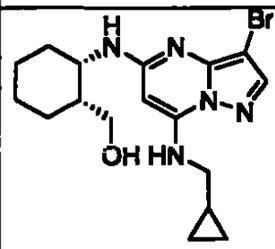
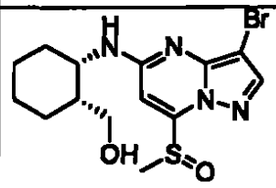
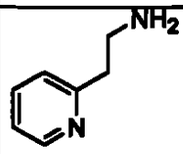
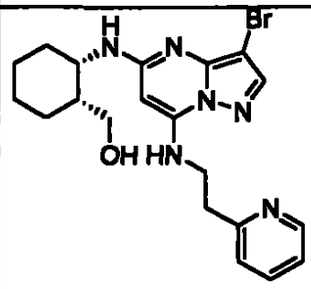
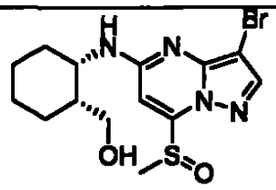
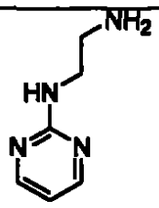
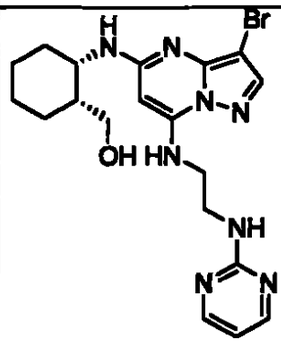
TABLA 1001

Ej.	Columna 2	Columna 3	Columna 4	COMPUESTO
1016				mp = 182-185 °C; M+H = 448
1017				mp = 187-189 °C; M+H = 445

682

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

683

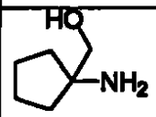
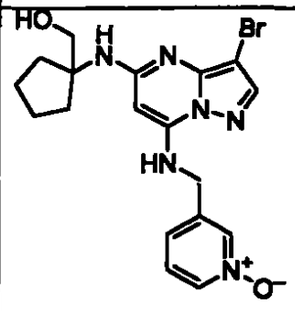
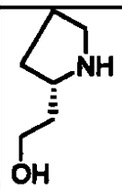
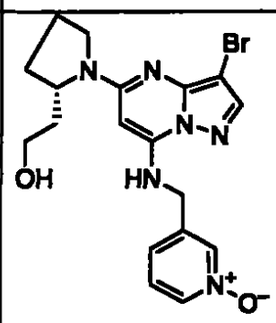
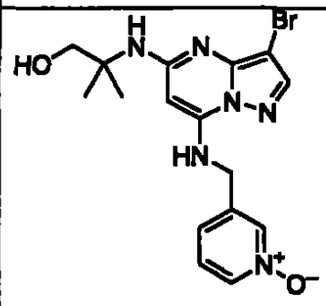
1023	 (±)		 (±)	mp = 203-205 °C; M+H = 432
1024	 (±)		 (±)	mp = 210-212 °C; M+H = 395
1025	 (±)		 (±)	mp = 82-84 °C; M+H = 446
1026	 (±)		 (±)	Mp = 86-90 °C; M+H = 462

684

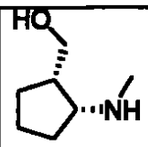
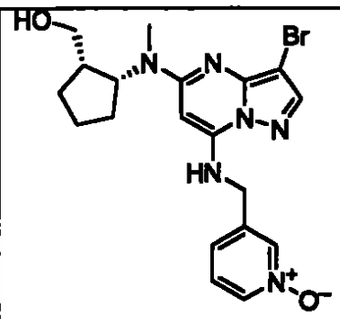
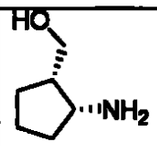
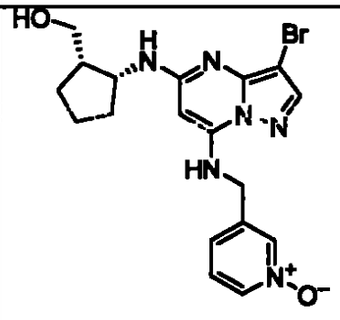
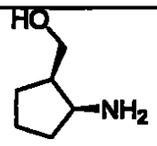
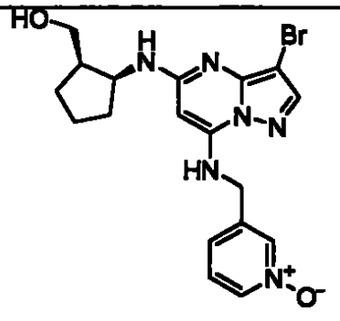
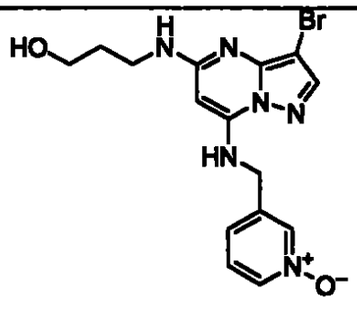
EJEMPLOS 1027-1038:

Esencialmente mediante las mismas condiciones expuestas en el Ejemplo 341, Pasos A y B sustituyendo solamente las aminas en la Columna 2 de la Tabla 1002 y el compuesto preparado en el Ejemplo Preparativo 193,10, se prepararon los compuestos en la columna 4 de la Tabla 1002.

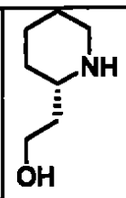
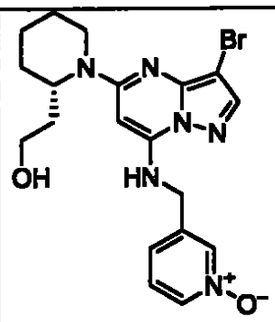
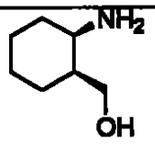
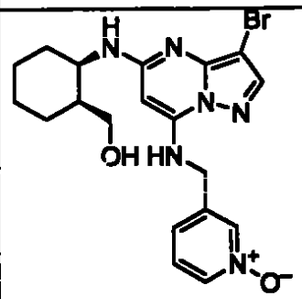
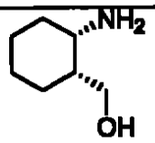
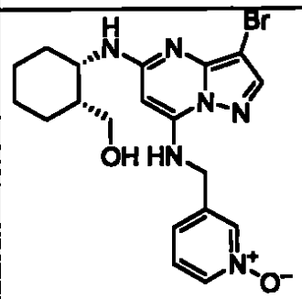
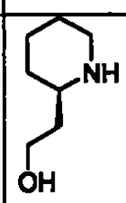
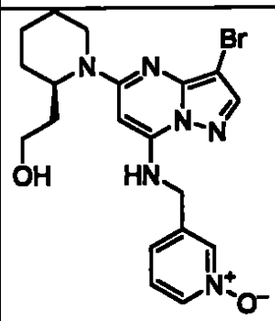
TABLA 1002

Ej.	Columna 2	Columna 4	COMPUESTO
1027			mp = 160-163 °C; M+H = 434
1028			mp = 122-124 °C; M+H = 434
1029			mp = 153-156 °C; M+H = 408

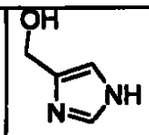
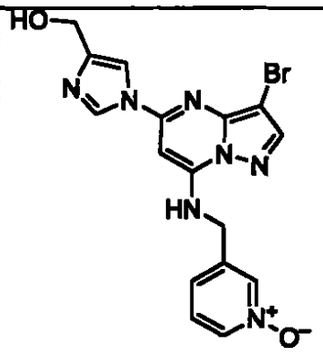
685

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

686

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

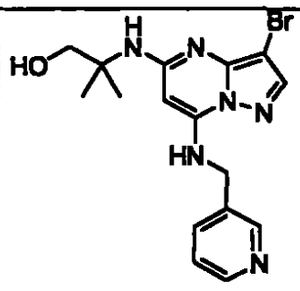
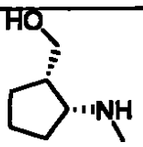
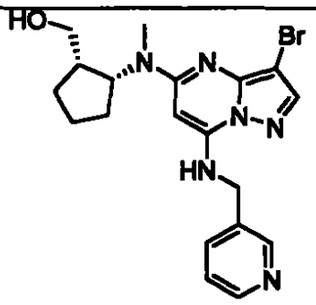
687

1038			

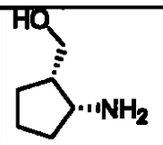
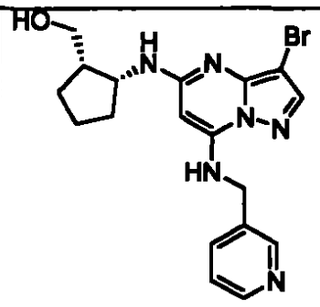
EJEMPLOS 1039-1041:

Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 340 sustituyendo solamente las aminas en 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	COMPUESTO
1039			mp = 210-212 °C; M+H = 392
1040	 (±)	 (±)	mp = 128-130 °C; M+H = 432

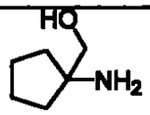
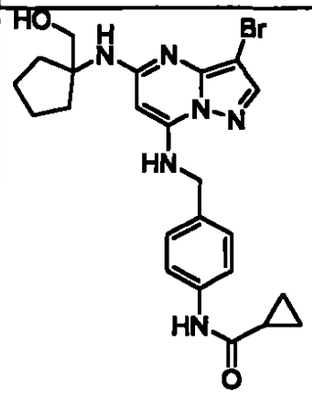
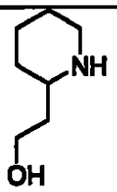
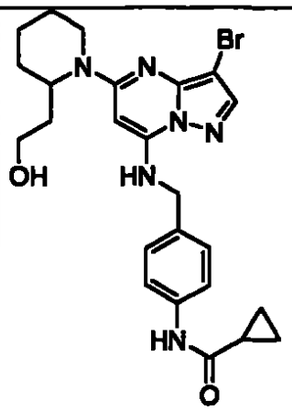
688

1041			mp = 148-151 °C; M+H = 18

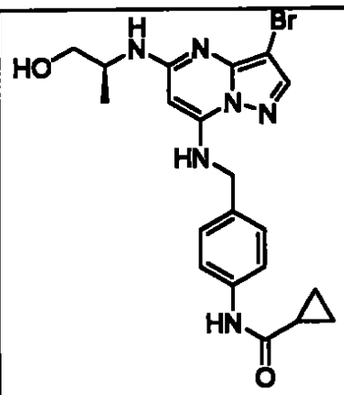
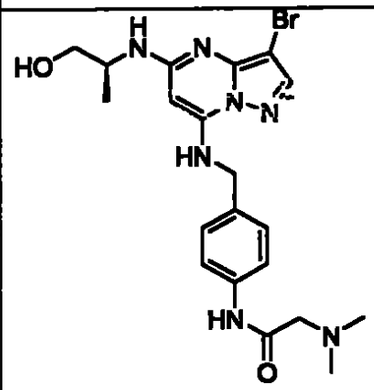
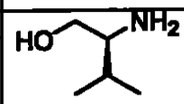
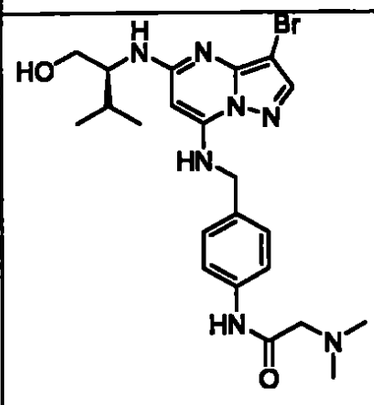
EJEMPLOS 1042-1057:

Esencialmente mediante el mismo procedimiento expuesto en el Ejemplo 340, usando solamente el 5-cloroderivado 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.

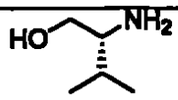
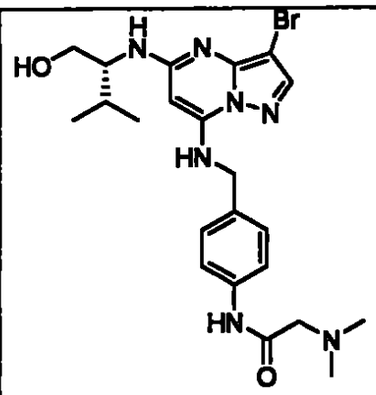
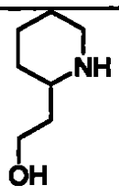
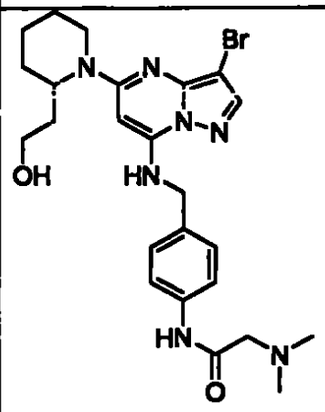
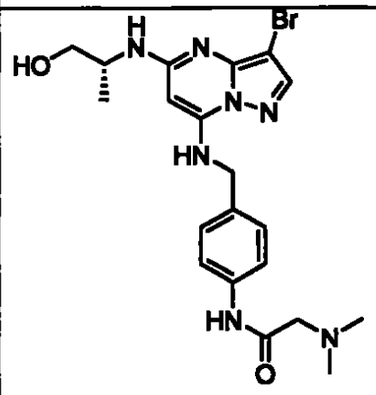
TABLA 1004

Ej.	Columna 2	Columna 4	COMPUESTO
1042			M+H= 500,3
1043			M+H= 514,1

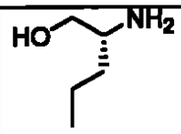
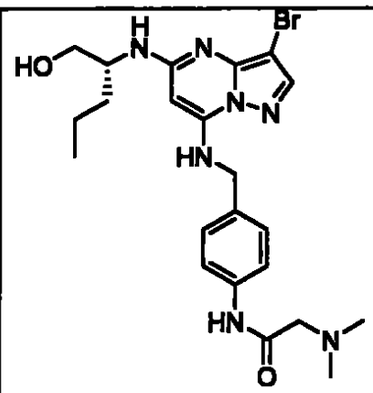
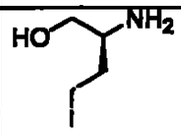
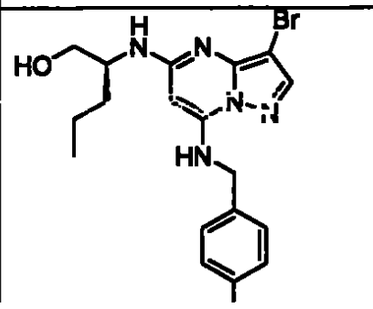
689

1044			M+H= 460,3
1045			M+H= 477,1
1046			M+H= 505,1

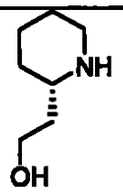
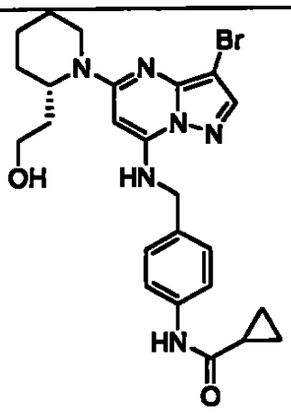
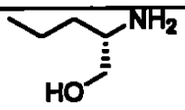
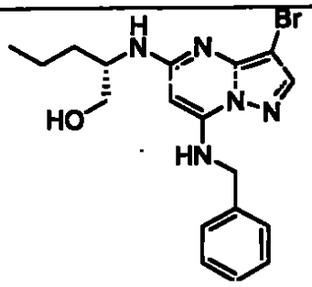
690

1047			M+H= 505,1
1048			M+H=531,1
1049			M+H= 477,1

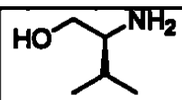
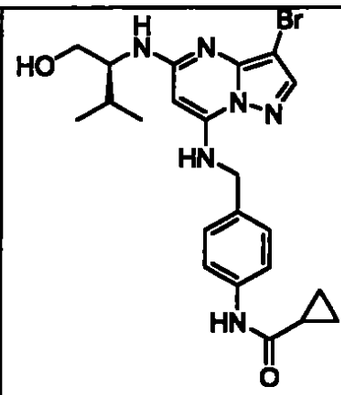
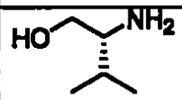
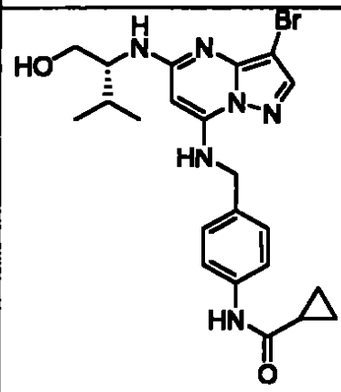
691

1050			M+H= 505,1
1051			M+H= 505,1

692 (875)

1053			M+H= 514,1
1054			M+H= 488,3

693

1056			M+H= 488,1
1057			M+H= 488,1

ENSAYO:

CONSTRUCCIONES DE BACULOVIRUS: *Se clonaron las ciclinas A y E en pFASTBAC (Invitrogen) mediante PCR, con la adición de una secuencia GluTAG (EYMPME) en el extremo del amino-terminal para permitir la purificación en columnas de afinidad anti-GluTAG. Las proteínas expresadas fueron de un tamaño de aproximadamente 46kDa (ciclina E) y 50kDa (ciclina A). CDK2 también se clonó en pFASTBAC mediante PCR, con el agregado de un rótulo de epítopo de hemaglutininaen el extremo de terminal carboxi (YDVPDYAS). La proteína expresada fue de un tamaño aproximado de 34kDa.*

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Diagnostics GmbH, Mannheim, Alemania). Las mezclas se agitaron durante 30-60 minutos para promover la formación del complejo ciclina-CDK2. Luego los lisatos mezclados se giraron de modo descendente 15000 RPM durante 10 minutos y se retuvo el sobrenadante. Luego, se usaron 5ml de perlas de anti-GluTAG (por un litro de células SF9) para capturar complejos de ciclina-CDK2. Las perlas unidas se lavaron tres veces en buffer de lisis. Las proteínas se eluyeron de manera competitiva con buffer de lisis que contiene 100-200ug/ml del péptido GluTAG. El eluato se dializó hasta el día siguiente en 2 litros de buffer de quinasa conteniendo Tris 50mM pH 8,0, DTT 1mM, MgCl210mM, ortovanadato de sodio 100uM y glicerol 20%. La enzima se almacenó en alícuotas a –70°C.

ENSAYO IN VITRO DE QUINASA: Los ensayos de quinasa CDK2 (ya sea ciclina A or E-dependiente) se llevaron a cabo en placas de 96 pocillos de unión de proteína baja (Corning Inc, Corning, New York). La enzima se diluyó a una concentración final de buffer quinasa de 50 µg/ml contienendo Tris 50mM pH 8,0, $MgCl_2$ 10mM, DTT 1mM, y ortovanadato de sodio 0,1mM. el sustrato que se usó en estas reacciones fue un péptido biotinilado derivado de Histona H1 (de Amersham, UK). El sustrato se disolvió sobre hielo y se diluyó 2 µM en buffer de quinasa. Los compuestos se diluyeron en DMSO 10% para cocnentraciones deseables. Para cada reacción de quinasa, se mezclaron 20 µl de la solución enzimática 50 µg/ml (1 µg de enzima) y 20 µl de la solución del sustrato 1 µM, luego se combinaron con 10 µl del compuesto diluido en cada pocillo para analizar. La reacción de quinasa se inició mediante la adición de 50 µl de 4 µM ATP y 1 µCi de 33P-ATP (de Amersham, UK). Se dejó correr la reacción durante 1 hora a temperatura ambiente. La reacción se detuvo mediante la adición de 200 µl de buffer de terminación conteniendo 0,1% Triton X-100, ATP 1mM, EDTA 5mM, y 5 mg/ml de perlas SPA recubiertas con estreptavidina (de Amersham, UK) durante 15 minutos. Las perlas SPA se capturaron luego sobre una placa de filtrado GF/B de 96 pocillos (Packard/Perkin Elmer Life Sciences) usando un cosechador universal Filtermate (Packard/Perkin Elmer Life Sciences.). Se eliminaron señales no específicas mediante el lavado de las perlas dos veces con NaCl 2M , luego dos veces con NaCl 2 M con ácido fosfórico 1%. La señal

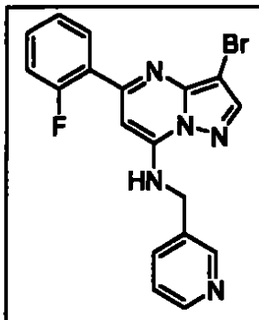
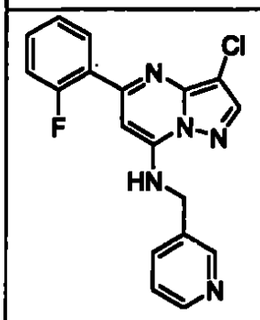
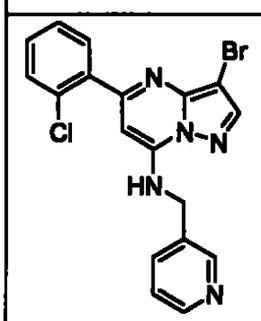
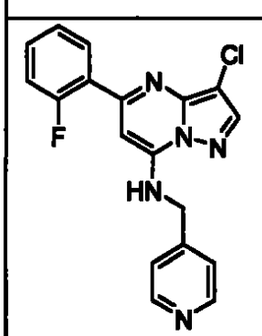
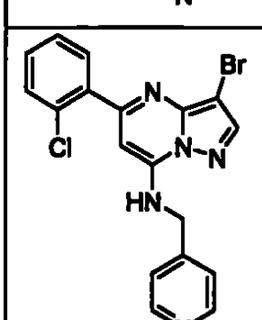
695 696

radioactiva se mensuó entonces usando un contador de centelleo líquido de 96 pocillos TopCount (from Packard/Perkin Elmer Life Sciences).

DETERMINACIÓN DE LOS IC_{50}: Las curvas de dosis-respuesta se plotearon a partir de los datos de inhibición generados, cada uno en duplicado, a partir de diluciones en serie de 8 puntos de compuestos inhibidores. La concentración del compuesto se ploteó contra el % de actividad quinasa, se calculó mediante CPM de las muestras tratadas dividido por CPM de las muestras sin tratar. Para generar los valores de IC_{50}, se adaptaron las curvas de dosis-respuesta a una curva sigmoide estándar y los valores de IC_{50} se derivan mediante el análisis de regresión no lineal. Los valores de IC_{50} que se obtuvieron de esa 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 mencionado anteriormente.

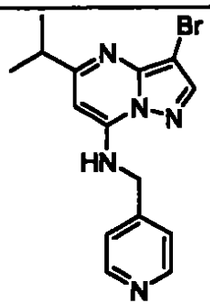
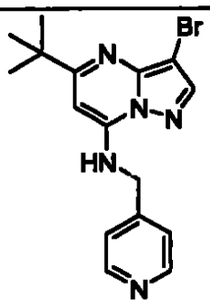
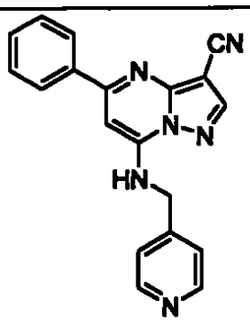
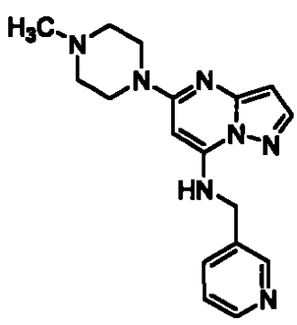
Tabla 87

696 697

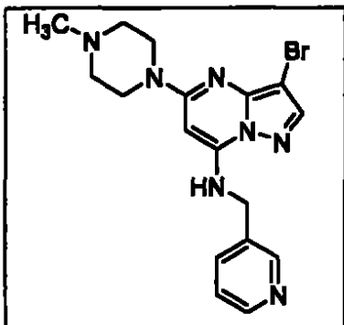
	4	0,011
	5	0,021
	8	0,003
	6	0,064 0,029
	7	0,01 0,006

697

698

	10	0,042
	12	0,17
	16	0,62
	1	5,6

698

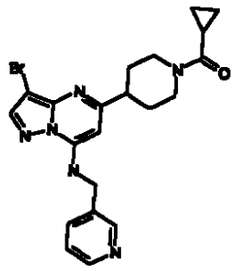
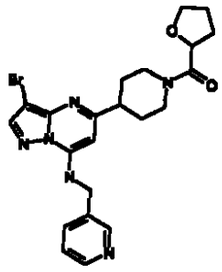
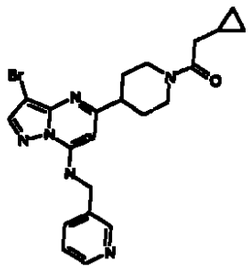
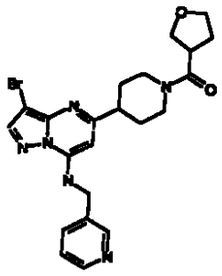
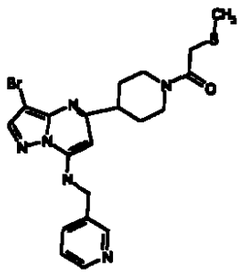
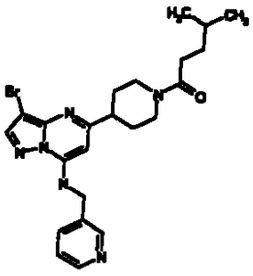
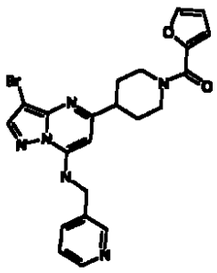
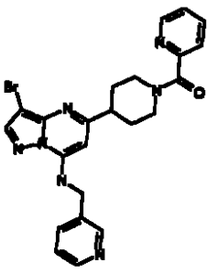
	3	0,14

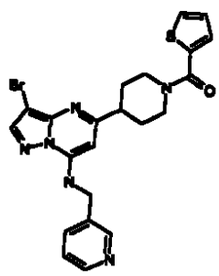
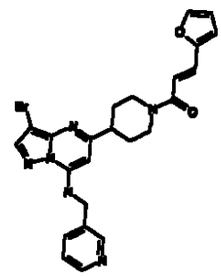
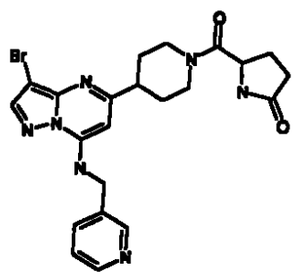
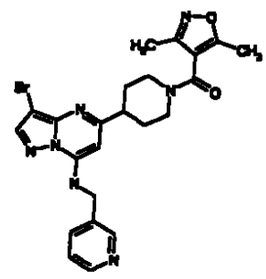
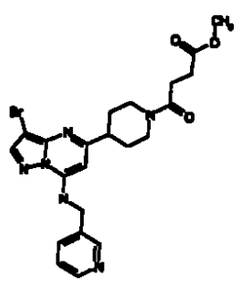
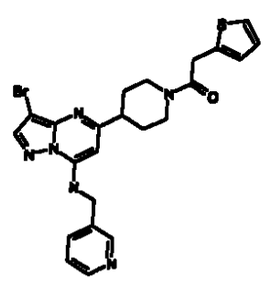
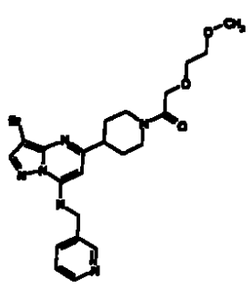
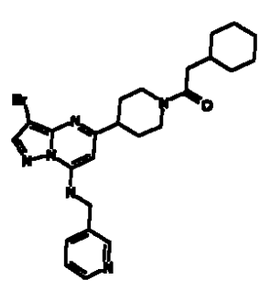
Según se demostró anteriormente mediante los valores de ensayo, los compuestos de la presente invención exhiben excelentes propiedades inhibidoras de CDK.

Mientras que la presente invención ha sido descripta de manera conjunta con las realizaciones específicas expuestas anteriormente, muchas alternativas, modificaciones y otras variaciones de las mismas serán evidentes para aquellos con experiencia ordinaria en la técnica. Se pretende que todas dichas alternativas, modificaciones y variaciones se comprendan en el espíritu y alcance de la presente invención.

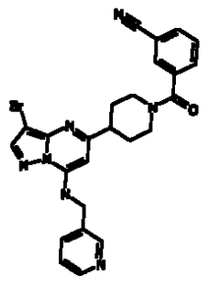
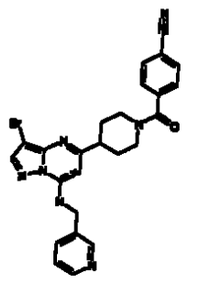
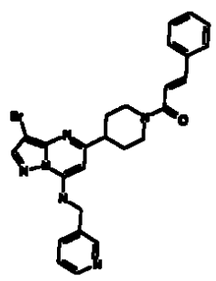
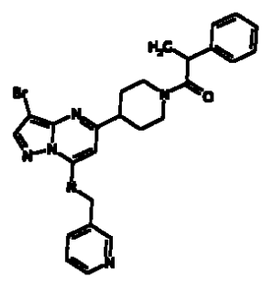
699

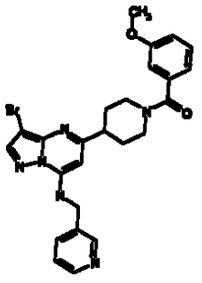
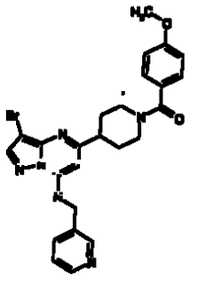
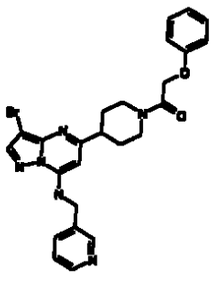
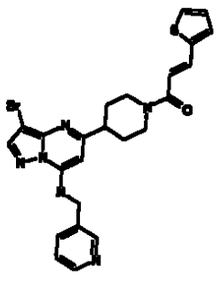
TABLA 43

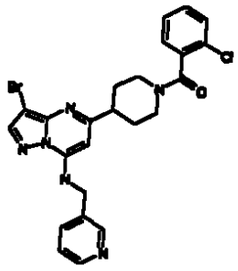
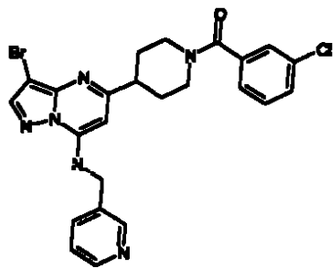
Ej.	Compuesto	m/z	Ej.	Compuesto	m/z
4301		457,25	4305		487,27
4302		471,26	4306		487,27
4303		477,26	4307		487,27
4304		483,27	4308		494,27

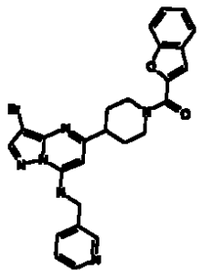
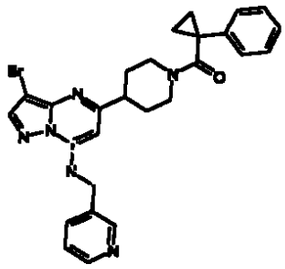
Ej.	Producto	m/z	Ej.	Producto	m/z
4309		499,27	4313		509,28
4310		500,27	4314		512,28
4311		503,28	4315		513,28
4312		505,28	4316		513,28

701

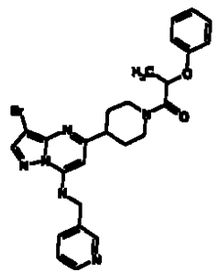
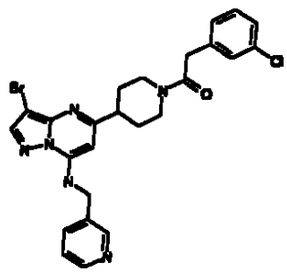
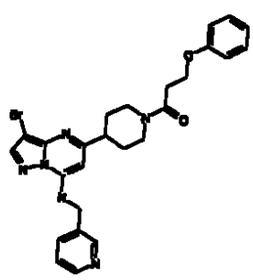
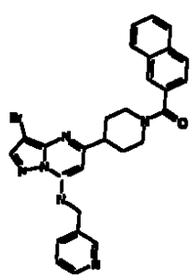
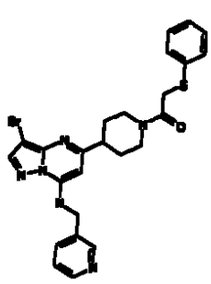
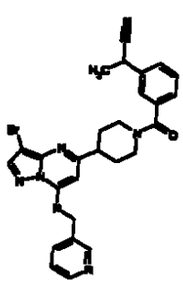
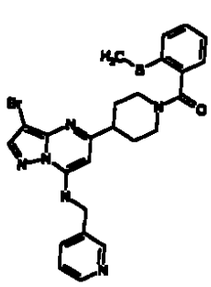
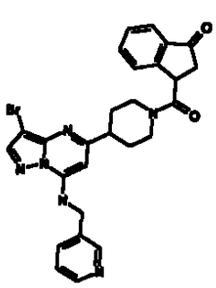
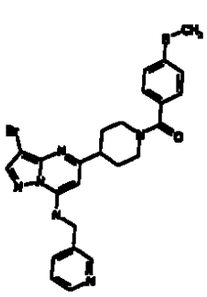
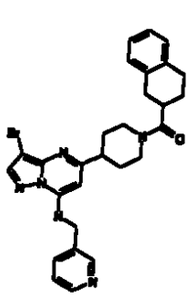
Ej.	Producto	m/z
4317		518,28
4318		518,28
4319		519,29
4320		521,29

Ej.	Producto	m/z
4321		523,29
4322		523,29
4323		523,29
4324		525,29

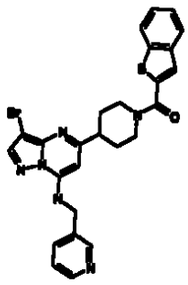
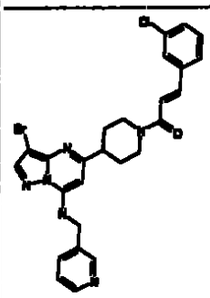
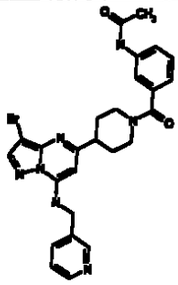
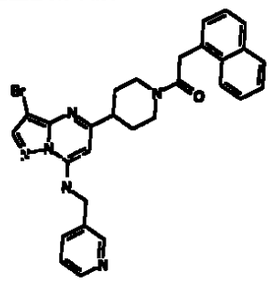
Producto	1.Ej. 2. m/z
	1. 4325 2. 527.29
	1. 4326 2. 527.29
	

Producto	1.Ej. 2. m/z
	1. 4330 2. 533.29
	4331
	

703
704

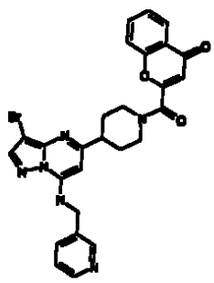
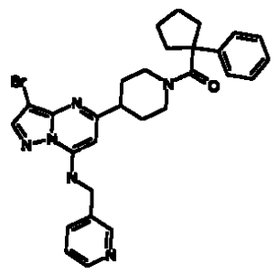
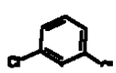
Producto	1.Ej. 2. m/z	Producto	1.Ej. 2. m/z
	1. 4335 2.537.3		1. 4340 2. 541.3
	1.4336 2. 537.3		1. 4341 2. 543.3
	1. 4337 2. 539.3		1. 4342 2. 546.3
	1. 4338 2. 539.3		1. 4343 2. 547.3
	1. 4339 2. 539.3		1. 4344 2. 547.3

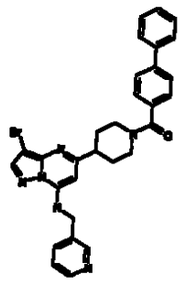
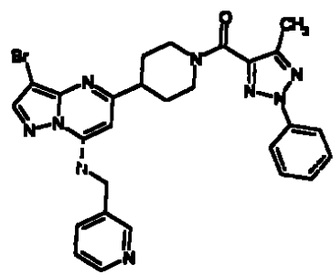
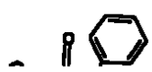
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705

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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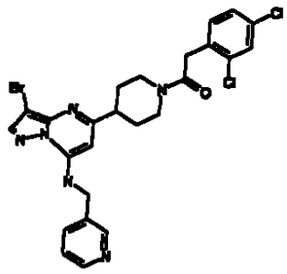
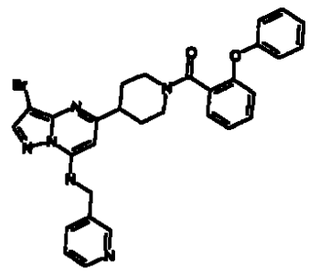
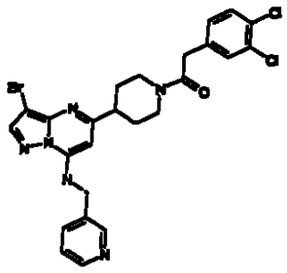
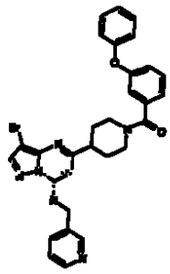
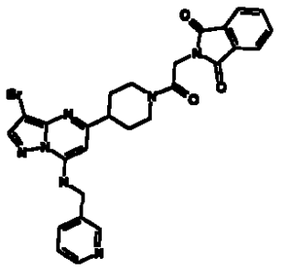
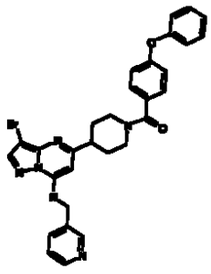
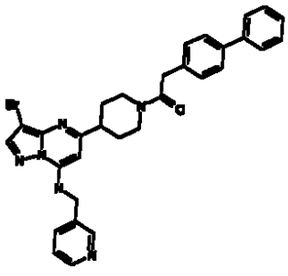
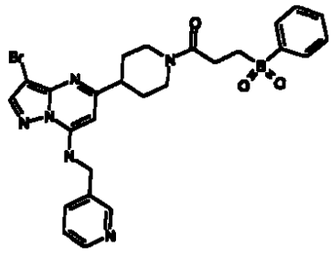
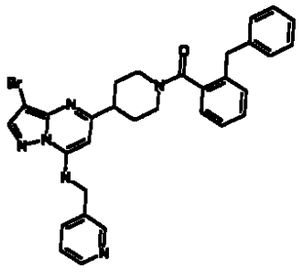
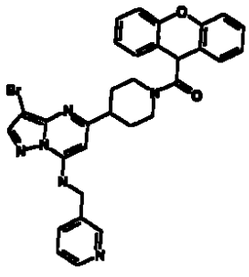
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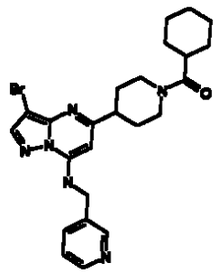
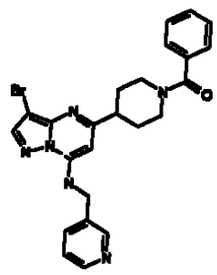
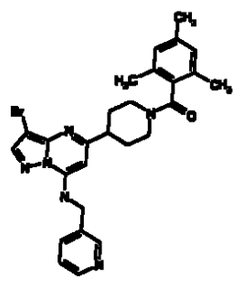
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	1. 4356 2. 561.31
	

Producto	1. Ej. 2. m/z
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	1. 4361 2. 574.32
	

706

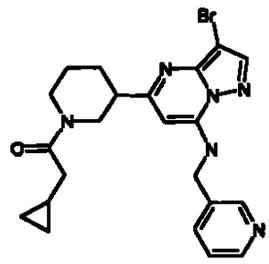
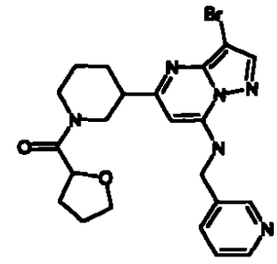
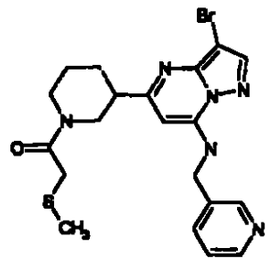
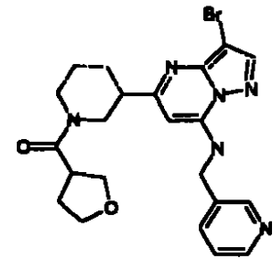
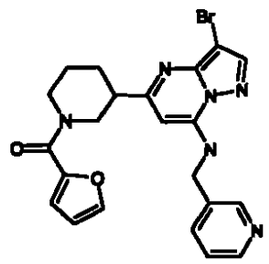
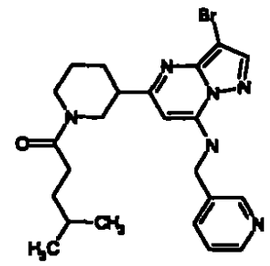
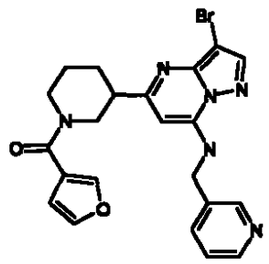
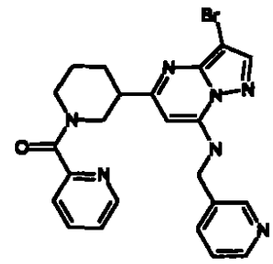
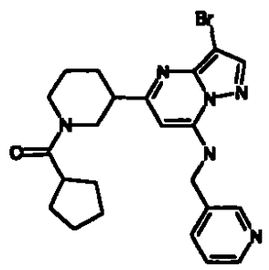
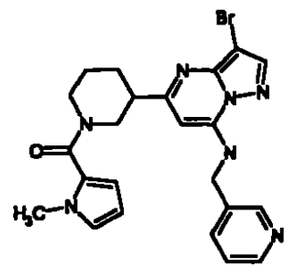
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	1. 43666 2. 575.32		1. 4371 2. 583.32
	1. 4367 2. 574.32		1. 4372 2. 585.32
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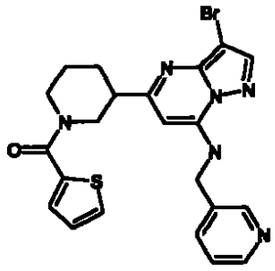
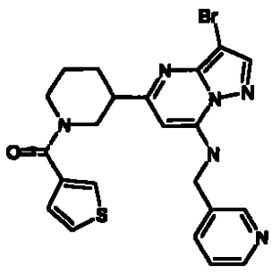
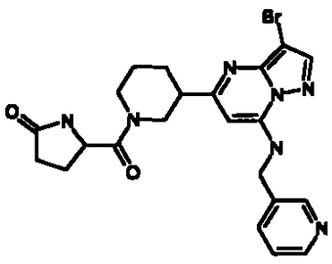
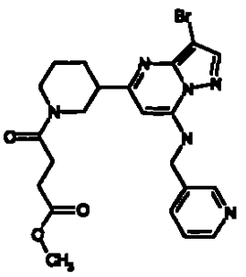
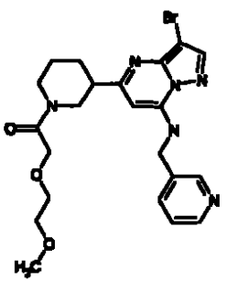
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	1. 4377 2. 535.29

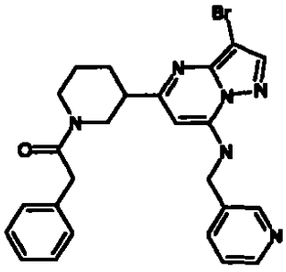
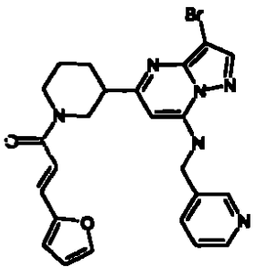
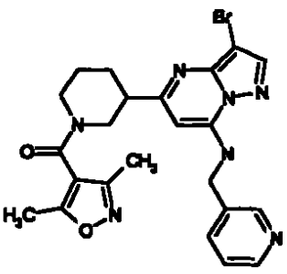
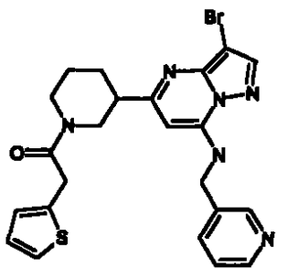
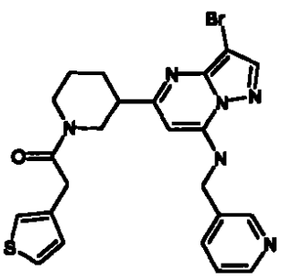
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TABLA 44

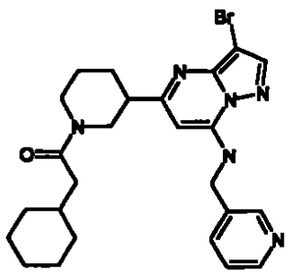
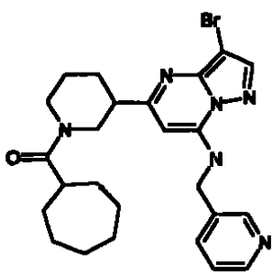
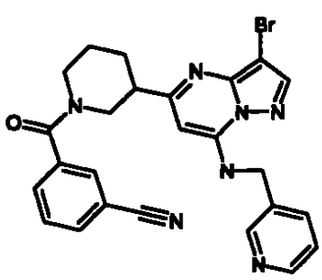
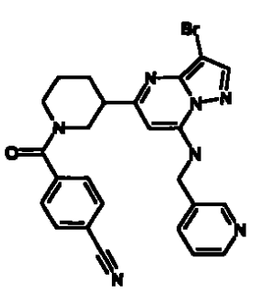
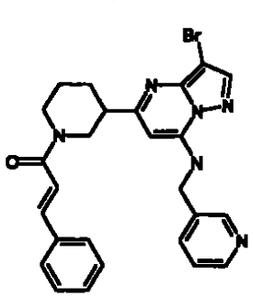
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	1. 4402 2. 475.26		1. 4407 2. 487.27
	1. 4403 2. 483.27		1. 4408 2. 487.27
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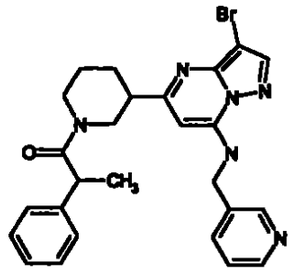
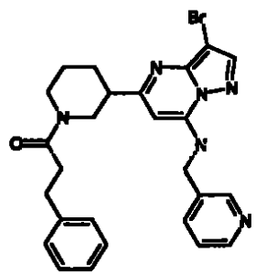
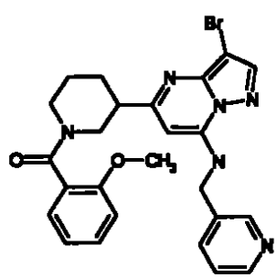
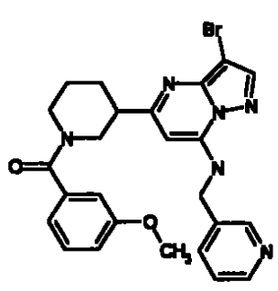
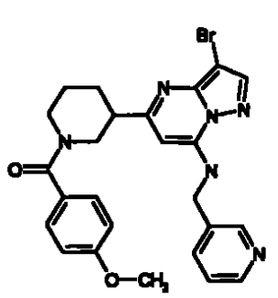
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Producto	1. Ej 2. m/z
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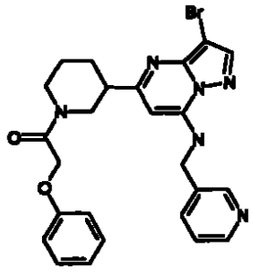
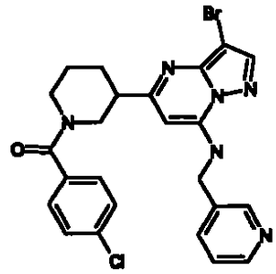
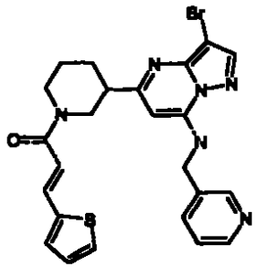
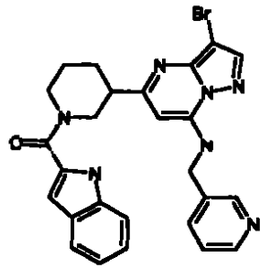
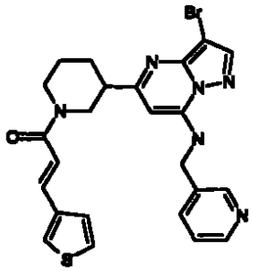
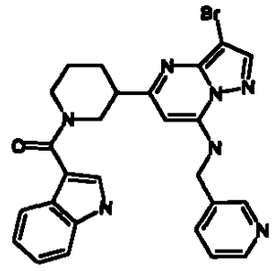
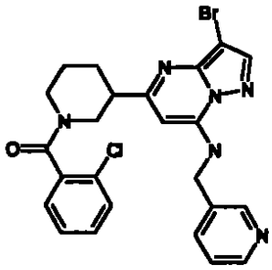
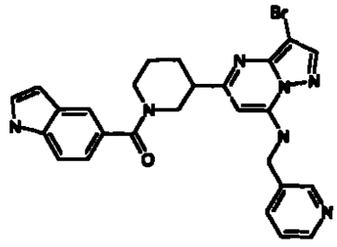
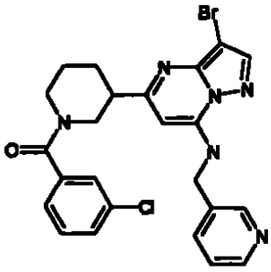
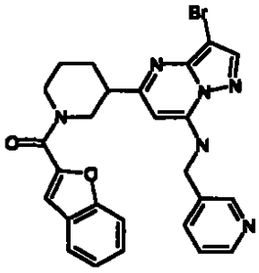
Producto	1. Ej. 2. m/z
	1. 4416 2. 507.28
	1. 4417 2. 509.3
	1. 4418 2. 512.28
	1. 4419 2. 513.28
	1. 4420 2. 513.28

710

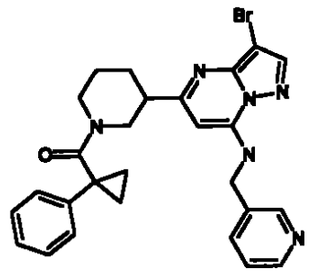
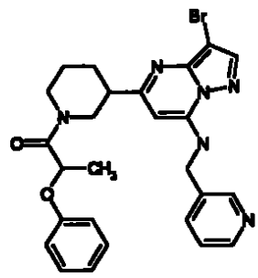
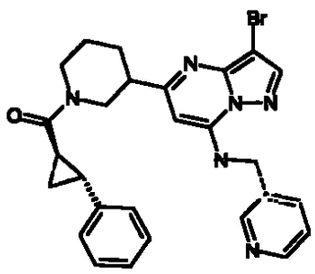
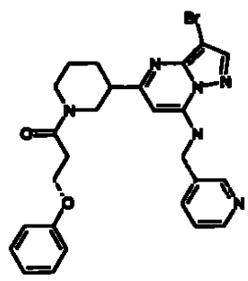
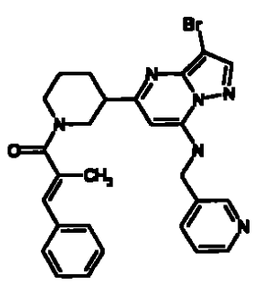
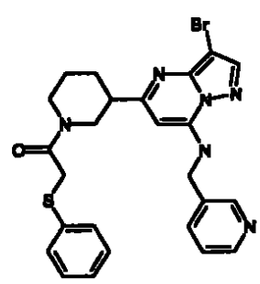
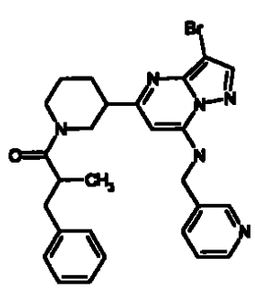
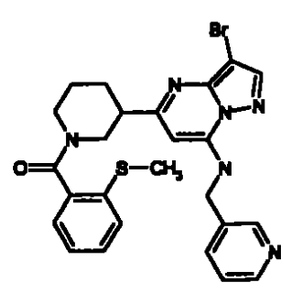
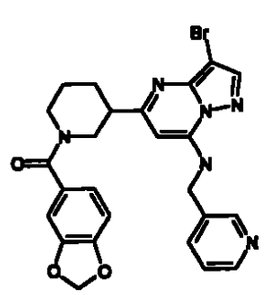
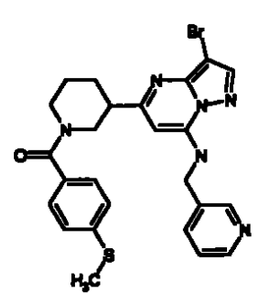
Producto	1. Ej 2. m/z
	1. 4421 2. 513.28
	1. 4422 2. 513.28
	1. 4423 2. 518.28
	1. 4424 2. 518.28
	1. 4425 2. 519.3

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

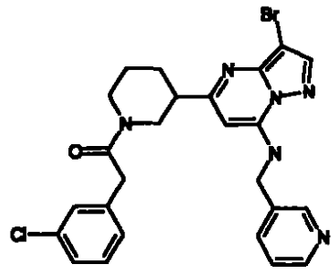
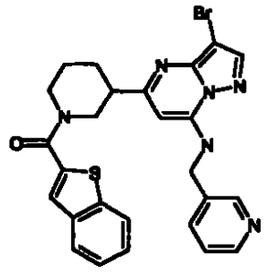
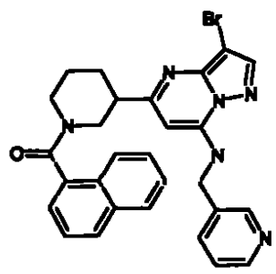
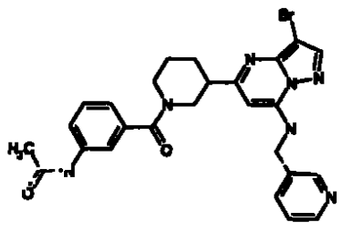
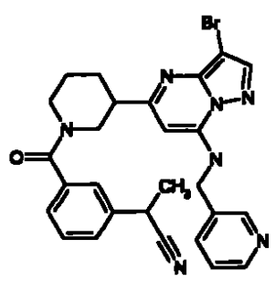
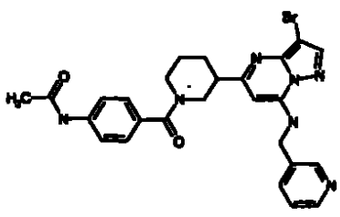
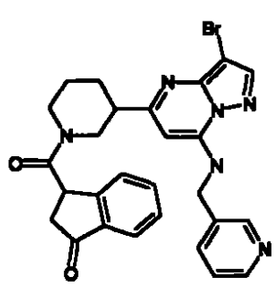
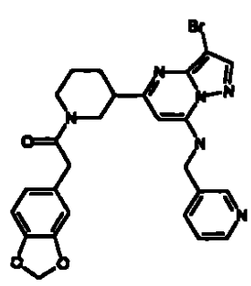
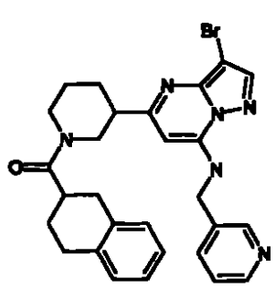
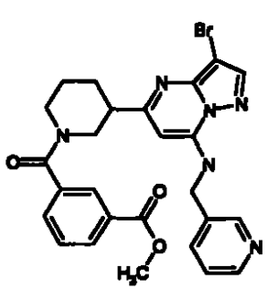
711

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. 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

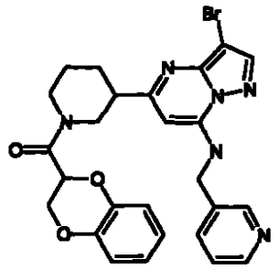
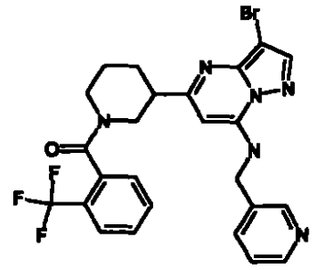
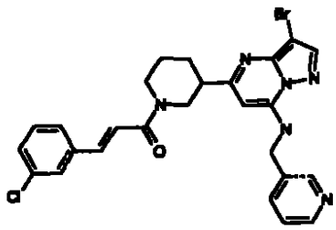
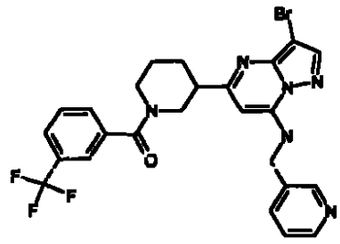
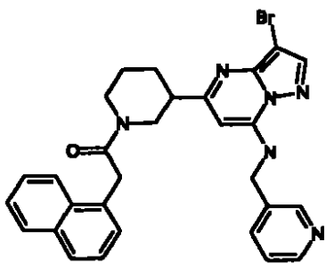
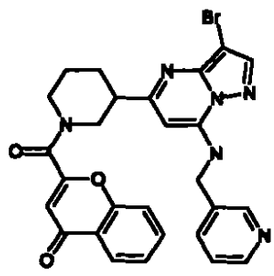
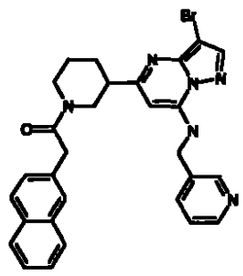
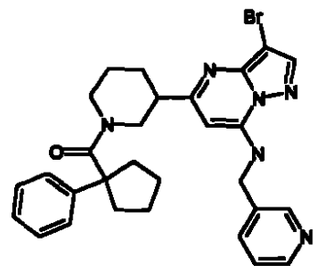
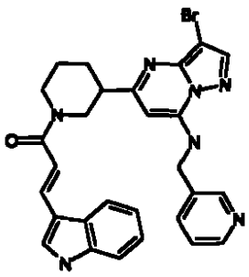
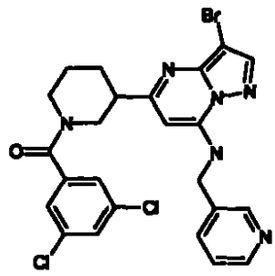
712

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

713

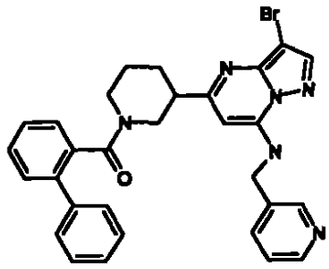
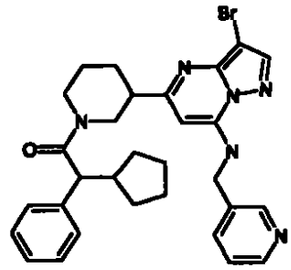
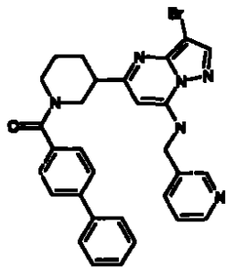
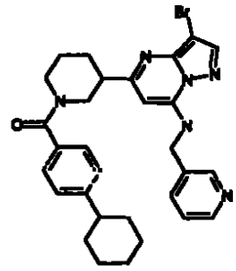
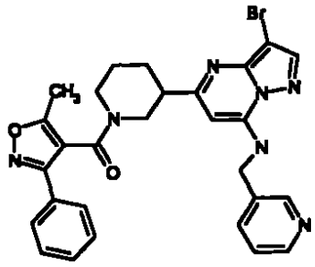
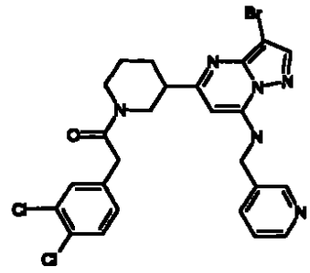
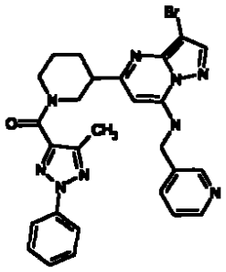
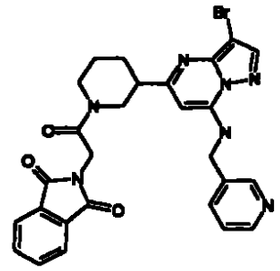
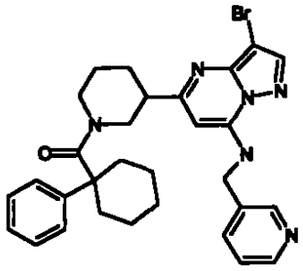
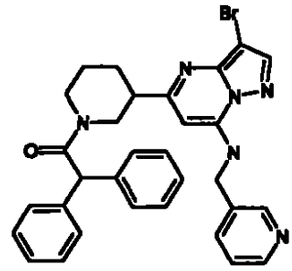
Producto	1. Ej 2. m/z	Producto	1. Ej. 2. m/z
	1. 4451 2. 541.3		1. 4456 2. 549.3
	1. 4451 2. 543.3		1. 4457 2. 550.3
	1. 4453 2. 546.3		1. 4458 2. 550.3
	1. 4454 2.547.3		1. 4459 2. 551.3
	1. 4455 2.547.3		1. 4460 2. 551.3

714

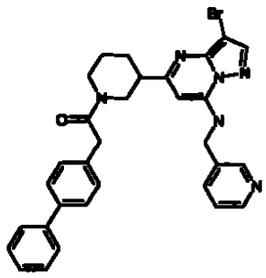
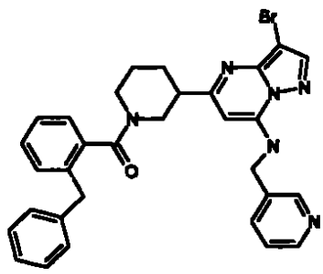
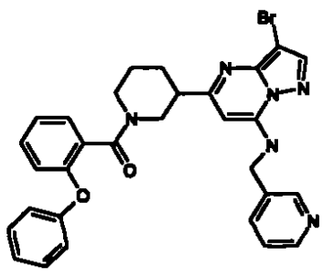
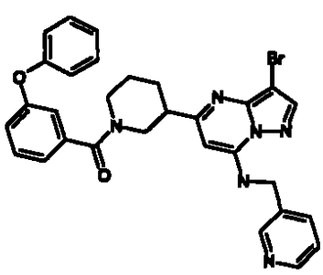
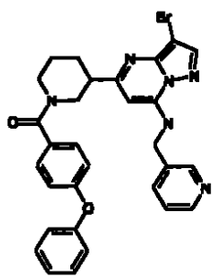
Producto	1. Ej 2. m/z	Producto	1. Ej. 2. m/z
	1. 4461 2. 549.3		1. 4466 2. 561.31
	1. 4462 2. 553.3		1. 4467 2. 561.31
	1. 4463 2. 557.3		1. 4468 2. 561.31
	1. 4464 2. 557.31		1. 4469 2. 561.31
	1. 4465 2. 558.31		1. 4470 2. 562.3

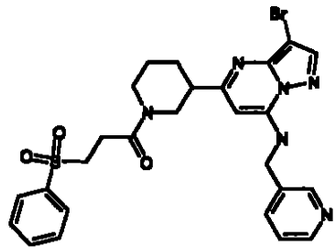
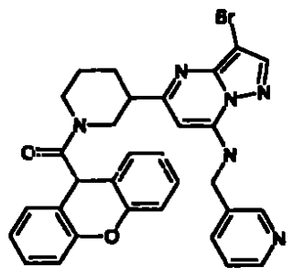
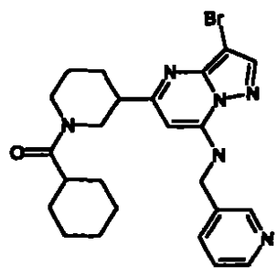
715

216

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

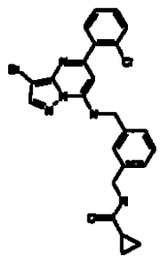
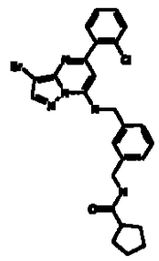
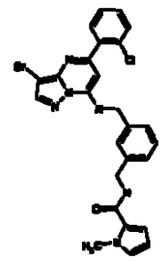
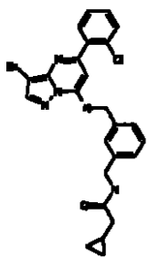
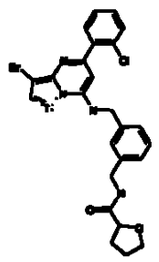
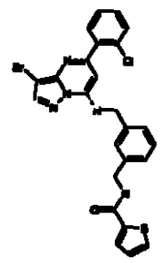
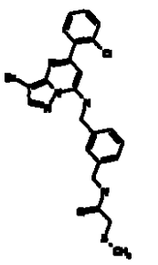
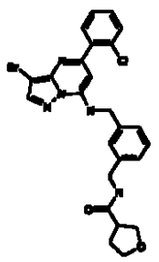
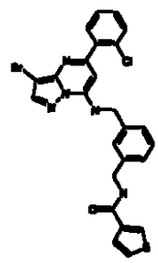
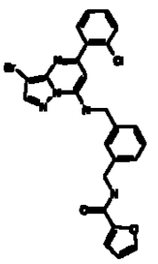
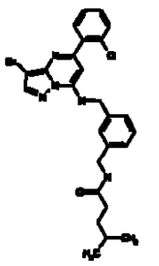
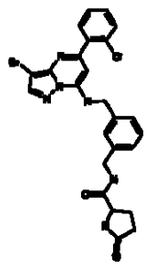
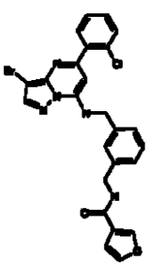
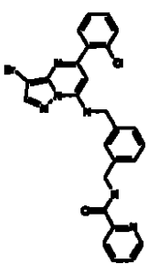
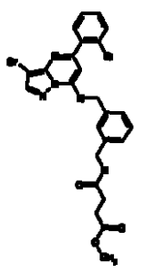
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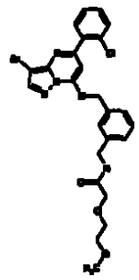
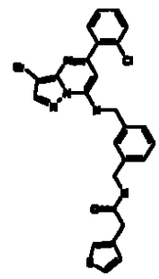
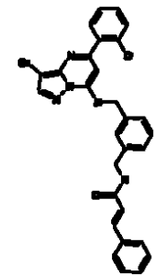
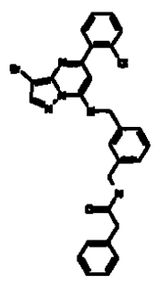
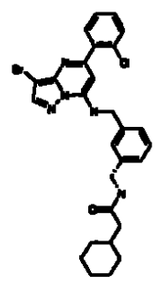
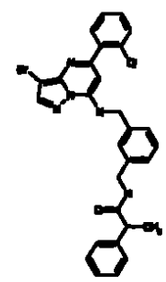
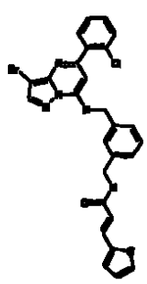
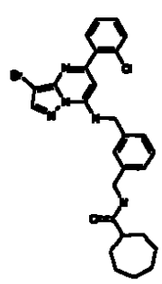
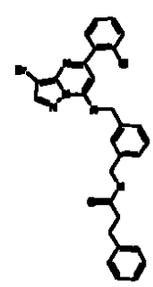
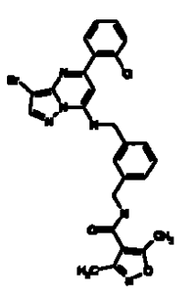
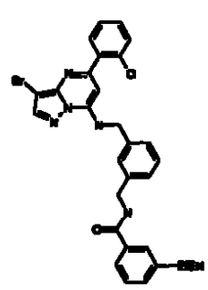
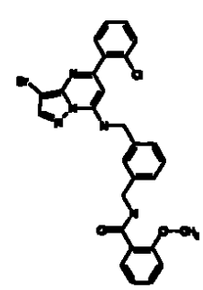
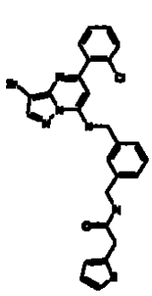
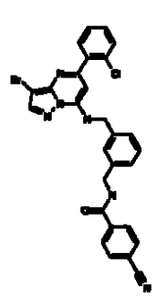
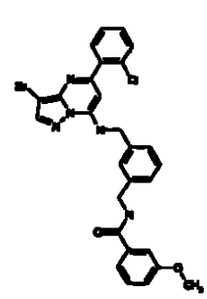
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717

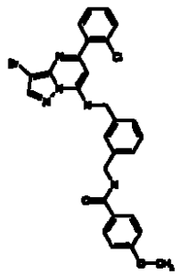
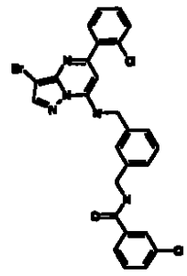
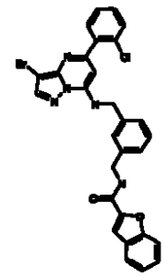
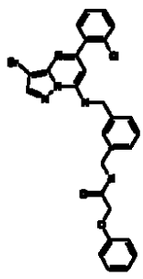
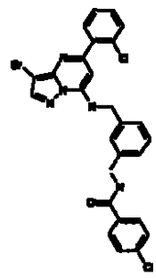
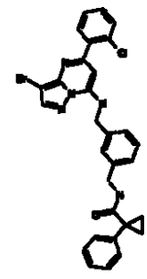
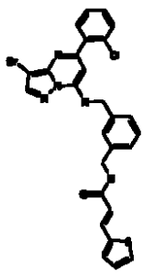
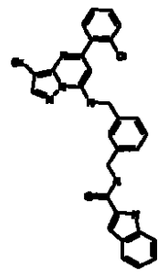
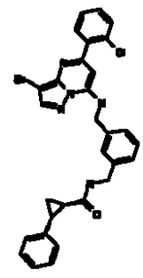
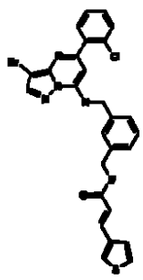
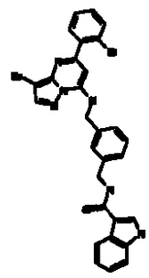
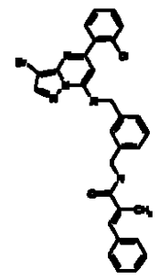
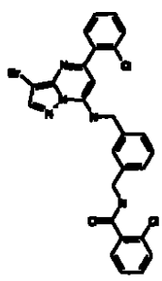
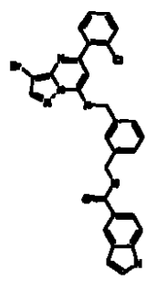
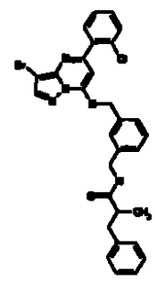
TABLA 45

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	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
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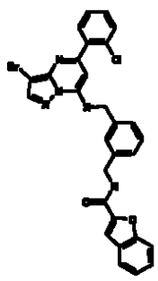
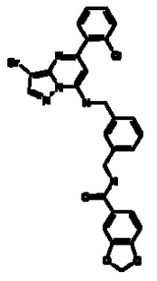
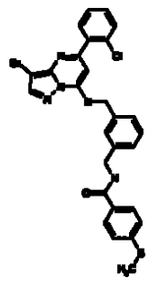
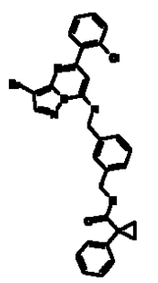
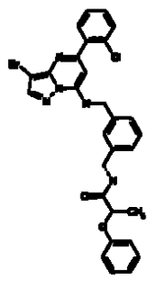
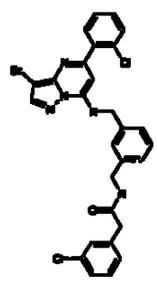
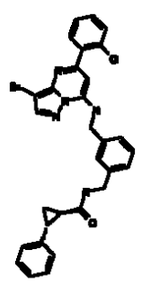
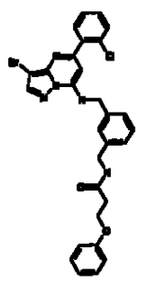
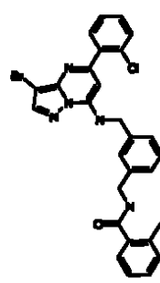
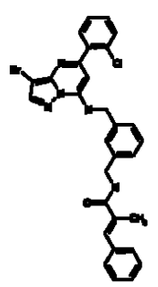
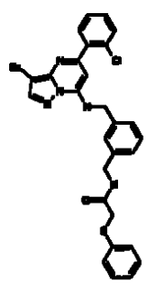
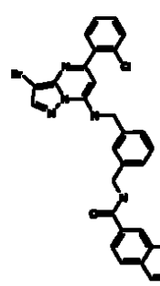
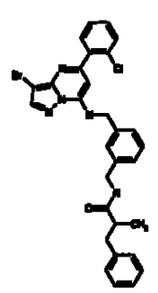
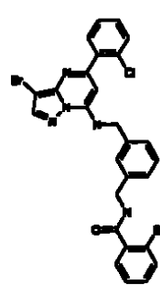
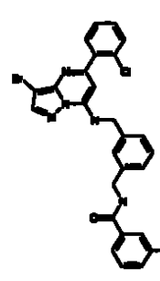
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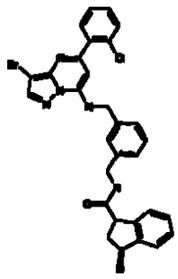
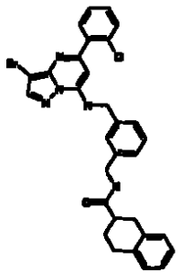
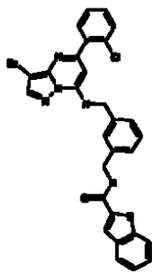
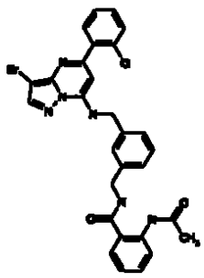
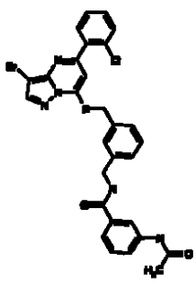
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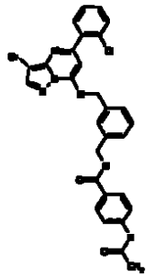
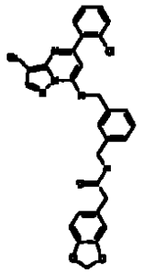
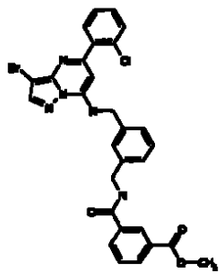
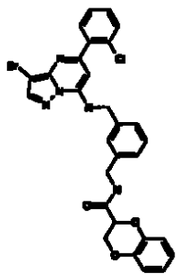
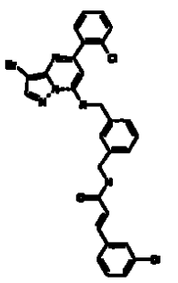
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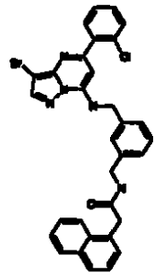
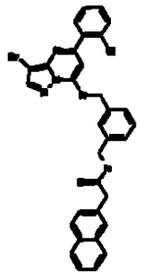
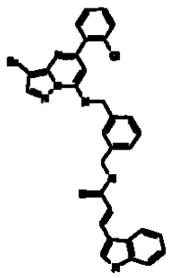
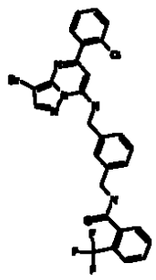
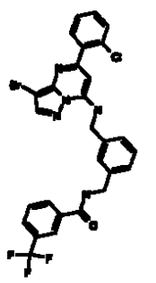
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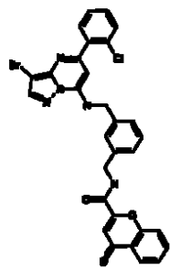
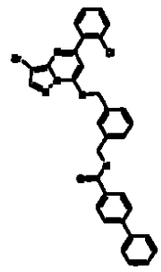
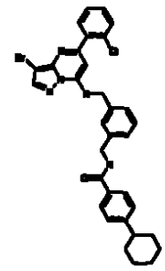
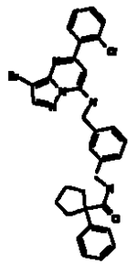
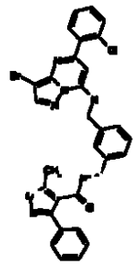
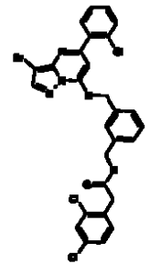
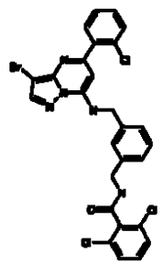
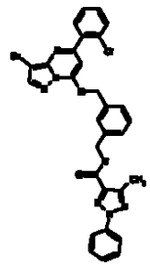
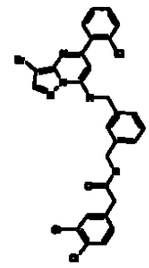
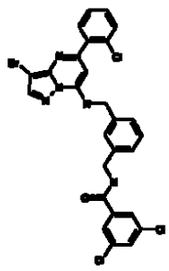
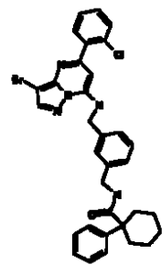
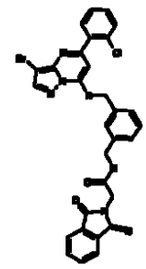
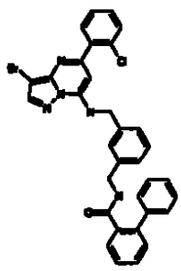
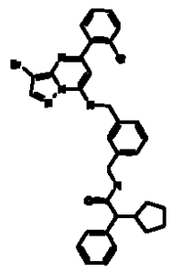
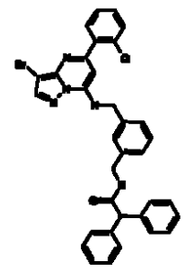
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	1. 4548 2. 588.32		1. 4553 2. 592.33		1. 4558 2. 596.33
	1. 4549 2. 588.32		1. 4554 2. 594.33		1. 4559 2. 598.33
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Producto	1. Ej. 2. m/z
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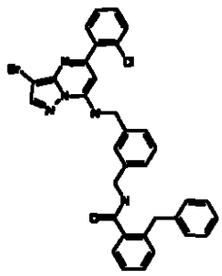
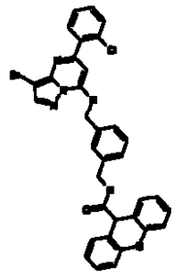
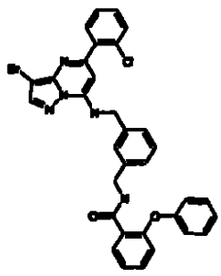
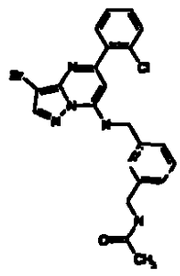
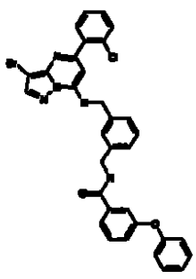
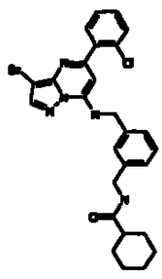
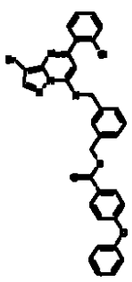
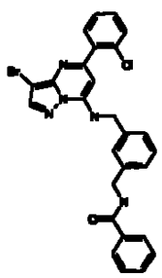
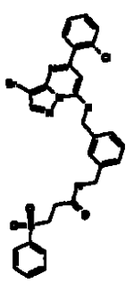
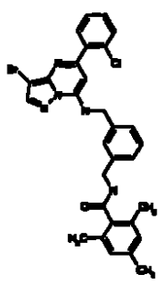
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Producto	1. Ej. m/z
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722

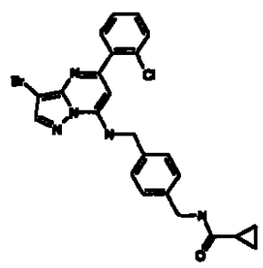
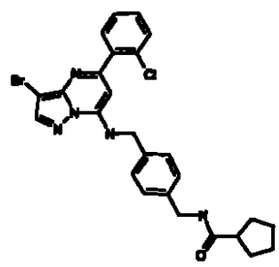
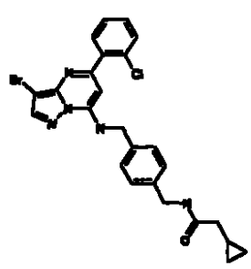
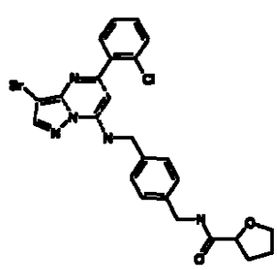
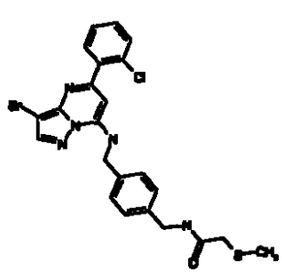
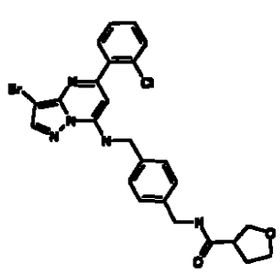
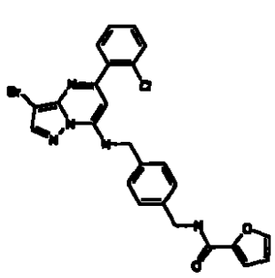
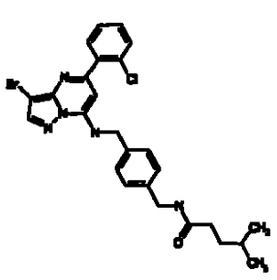
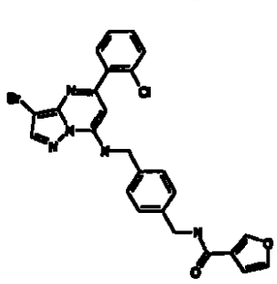
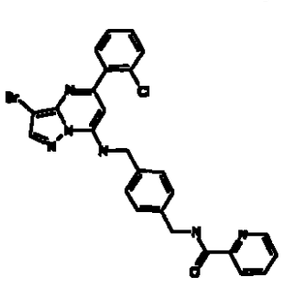
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	1. 4577 2. 616.34		1. 4582 2. 629.35		1. 4587 2. 630.35
	1. 4578 2. 616.34		1. 4583 2. 629.35		1. 4588 2. 630.35
	1. 4579 2. 616.34		1. 4584 2. 630.35		1. 4589 2. 631.35
	1. 4580 2. 624.34		1. 4585 2. 630.35		1. 4590 2. 638.35

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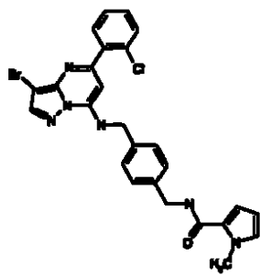
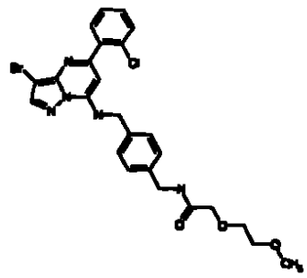
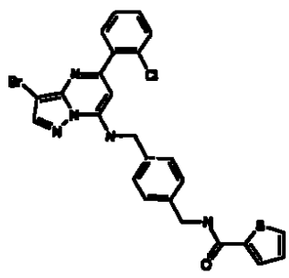
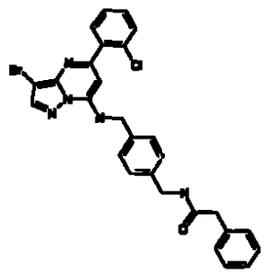
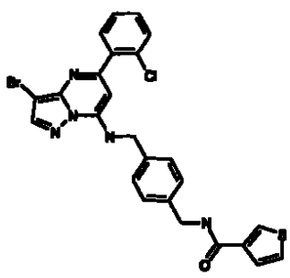
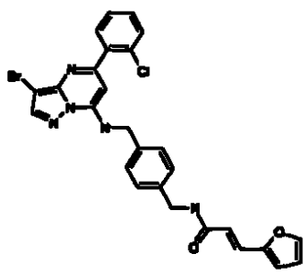
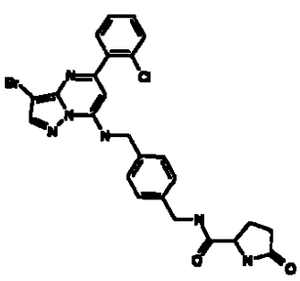
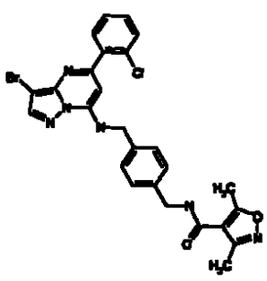
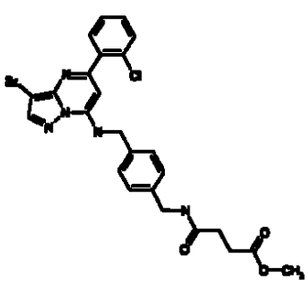
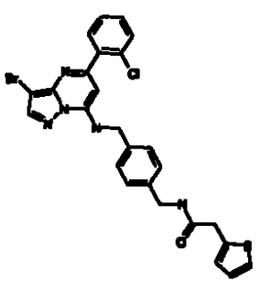
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	1. 4592 2. 640.35		1. 4597 2. 486.27
	1. 4593 2. 640.35		1. 4598 2. 554.3
	1. 4594 2. 640.35		1. 4599 2. 548.3
	1. 4595 2. 640.35		1. 45100 2.

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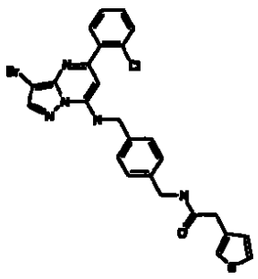
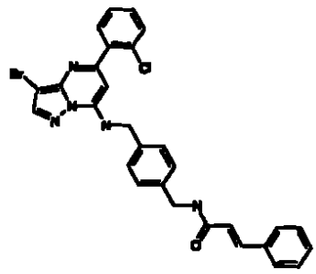
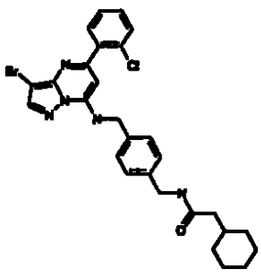
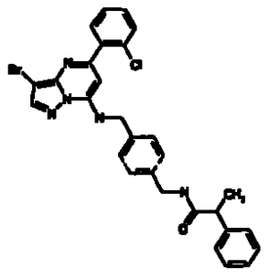
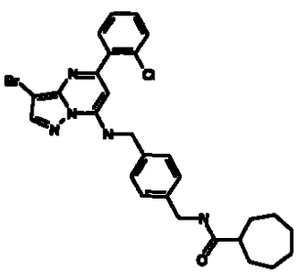
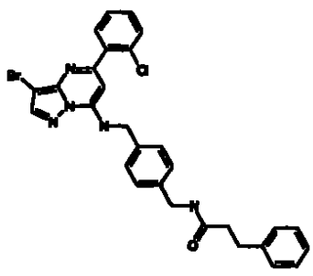
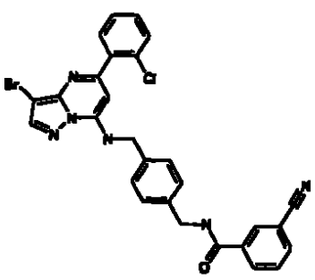
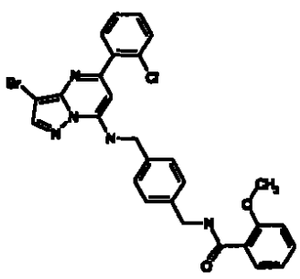
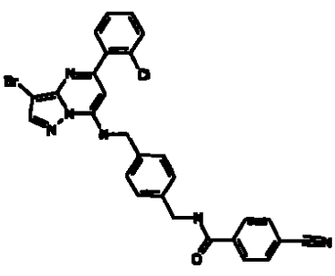
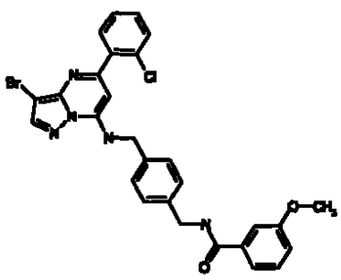
TABLA 46

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	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

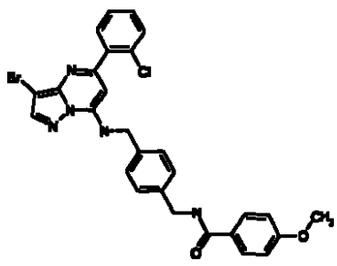
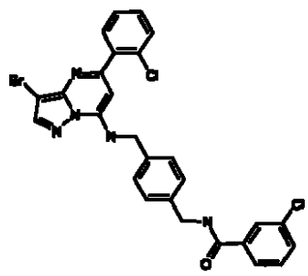
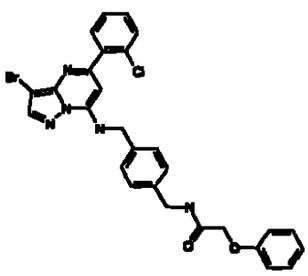
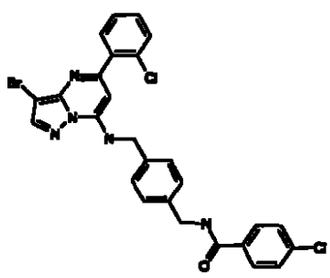
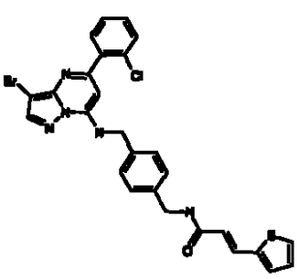
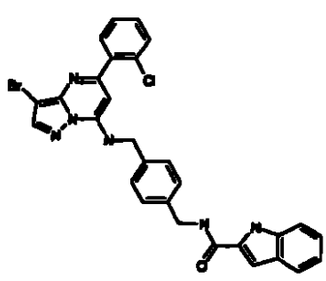
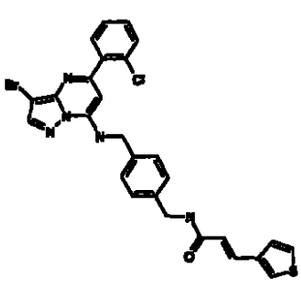
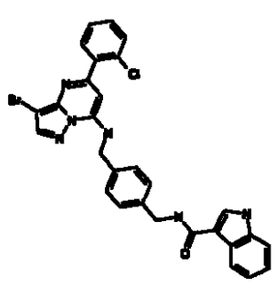
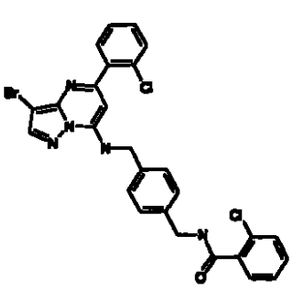
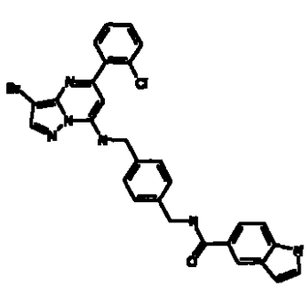
725

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	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

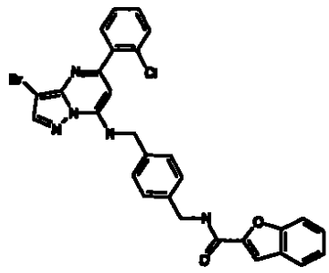
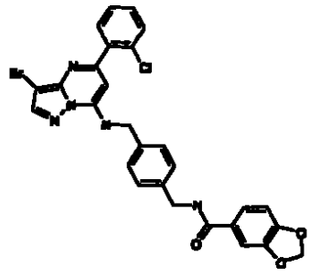
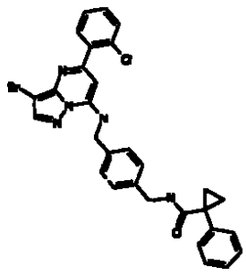
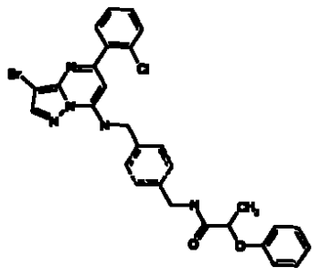
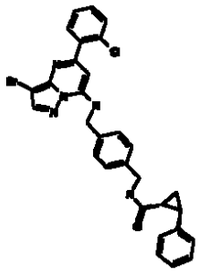
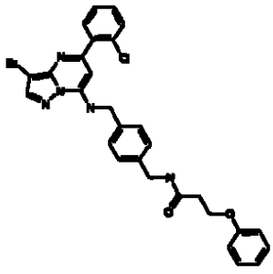
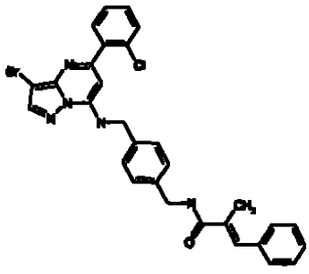
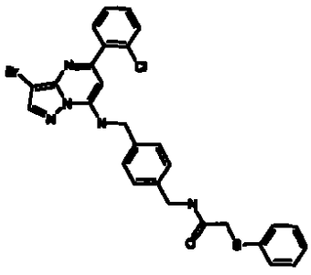
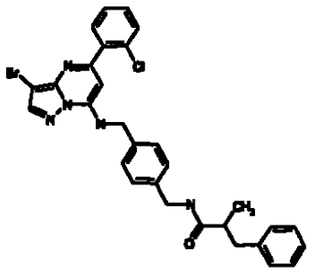
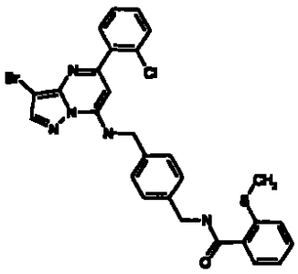
726

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	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

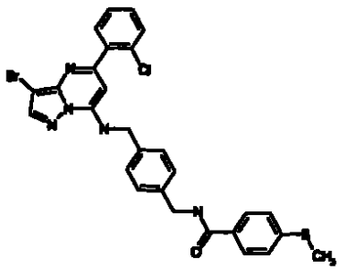
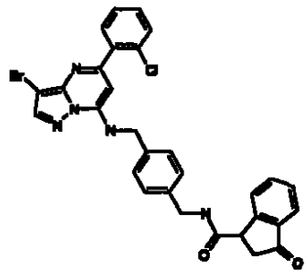
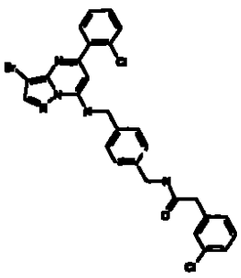
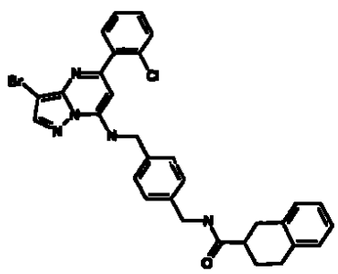
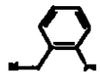
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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4631 2. 578.32		1. 4636 2. 582.32
	1. 4632 2. 578.32		1. 4637 2. 582.32
	1. 4633 2. 580.32		1. 4638 2. 587.32
	1. 4634 2. 580.32		1. 4639 2. 585.3
	1. 4635 2. 582.32		1. 4640 2. 585.3

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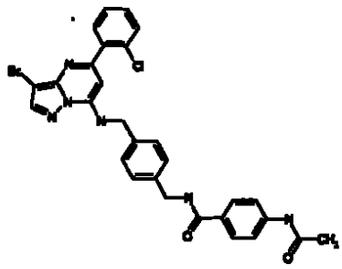
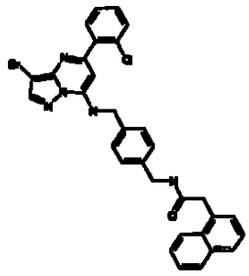
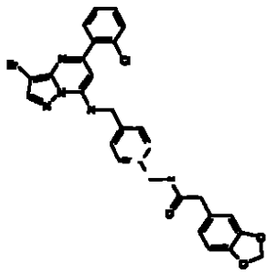
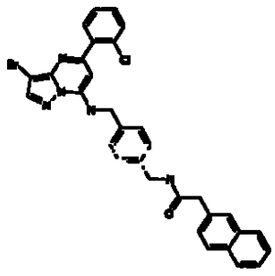
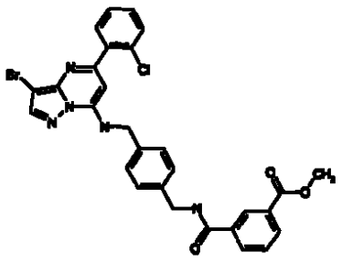
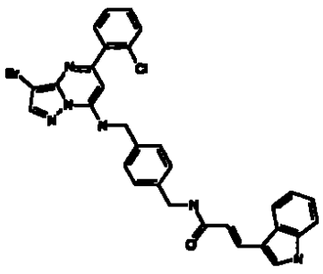
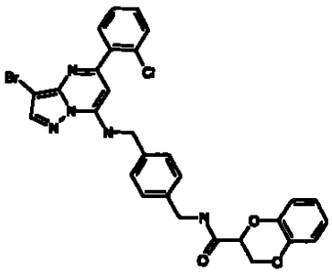
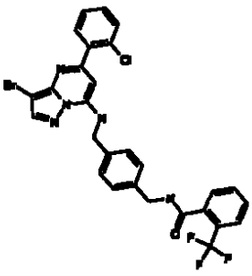
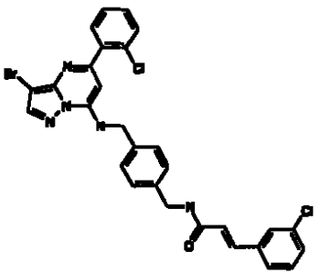
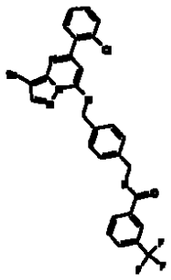
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	1. 4642 2. 588.32		1. 4647 2. 592.33
	1. 4643 2. 588.32		1. 4648 2. 592.33
	1. 4644 2,. 588.32		1. 4649 2.
	1. 4645 2. 590.32		1. 4650 2. 594.33

729

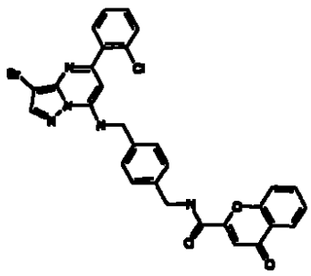
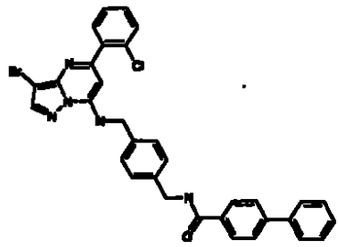
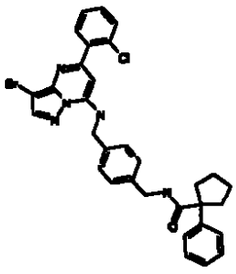
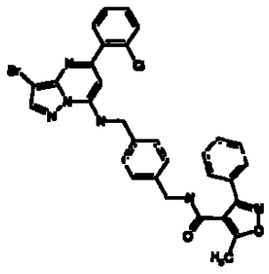
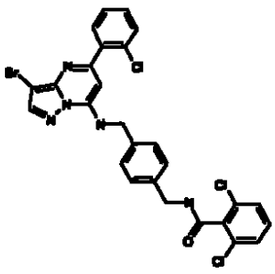
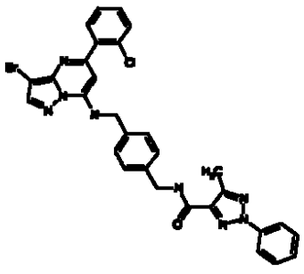
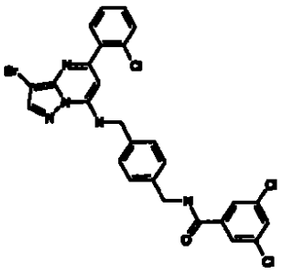
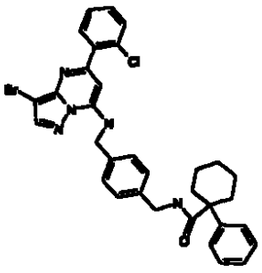
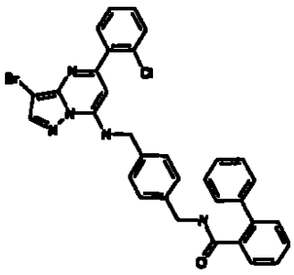
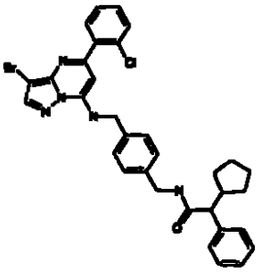
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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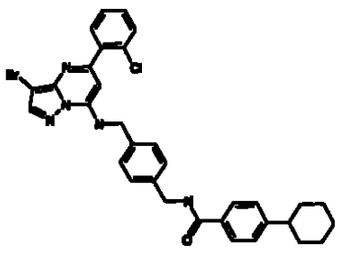
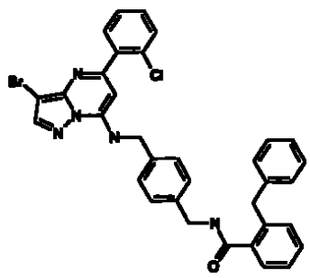
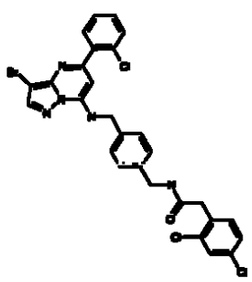
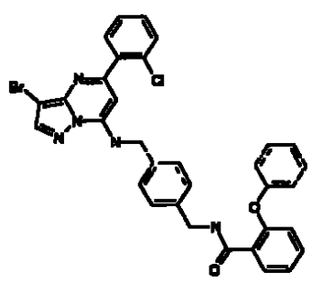
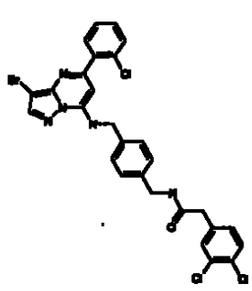
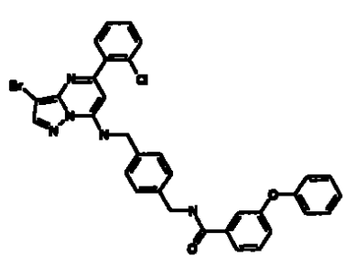
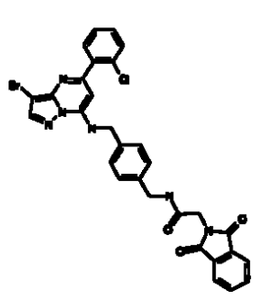
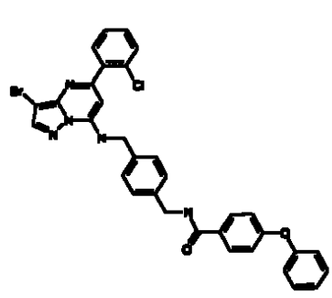
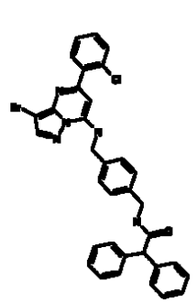
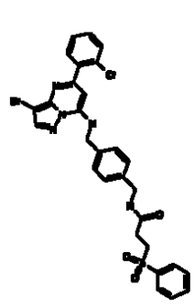
730

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 4662 2. 606.33		1. 4667 2. 613.34
	1. 4663 2. 606.33		1. 4668 2. 613.34
	1. 4664 2. 606.33		1. 4669 2. 616.34
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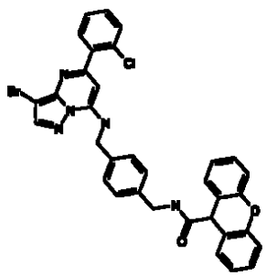
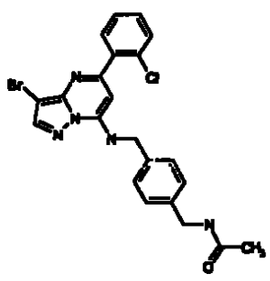
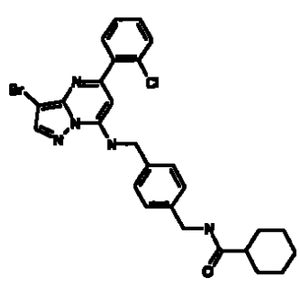
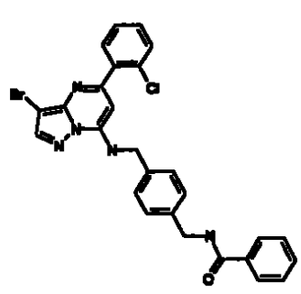
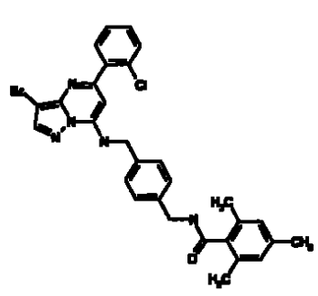
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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 4672 2. 616.34		1. 4677 2. 629.35
	1. 4673 2. 616.34		1. 4678 2. 629.35
	1. 4674 2. 616.34		1. 4679 2. 630.35
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732

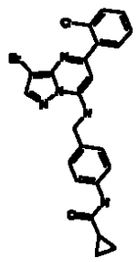
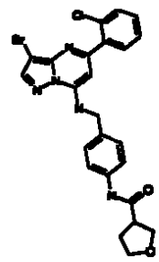
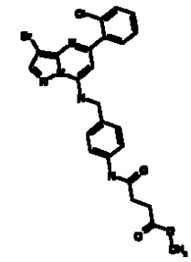
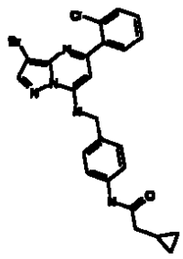
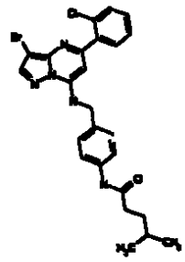
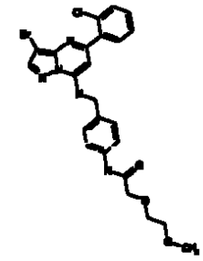
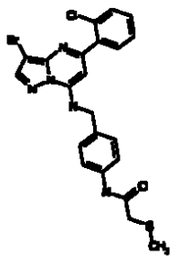
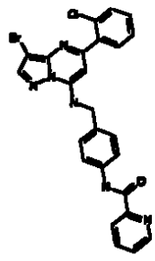
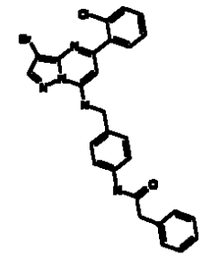
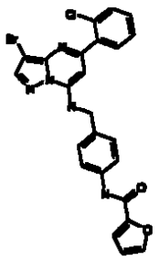
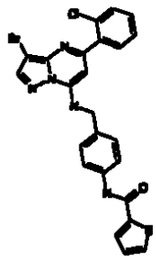
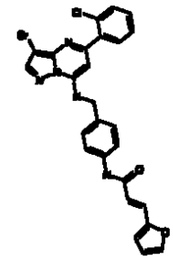
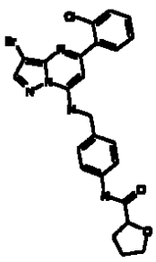
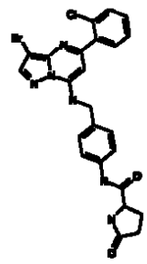
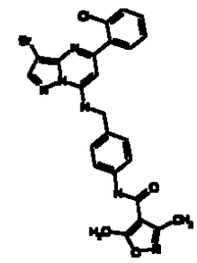
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 4682 2. 630.35		1. 4687 2. 640.35
	1. 4683 2. 630.35		1. 4688 2. 640.35
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733

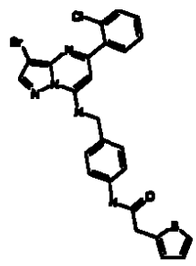
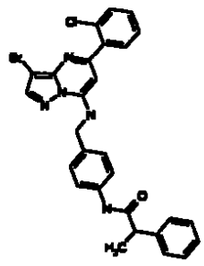
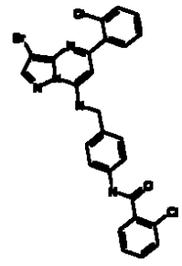
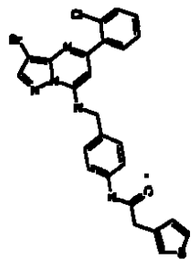
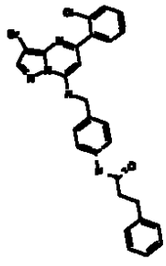
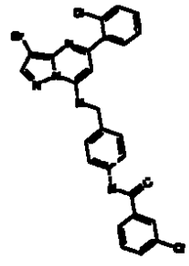
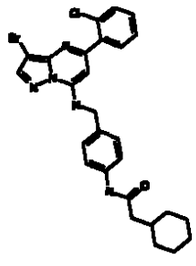
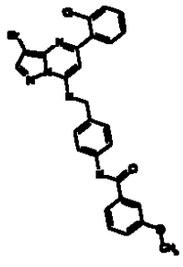
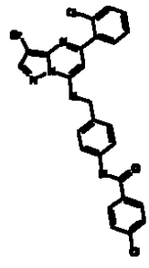
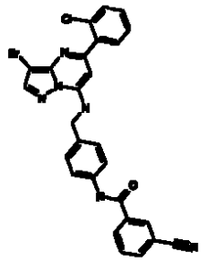
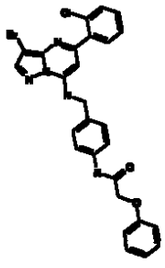
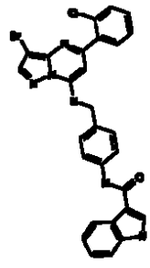
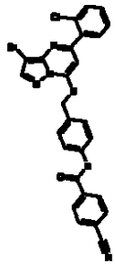
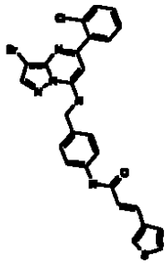
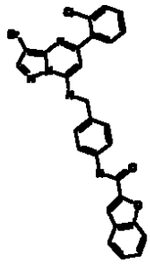
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	1. 4693 2. 554.3
	1. 4694 2. 548.3
	1. 4695 2. 590.32

734

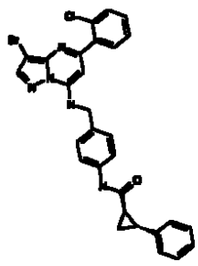
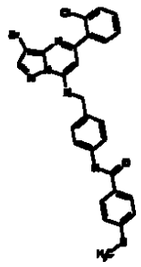
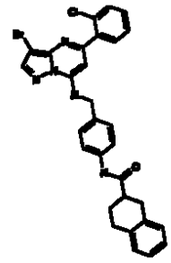
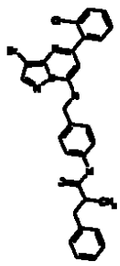
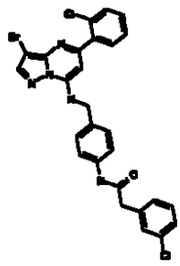
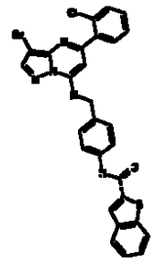
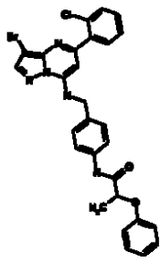
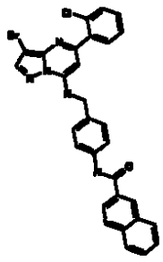
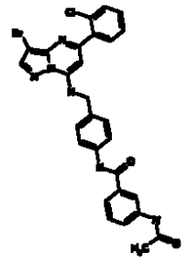
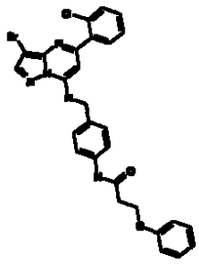
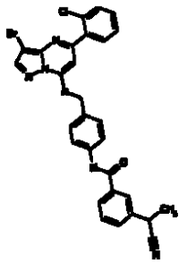
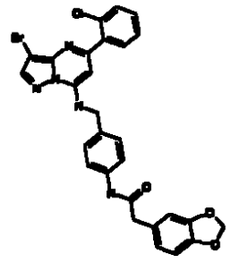
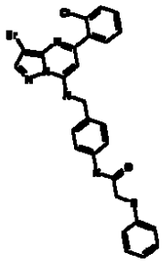
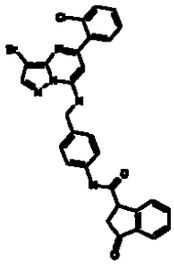
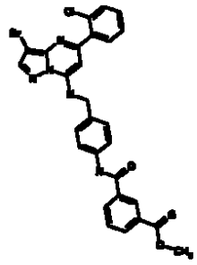
TABLA 47

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

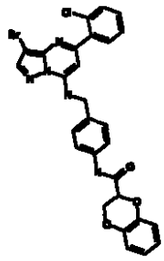
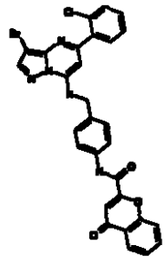
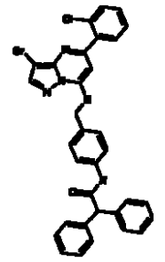
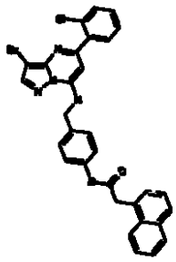
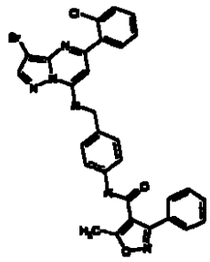
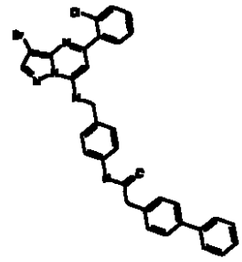
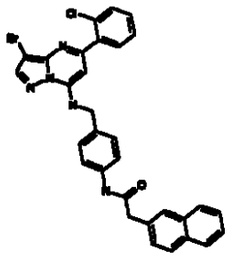
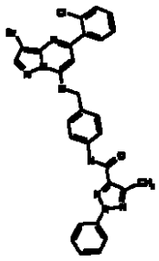
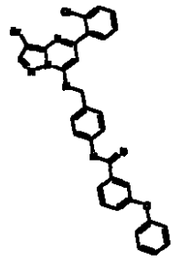
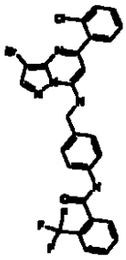
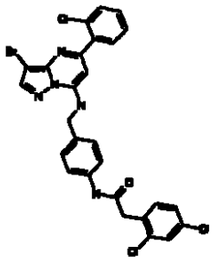
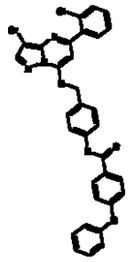
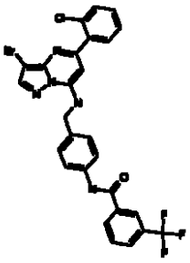
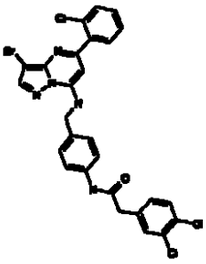
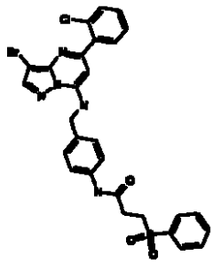
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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2 m/z
	1. 4716 2. 554.3		1. 4721 2. 562.31		1. 4726 : 568.31
	1. 4717 2. 554.3		1. 4722 2. 562.31		1. 4727 : 568.31
	1. 4718 2. 554.3		1. 4723. 2 564.31		1. 4728 : 568.31
	1. 4719 2. 559.31		1. 4724 2. 564.31		1. 4729 : 573.32
	1. 4720 2. 559.31		1. 4725 2. 566.31		1. 4730 : 574.32

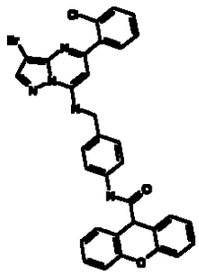
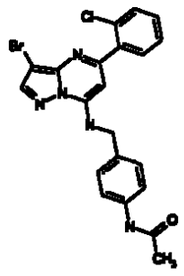
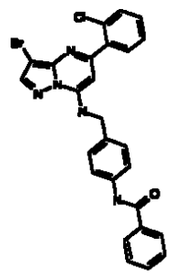
736

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 : 588.32
	1. 4732 2. 576.32		1. 4737 2. 582.32		1. 4742 : 590.32
	1. 4733 2. 578.32		1. 4738 2. 584.32		1. 4743 . 591.33
	1. 4734 2. 578.32		1. 4739 2. 585.32		1. 4744 . 592.33
	1. 4735 2. 580.32		1. 4740 2. 588.32		1. 4745 . 592.33

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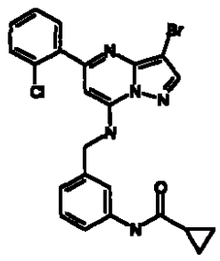
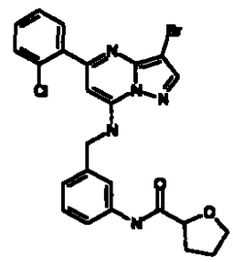
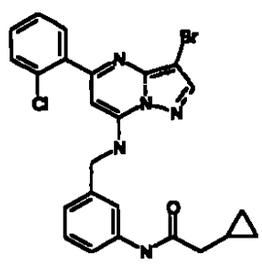
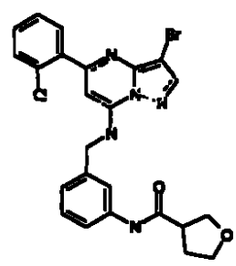
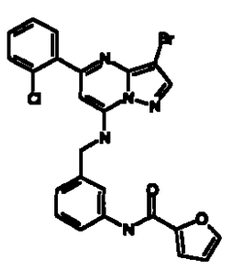
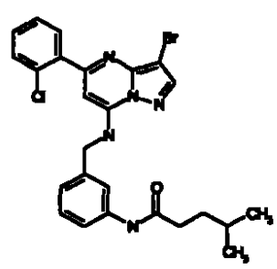
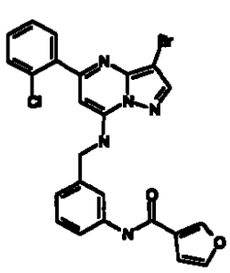
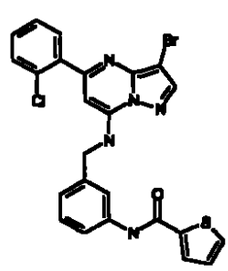
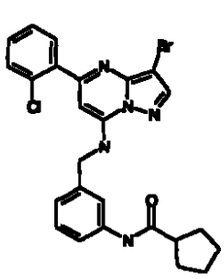
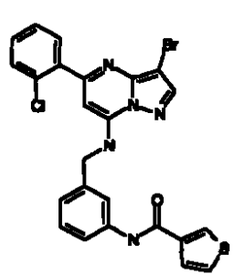
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2 m/z
	1. 4746 2. 592.33		1. 4751 2. 602.33		1. 4756 : 624.34
	1. 4747 2. 598.33		1. 4752 2. 615.34		1. 4757 : 624.34
	1. 4748 2. 598.33		1. 4753 2. 615.34		1. 4758 : 626.34
	1. 4749 2. 602.33		1. 4754 2. 616.34		1. 4759 . 624.34
	1. 4750 2. 602.33		1. 4755 2. 616.34		1. 4760 . 626.34

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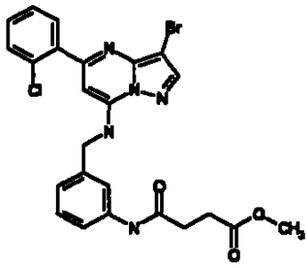
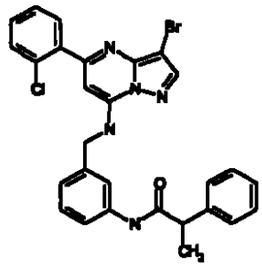
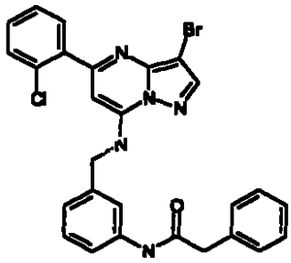
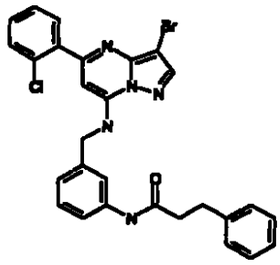
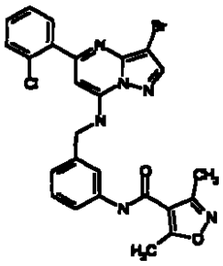
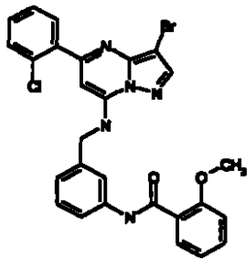
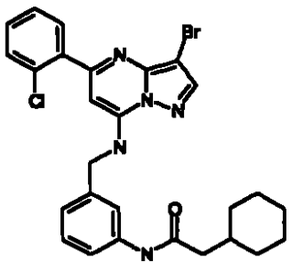
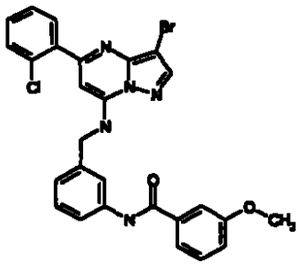
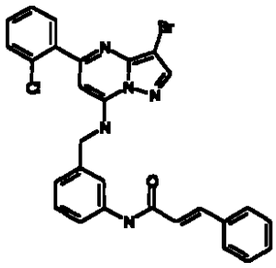
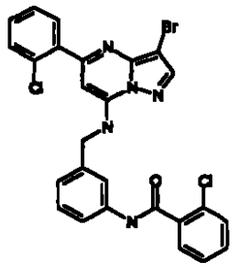
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	1. 4762 2. 472.26
	1. 4763 2. 534.29

739

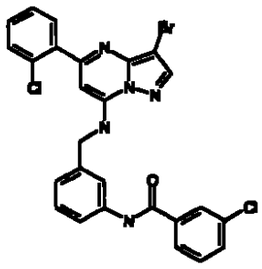
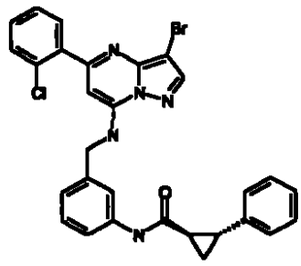
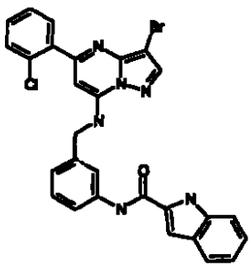
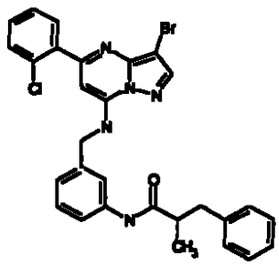
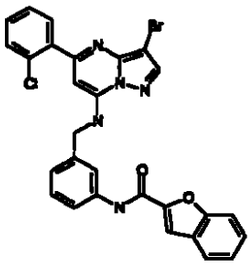
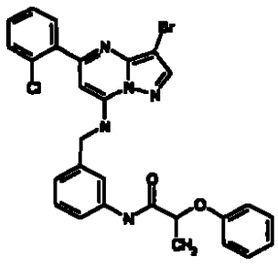
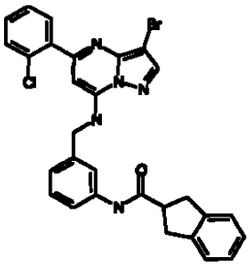
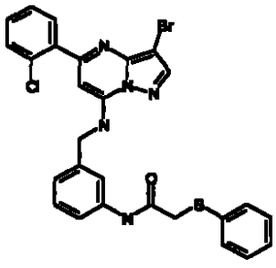
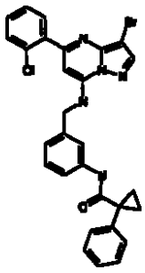
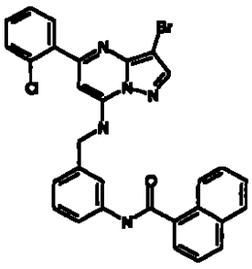
TABLA 48

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	1. 4802 2. 512.28		1.. 4807 2. 528.29
	1. 4803 2. 524.29		1. 4806 2. 528.29
	1. 4804 2. 524.29		1. 4809 2. 540.3
	1. 4805 2. 526.29		1. 4810 2. 540.3

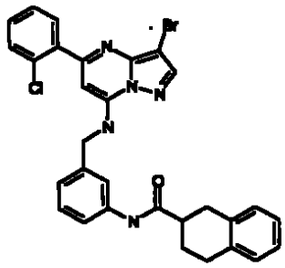
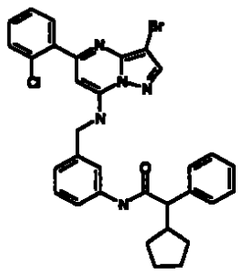
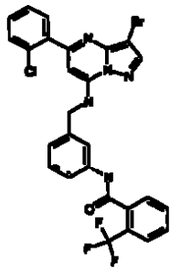
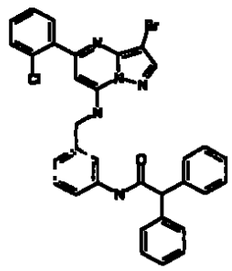
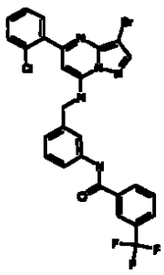
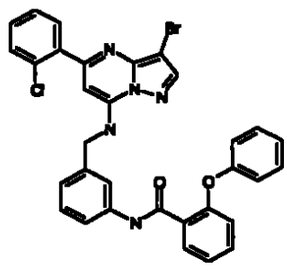
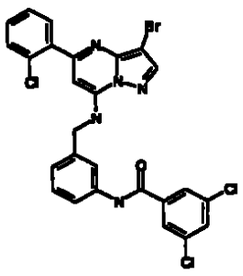
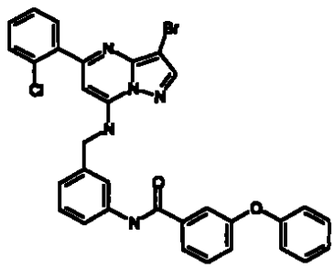
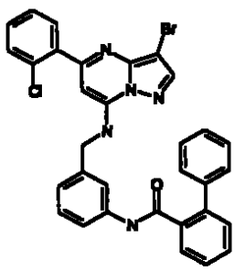
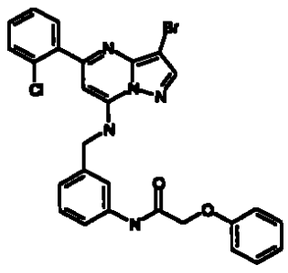
740

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	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

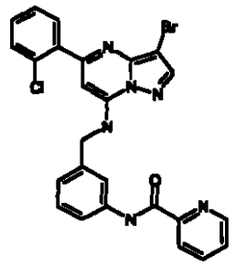
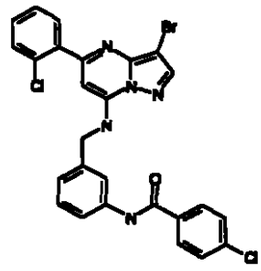
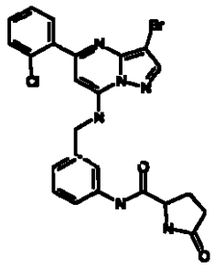
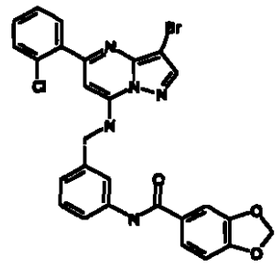
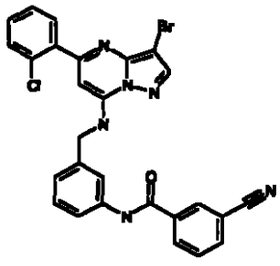
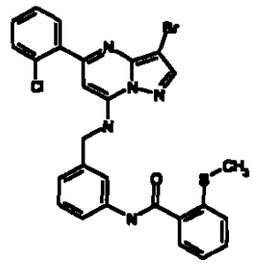
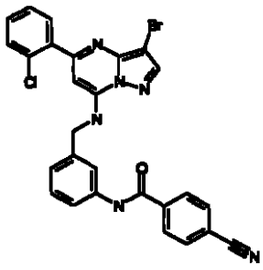
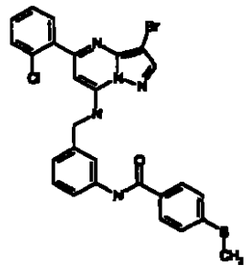
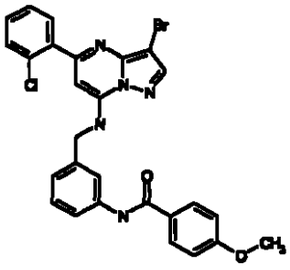
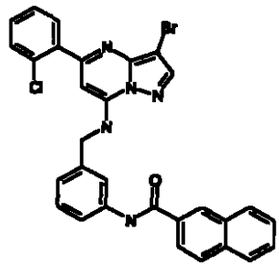
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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 4822 2. 573.32		1. 4828 2. 575.32
	1. 4821 2. 574.32		1. 4829 2. 578.32
	1. 4824 2. 574.32		1. 4829 2. 580.32
	1. 4825 2. 574.32		1. 4830 2. 584.32

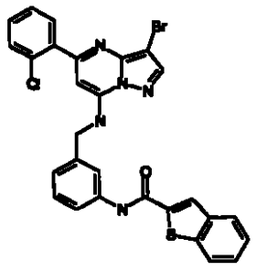
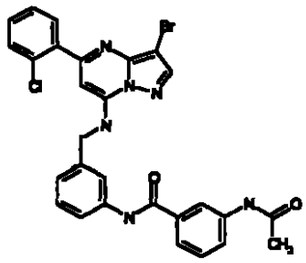
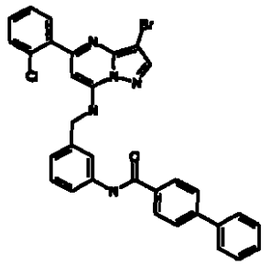
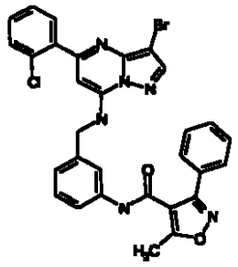
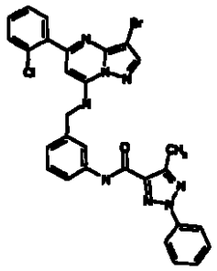
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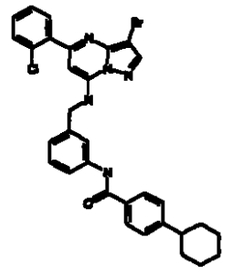
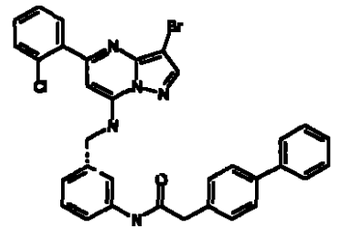
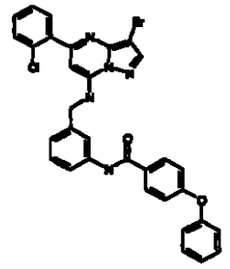
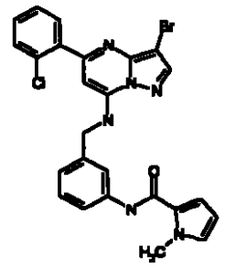
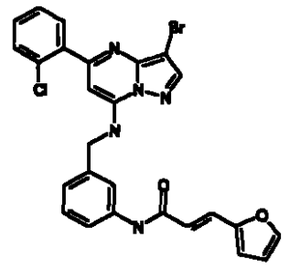
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 4832 2. 602.33		1. 4837 2. 624.34
	1. 4833 2. 602.33		1. 4838 2. 626.34
	1. 4834 2. 602.33		1. 4839 2. 626.34
	1. 4835 2. 610.34		1. 4840 2. 564.31

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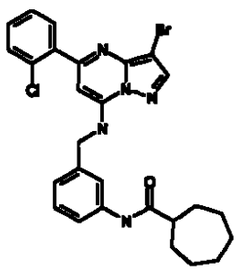
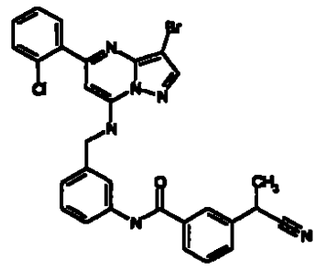
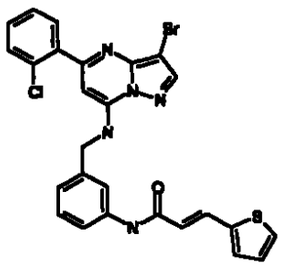
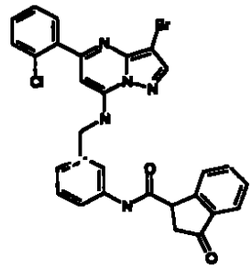
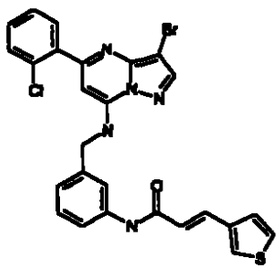
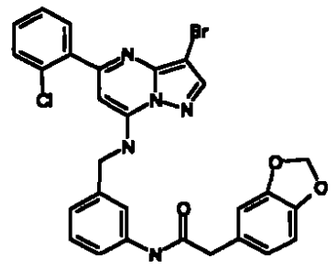
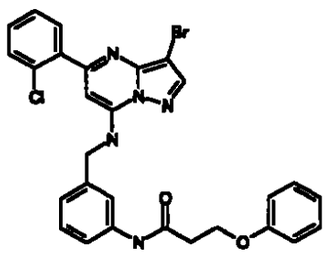
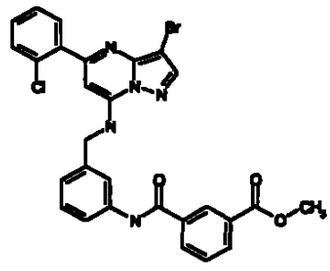
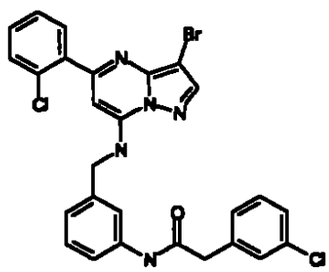
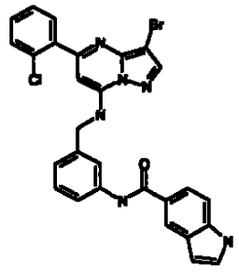
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	1. 4843 2. 559.31		1. 4848 2. 580.32
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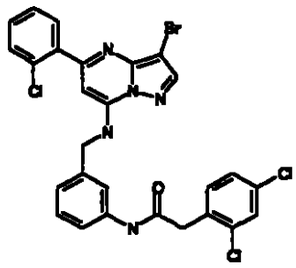
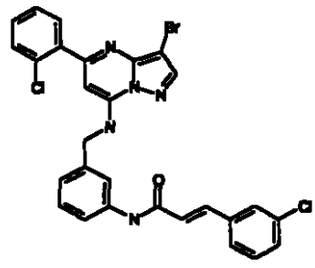
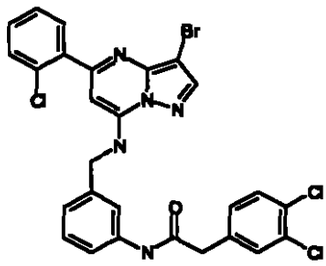
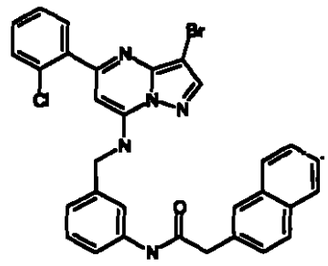
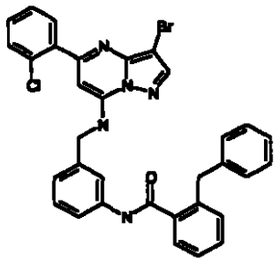
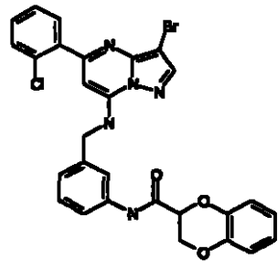
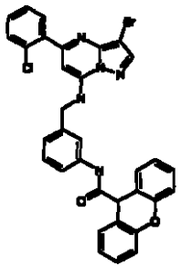
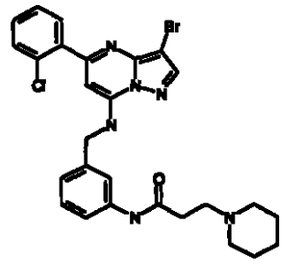
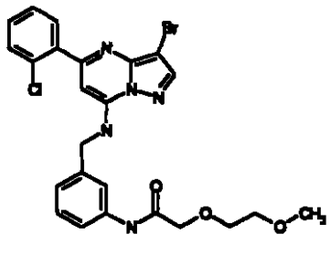
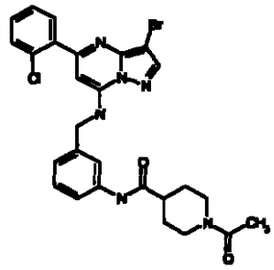
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	1. 4852 2. 591.33
	1. 4853 2. 610.34
	1. 4854 2. 615.34
	1. 4855 2. 615.34

Producto	1. Ej. 2. m/z
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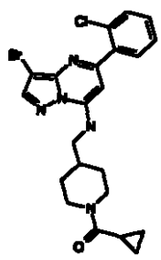
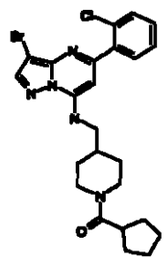
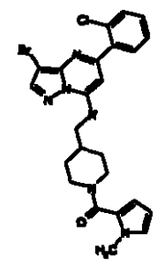
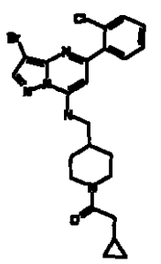
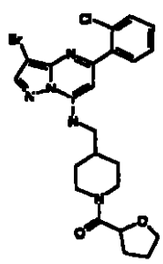
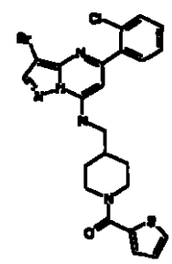
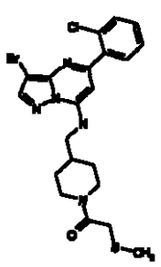
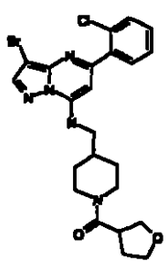
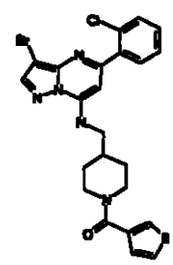
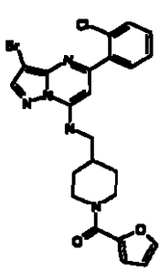
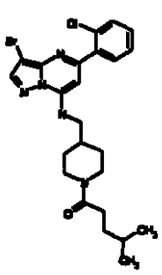
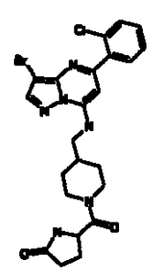
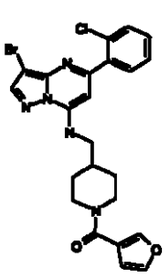
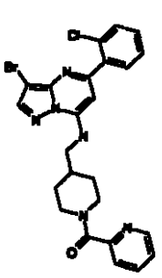
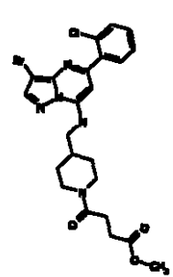
795

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 4863 2. 566.31		1. 4868 2. 592.33
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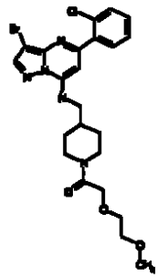
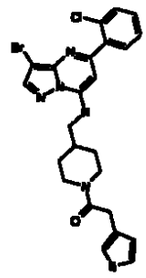
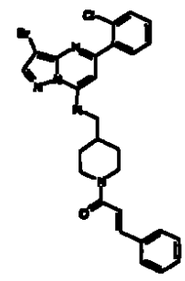
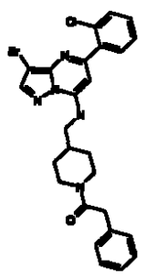
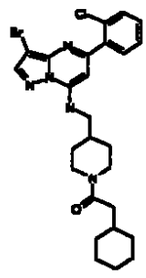
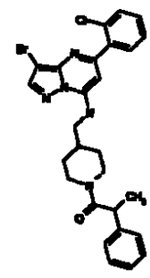
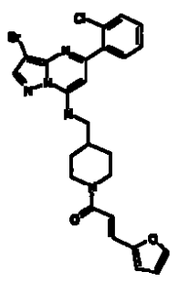
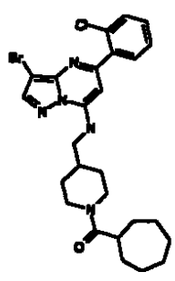
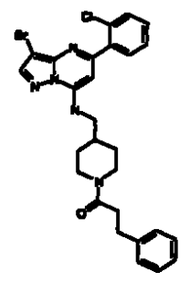
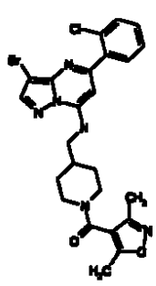
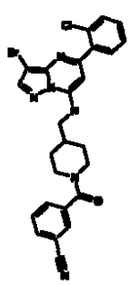
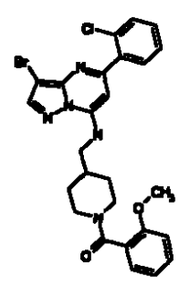
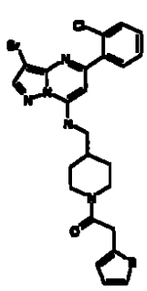
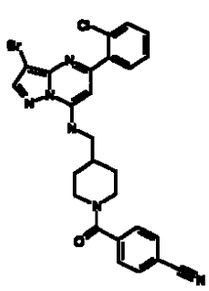
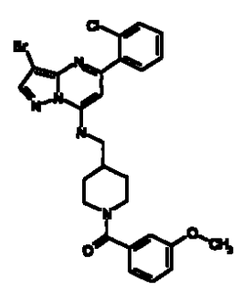
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	1. 4872 2. 616.34		1. 4877 2. 598.33
	1. 4873 2. 624.34		1. 4878 2. 592.33
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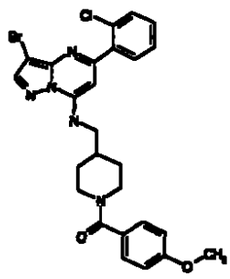
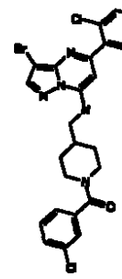
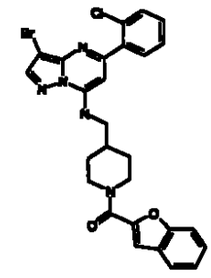
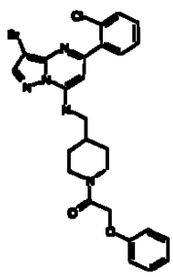
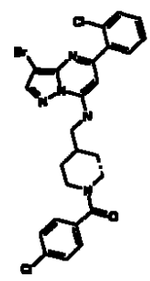
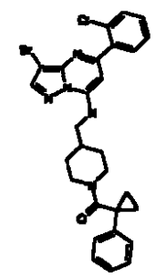
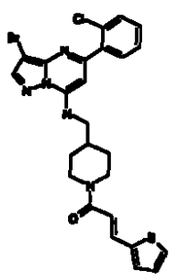
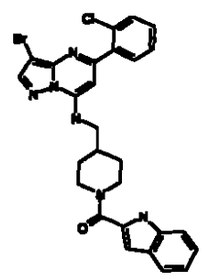
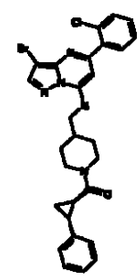
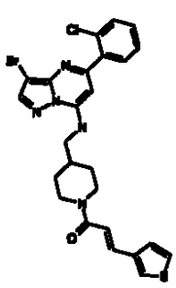
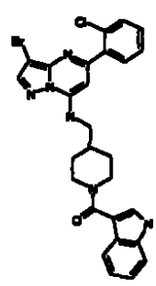
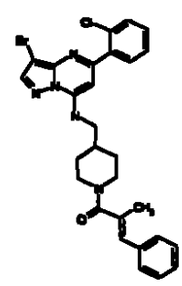
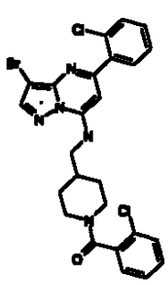
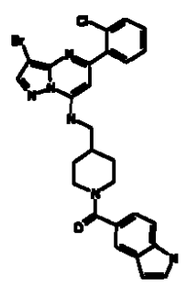
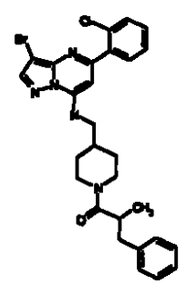
TABLA 49

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	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

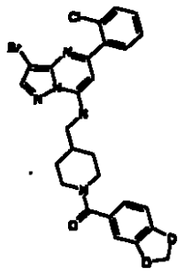
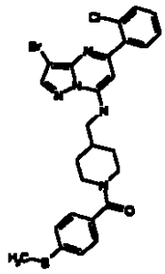
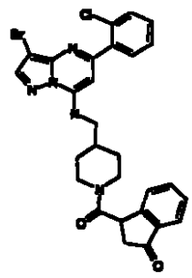
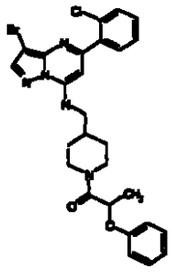
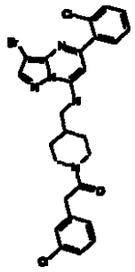
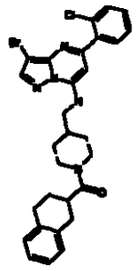
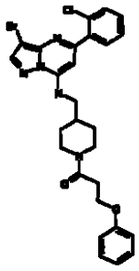
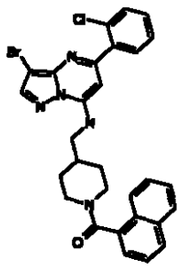
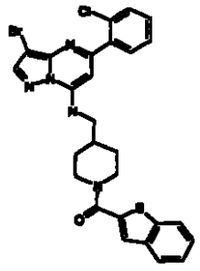
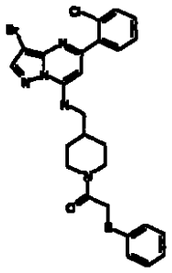
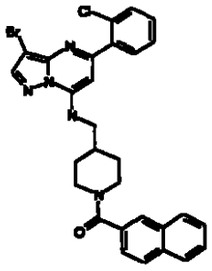
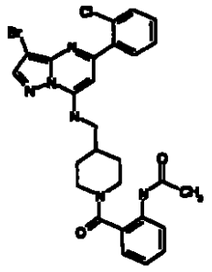
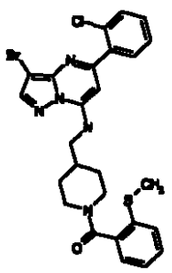
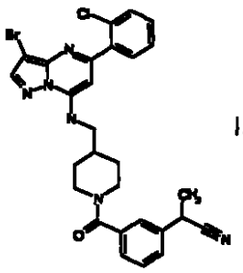
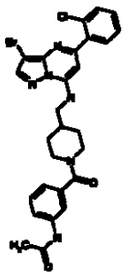
748

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	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
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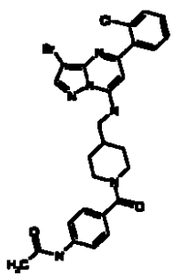
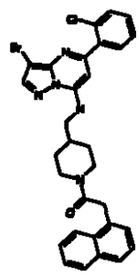
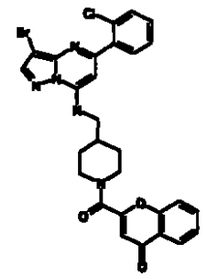
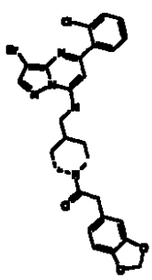
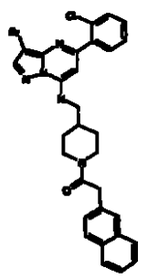
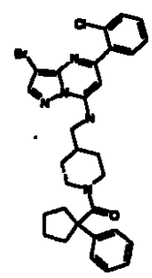
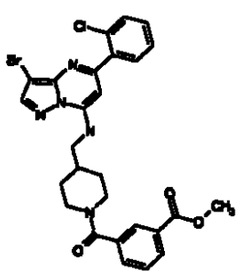
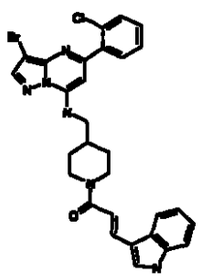
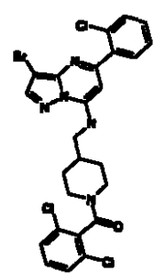
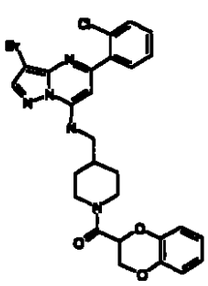
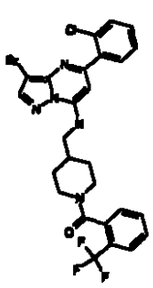
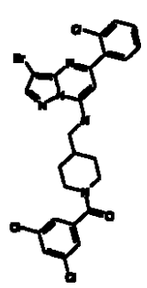
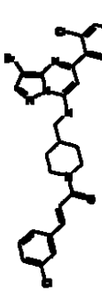
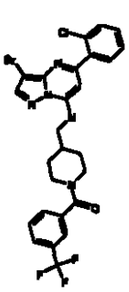
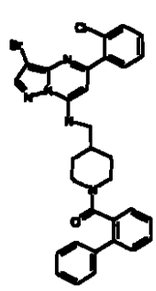
799

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej m/.
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	1. 4932 2. 556.31		1. 4937 2. 560.31		1. 494 566.
	1. 4933 2. 558.31		1. 4938 2. 565.31		1. 494 566.
	1. 4934 3. 558.31		1. 4939 2. 565.3		1. 494 566.
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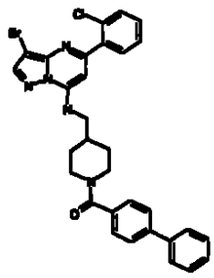
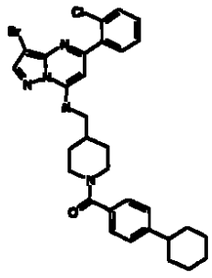
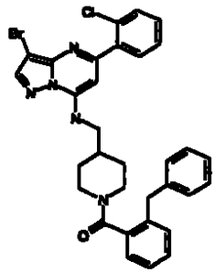
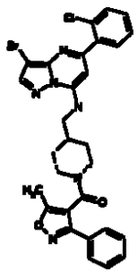
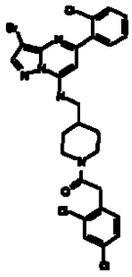
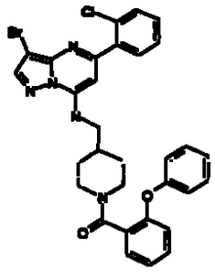
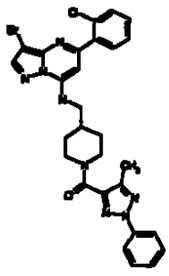
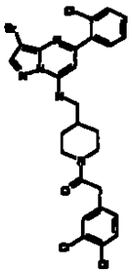
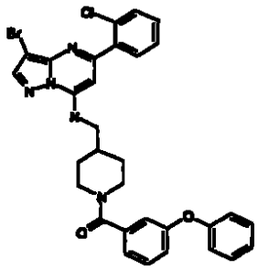
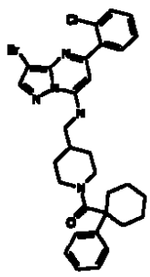
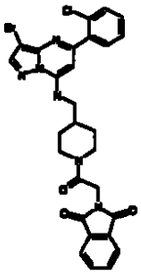
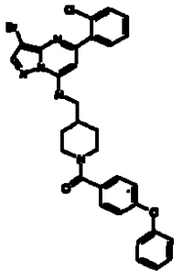
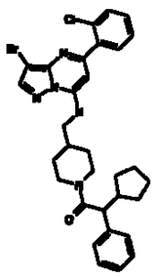
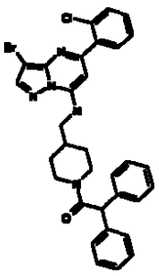
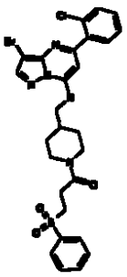
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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 4947 2. 570.31		1. 4952 2. 574.32		1. 4957 2. 580.32
	1. 4948 2. 570.31		1. 4953 2. 576.32		1. 4958 2. 582.32
	1. 4949 2. 572.31		1. 4954 2. 576.32		1. 4959 2. 583.32
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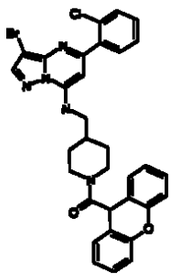
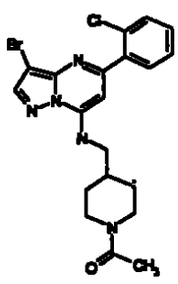
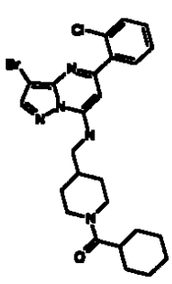
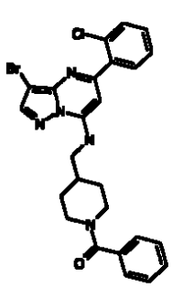
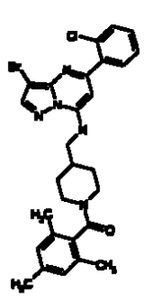
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	1. 4963 2. 584.32		1. 4968 2. 591.3		1. 4973 2. 594.33
	1. 4964 2. 584.32		1. 4969 2. 594.33		1. 4974 2. 594.33
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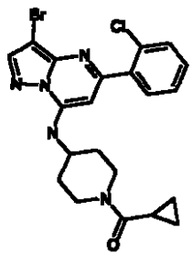
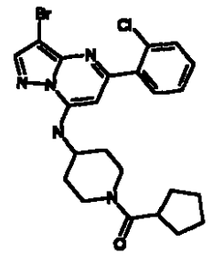
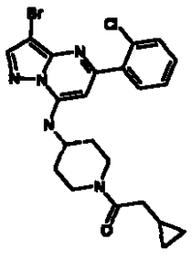
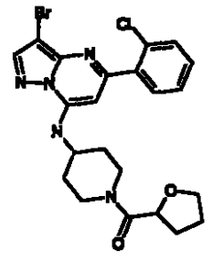
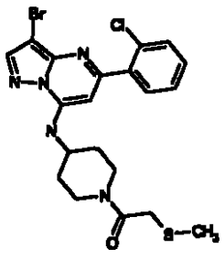
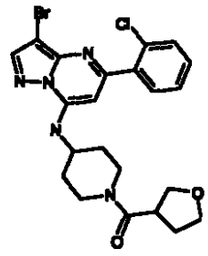
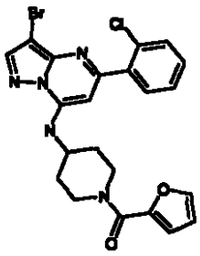
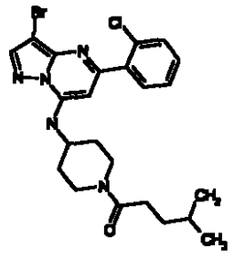
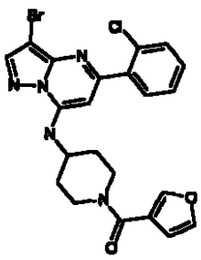
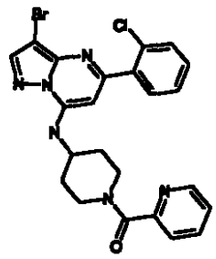
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	1. 4977 2. 607.33		1. 4982 2. 608.33		1. 4987 2. 618.34
	1. 4978 2. 607.33		1. 4983 2. 608.33		1. 4988 2. 618.34
	1. 4979 2. 605.33		1. 4984 2. 609.33		1. 4089 2. 618.34
	1. 4980 2. 608.33		1. 4985 2. 616.34		1. 4990 2. 618.34

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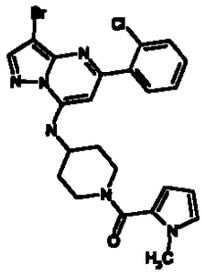
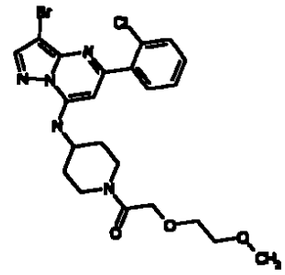
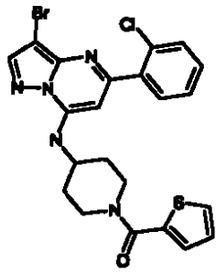
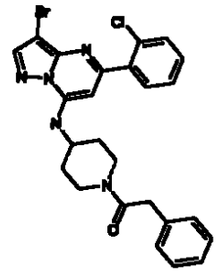
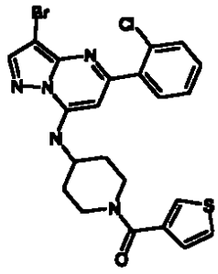
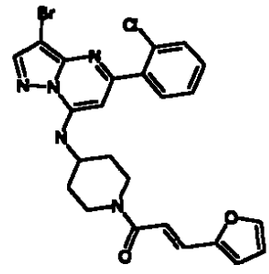
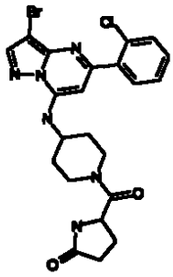
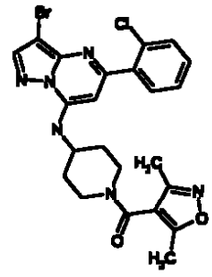
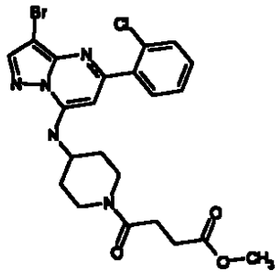
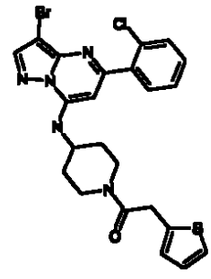
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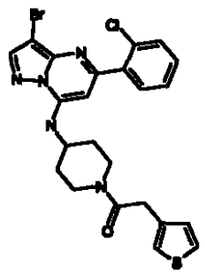
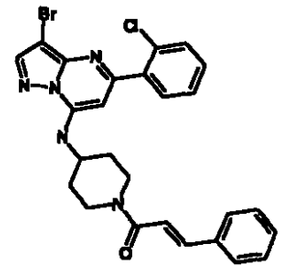
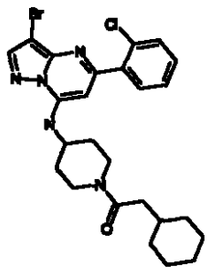
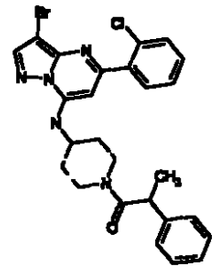
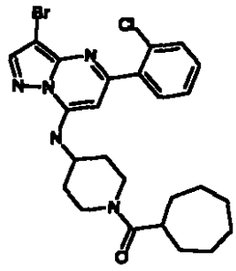
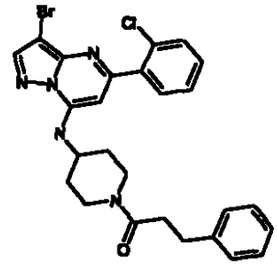
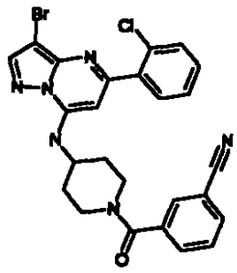
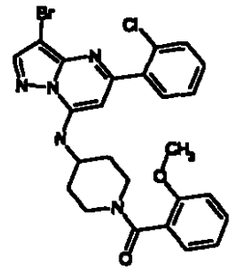
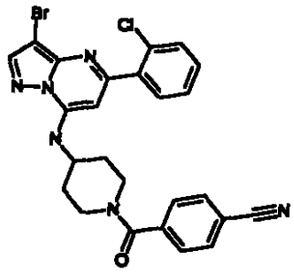
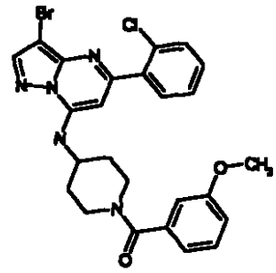
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TABLA 50

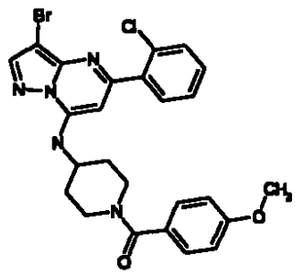
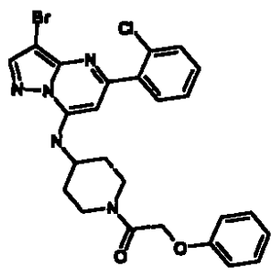
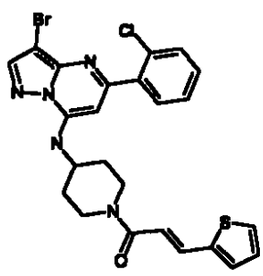
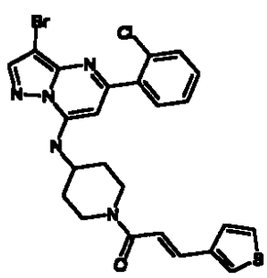
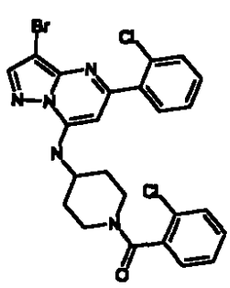
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	1. 5003 2. 496.27		1. 5008 2. 506.28
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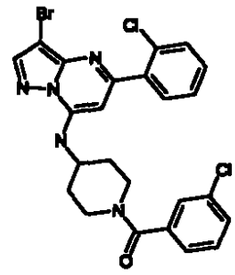
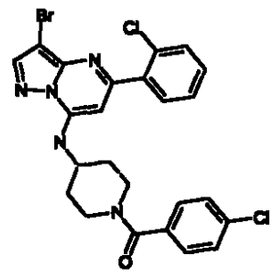
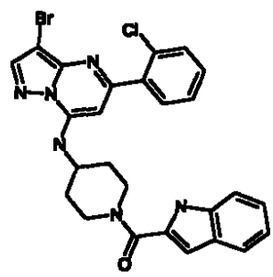
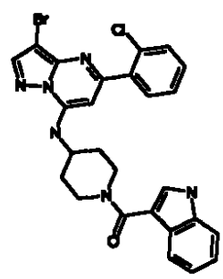
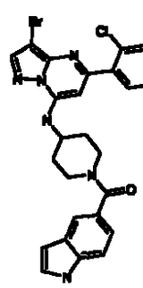
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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 5013 2. 518.28		1. 5018 2. 528.29
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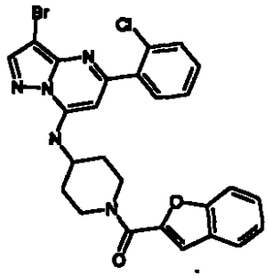
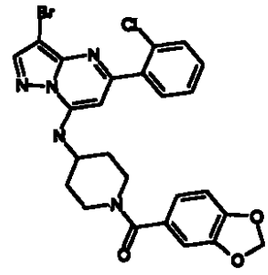
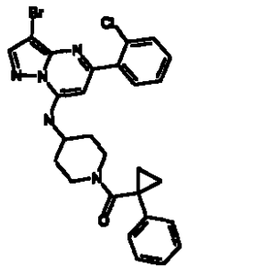
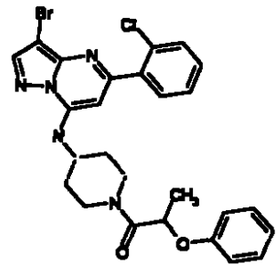
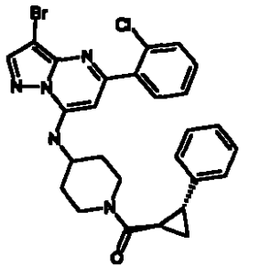
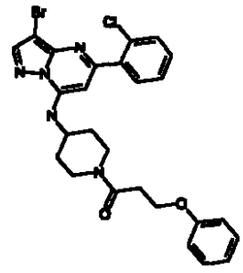
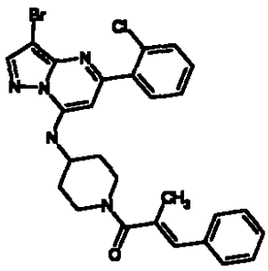
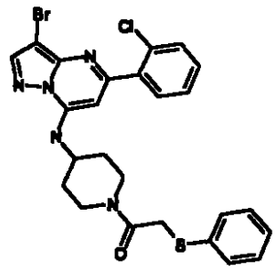
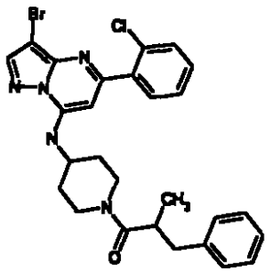
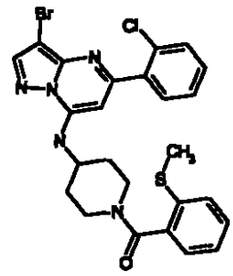
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 5022 2. 532.29		1. 5027 2. 540.3
	1. 5023 2. 532.29		1. 5028 2. 540.3
	1. 5024 2. 537.3		1. 5029 2. 542.3
	1. 5025 2. 537.3		1. 5030 2. 542.3

757

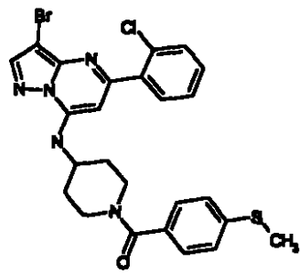
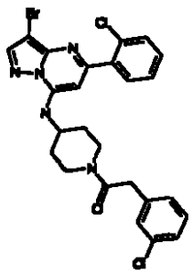
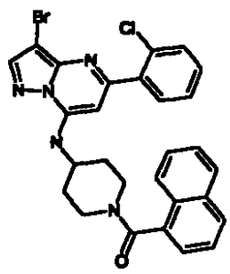
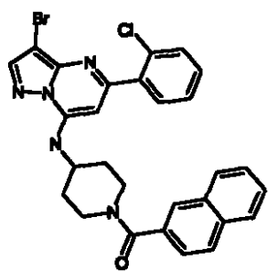
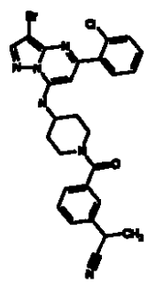
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	1. 5034 2. 544.3
	1. 5035 2 .546.3

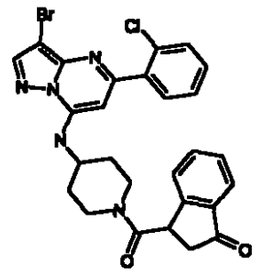
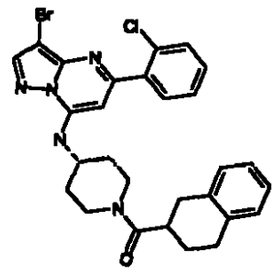
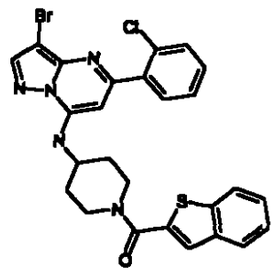
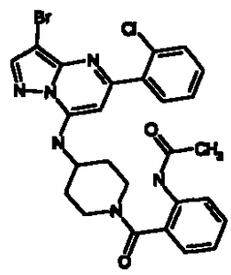
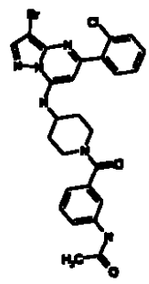
Producto	1. Ej. 2. m/z
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	1. 5037 2 .546.3
	1. 5038 2. 551.3
	1. 5039 2. 551.3
	1. 5040

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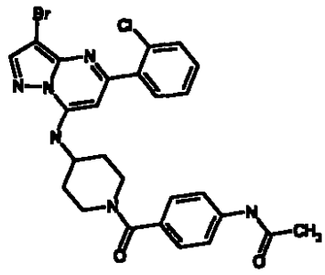
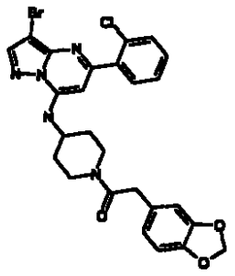
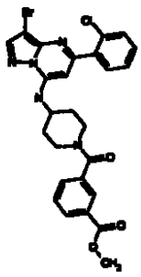
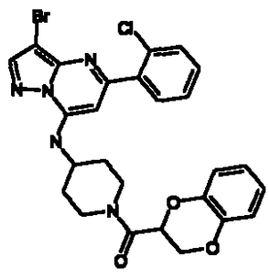
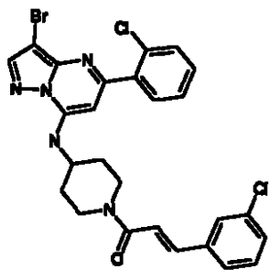
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5041 2. 552.3		1. 5046 2. 556.31
	1. 5042 2. 552.3		1. 5047 2. 556.31
	1. 5043 2. 552.3		1. 5048 2. 556.31
	1. 5044 2. 552.3		1. 5049 2. 558.31
	1. 5045 2. 554.3		1. 5050 2. 558.31

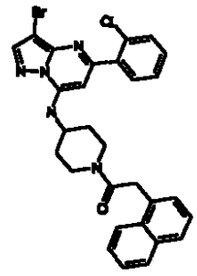
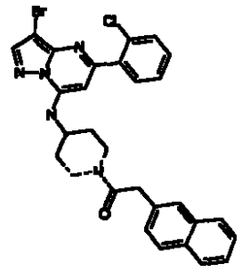
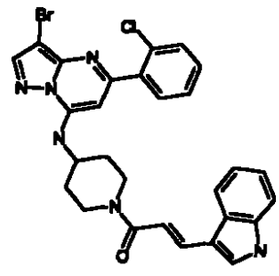
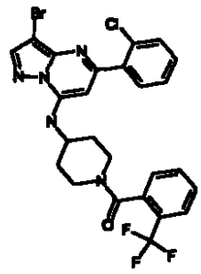
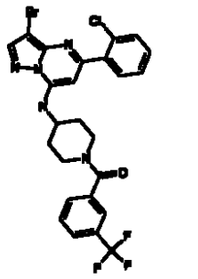
759

Producto	1. Ej. 2. m/z
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	1. 5052 2. 560.31
	1. 5053 2. 562.31
	1. 5054 2. 562.31
	1. 5055 2. 565.31

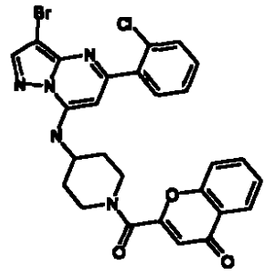
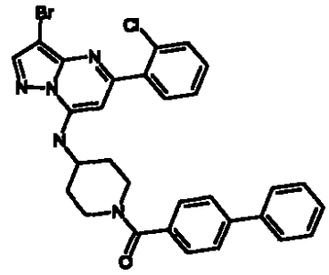
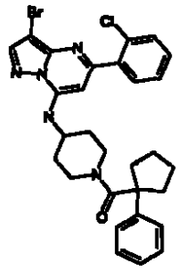
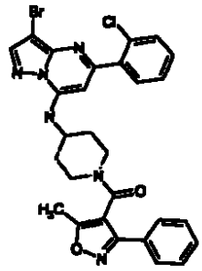
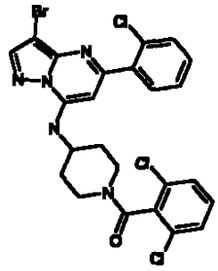
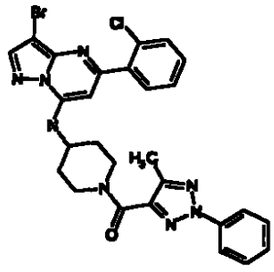
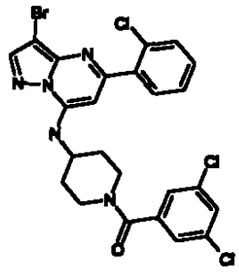
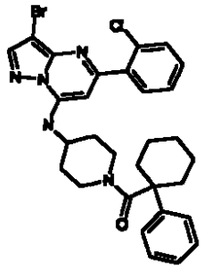
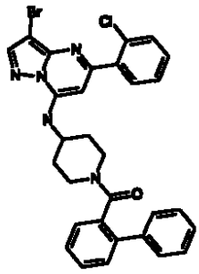
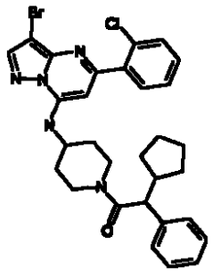
Producto	1. Ej. 2. m/z
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	1. 5058 2. 568.31
	1. 5059 2. 569.31
	1. 5060 2. 569.31

760

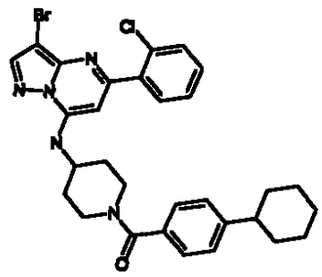
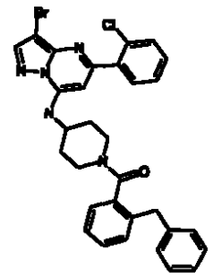
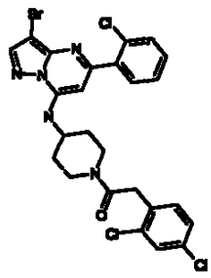
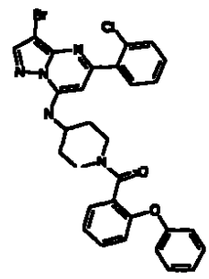
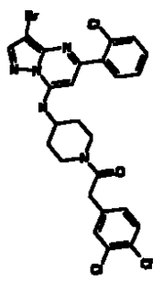
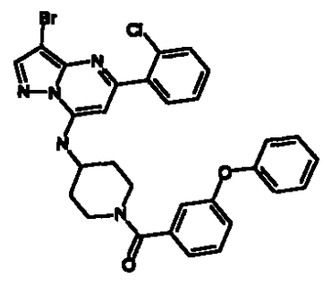
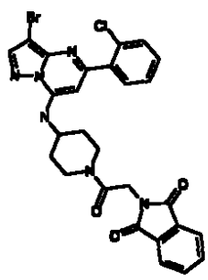
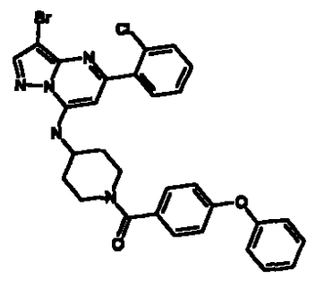
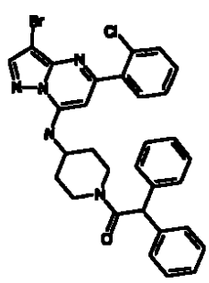
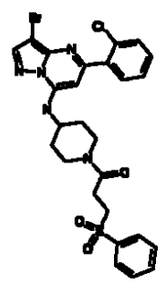
Producto	1. Ej. 2. m/z
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	1. 5062 2. 570.31
	1. 5063 2. 570.31
	1. 5064 2. 570.31
	1. 5065 572.31

Producto	1. Ej. 2. m/z
	1. 5066 2. 576.32
	1. 5067 2. 576.32
	1. 5068 2. 577.32
	1. 5069 2. 580.32
	1. 5070 2. 580.32

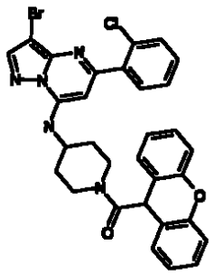
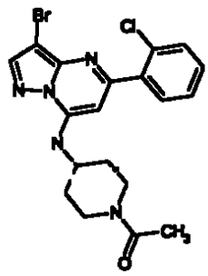
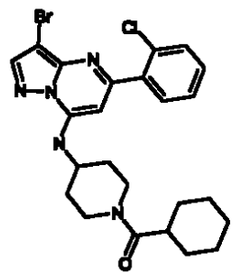
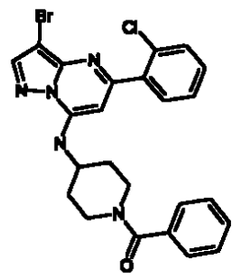
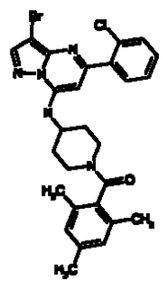
761

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	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

762

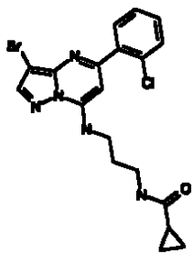
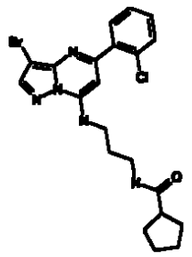
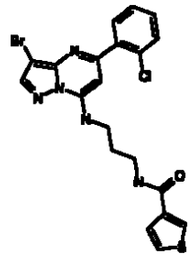
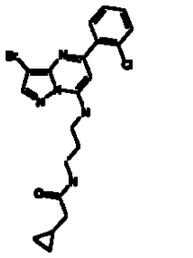
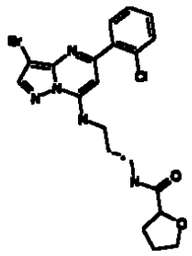
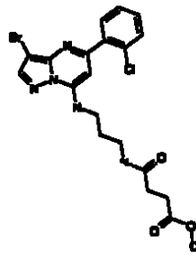
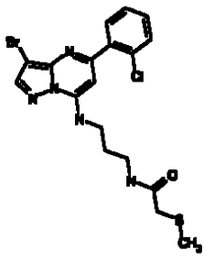
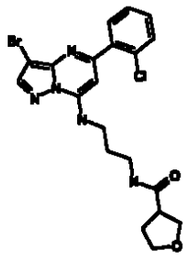
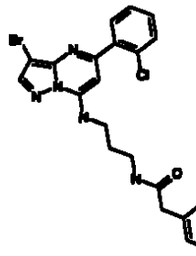
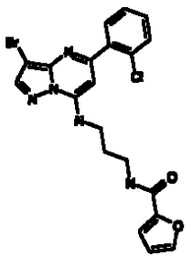
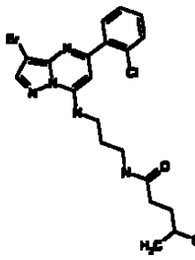
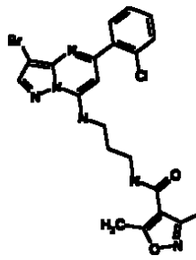
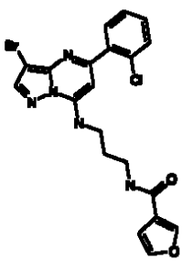
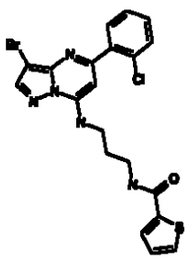
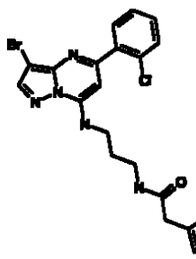
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	1. 5083 2. 594.33		1. 5088 2. 604.33
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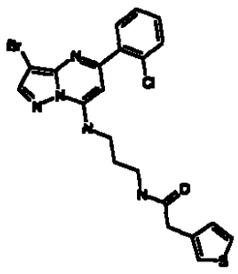
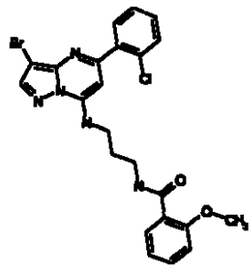
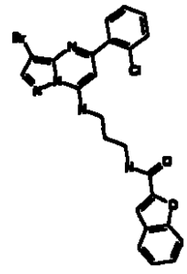
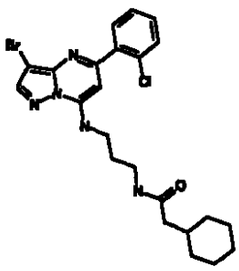
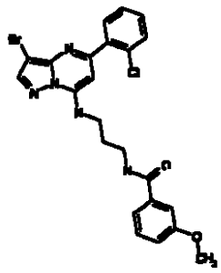
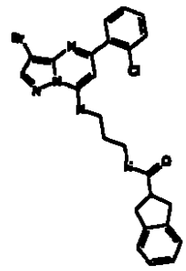
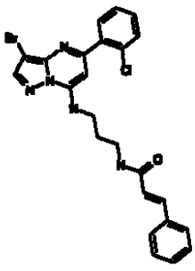
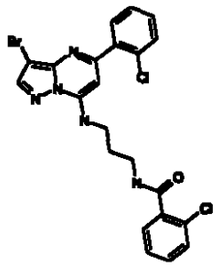
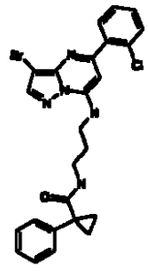
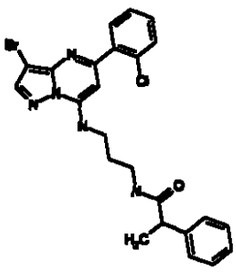
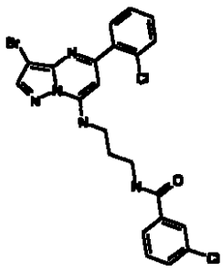
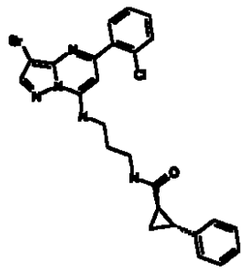
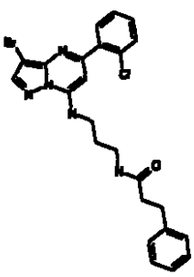
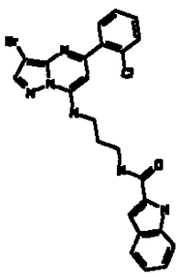
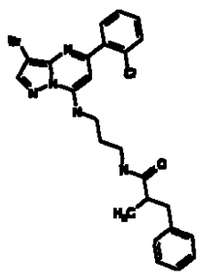
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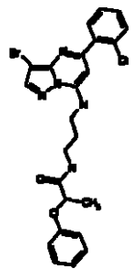
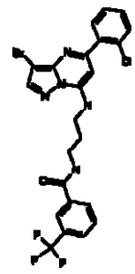
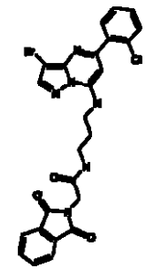
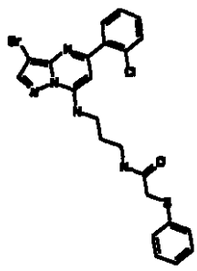
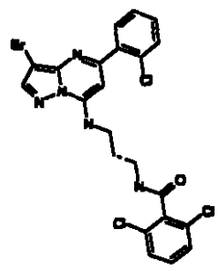
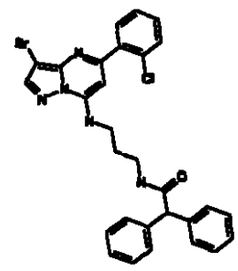
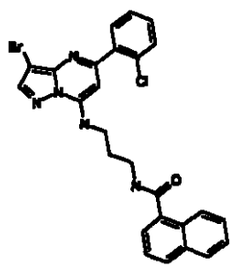
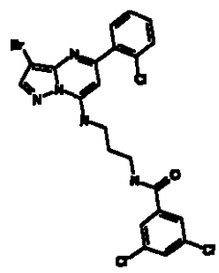
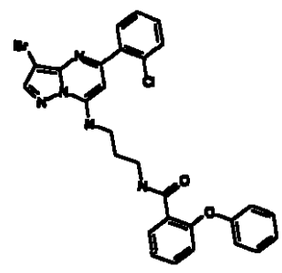
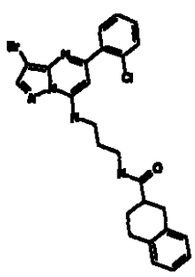
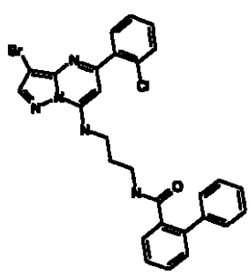
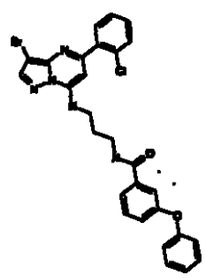
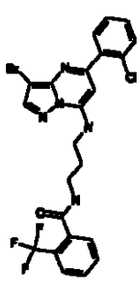
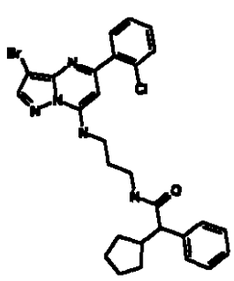
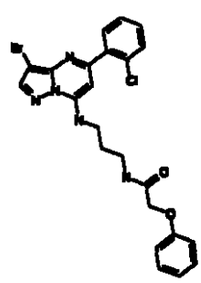
TABLA 51

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	1. 5102 2. 462.8		1. 5107 2. 478.8		1. 5112 2. 494.8
	1. 5103 2. 466.8		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
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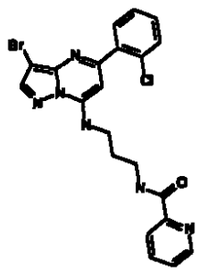
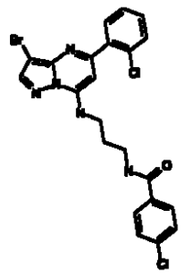
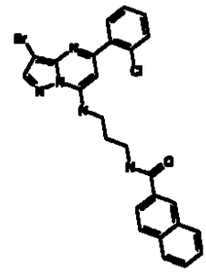
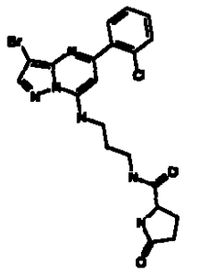
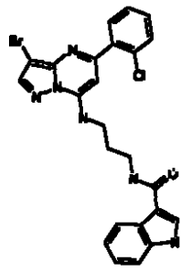
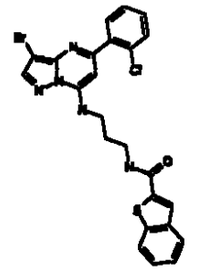
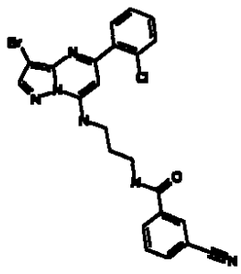
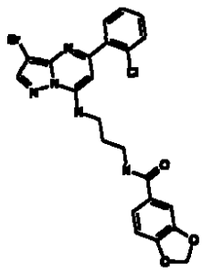
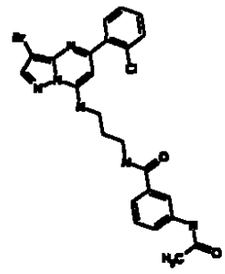
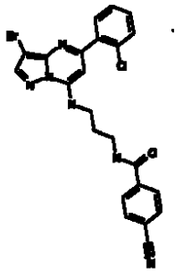
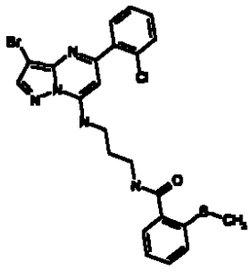
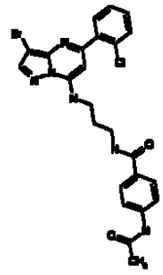
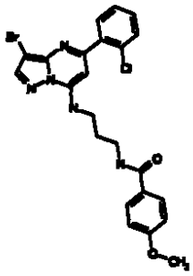
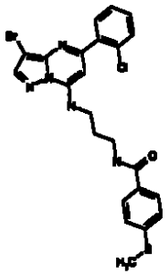
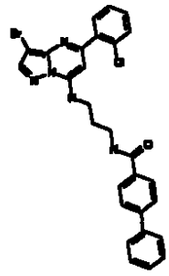
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	1. 5118 2. 510.8		1. 5123 2. 519.2		1. 5128 2 . 524.9
	1. 5119 2. 512.8		1. 5124 2. 519.2		1. 5129 2. 524.9
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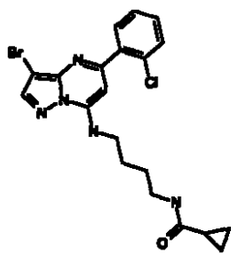
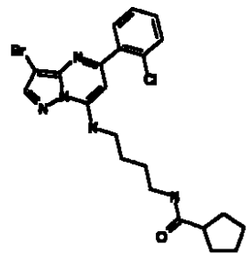
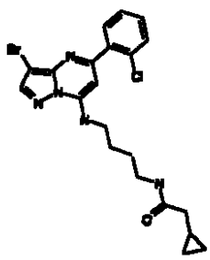
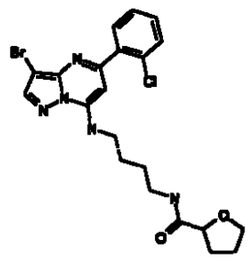
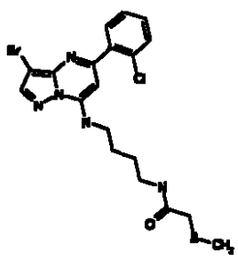
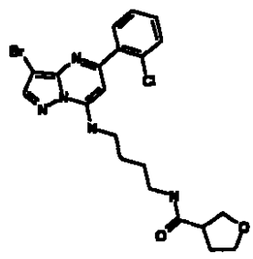
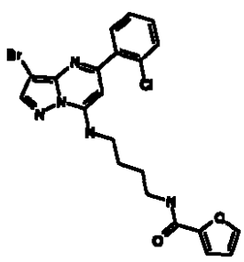
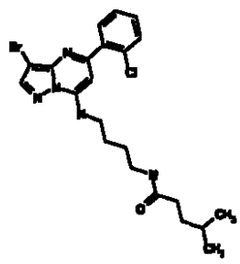
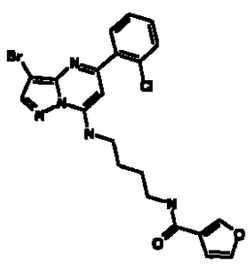
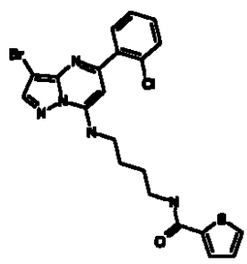
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	1. 5132 2. 530.9		1. 5137 2. 553.7		1. 5142 2. 574.9
	1. 5133 2. 534.8		1. 5138 2. 553.7		1. 5143 2. 576.9
	1. 5134 2. 538.9		1. 5139 2. 560.9		1. 5144 2. 576.9
	1. 5135 2. 552.8		1. 5140 2. 566.9		1. 5145 2. 514.8

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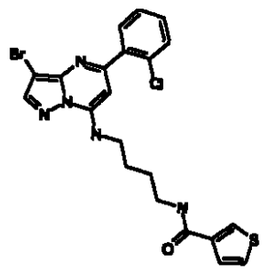
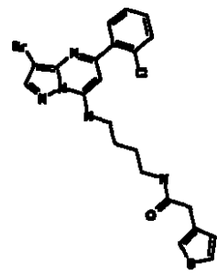
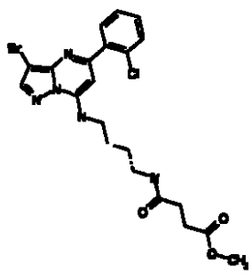
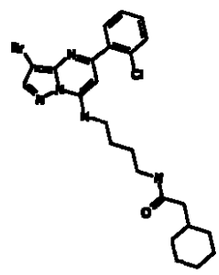
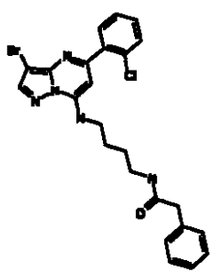
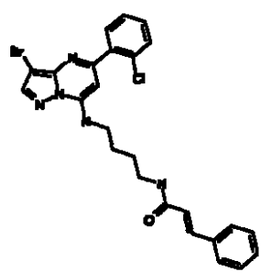
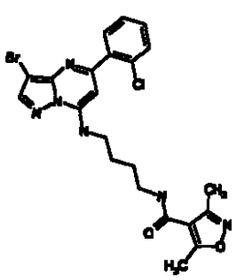
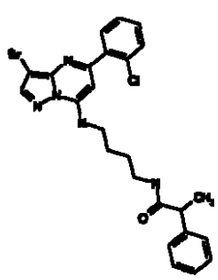
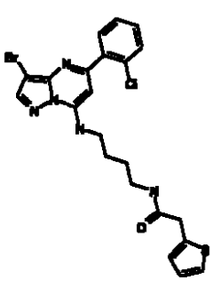
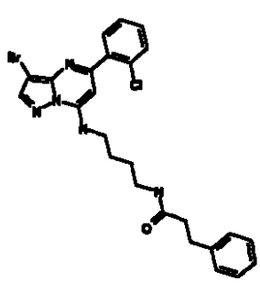
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5146 2. 485.8		1. 5151 2. 519.2		1. 5156 2. 534.8
	1. 5147 2. 491.8		1. 5152 2. 523.8		1. 5157 2. 540.9
	1. 5148 2. 509.8		1. 5153 2. 528.8		1. 5158 2. 541.8
	1. 5149 2. 509.8		1. 5154 2. 530.9		1. 5159 2. 541.8
	1. 5150 2. 514.8		1. 5155 2. 530.9		1. 5160 2. 560.9

768 769

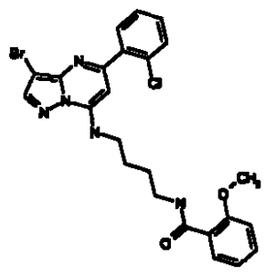
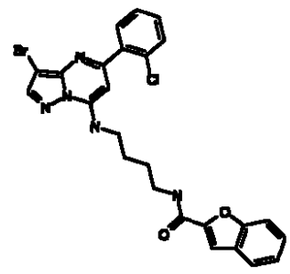
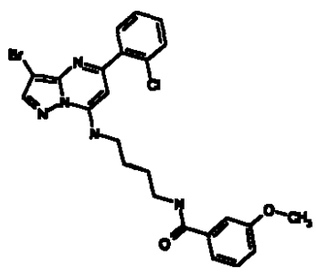
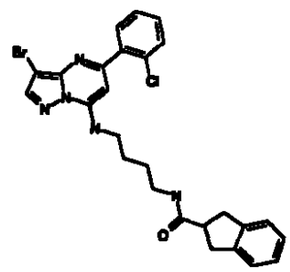
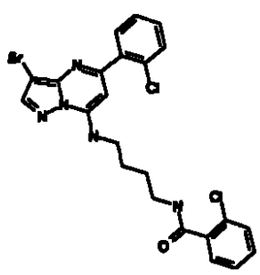
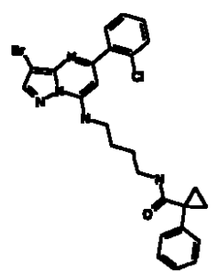
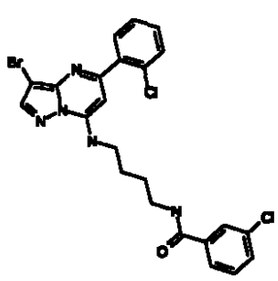
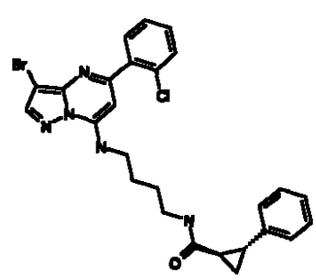
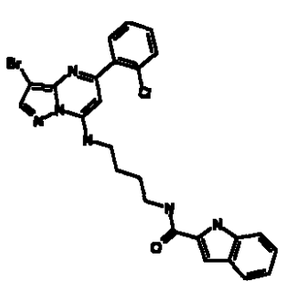
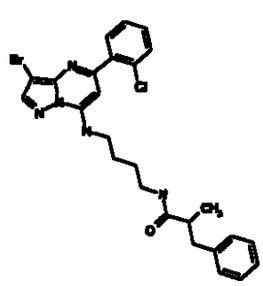
TABLA 52

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 5202 2. 476.5		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
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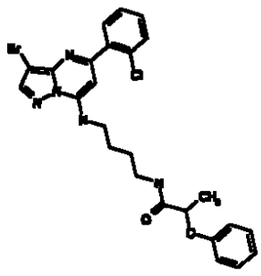
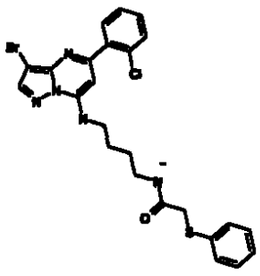
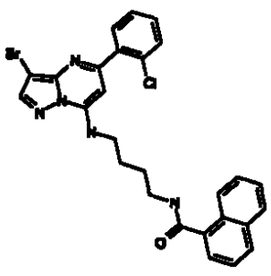
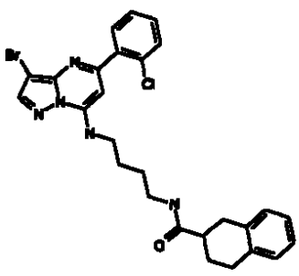
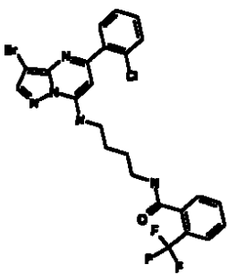
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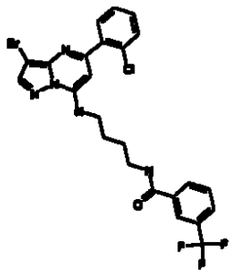
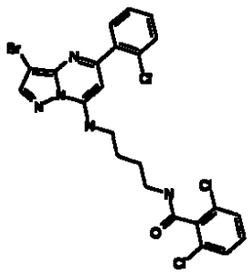
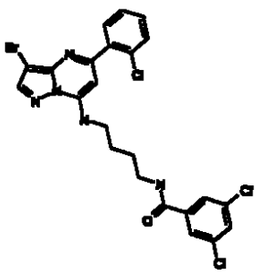
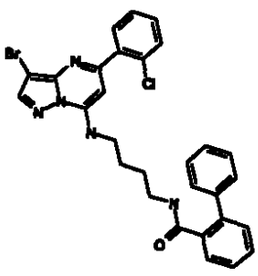
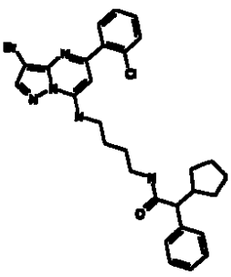
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	2. 5212 2. 508.9		1. 5217 2. 518.9
	1. 5213 2. 512.8		1. 5218 2. 524.9
	1. 5214 2. 517.8		1. 5219 2. 526.9
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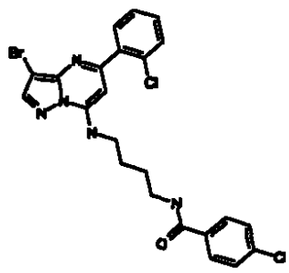
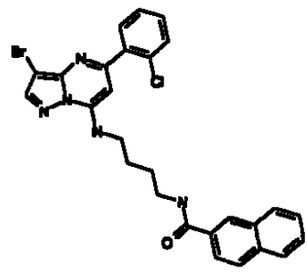
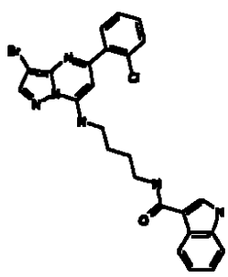
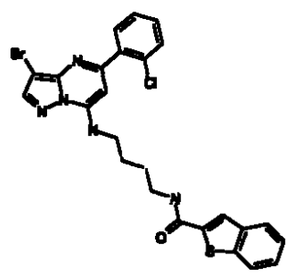
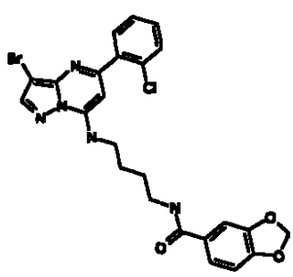
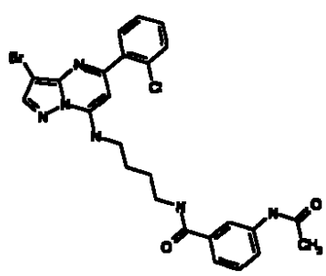
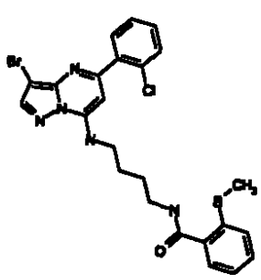
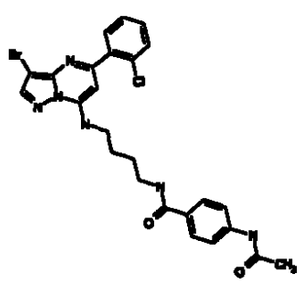
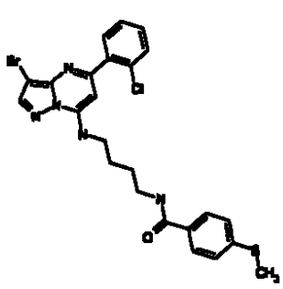
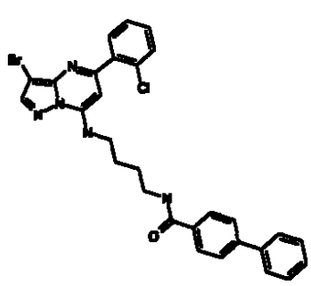
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	1. 5222 2. 528.8		1. 5227 2. 538.9
	1. 5223 2. 533.3		1. 5228 2. 536.9
	1. 5224 2. 533.3		1. 5229 2. 538.9
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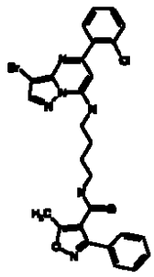
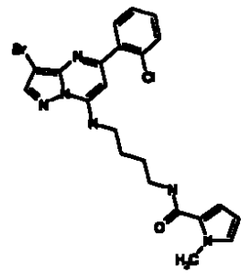
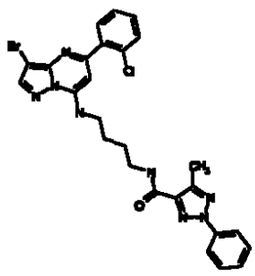
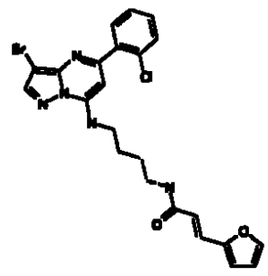
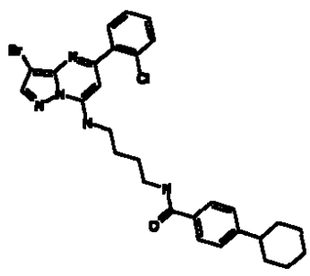
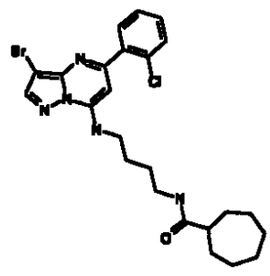
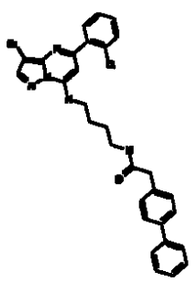
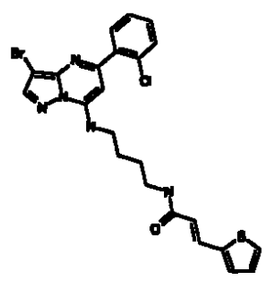
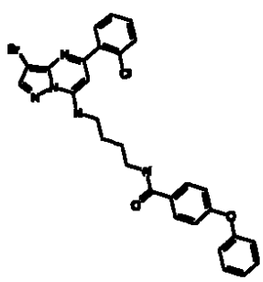
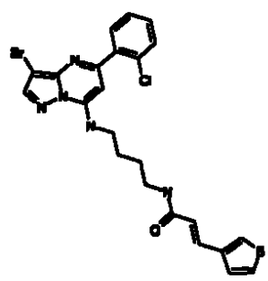
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	1. 5233 2. 548.9
	1. 5234 2. 552.9
	1. 5235 2. 566.8

Producto	1. Ej. 2. m/z
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	1. 5237 2. 567 7
	1. 5238 2. 567.7
	1. 5239 2. 574.9
	1. 5240 2. 581

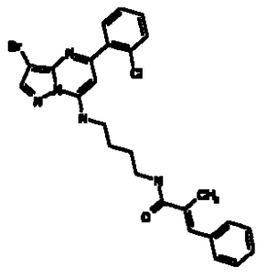
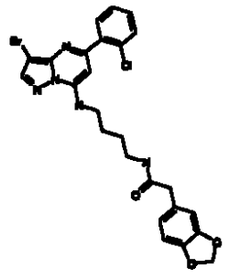
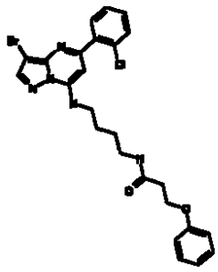
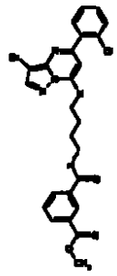
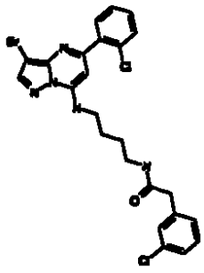
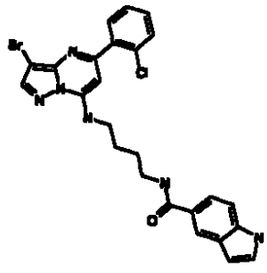
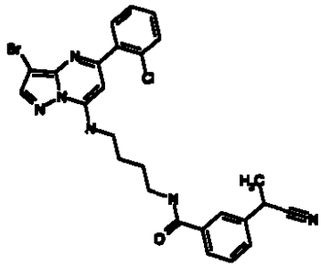
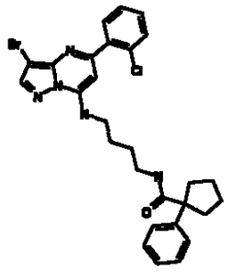
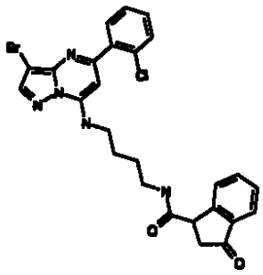
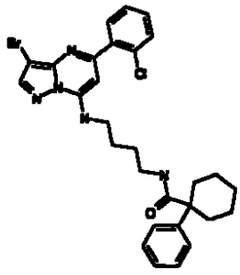
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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5241 2. 533.3		1. 5246 2. 548.9
	1. 5242 2. 537.9		1. 5247 2. 554.9
	1. 5243 2. 542.8		1. 5248 2. 555.9
	1. 5244 2. 544.9		1. 5249 2. 555.9
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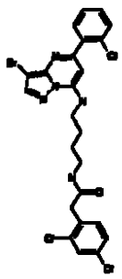
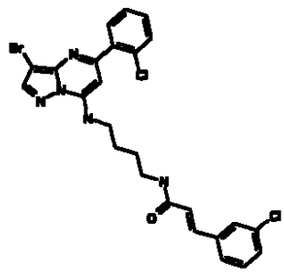
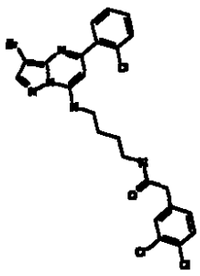
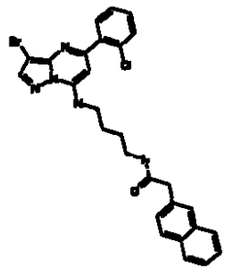
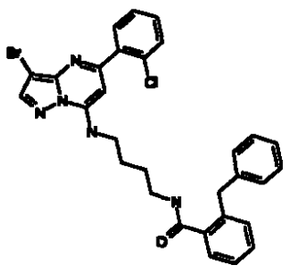
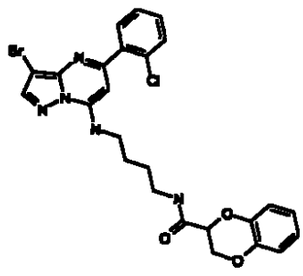
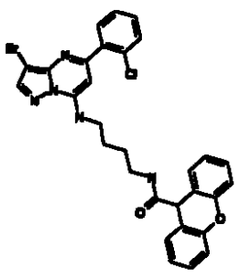
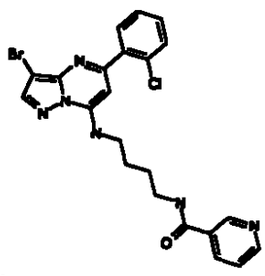
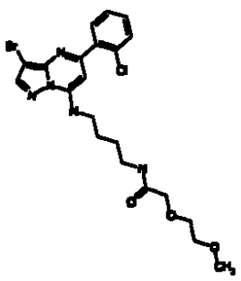
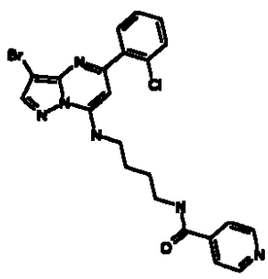
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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 5253 2. 581		1. 5258 2. 518.9
	1. 5254 2. 588.9		1. 5259 2. 530.9
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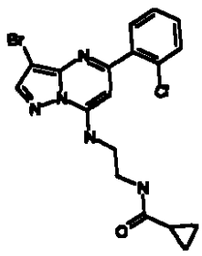
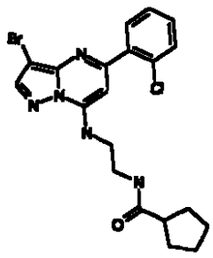
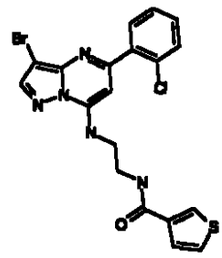
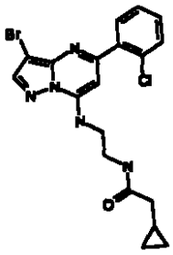
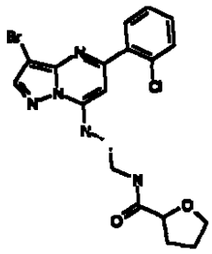
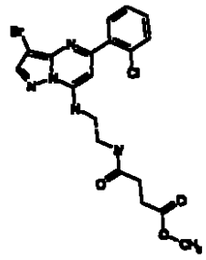
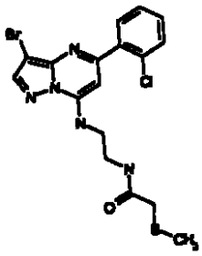
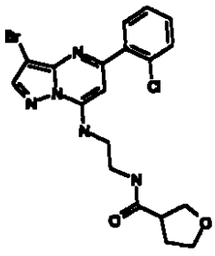
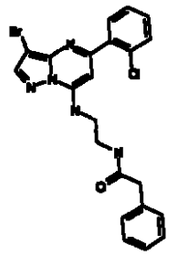
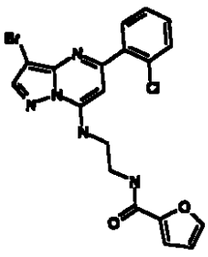
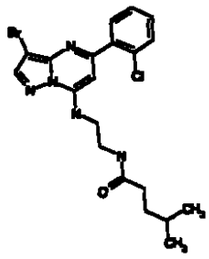
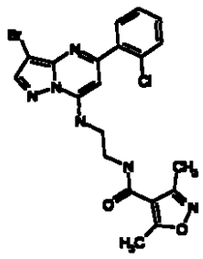
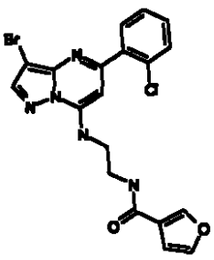
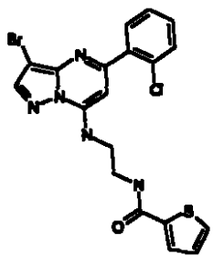
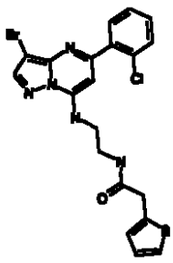
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 5262 2. 542.3		1. 5267 2. 556.9
	1. 5263 2. 547.3		1. 5268 2. 537.9
	1. 5264 2. 551.9		1. 5269 2. 566.9
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775

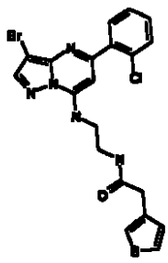
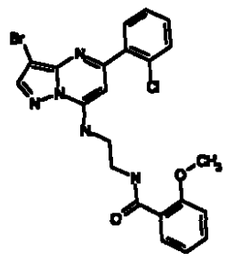
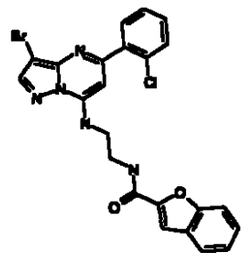
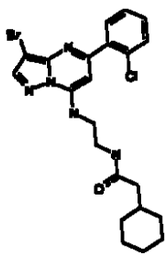
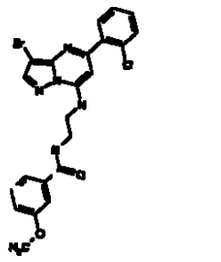
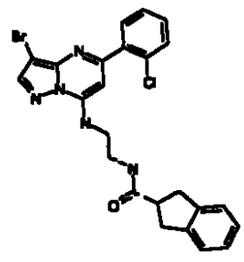
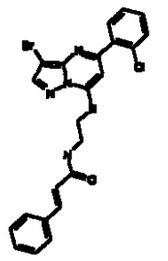
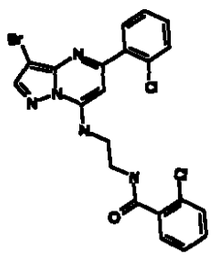
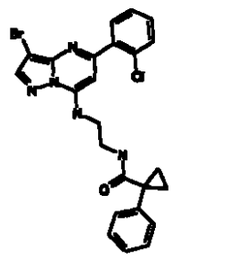
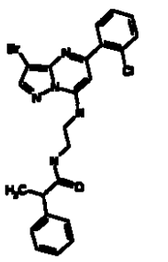
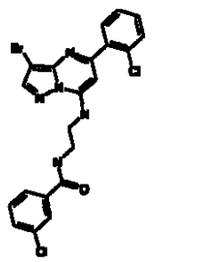
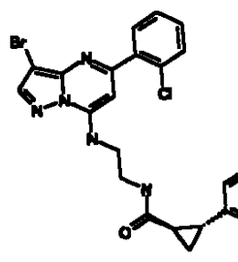
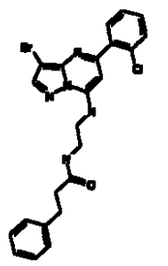
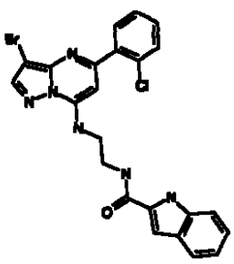
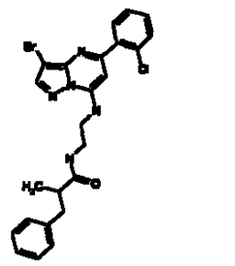
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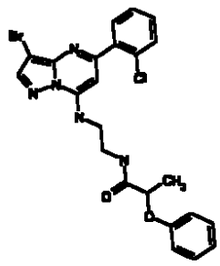
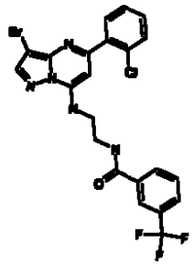
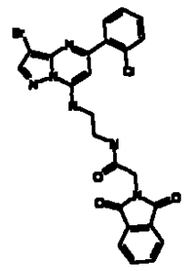
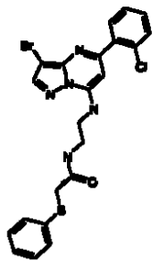
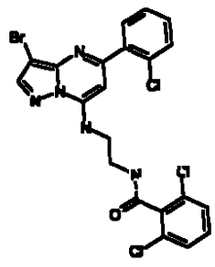
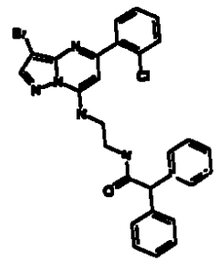
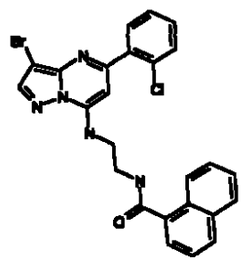
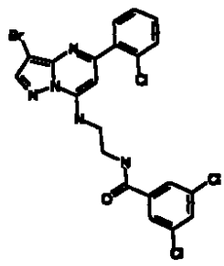
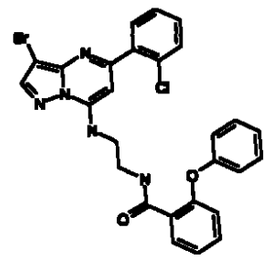
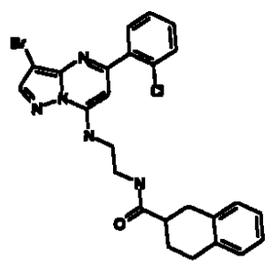
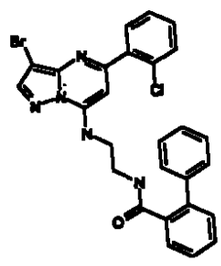
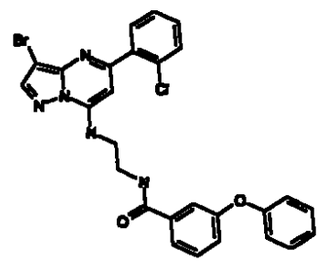
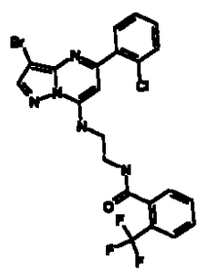
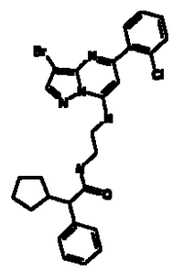
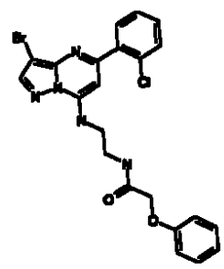
TABLA 53

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	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
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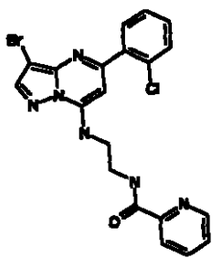
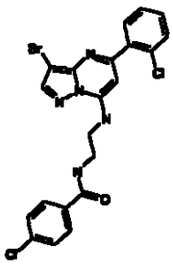
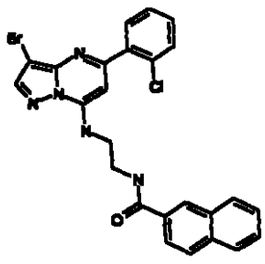
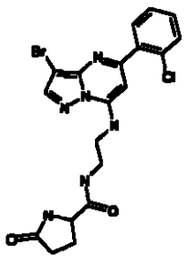
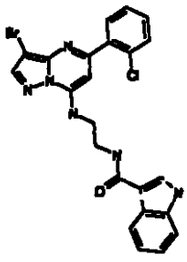
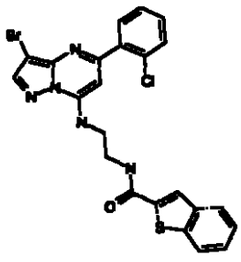
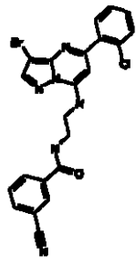
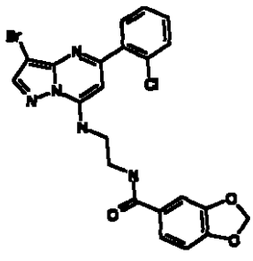
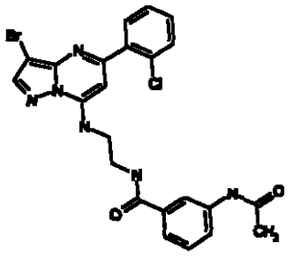
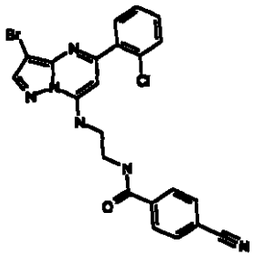
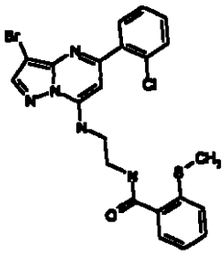
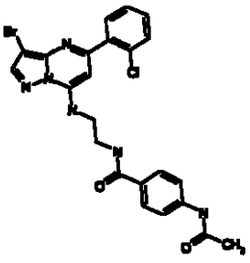
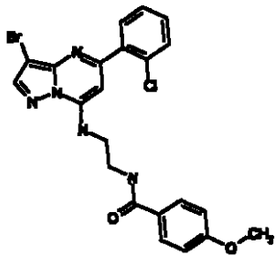
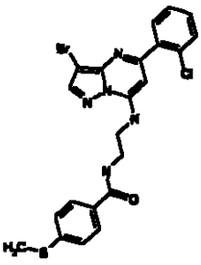
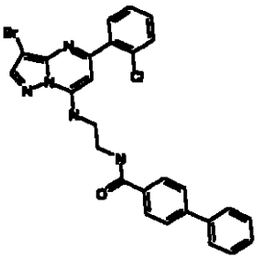
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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 5317 2. 490.8		1. 5322 2. 500.8		1. 5327 2. 510.8
	1. 5318 2. 496.8		1. 5323 2. 505.2		1. 5328 2. 510.8
	1. 5319 2. 498.8		1. 5324 2. 505.2		1. 5329 2. 510.8
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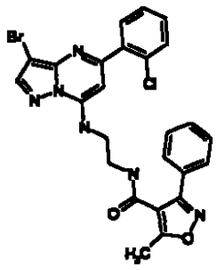
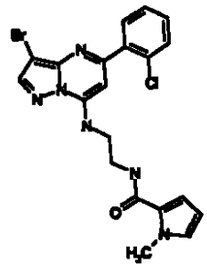
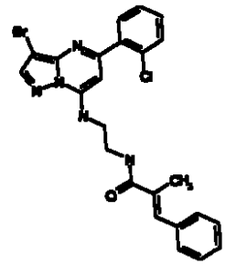
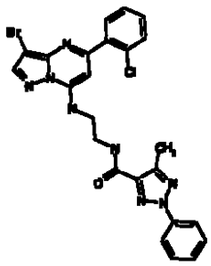
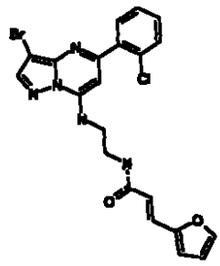
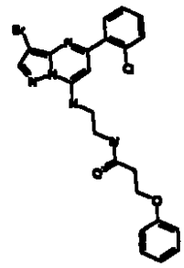
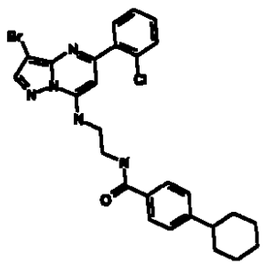
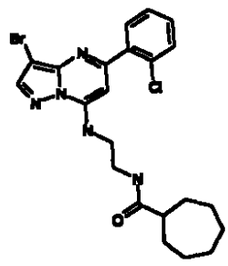
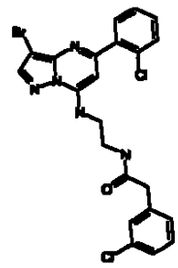
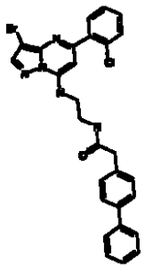
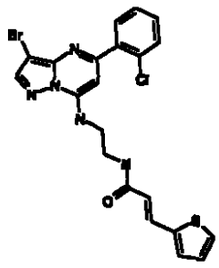
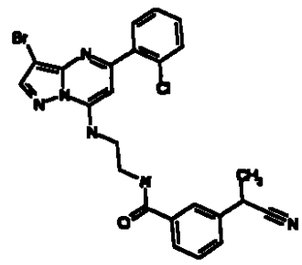
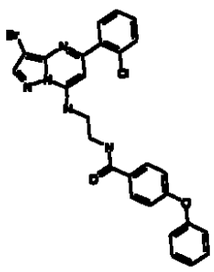
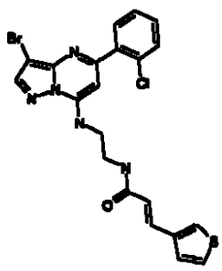
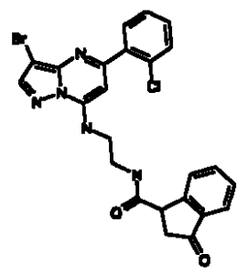
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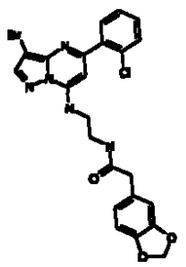
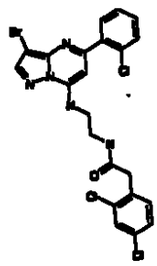
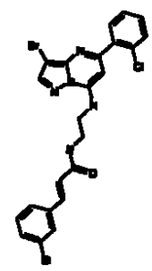
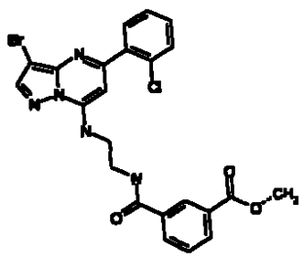
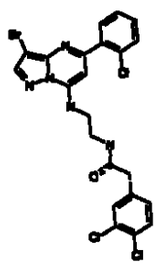
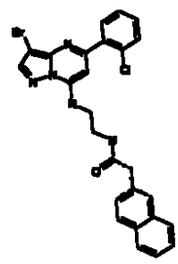
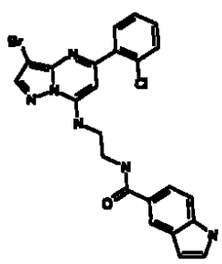
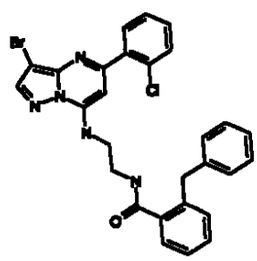
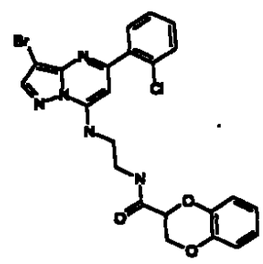
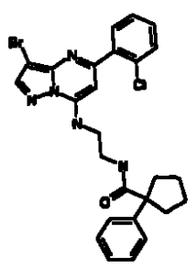
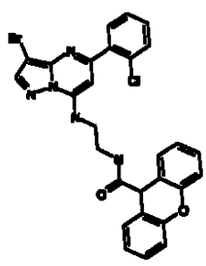
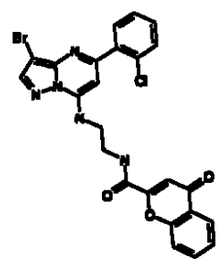
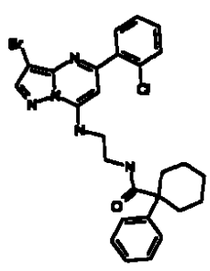
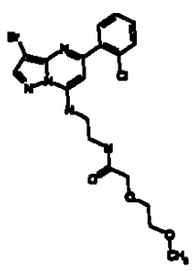
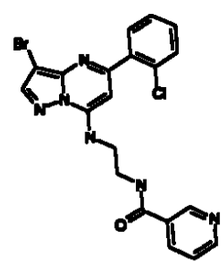
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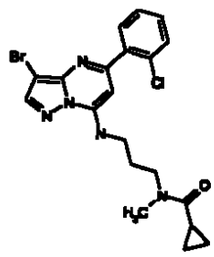
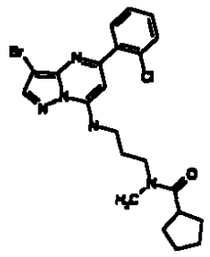
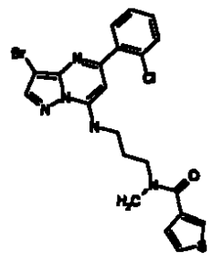
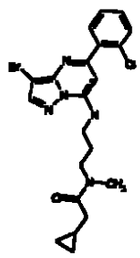
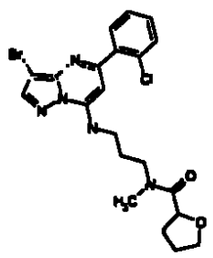
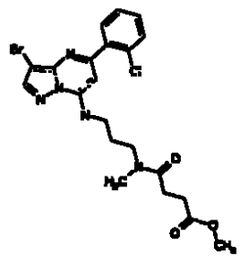
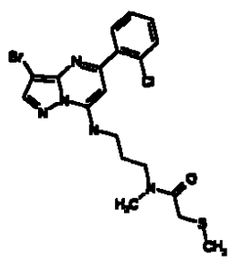
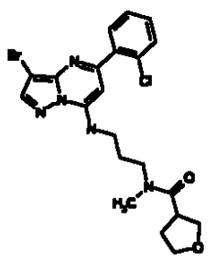
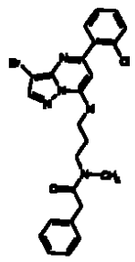
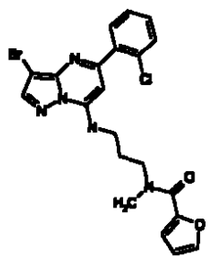
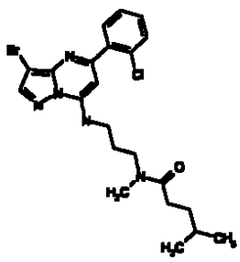
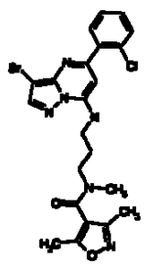
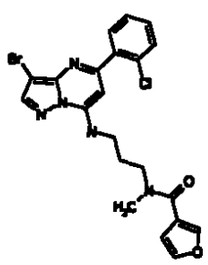
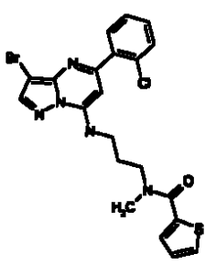
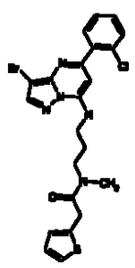
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	1. 5364 2. 560.9		1. 5369 2. 502.8		1. 5374 2 523.8
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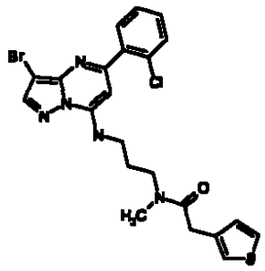
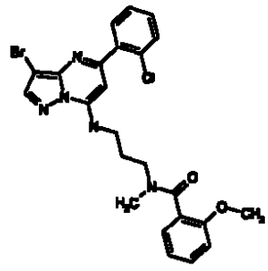
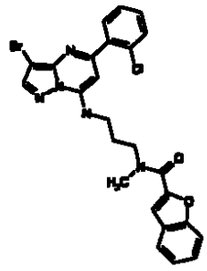
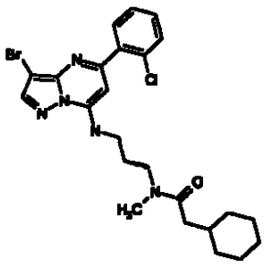
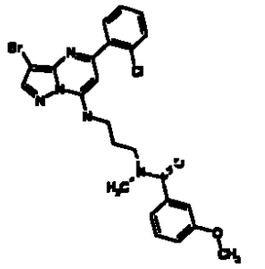
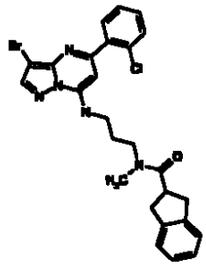
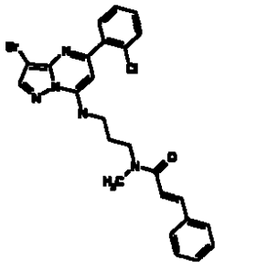
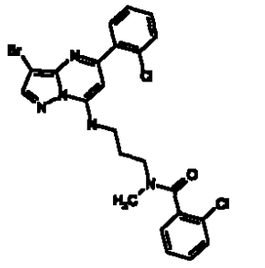
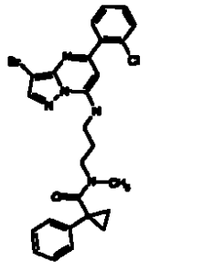
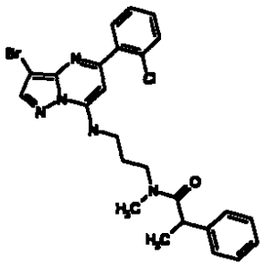
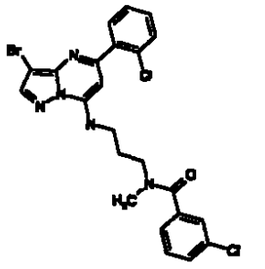
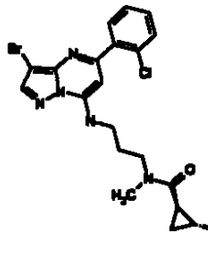
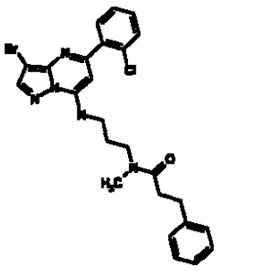
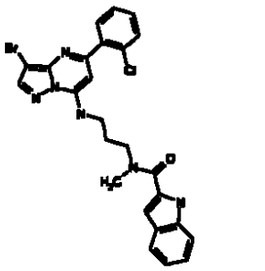
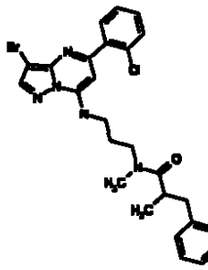
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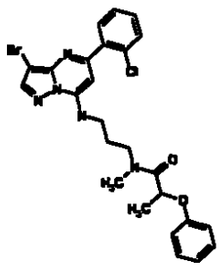
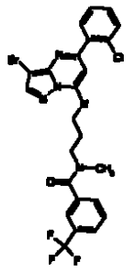
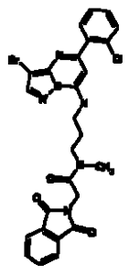
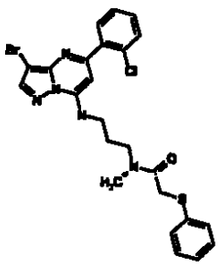
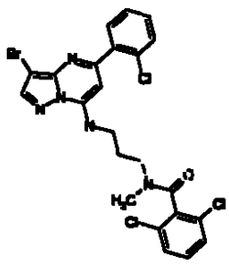
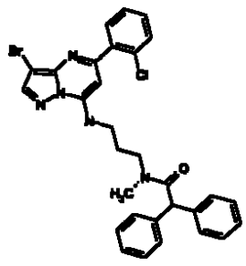
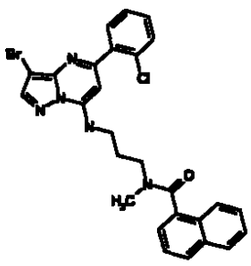
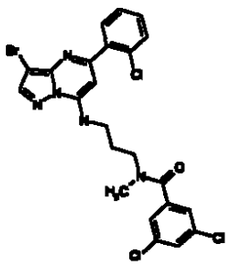
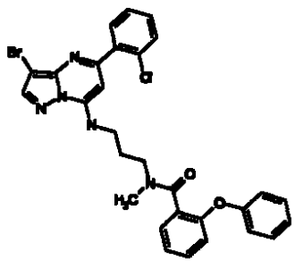
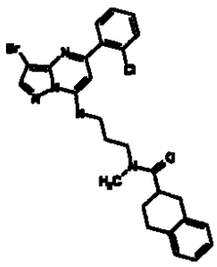
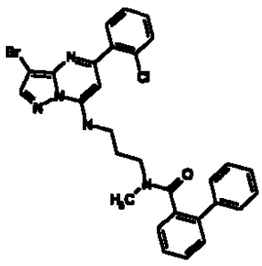
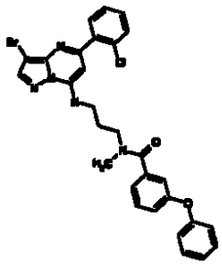
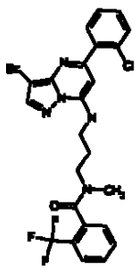
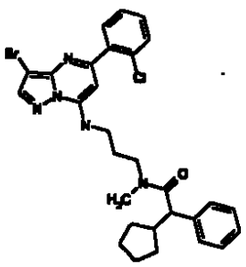
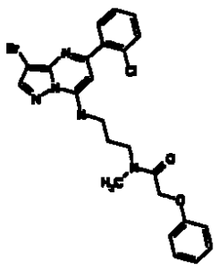
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	1. 5403 2. 483.3		1. 5408 2. 493.3		1. 5413 2. 513.3
	1. 5404 2. 489.3		1. 5409 2. 493.3		1. 5414 2. 518.3
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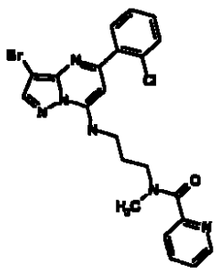
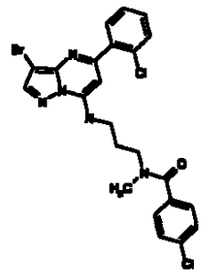
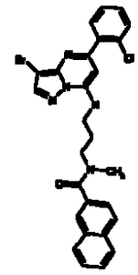
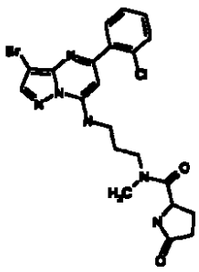
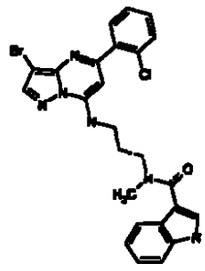
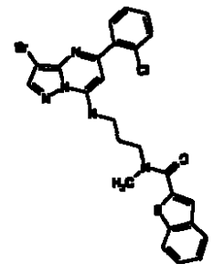
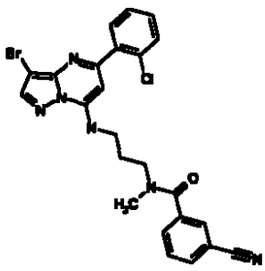
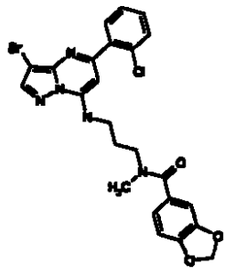
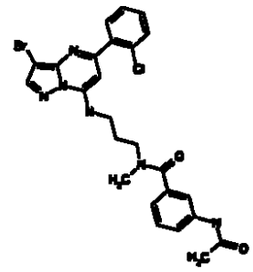
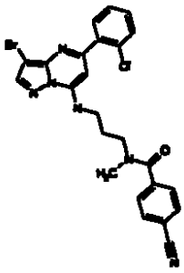
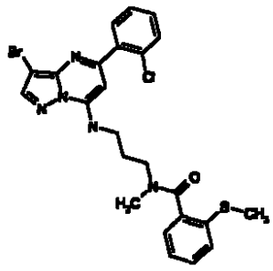
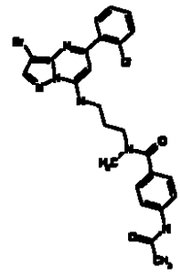
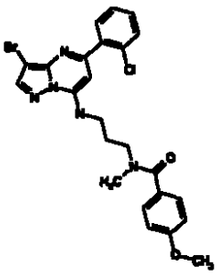
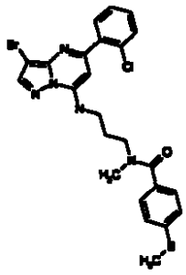
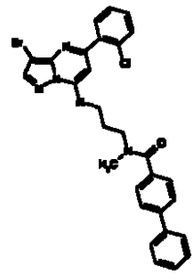
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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 5418 2. 525.3		1. 5423 2. 533.3		1. 5428 2. 539.3
	1. 5419 2. 527.3		1. 5424 2. 533.3		1. 5429 2. 539.3
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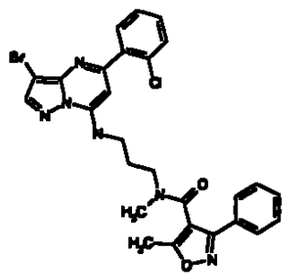
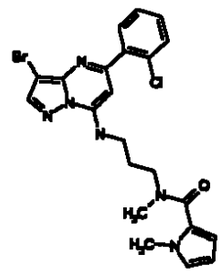
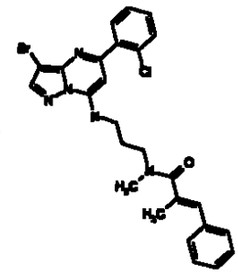
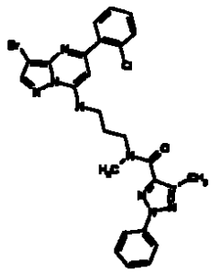
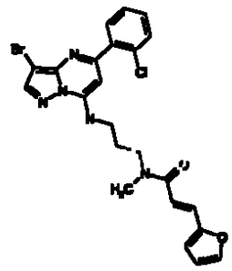
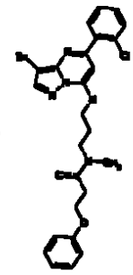
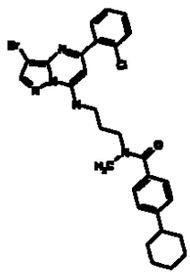
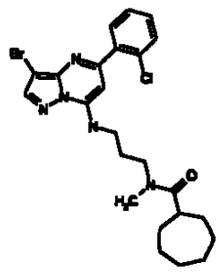
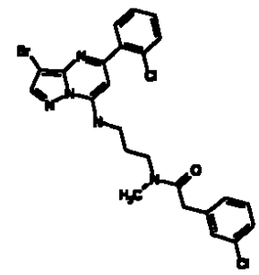
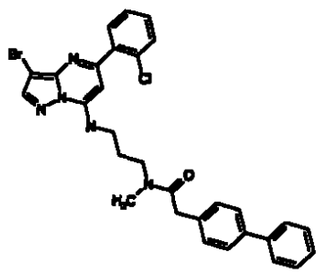
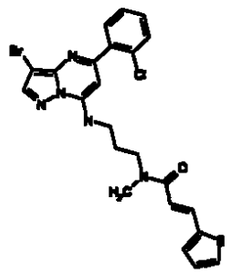
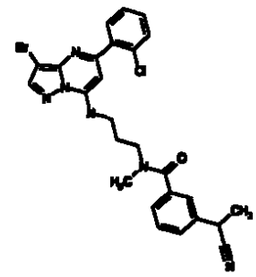
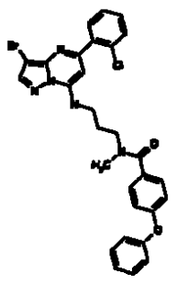
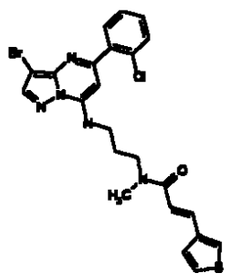
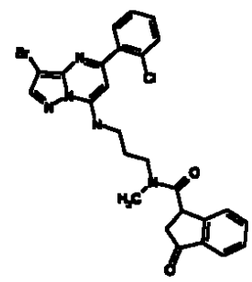
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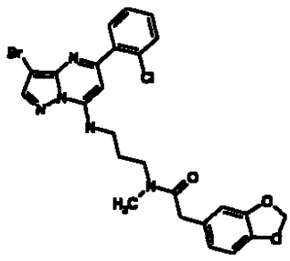
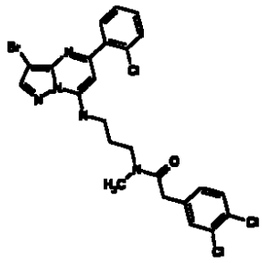
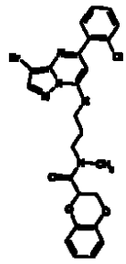
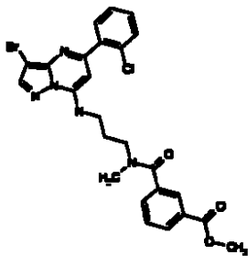
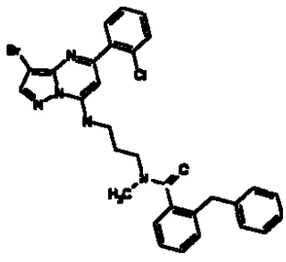
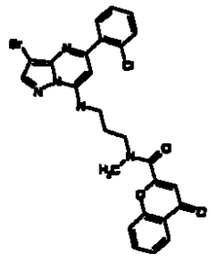
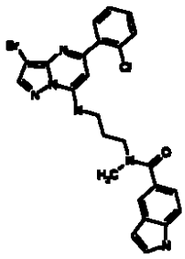
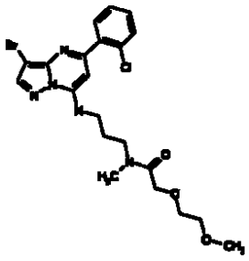
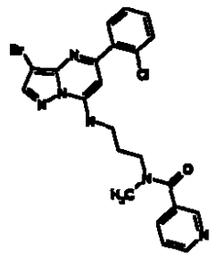
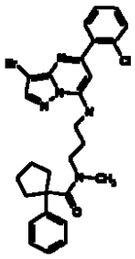
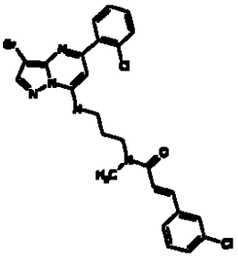
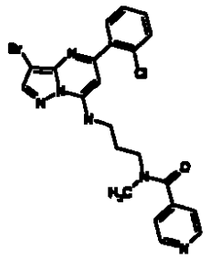
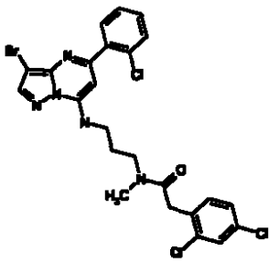
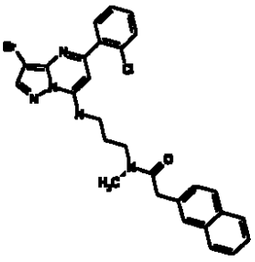
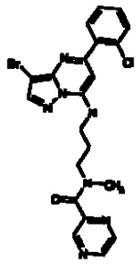
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	1. 5434 2. 553.3		1. 5439 2. 575.3		1. 5444 2 591.3
	1. 5435 2. 567.3		1. 5440 2. 581.3		1. 5445 2 529.3

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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 5448 2. 524.3		1. 5453 2. 543.3		1. 5458 2. 556.3
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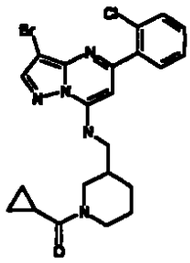
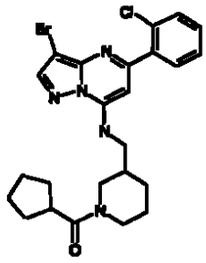
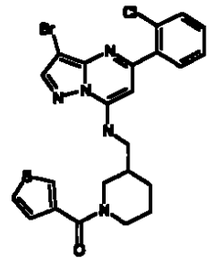
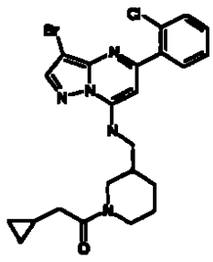
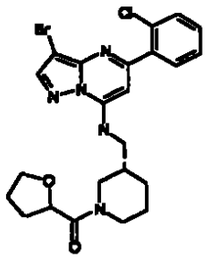
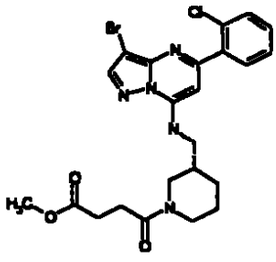
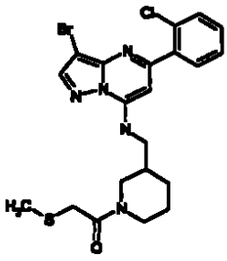
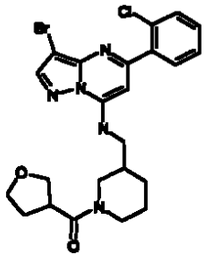
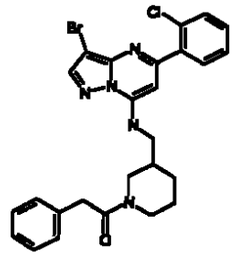
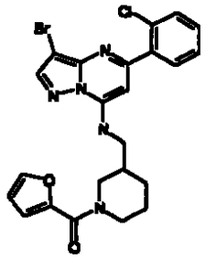
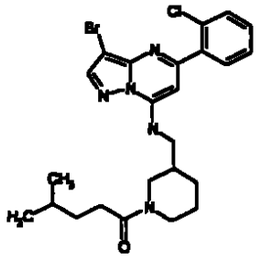
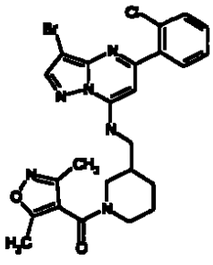
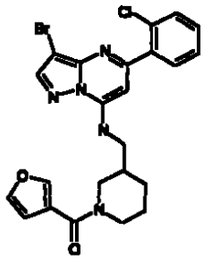
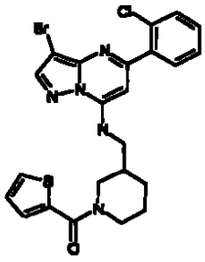
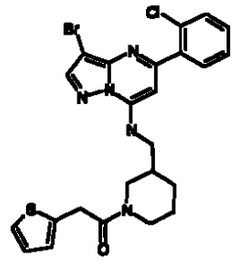
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	1. 5463 2. 581.3		1. 5468 2. 519.3		1. 5473 2 547.3
	1. 5464 2. 589.3		1. 5469 2. 531.3		1. 5474 2 552.3
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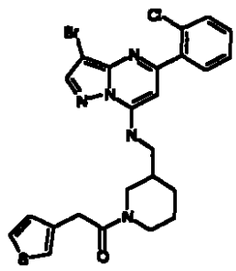
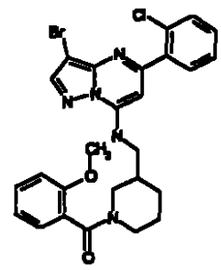
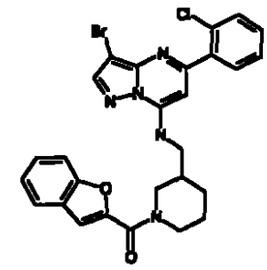
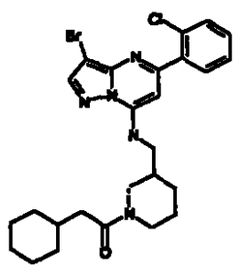
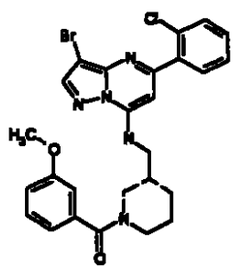
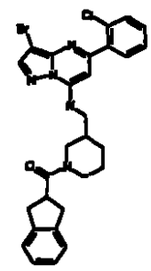
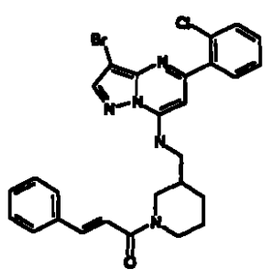
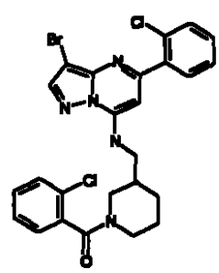
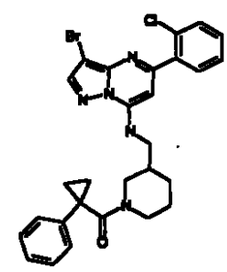
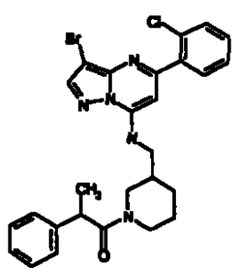
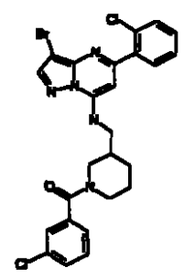
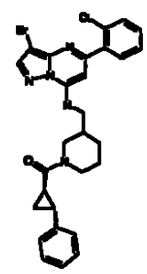
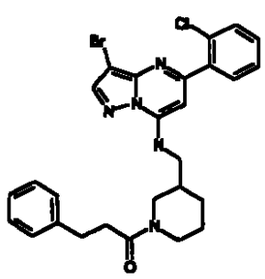
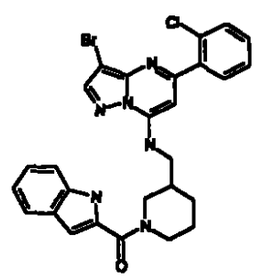
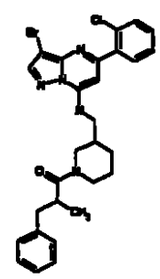
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	1. 5477 2. 557.3		1. 5482 2. 589.3		1. 5487 2. 891.5
	1. 5478 2. 538.3		1. 5483 2. 511.3		1. 5488 2. 500.3
	1. 5479 2. 567.3		1. 5484 2. 559.3		1. 5489 2. 500.3
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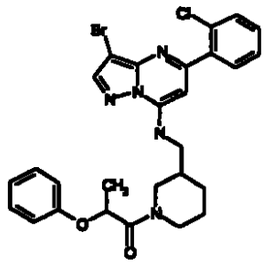
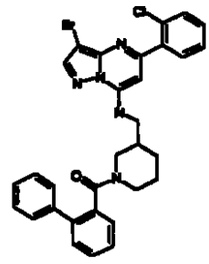
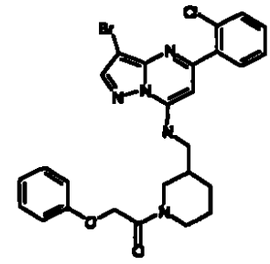
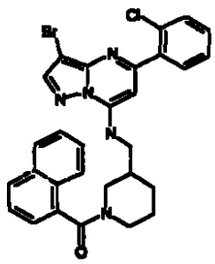
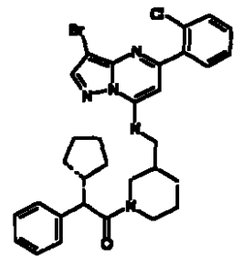
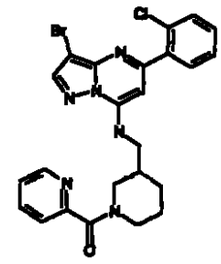
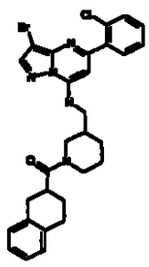
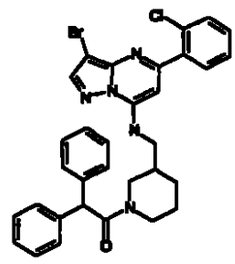
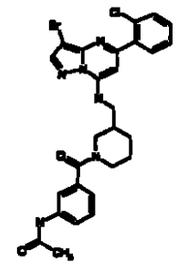
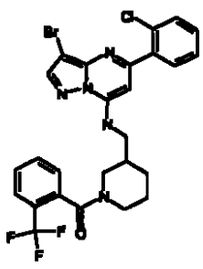
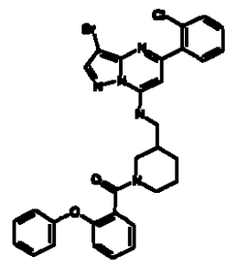
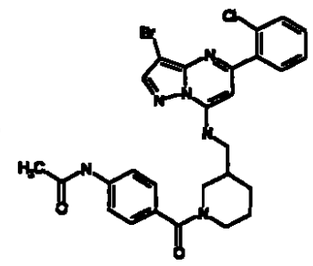
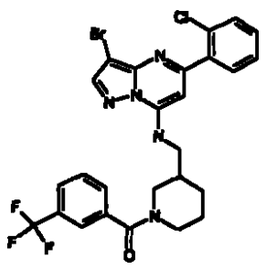
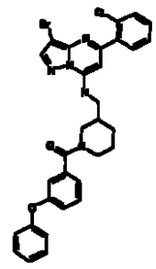
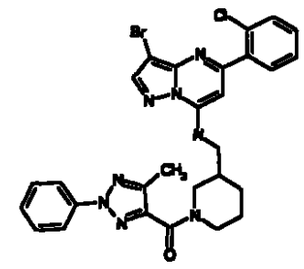
TABLA55

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	1. 5503 2. 508.87		1. 5508 2. 516.84		1. 5513 2. 538.87
	1. 5504 2. 514.81		1. 5509 2. 518.88		1. 5514 2. 543.85
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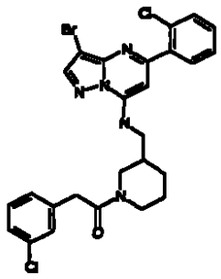
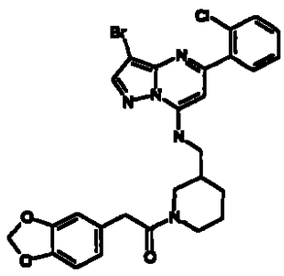
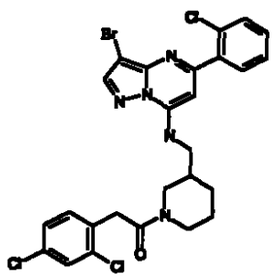
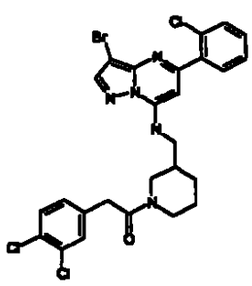
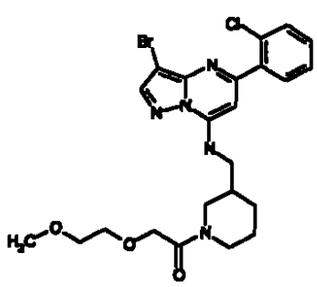
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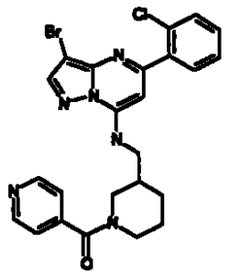
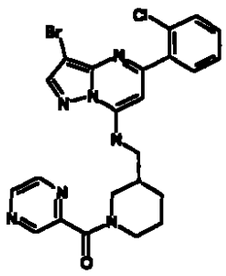
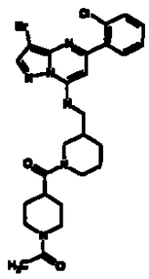
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	1. 5517 2. 544.92		1. 5522 2. 554.87		1. 5527 2. 564.91
	1. 5518 2. 550.89		1. 5523 2. 559.29		1. 5528 2. 564.91
	1. 5519 2. 552.9		1. 5524 2. 559.29		1. 5529 2. 564.91
	1. 5520 2. 552.9		1. 5525 2. 563.88		1. 5530 2. 566.93

790

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
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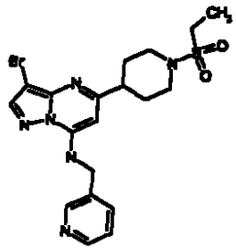
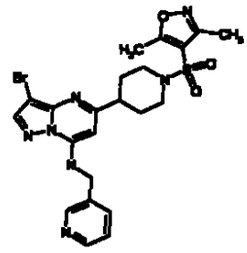
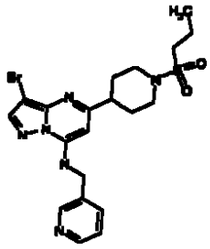
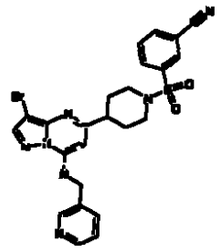
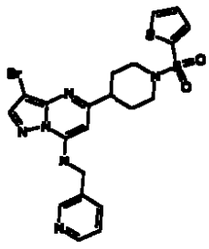
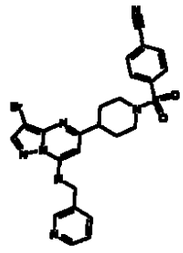
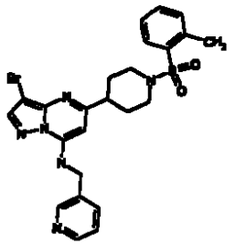
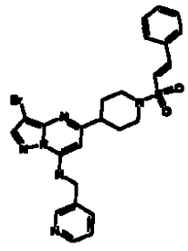
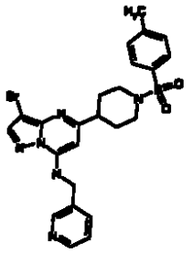
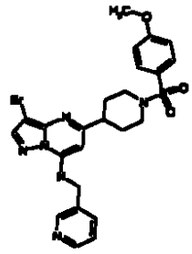
791 792

Producto	1. Ej. 2. m/z
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	1. 5547 2. 592.99
	1. 5548 2. 607.76
	1. 5549 2. 607.76
	1. 5550 2. 536.86

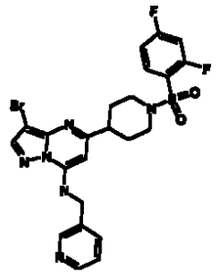
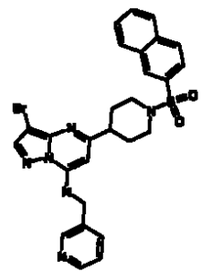
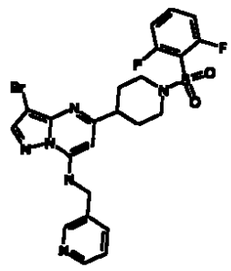
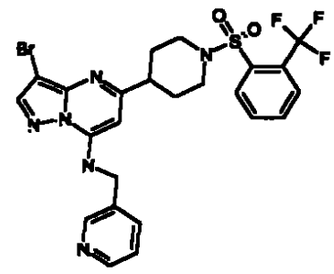
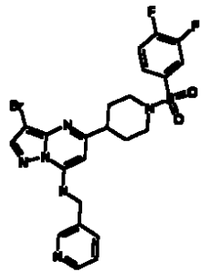
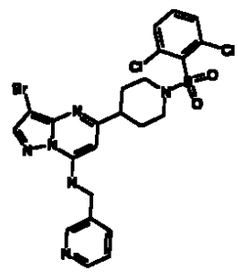
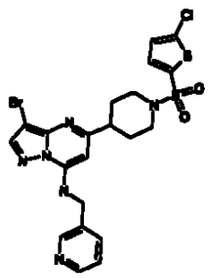
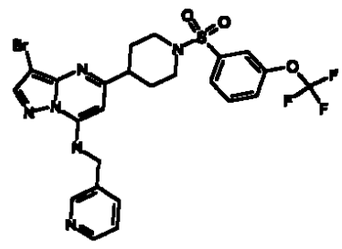
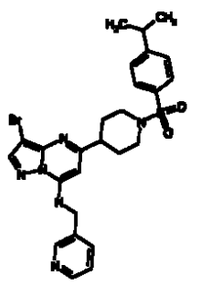
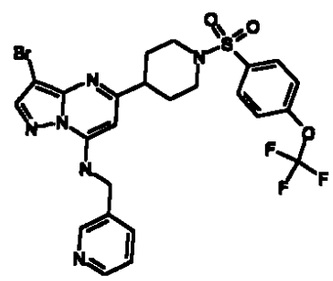
Producto	1. Ej. 2. m/z
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	1. 5552 2. 526.82
	1. 5553 2. 573.92

792

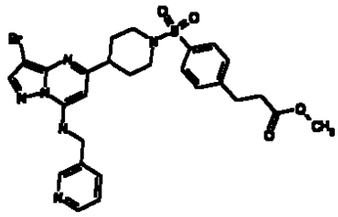
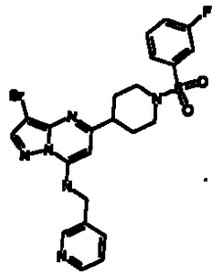
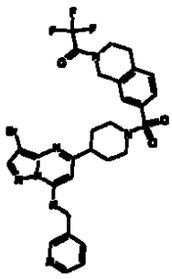
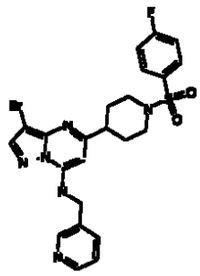
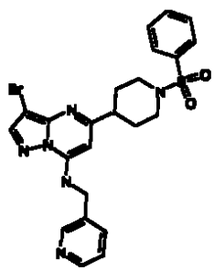
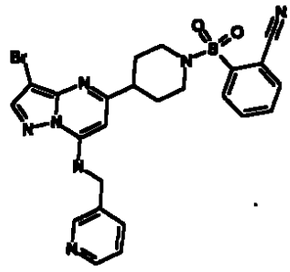
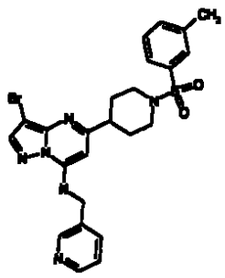
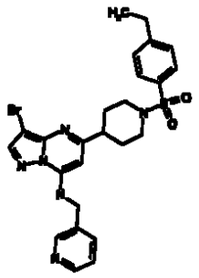
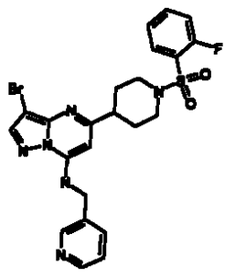
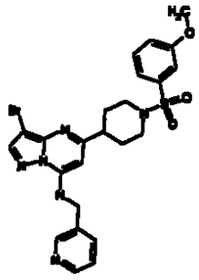
TABLA 56

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. 455.27		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

793

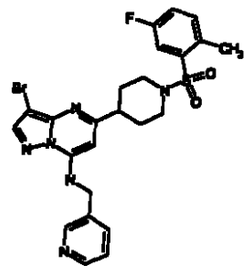
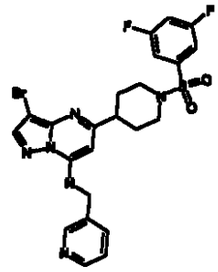
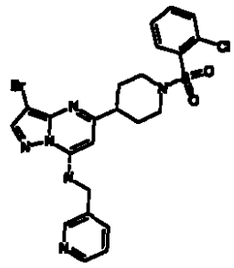
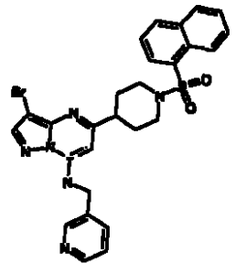
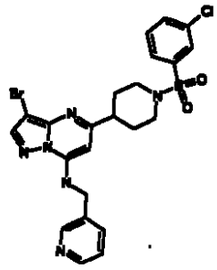
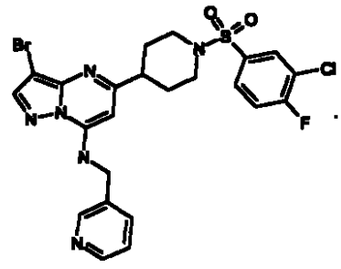
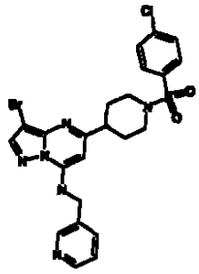
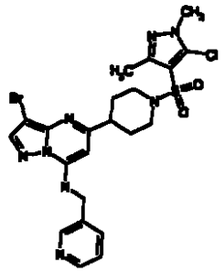
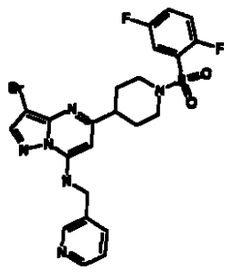
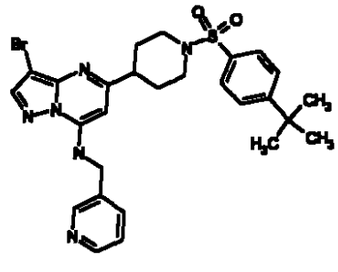
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5611 2. 565.31		1 .5616 2. 579.32
	1. 5612 2. 565.31		1. 5617
	1. 5613 2. 565.31		1. 5618
	1. 5614 2. 569.31		1. 5619
	1. 5615 2. 571.31		1. 5620

794

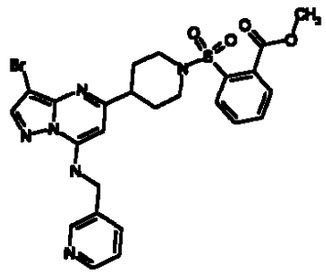
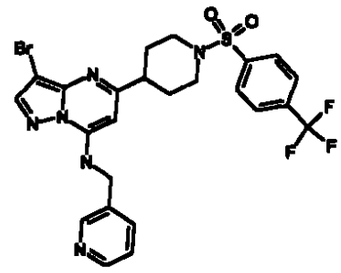
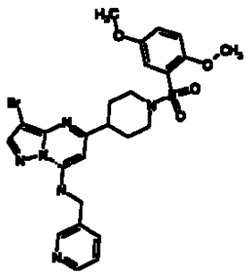
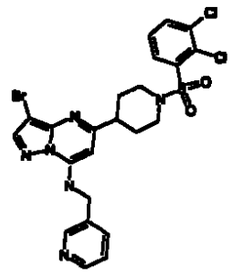
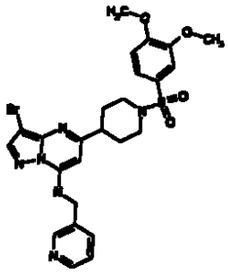
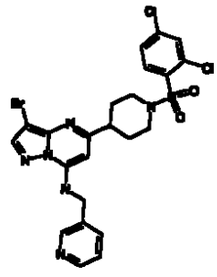
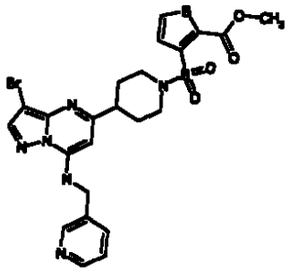
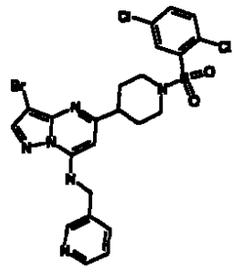
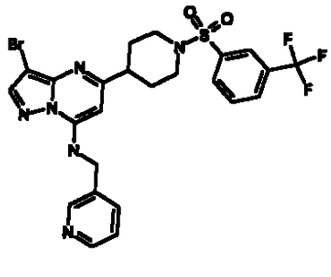
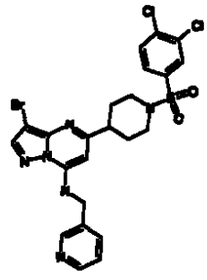
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5621 2. 615.34		1. 5626 2. 547.3
	2. 5622 2. 680.37		1. 5627 2. 547.3
	1. 5623 2. 529.29		1. 5628 2. 554.3
	1. 5624 2. 543.3		1. 5629 2. 555.31
	1. 5625 2. 547.3		1. 5630 2. 559.31

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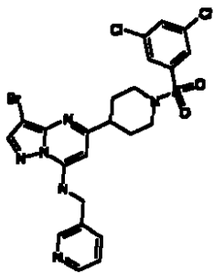
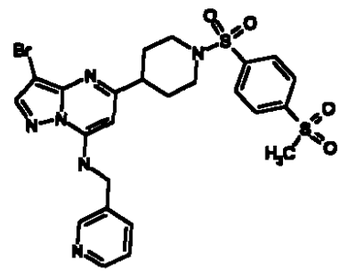
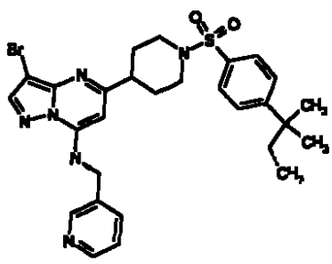
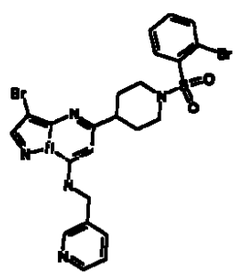
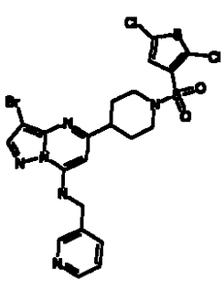
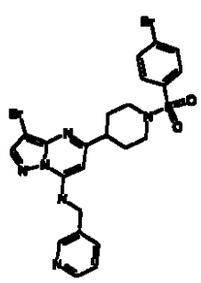
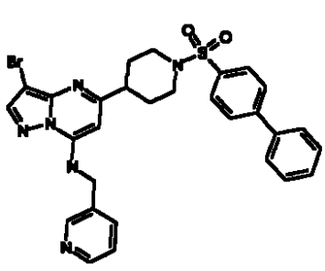
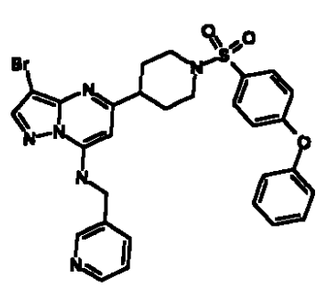
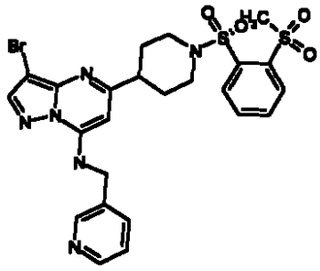
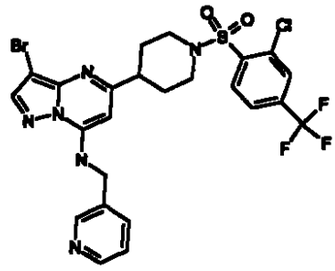
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	1. 5632 2. 563.31		1. 5637 2. 579.32
	1. 5633 2. 563.31		1. 5638 2. 581.32
	1. 5634 2. 563.31		1. 5639 2. 581.32
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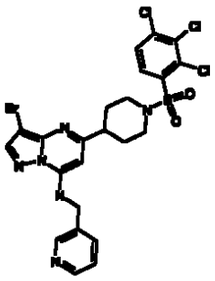
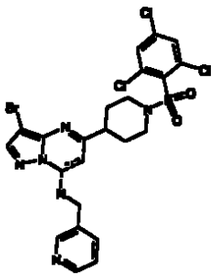
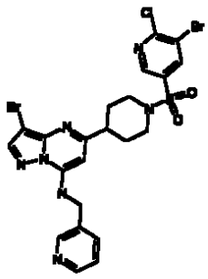
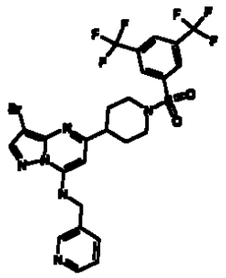
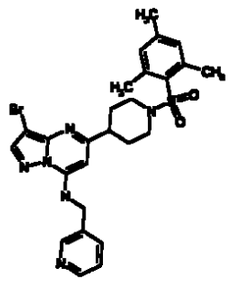
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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 5642 2. 599.32		1. 5647 2. 597.33
	1. 5643 2. 589.32		1. 5648 2. 597.33
	1. 5644 2. 593.33		1. 5649 2. 597.33
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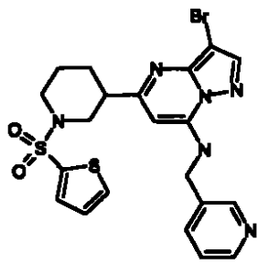
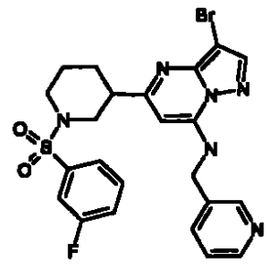
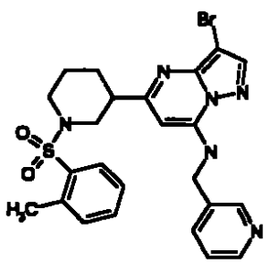
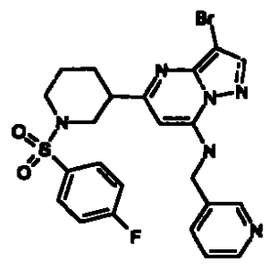
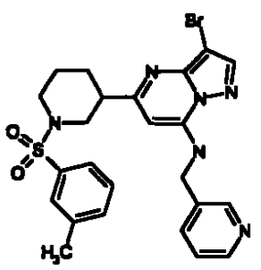
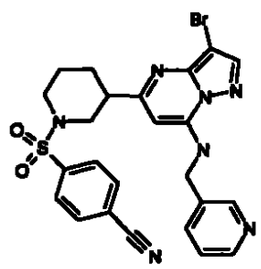
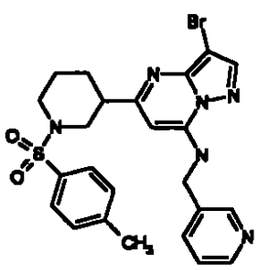
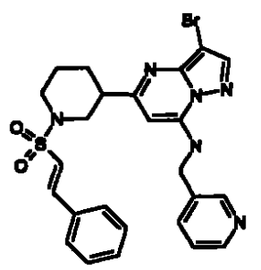
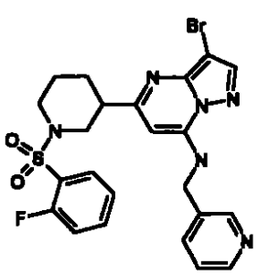
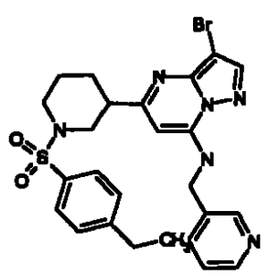
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	1. 5652 2. 599.33		1. 5657 2. 607.33
	1. 5653 2. 603.33		1. 5658 2. 607.33
	1. 5654 2. 605.33		1. 5659 2. 621.34
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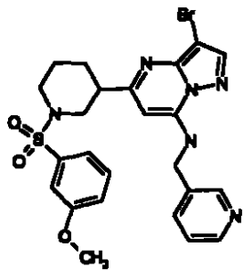
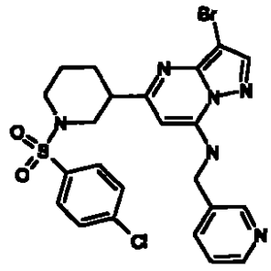
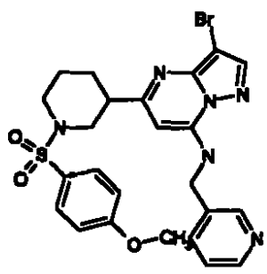
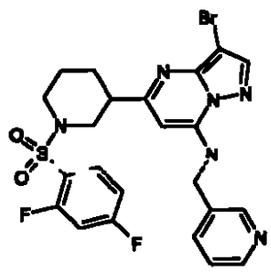
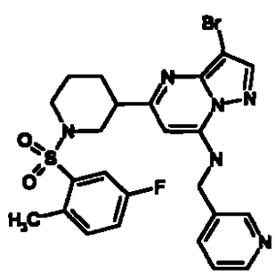
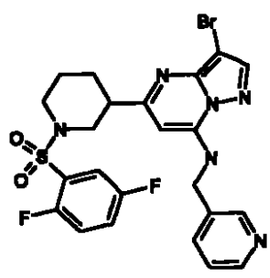
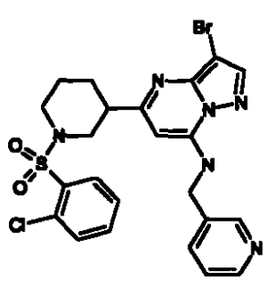
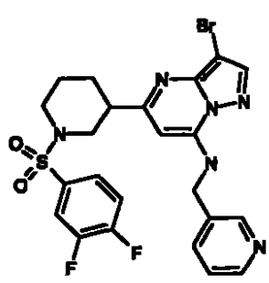
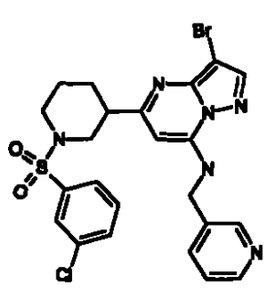
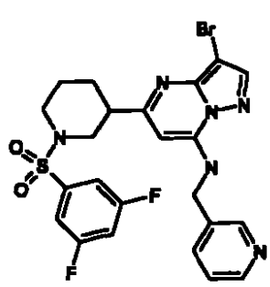
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	1. 5662 2. 631.35
	1. 5663 2. 642.35
	1. 5664 2. 665.37
	1. 5665 2. 571.31

799

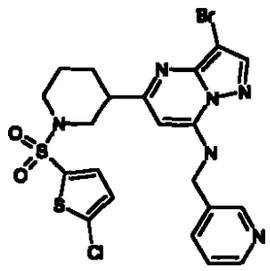
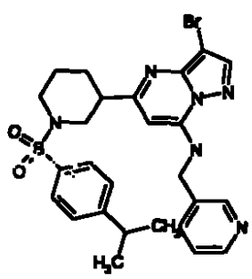
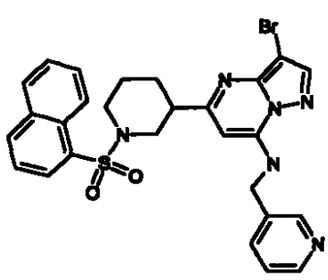
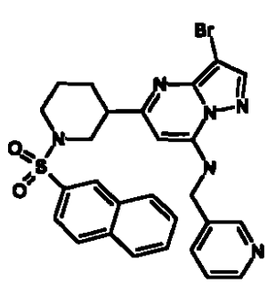
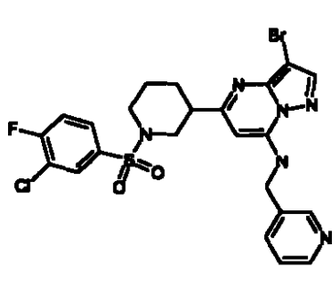
TABLA 57

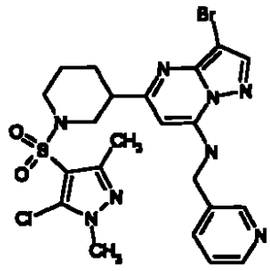
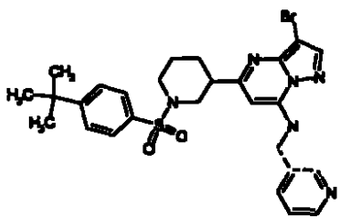
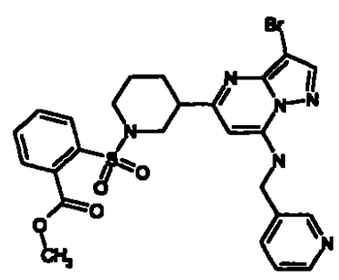
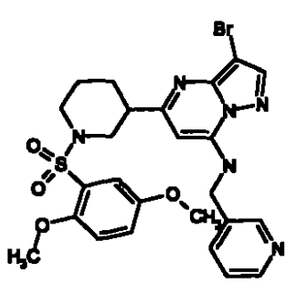
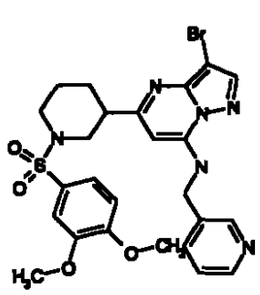
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 5702 2. 540.3		1. 5707 2. 547.3
	1. 5703 2. 543.3		1. 5708 2. 554.3
	1. 5704 2. 543.3		1. 5709 2. 555.31
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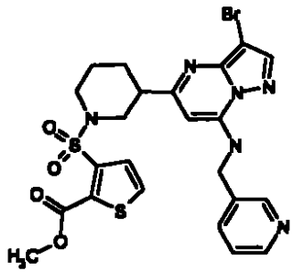
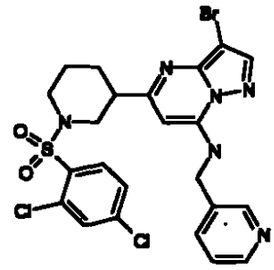
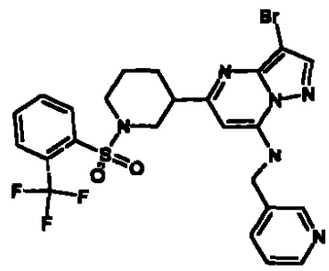
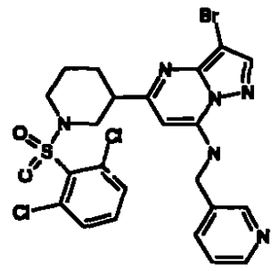
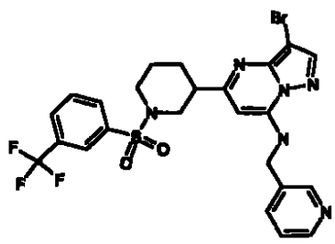
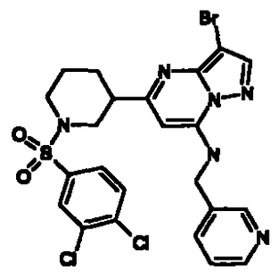
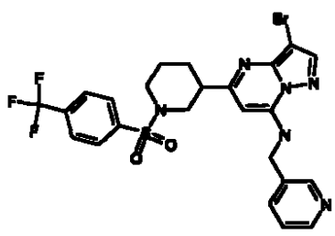
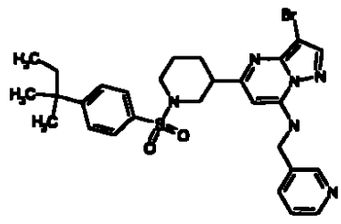
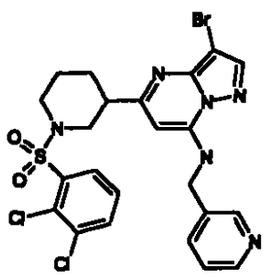
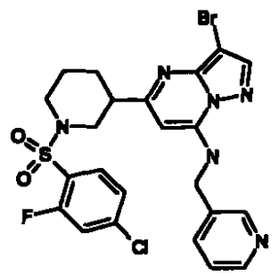
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 5712 2. 559.31		1. 5717 2. 565.31
	1. 5713 2. 561.31		1. 5718 2. 565.31
	1. 5714 2. 562.31		1. 5719 2. 565.31
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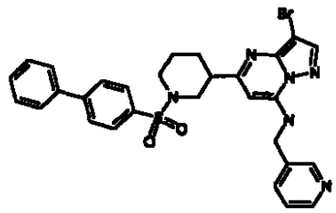
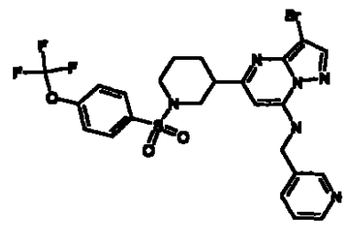
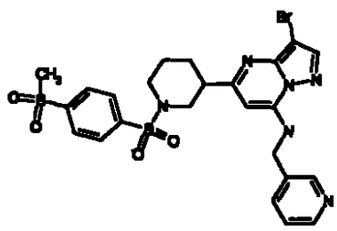
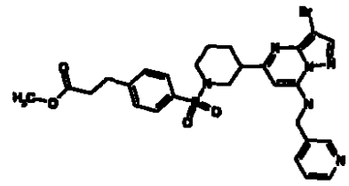
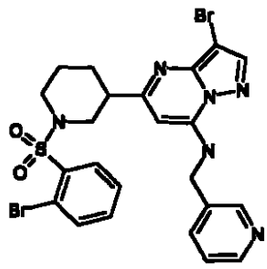
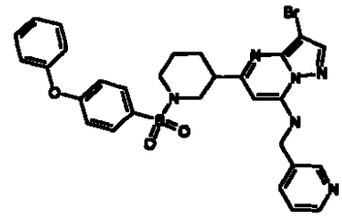
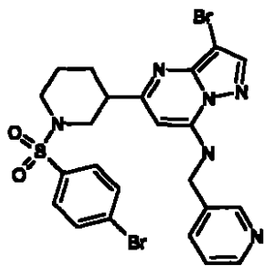
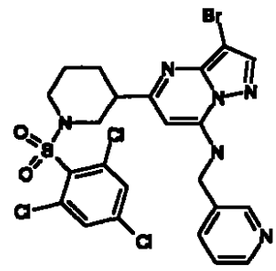
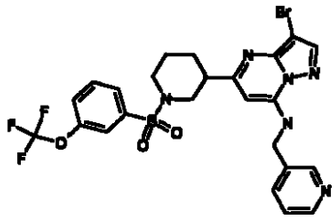
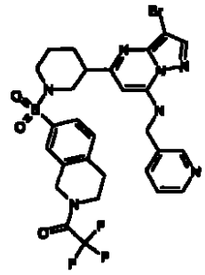
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	1. 5724 2. 579.32
	1. 5725 2. 581.32

Producto	1. Ej. 2. m/z
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	1. 5728 2. 587.32
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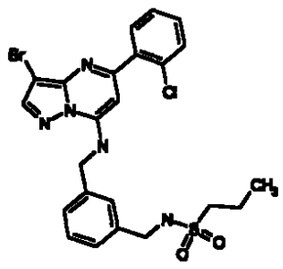
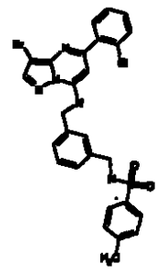
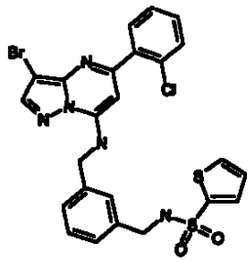
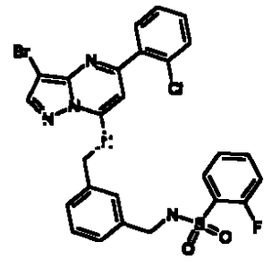
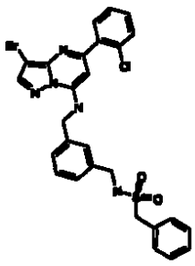
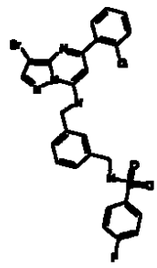
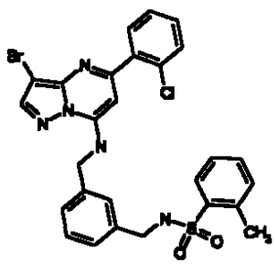
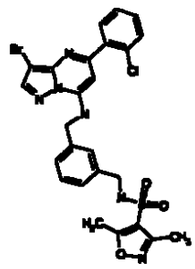
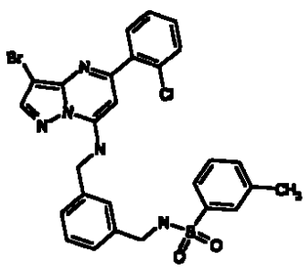
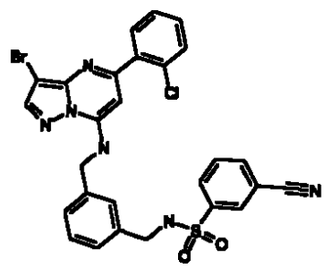
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	1. 5732 2. 597.33		1. 5737 2. 597 33
	1. 5733 2. 595.33		1. 5738 2. 596.33
	1. 5734 2. 597.33		1. 5739 2. 597.33
	1. 5735 2. 597.33		1. 5740 2. 581.32

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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
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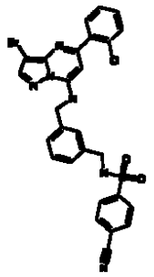
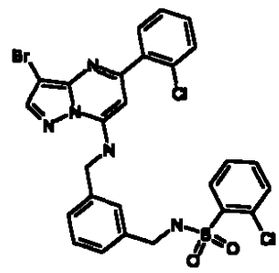
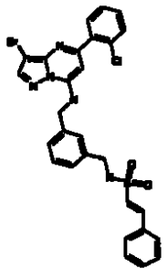
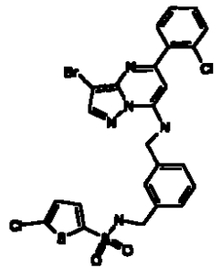
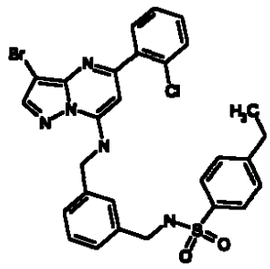
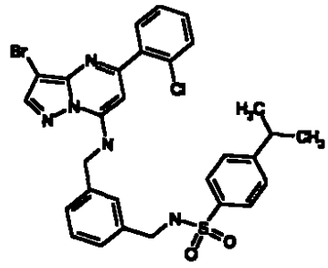
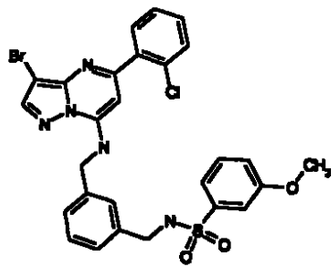
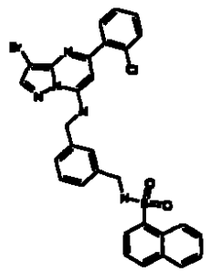
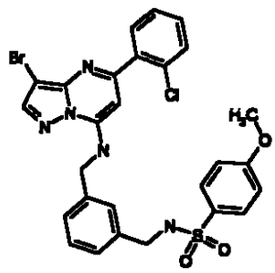
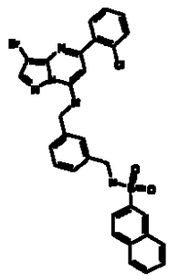
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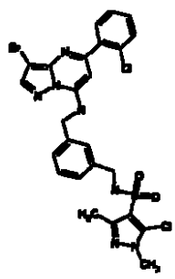
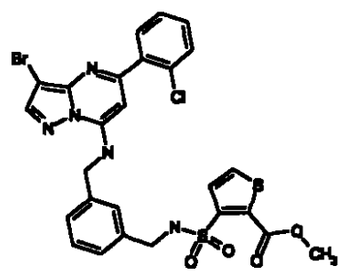
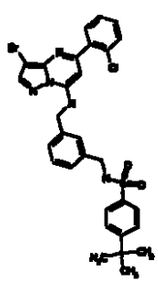
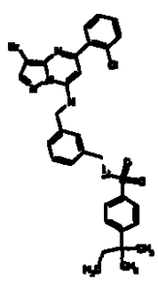
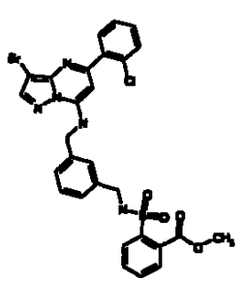
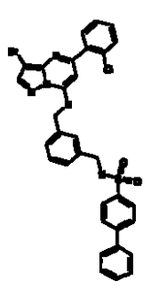
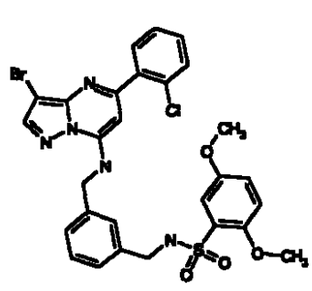
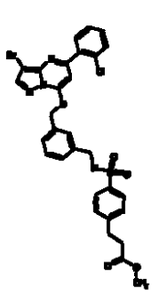
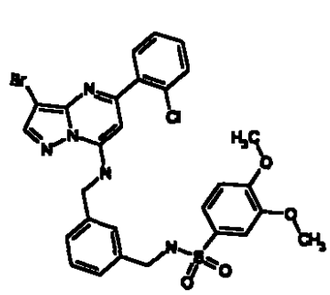
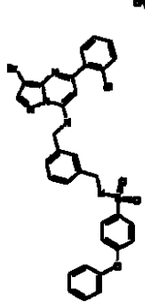
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	1. 5802 2. 590.32		10 5807 2. 602.33
	1. 5803 2. 598.33		1. 5808 2. 602.33
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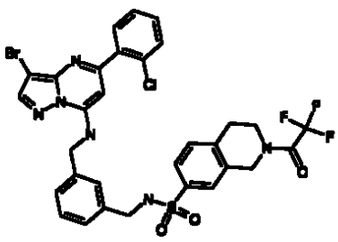
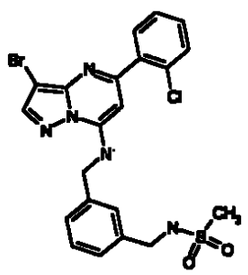
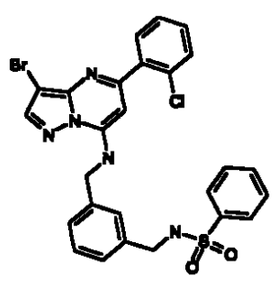
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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 5812 2. 610.34		1. 5817 2. 624.34
	1. 5813 2. 612.34		1. 5818 2. 626.34
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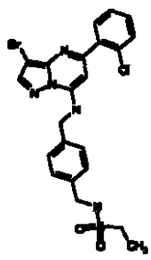
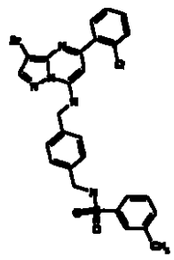
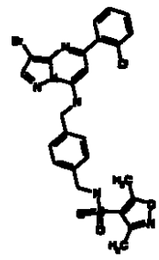
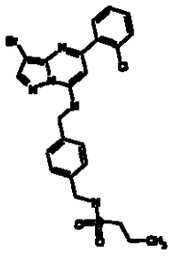
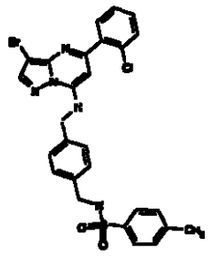
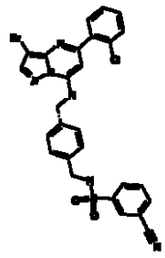
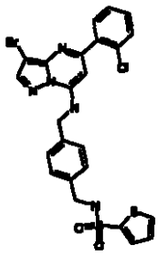
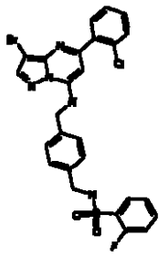
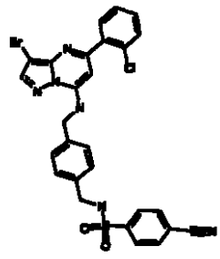
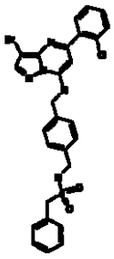
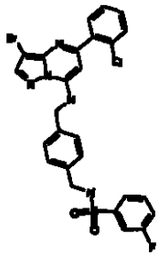
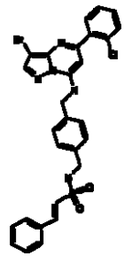
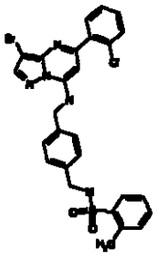
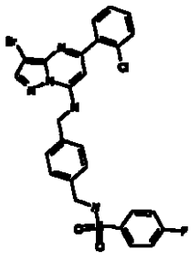
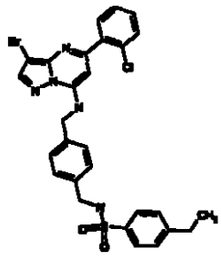
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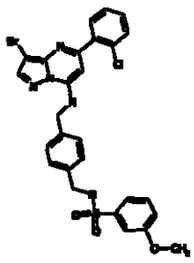
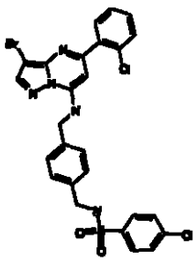
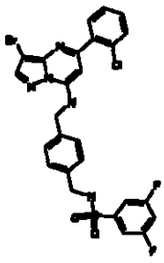
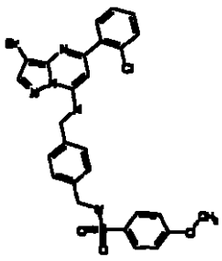
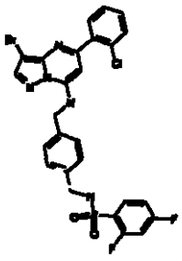
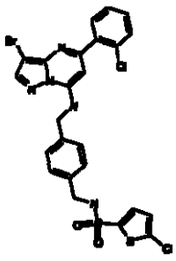
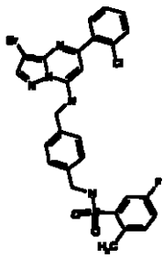
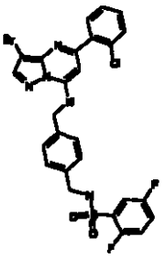
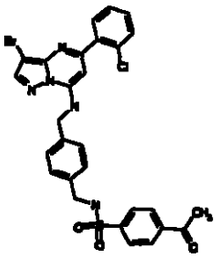
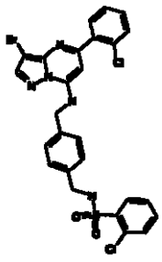
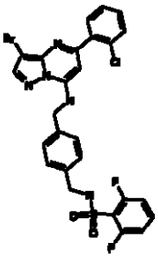
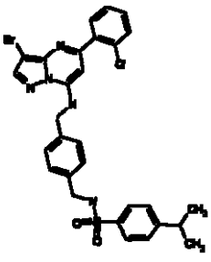
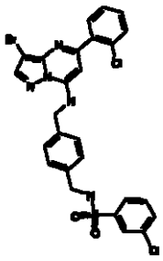
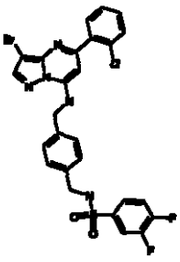
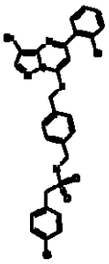
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TABLA 59

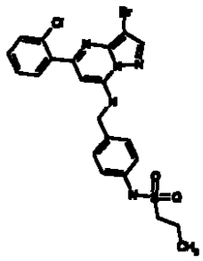
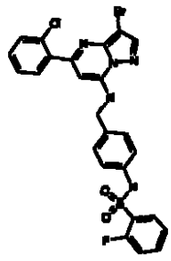
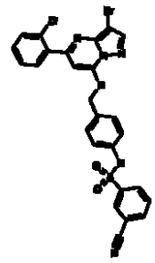
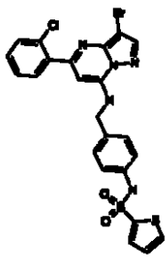
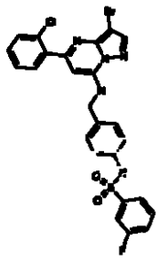
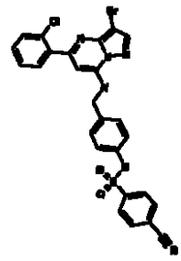
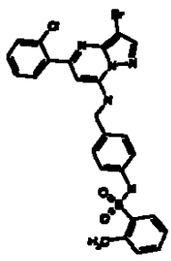
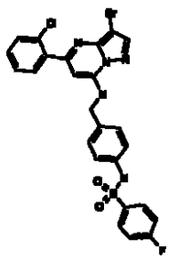
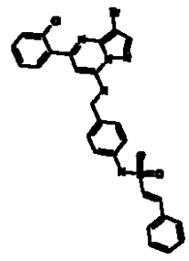
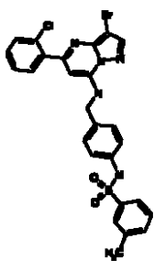
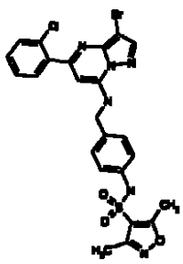
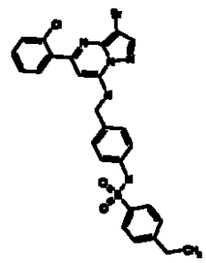
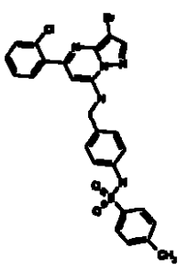
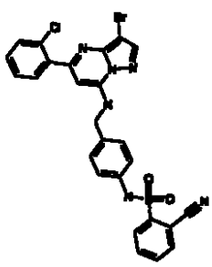
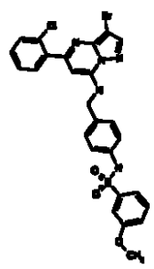
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	1. 5903 2. 590.32		1. 5908 2. 602.33		1. 5913 2. 609.33
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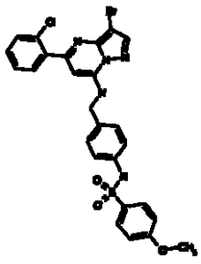
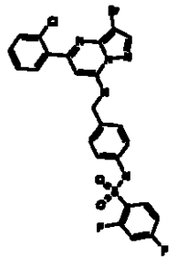
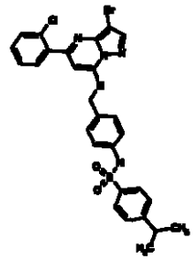
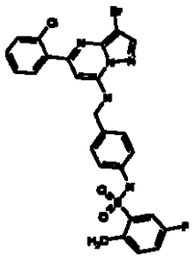
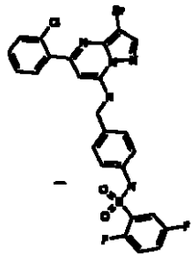
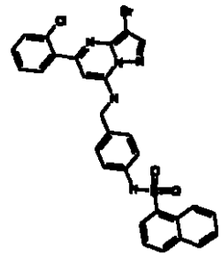
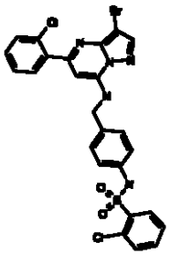
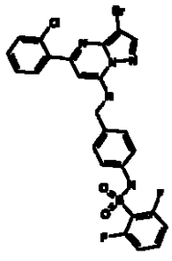
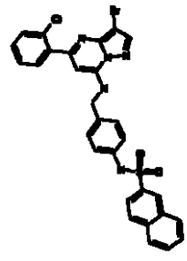
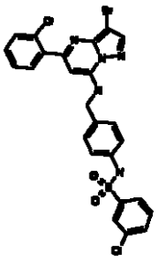
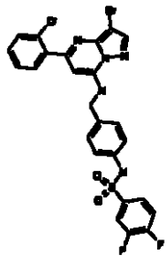
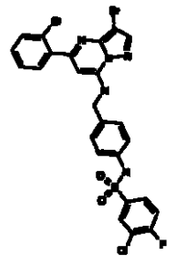
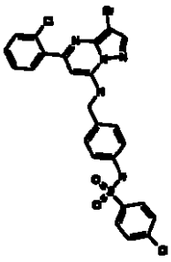
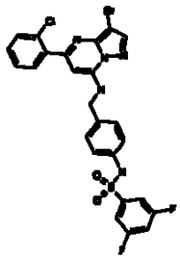
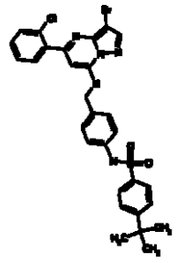
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	1. 5919 2. 618.34		1. 5924 2. 620.34		1. 5929 2. 626.34
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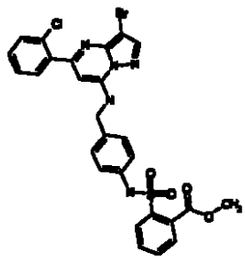
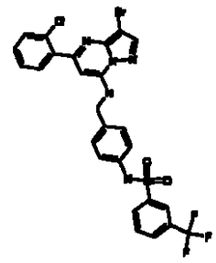
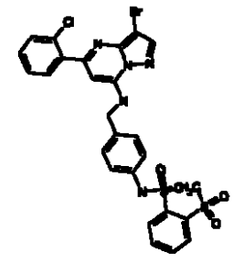
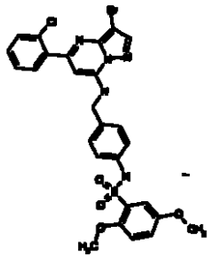
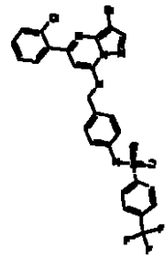
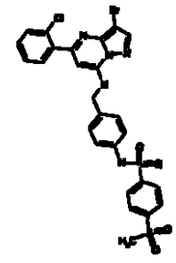
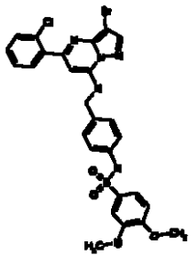
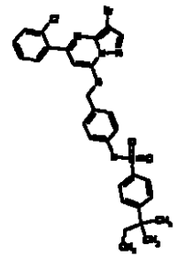
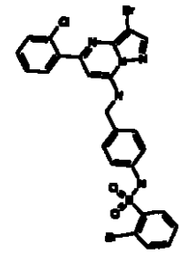
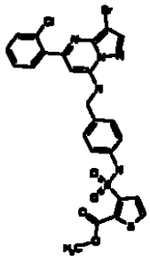
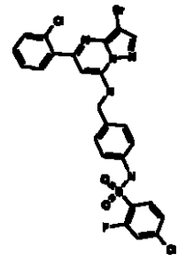
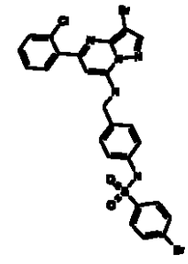
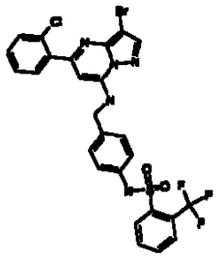
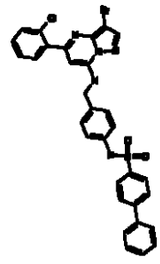
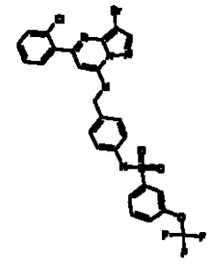
TABLA 60

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. 596.33
	1. 6005 2. 584.32		1. 6010 2. 595.33		1. 6015 2. 600.33

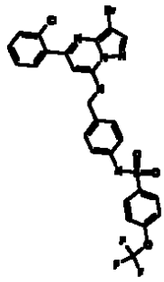
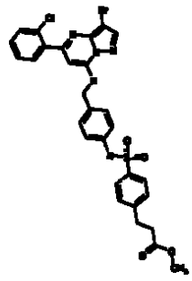
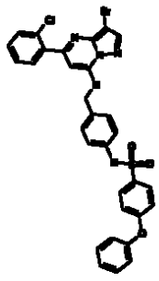
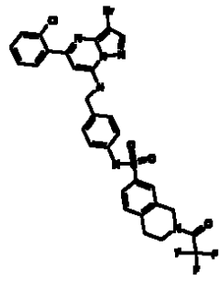
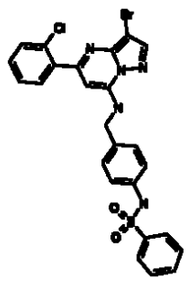
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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6016 2. 600.33		1. 6021 2. 606.33		1. 6026 2. 612.34
	1. 6017 2. 602.33		1. 6022 2. 606.33		1. 6027 2. 620.34
	1. 6018 2. 604.33		1. 6023 2. 606.33		1. 6028 2. 620.34
	1. 6019 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

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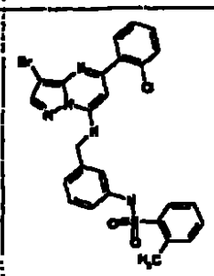
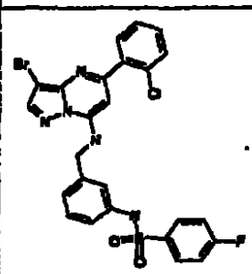
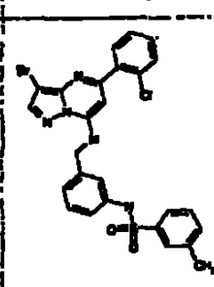
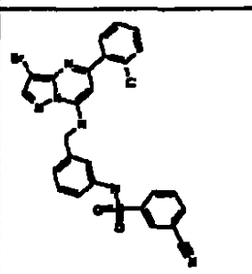
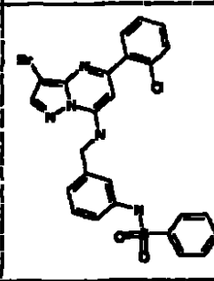
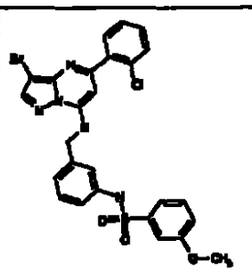
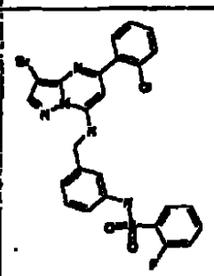
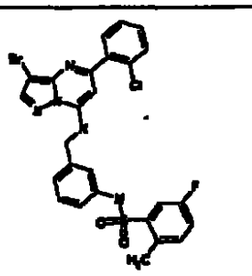
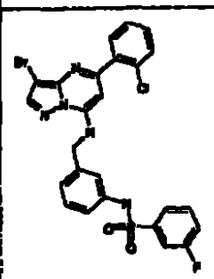
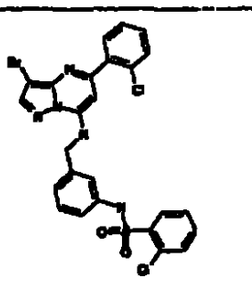
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6031 2. 628.35		1. 6036 2. 638.35		1. 6041 2. 648.36
	1. 6032 2. 630.35		1. 6037 2. 638.35		1. 60425 2. 648.36
	1. 6033 2. 630.35		1. 6038 2. 638.35		1. 6043 2. 648.36
	1. 6034 2. 634.35		1. 6039 2. 622.34		1. 6044 2. 648.36
	1. 6035 2. 638.35		1. 6040 2. 646.36		1. 6045 2. 654.36

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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

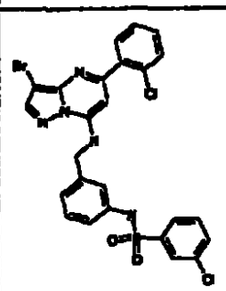
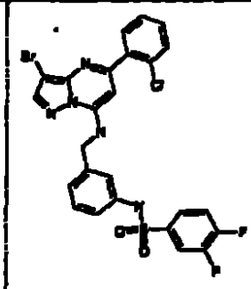
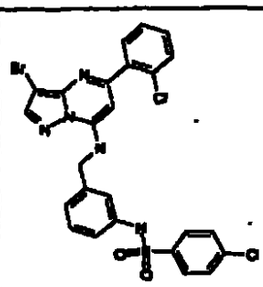
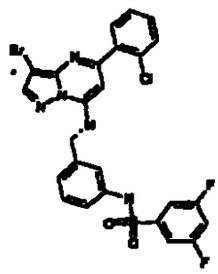
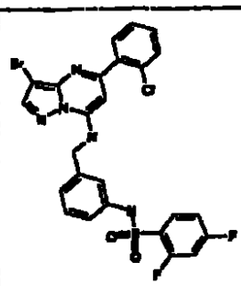
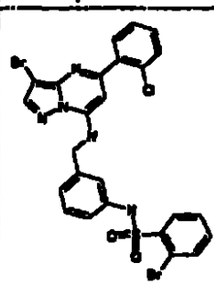
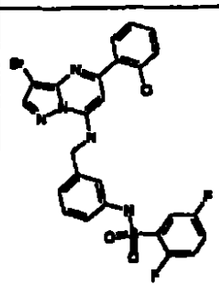
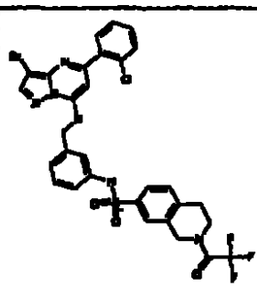
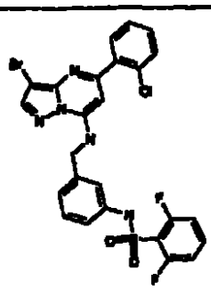
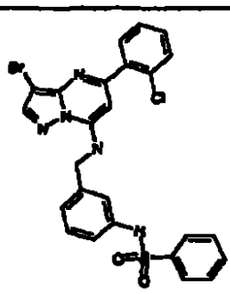
814

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

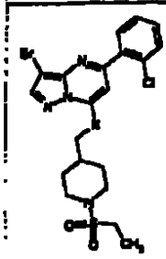
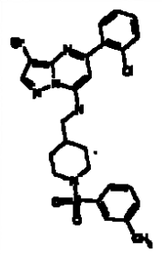
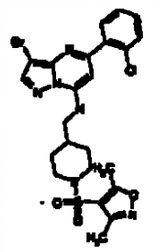
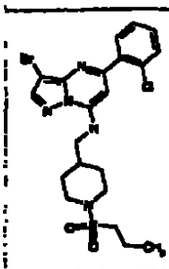
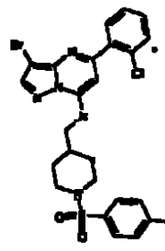
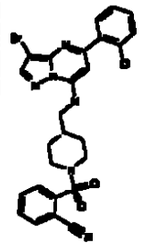
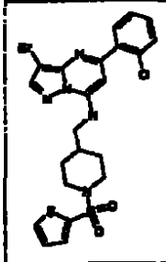
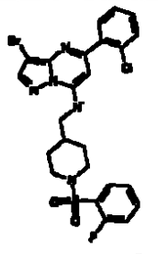
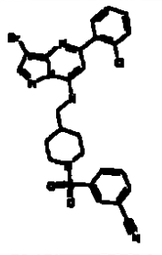
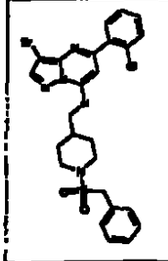
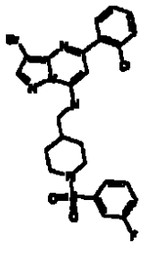
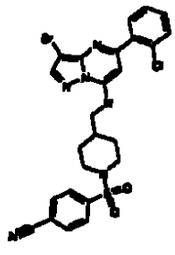
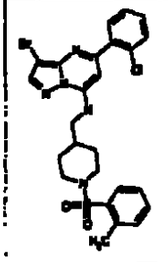
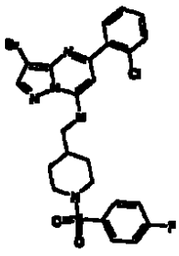
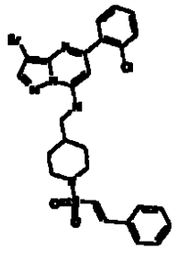
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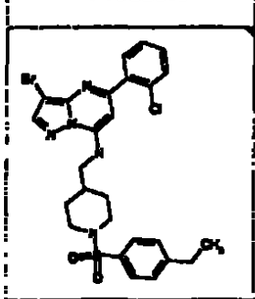
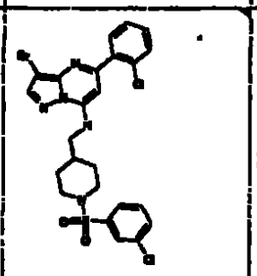
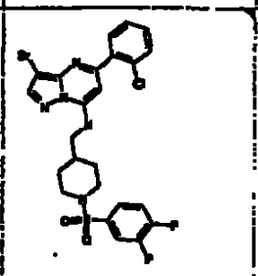
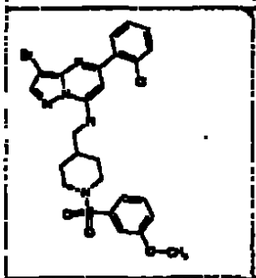
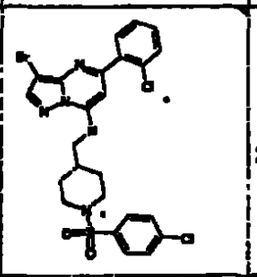
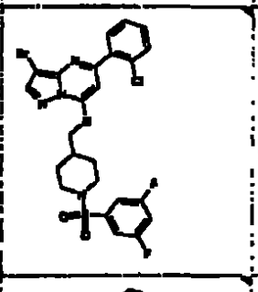
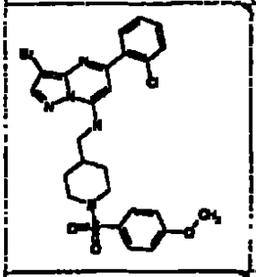
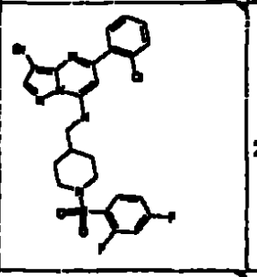
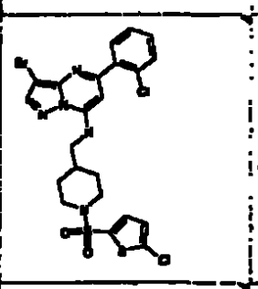
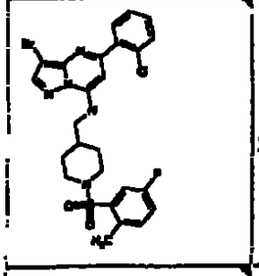
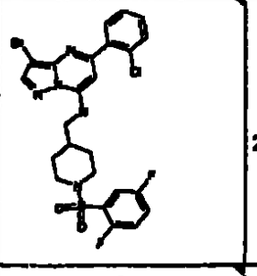
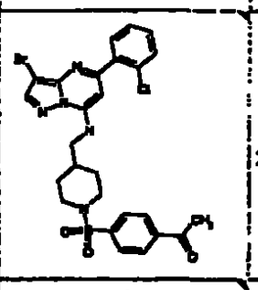
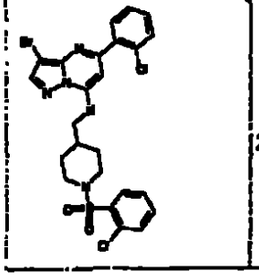
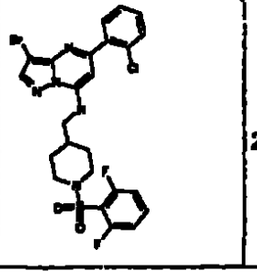
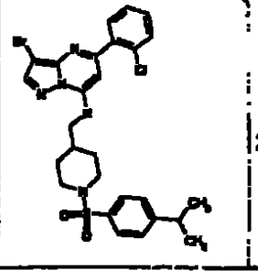
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	1. 6112 2. 604.33		1. 6117 2. 606.33
	1. 6113 2. 606.33		1. 6118 2. 648.36
	1. 6114 2. 606.33		1. 6119 2. 721.4
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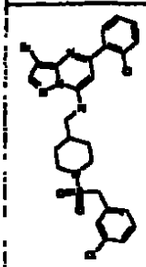
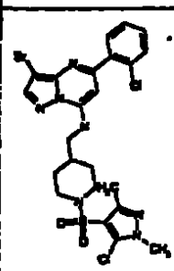
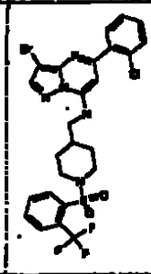
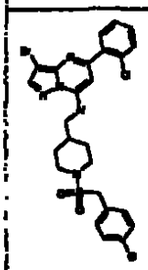
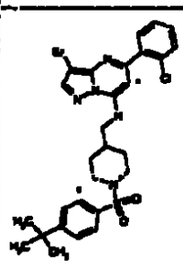
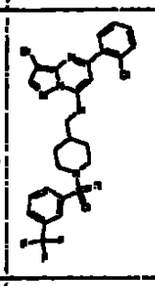
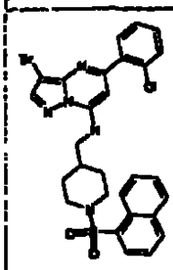
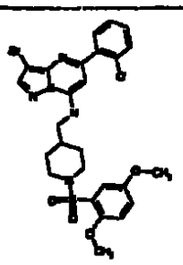
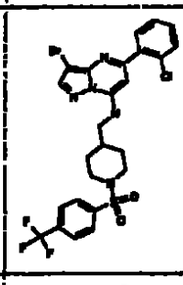
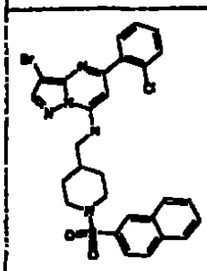
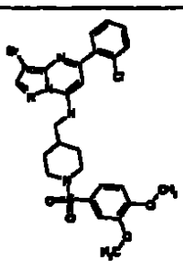
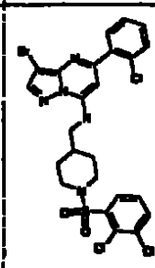
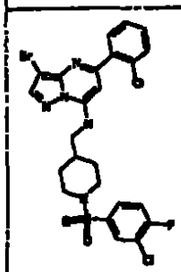
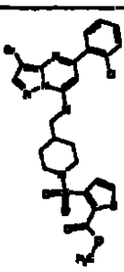
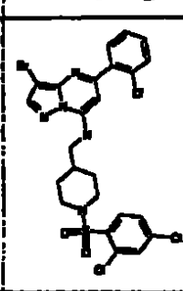
TABLA 62

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	1. 6202 2. 528.29		1. 6207 2. 576.32		1. 6212 2. 587.32
	1. 6203 2. 566.31		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
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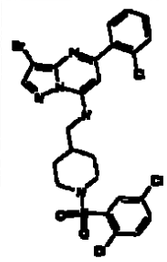
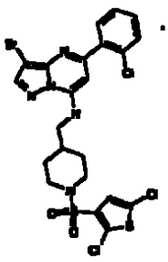
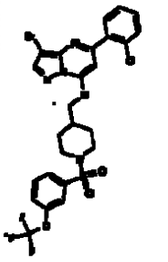
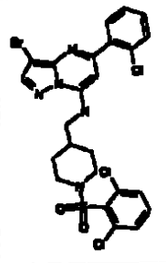
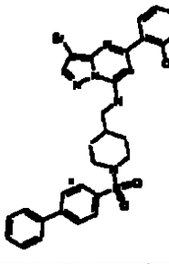
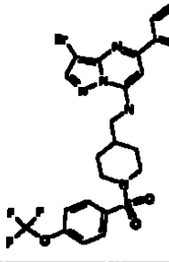
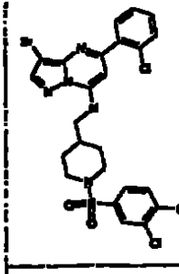
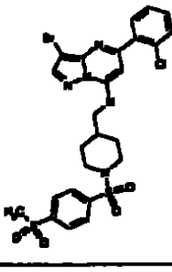
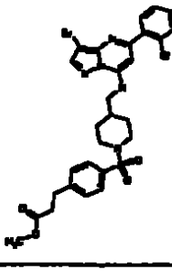
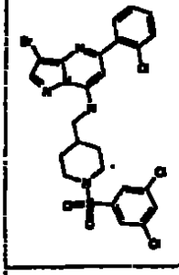
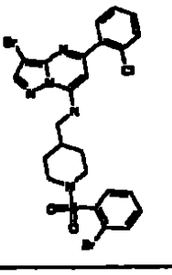
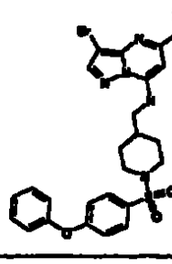
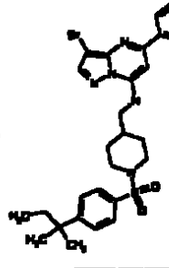
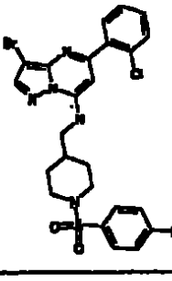
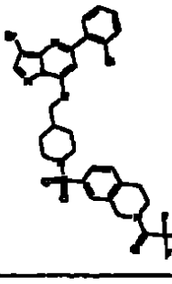
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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 6217 2. 592.33		1. 6222 2. 596.33		1. 6227 2. 596.33
	1. 6218 2. 592.33		1. 6223 2. 596.33		1. 6228 2. 602.33
	1. 6219 2. 592.33		1. 6224 2. 596.33		1. 6229 2. 604.33
	1. 6220 2. 594.33		1. 6225 2. 596.33		1. 6230 2. 604.33

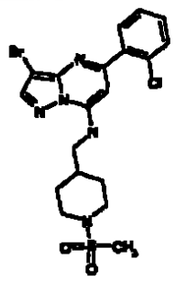
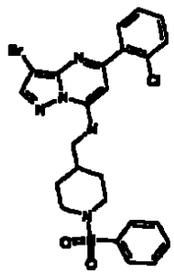
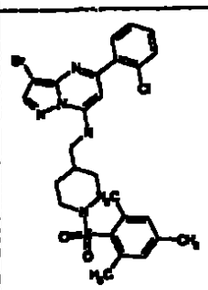
818

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	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

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Product	1. 日. 2. m/z	Product	1. 日. 2. m/z	Product	1. 日. 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. 648.36
	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

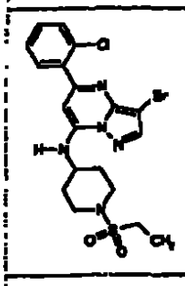
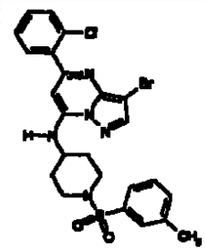
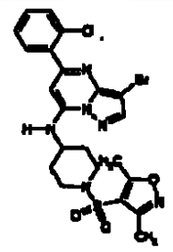
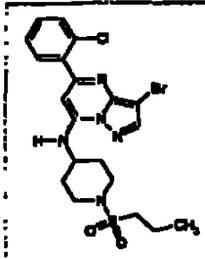
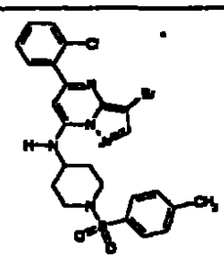
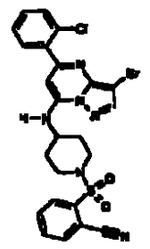
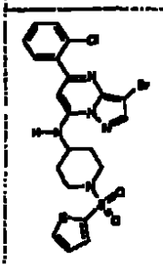
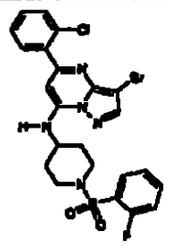
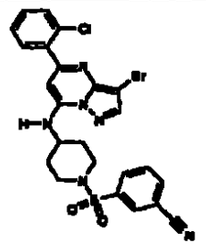
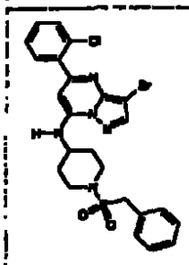
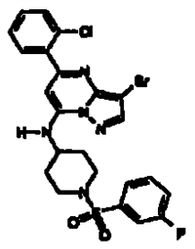
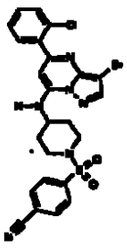
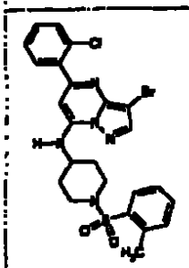
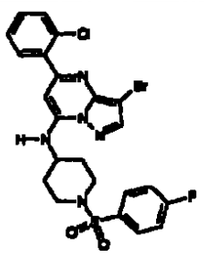
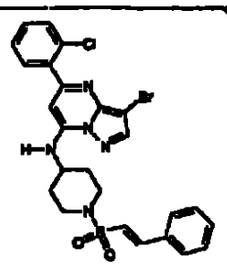
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	1. 6262 2. 562.31
	1. 6263 2. 604.33

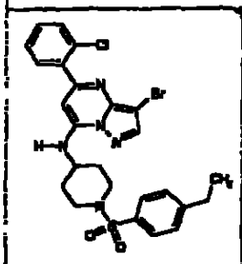
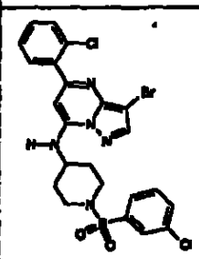
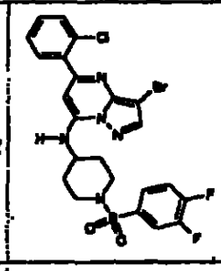
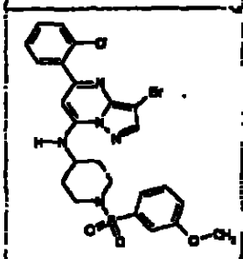
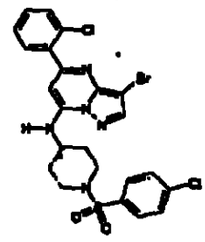
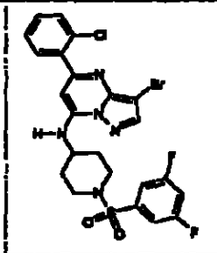
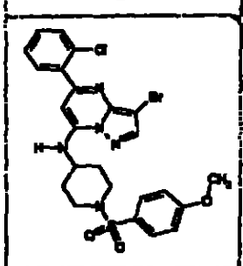
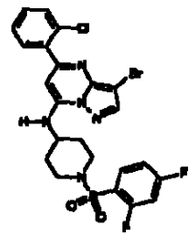
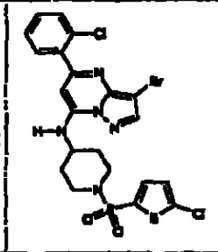
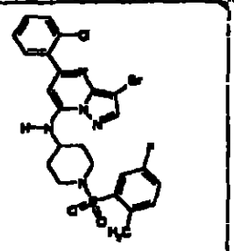
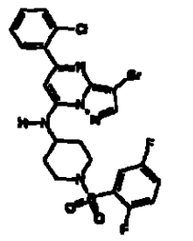
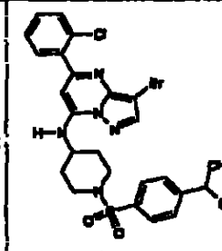
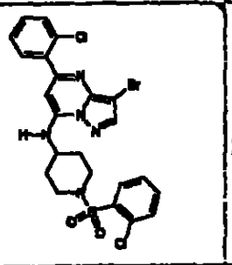
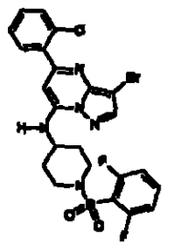
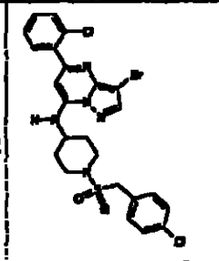
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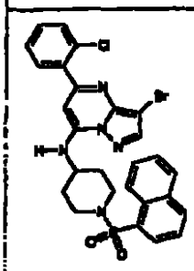
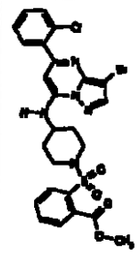
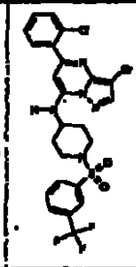
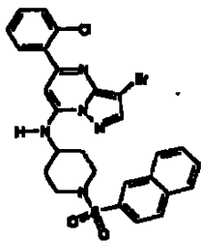
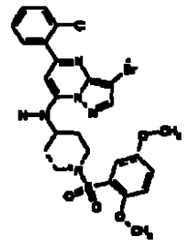
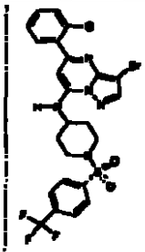
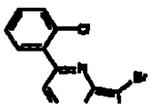
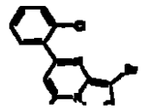
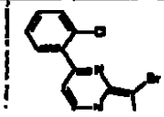
TABLA 63

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. 587.31
	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
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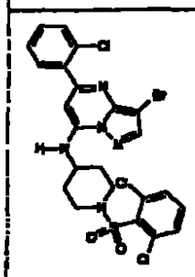
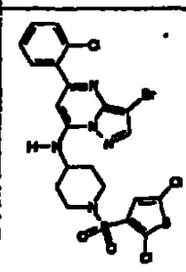
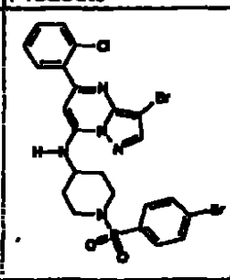
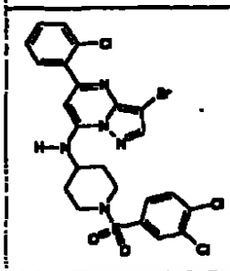
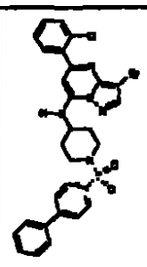
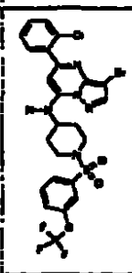
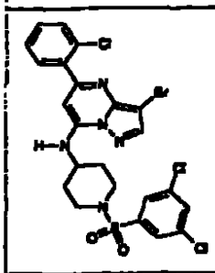
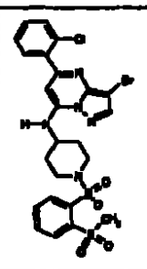
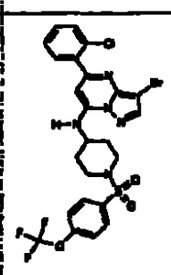
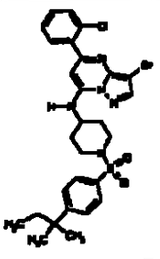
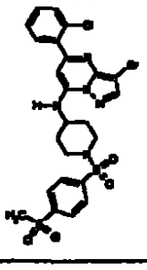
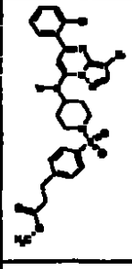
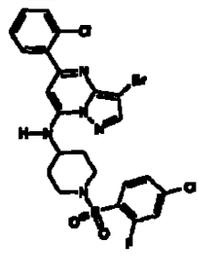
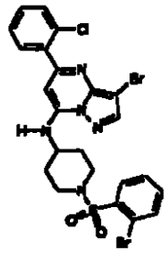
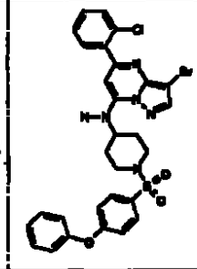
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Product a	1. 타. 2. m/z	Product b	1. 타. 2. m/z	Product c	1. 타. 2. m/z
	1. 6316 2. 576.32		1. 6321 2. 582.32		1. 6326 2. 584.32
	1. 6317 2. 578.32		1. 6322 2. 582.32		1. 6327 2. 584.32
	1. 6318 2. 578.32		1. 6323 2. 584.32		1. 6328 2. 588.32
	1. 6319 2. 580.32		1. 6324 2. 582.32		1. 6329 2. 590.32
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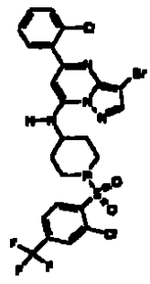
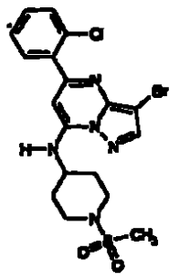
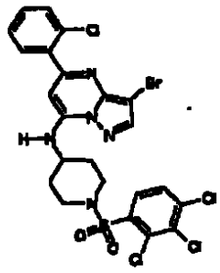
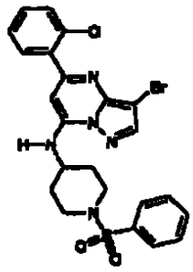
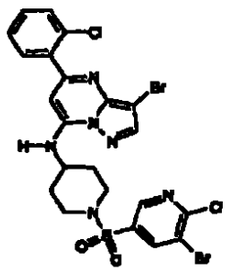
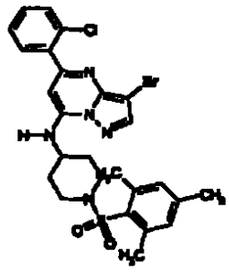
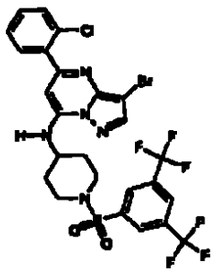
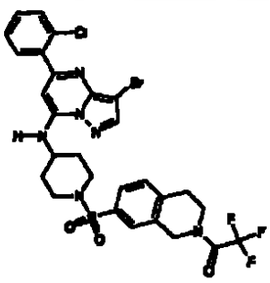
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	1. 6332 2. 598.33		1. 6337 2. 606.33		1. 6342 2. 616.34
					

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Product	1. 타. 2. m/z	Product	1. 타. 2. m/z	Product	1. 타. 2. m/z
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	1. 6347 2. 616.34		1. 6352 2. 624.34		1. 6357 2. 632.35
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	1. 6349 2. 618.34		1. 6354 2. 626.34		1. 6359 2. 634.35
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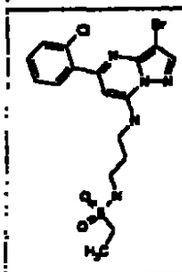
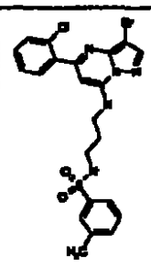
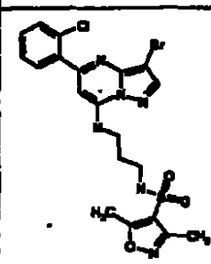
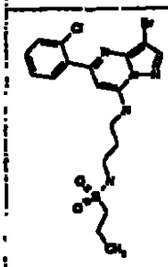
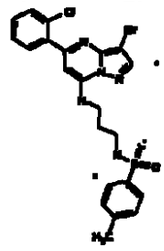
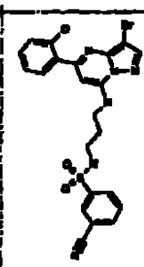
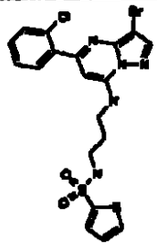
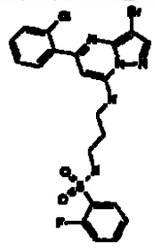
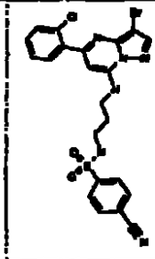
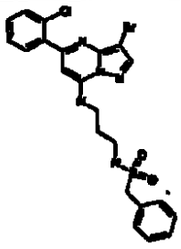
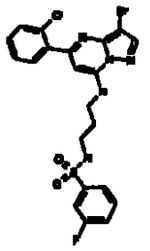
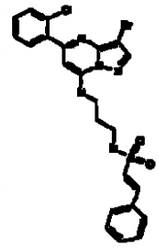
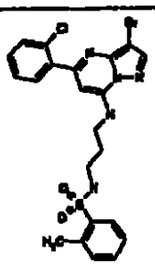
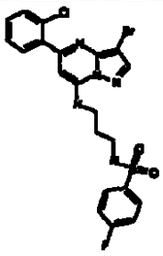
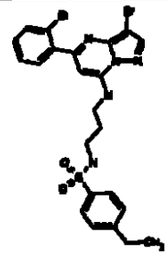
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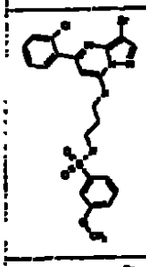
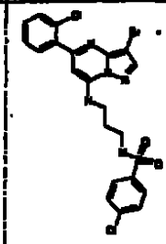
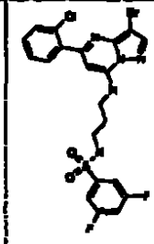
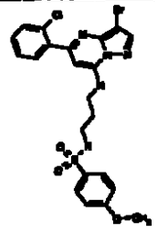
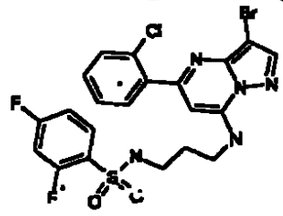
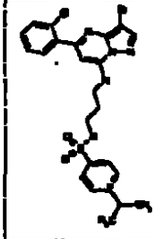
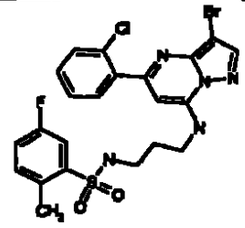
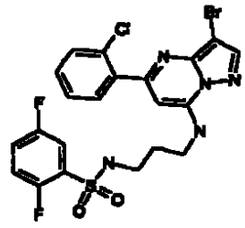
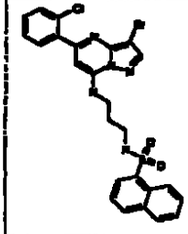
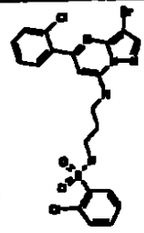
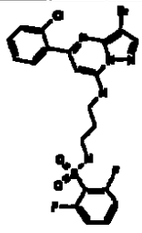
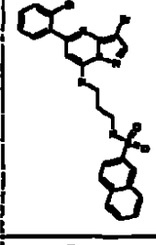
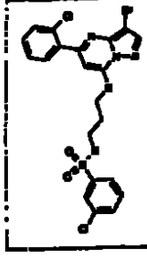
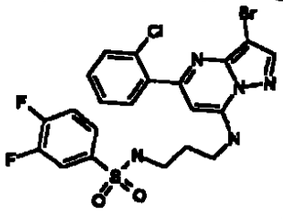
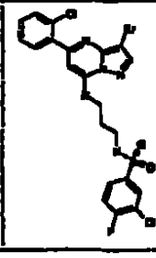
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TABLA 64

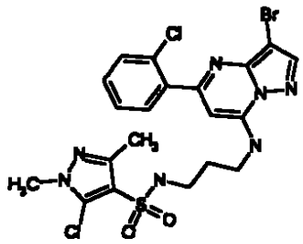
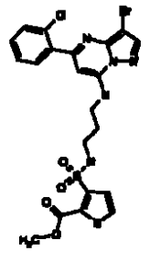
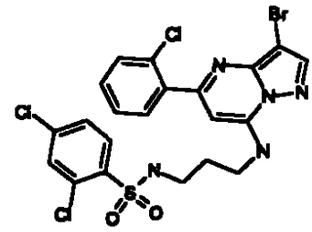
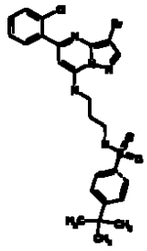
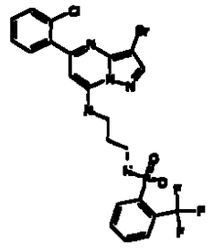
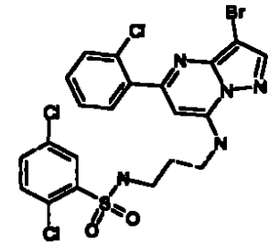
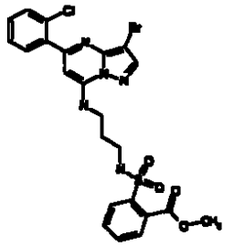
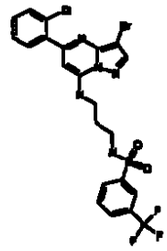
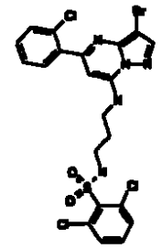
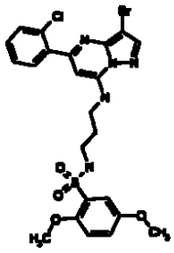
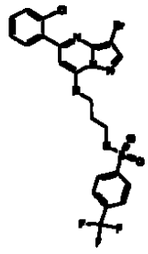
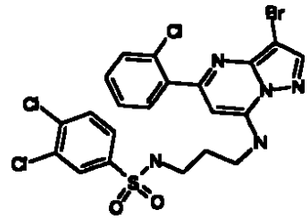
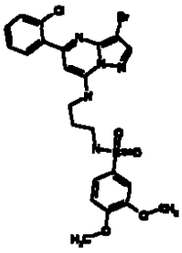
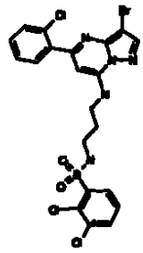
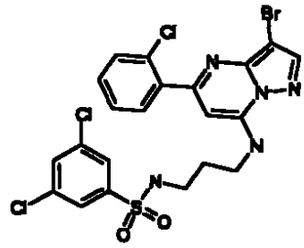
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	1. 6403 2. 528.29		1. 6408 2. 540.3		1. 6413 2. 547.3
	1. 6404 2. 536.29		1. 6409 2. 540.3		1. 6414 2. 548.3
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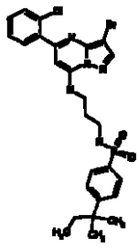
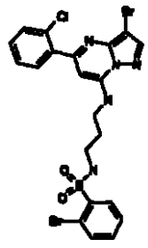
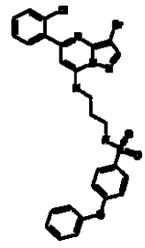
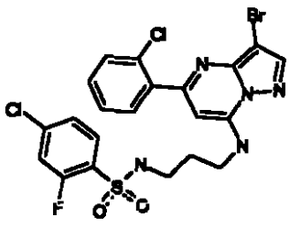
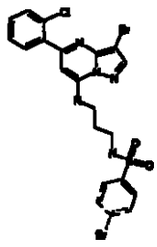
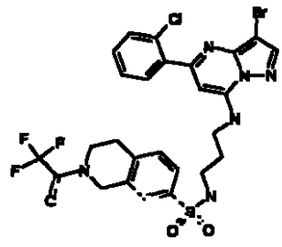
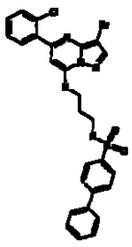
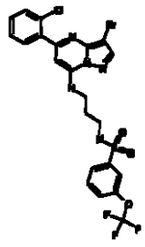
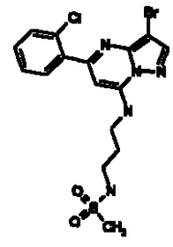
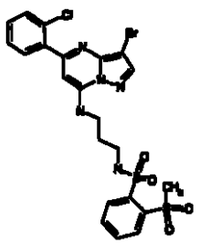
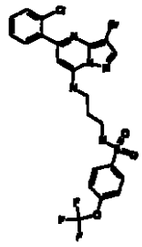
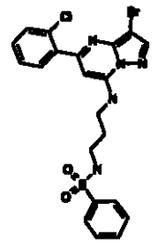
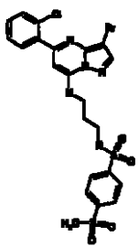
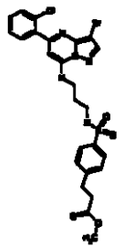
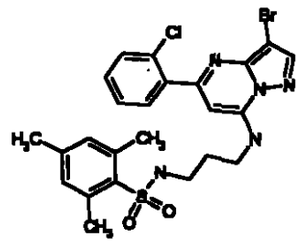
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	1. 6418 2. 554.3		1. 6423 2. 556.31		1. 6428 2. 572.31
	1. 6419 2. 556.31		1. 6424 2. 556.31		1. 6429 2. 572.31
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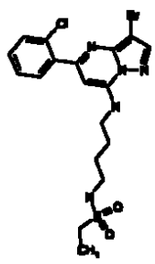
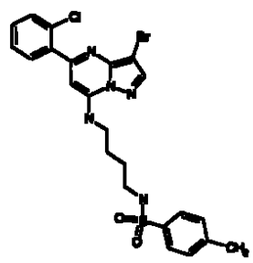
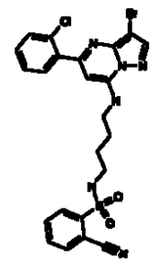
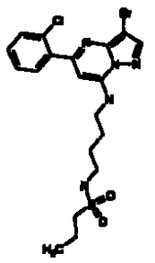
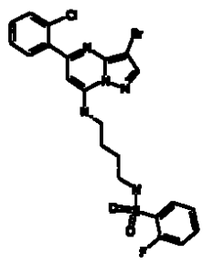
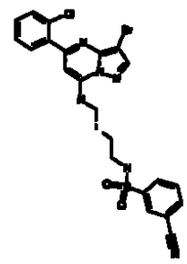
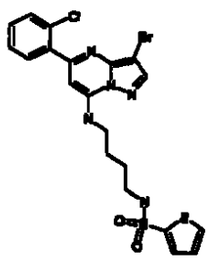
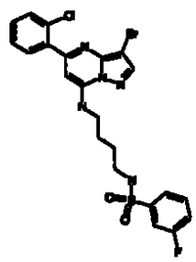
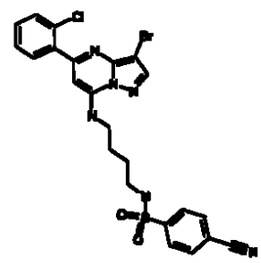
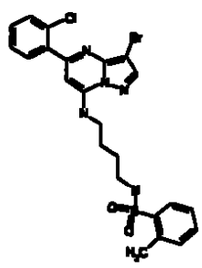
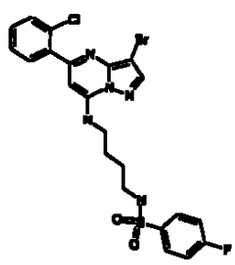
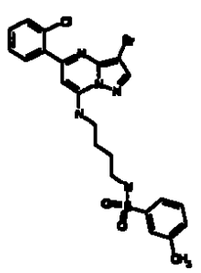
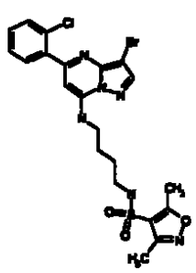
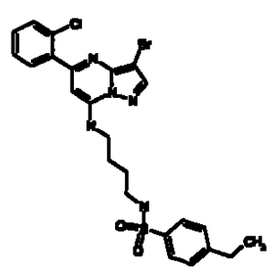
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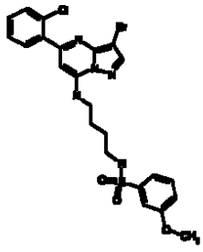
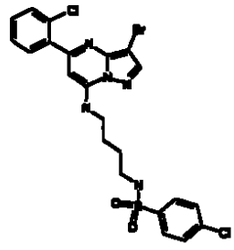
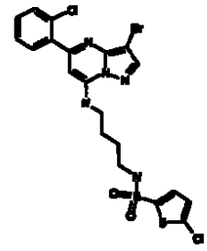
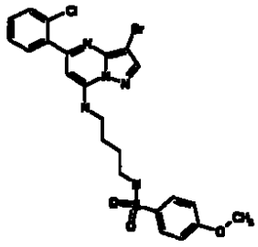
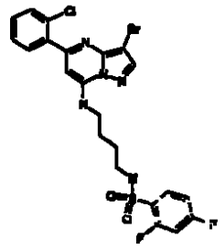
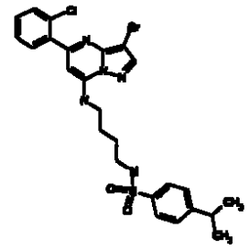
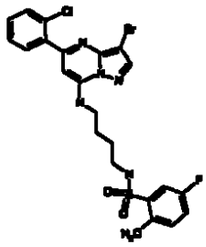
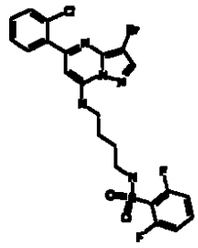
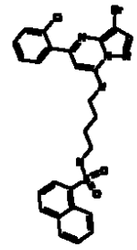
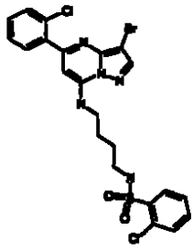
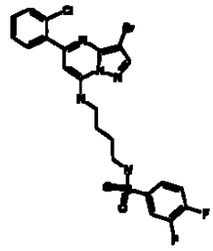
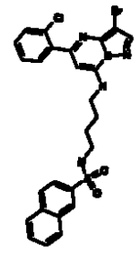
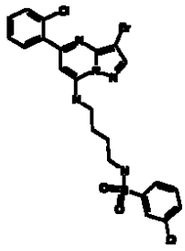
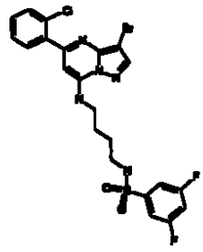
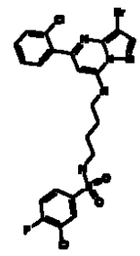
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	1. 6448 2. 598.33		1. 6453 2. 606.33		1. 6458 2 460.25
	1. 6449 2. 600.33		1. 6454 2. 606.33		6459 2.
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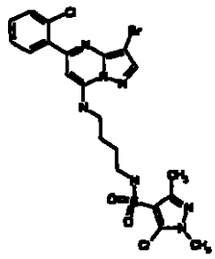
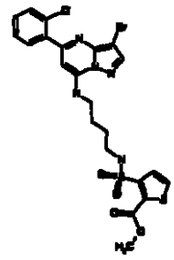
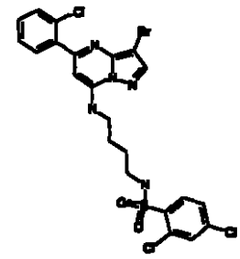
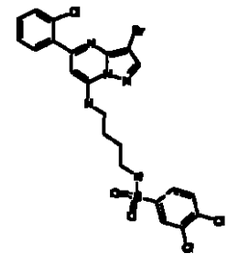
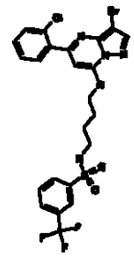
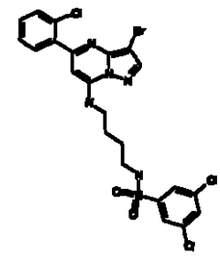
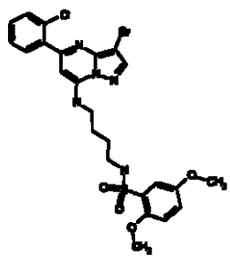
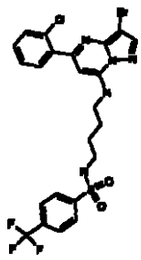
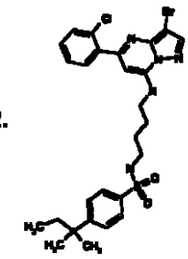
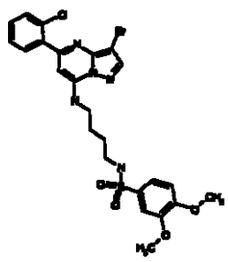
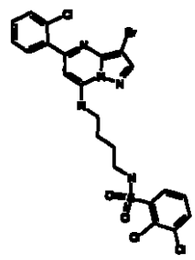
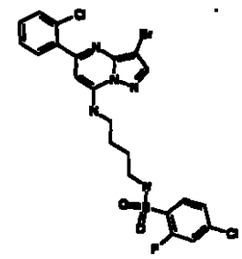
TABLA 65

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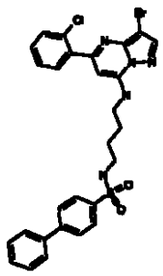
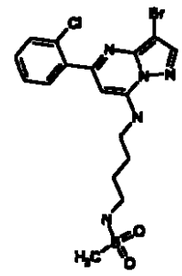
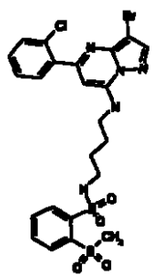
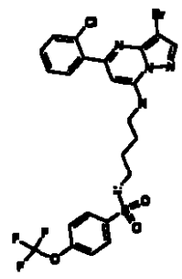
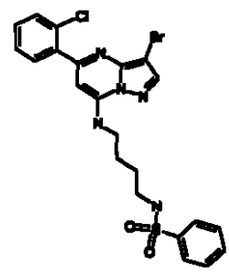
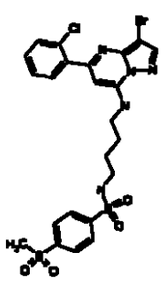
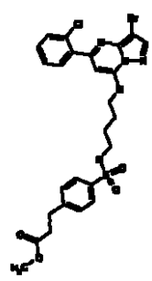
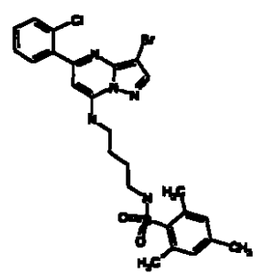
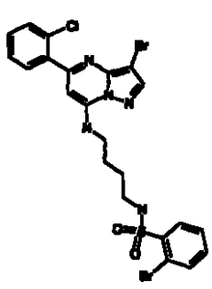
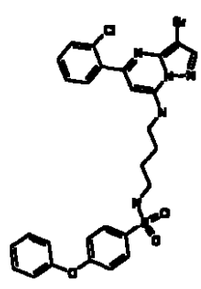
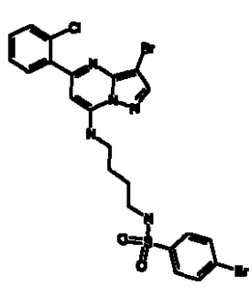
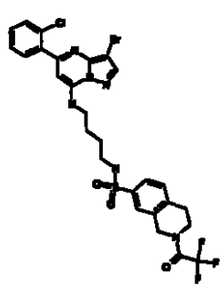
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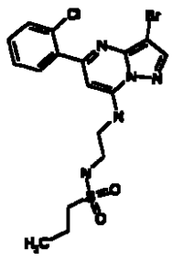
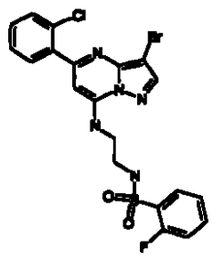
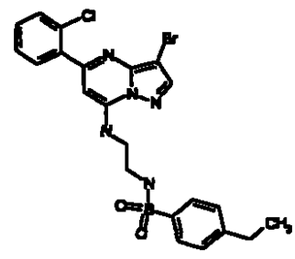
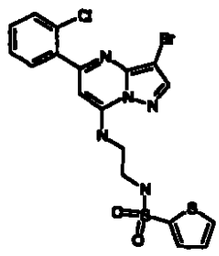
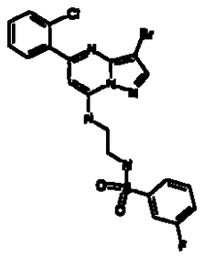
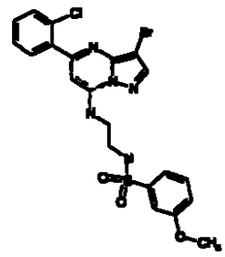
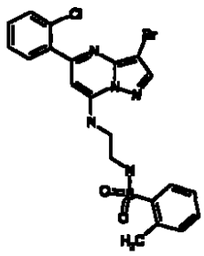
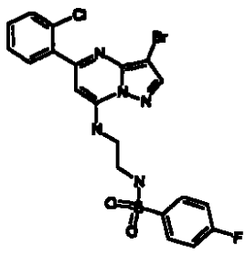
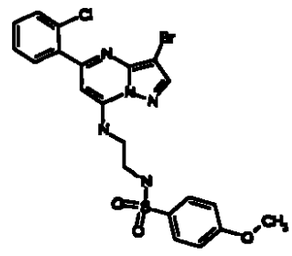
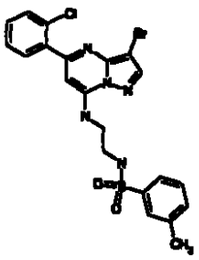
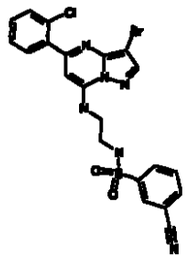
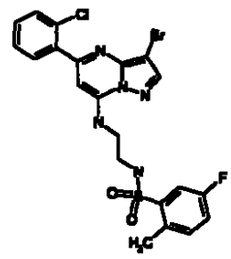
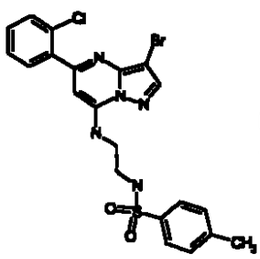
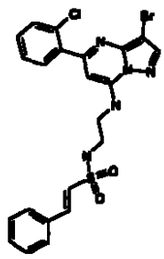
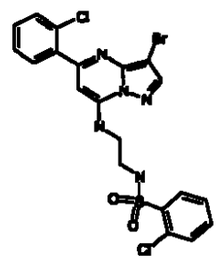
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	1. 6534 2. 596.33		1. 6539 2. 604.33		1. 6544 2. 606.33
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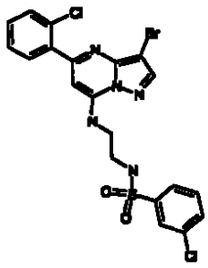
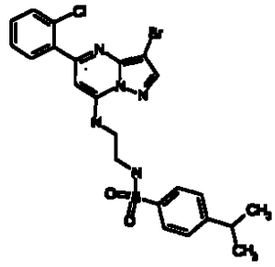
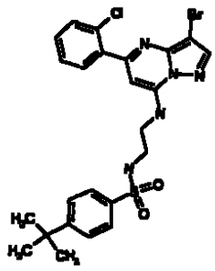
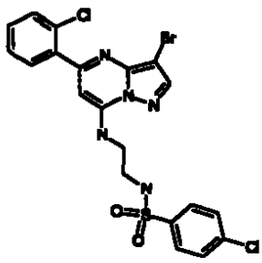
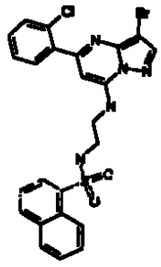
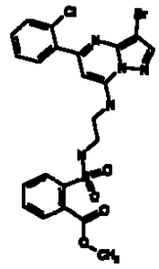
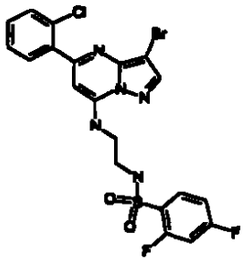
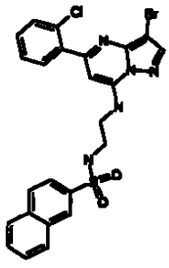
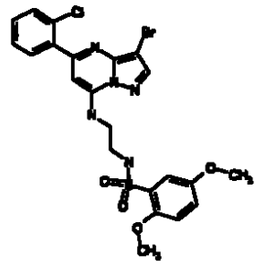
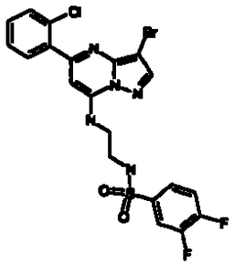
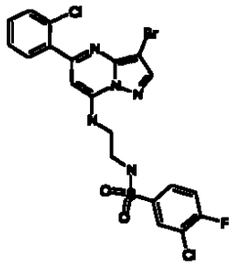
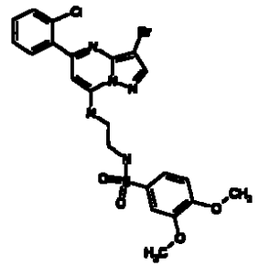
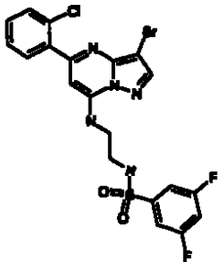
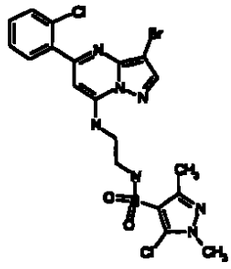
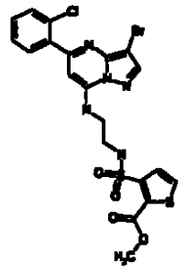
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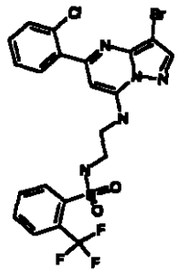
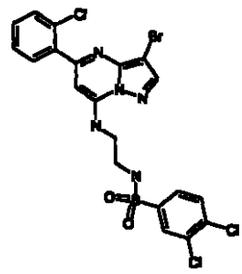
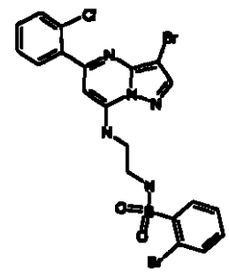
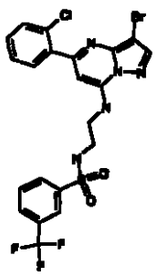
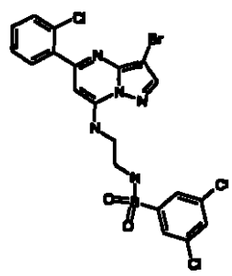
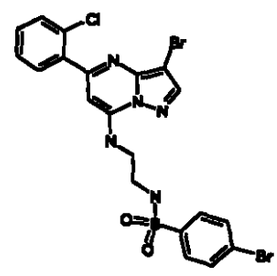
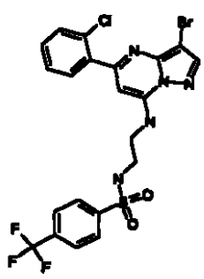
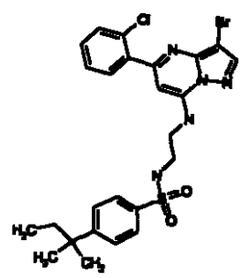
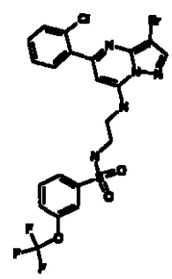
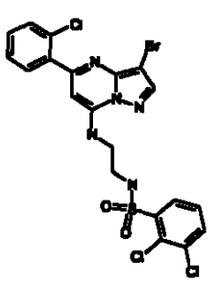
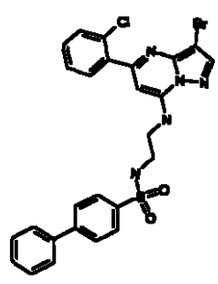
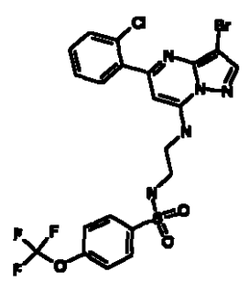
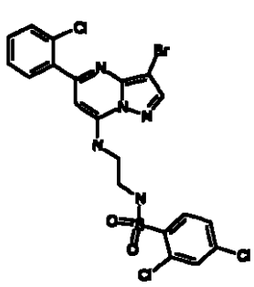
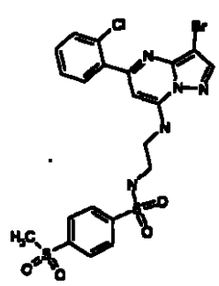
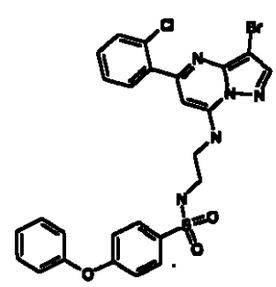
TABLA 67

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 6702 2. 514.28		1. 6707 2. 526.29		1. 6712 2. 536.3
	1. 6703 2. 522.29		1. 6708 2. 526.29		1. 6713 2. 536.3
	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

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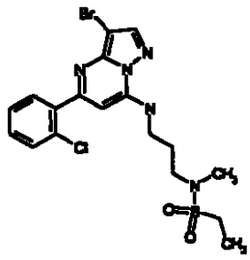
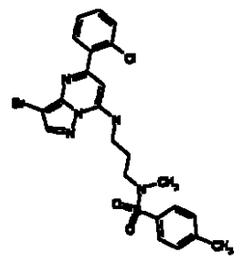
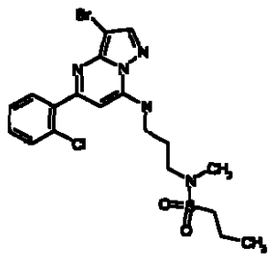
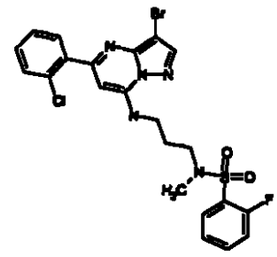
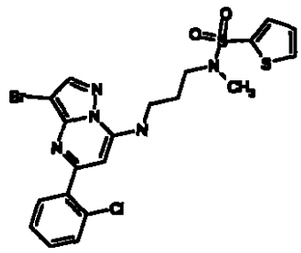
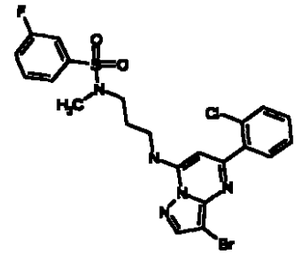
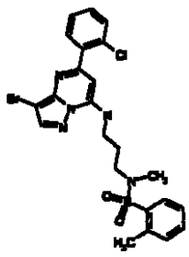
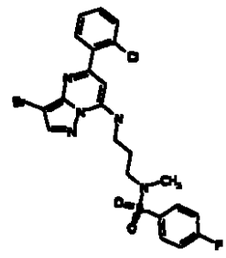
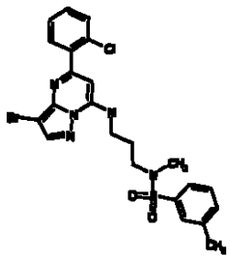
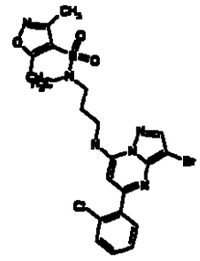
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	1. 6716 2. 542.3		1. 6721 2. 550.3		1. 6726 2. 564.31
	1. 6717 2. 542.3		1. 6722 2. 558.31		1. 6727 2. 566.31
	1. 6718 2. 544.3		1. 6723 2. 558.31		1. 6728 2. 568.31
	1. 6719 2. 544.3		1. 6724 2. 560.31		1. 6729 2. 568.31
	1. 6720 2. 544.3		1. 6725 2. 560.31		1. 6730 2. 572.31

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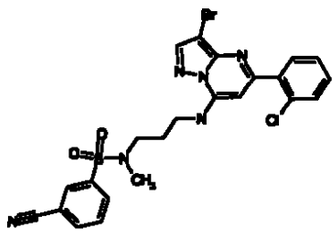
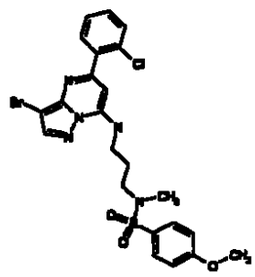
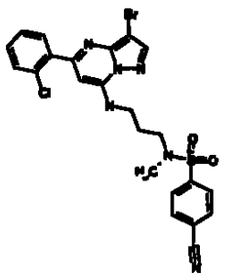
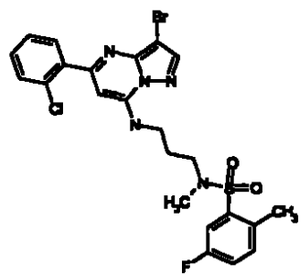
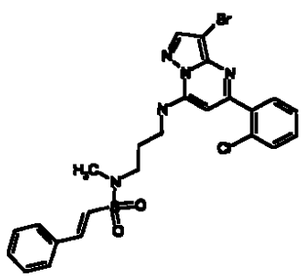
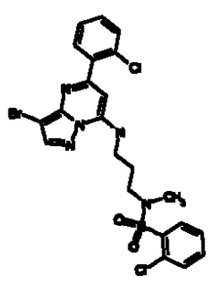
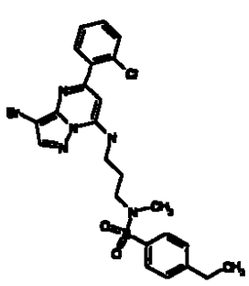
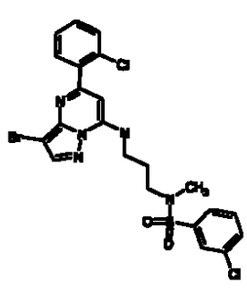
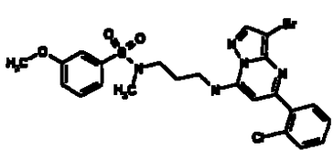
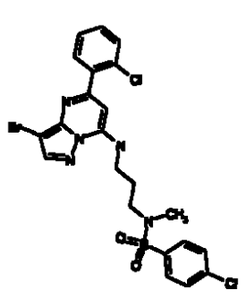
Producto	1. Ej. 2. m/z	Product	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6731 2. 576.32		1. 6736 2. 576.32		1. 6741 2. 586.32
	1. 6732 2. 576.32		1. 6737 2. 576.32		1. 6742 2. 586.32
	1. 6733 2. 576.32		1. 6738 2. 576.32		1. 6743 2. 592.33
	1. 6734 2. 576.32		1. 6739 2. 584.32		1. 6744 2. 592.33
	1. 6735 2. 576.32		1. 6740 2. 586.32		1. 6745 2. 600.33

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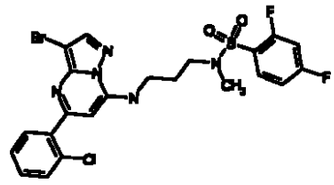
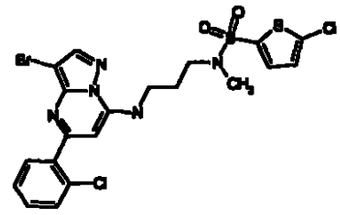
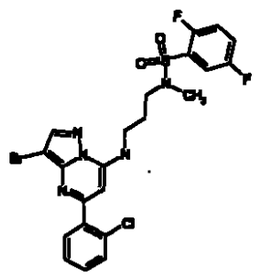
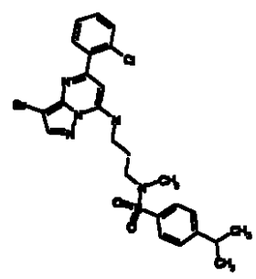
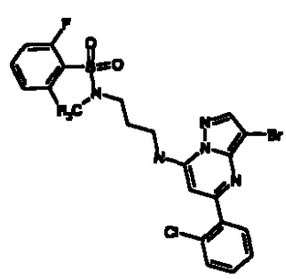
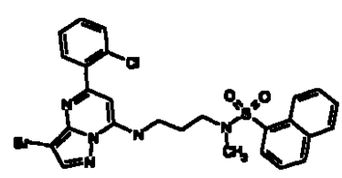
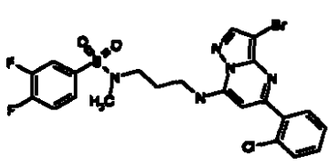
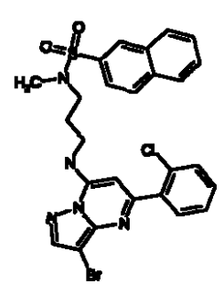
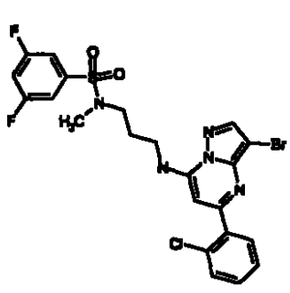
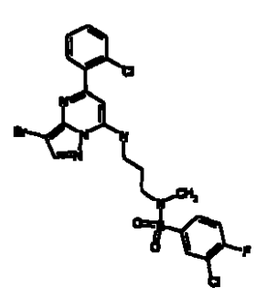
TABLA 68

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	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

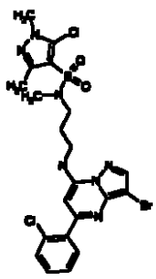
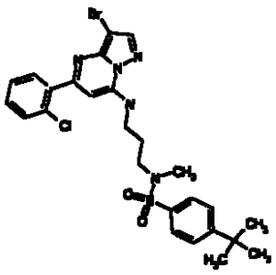
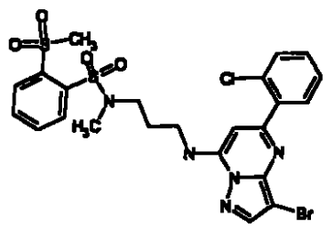
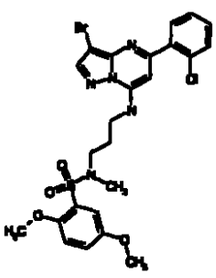
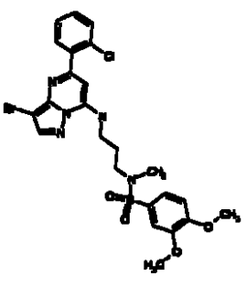
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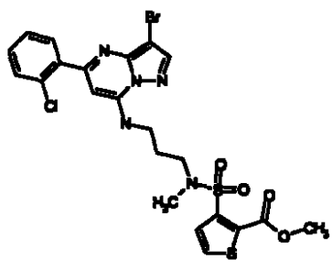
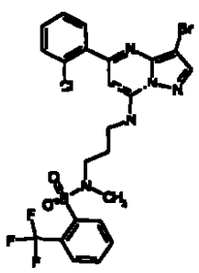
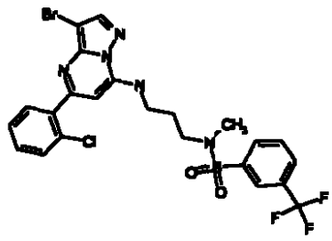
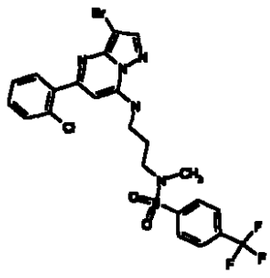
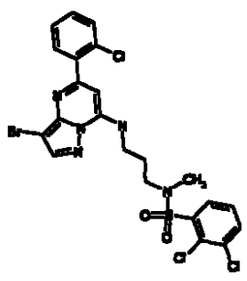
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6811 2. 561.31		1. 6816 2. 586.31
	1. 6812 2. 561.31		1. 6817 2. 588.31
	1. 6813 2. 562.31		1. 6818 2. 570.31
	1. 6814 2. 584.31		1. 6819 2. 570.31
	1. 6815 2. 566.31		1. 6820 2. 570.31

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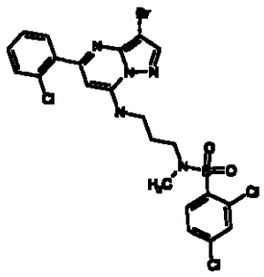
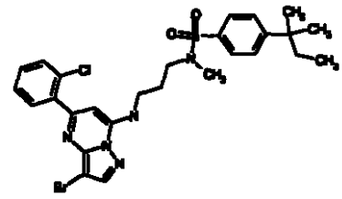
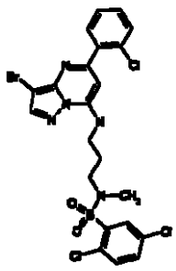
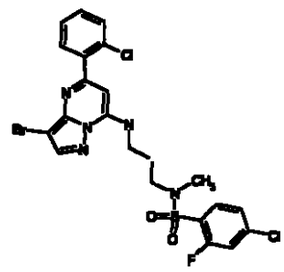
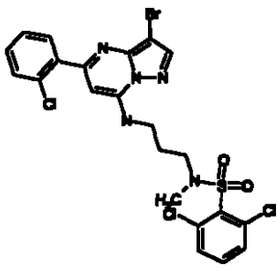
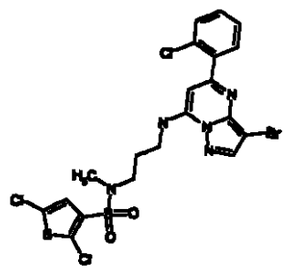
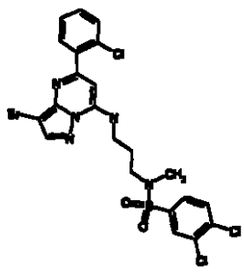
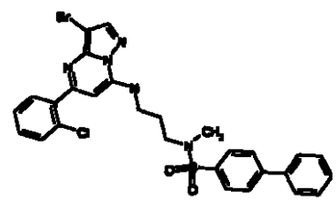
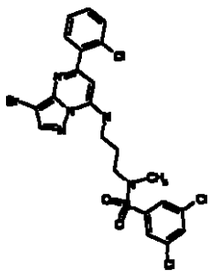
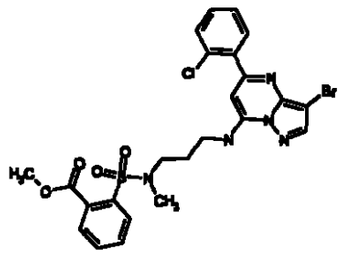
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	1. 6822 2. 572.31		1. 6827 2. 578.32
	1. 6823 2. 572.31		1. 6828 2. 586.32
	1. 6824 2. 572.31		1. 6829 2. 586.32
	1. 6825 2. 572.31		1. 6830 2. 588.32

840

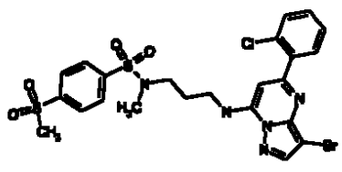
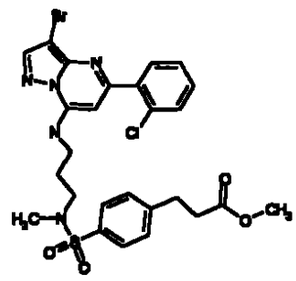
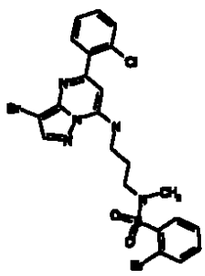
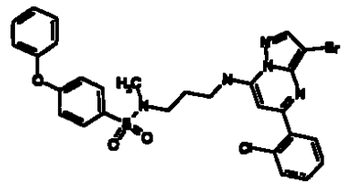
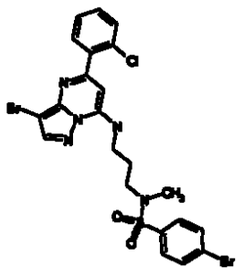
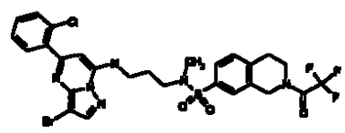
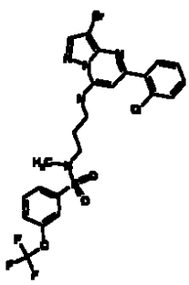
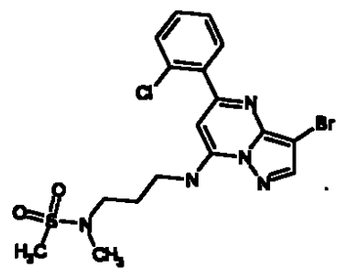
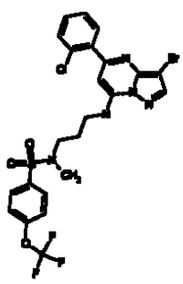
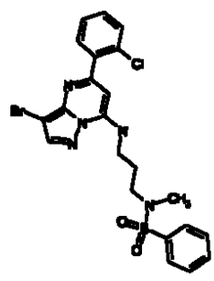
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	1. 6832 2. 592.33
	1. 6833 2. 614.34
	1. 6834 2. 596.33
	1. 6835 2. 596.33

Producto	1. Ej. 2. m/z
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	1. 6837 2. 602.33
	1. 6838 2. 604.33
	1. 6839 2. 604.33
	1. 6840 2. 604.33

841

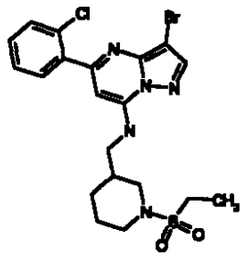
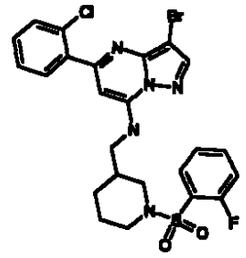
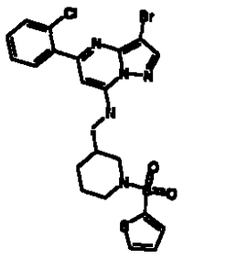
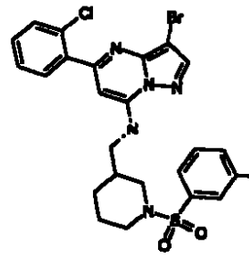
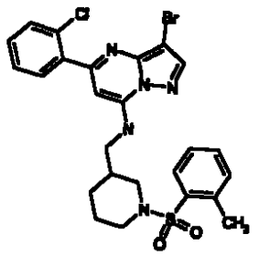
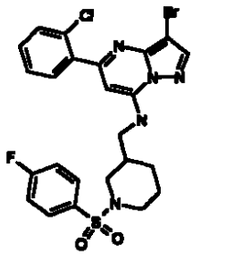
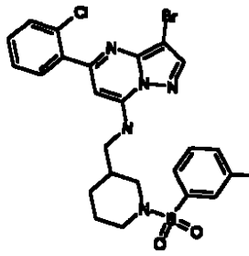
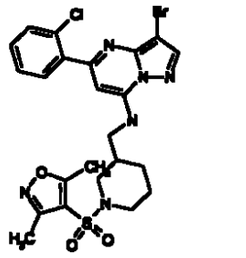
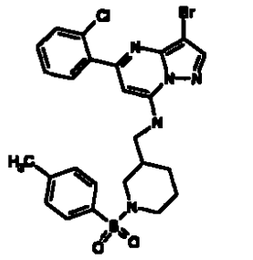
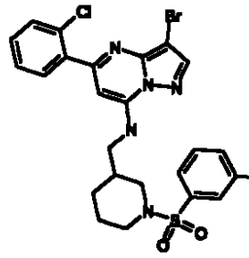
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 6842 2. 604.33		1. 6847 2. 588.32
	1. 6843 2. 605.33		1. 6848 2. 610.34
	1. 6844 2. 604.33		1. 6849 2. 612.34
	1. 6845 2. 604.33		1. 6850 2. 594.33

892

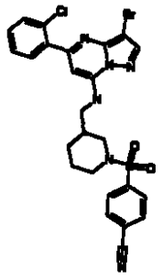
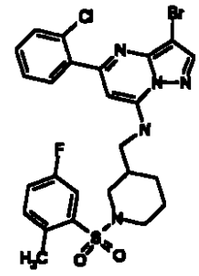
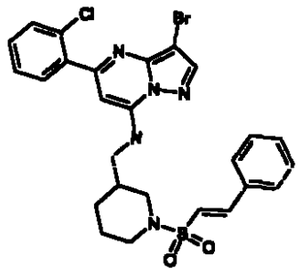
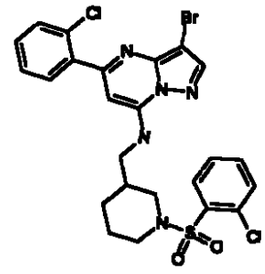
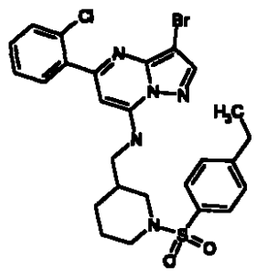
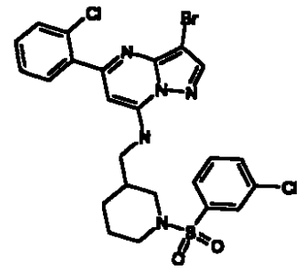
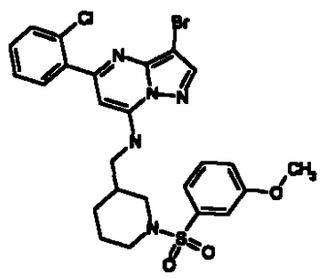
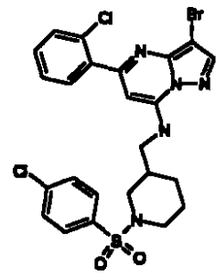
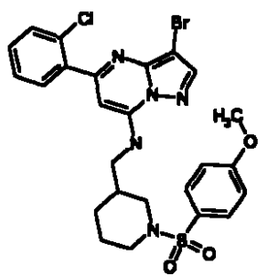
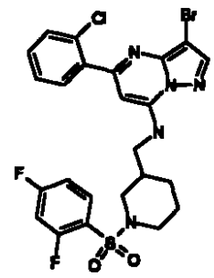
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6851 2. 614.34		1. 6856 2. 620.34
	1. 6852 2. 614.34		1. 6856 2. 628.35
	1. 6853 2. 614.34		1. 6857 2. 687.38
	1. 6854 2. 620.34		1. 6859 2. 474.26
	1. 6855 2. 620.34		1. 6860 2. 536.29

843

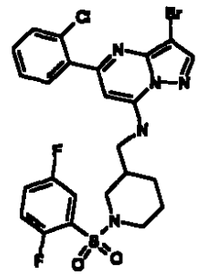
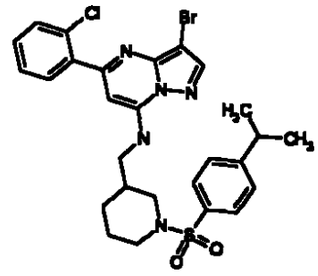
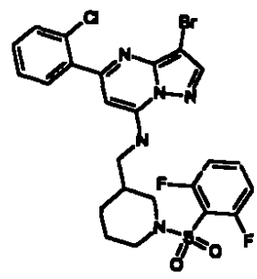
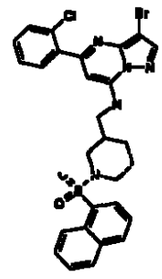
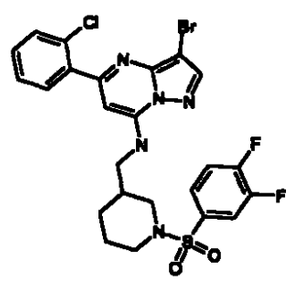
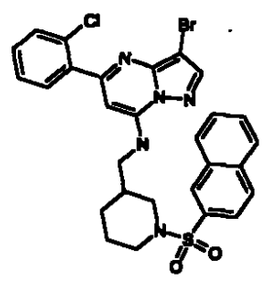
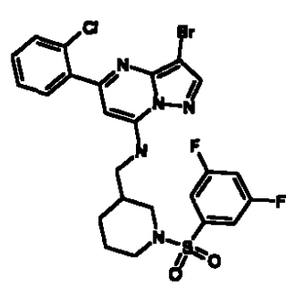
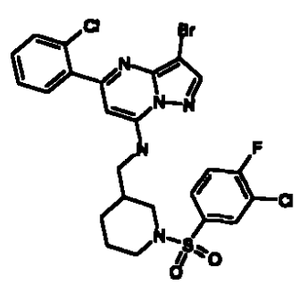
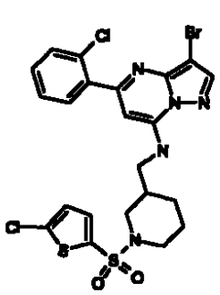
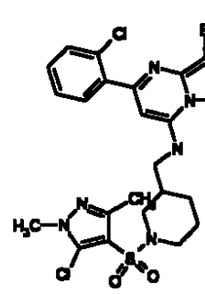
TABLA 69

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	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

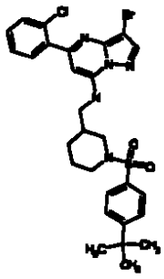
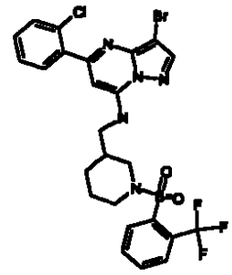
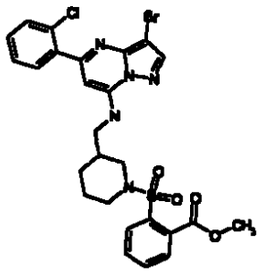
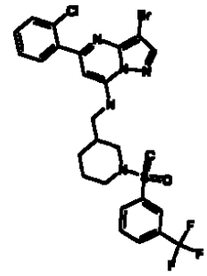
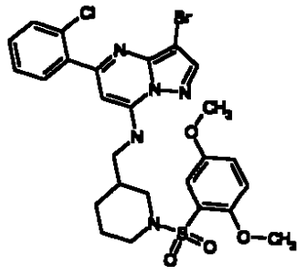
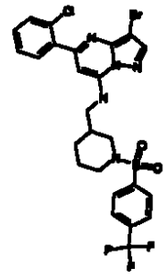
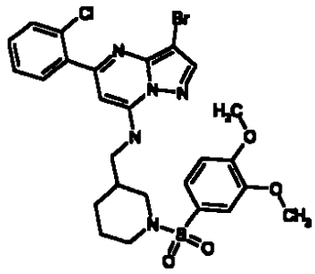
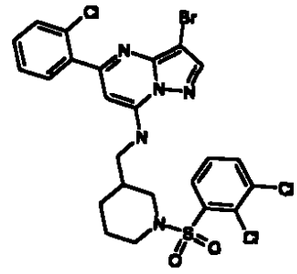
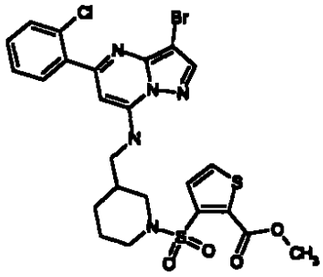
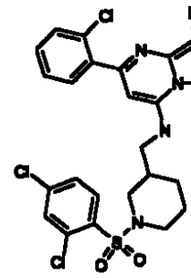
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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 6912 2. 588.32		1. 6917 2. 596.33
	1. 6913 2. 590.32		1. 6918 2. 596.33
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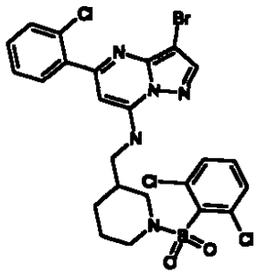
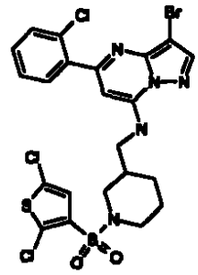
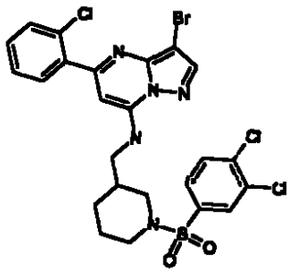
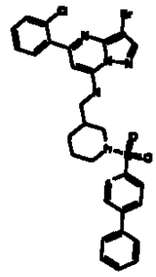
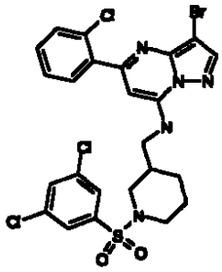
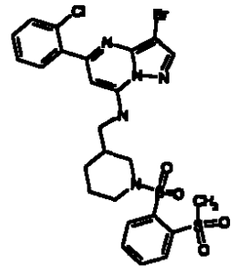
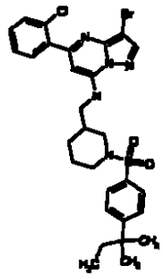
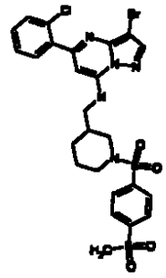
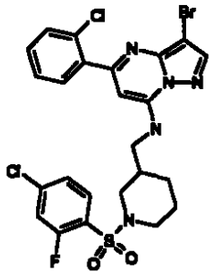
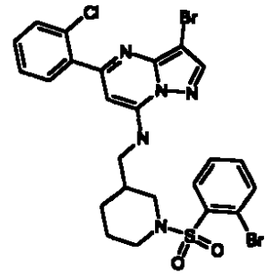
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	1. 6923 2. 598.33		1. 6928 2. 612.34
	1. 6924 2. 598.33		1. 6929 2. 614.34
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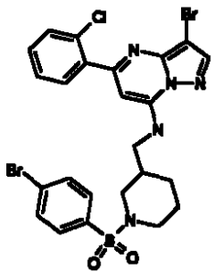
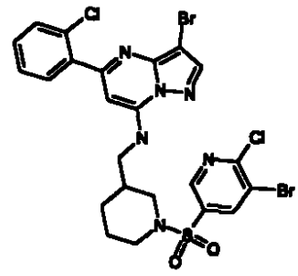
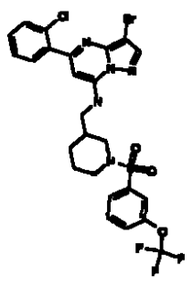
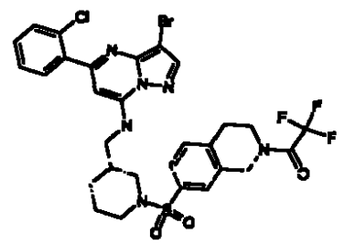
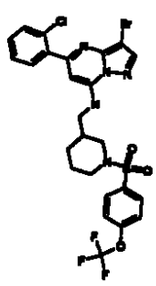
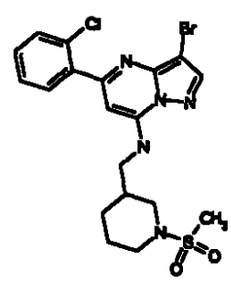
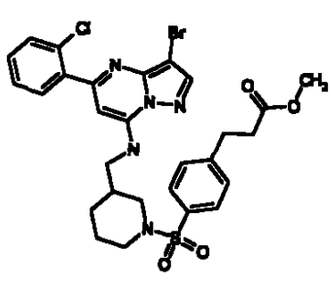
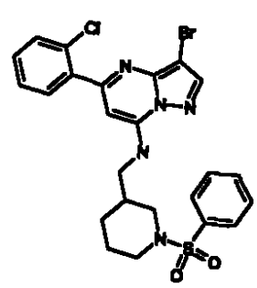
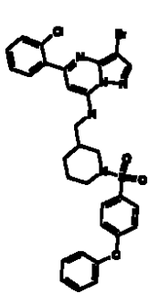
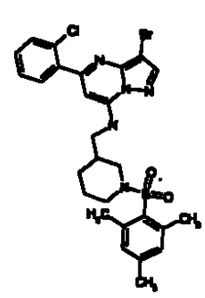
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	1. 6932 2. 620.34		1. 6937 2. 630.35
	1. 6933 2. 622.34		1. 6938 2. 630.35
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897

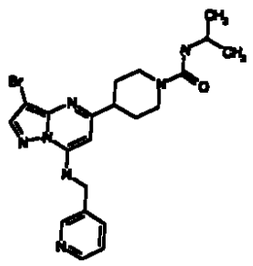
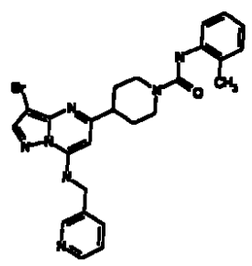
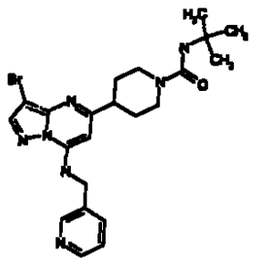
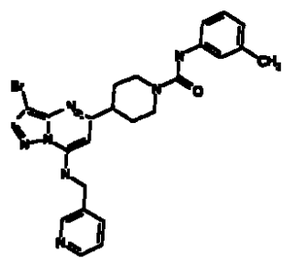
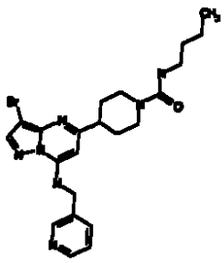
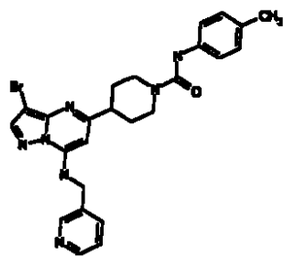
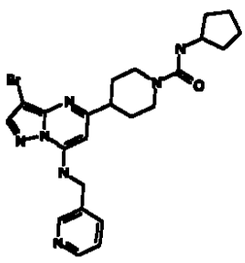
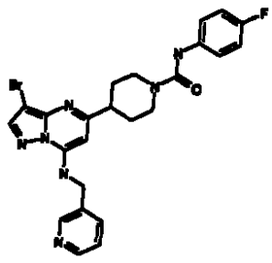
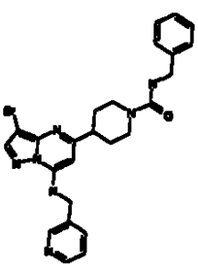
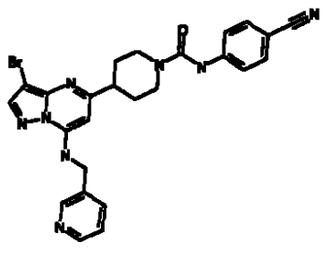
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	1. 6942 2. 630.35		1. 6947 2. 636.35
	1. 6943 2. 630.35		1. 6948 2. 640.35
	1. 6944 2. 632.35		1. 6949 2. 640.35
	1. 6945 2. 614.34		1. 6950 2. 640.35

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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	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
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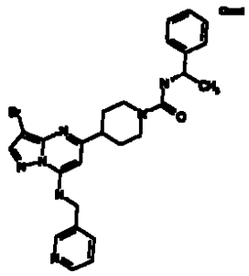
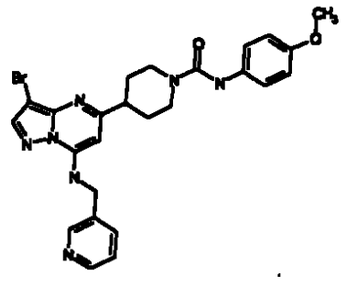
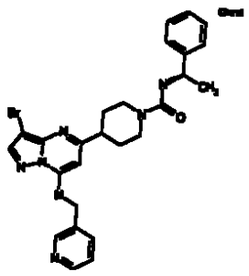
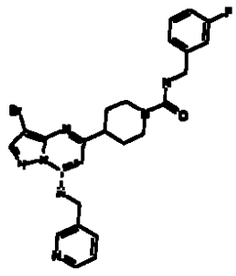
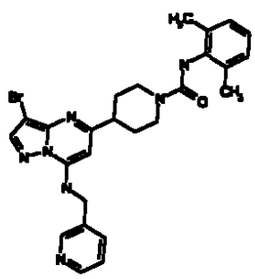
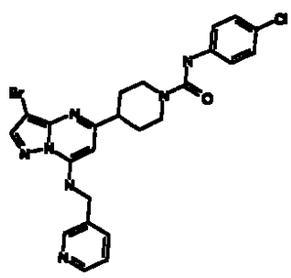
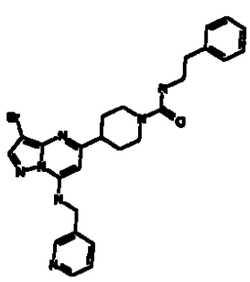
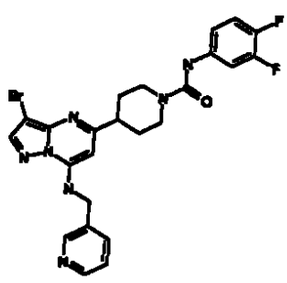
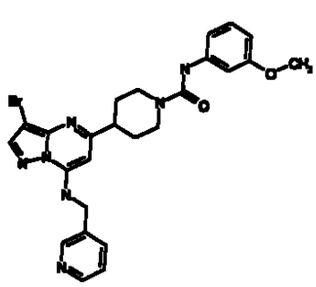
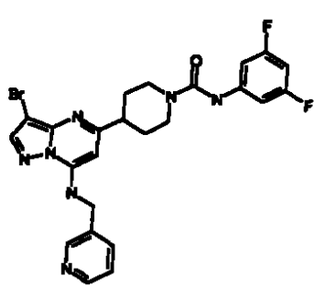
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TABLA 70

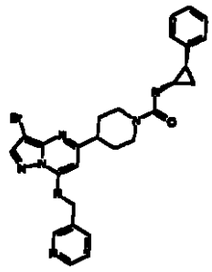
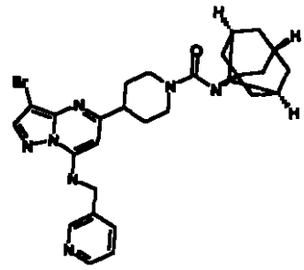
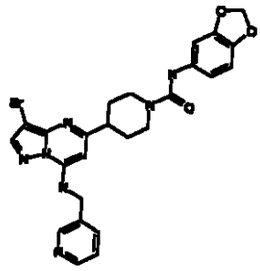
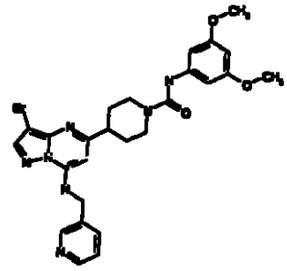
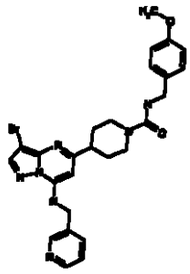
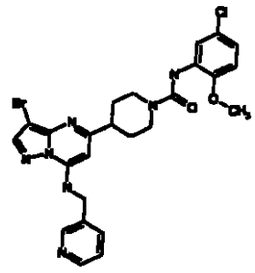
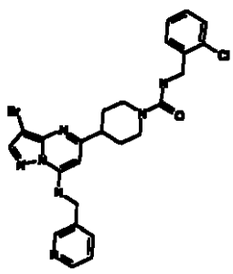
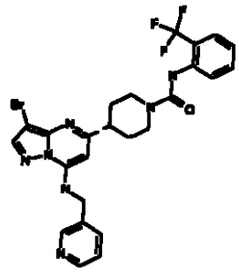
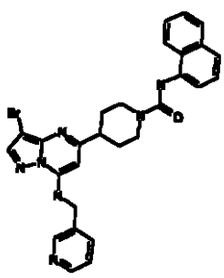
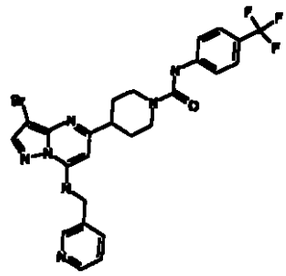
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 7003 2. 488.27		1. 7008 2. 520.29
	1. 7004 2. 500.27		1. 7009 2. 526.29
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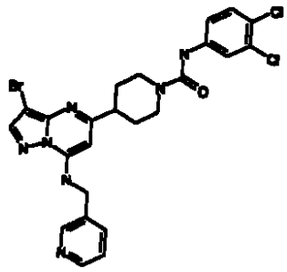
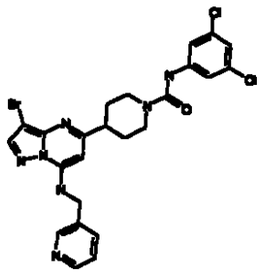
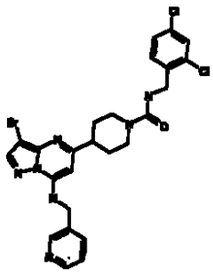
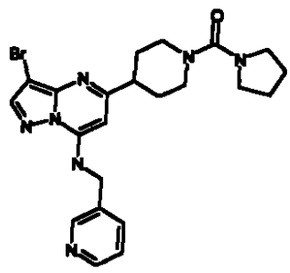
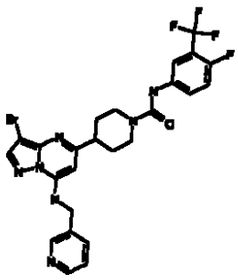
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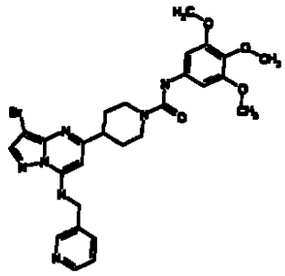
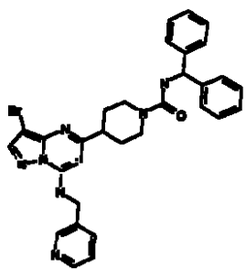
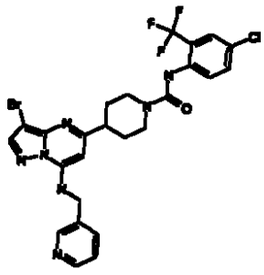
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	1. 7012 2. 536.29		1. 7017 2. 540.3
	1. 7013 2. 536.29		1. 7018 2. 542.3
	1. 7014 2. 536.29		1. 7019 2. 544.3
	1. 7015 2. 536.29		1. 7020 2. 544.3

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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

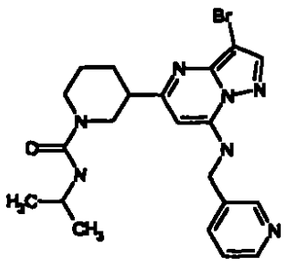
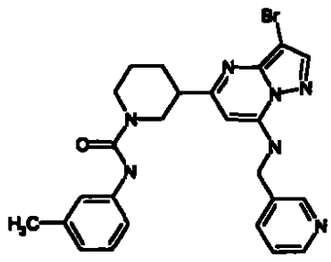
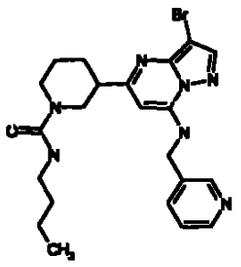
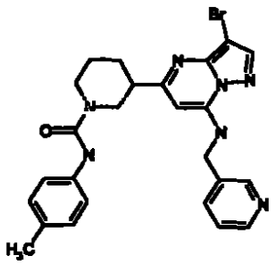
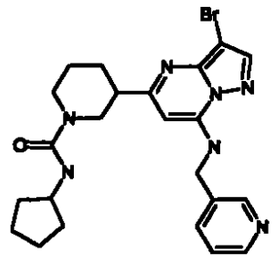
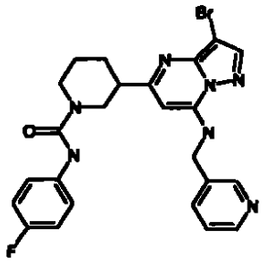
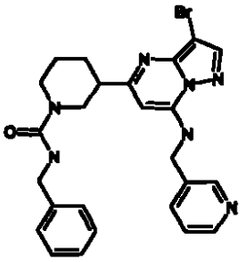
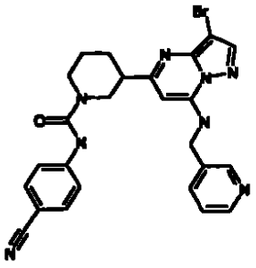
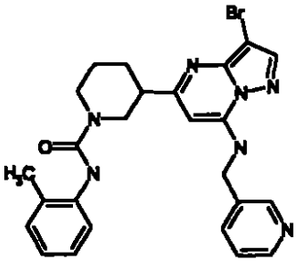
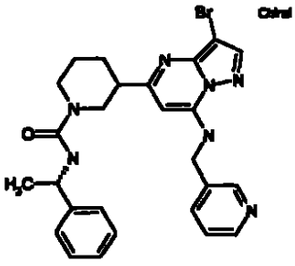
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Producto	1. Ej. 2. m/z
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	1. 7032 2. 576.32
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	1. 7034 2. 486.27
	1. 7035 2. 594.33

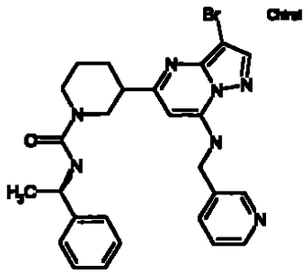
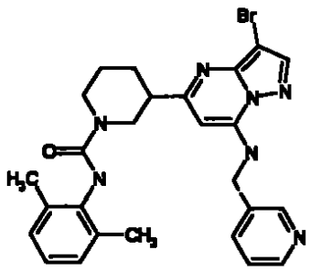
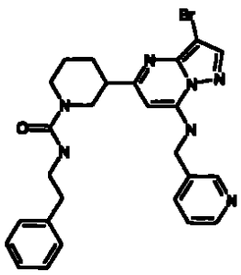
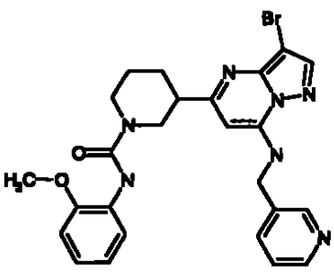
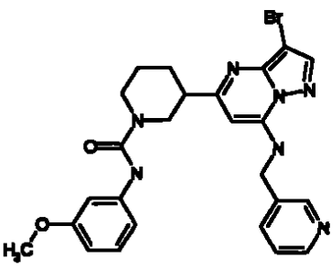
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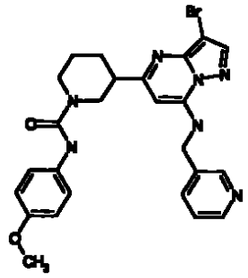
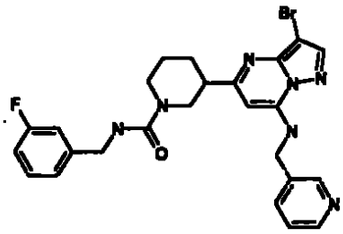
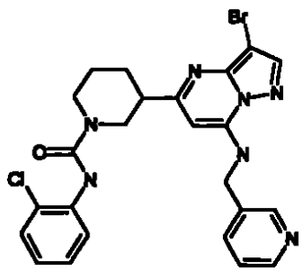
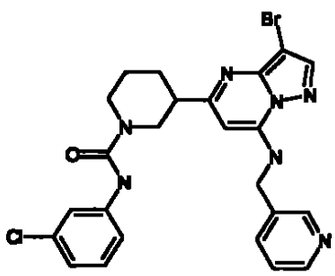
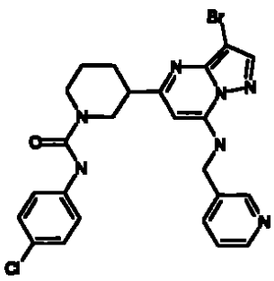
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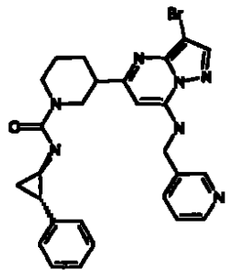
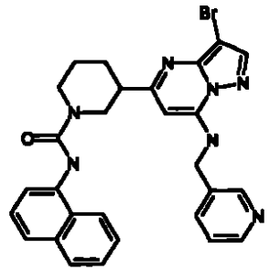
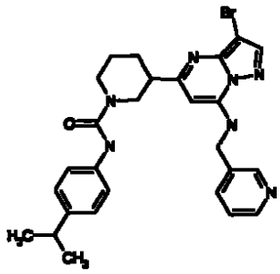
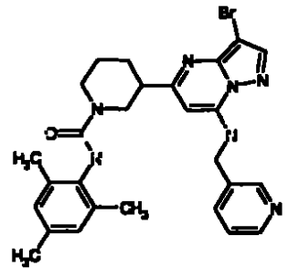
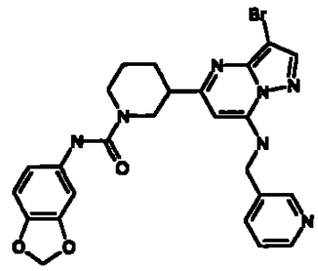
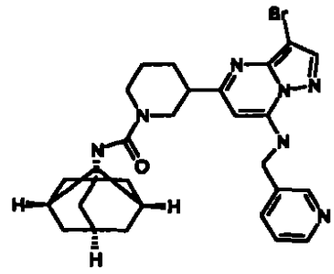
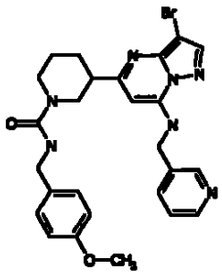
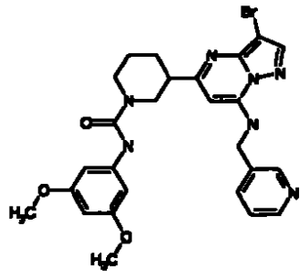
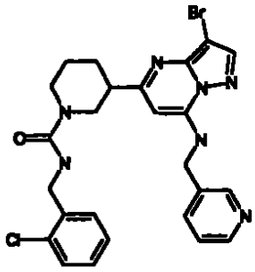
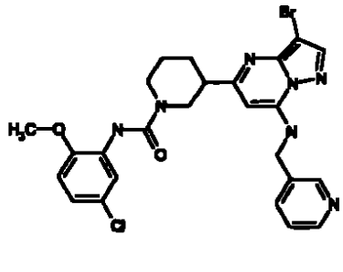
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	1. 7102 2. 488.27		1. 7107 2. 522.29
	1. 7103 2. 500.27		1. 7108 2. 526.3
	1. 7104 2. 522.29		1. 7109 2. 533.29
	1. 7105 2. 522.29		1. 7110 2. 536.29

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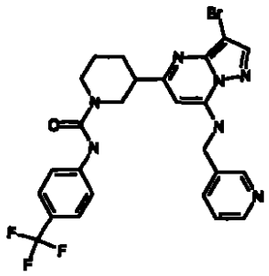
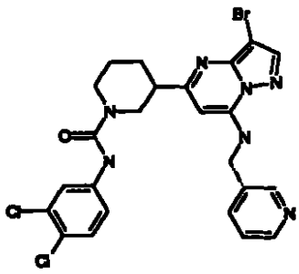
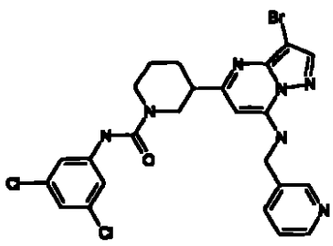
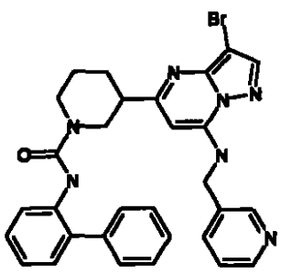
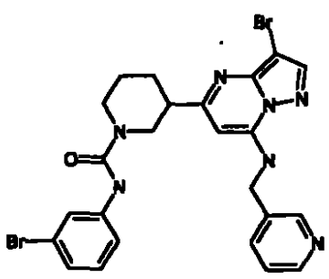
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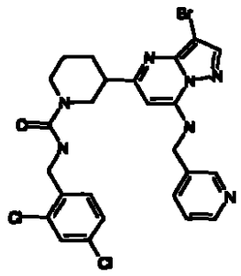
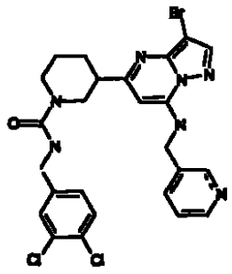
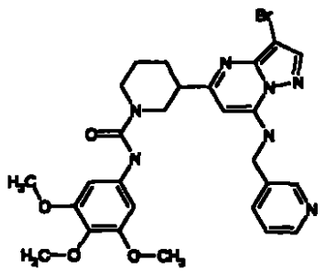
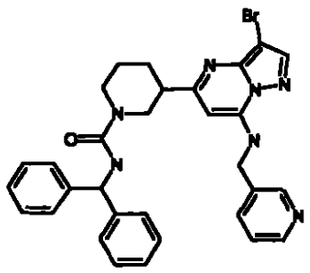
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	1. 7118 2. 542.3
	1. 7119 2. 542.3
	1. 7120 2. 542.3

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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

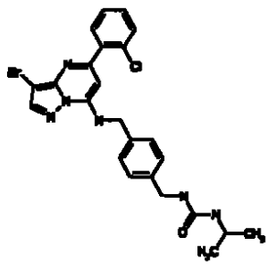
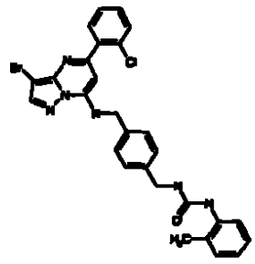
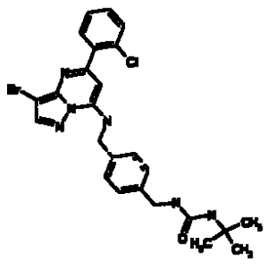
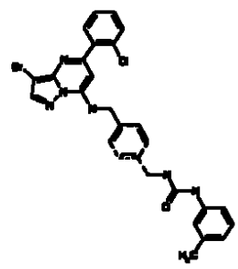
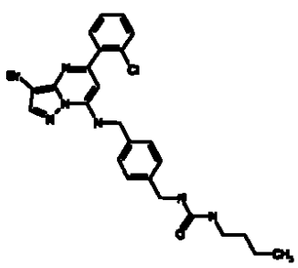
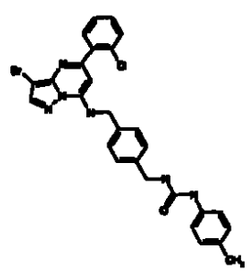
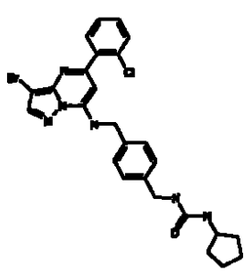
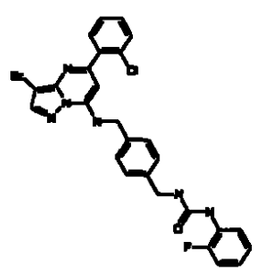
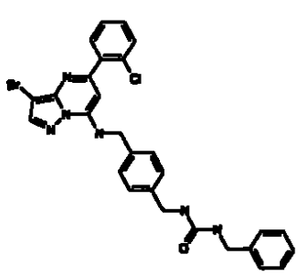
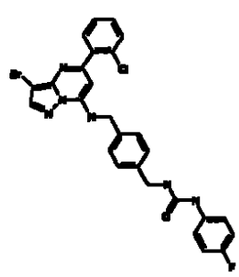
856

Producto	1. Ej. 2. m/z
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	1. 7132 2. 576.32
	1. 7133 2. 576.32
	1. 7134 2. 584.32
	1. 7135 2. 585.3

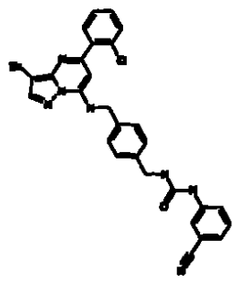
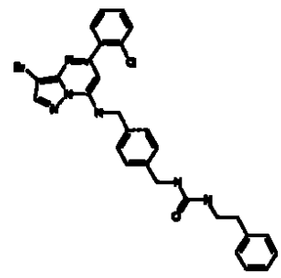
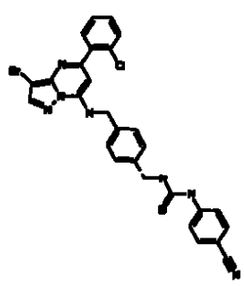
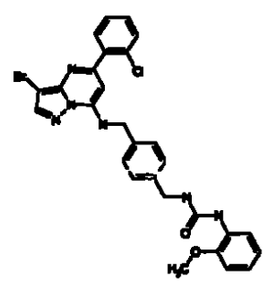
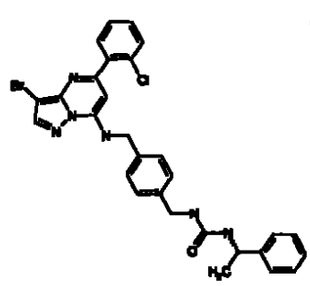
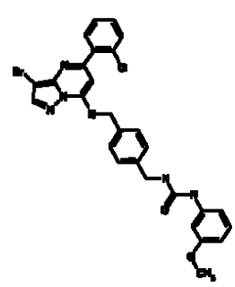
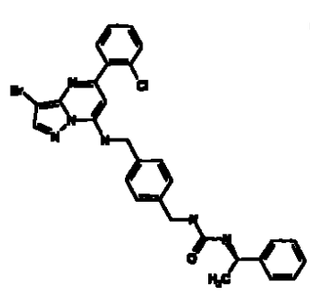
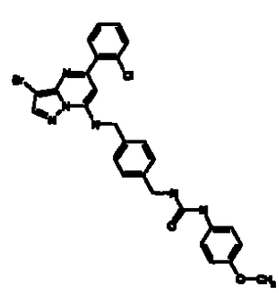
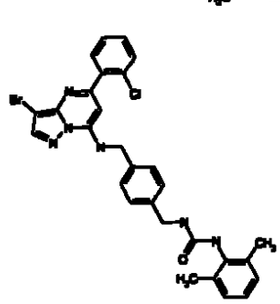
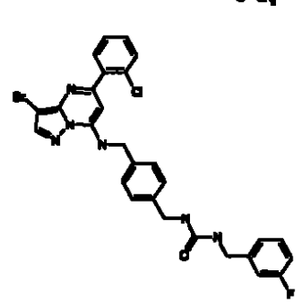
Producto	1. Ej. 2. m/z
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	1. 7137 2. 590.32
	1. 7138 2. 598.33
	1. 7139 2. 598.33

857

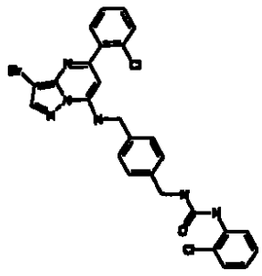
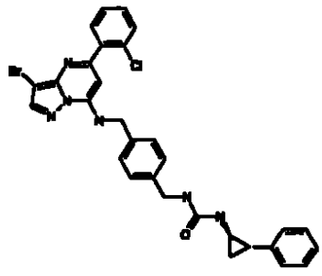
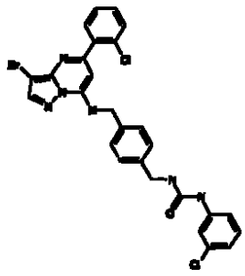
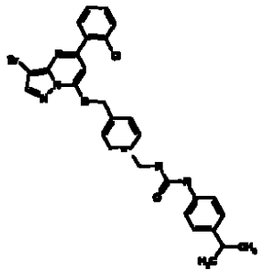
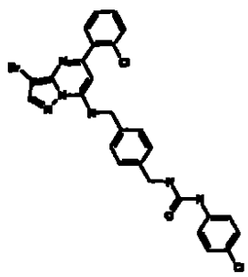
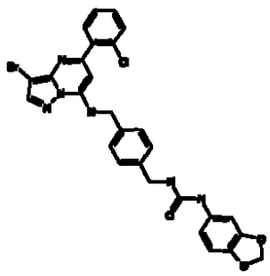
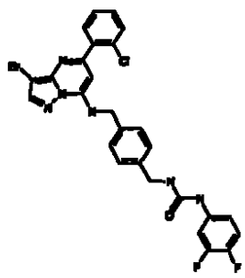
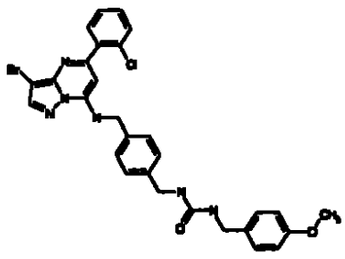
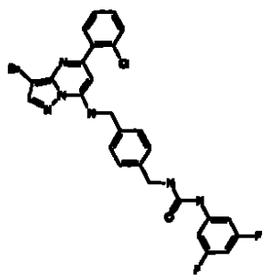
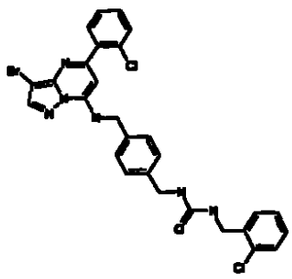
TABLA 72

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

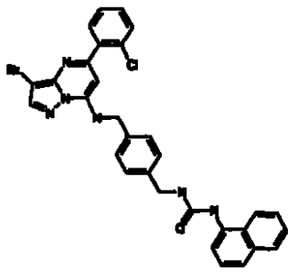
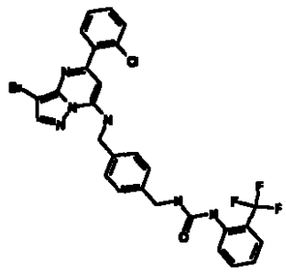
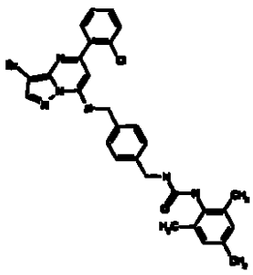
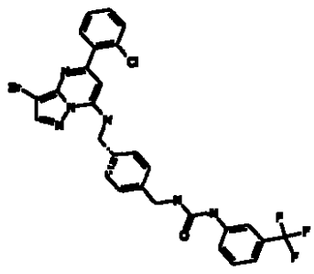
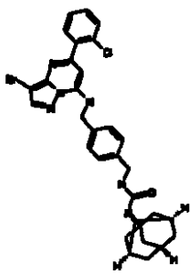
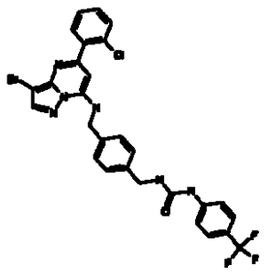
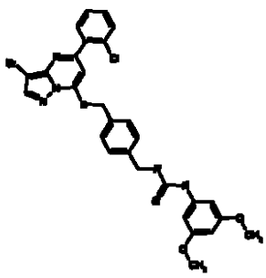
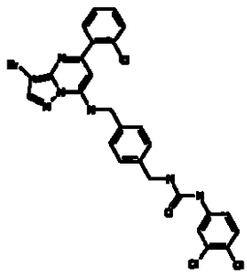
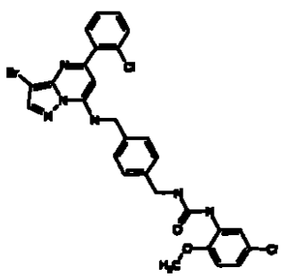
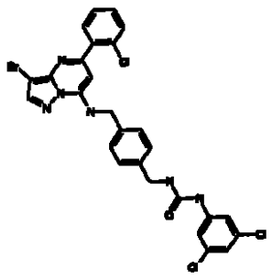
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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7211 2. 588.32		1. 7216 2. 591.33
	1. 7212 2. 588.32		1. 7217 2. 593.33
	1. 7213 2. 591.33		1. 7218 2. 593.33
	1. 7214 2. 591.33		1. 7219 2. 593.33
	1. 7215 2. 591.33		1. 7220 2. 595.33

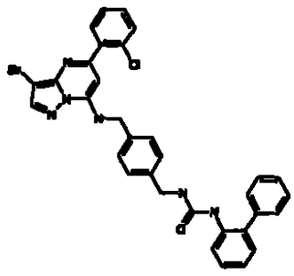
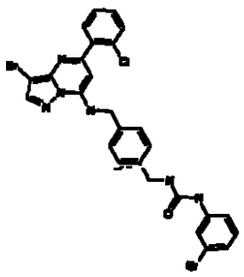
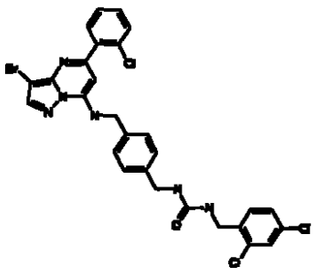
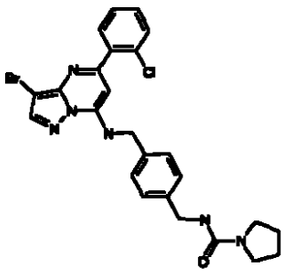
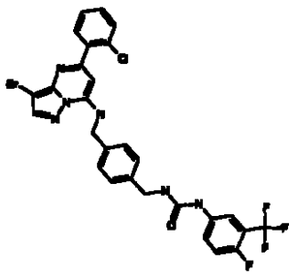
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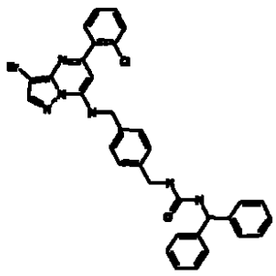
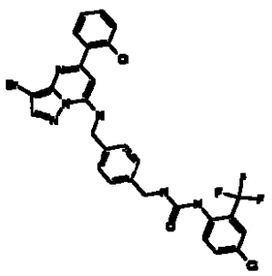
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	1. 7222 2. 597.33		1. 7227 2. 603:33
	1. 7223 2. 597.33		1. 7228 2. 607.33
	1. 7224 2. 599.33		1. 7229 2. 607.14
	1. 7225 2. 599.33		1. 7230 2. 611.34

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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

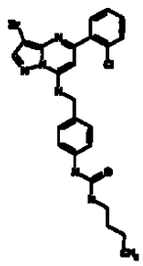
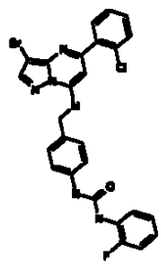
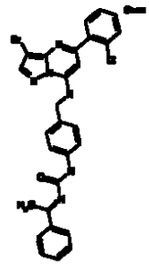
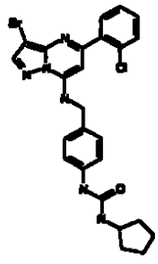
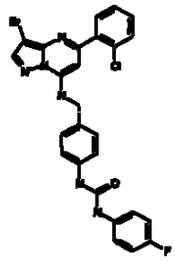
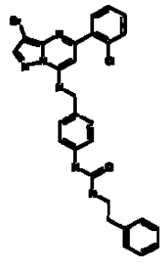
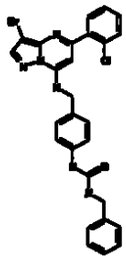
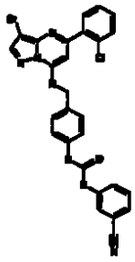
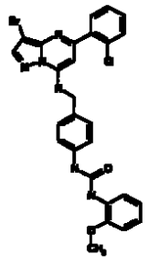
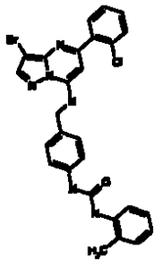
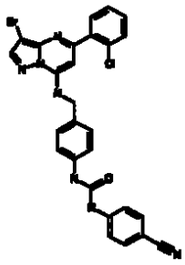
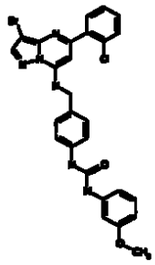
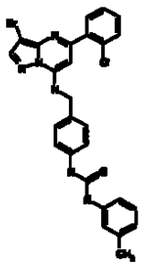
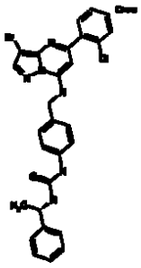
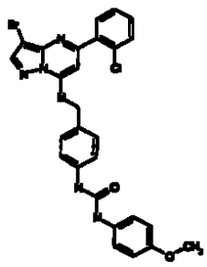
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	1. 7245 2. 649.36

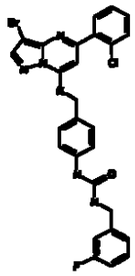
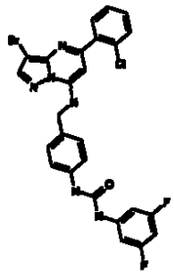
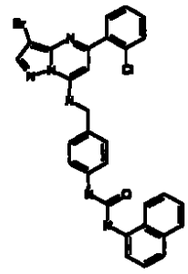
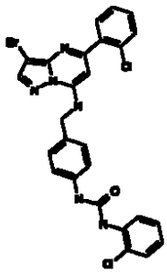
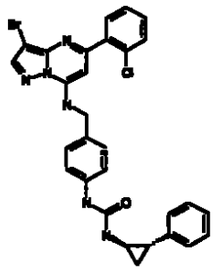
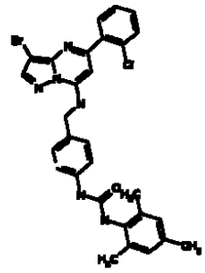
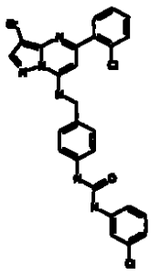
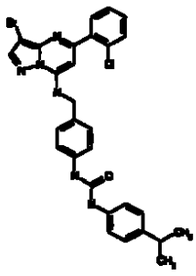
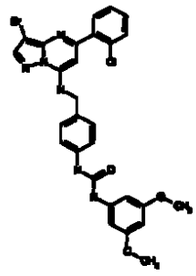
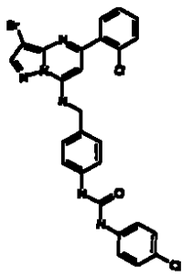
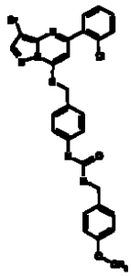
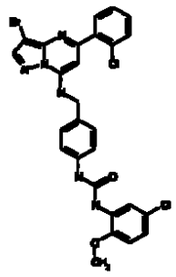
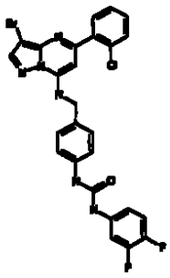
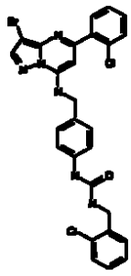
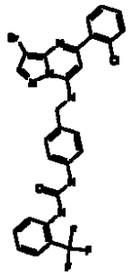
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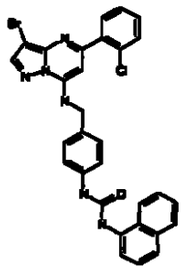
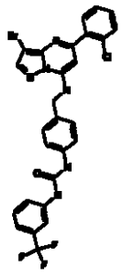
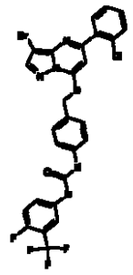
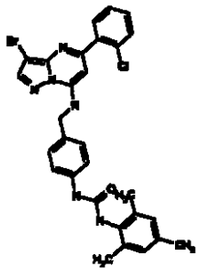
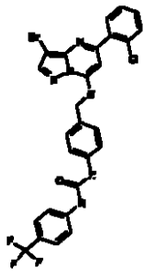
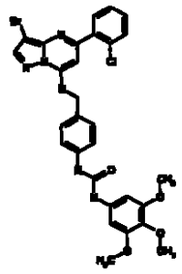
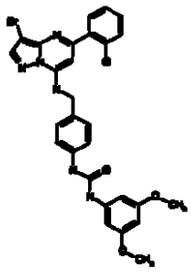
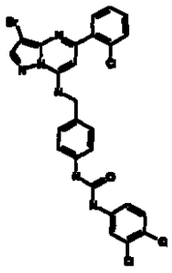
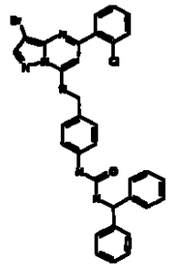
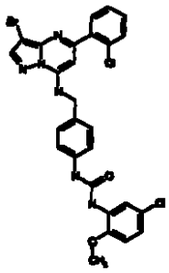
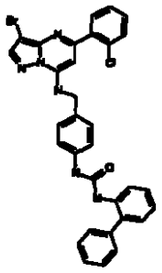
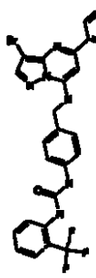
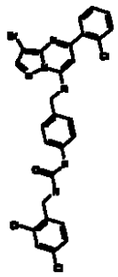
862

TABLA 73

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	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
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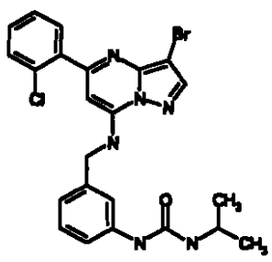
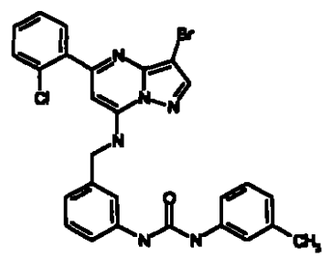
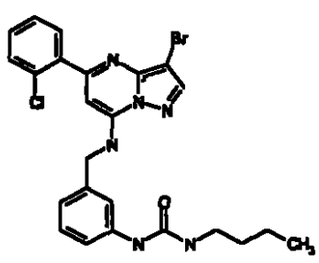
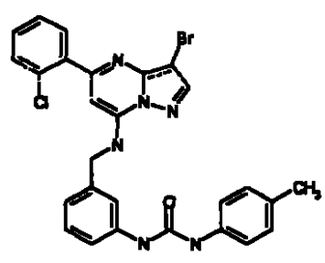
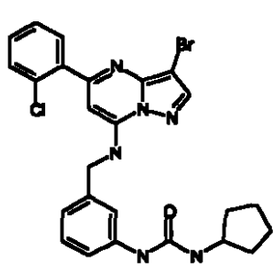
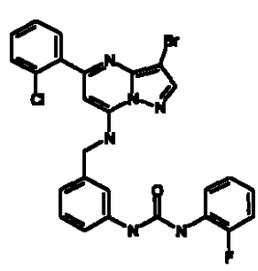
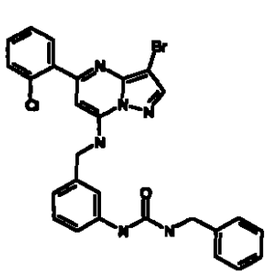
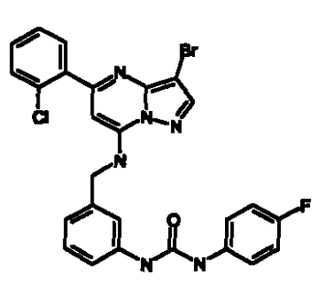
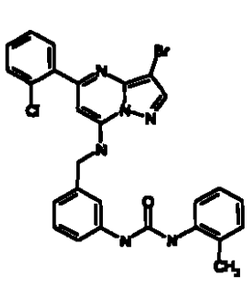
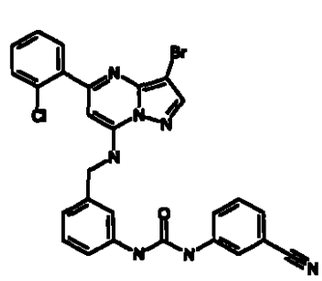
863
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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7316 2. 581.32		1. 7321 2. 585.32		1. 7326 2. 599.33
	1. 7317 2. 583.32		1. 7322 2. 589.32		1. 7327 2. 591.33
	1. 7318 2. 583.32		1. 7323 2. 591.33		1. 7328
	1. 7319 2. 583.32		1. 7324 2. 593.33		1.7329 2. 613.34
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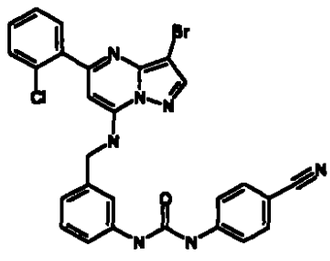
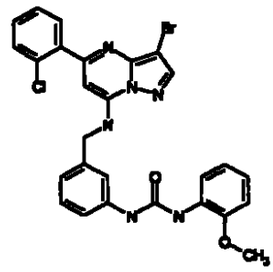
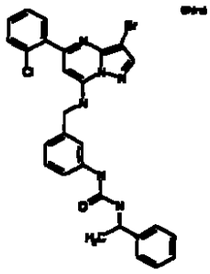
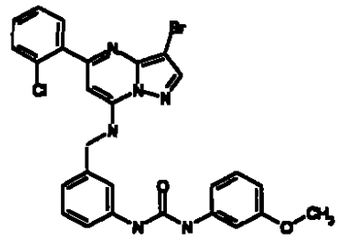
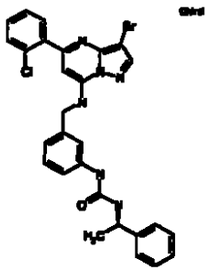
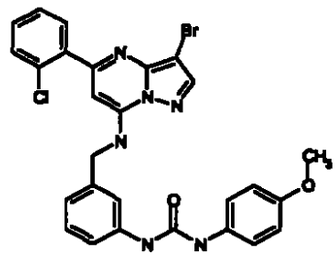
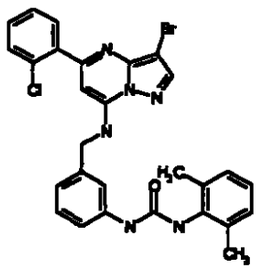
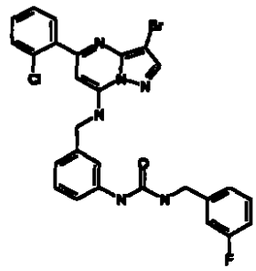
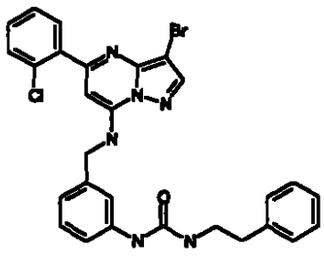
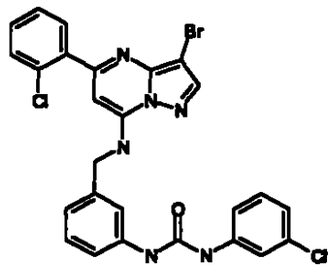
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7331 2. 599.33		1. 7336 2. 617.34		1. 73412. 635.35
	1. 7332 2. 591.33		1. 7337 2. 617.34		1. 7342 2. 639.35
	1. 7333 2. 609.33		1. 7338 2. 617.34		1. 7343 2. 639.35
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865

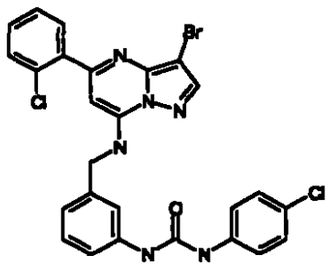
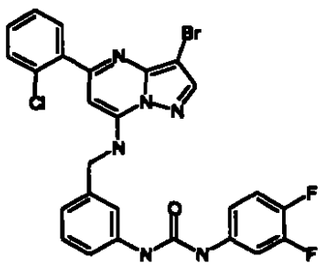
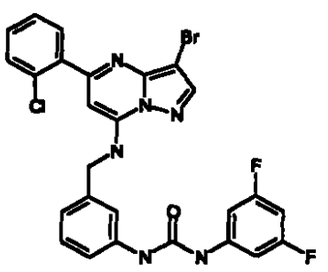
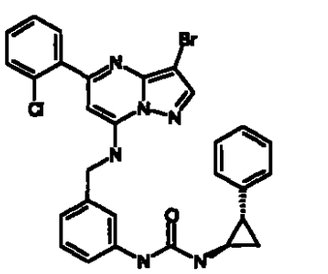
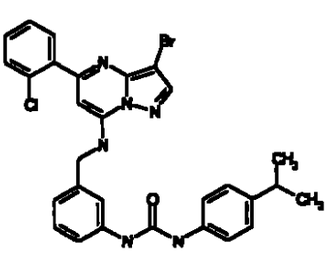
TABLA 74

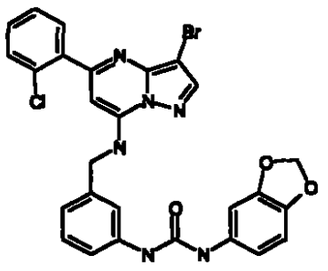
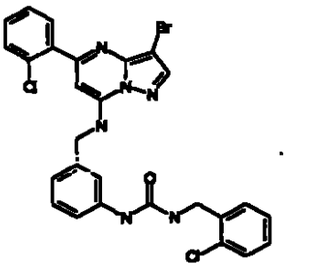
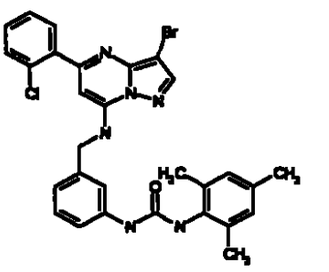
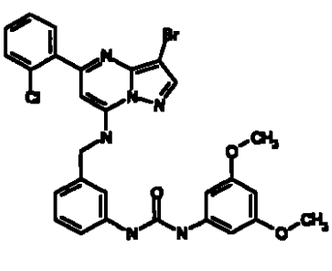
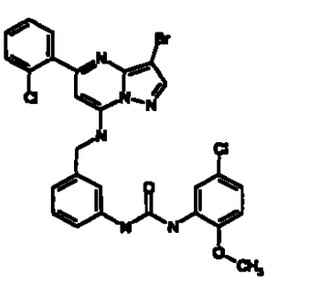
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	1. 7401 2. 515.28		1. 7406 2. 563.31
	1. 7402 2. 529.29		1. 7407 2. 563.31
	1. 7403 2. 541.3		1. 7408 2. 567.31
	1. 7404 2. 563.13		1. 7409 2. 567.31
	1. 7405 2. 563.31		1. 7410 2. 574.32

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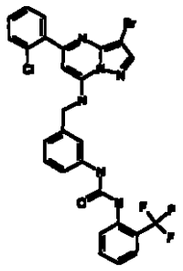
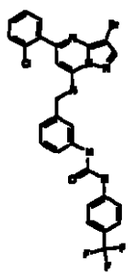
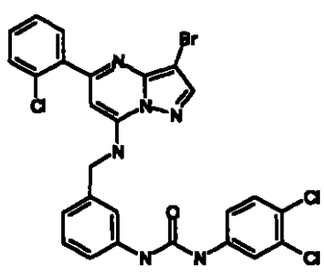
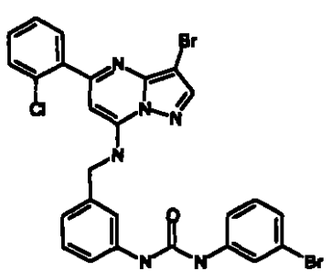
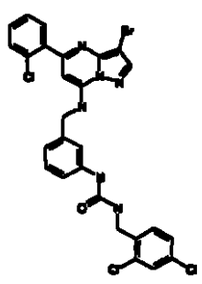
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7411 2. 574.32		1. 7416 2. 579.32
	1. 7412 2. 577.14		1. 741 7 2. 579.32
	1. 7413 2. 577.32		1. 7418 2. 579.32
	1. 7414 2. 577.32		1. 7419 2. 581.32
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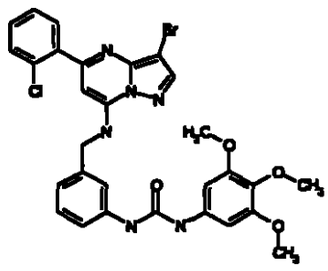
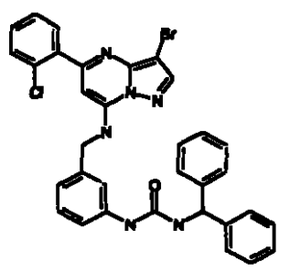
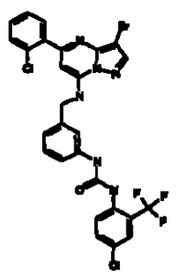
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Producto	1. Ej. 2. m/z
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	1. 7422 2. 585.32
	1. 7423 2. 585.32
	1. 7424 2. 589.32
	1. 7425 2. 591.33

Producto	1. Ej. 2. m/z
	1. 7426 2. 593.33
	1. 7427 2. 597.33
	1. 7428 2. 591.33
	1. 7429 2. 609.33
	1. 7430 2. 613.34

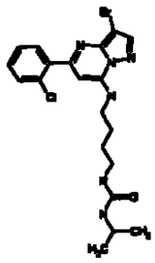
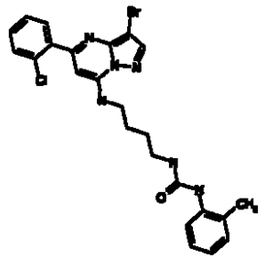
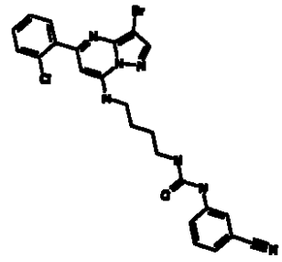
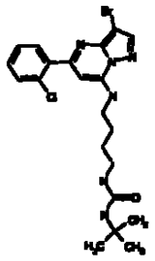
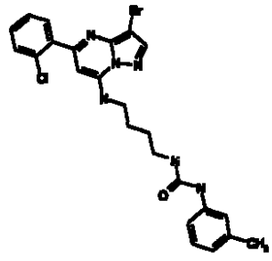
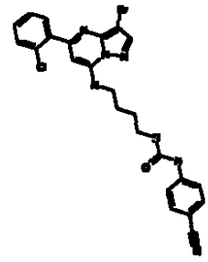
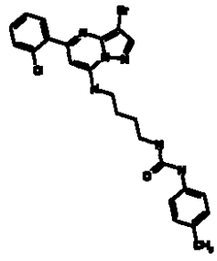
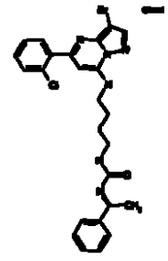
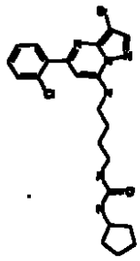
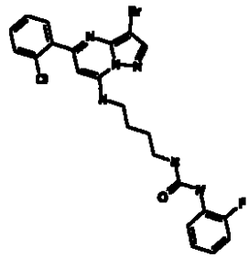
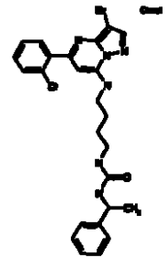
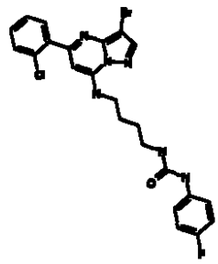
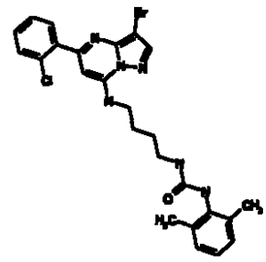
868

Producto	1. Ej. 2. m/z
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	1. 7432 2. 617.34
	1. 7433 2. 617.34
	1. 7434 2. 627.34
	1. 7435 2. 631.35

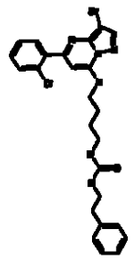
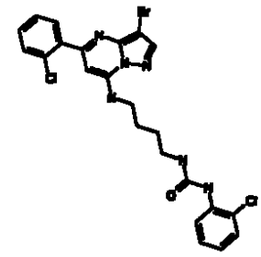
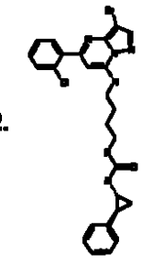
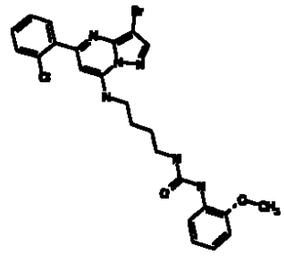
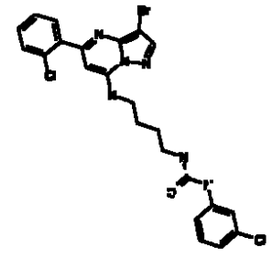
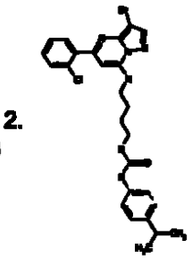
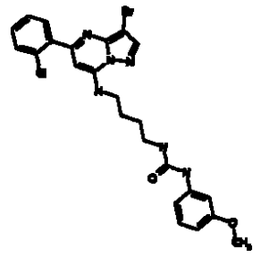
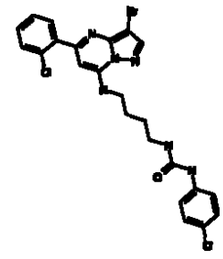
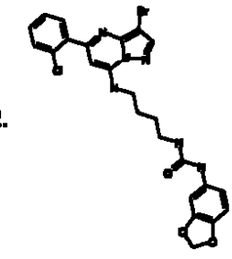
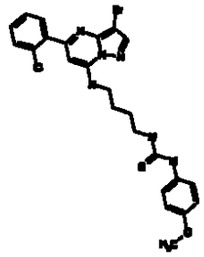
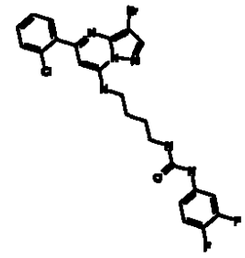
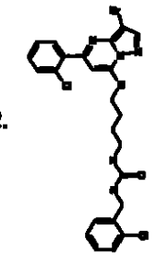
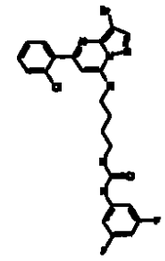
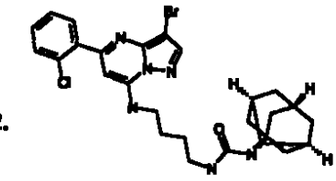
Producto	1. Ej. 2. m/z
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	1. 7437 2. 659.35
	1. 7438 2. 651.36

869/870

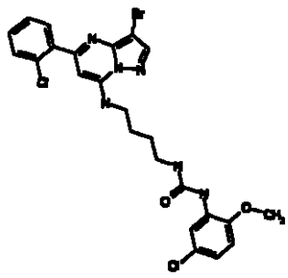
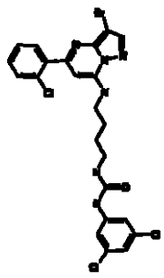
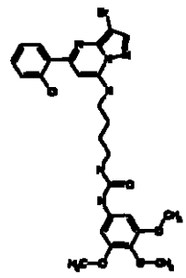
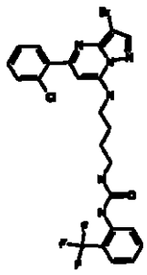
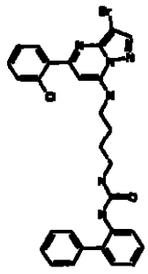
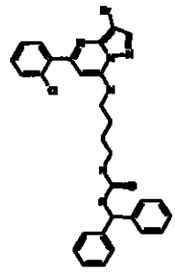
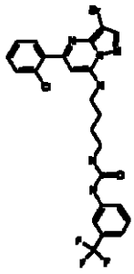
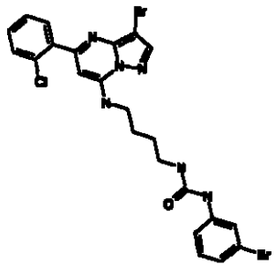
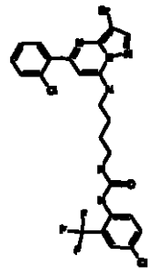
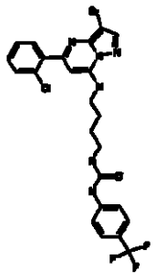
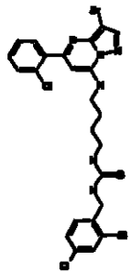
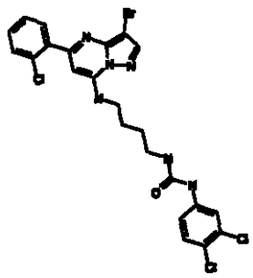
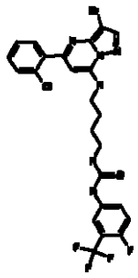
TABLA75

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	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

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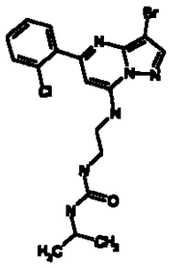
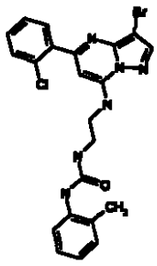
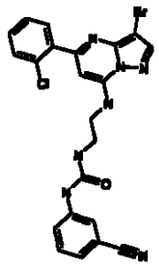
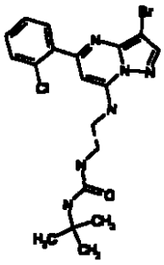
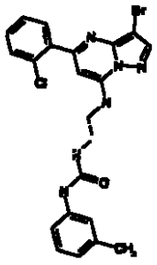
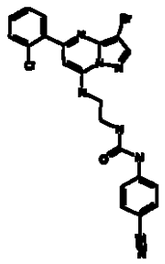
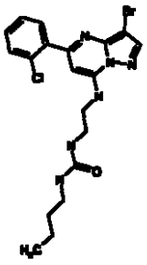
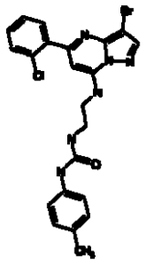
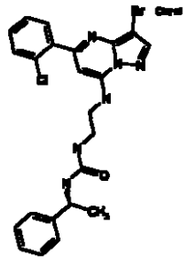
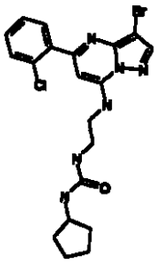
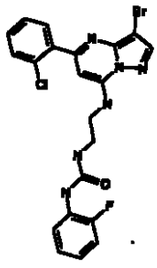
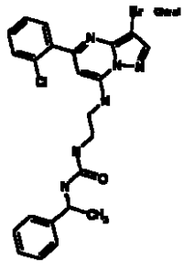
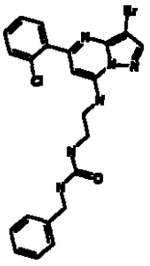
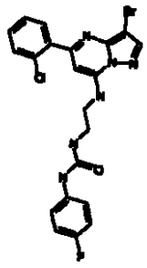
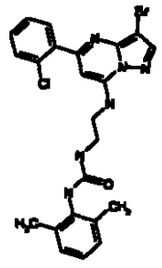
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2 m/z
	1. 7516 2. 543.3		1. 7521 2. 549.3		1. 7526 555.3
	1. 7517 2. 545.3		1. 7522 2. 549.3		1. 7527 557.3
	1. 7518 2. 545.3		1. 7523 2. 549.3		1. 7528 559.3
	1. 7519 2. 545.3		1. 7524 2. 551.3		1. 7529 560.3
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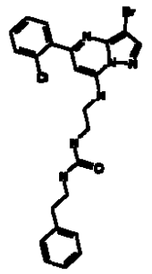
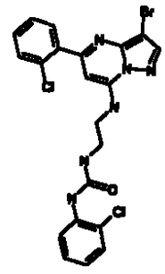
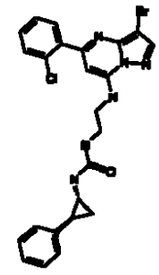
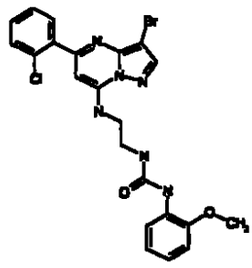
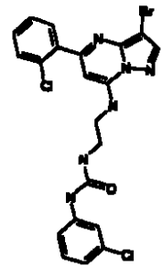
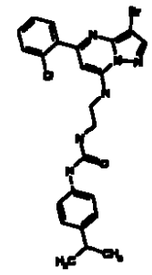
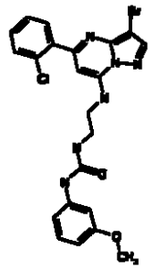
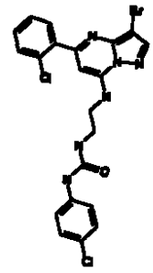
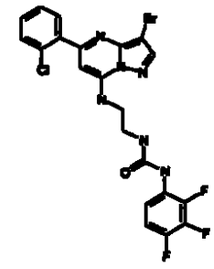
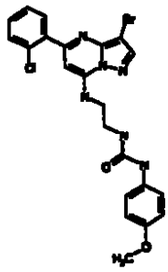
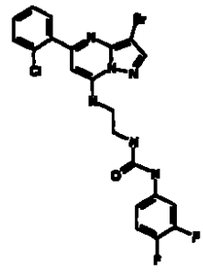
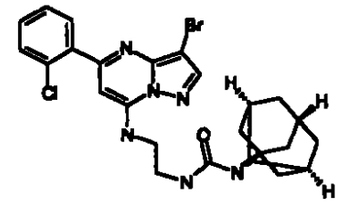
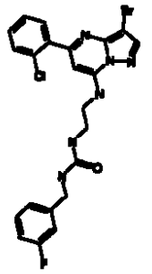
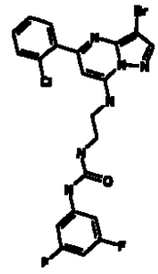
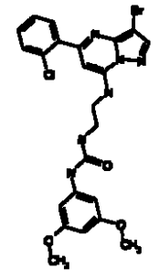
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7531 2. 579.32		1. 7536 2. 583.32		1. 7541 2. 605.33
	1. 7532 2. 583.32		1. 7537 2. 591.33		1. 7542 2. 605.33
	1. 7533 2. 583.32		1. 7538 2. 593.33		1. 7543 2. 614.34
	1. 7534 2. 583.32		1. 7539 2. 597.33		
	1. 7535 2. 583.32		1. 7540 2. 601.33		

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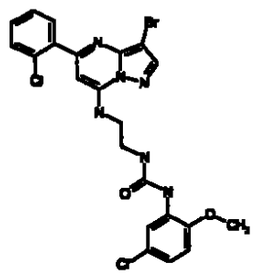
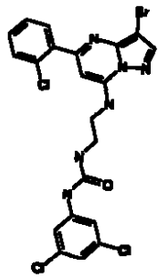
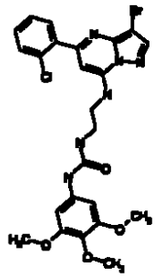
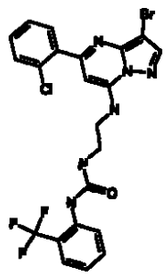
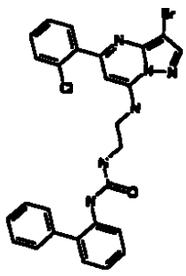
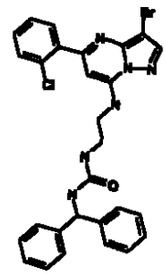
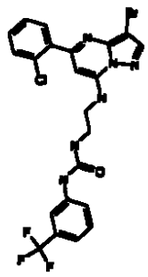
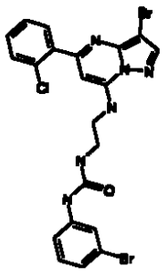
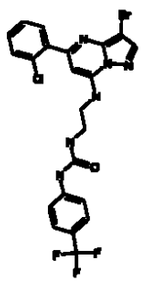
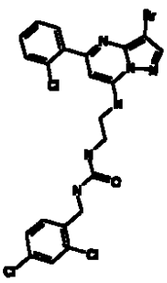
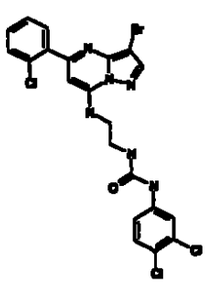
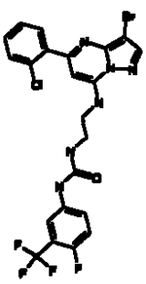
TABLA 76

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. 512.23
	1. 7603 2. 467.26		1. 7608 2.501.28		1. 7613 2. 515.28
	1. 7604 2. 479.26		1. 7609 2. 505.26		1. 7614 2. 515.28
	1. 7605 2. 501.28		1. 7610 2. 505.28		1. 7615 2. 515.28

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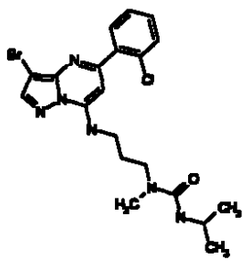
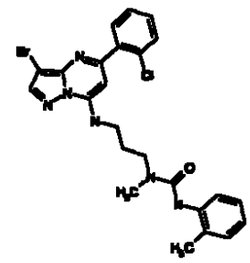
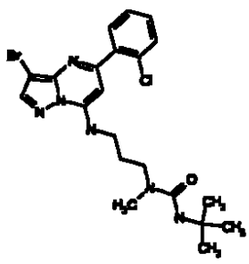
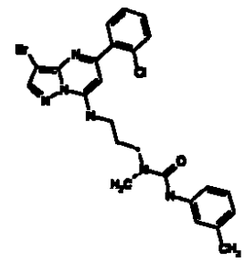
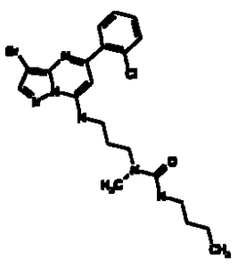
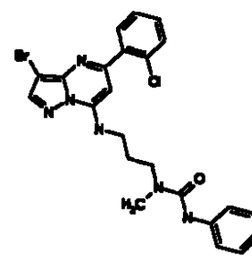
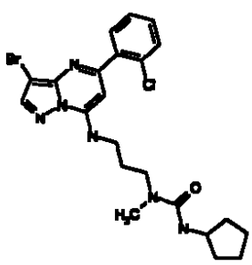
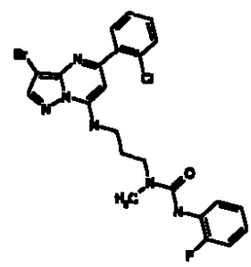
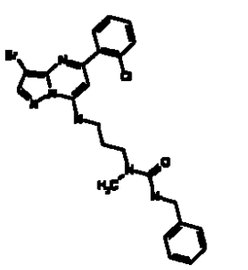
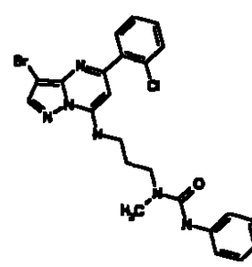
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	1. 761 6 2. 515.28		1. 7621 2. 521.29		1. 7626 2. 527.29
	1. 7617 2. 517.28		1. 7622 2. 521.29		1. 7627 2. 529.29
	1. 7618 2. 517.28		1. 7623 2. 521.29		1. 7628 2. 541.3
	1. 7619 2. 517.28		1. 7624 2. 523.29		1. 7629 2. 545.3
	1. 7620 2. 519.29		1. 7625 2. 523.29		1. 7630 2. 547.3

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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. 583.31		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		

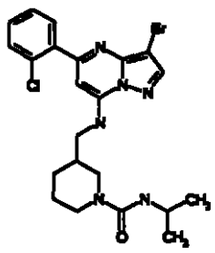
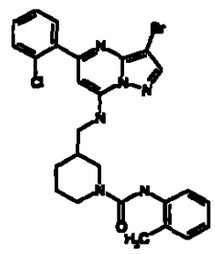
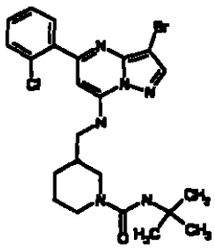
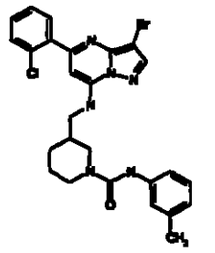
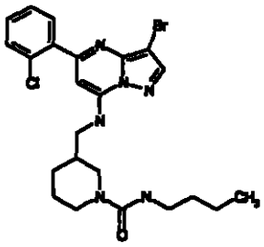
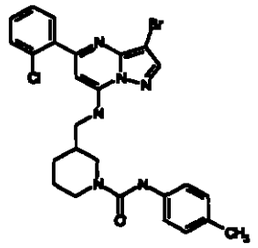
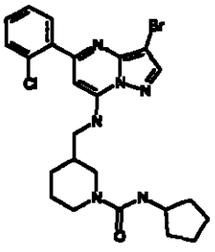
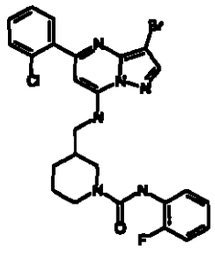
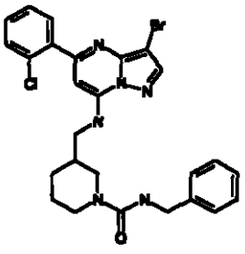
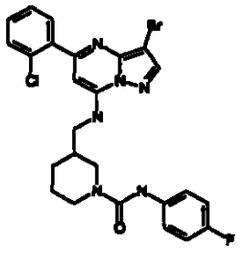
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TABLA 77

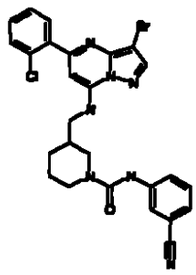
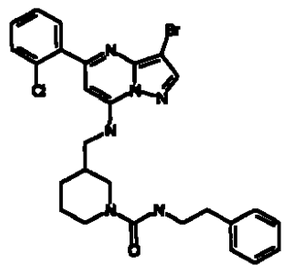
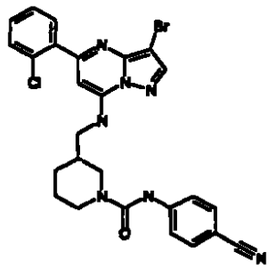
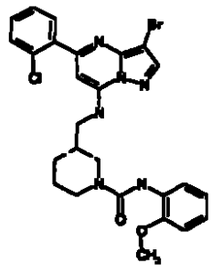
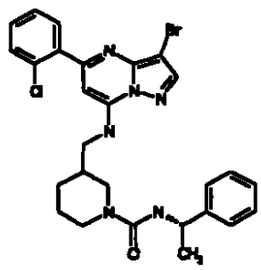
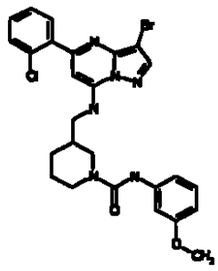
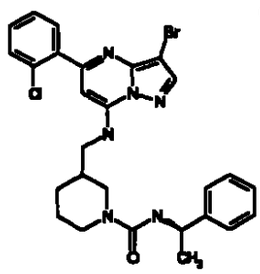
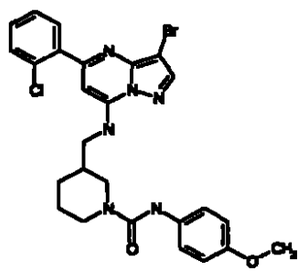
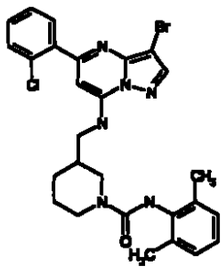
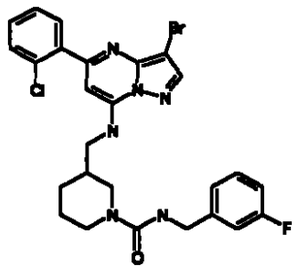
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7701 2. 481.26		1. 7706 2. 529.29
	1. 7702 2. 495.27		1. 7707 2. 529.29
	1. 7703 2. 495.27		1. 7708 2. 529.29
	1. 7704 2. 507.28		1. 7709 2. 533.29
	1. 7705 2. 529.29		1. 7710 2. 533.29

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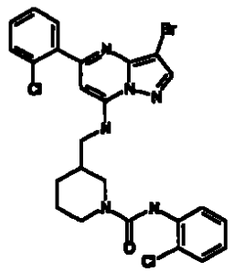
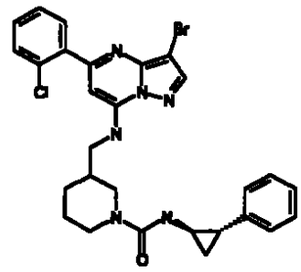
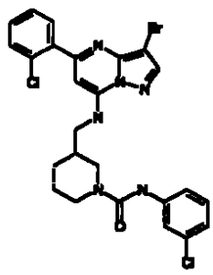
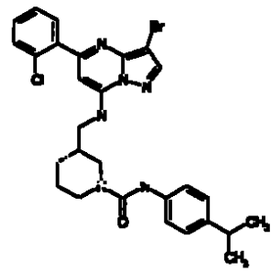
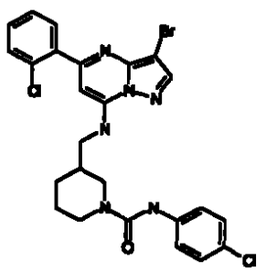
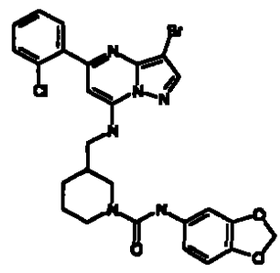
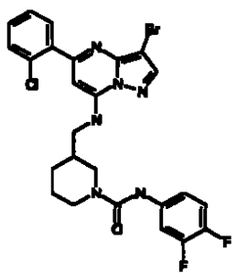
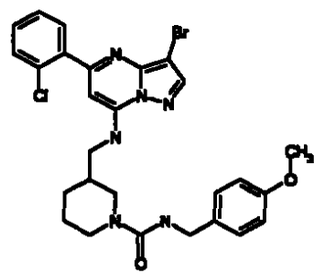
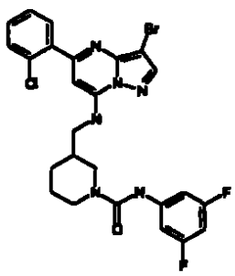
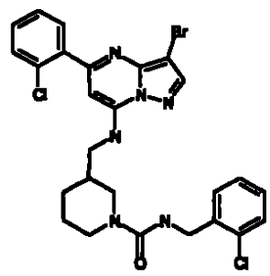
TABLA 78

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

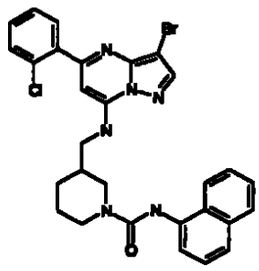
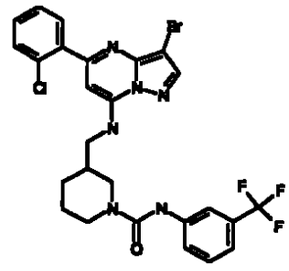
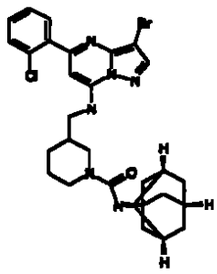
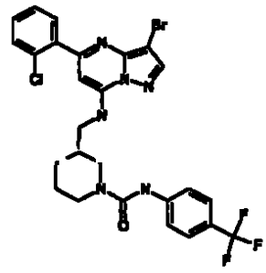
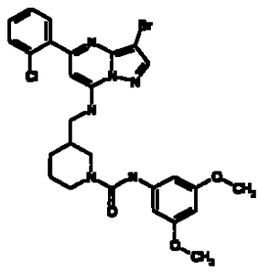
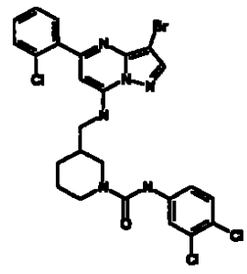
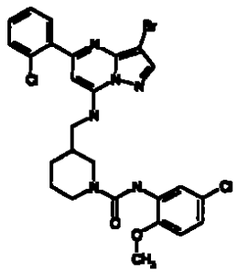
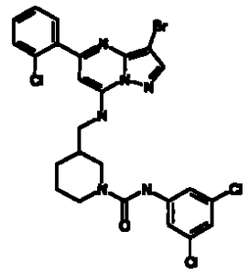
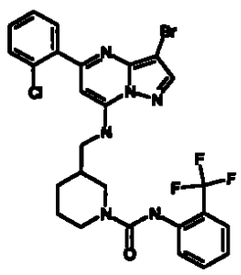
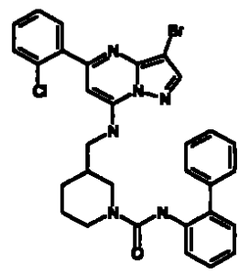
877

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

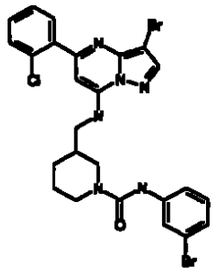
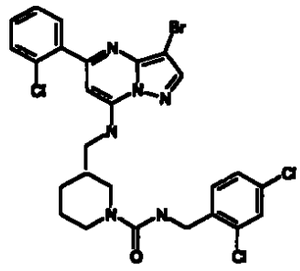
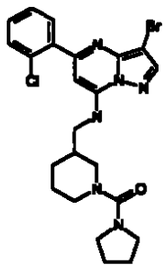
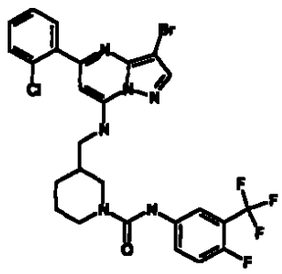
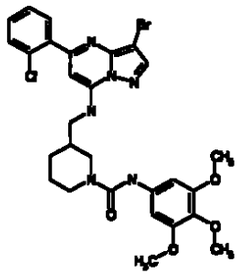
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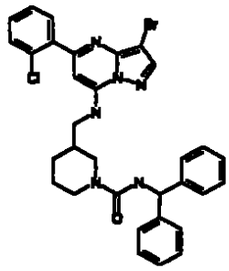
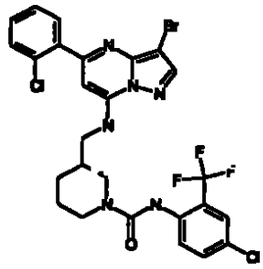
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 7822 2. 575.32		1. 7827 2. 583.32
	1. 7823 2. 575.32		1. 7828 2. 585.32
	1. 7824 2. 577.32		1. 7829 2. 585.32
	1. 7825 2. 577.32		1. 7830 2. 589.32

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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

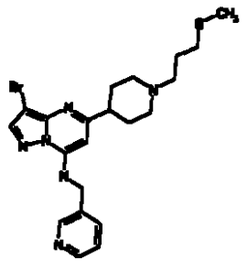
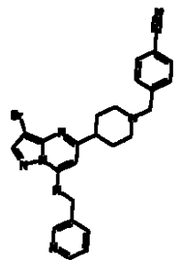
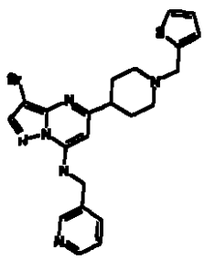
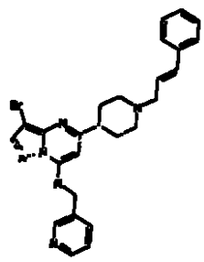
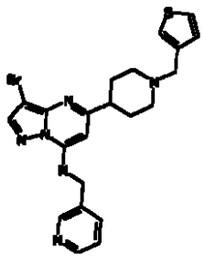
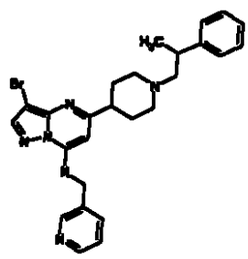
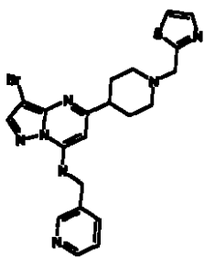
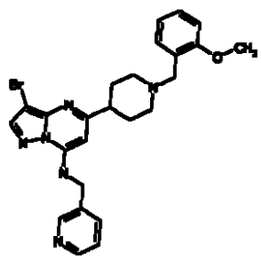
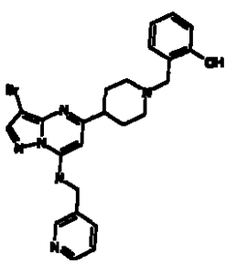
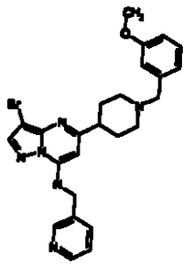
880

Producto	1. Ej. 2. m/z
	1. 7841 2. 619.34
	1. 7842 2. 623.34
	1. 7843 2. 519.29
	1. 7844 2. 627.34
	1. 7845 2. 631.35

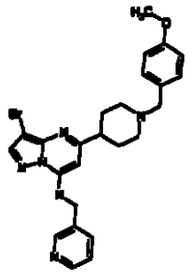
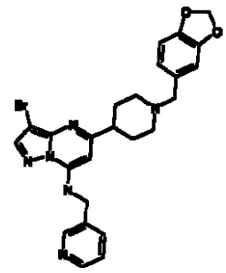
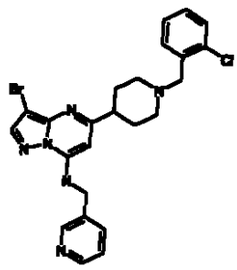
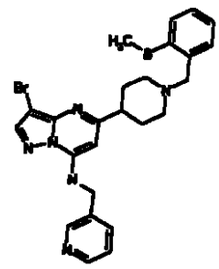
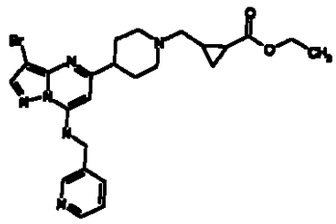
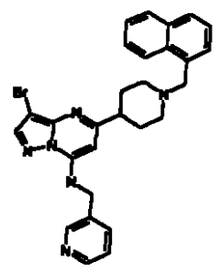
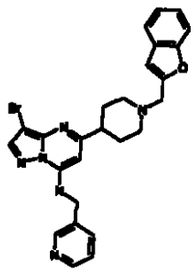
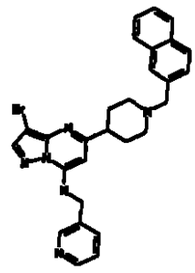
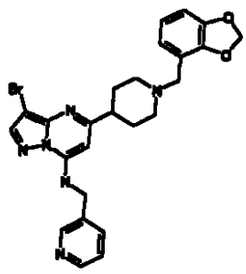
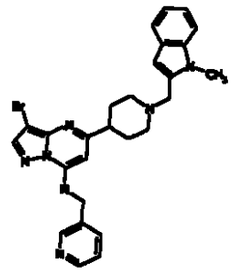
Producto	1. Ej. 2. m/z
	1. 7846 2. 631.35
	1. 7847 2. 643.35

881

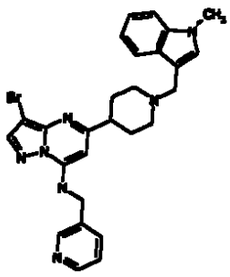
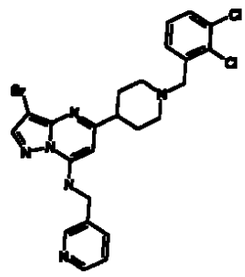
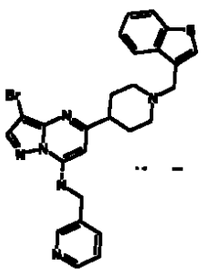
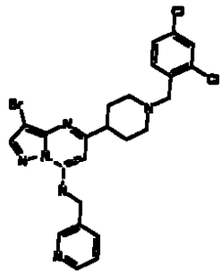
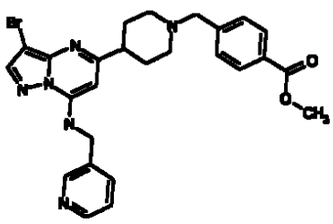
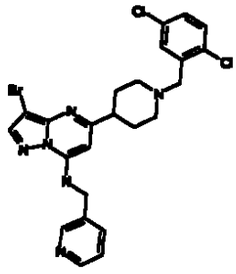
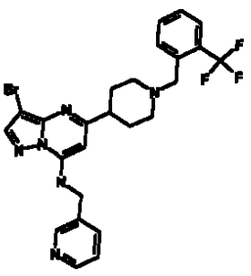
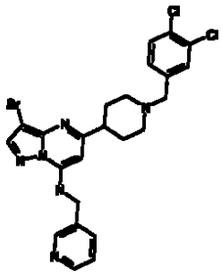
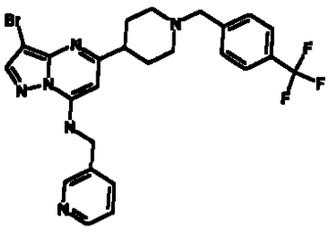
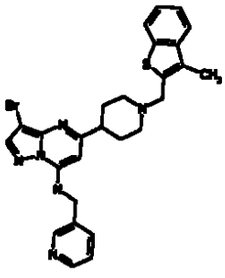
TABLA 79

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

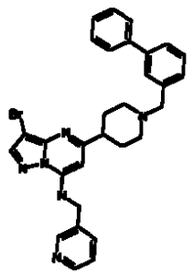
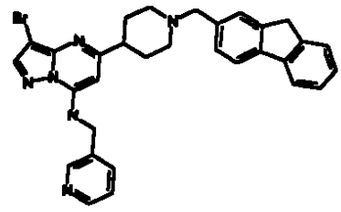
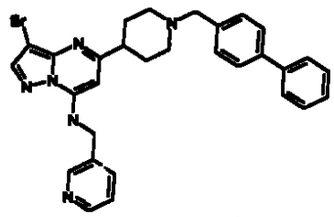
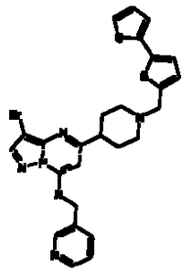
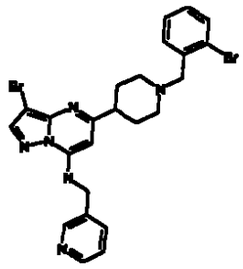
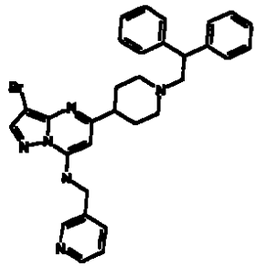
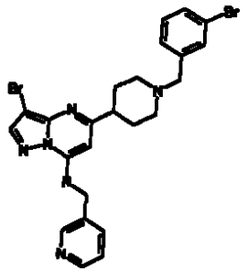
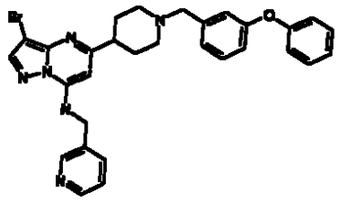
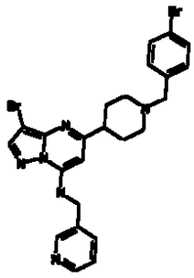
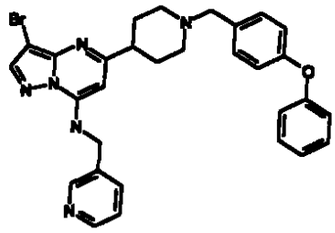
882

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

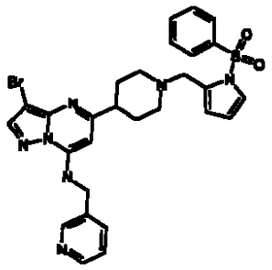
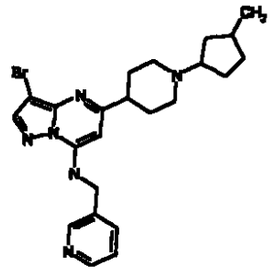
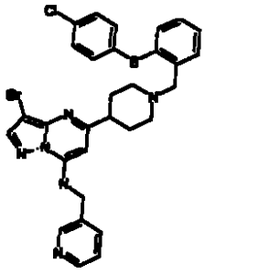
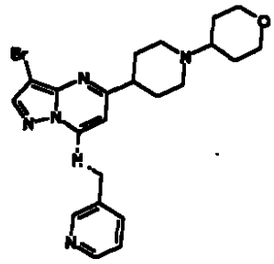
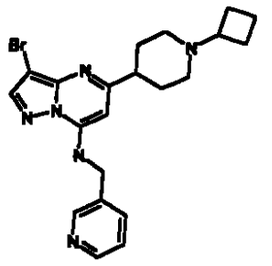
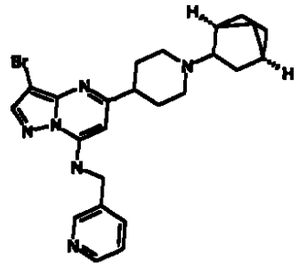
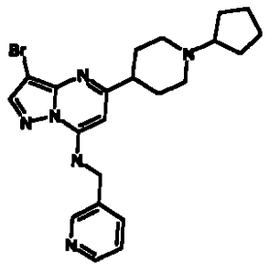
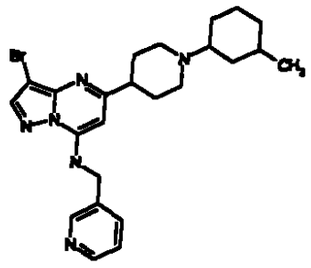
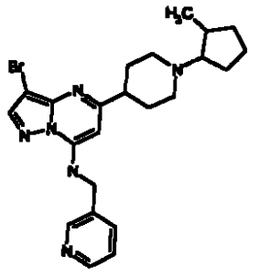
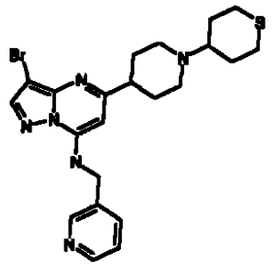
883

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	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

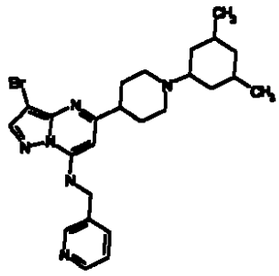
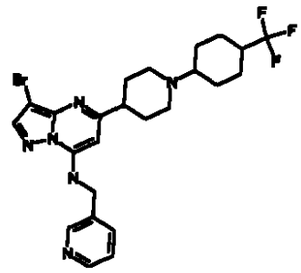
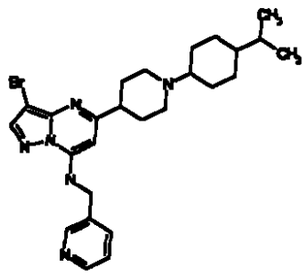
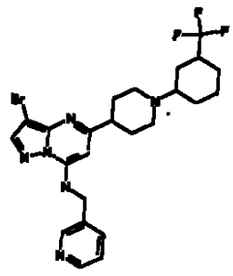
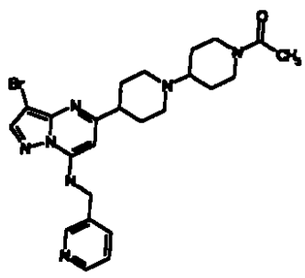
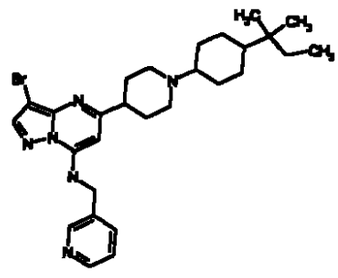
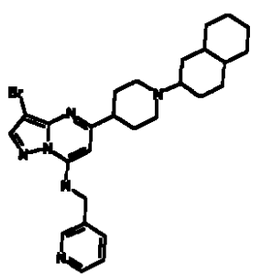
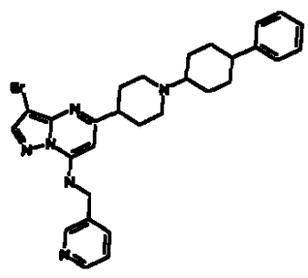
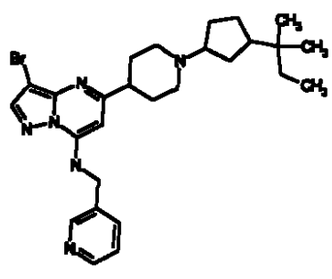
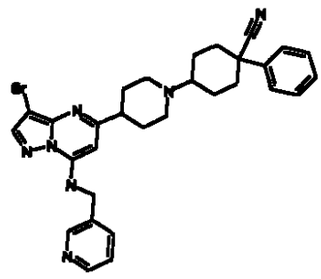
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	1. 7932 2. 555.31		1. 7937 2. 567.31
	1. 7933 2. 557.31		1. 7938 2. 569.31
	1. 7934 2. 557.31		1. 7939 2. 571.31
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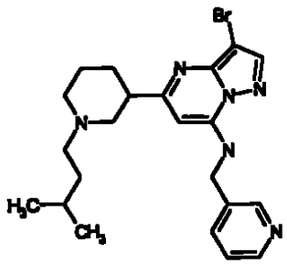
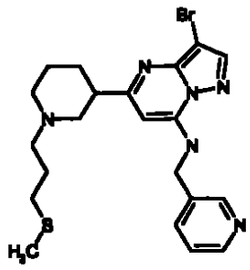
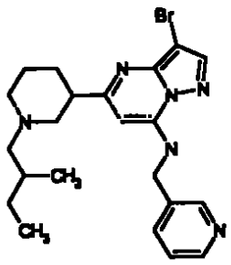
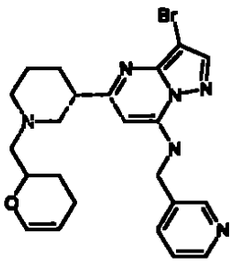
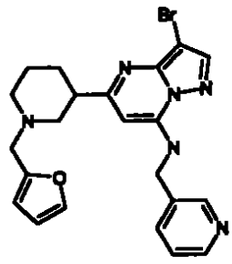
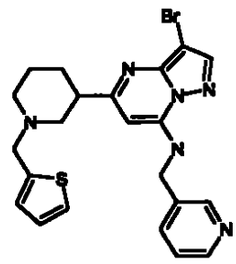
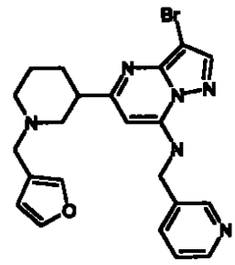
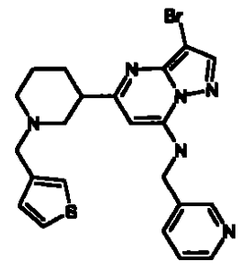
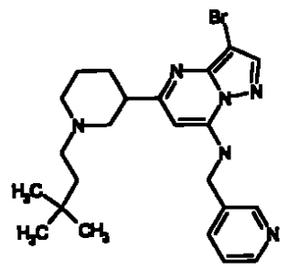
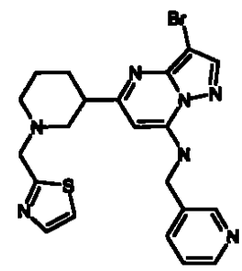
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	1. 7942 2. 621.34		1. 7947 2. 473.26
	1. 7943 2. 443.24		1. 7948 2. 483.27
	1. 7944 2. 457.25		1. 7949 2. 485.27
	1. 7945 2. 471.26		1. 7950 2. 489.27

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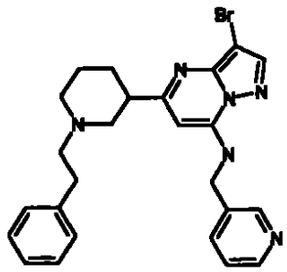
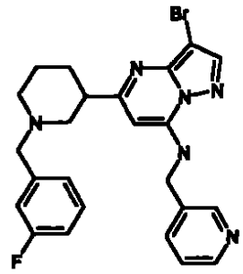
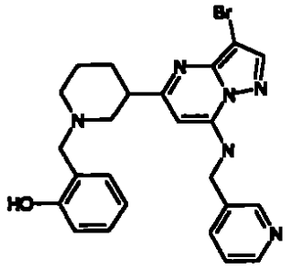
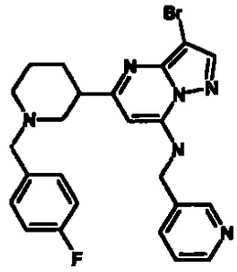
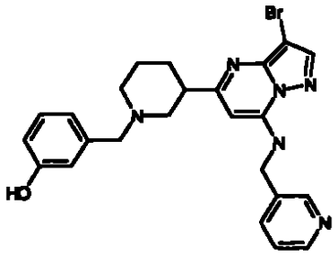
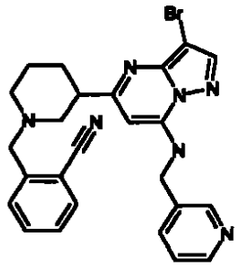
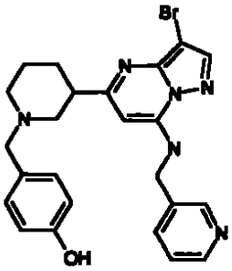
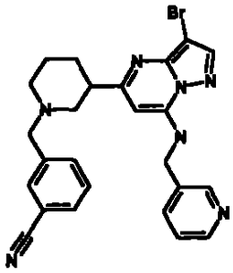
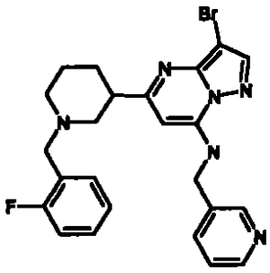
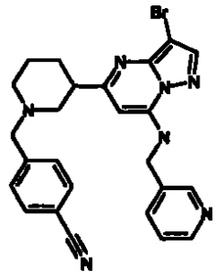
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 7952 2. 513.28		1. 7957 2. 539.3
	1. 7953 2. 514.28		1. 7958 2. 541.3
	1. 7954 2. 525.29		1. 7959 2. 547.3
	1. 7955 2. 525.29		1. 7960 2. 572.31

887

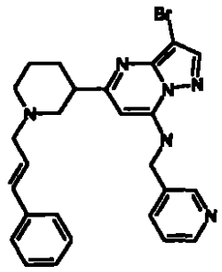
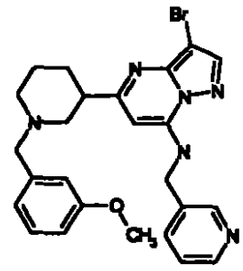
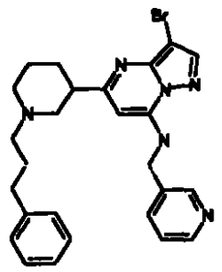
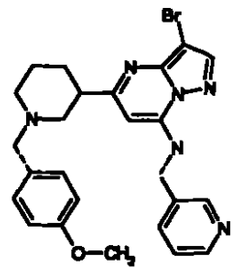
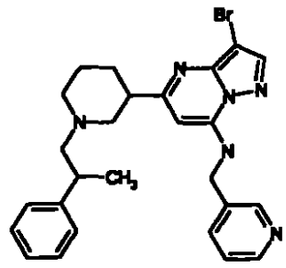
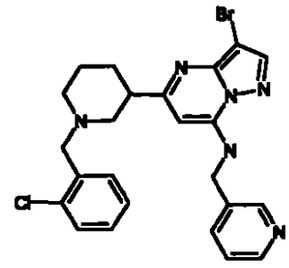
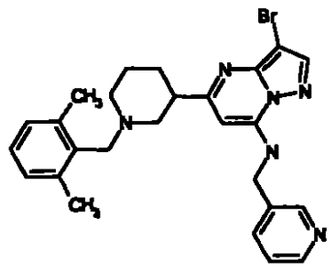
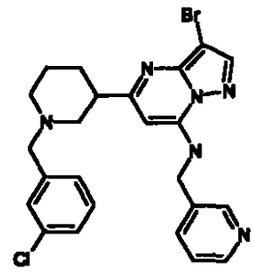
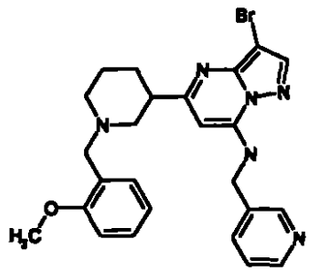
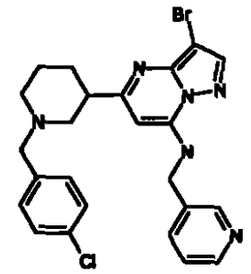
TABLA 80

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
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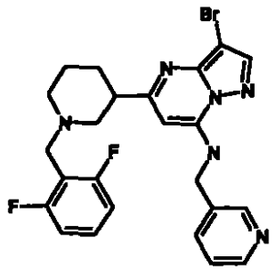
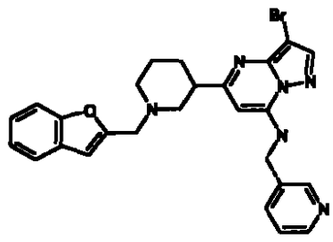
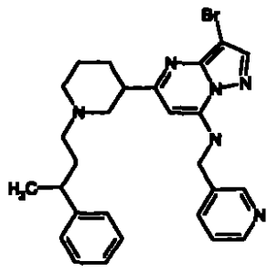
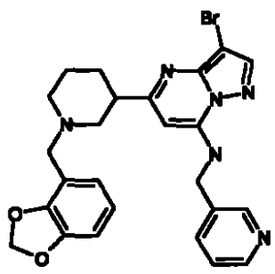
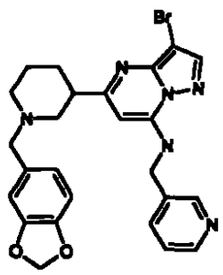
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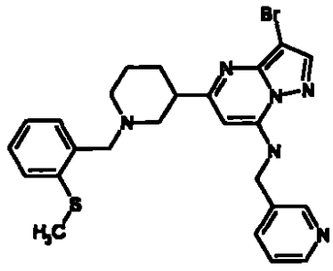
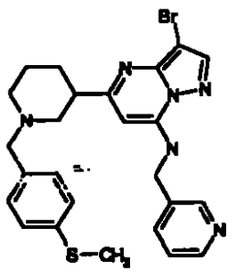
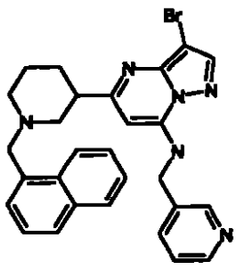
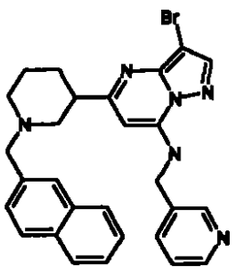
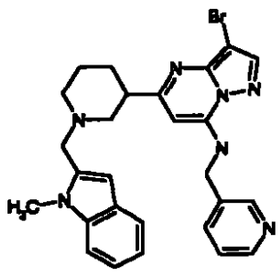
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	1. 8012 2. 495.27		1. 8017 2. 495.27
	1. 8013 2. 495.27		1. 8018 2. 502.28
	1. 8014 2. 495.27		1. 8019 2. 502.28
	1. 8015 2. 495.27		1. 8020 2. 502.28

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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
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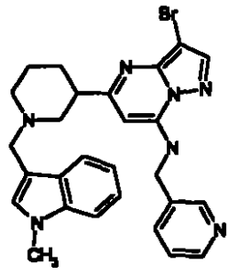
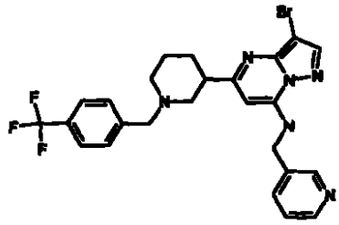
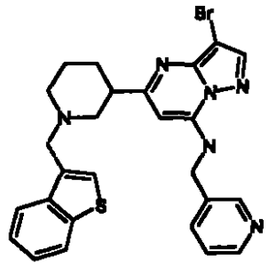
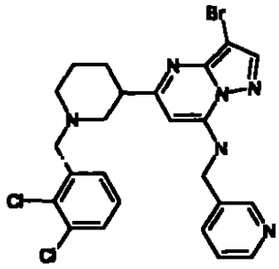
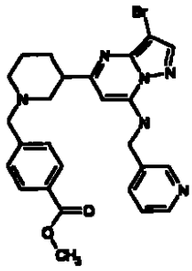
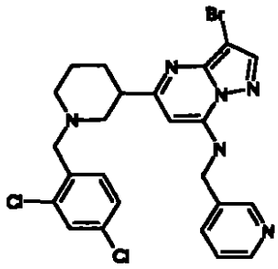
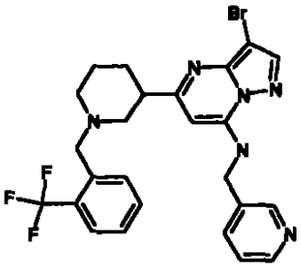
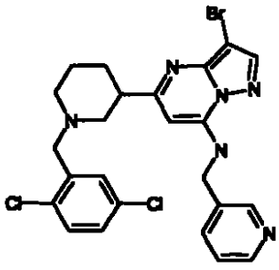
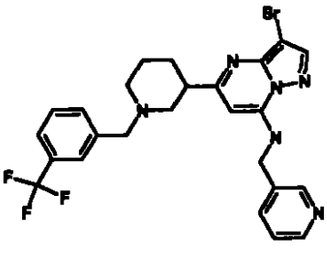
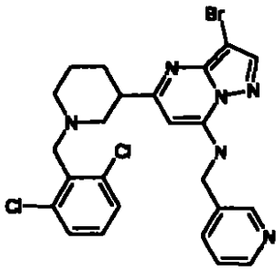
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Producto	1. Ej. 2. m/z
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	1. 8034 2. 523.29
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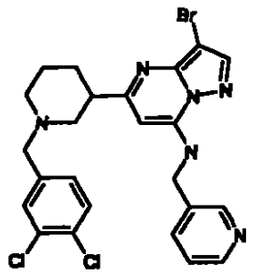
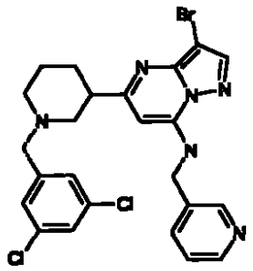
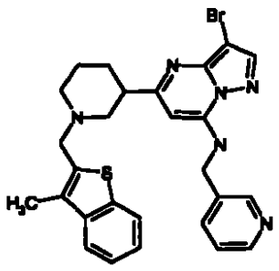
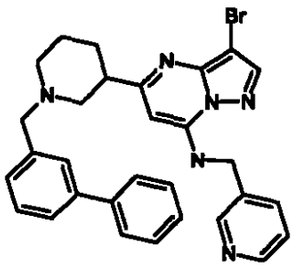
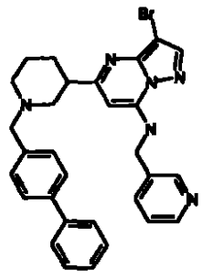
Producto	1. Ej. 2. m/z
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	1. 8040 2. 530.29

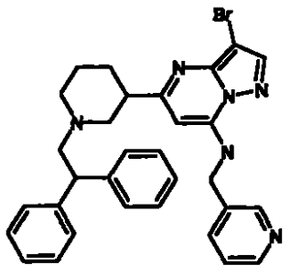
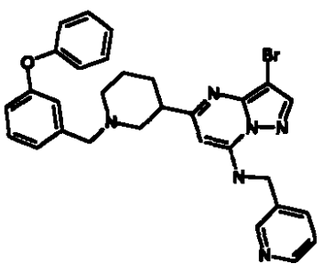
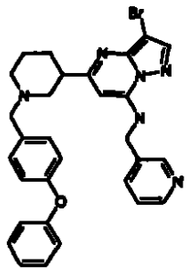
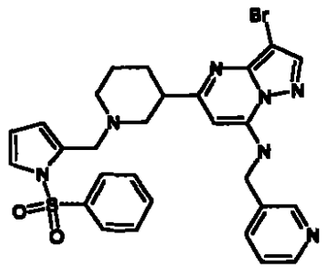
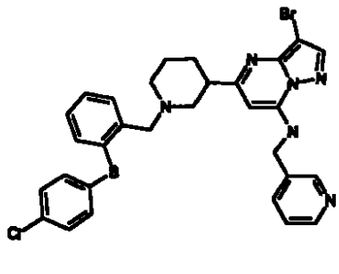
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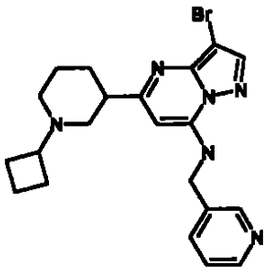
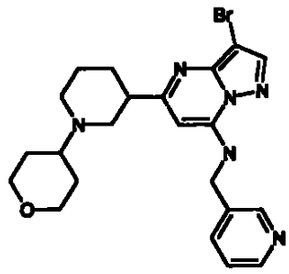
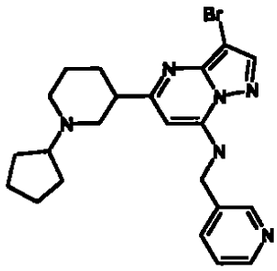
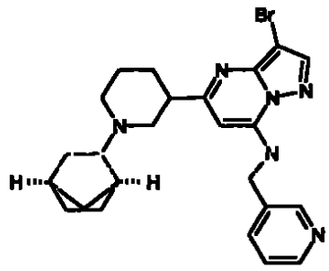
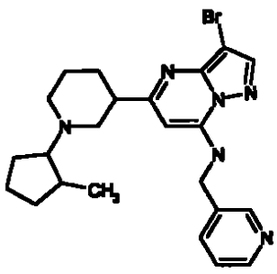
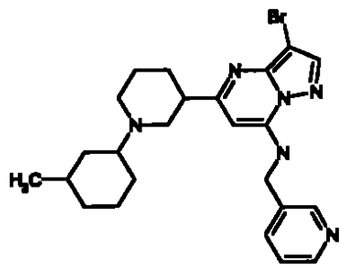
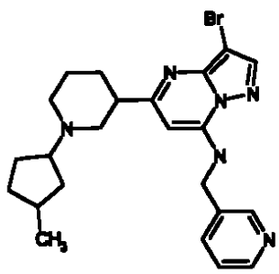
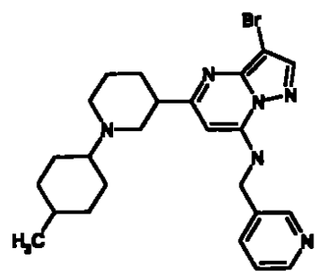
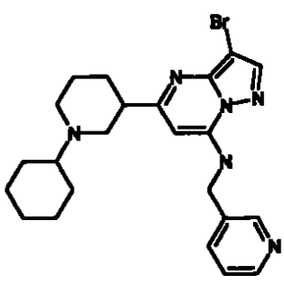
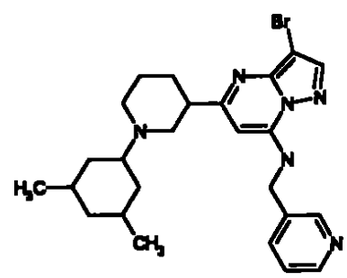
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 8042 2. 535.29		1. 8047 2. 544.3
	1. 8043 2. 537.3		1. 8048 2. 547.3
	1. 8044 2. 547.3		1. 8049 2. 547.3
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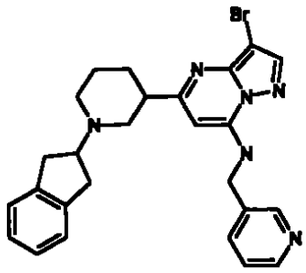
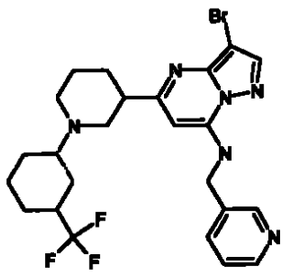
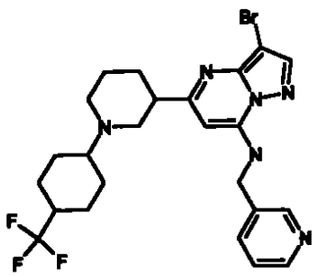
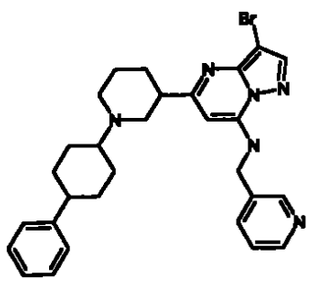
Producto	1. Ej. 2. m/z
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	1. 8054 2. 555.31
	1. 8055 2. 553.3

Producto	1. Ej. 2. m/z
	1. 8056 2. 569.31
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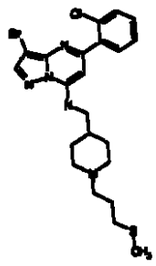
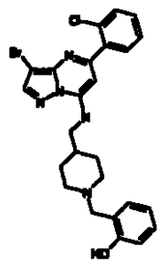
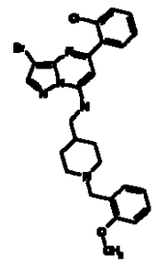
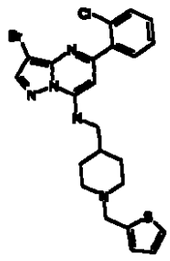
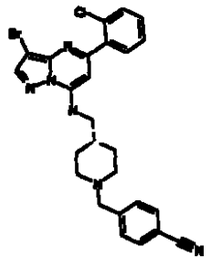
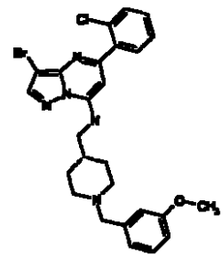
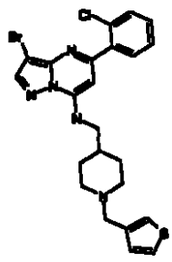
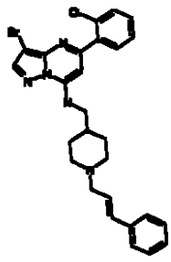
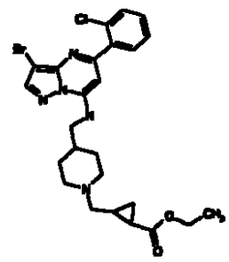
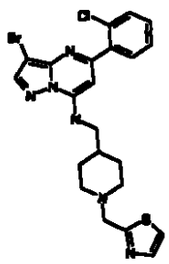
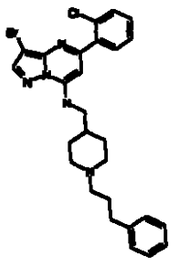
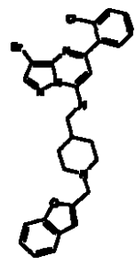
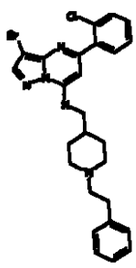
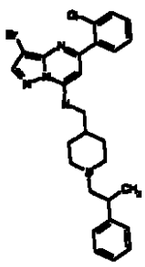
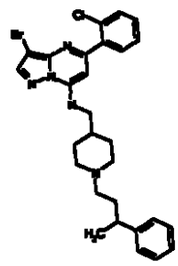
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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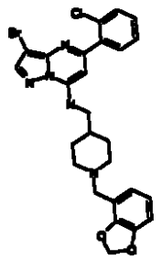
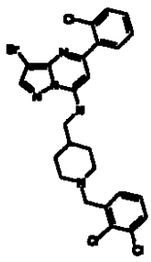
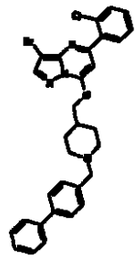
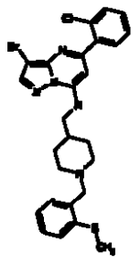
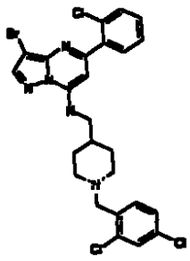
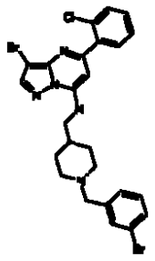
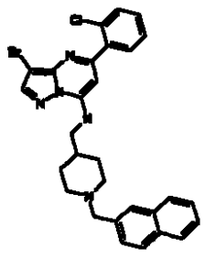
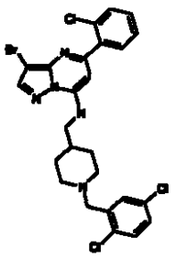
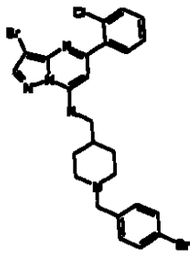
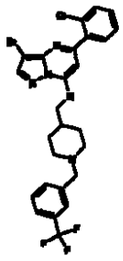
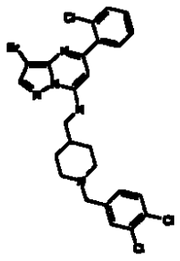
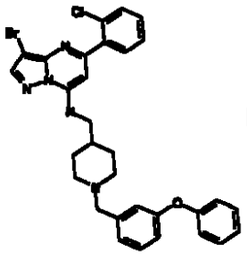
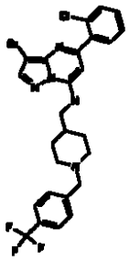
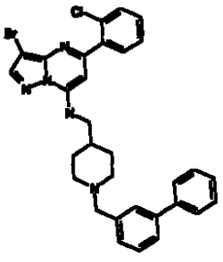
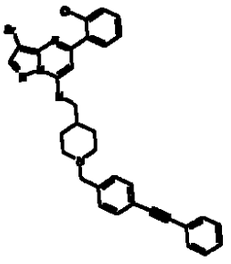
Producto	1. Ej. 2. m/z
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	1. 8072 2. 537.3
	1. 8073 2. 537.3
	1. 8074 2. 547.3

895

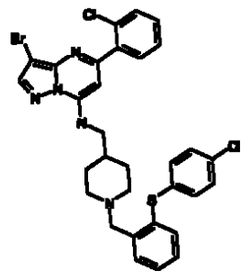
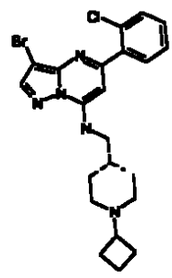
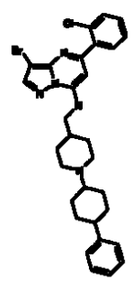
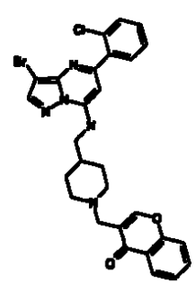
TABLA81

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. 536.3		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

896

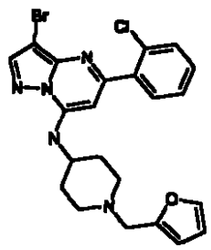
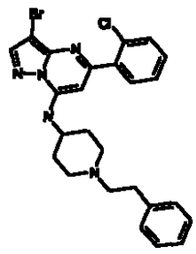
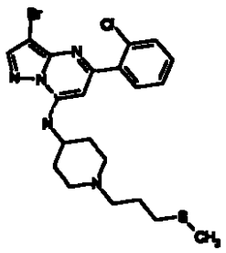
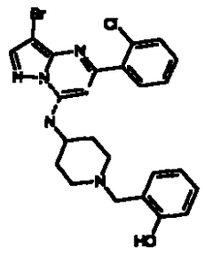
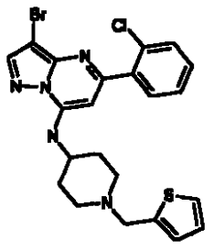
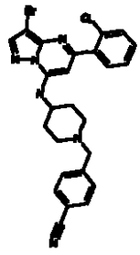
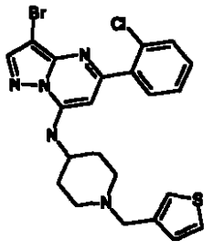
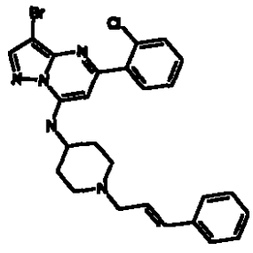
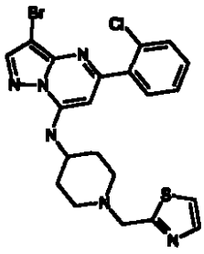
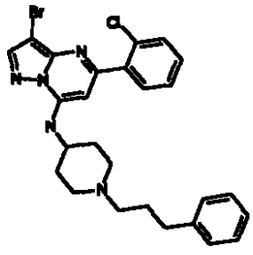
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8116 2. 556.31		1. 8121 2. 580.32		1. 8126 2. 588.32
	1. 8117 2. 556.31		1. 8122 2. 580.32		1. 8127 2. 590.32
	1. 8118 2. 582.31		1. 8123 2. 580.32		1. 8128 2. 590.32
	1. 8119 2. 580.32		1. 8125 2. 580.32		I. 8129 2. 604.33
	1. 8120 2. 580.32		1. 8126 2. 588.32		1. 8130 2. 612.34

897

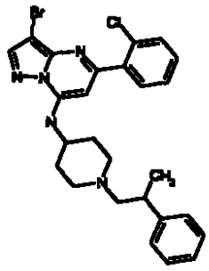
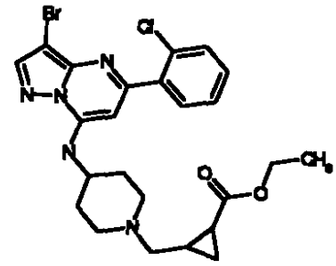
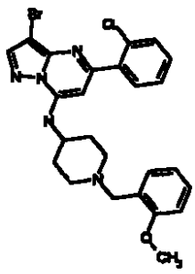
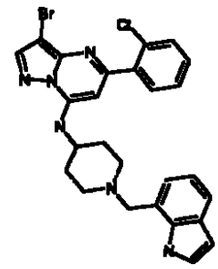
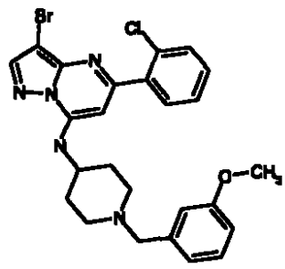
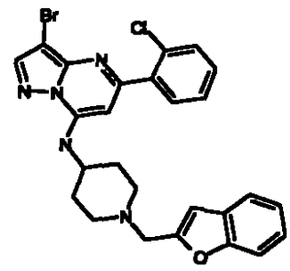
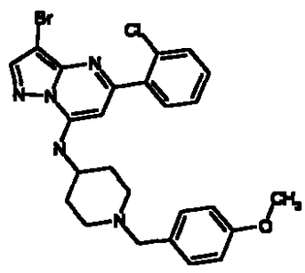
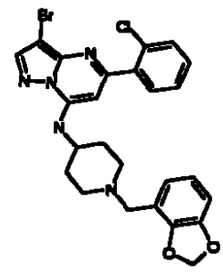
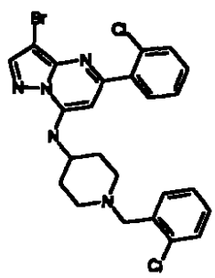
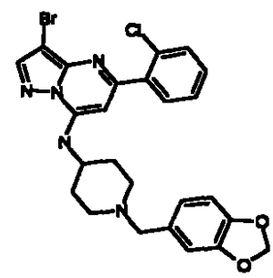
Producto	1. Ej. 2. m/z
	1. 8131 2. 654.36
	1. 8132 2. 476.26
	1. 8133 2. 580.32
	1. 8134 2. 580.32

898

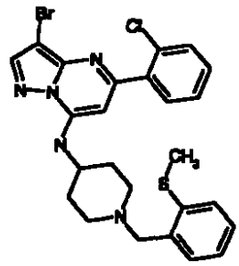
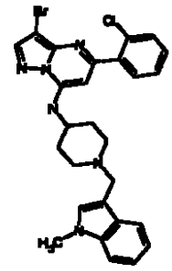
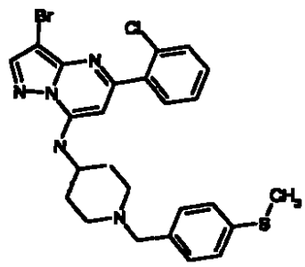
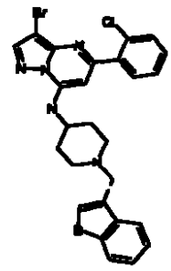
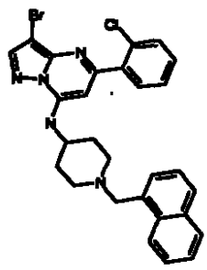
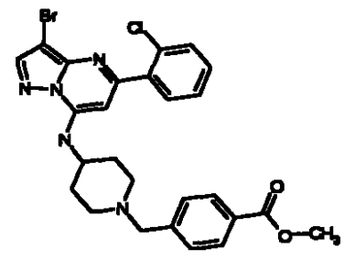
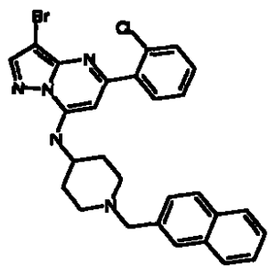
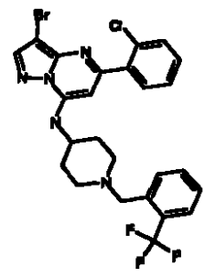
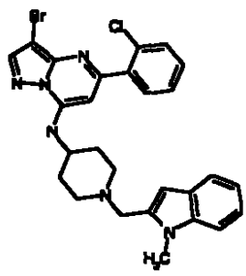
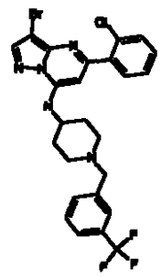
TABLA 82

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. 498.27		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

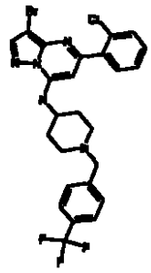
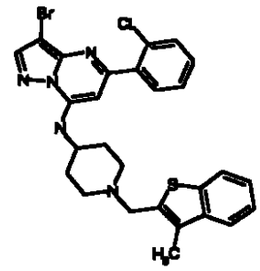
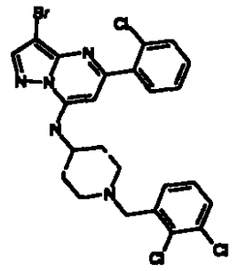
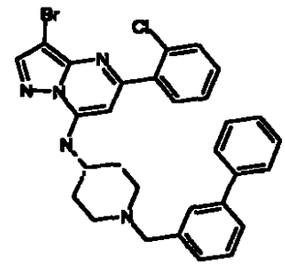
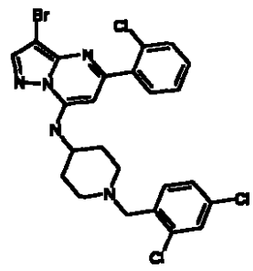
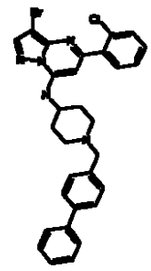
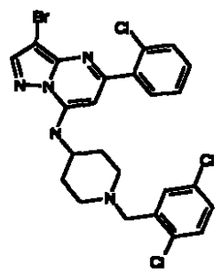
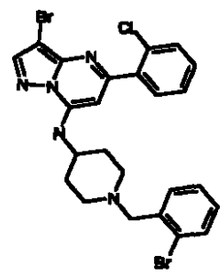
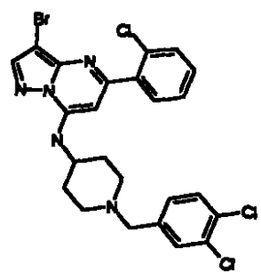
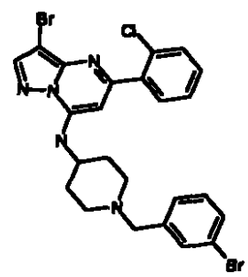
899 900

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

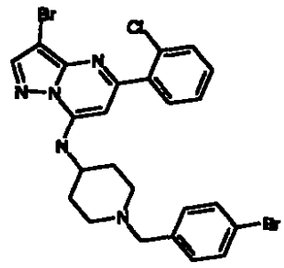
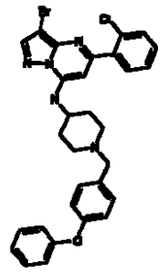
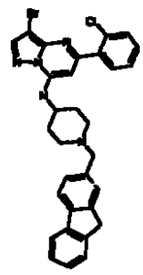
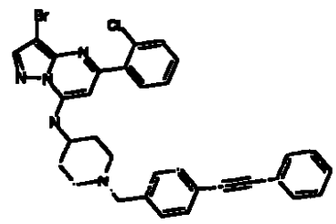
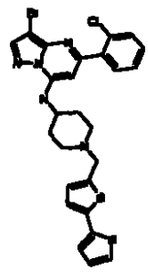
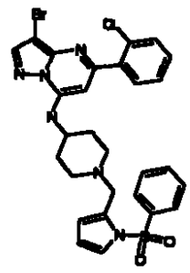
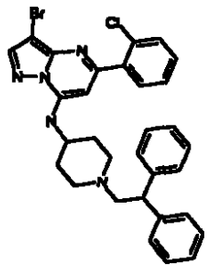
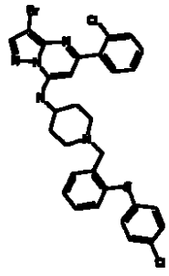
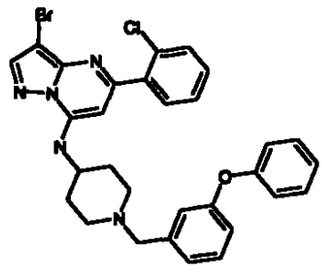
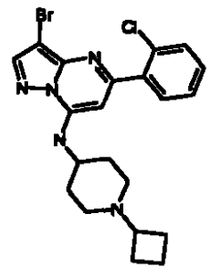
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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 8222 2. 544.3		1. 8227 2. 554.3
	1. 8223 2. 548.3		1. 8228 2. 558.31
	1. 8224 2. 548.3		1. 8229 2. 566.31
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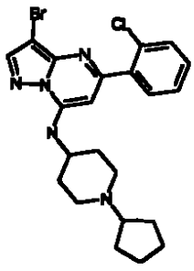
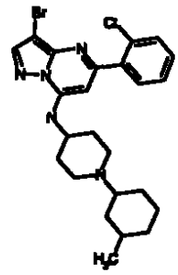
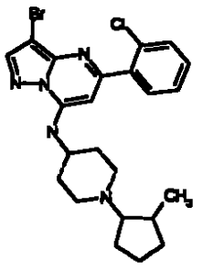
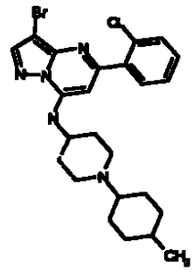
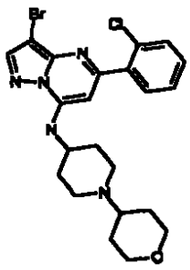
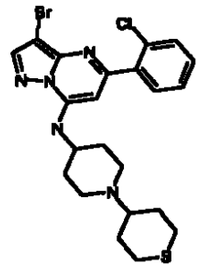
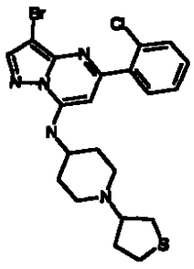
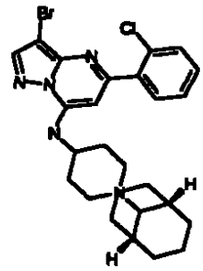
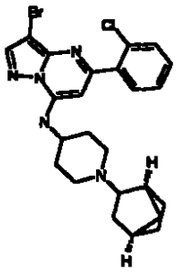
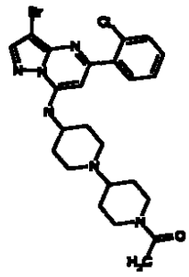
901 902

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 8233 2. 566.31		1. 8238 2. 574.32
	1. 8243 2. 566.31		1. 8239 2. 576.32
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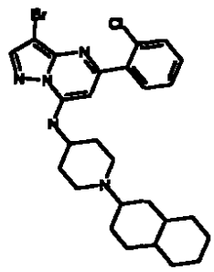
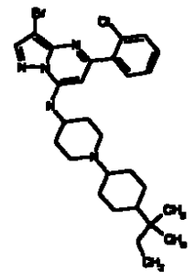
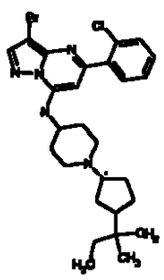
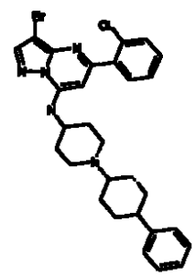
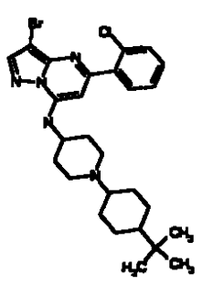
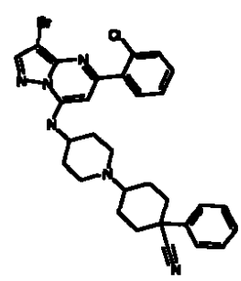
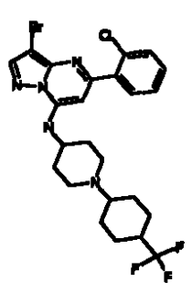
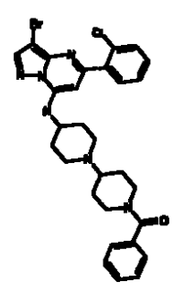
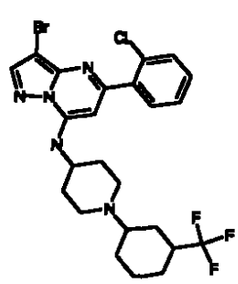
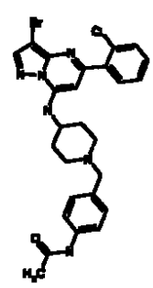
902
903

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 8242 2. 586.32		1. 8247 2. 586.33
	1. 8243 2. 586.32		1. 8248 2. 627.34
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903

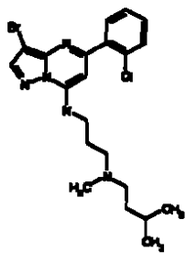
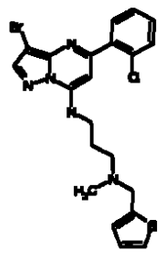
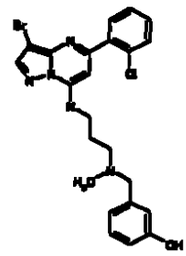
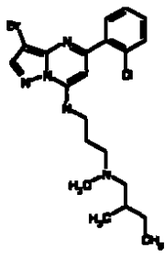
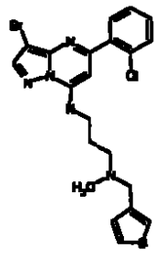
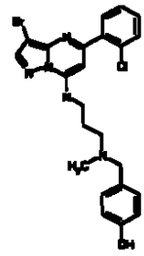
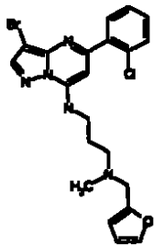
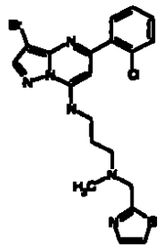
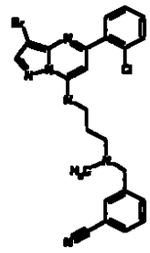
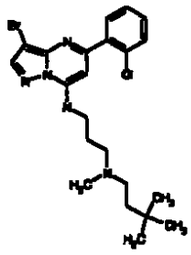
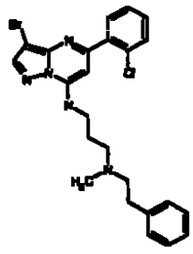
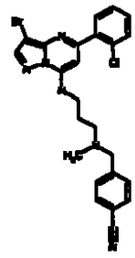
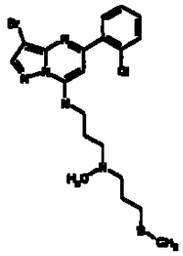
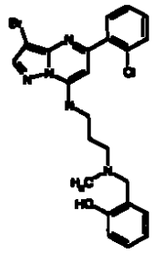
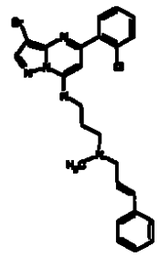
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 8253 2. 492.27		1. 8258 2. 508.28
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905

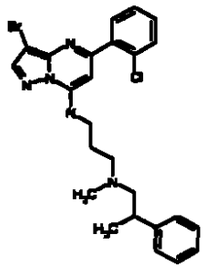
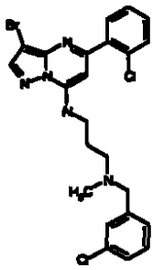
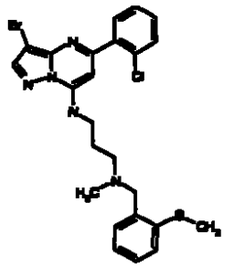
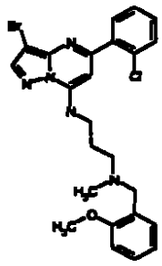
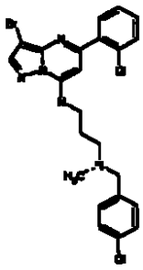
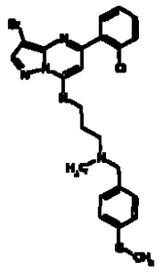
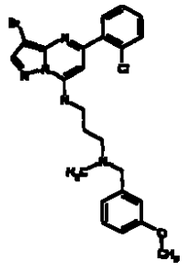
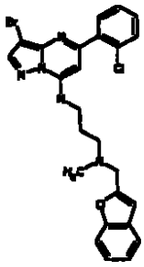
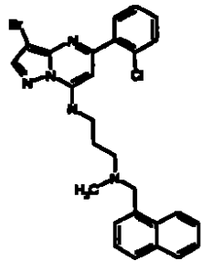
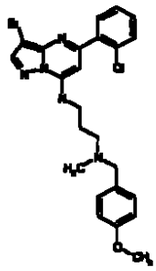
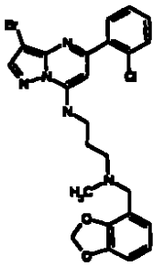
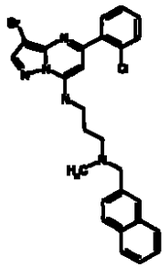
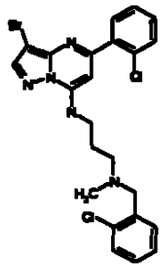
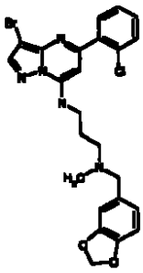
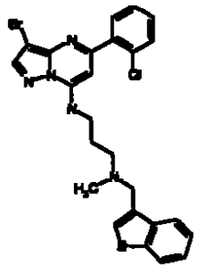
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	1. 8263 2. 546.3		1. 8268 2. 591.33
	1. 8264 2. 558.31		1. 8269 2. 595.33
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TABLA 83

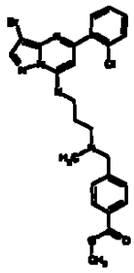
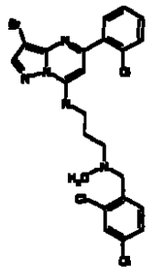
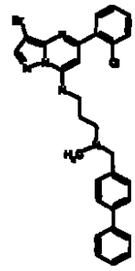
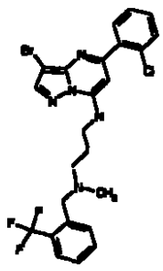
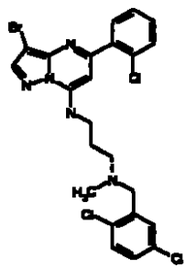
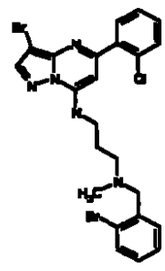
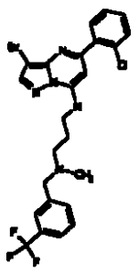
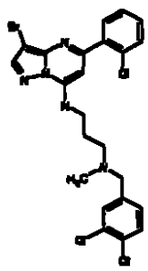
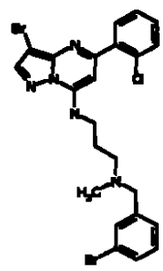
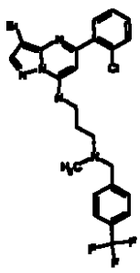
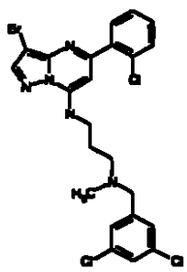
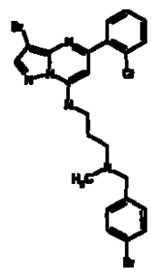
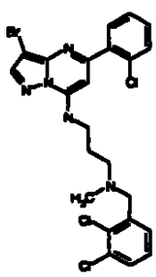
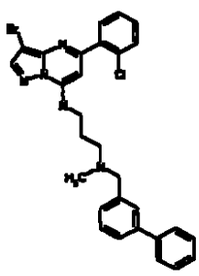
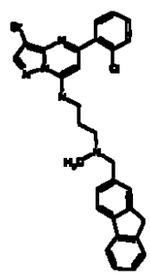
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	1. 8303 2. 475.827		1. 8308 2. 492.787		1. 8313 2. 510.822
	1. 8304 2. 479.89		1. 8309 2. 499.846		1. 8314 2. 510.821
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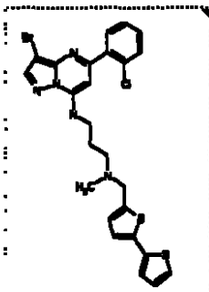
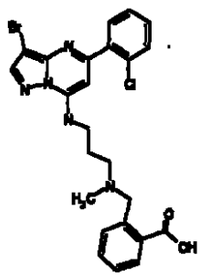
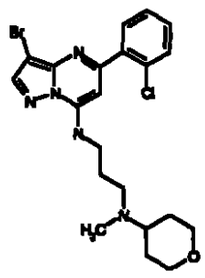
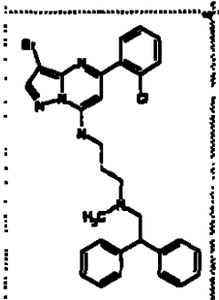
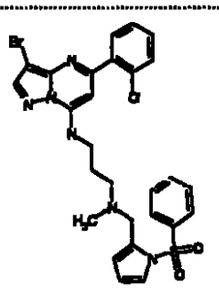
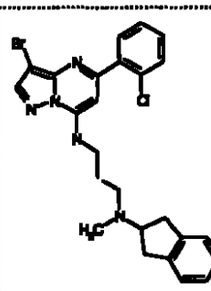
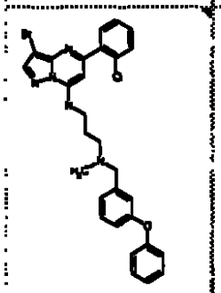
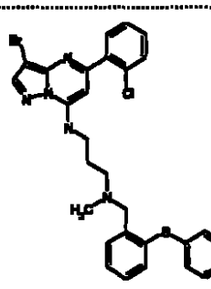
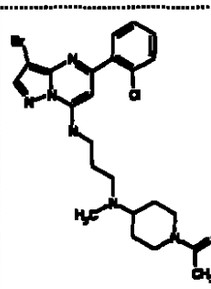
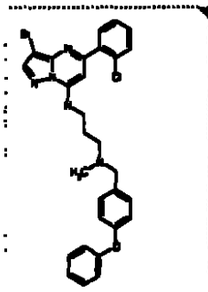
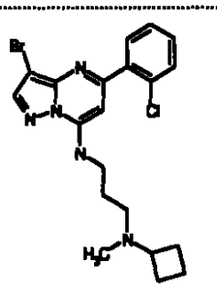
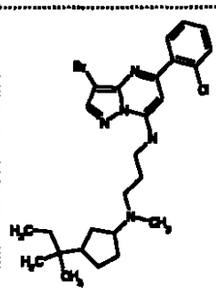
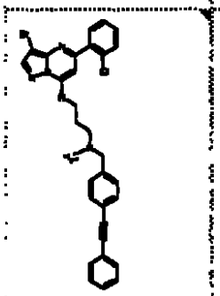
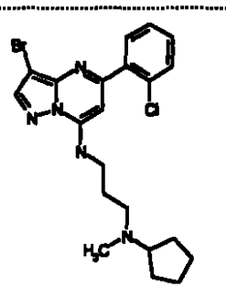
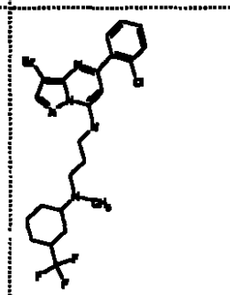
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	1. 8317 2. 515.832		1. 8322 2. 519.791		1. 8327 2. 531.812
	1. 8318 2. 515.832		1. 8323 2. 525.813		1. 8328 2. 535.83
	1. 8319 2. 515.837		1. 8324 2. 529.806		1. 8329 2. 535.831
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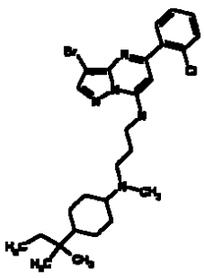
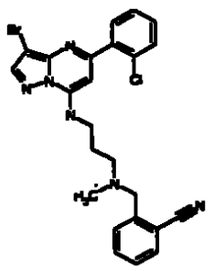
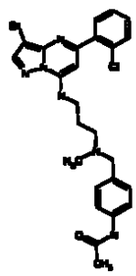
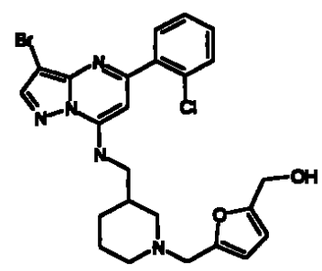
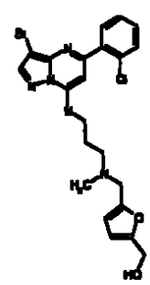
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Producto	1. Ej. 2. m/z	Producto	1. Ex. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 8333 2. 553.796		1. 8338 2. 554.738		1. 8343 2. 564.704
	1. 8334 2. 553.795		1. 8339 2. 554.727		1. 8344 2. 564.72
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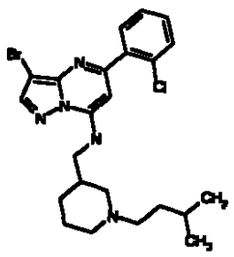
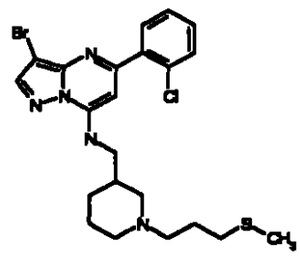
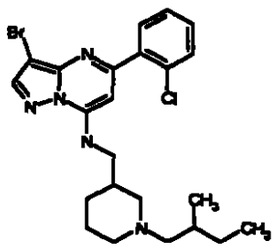
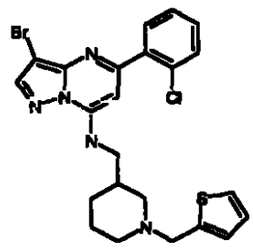
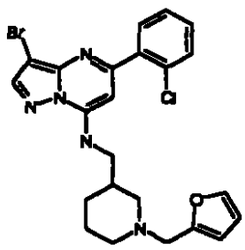
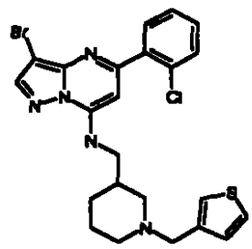
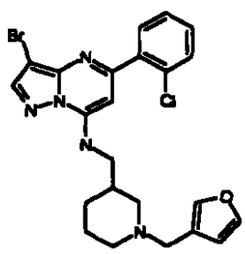
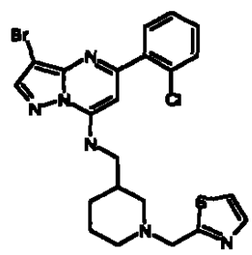
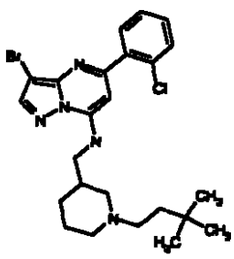
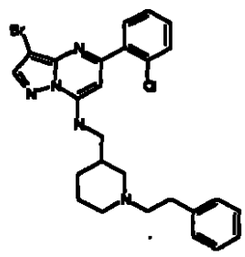
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	1. 8347 2. 575.839		1. 8352 2. 614.763		1. 8357 2. 511.842
	1. 8348 2. 577.818		1. 8353 2. 628.727		1. 8358 2. 520.859
	1. 8349 2. 577.814		1. 8354 2. 449.857		1. 8359 2. 533.903
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909

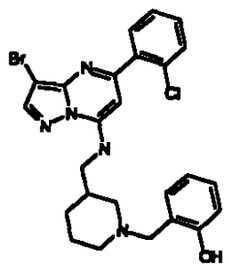
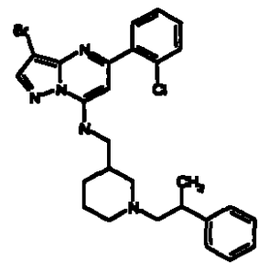
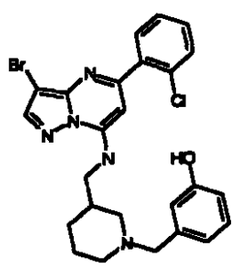
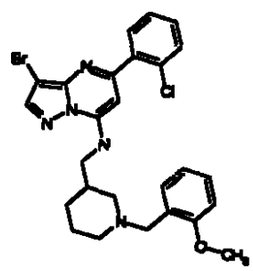
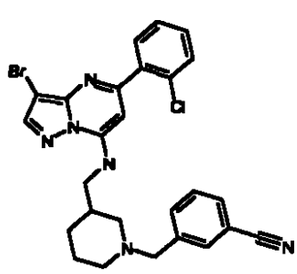
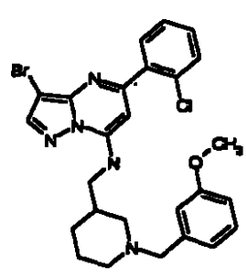
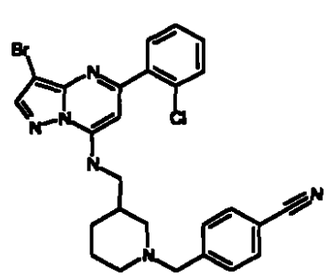
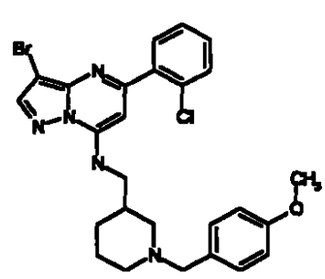
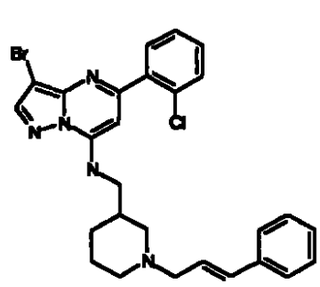
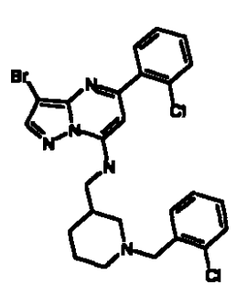
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	1. 8362 2. 510.817
	1. 8363 2. 542.833
	1. 8364 2. 573.815
	1. 8365 2. 547.798

910

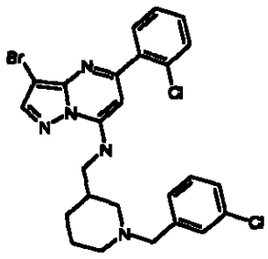
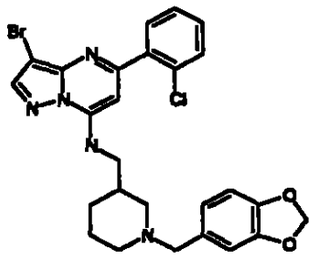
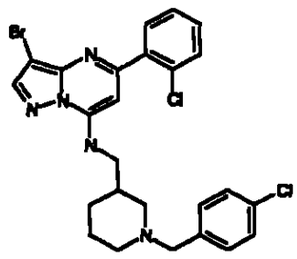
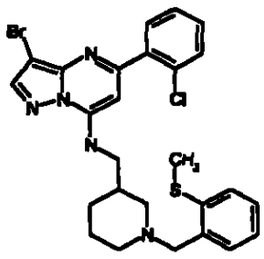
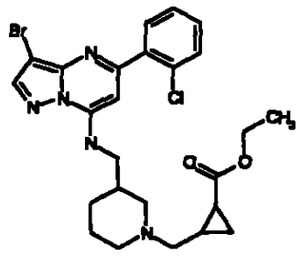
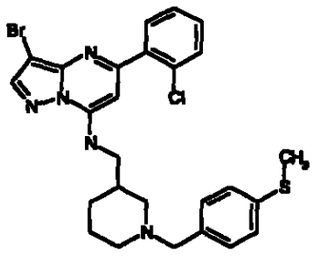
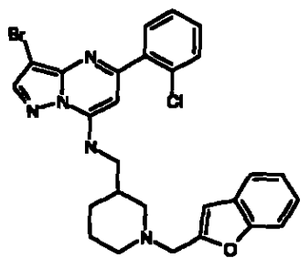
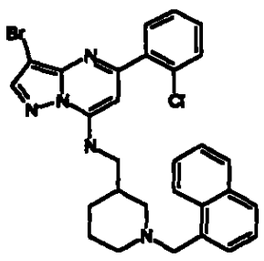
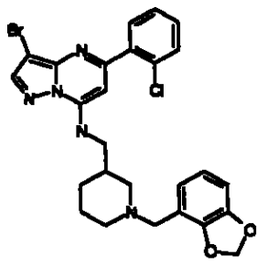
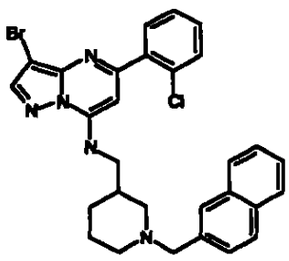
TABLA 84

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
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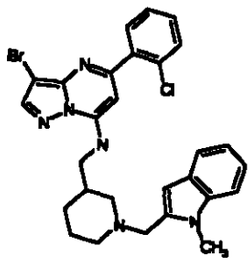
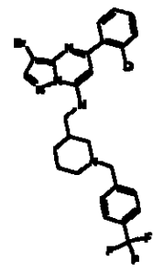
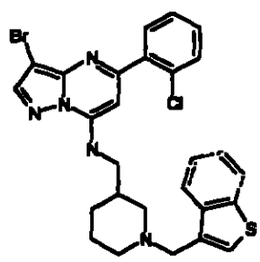
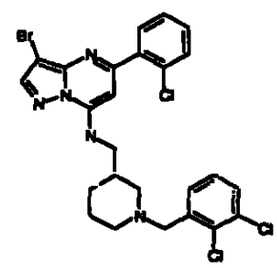
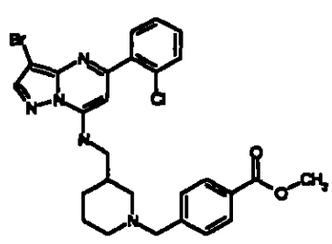
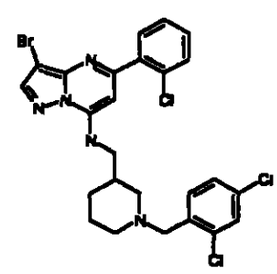
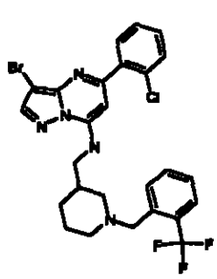
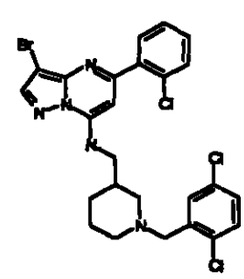
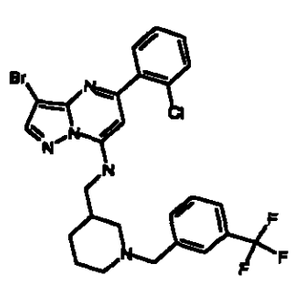
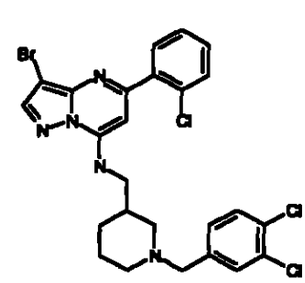
911 912

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 8412 2. 527.333		1. 8417 2. 541.84
	1. 8413 2. 536.833		1. 8416 2. 541.843
	1. 8414 2. 536.829		1. 8419 2. 541.843
	1. 8415 2. 537.845		1. 8420 2. 546.786

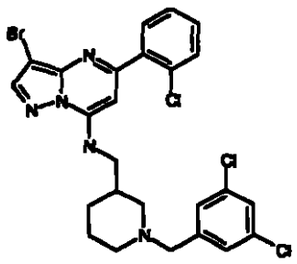
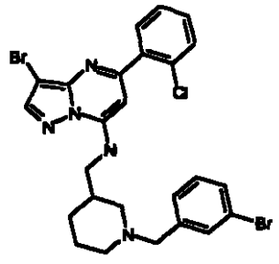
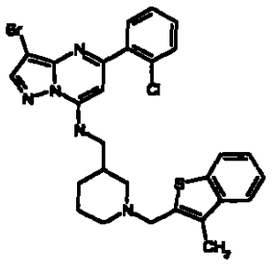
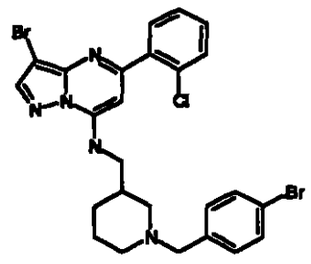
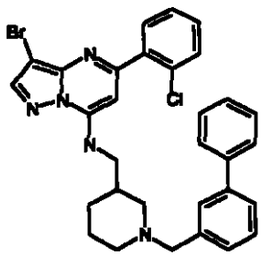
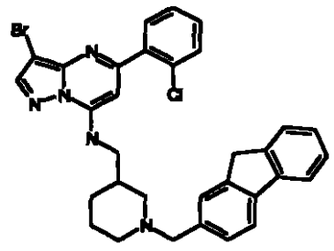
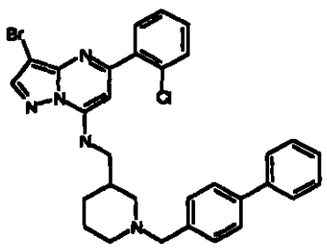
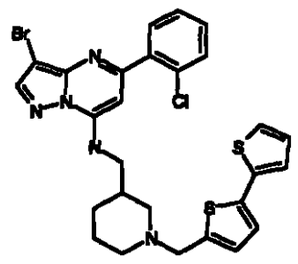
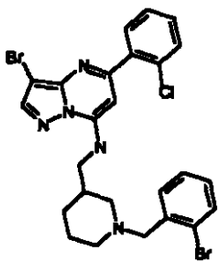
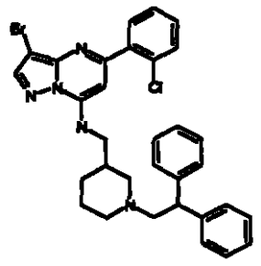
912

Producto	1. Ej. 2. m/z	Producto	1. Ej. 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

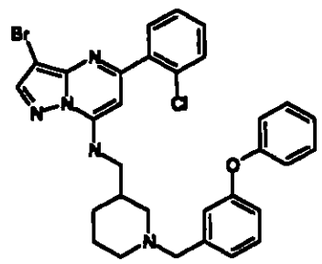
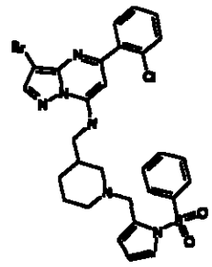
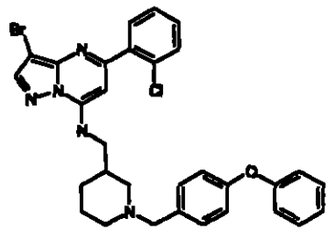
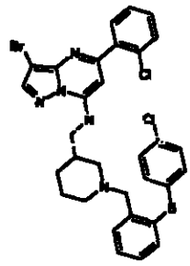
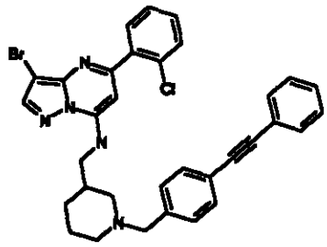
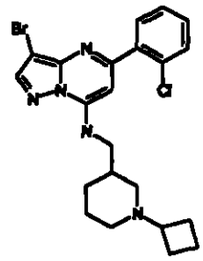
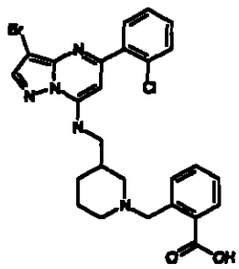
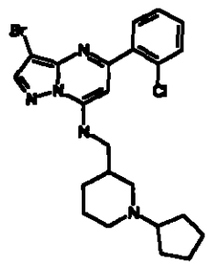
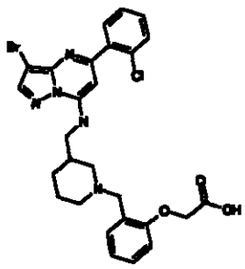
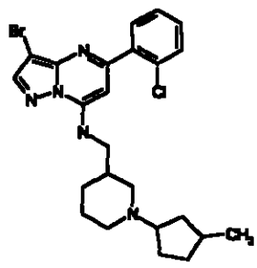
913

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

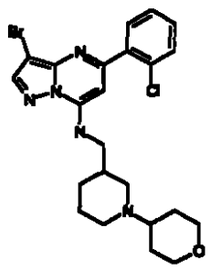
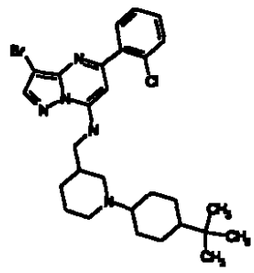
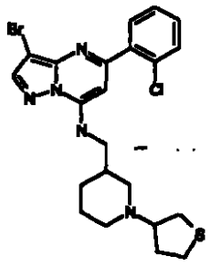
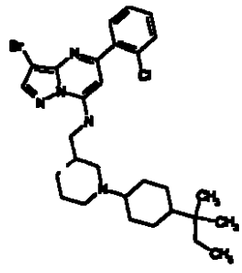
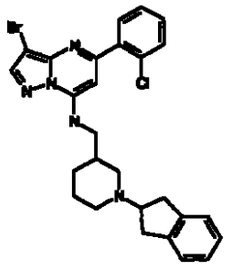
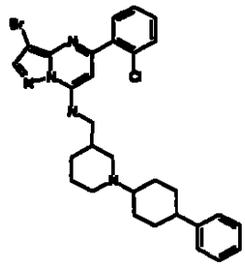
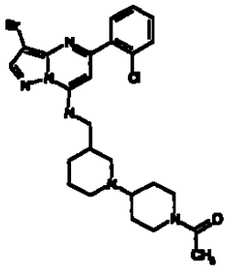
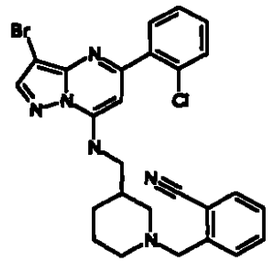
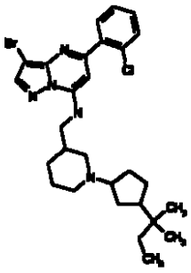
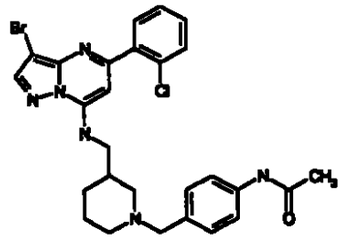
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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 8442 2. 581.805		1. 8447 2. 590.724
	1. 8443 2. 587.844		1. 8448 2. 599.834
	1. 8444 2. 587.835		1. 8449 2. 599.749
	1. 8445 2. 590.723		1. 8450 2. 601.854

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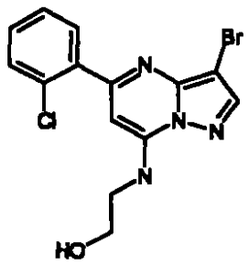
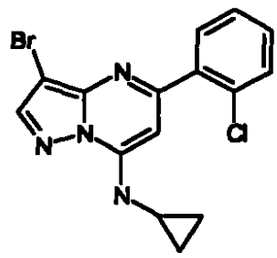
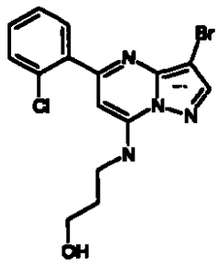
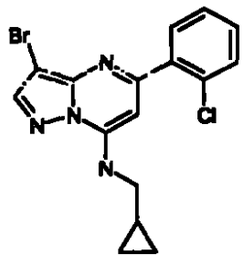
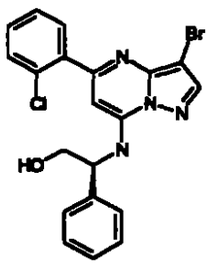
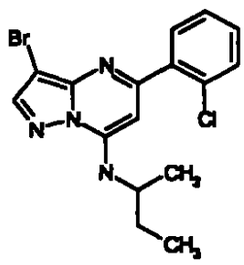
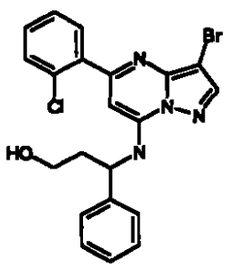
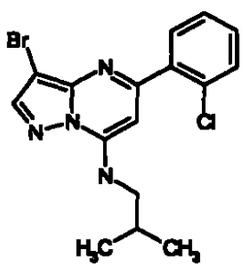
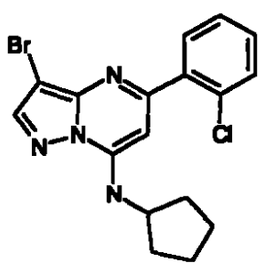
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	1. 8451 2. 603.831		1. 8456 2. 640.779
	1. 8452 2. 603.83		1. 8457 2. 654.748
	1. 8453 2. 611.83		1. 8458 2. 475.871
	1. 8454 2. 555.824		1. 8459 2. 489.879
	1. 8455 2. 585.817		1. 8460 2. 503.885

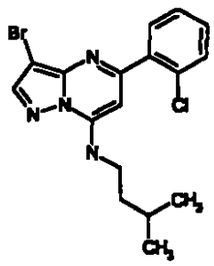
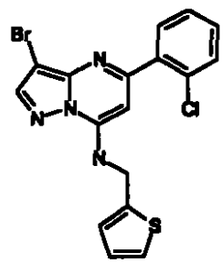
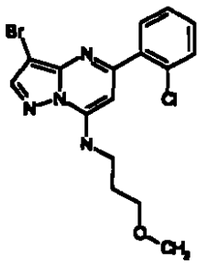
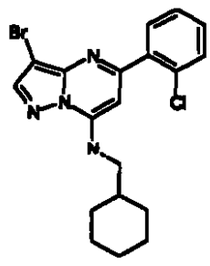
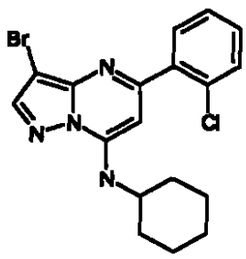
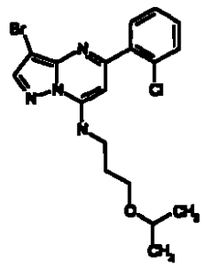
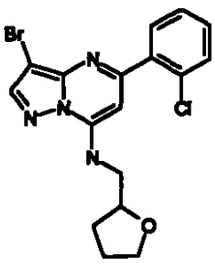
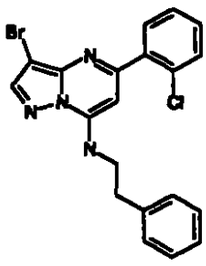
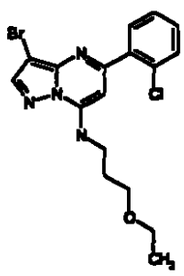
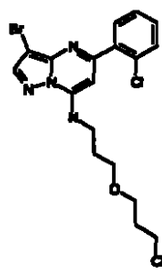
916

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 8463 2. 537.859		1. 8468 2. 579.876
	1. 8464 2. 546.877		1. 8469 2. 536.831
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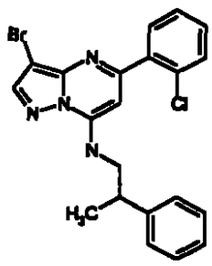
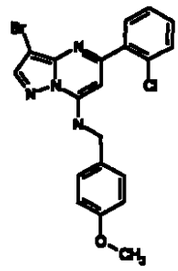
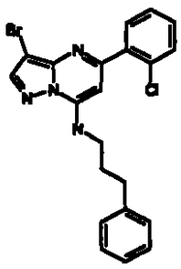
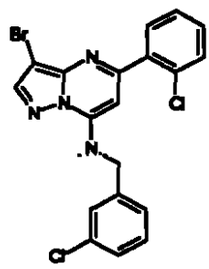
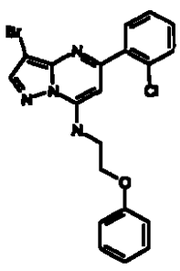
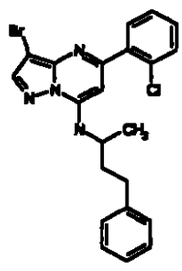
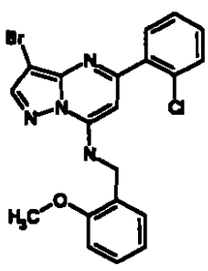
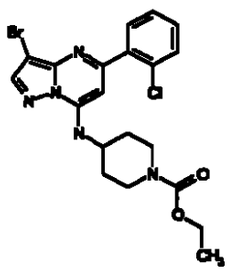
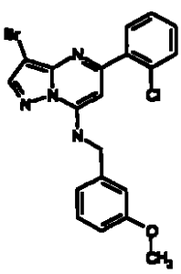
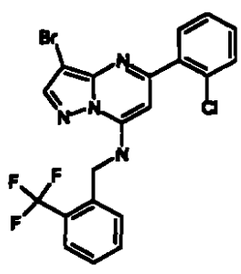
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TABLA 85

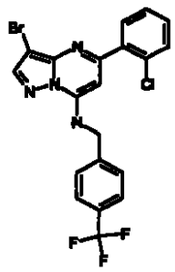
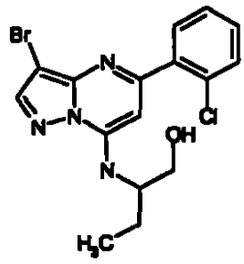
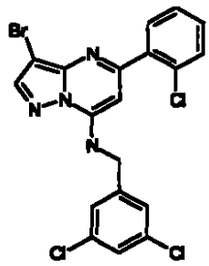
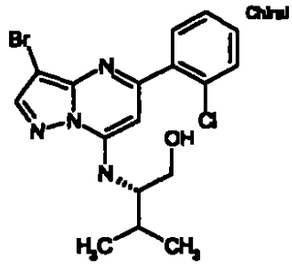
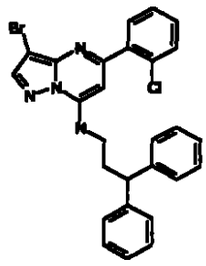
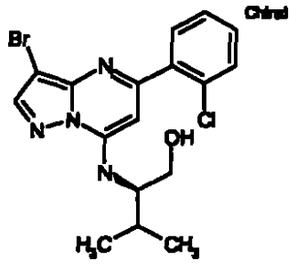
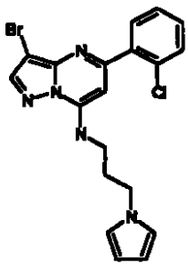
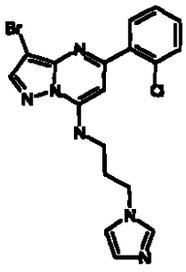
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	1. 8502 2. 381.2		1. 8507 2. 323.1
	1. 8503 2. 443.2		1. 8508 2. 365.2
	1. 8504 2. 457.3		1. 8509 2. 379.21
			1. 8510 2. 381.21

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

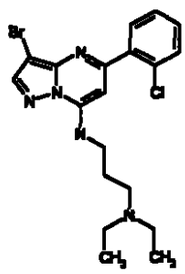
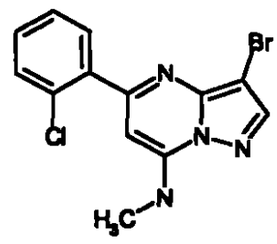
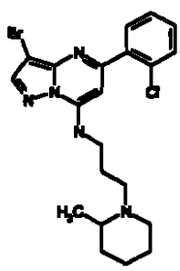
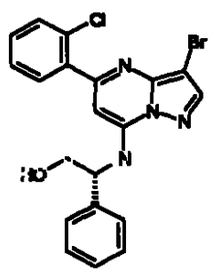
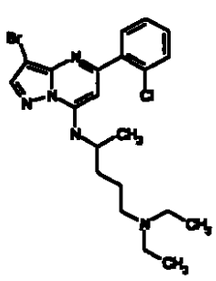
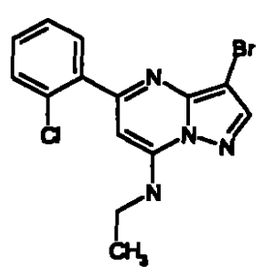
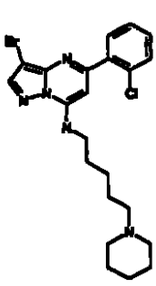
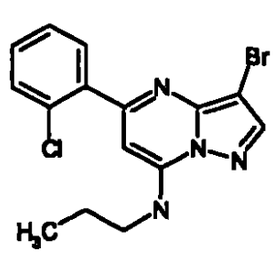
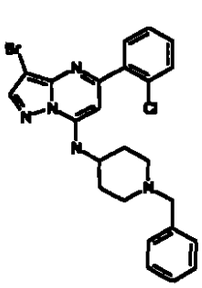
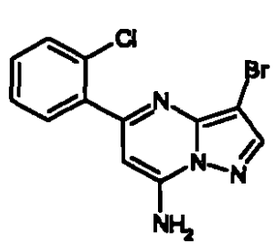
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Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
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	1. 8522 2. 439.24		1. 8527 2 .444.24
	1. 8523 2. 443.24		1. 8528 2. 444.24
	1. 8524 2. 443.24		1. 8529 2. 446.25
	1. 8525 2. 445.24		1. 8530 2. 457.25

920

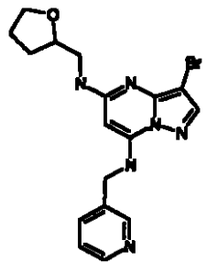
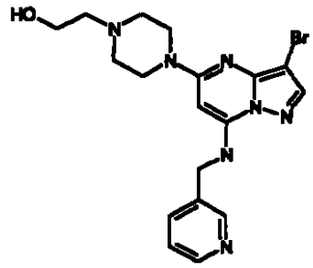
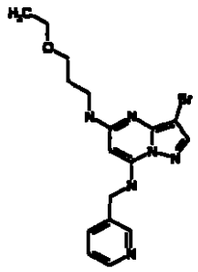
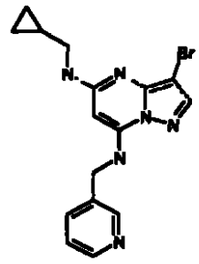
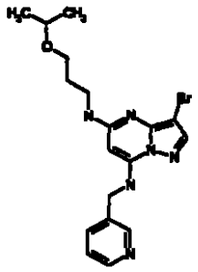
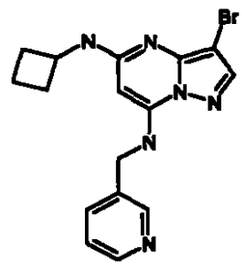
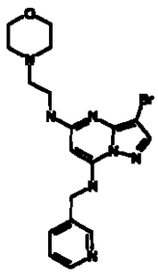
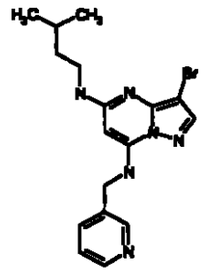
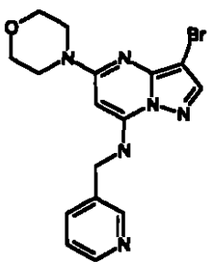
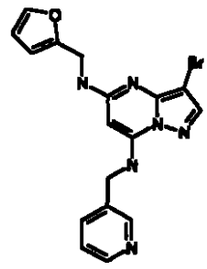
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	1. 8532 2. 483.27		1. 8537 2. 429.24
	1. 8533 2. 483.27		1. 8538 2. 397.22
			1. 8539 2. 411.23
			1. 8540 2. 411.23

921

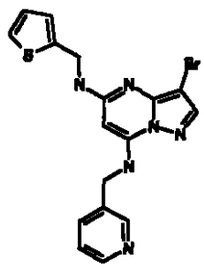
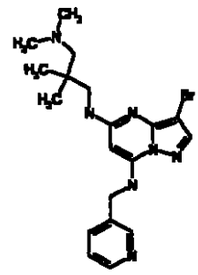
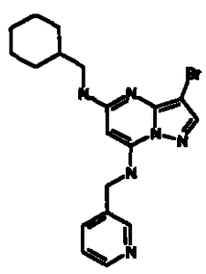
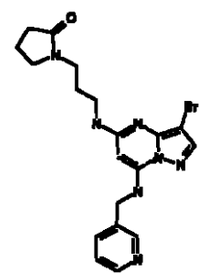
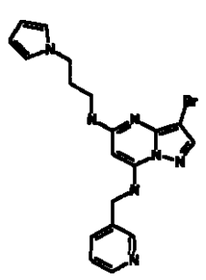
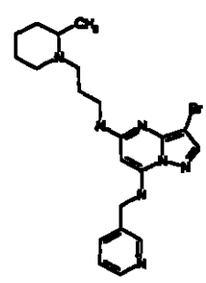
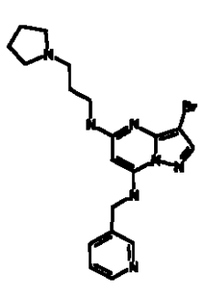
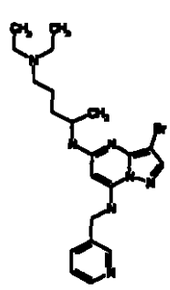
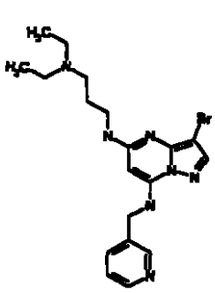
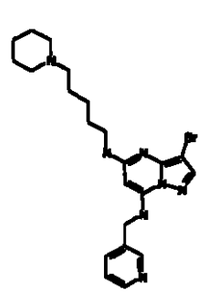
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8541 2. 432.24		1. 8547 2. 478.26
	1. 8542 2. 433.24		1. 8548 2. 498.27
	1. 8543 2. 438.24		1. 8549 2. 385.1
	1. 8545 2. 464.26		1. 8549 2. 337.1
	1. 8546 2. 466.26		1. 8550 2. 351.1

922

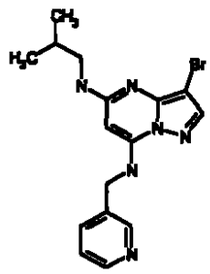
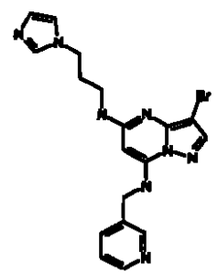
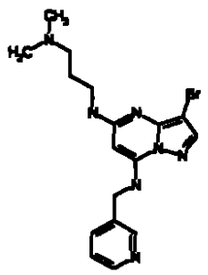
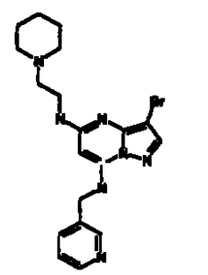
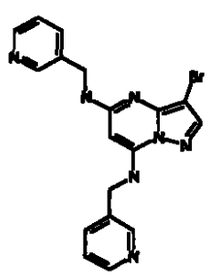
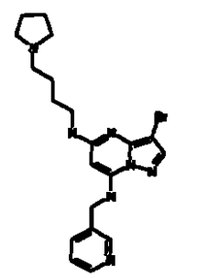
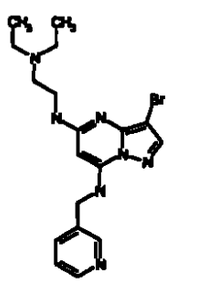
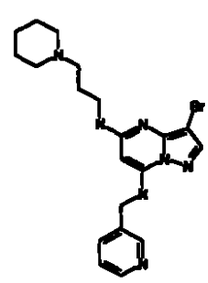
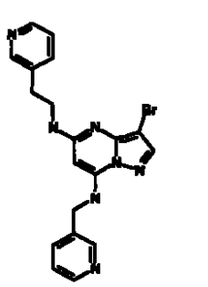
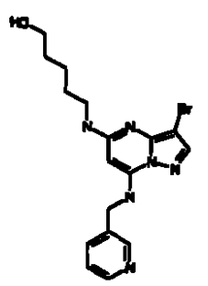
TABLA 86

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

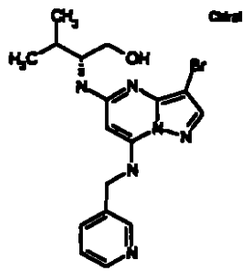
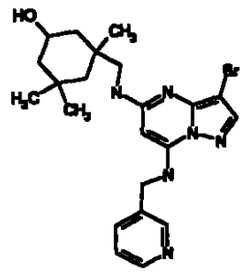
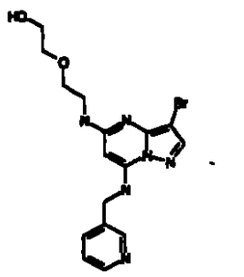
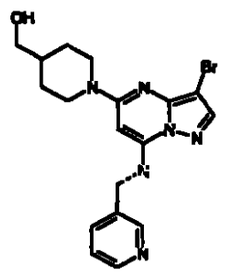
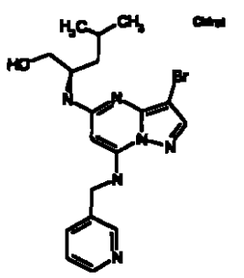
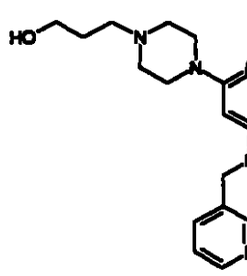
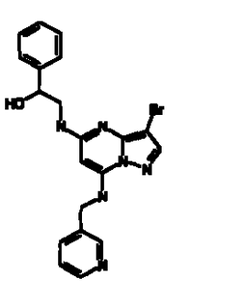
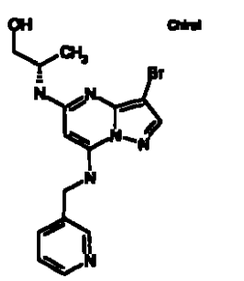
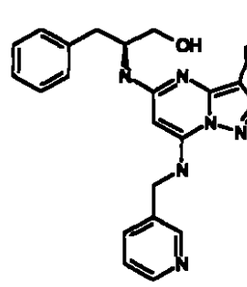
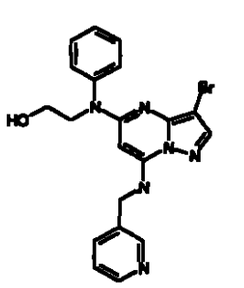
923

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

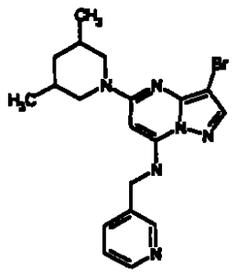
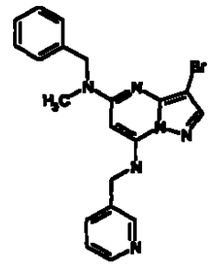
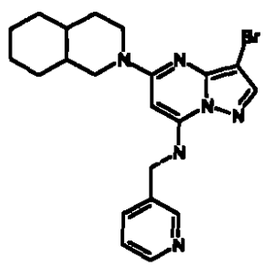
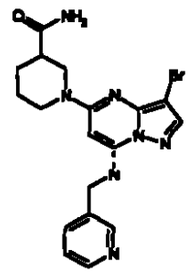
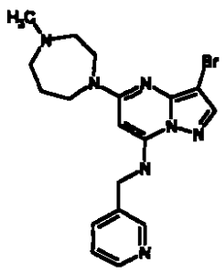
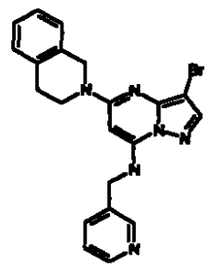
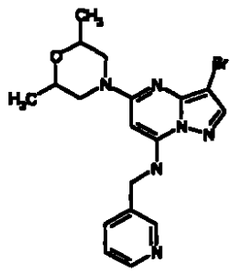
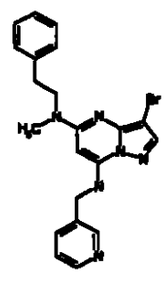
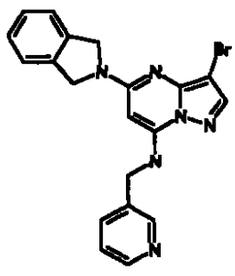
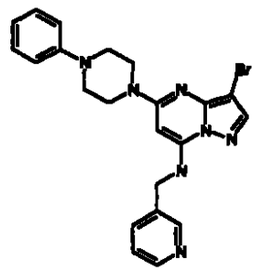
924

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

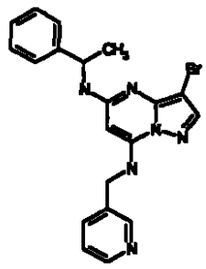
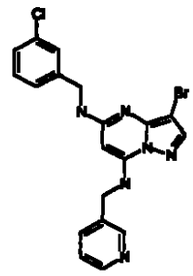
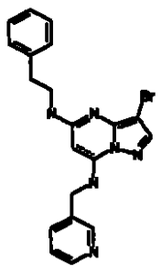
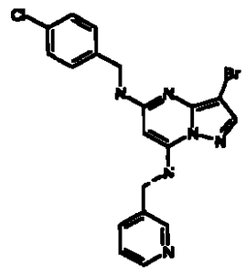
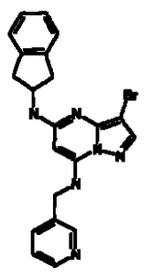
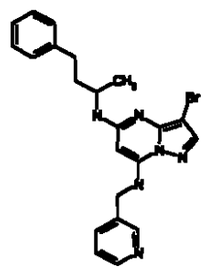
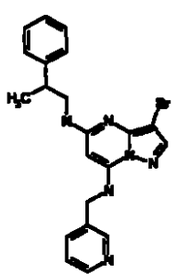
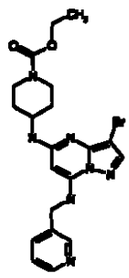
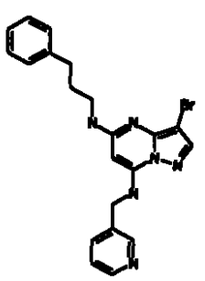
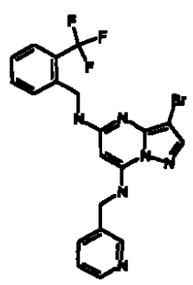
925

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

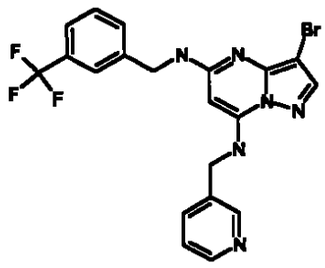
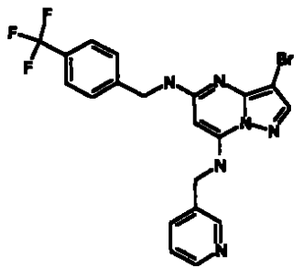
926

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

927

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

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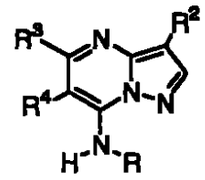
Producto	1. Ej. 2. m/z
	1. 8661 2. 477.26
	1. 8662 2. 479.25

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930

REIVINDICACIONES

Habiendo así especialmente descrito y determinado la naturaleza de la presente invención y la forma como la misma ha de ser llevada a la práctica, se declara reivindicar como de propiedad y derecho exclusivo.

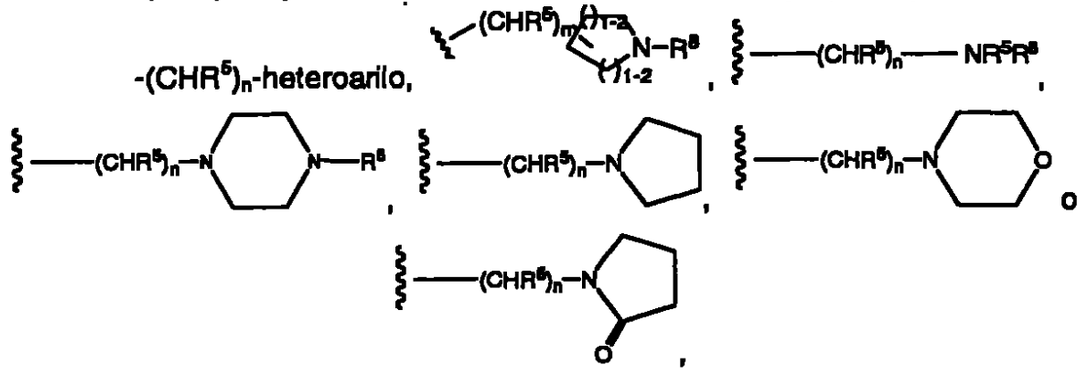
1. Un compuesto representado mediante la fórmula estructural:



o una sal aceptable para uso farmacéutico o solvato de dicho compuesto,

en el cual:

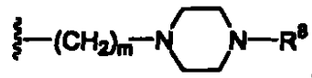
R es H, alquilo, alquenilo, alquinilo, arilalquilo, arilalquenilo, cicloalquilo, cicloalquilalquilo, alquenilalquilo, alquinilalquilo, heterociclilo, heterociclilalquilo, heteroarilalquilo (incluyendo el N-óxido de dicho heteroarilo), -$(CHR^5)_n$-arilo, -$(CHR^5)_n$-heteroarilo,

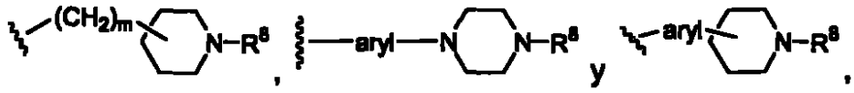


donde cada uno de dichos alquilo, alquenilo, alquinilo, arilo, cicloalquilo, heterociclilo y heteroarilo puede ser no sustituido o sustituido opcionalmente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo que consiste en halógeno, alquilo, 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 $-N(R^5)C(O)NR^5R^{10}$;

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R^2 se selecciona del grupo que consiste en 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 se seleccionan independientemente del listado de R^9 que se muestra a continuación, arilo sustituido con 1-3 grupos arilo o heteroarilo que pueden ser iguales o diferentes y se seleccionan independientemente 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 se seleccionan independientemente de grupos fenilo, piridilo, tiofenilo, furanilo y tiazolo, heteroarilo fusionado con un grupo arilo o heteroarilo,

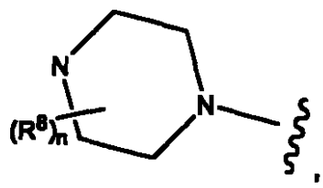
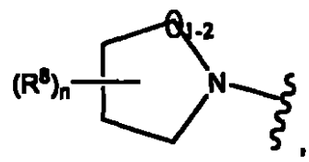
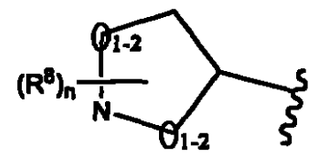
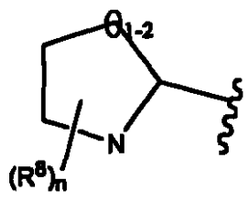




donde uno o más de los arilo y/o uno o más de los heteroarilo en las definiciones mencionadas anteriormente para R^2 puede ser no sustituido o sustituido opcionalmente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo que consiste en halógeno, -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 se selecciona 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,

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y


donde cada uno de dichos alquilo, cicloalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heteroarilo y heteroarilalquilo para R^3 y los restos heterociclilo cuyas estructuras se muestran en forma inmediatamente anterior para R^3 puede ser no sustituido o sustituido independientemente de manera opcional con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, CN, $-OCF_3$, $-(CR^4R^5)_pOR^5$, $-OR^5$, $-NR^5R^6$, $-(CR^4R^5)_pNR^5R^6$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^6$, con la salvedad de que ningún carbono adyacente al átomo de nitrógeno en un anillo heterociclilo posea un resto $-OR^5$;

R^4 es H, halo o alquilo;

R^5 es H, alquilo, arilo o cicloalquilo;

R^6 se selecciona del grupo que consiste en H, 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 puede ser no sustituido o sustituido opcionalmente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, heterociclilalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^{10}$, $-C(R^4R^5)_p-R^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)R^5$,

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$-C(O)NR^5R^{10}$, $-SO_3H$, $-SR^{10}$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^{10}$;

R^{10} se selecciona 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 puede ser no sustituido o sustituido opcionalmente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente 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 el resto $-NR^5R^{10}$, o (ii) R^5 y R^8 en el resto $-NR^5R^8$, se pueden unir para formar un resto cicloalquilo o heterociclilo, siendo cada uno de dichos restos cicloalquilo o heterociclilo no sustituidos o sustituidos opcionalmente de manera independiente con uno o más grupos R^9;

R^7 se selecciona 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 puede ser no sustituido o sustituido independientemente de manera opcional con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente 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 se selecciona 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

933

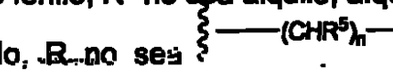
$-S(O_2)R^7$;

R^9 se selecciona del grupo que consiste en halógeno, -CN, $-NR^5R^{10}$, $-C(O_2)R^6$, $-C(O)NR^5R^{10}$, $-OR^6$, $-SR^6$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^{10}$;

m es 0 a 4;

n es 1 a 4; y

p es 1 a 4,

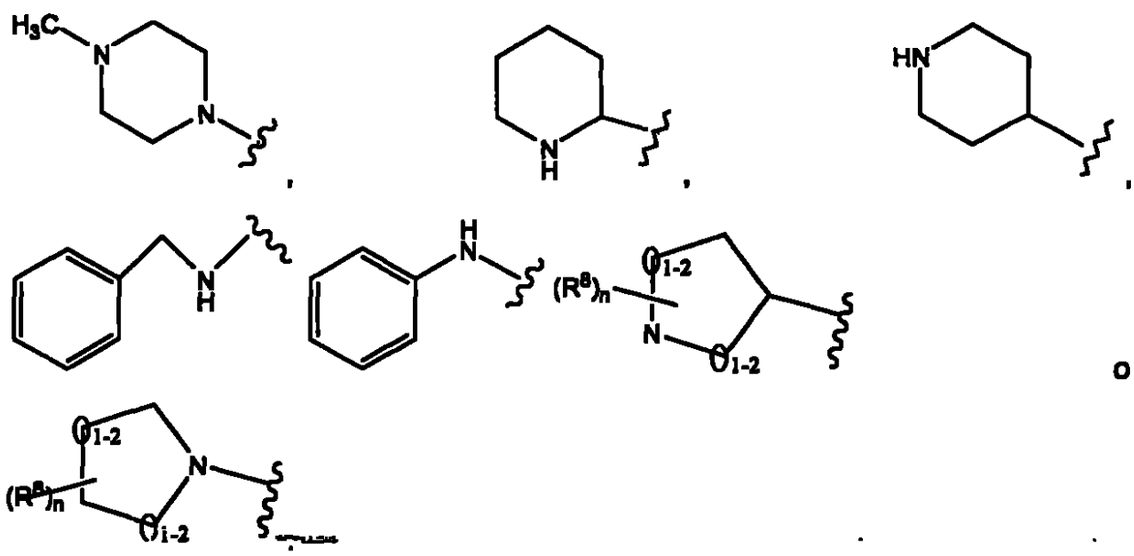
con la salvedad de que cuando R^2 es fenilo, R^3 no sea alquilo, alquinilo o halógeno, y que cuando R^2 es arilo, R no sea  , con la salvedad adicional de que cuando R es arilalquilo, entonces cualquier sustituyente heteroarilo en el arilo de dicho arilalquilo contiene al menos tres heteroátomos.

2. El compuesto de la reivindicación 1, en el cual R es $-(CHR^5)_n$-arilo, $-(CHR^5)_n$-heteroarilo, alquilo, cicloalquilo, heterociclilo o heteroarilalquilo (incluyendo el N-óxido de dicho heteroarilo), donde cada uno de dichos alquilo, arilo, cicloalquilo, heterociclilo y heteroarilo puede ser no sustituido o sustituido opcionalmente con uno o más restos según se enunció en la reivindicación 1;

R^2 es halógeno, alquilo, haloalquilo, CN, cicloalquilo, heterociclilo o alquinilo;

R^3 es H, alquilo inferior, arilo, heteroarilo, cicloalquilo, $-NR^5R^6$,

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donde dicho alquilo, arilo, heteroarilo, cicloalquilo y las estructuras del heterociclilo mostradas en forma inmediatamente anterior para R^3 se sustituyen opcionalmente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente 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 salvedad de que ningún carbono adyacente a un átomo de nitrógeno en un anillo heterociclilo posea un resto $-OR^5$;

R^4 es H o alquilo inferior;

R^5 es H, alquilo inferior o cicloalquilo;

n es 1 a 2; y

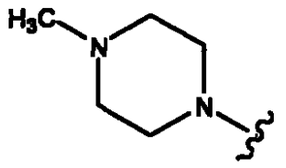
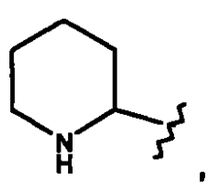
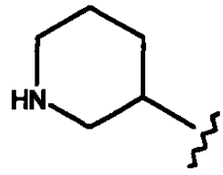
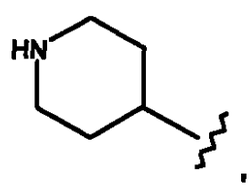
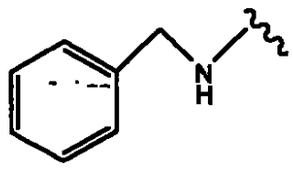
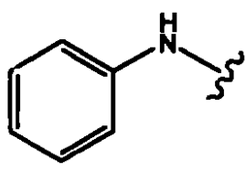
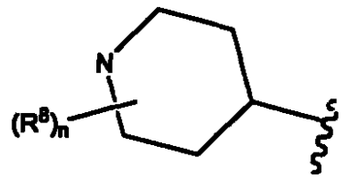
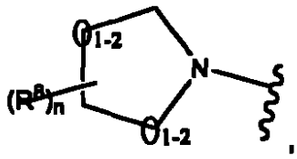
p es 1 o 2.

3. El compuesto de la reivindicación 2, en el cual R es hidroxialquilo, $-(CHR^5)_n$-arilo o $-(CHR^5)_n$-heteroarilo, donde cada uno de dicho arilo y heteroarilo es no sustituido o sustituido con uno o más grupos que pueden ser iguales o diferentes, seleccionándose cada grupo independientemente del grupo que consiste en heteroarilo, amina, heterociclilo, $-C(O)N(R^5R^6)$, $-S(O_2)R^5$, $-S(O_2)N(R^5R^6)$, alcoxi y halo.

935

4. El compuesto de la reivindicación 2, en el cual R^2 es Br, Cl, CF_3, CN, alquilo inferior, ciclopropilo, alquinilo, alquilo sustituido con $-OR^6$ o tetrahidrofuranilo.

5. El compuesto de la reivindicación 2, en el cual R^3 es H, alquilo inferior, arilo, heteroarilo, cicloalquilo,

donde cada uno de dichos alquilo, arilo, heteroarilo, cicloalquilo y las estructuras del heterociclilo que se muestran en forma inmediatamente anterior para R^3 se sustituyen opcionalmente con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo que consiste en halógeno, CF_3, OCF_3, alquilo inferior, CN y OR^5, con la salvedad de que ningún carbono adyacente a un átomo de nitrógeno en un anillo heterociclilo posea un resto $-OR^5$.

6. El compuesto de la reivindicación 2, en el cual R^4 es H o alquilo inferior.

7. El compuesto de la reivindicación 2, en el cual R^5 es H.

8. El compuesto de la reivindicación 2, en el cual n es 1.

9. El compuesto de la reivindicación 1, en el cual p es 1.

10. El compuesto de la reivindicación 2, en el cual R es bencilo o hidroxialquilo.

936

11. El compuesto de la reivindicación 2, en el cual R es pirid-3-ilmetilo, donde dicho piridilo puede ser no sustituido o sustituido de manera opcional con uno o más restos según se enunció en la reivindicación 1.

12. El compuesto de la reivindicación 2, en el cual R es pirid-4-ilmetilo, donde dicho piridilo puede ser no sustituido o sustituido de manera opcional con uno o más restos según se enunció en la reivindicación 1.

13. El compuesto 2, en el cual R es el N-óxido del pirid-2-ilmetilo, pirid-3-ilmetilo o pirid-4-ilmetilo, donde cada uno de dichos grupos piridilo puede ser no sustituido o sustituido de manera opcional con uno o más restos según se enunció en la reivindicación 1.

14. El compuesto de la reivindicación 4, en el cual dicho R^2 es Br.

15. El compuesto de la reivindicación 4, en el cual dicho R^2 es Cl.

16. El compuesto de la reivindicación 4, en el cual R^2 es etilo.

17. El compuesto de la reivindicación 4, en el cual R^2 es ciclopropilo.

18. El compuesto de la reivindicación 4, en el cual R^2 es etinilo.

19. El compuesto de la reivindicación 2, en el cual R^3 es alquilo inferior, cicloalquilo, heterociclilo, arilo o $-N(R^5R^6)$.

20. El compuesto de la reivindicación 19, en el cual R^3 es isopropilo.

21. El compuesto de la reivindicación 19, en el cual R^3 es ciclohexilo o norbornilo, donde cada uno de dichos ciclohexilo o norbornilo puede ser no sustituido o sustituido con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo que consiste en alquilo e hidroxialquilo.

22. El compuesto de la reivindicación 19, en el cual R^3 es fenilo no sustituido.

23. El compuesto de la reivindicación 19, en el cual R^3 es un fenilo sustituido con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo que consiste en F, Br, Cl y CF_3.

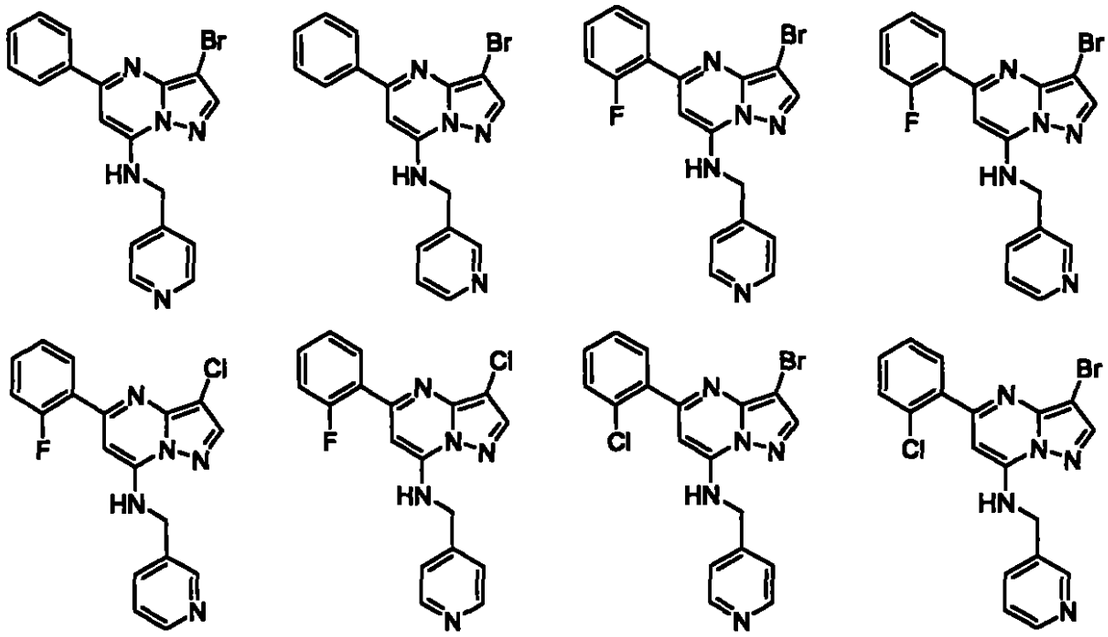
937

24. El compuesto de la reivindicación 19, en el cual R^5 de dicho –N(R^5R^6) es H o hidroxialquilo, y R^6 de dicho –N(R^5R^6) se selecciona del grupo que consiste en alquilo, hidroxialquilo, cicloalquilo y metilendioxi, donde cada uno de dichos alquilo y cicloalquilo puede ser no sustituido o sustituido con uno o más restos que pueden ser iguales o diferentes, seleccionándose cada resto independientemente del grupo que consiste en amina, etoxicarbonilo, amida, hidroxialquilo, hidroxi.

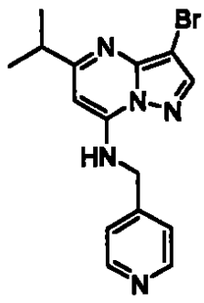
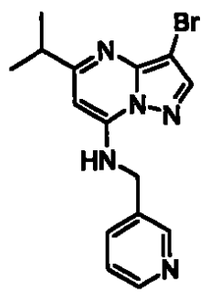
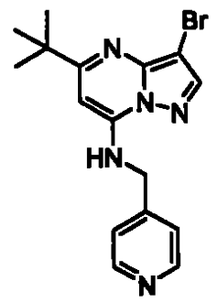
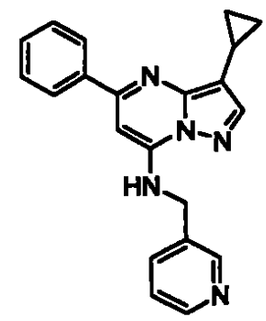
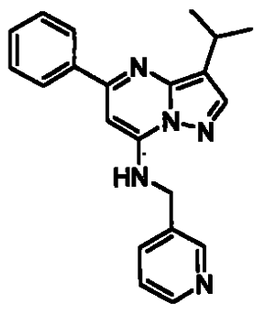
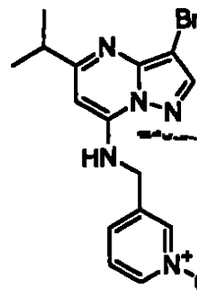
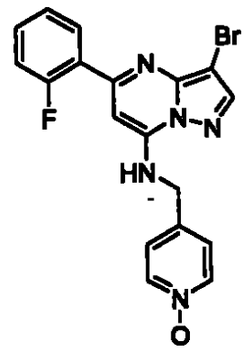
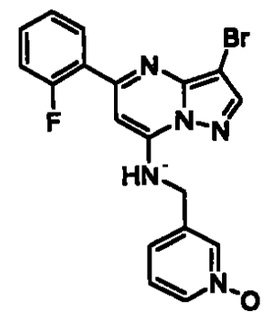
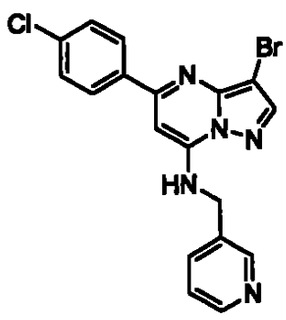
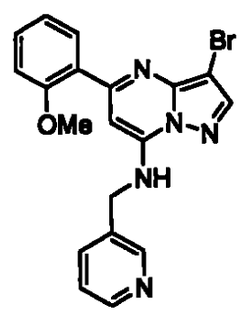
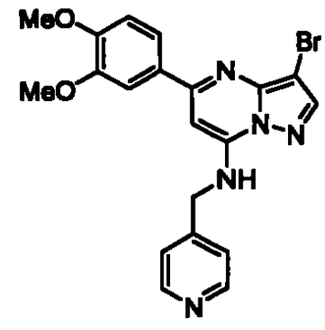
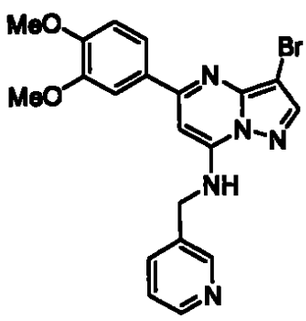
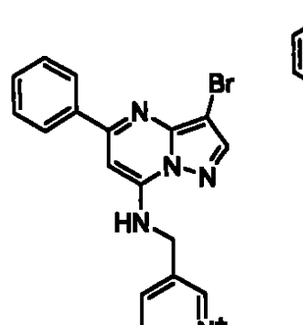
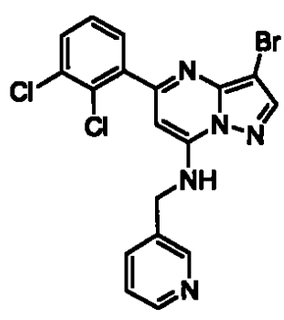
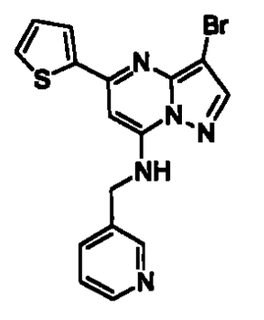
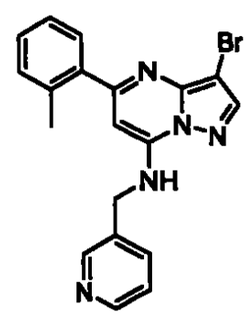
25. El compuesto de la reivindicación 19, en el cual R^5 y R^6 de dicho –N(R^5R^6) se unen para formar un resto heterociclilo, donde dicho resto heterociclilo puede ser no sustituido o sustituido independientemente de manera opcional con uno o más grupos que pueden ser iguales o diferentes, seleccionándose cada grupo del grupo que consiste en hidroxialquilo, amida, -C(O)R^5, >C(CH_3)$_2$, -S(O_2)R^5, -S(O_2)N(R^5R^6), –C(=NH)N(R^5R^6) y –C(=N-CN)N(R^5R^6).

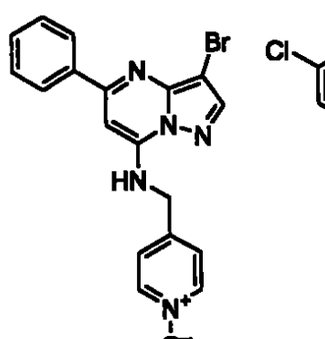
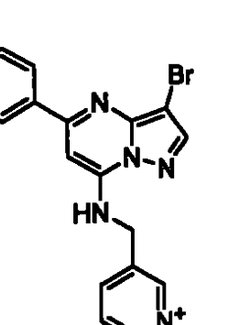
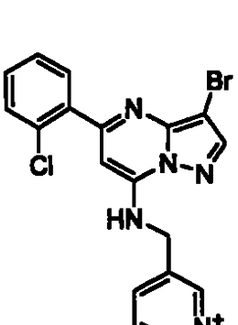
26. El compuesto de la reivindicación 25, en el cual dicho resto heterociclilo formado por R^5 y R^6 es un anillo de pirrolidina o piperidina.

27. Un compuesto de fórmula:

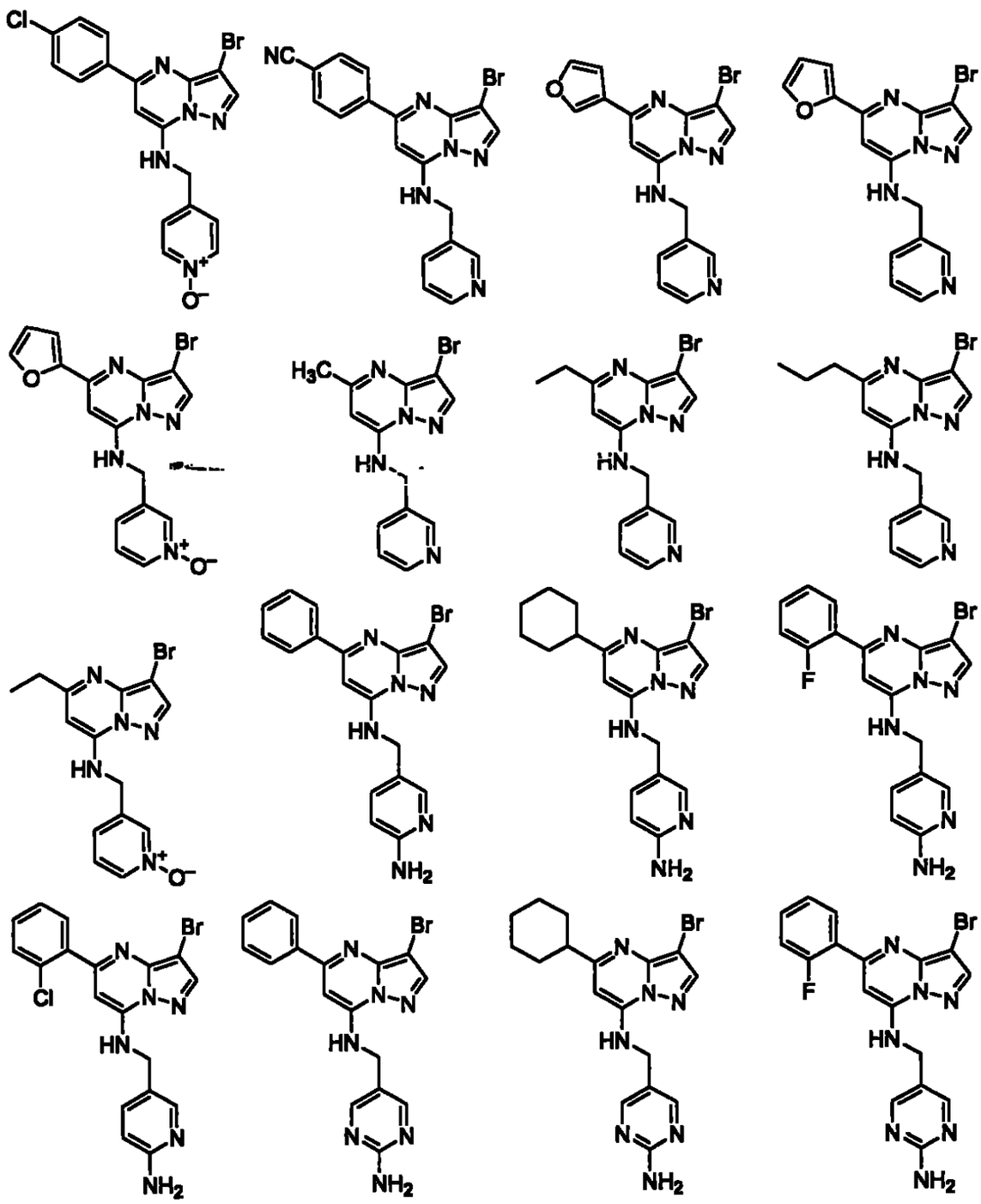


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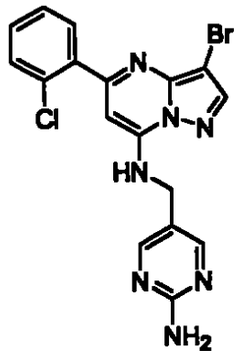
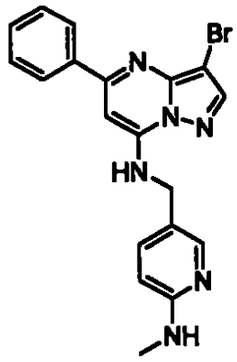
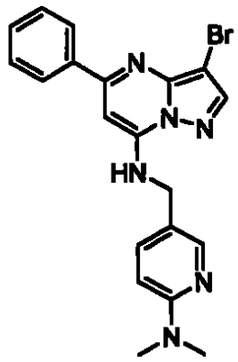
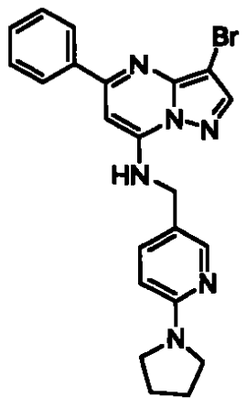
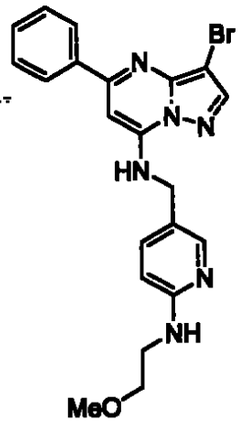
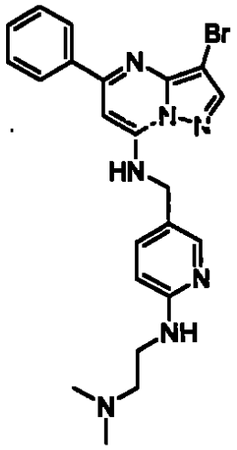
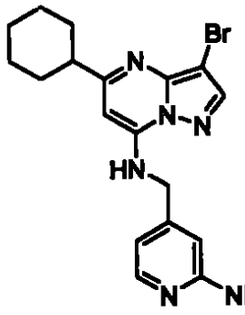
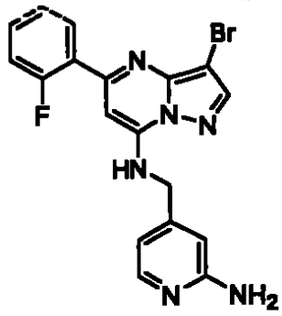
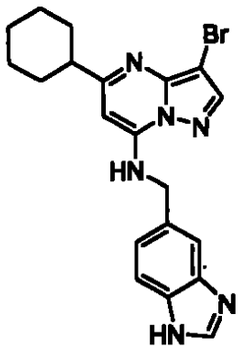
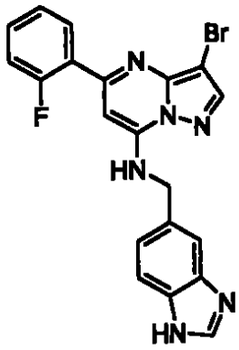
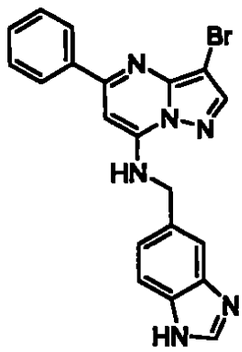
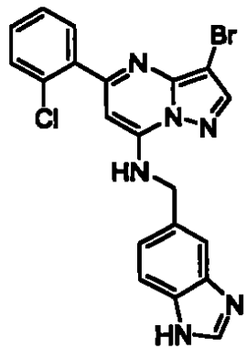
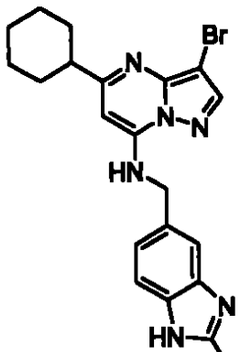
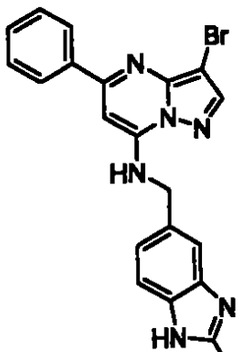
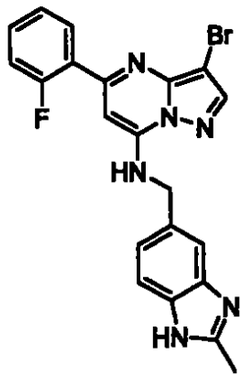
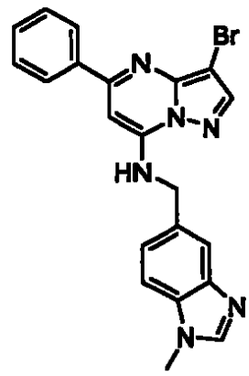

















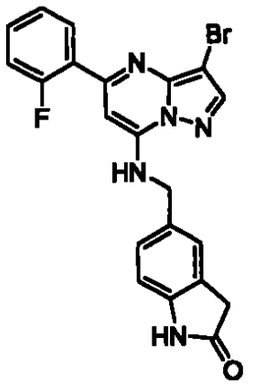
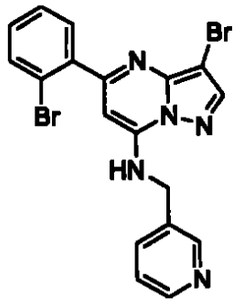
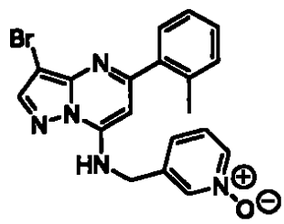
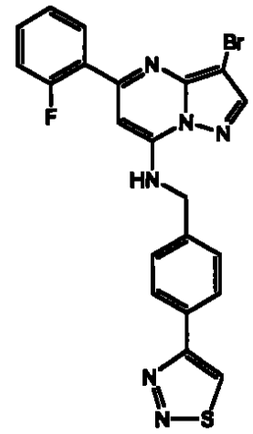
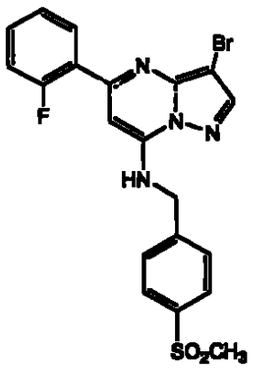
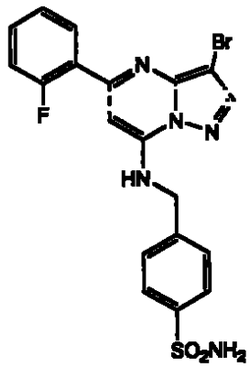
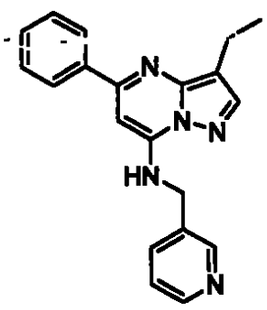
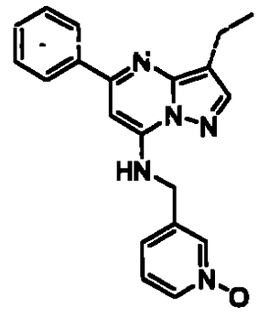
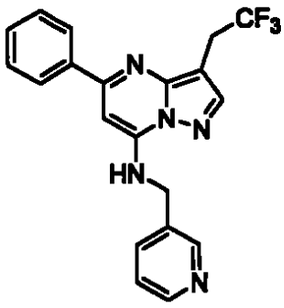
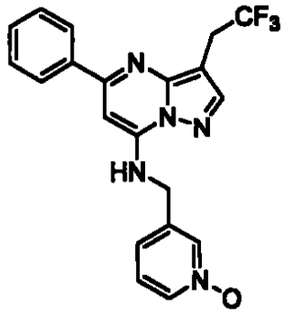
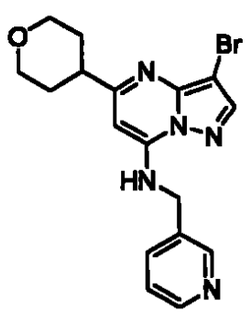
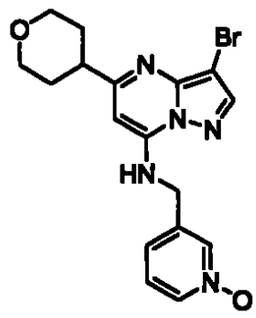
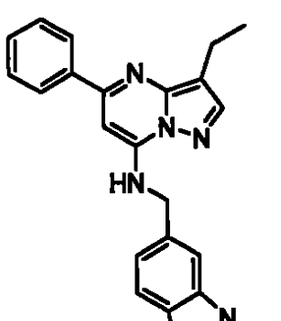
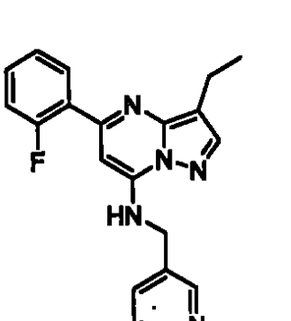
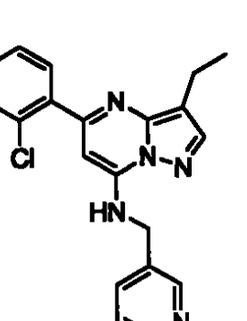
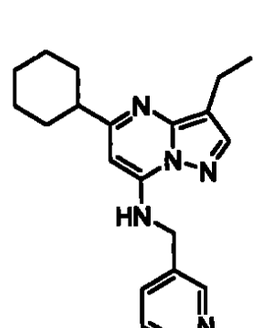




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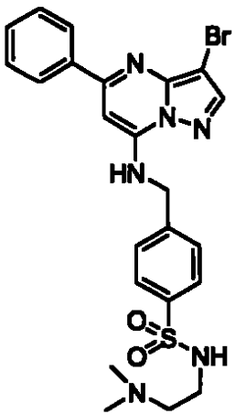
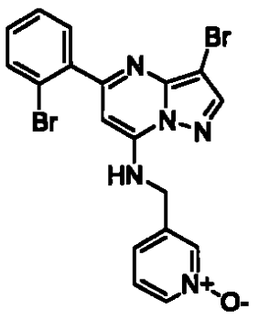
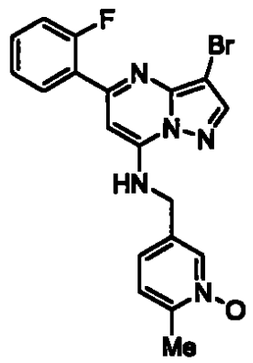
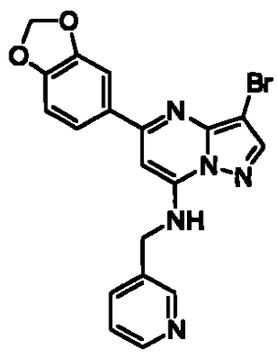
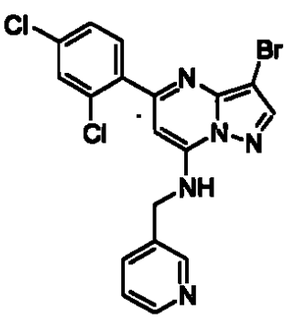
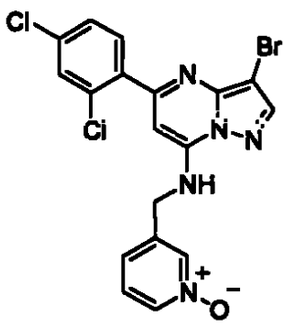
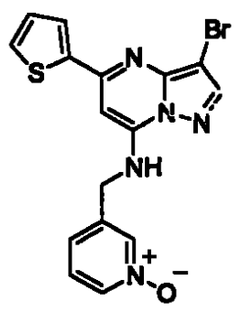
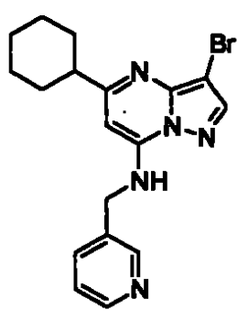
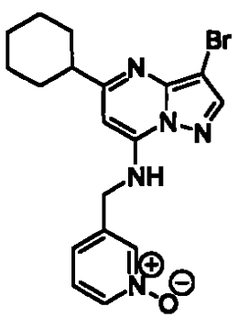
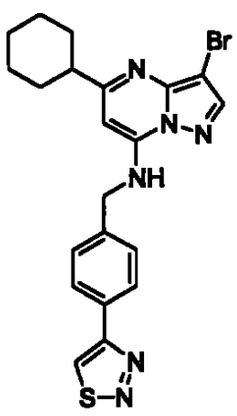
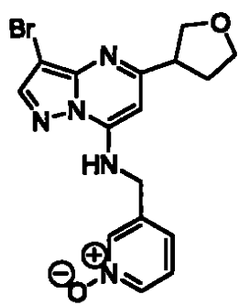
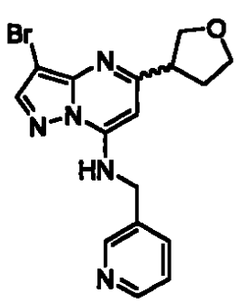
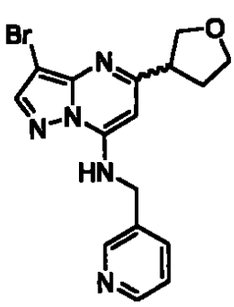
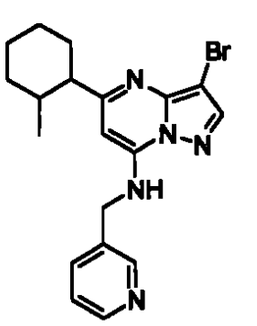
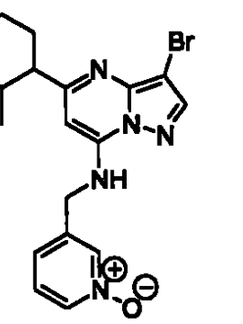
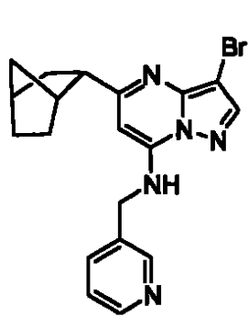

















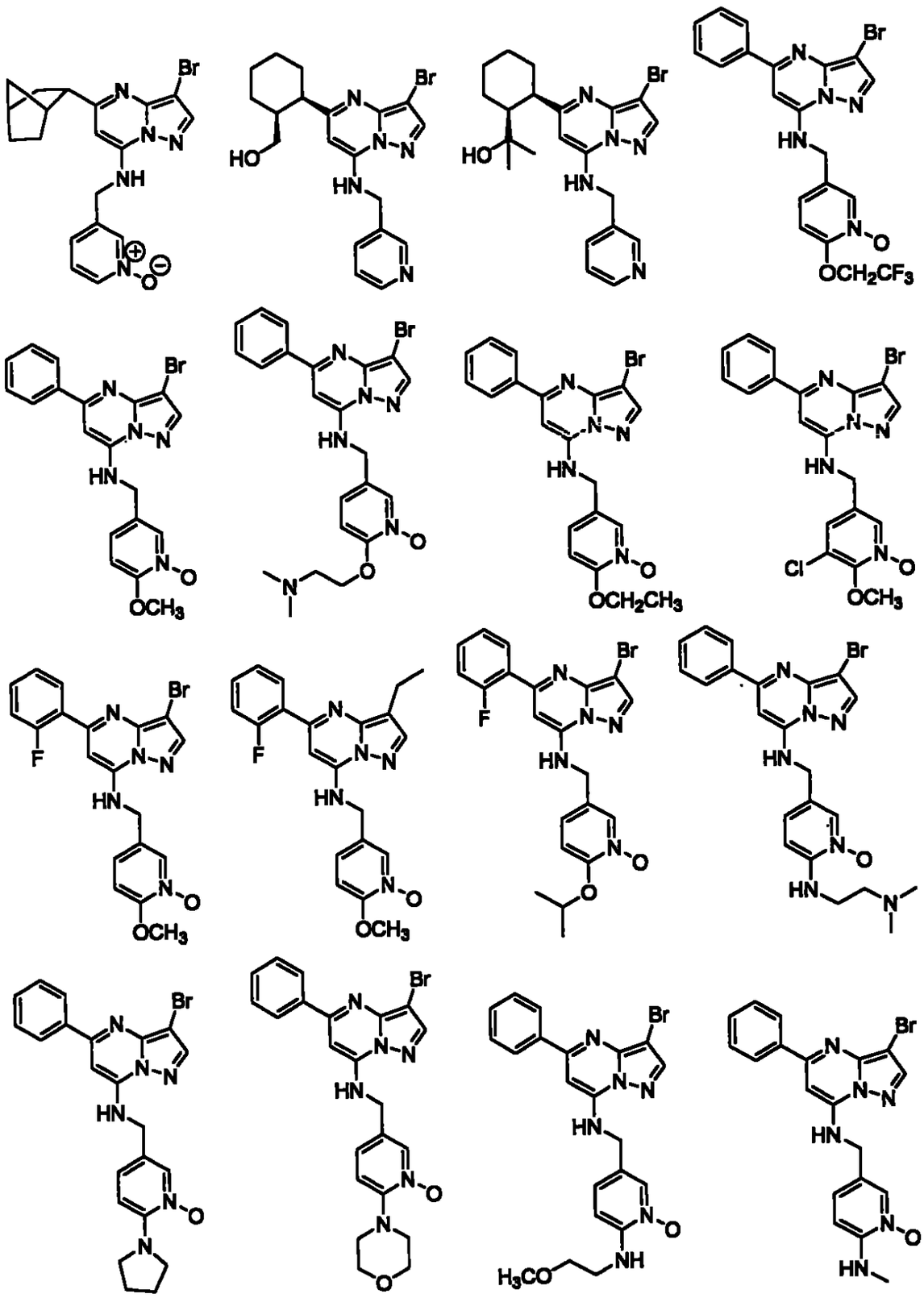


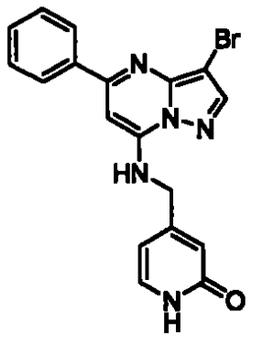
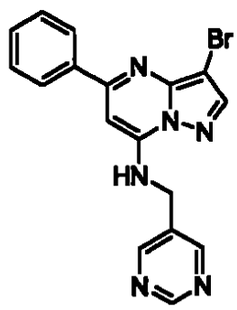
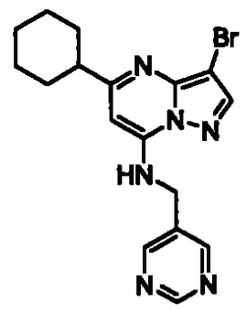
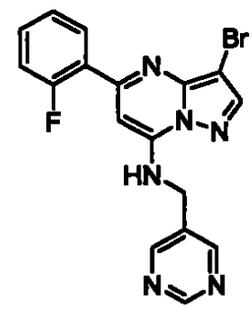
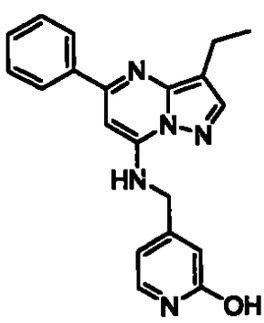
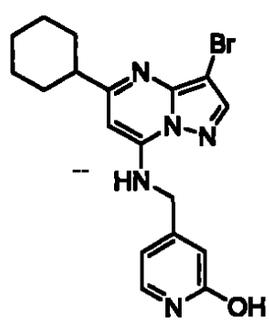
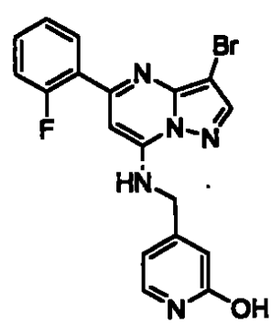
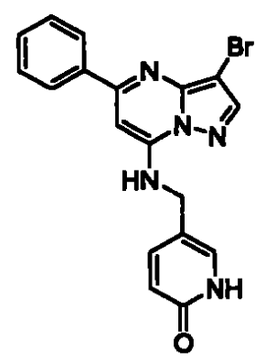
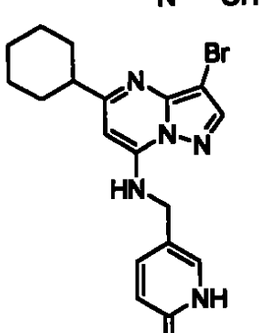
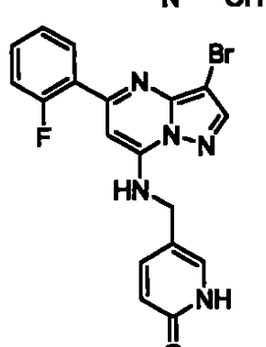
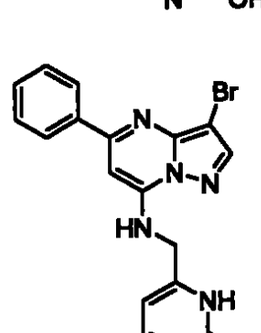
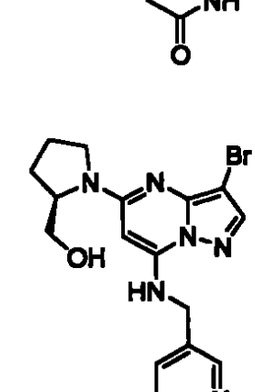
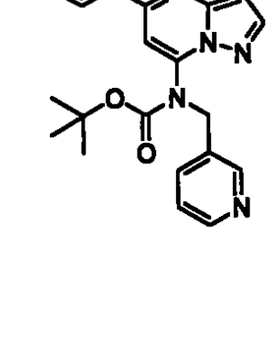
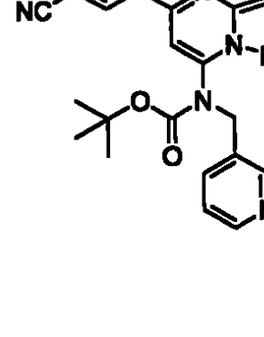
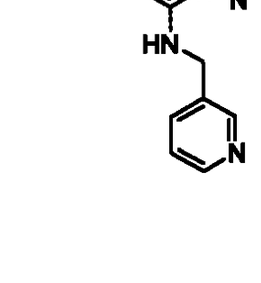
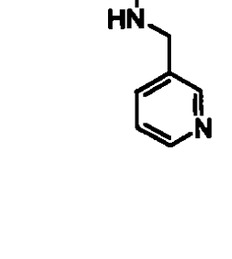


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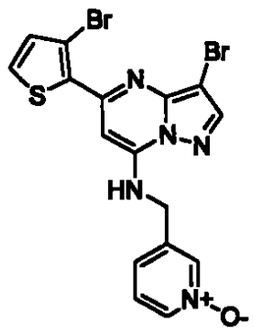
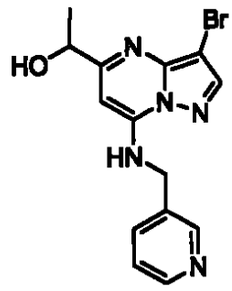
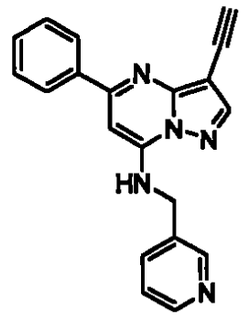
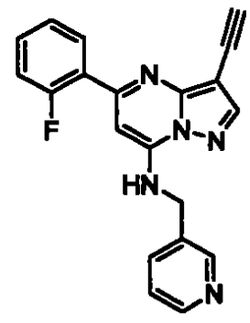
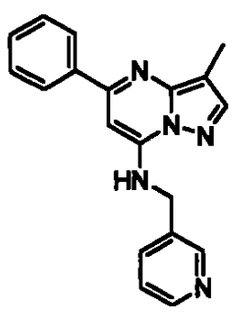
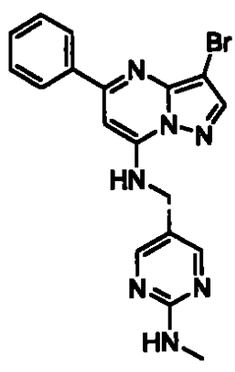
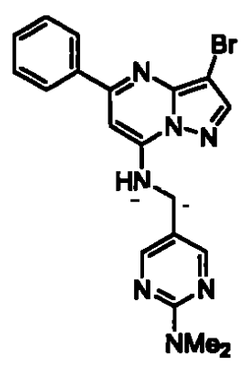
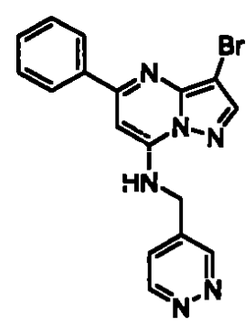
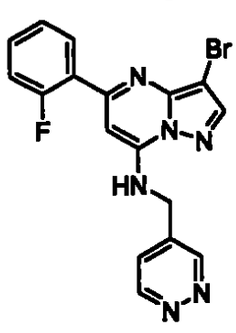
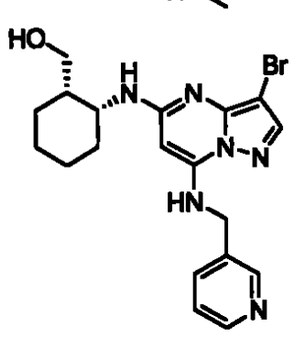
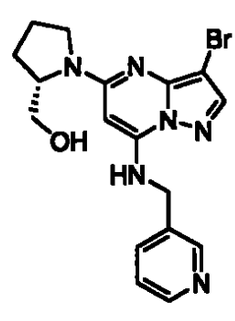
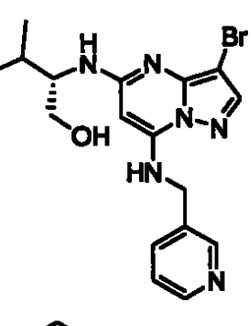
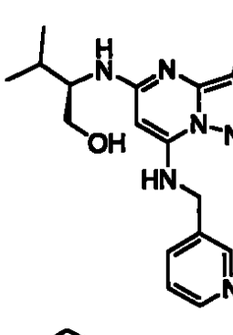
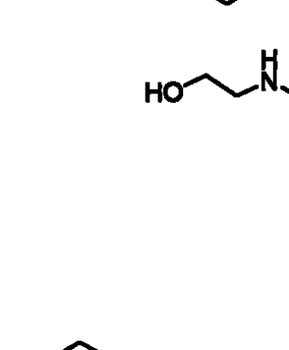
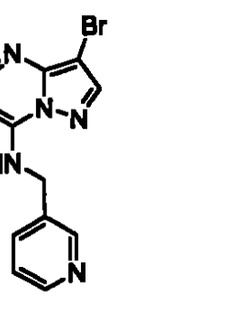
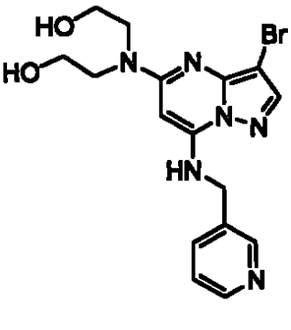
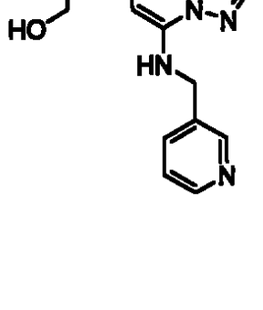
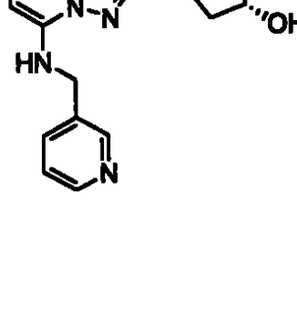
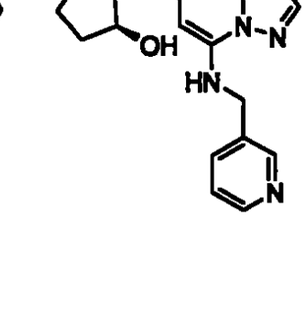

















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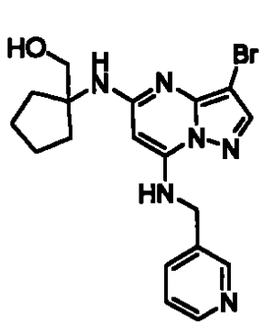


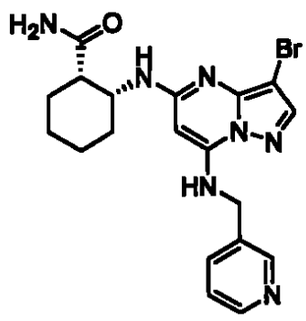

















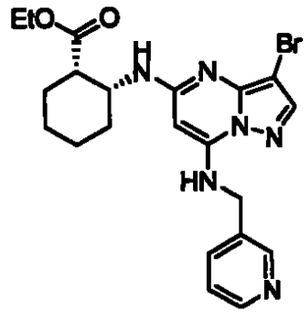
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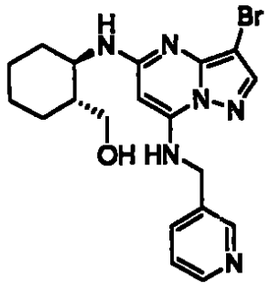




















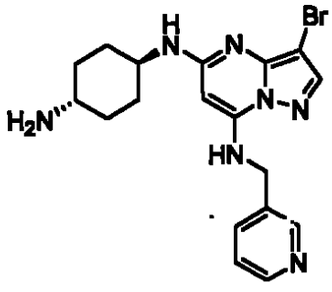
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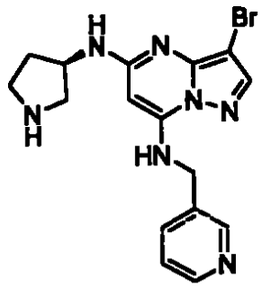


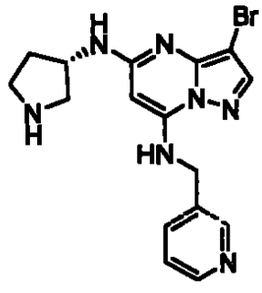


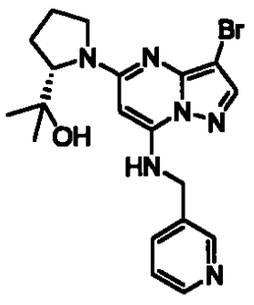


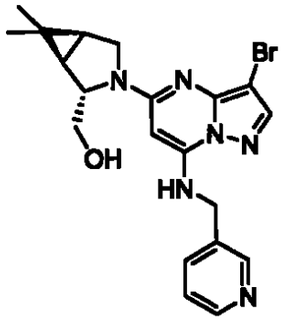


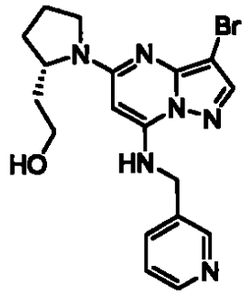


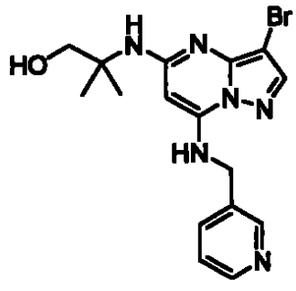


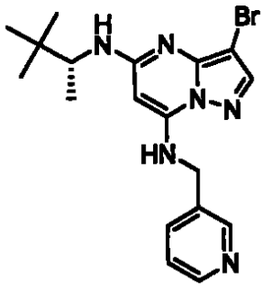


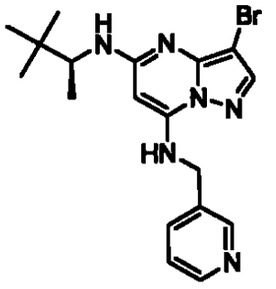


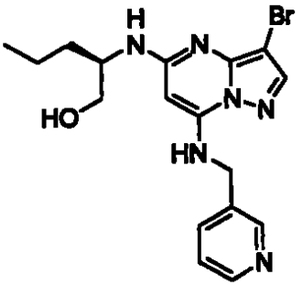


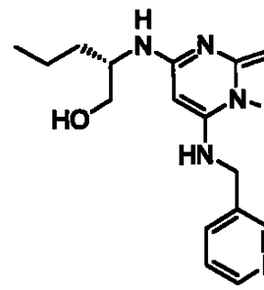


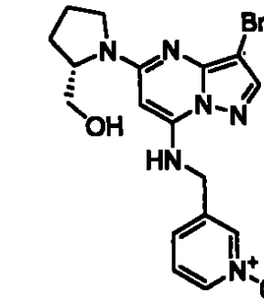


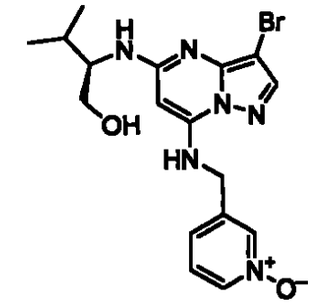


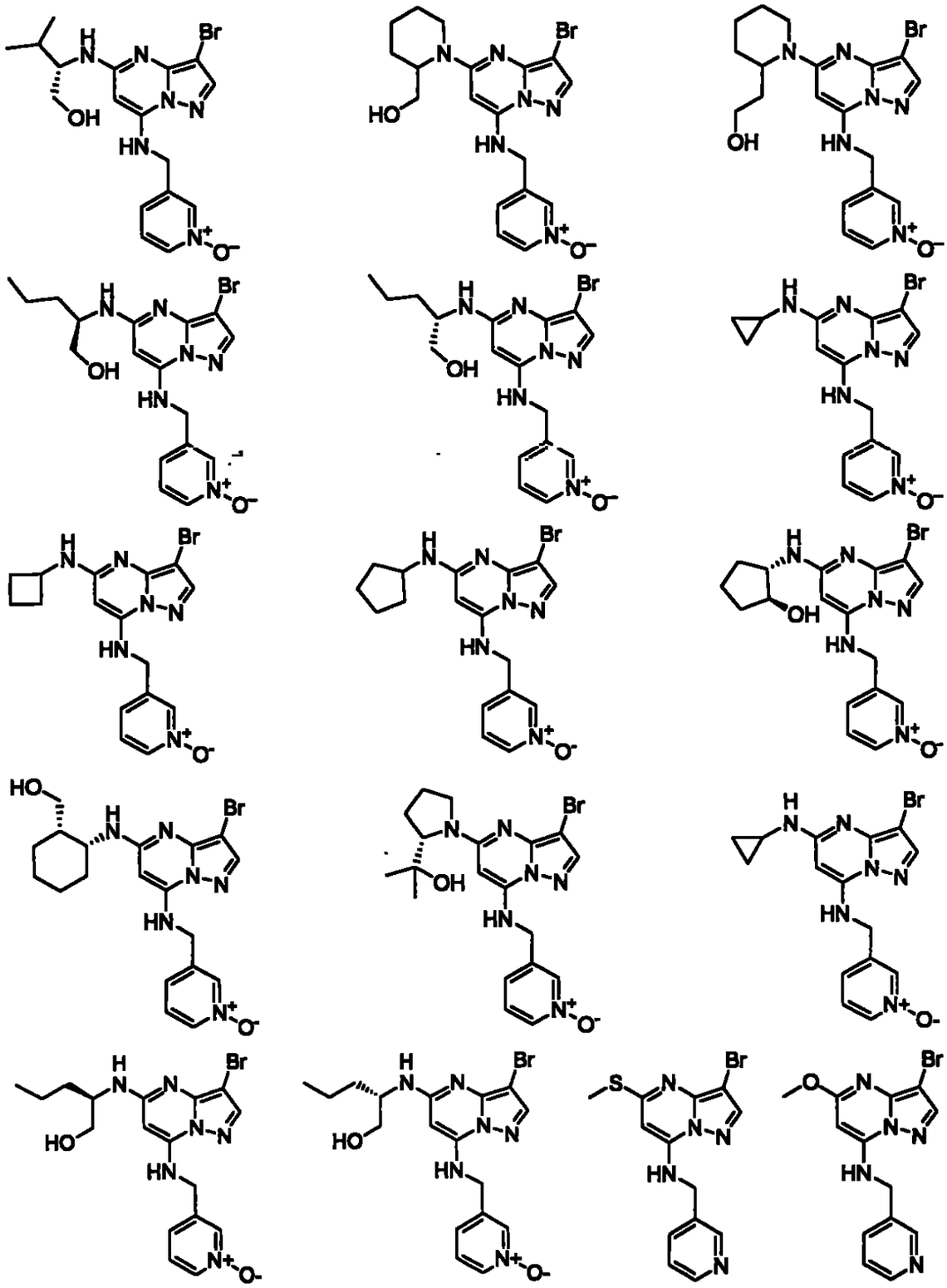




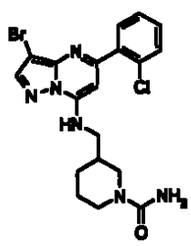
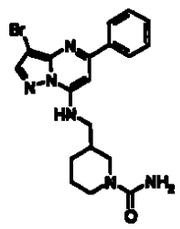
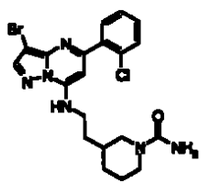
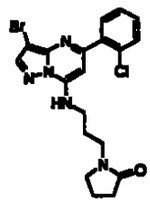
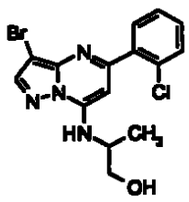


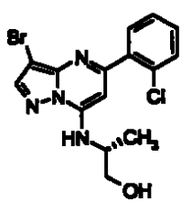
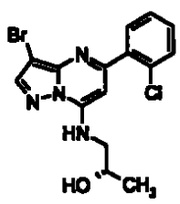
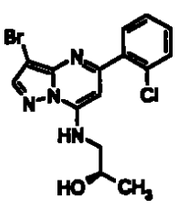
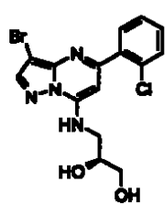
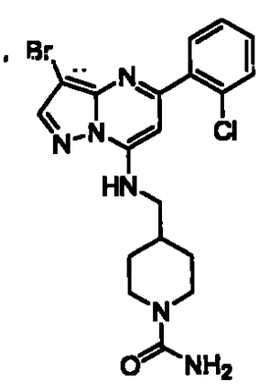
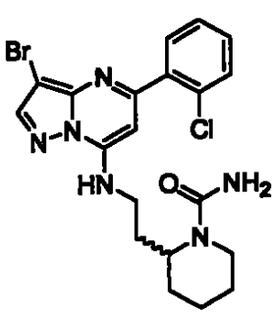
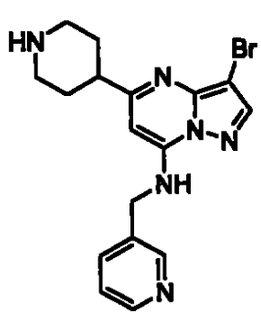
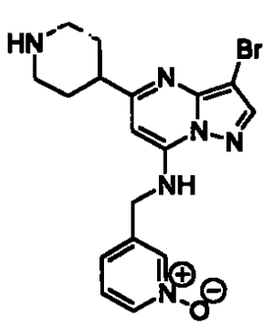
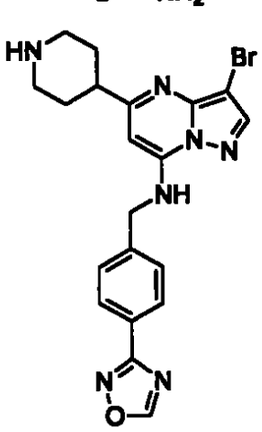
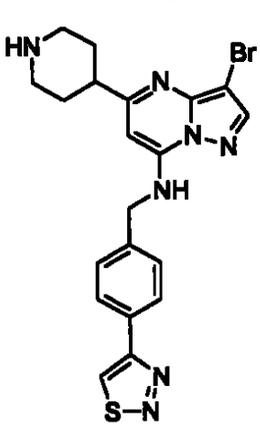
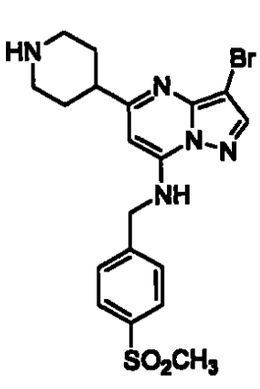
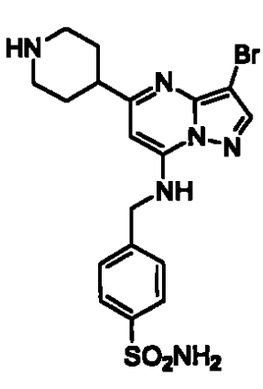
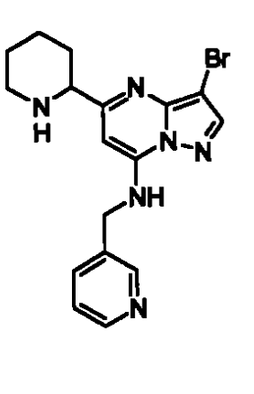
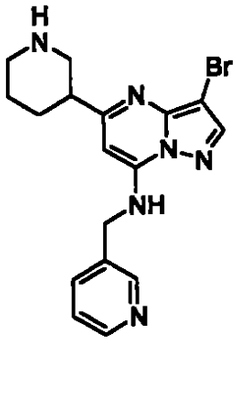
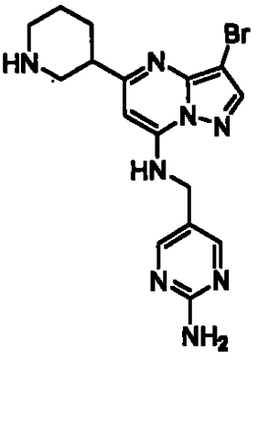
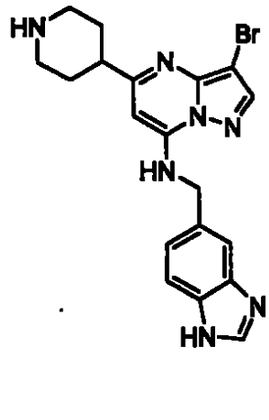


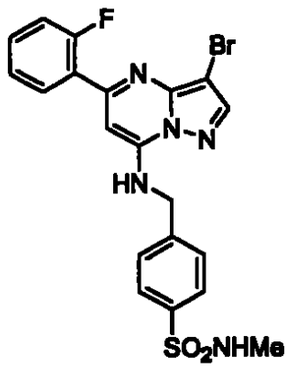


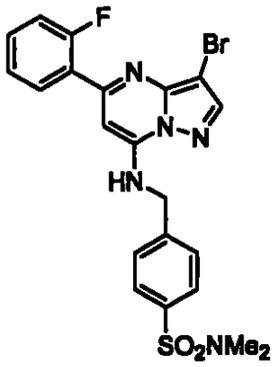


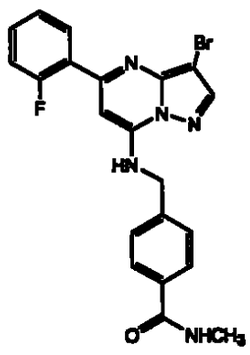
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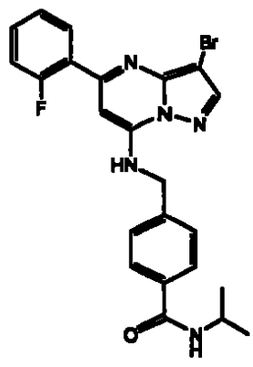






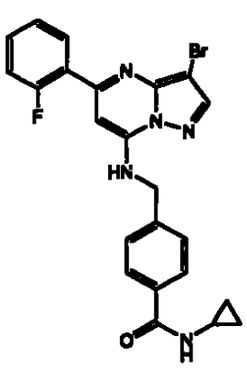

















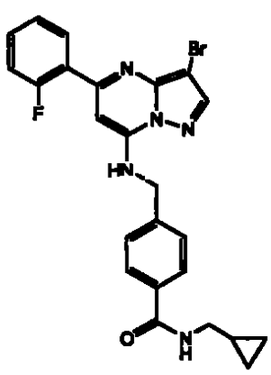

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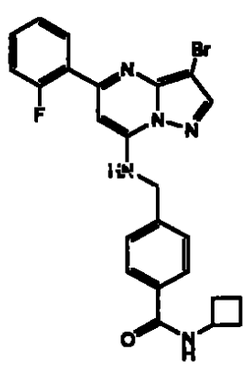

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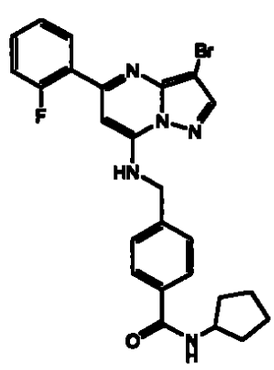

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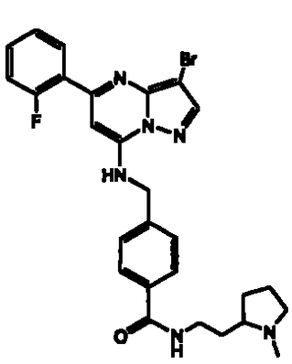

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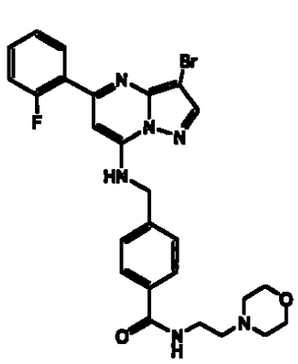

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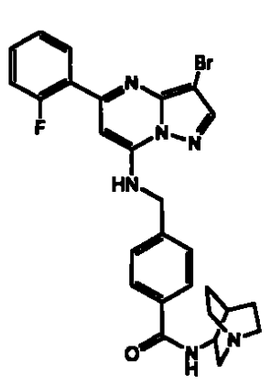

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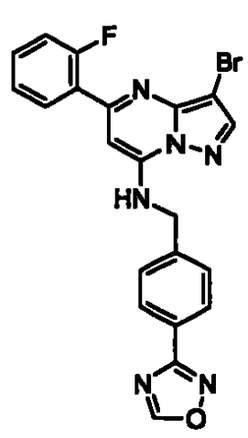

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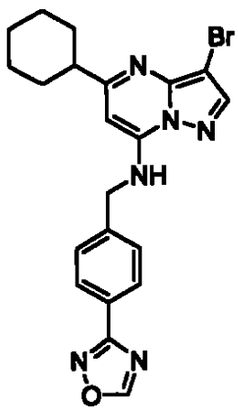
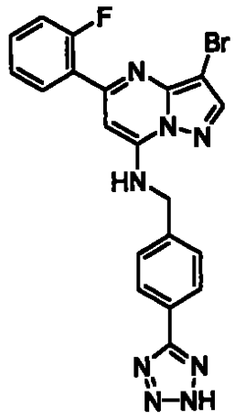
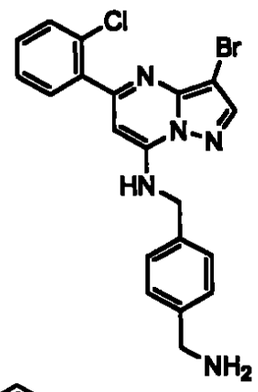
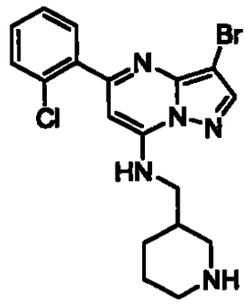
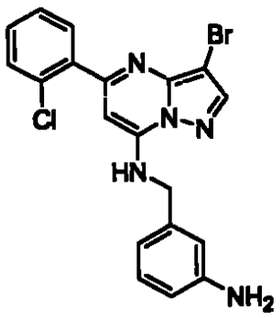
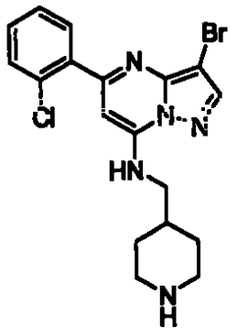
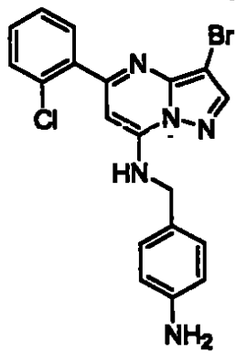
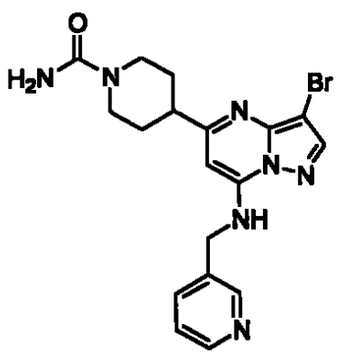
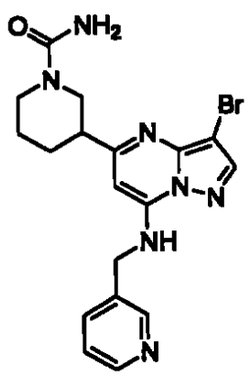
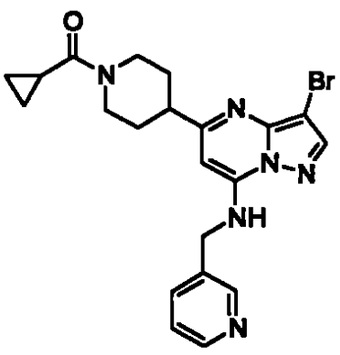
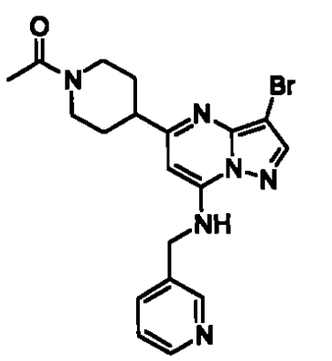
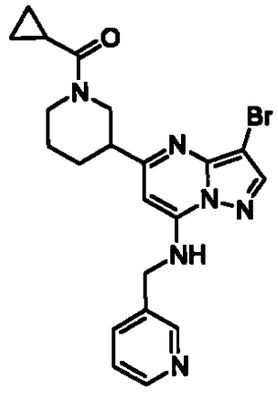
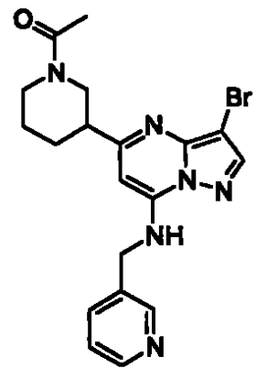

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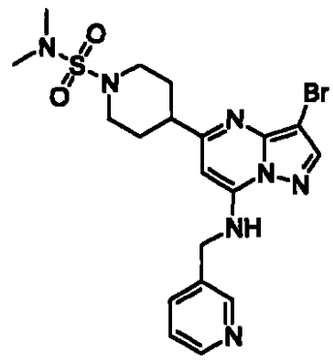

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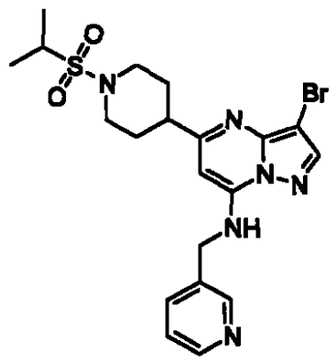

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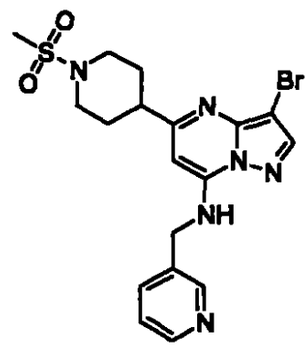
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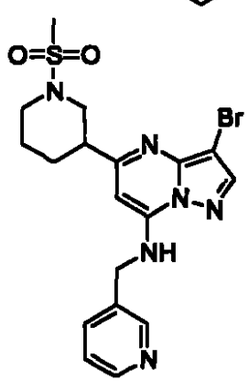














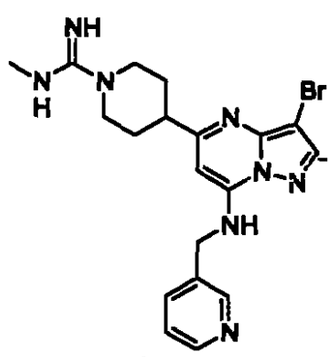
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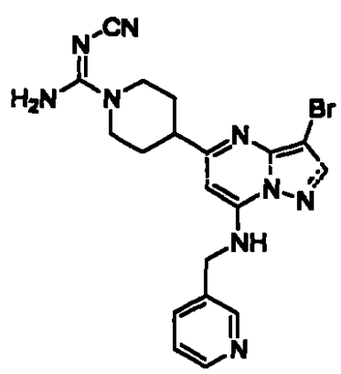


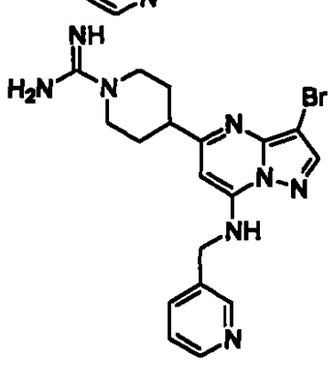


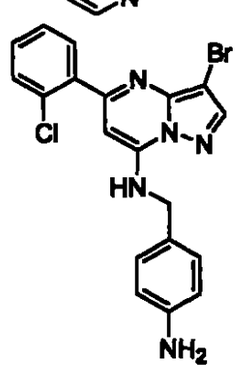


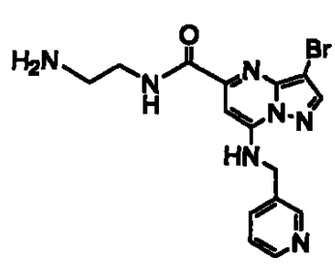


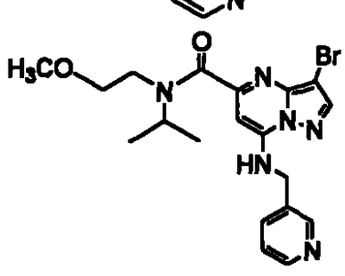








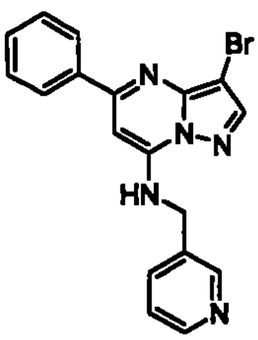
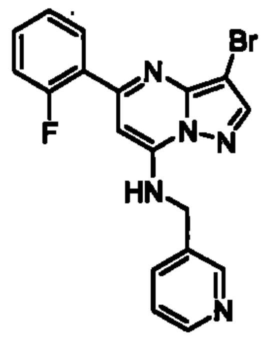
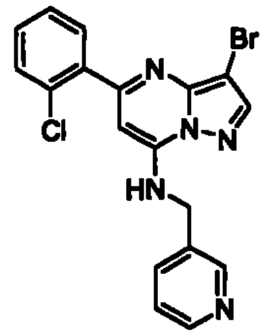
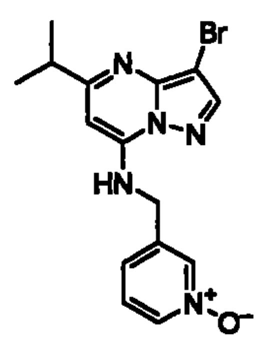


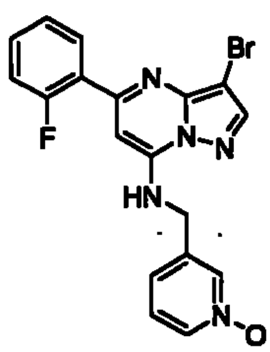
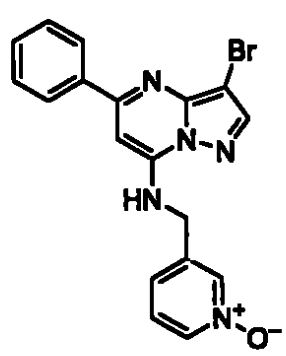
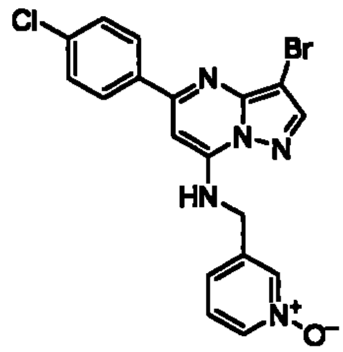
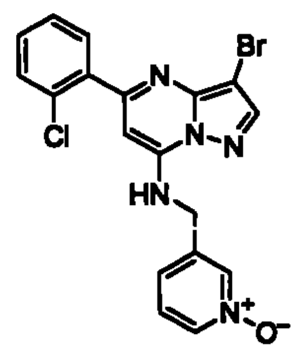


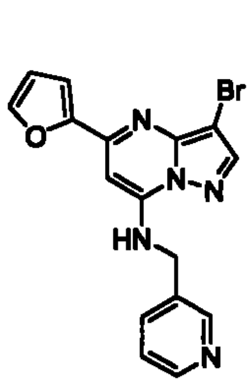
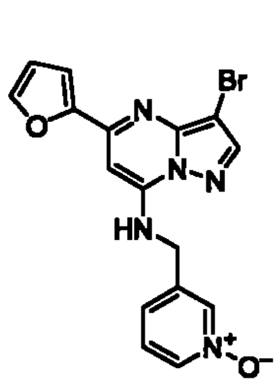
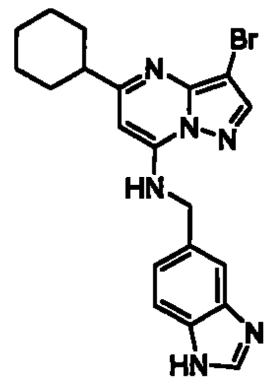
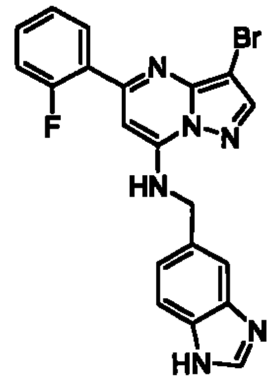
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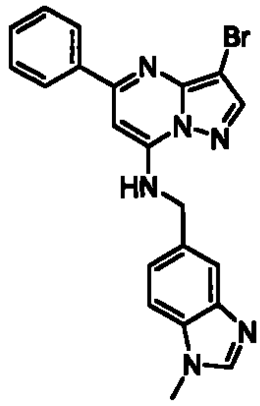
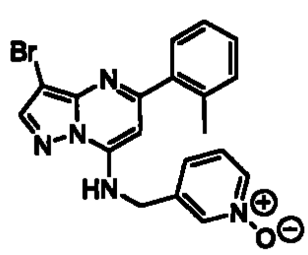
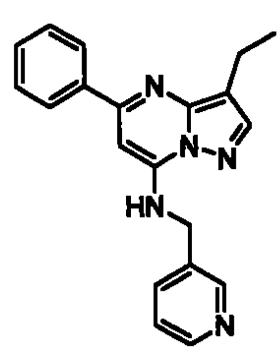
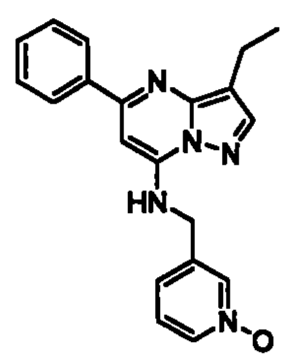
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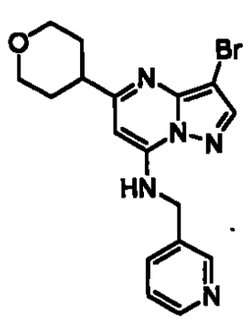
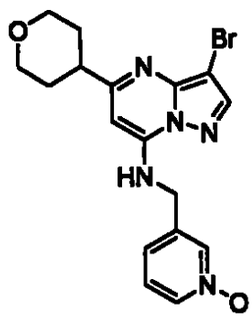
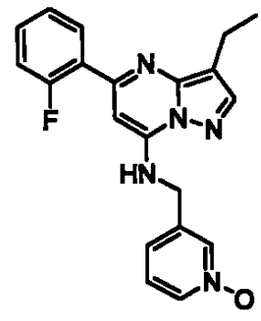
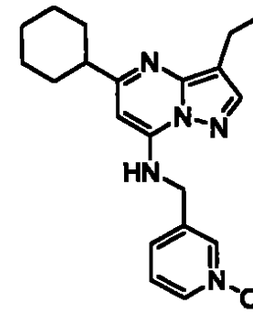
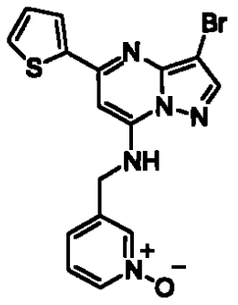
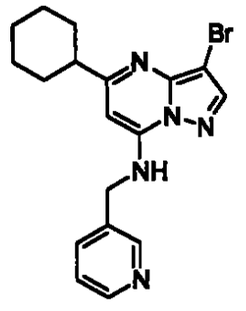
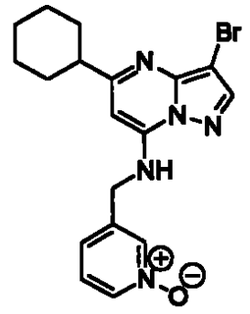
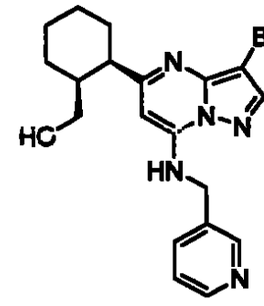
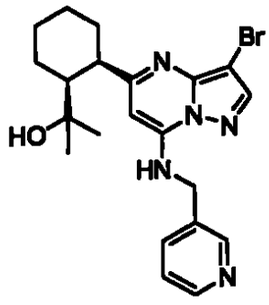
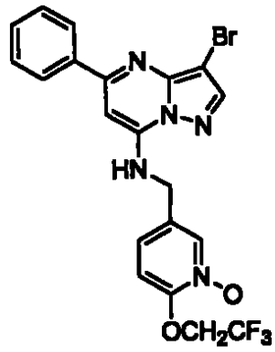
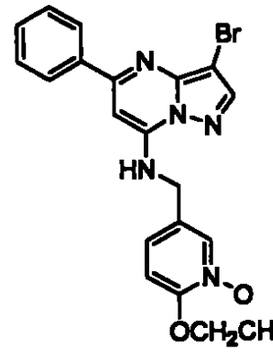
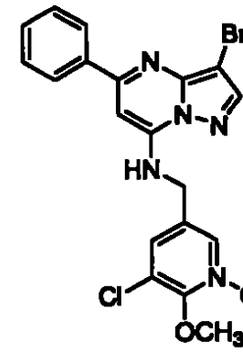
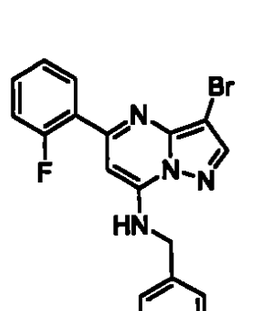
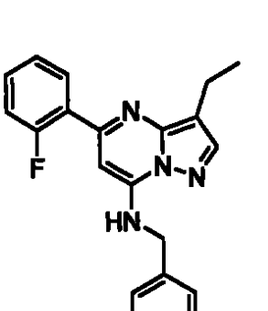
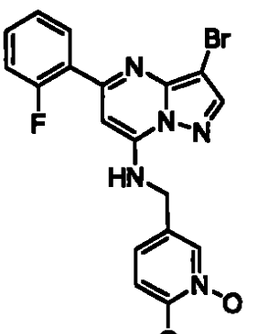
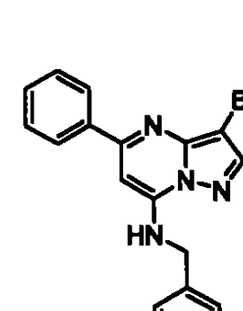





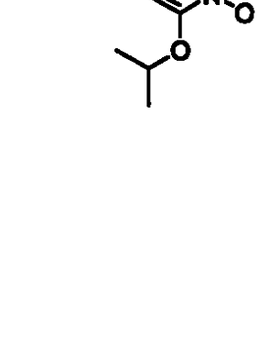





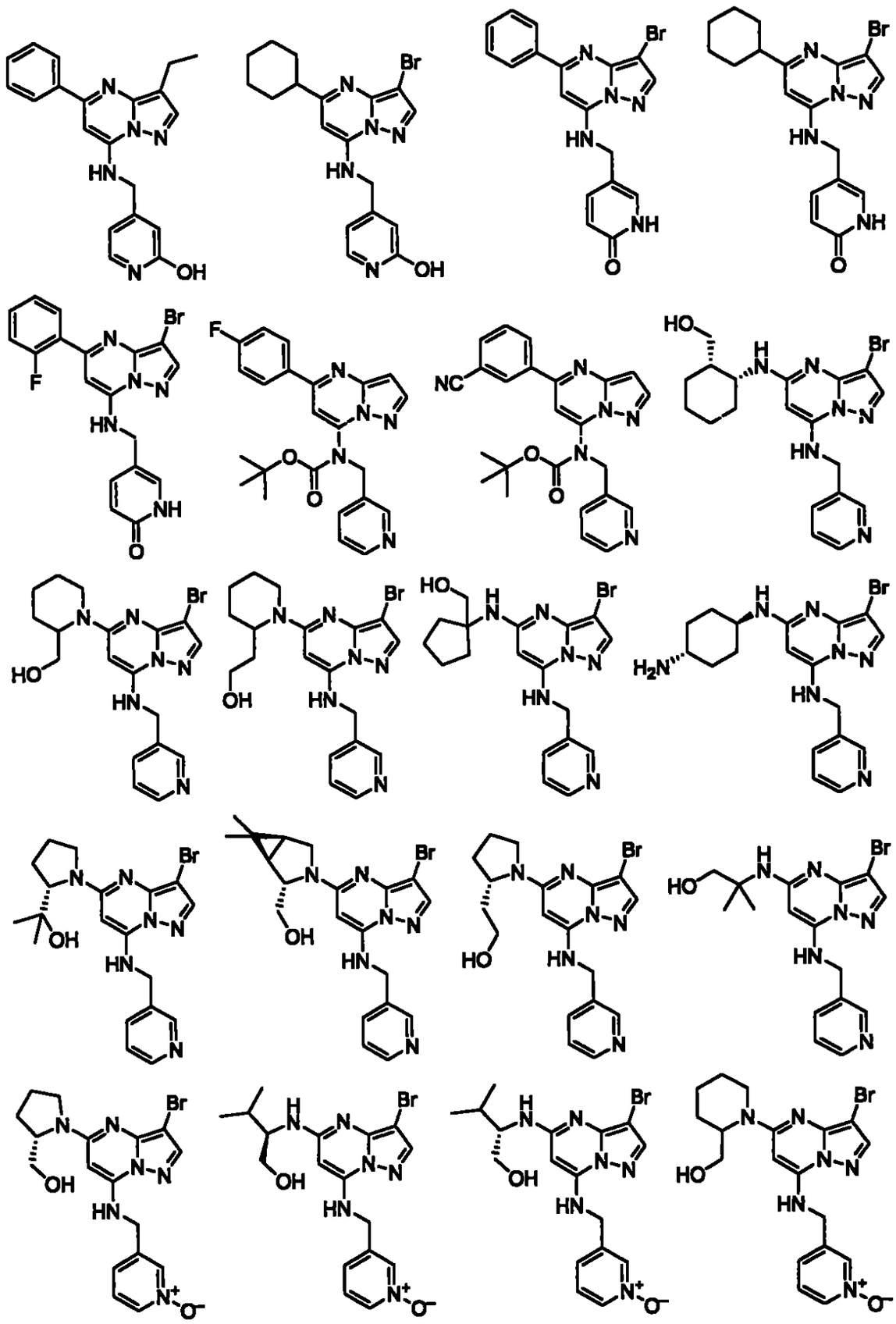





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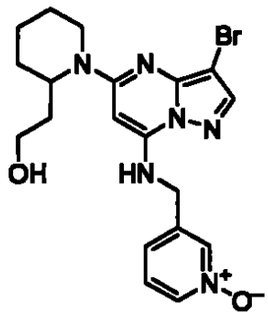



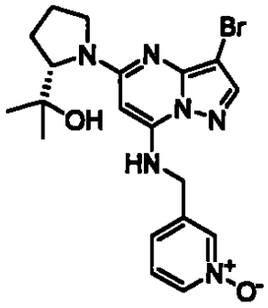

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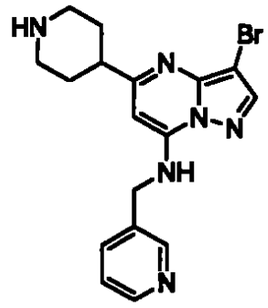


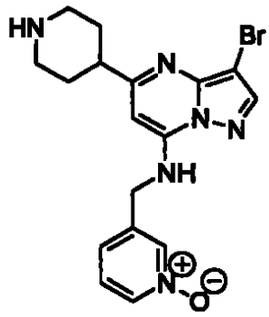
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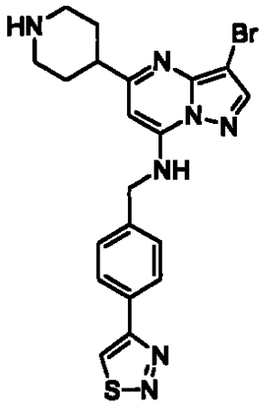
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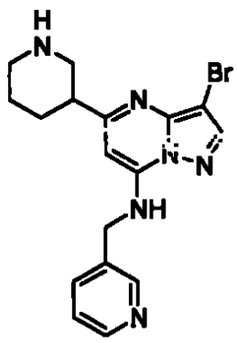


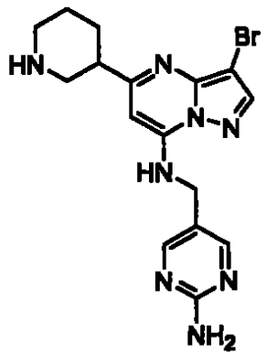


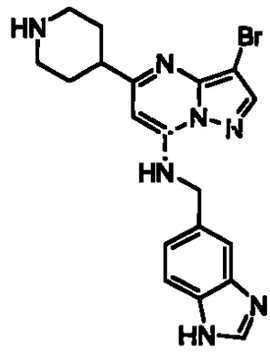


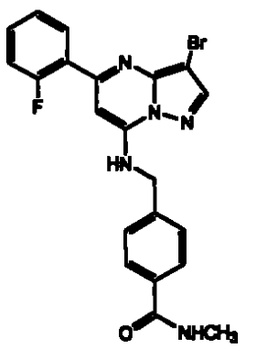


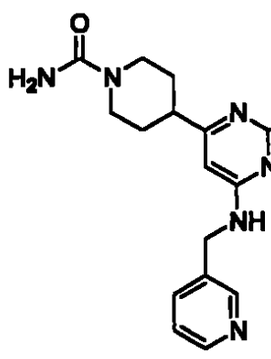


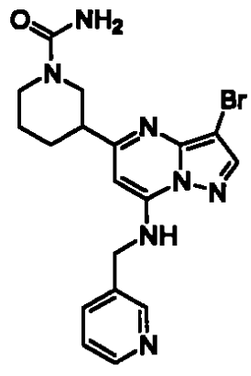




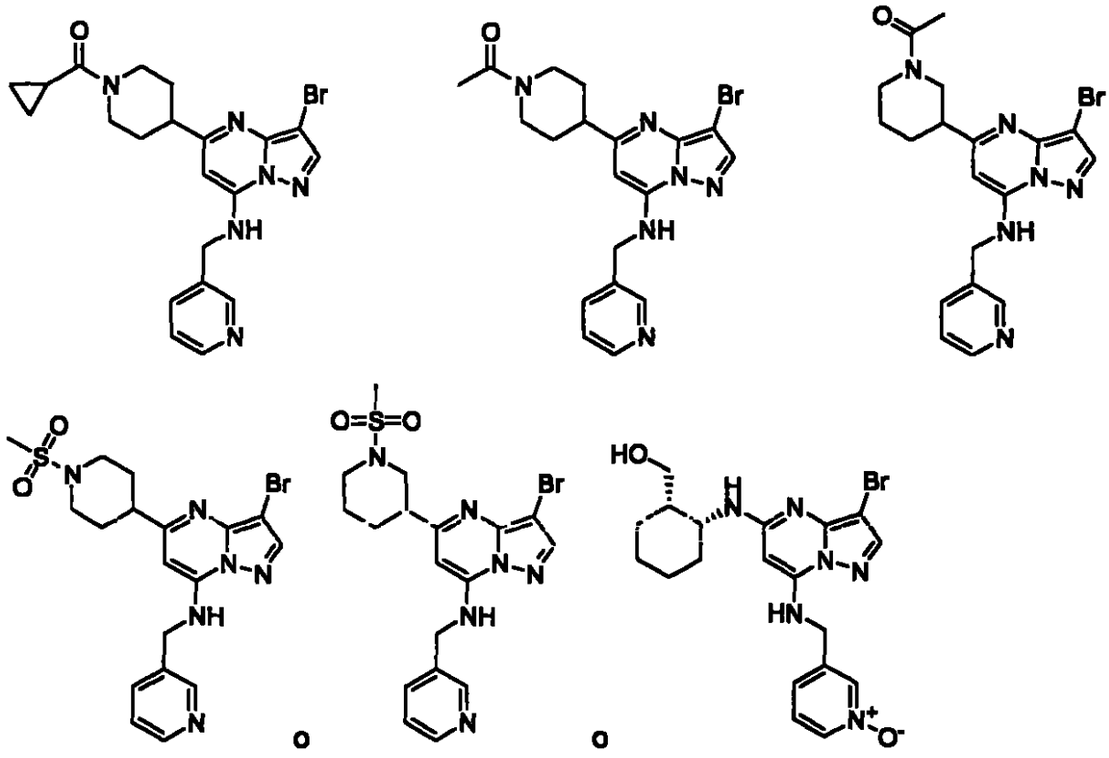






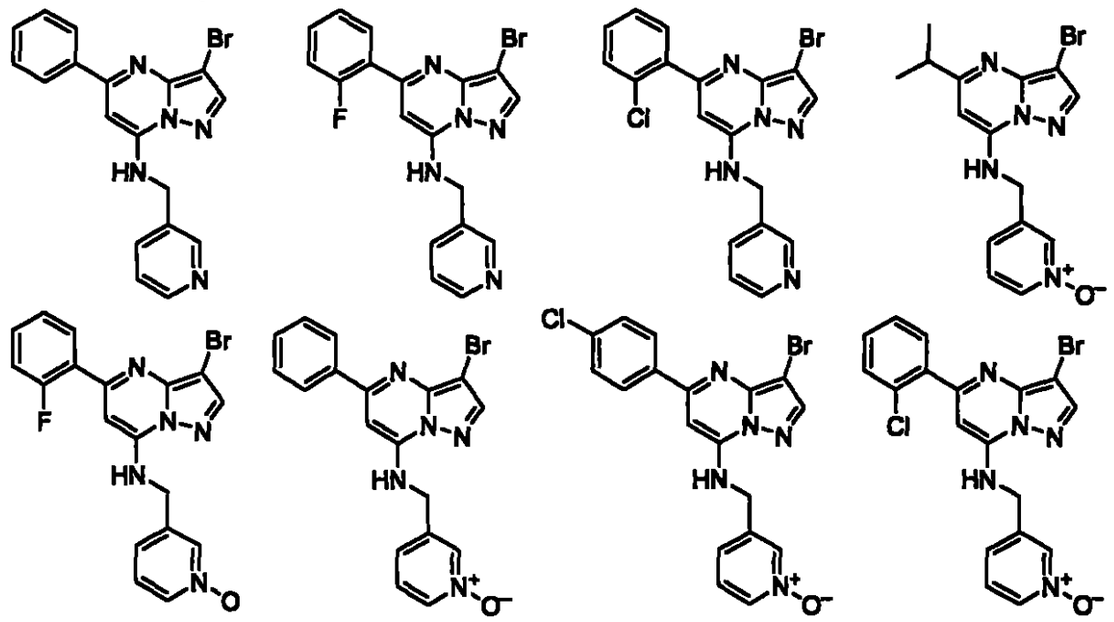


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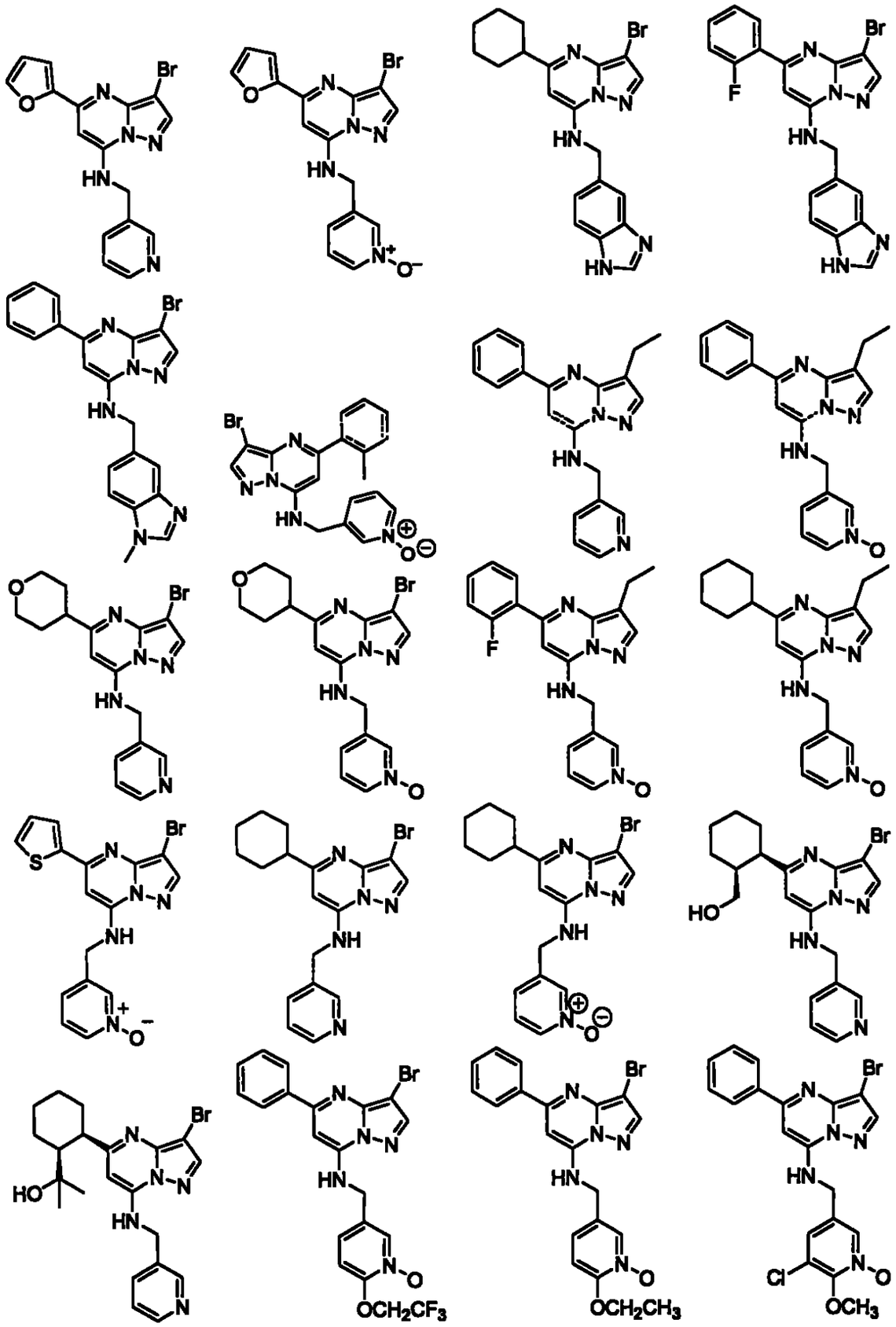


o una sal aceptable para uso farmacéutico o solvato del mismo.

29. Un compuesto de fórmula:

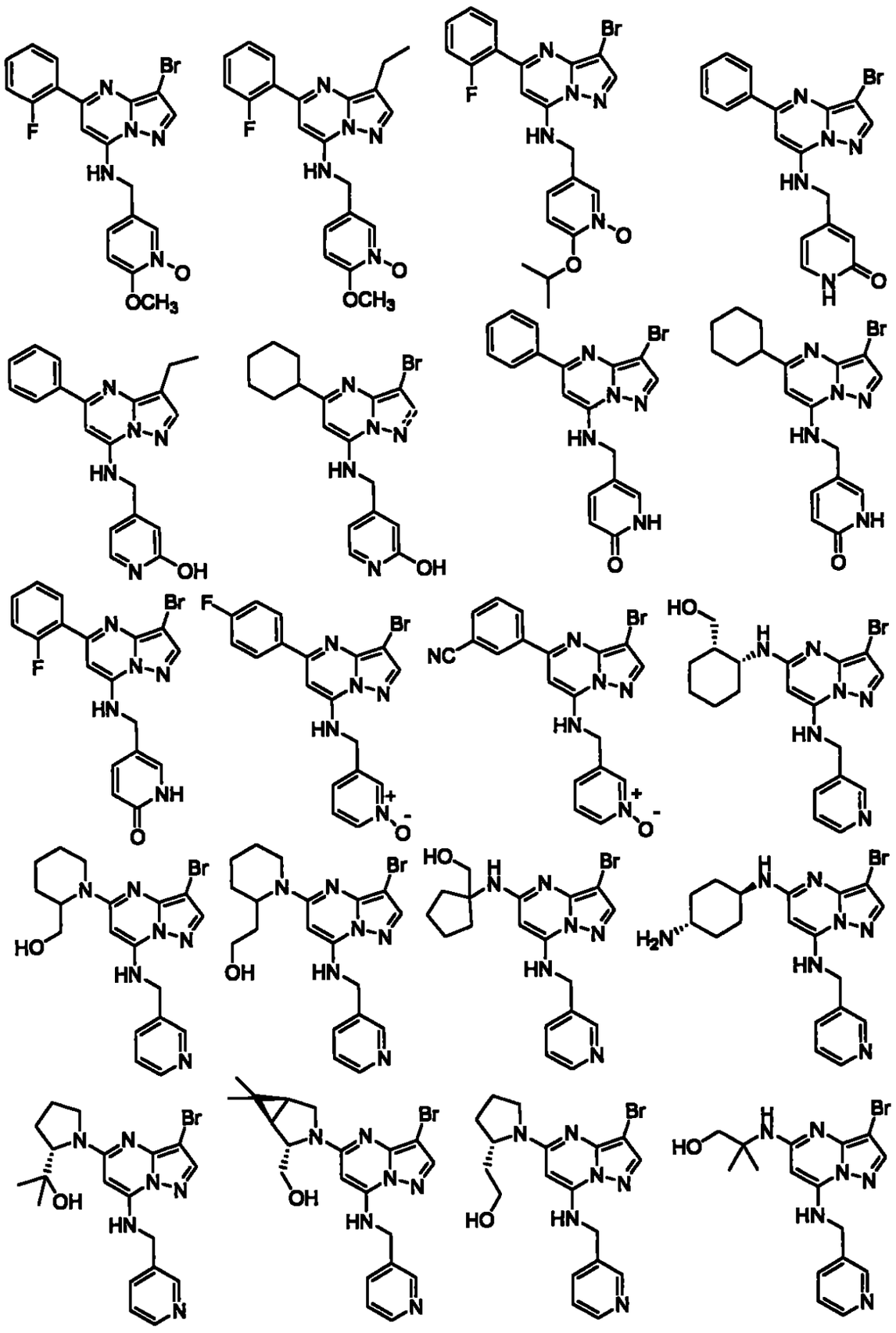


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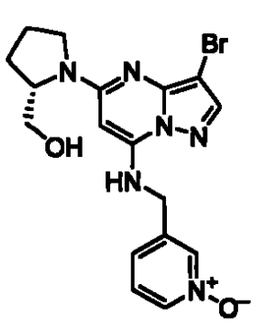
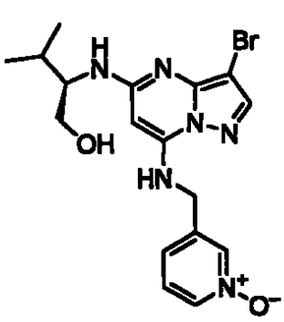
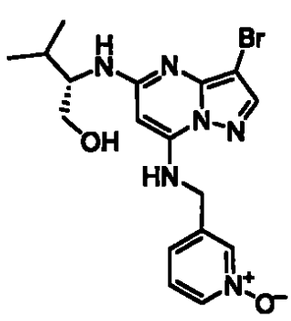
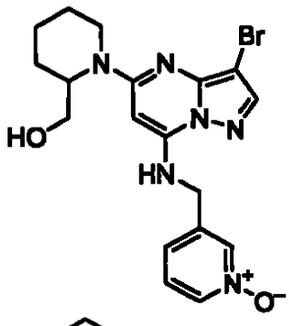
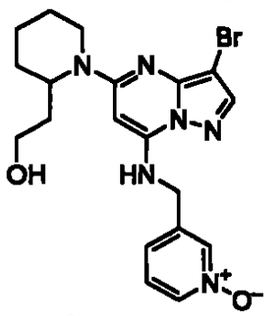
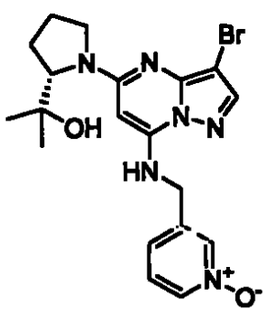
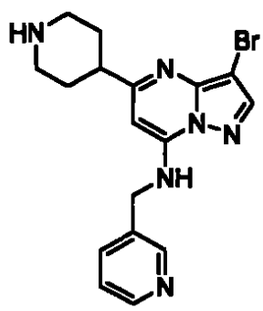
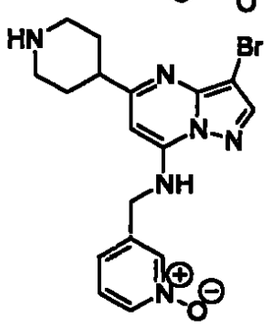
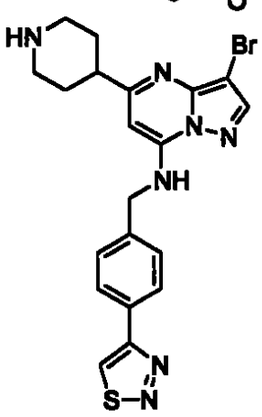
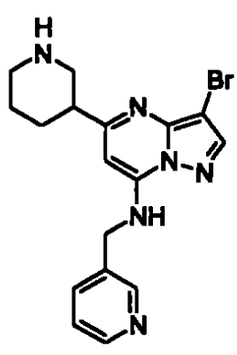
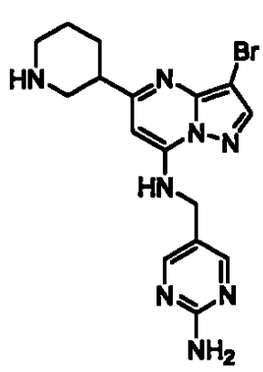
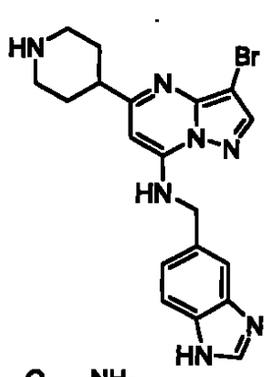
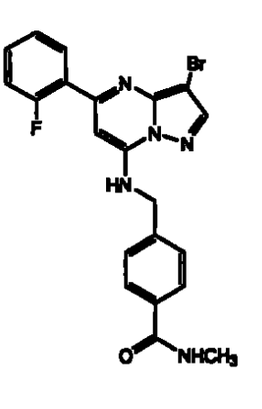
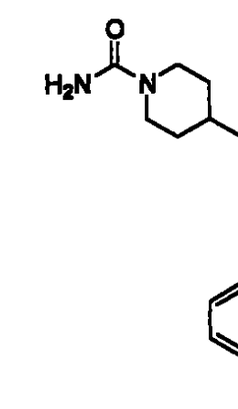
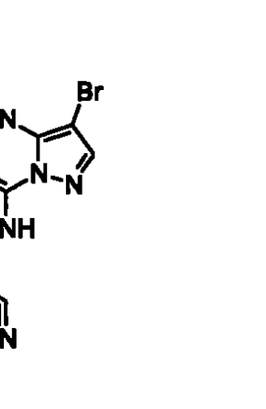
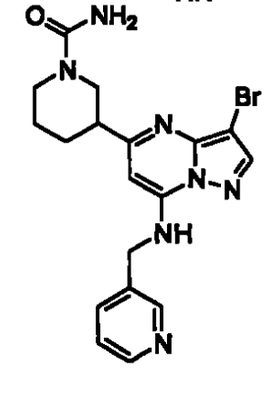


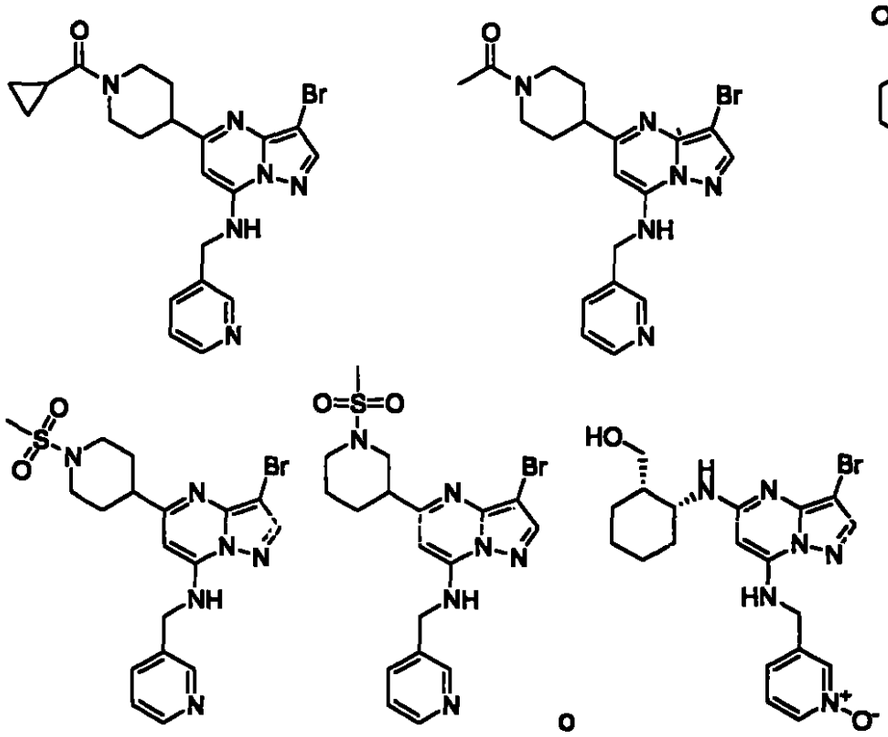
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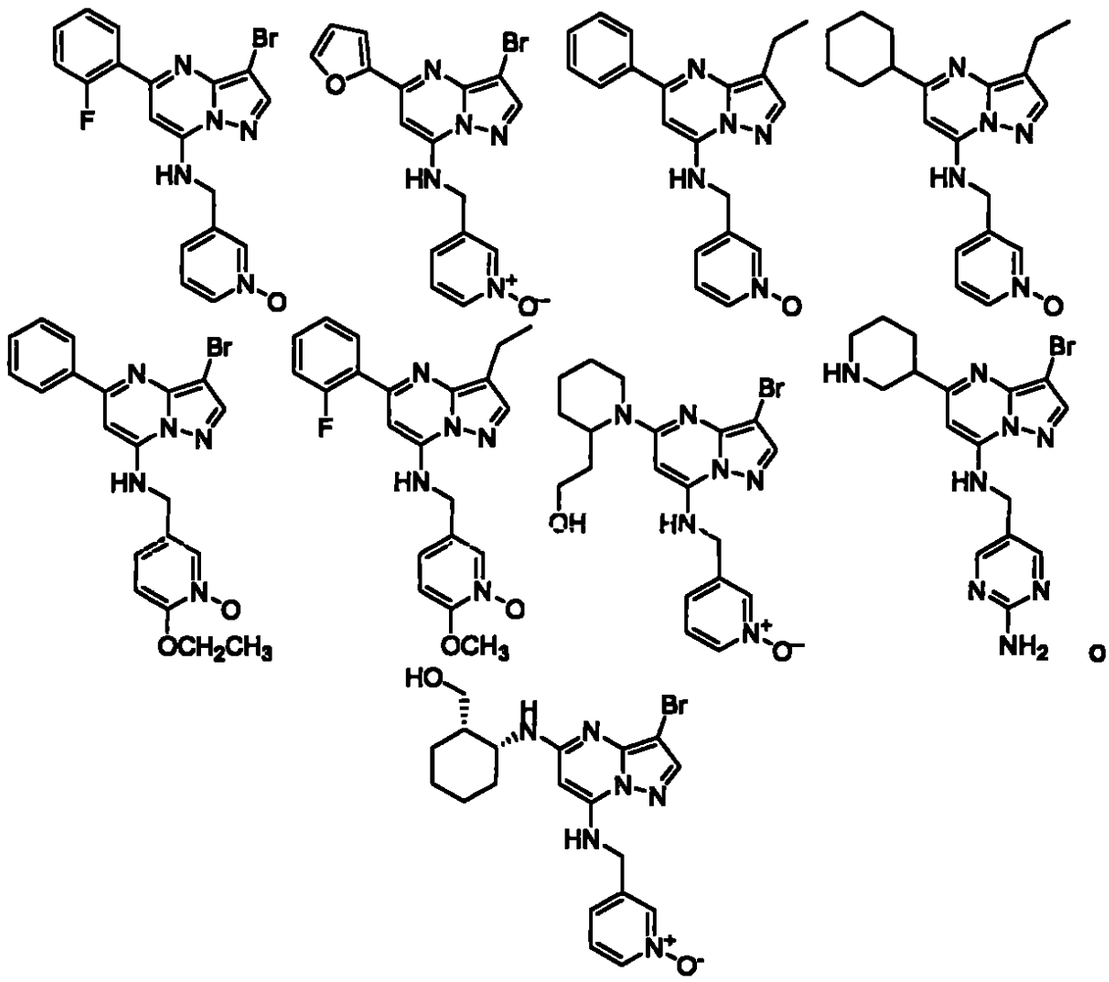
959



o una sal aceptable para uso farmacéutico o solvato del mismo.

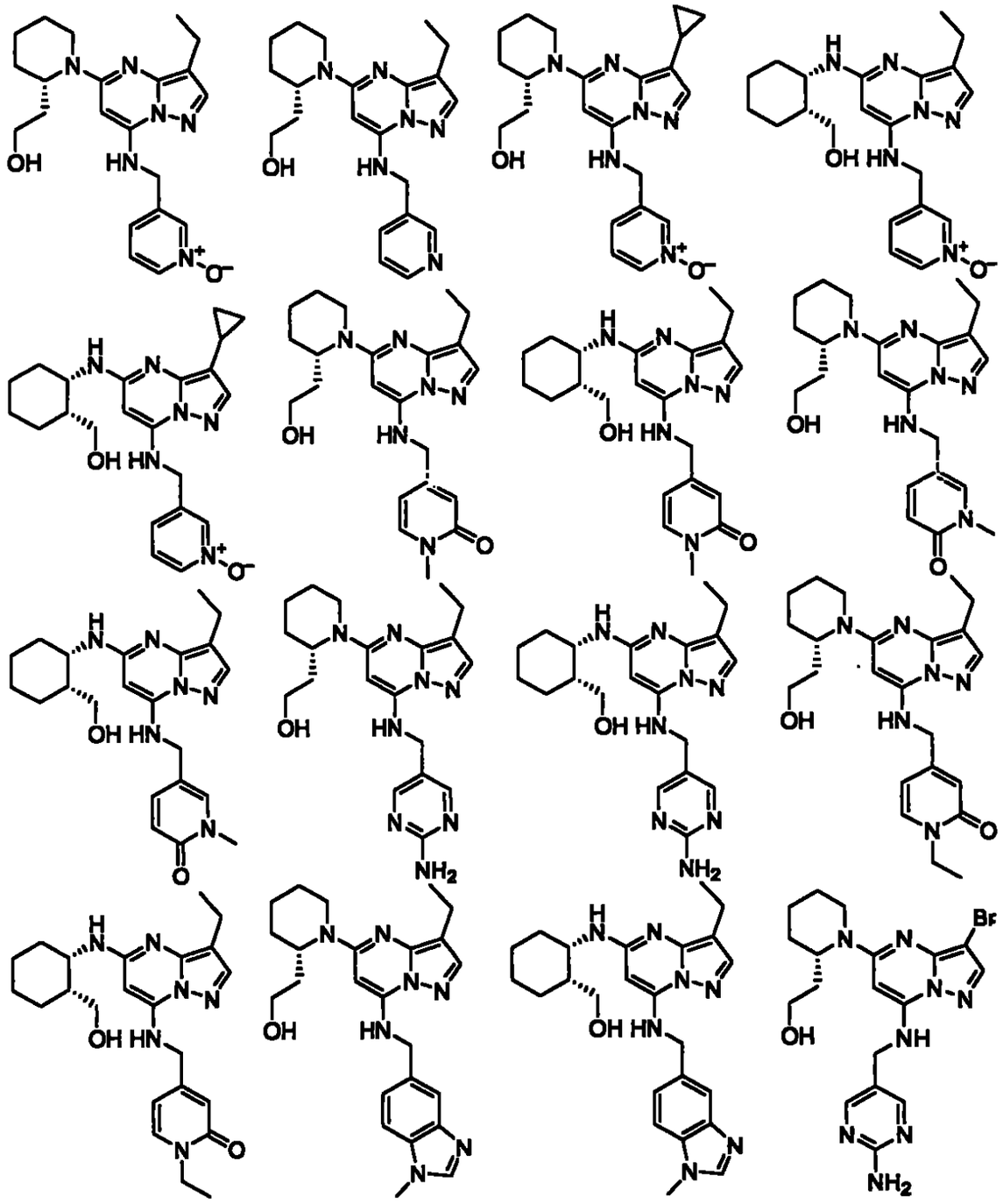
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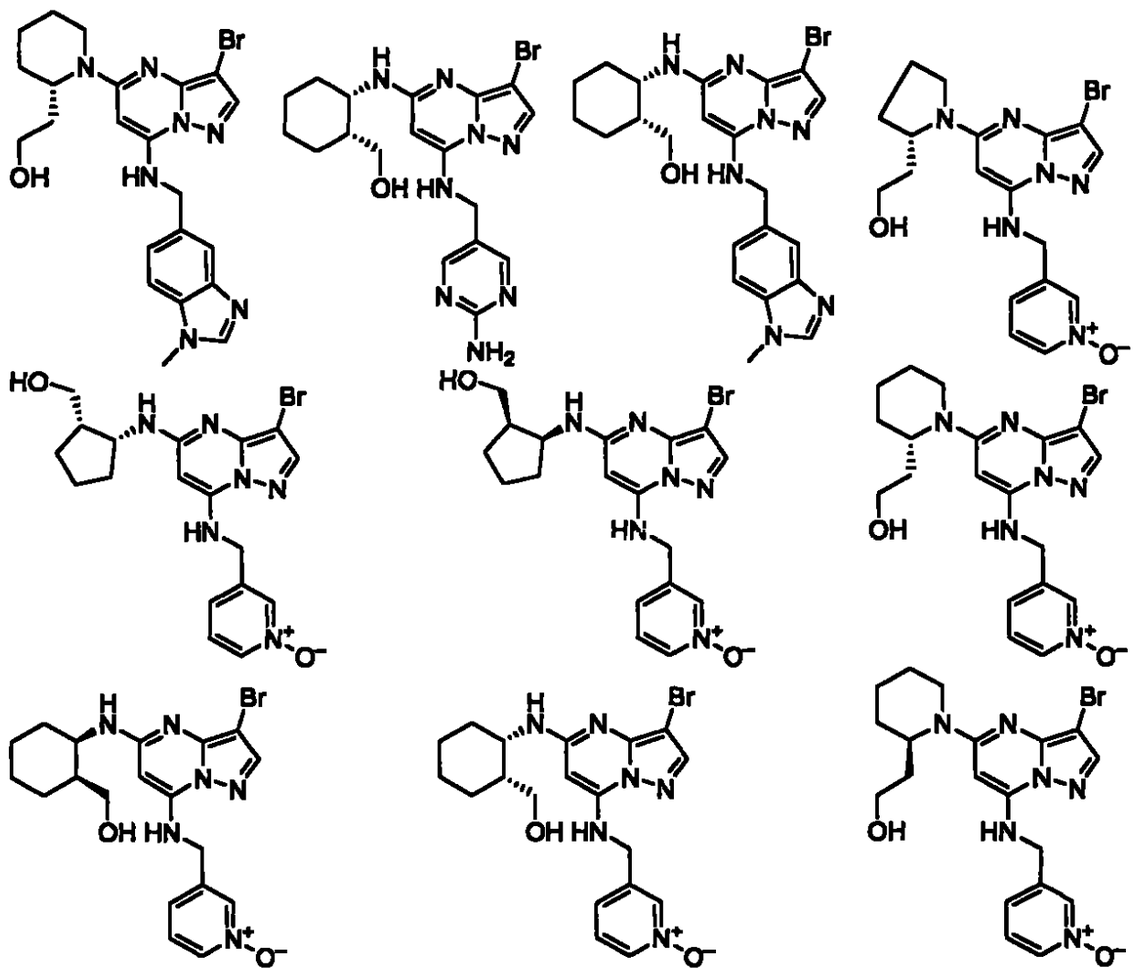


o una sal aceptable para uso farmacéutico o solvato del mismo.

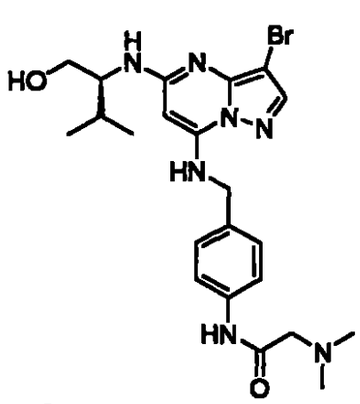
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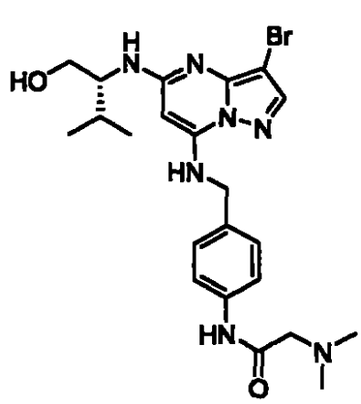
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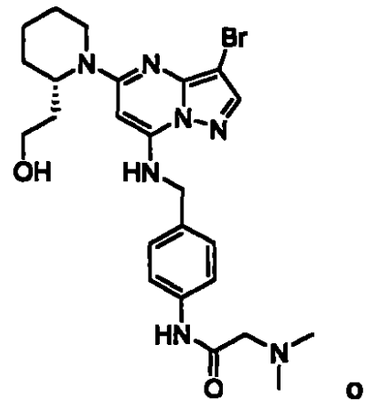




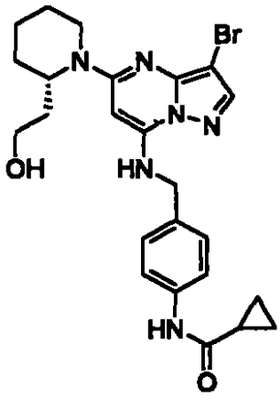
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o



o una sal aceptable para uso farmacéutico o solvato del mismo.

32. Un método para inhibir una o más quinasas ciclina-dependientes, que comprende administrar una cantidad efectiva terapéuticamente de al menos un compuesto de la reivindicación 1 a un paciente que necesita tal inhibición.

33. Un método para tratar una o más enfermedades asociadas con una quinasa ciclina-dependiente, que comprende administrar una cantidad efectiva terapéuticamente de al menos un compuesto de la reivindicación 1 a un paciente que necesita tal tratamiento.

34. El método de la reivindicación 33, en el cual dicha quinasa ciclina-dependiente es CDK2.

35. El método de la reivindicación 33, en el cual dicha quinasa ciclina-dependiente es la proteína quinasa activada por mitógenos (MAPK/ERK).

36. El método de la reivindicación 33, en el cual dicha quinasa ciclina-dependiente es la glucógeno sintasa quinasa 3 (GSK3beta).

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37. El método de la reivindicación 33, en el cual dicha enfermedad se selecciona del grupo que consiste en:

cáncer de vejiga, mama, colon, riñón, hígado, pulmón, cáncer pulmonar microcítico, esófago, vesícula biliar, ovario, páncreas, estómago, cuello del útero, tiroides, próstata y piel, incluyendo carcinoma celular de células escamosas;

leucemia, leucemia linfocítica aguda, leucemia linfoblástica aguda, linfoma de células B, linfoma de células T, linfoma de Hodgkin, linfoma no Hodgkin, linfoma de células pilosas y linfoma de Burkett;

leucemia mielógena aguda y crónica, síndrome mielodisplásico y leucemia promielocítica;

fibrosarcoma, rabdomiosarcoma;

astrocitoma, neuroblastoma, glioma y schwannomas;

melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentoso, queratoctantoma, cáncer folicular tiroideo y sarcoma de Kaposi.

38. Un método para tratar uno o más enfermedades asociadas con quinasas ciclina-dependientes, que comprende administrar a un mamífero que necesita tal tratamiento,

una cantidad de un primer compuesto, que es un compuesto de la reivindicación 1, o una sal aceptable para uso farmacéutico o solvato del mismo; y

una cantidad de al menos un segundo compuesto, siendo dicho segundo compuesto un agente anti-neoplásico;

donde las cantidades del primer compuesto y de dicho segundo compuesto producen un efecto terapéutico.

39. El método de la reivindicación 38, que además comprende terapia de radiación.

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40. El método de la reivindicación 38, en el cual dicho agente anti-neoplásico se selecciona del grupo que consiste en un agente citostático, cisplatino, doxorubicina, taxotere, taxol, etopósido, CPT-11, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epotilonas, tamoxifeno, 5-fluorouracilo, metoxtrexato, 5FU, temozolomida, ciclofosfamida, SCH 66336, R115777, L778,123, BMS 214662, Iressa, Tarceva, anticuerpos para EGFR, Gleevec, intron, ara-C, adriamicina, citoxan, gemcitabina, mostaza de Uracilo, Clormetina, Ifosfamida, Melfalan, Clorambucil, Pipobroman, Trietilenmelamina, Trietilentiofosforamina, Busulfan, Carmustina, Lomustina, estreptozocina, Dacarbazina, Floxuridina, Citarabina, 6-Mercaptopurina, 6-Tioguanina, Fludarabina fosfato, oxaliplatino, leucovirin, ELOXATIN™, Pentostatina, Vinblastina, Vincristina, Vindesina, Bleomicina, Dactinomicina, Daunorubicina, Doxorubicina, Epirubicina, Idarubicina, Mitramicina, Deoxicoformicina, Mitomicina-C, L-Asparaginasa, Tenipósido, 17α-Etinilestradiol, Dietilstilbestrol, Testosterona, Prednisona, Fluoximesterona, Dromostanolona propionato, Testolactona, Megestrolacetato, Metilprednisolona, Metiltestosterona, Prednisolona, Triamcinolona, Clorotrianiseno, Hidroxiprogesterona, Aminoglutetimida, estramustina, Medroxiprogesteronacetato, Leuprolida, Flutamida, Toremifeno, goserelin, Cisplatino, Carboplatino, Hidroxiurea, Amsacrina, Procarbazina, Mitotano, Mitoxantrona, Levamisol, Navelbeno, CPT-11, Anastrazol, Letrazol, Capecitabina, Reloxafina, Droloxafina o Hexametilmelamina.

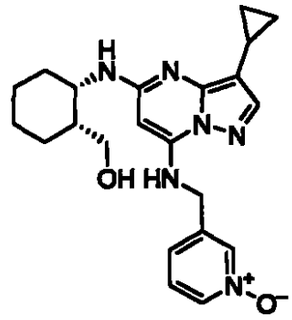
41. Una composición farmacéutica que comprende una cantidad efectiva terapéuticamente de al menos un compuesto de la reivindicación 1 en combinación con al menos un vehículo aceptable para uso farmacéutico.

42. La composición farmacéutica de la reivindicación 39, que comprende adicionalmente uno o más agentes anti-neoplásicos seleccionados del grupo que consiste en un agente citostático, cisplatino, doxorubicina, taxotere, taxol,

etopósido, CPT-11, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epotilonas, tamoxifeno, 5-fluorouracilo, metoxtrexato, 5FU, temozolomida, ciclofosfamida, SCH 66336, R115777, L778,123, BMS 214662, Iressa, Tarceva, anticuerpos para EGFR, Gleevec, intron, ara-C, adriamicina, citoxan, gemcitabina, mostaza de Uracilo, Clormetina, Ifosfamida, Melfalan, Clorambucil, Pipobroman, Trietilenmelamina, Trietilentiofosforamina, Busulfan, Carmustina, Lomustina, estreptozocina, Dacarbazina, Floxuridina, Citarabina, 6-Mercaptopurina, 6-Tioguanina, fosfato de Fludarabina, Pentostatina, Vinblastina, Vincristina, Vindesina, Bleomicina, Dactinomicina, Daunorubicina, Doxorubicina, Epirubicina, Idarubicina, Mitramicina, Desoxicoformicina, Mitomicina-C, L-Asparaginasa, Tenipósido, 17α-Etinilestradiol, Dietilstilbestrol, Testosterona, Prednisona, Fluoximesterona, Dromostanolon propionato, Testolactona, Megestrolacetato, Metilprednisolona, Metiltestosterona, Prednisolona, Triamcinolona, Clorotrianiseno, Hidroxiprogesterona, Aminoglutetimida, Estramustina, Medroxiprogesteronacetato, Leuprolida, Flutamida, Toremifeno, goserelin, Cisplatino, Carboplatino, Hidroxiurea, Amsacrine, Procarbazina, Mitotano, Mitoxantrona, Levamisol, Navelbeno, CPT-11, Anastrazol, Letrazol, Capecitabina, Reloxafina, Droloxafina o Hexametilmelamina.

43. Un compuesto de la reivindicación 1 en forma purificada.

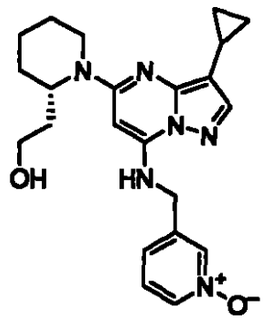
44. Un compuesto de fórmula:



o una sal aceptable para uso farmacéutico o solvato del mismo.

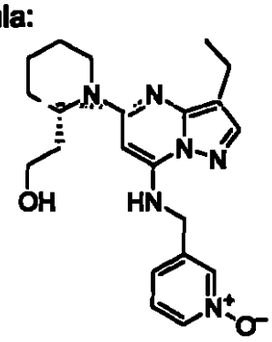
45. Un compuesto de fórmula:

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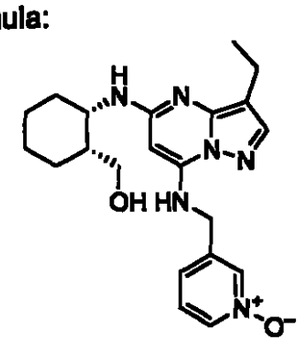
o una sal aceptable para uso farmacéutico o solvato del mismo.

46. Un compuesto de fórmula:



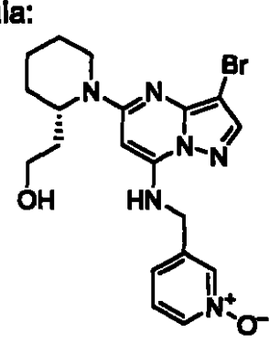
o una sal aceptable para uso farmacéutico o solvato del mismo.

47. Un compuesto de fórmula:



o una sal aceptable para uso farmacéutico o solvato del mismo.

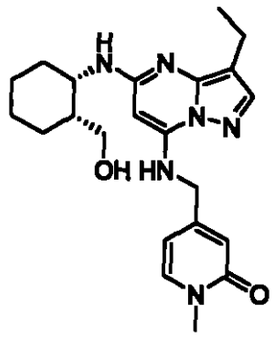
48. Un compuesto de fórmula:



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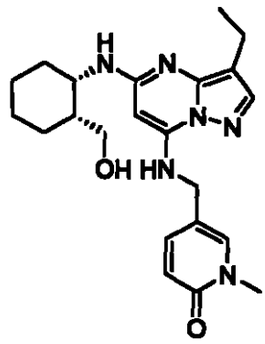
o una sal aceptable para uso farmacéutico o solvato del mismo.

49. Un compuesto de fórmula:



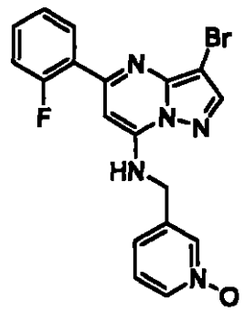
o una sal aceptable para uso farmacéutico o solvato del mismo.

50. Un compuesto de fórmula:



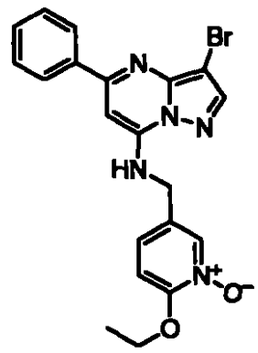
o una sal aceptable para uso farmacéutico o solvato del mismo.

51. Un compuesto de fórmula:



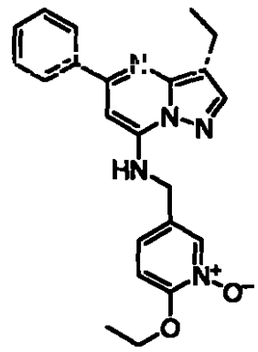
o una sal aceptable para uso farmacéutico o solvato del mismo.

52. Un compuesto de fórmula:



o una sal aceptable para uso farmacéutico o solvato del mismo.

53. Un compuesto de fórmula:



o una sal aceptable para uso farmacéutico o solvato del mismo.

p.p. de: SCHERING CORPORATION &
PHARMACOPEIA DRUG DISCOVERY, INC.

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RESUMEN DE LA INVENCIÓN

En sus numerosas realizaciones, la presente invención provee una clase novedosa de compuestos derivados de pirazolo[1,5-a]pirimidina como inhibidores de quinasas ciclina-dependientes, métodos para preparar tales compuestos, composiciones farmacéuticas que contienen uno o más de tales compuestos, métodos para preparar formulaciones farmacéuticas que comprenden uno o más de tales compuestos y métodos de tratamiento, prevención, inhibición o alivio de una o más enfermedades asociadas con las CDKs usando tales compuestos o composiciones farmacéuticas.

TRATADO DE CO PERACIÓN DE PATENTES
PCT

NOTIFICACIÓN DE TRANSMISIÓN DEL REPORTE PRELIMINAR INTERNACIONAL DE PATENTABILIDAD
(PCT Regla 71.1)
De: AUTORIDAD DE REVISION PRELIMINAR INTERNACIONAL

Para:
KALYANARAMAN, Palaiyur S.
SCHERING CORPORATION
Departamento de Patente K-6-1 1990
2000 Galloping Hill Road
Kenilworth, New Jersey 07033-0530
Estados Unidos de América.

Sello de recibido de fecha 13 de junio de 2006

Fecha de expedición: 09.06.2006
Referencia del expediente del solicitante o mandatario: OC01617K1
Solicitud Internacional No.: PCT/US2005/003859
Fecha de presentación internacional: 08.02.2005
Fecha de prioridad: 11.02.2004
Solicitante: SCHERING CORPORATION

1. Se notifica al solicitante que la Administración Encargada del Examen Preliminar Internacional ha emitido el informe de examen preliminar internacional para la solicitud internacional y se lo transmite adjunto, acompañado, si procede, de sus anexos.

2. Se transmite una copia del presente informe y, si procede, de sus anexos, a la Oficina Internacional para comunicación a todas las Oficinas elegidas.

3. Si alguna Oficina elegida lo exige, la Oficina Internacional realizará una traducción en inglés del informe (con exclusión de sus anexos) y la transmitirá a las Oficinas interesadas.

4. **RECORDATORIO**

   Para iniciar la fase nacional ante cada Oficina elegida, el solicitante debe cumplir ciertos actos (presentación de la traducción y pago de las tasas nacionales) en el plazo de 30 meses desde la fecha de prioridad (o más tarde por lo que respecta a ciertas oficinas) (Artículo 39 (1)) (véase también el recordatorio enviado por la Oficina Internacional en el formulario PCT/IB/301).

Cuando deba entregarse una traducción de la solicitud internacional o una oficina elegida, se incluirá la traducción de cualquier anexo de informe de Examen Preliminar Internacional. Corresponde al solicitante preparar la traducción en cuestión y entregarla directamente a cada Oficina elegida interesada

Para más amplios detalles en lo relativo a los plazos aplicables y las exigencias de las oficinas elegidas, véase el Volumen II de la guía del solicitante PCT.

Se llama la atención del solicitante sobre el Artículo 33(5) que prevé que los criterios de novedad, actividad inventiva y de aplicación industrial definidos en el Artículo 33(2) a (4) sólo servirán a los efectos del examen preliminar internacional, y que "todo Estado contratante puede aplicar criterios adicionales o diferentes al objeto de decidir, en ese Estado, si la invención es patentable o no" (véase también el Artículo 27(5)). Tales criterios adicionales pueden afectar, por ejemplo, a las excepciones de patentabilidad, requisitos específicos relativos a la divulgación, la claridad de las reivindicaciones.

Nombre y dirección postal de la Administración encargada del Examen Preliminar Internacional:
Oficina de Patentes Europea
D-80298 – Munich
Tel: +49-89 2399 - 0, Tx: 523656 epmu d
Fax: +49-89 2399 – 4465.

Funcionario Autorizado: Ullrich, J
Tel: + 49 89 2399-8048

TRATAD DE COOPERACIÓN DE PATENTES
PCT
INFORME PRELIMINAR INTERNACIONAL SOBRE PATENTABILIDAD
(Capítulo II del Tratado de Cooperación en materia de Patentes) .
(PCT Artículo 36 y Regla 70)

Referencia del expediente del solicitante o mandatario: OC01617K1
Solicitud Internacional No.: PCT/US2005/003859
Fecha de presentación internacional: 08.02.2005
Fecha de prioridad: 11.02.2004
Clasificación Internacional de Patentes (IPC) o la vez clasificación nacional e IPC: INV. C07D 487/04 A61K 31/495 A61P 35/00.
Solicitante: SCHERING CORPORATION

1. El reporte de examen preliminar internacional ha sido preparado por esta Autoridad de Revisión Preliminar Internacional bajo el Artículo 35 y es transmitido al solicitante según el Artículo 36.

2. Este REPORTE consta de un total de 8 hojas, incluida la presente hoja de portada.

3. Este informe también contiene ANEXOS, que comprenden.

   a. ☐ (*remitido al solicitante y a la oficina internacional*) un total de hojas, descritas a continuación:

      ☐ hojas de la descripción, las reivindicaciones y/o los dibujos que han sido modificadas y que sirven de base al presente informe, y/o de hojas que contienen rectificaciones autorizadas por esta Administración (véase la Regla 70.16 y la Instrucción Administrativa 607 del PCT).

      ☐ hojas que reemplazan a otras hojas anteriores, pero que esta Administración considera que contienen modificaciones que se extienden más allá de la divulgación de la invención tal como fue originalmente presentada, según se indica en el punto 4 del Reglamento I y en el Recuadro Suplementario.

   b. ☐ (remitido únicamente a la Oficina Internacional) un total de (indicar tipo y soporte(s) electrónico(s)) , que contienen una lista de secuencias y/o tabla(s) relativa(s), solo en formato legible por ordenador, como se indica en el Recuadro Suplementario relativo a Listas de Secuencias (ver Instrucción Administrativa 802).

4. El presente informe contiene indicaciones relativas a los siguientes puntos:

☒	Recuadro I	Base de este informe
☐	Recuadro II	Prioridad
☒	Recuadro III	Ninguna formulación de opinión sobre la novedad, la actividad inventiva y la aplicación industrial
☐	Recuadro IV	Falta de unidad de Invención
☒	Recuadro V	Declaración motivada según el Artículo 35(2) sobre la novedad, la actividad inventiva y la aplicación industrial, citas y explicaciones en apoyo de esta declaración
☒	Recuadro VI	Ciertos documentos citados
☐	Recuadro VII	Defectos en la Solicitud Internacional
☐	Recuadro VIII	Observaciones relativas a la solicitud internacional

Fecha de radicación de la demanda: 07.09.2005
Fecha de elaboración de este reporte: 09.06.2006

Nombre y dirección postal de la Administración encargada del Examen Preliminar Internacional:
Oficina de Patentes Europea
D-80298 – Munich
Tel: +49-89 2399 - 0, Tx: 523656 epmu d
Fax: +49-89 2399 – 4465.

Funcionario Autorizado: Fritz, M.
Tel: + 49 89 2399-

Recuadro I. Base de este informe

1. Por lo que respecta al **idioma**, este informe se ha establecido sobre la base de la solicitud internacional en el idioma en el cual se depositó, salvo indicación en contra señalada a continuación.

☐ Este informe está basado en una traducción del idioma original al siguiente idioma , que es el de una traducción proporcionada a los fines de:

- ☐ búsqueda internacional (según Reglas 12.3 y 23.1 (b))
- ☐ publicación de la solicitud internacional (según Regla 12.4)
- ☐ examen preliminar internacional (según Reglas 55.2 y/o 55.3)

2. Por lo que respecta a los **elementos*** de la solicitud internacional, esta opinión se ha establecido sobre la base de (*las hojas de reemplazo que hayan sido enviadas a la Oficina receptora en respuesta a un requerimiento según el Artículo 14 se las denomina en este informe como "inicialmente presentadas" y no se anexan al informe):*

Descripción, Páginas

1 – 594 tal como se presentaron inicialmente

Reivindicaciones, Números

1 – 53 tal como se presentaron inicialmente

☐ una lista de secuencias y/o tabla(s) relativa(s) – ver Recuadro Suplementario relativo a Listas de Secuencias

3. ☐ Las modificaciones ha ocasionado la cancelación de:

- ☐ la descripción, páginas
- ☐ las reivindicaciones, Nos.
- ☐ los dibujos, hojas/fig.
- ☐ la lista de secuencias (especificar):
- ☐ tabla(s) relativa(s) a la lista de secuencias (especificar):

4. ☐ El presente informe ha sido establecido como si no se hubiesen presentado (algunas de) las modificaciones anexadas a este informe y listadas abajo, ya que se ha considerado que iban más allá de la divulgación de la invención tal como fue presentada, como se indica en el Recuadro Suplementario (Regla 70.2(c)).

☐ la descripción, páginas

☐ las reivindicaciones, Nos.
☐ los dibujos, hojas/fig.
☐ la lista de secuencias (especificar):
☐ tabla(s) relativa(s) a la lista de secuencias (especificar):

* Si se utiliza el punto 4, algunas o todas estas páginas pueden llevar el sello de "sustituida".

Recuadro No. III. Ninguna formulación de opinión sobre la novedad, la actividad inventiva y la aplicación industrial

1. Las preguntas con respecto a si el invento reivindicado parece ser novedoso, implica una actividad inventiva (no ser evidente), o ser susceptible de aplicación industrial, por lo que respecta.

☐ al conjunto de la solicitud internacional,
☒ a las reivindicaciones Nos. 32-40

debido a que:

☒ la solicitud internacional, o las reivindicaciones Nos. 32-40 con relación a la aplicación industrial en cuestión se refieren al objeto, respecto del cual no requiere examen preliminar internacional (especifique):

ver hoja separada

☐ a descripción, reivindicaciones, o los dibujos (indíquese cuales a continuación) o tales reivindicaciones Nos. en cuestión no son claras, de manera que no es posible formular una opinión significativa (especifique):

☐ las reivindicaciones, o las reivindicaciones Nos. en cuestión no son claras, de manera que no es posible formular una opinión significativa.

☐ no se ha emitido informe de búsqueda internacional para dichas reivindicaciones Nos.

☐ la lista de de secuencias nucleótidas y/o de aminoácidos no cumplen la norma estándar prevista en el Anexo C de las Instrucciones Administrativas por que:

La lista en papel ☐ no se presentó

☐ no cumple con la norma estándar

La lista en formato legible por ordenador

☐ no se presentó

☐ no cumple con la norma estándar

☐ las tablas relativas a las listas de secuencias de nucleótidas y/o de aminoácidos, si únicamente se han presentado en formato legible por ordenador, no cumplen con los requisitos técnicos previstos en el Anexo C-*bis* de las Instrucciones Administrativas.

☒ Ver recuadro suplementario para más detalles.

Recuadro No. V Declaración razonada según el Artículo 35 (2) con respecto a la novedad, nivel inventivo o aplicación industrial: anterioridades y explicaciones que soportan tal declaración

1. Declaración

Novedad (N)	Si:	Reivindicaciones 4, 8-9, 11-18, 20-40, 42, 44-53
	No:	Reivindicaciones 1-3, 5-7, 10, 19, 41, 43
Nivel Inventivo (NI)	Si:	Reivindicaciones 4, 8-9, 11-18, 20-40, 42, 44-53
	No:	Reivindicaciones 1-3, 5-7, 10, 19, 41, 43
Aplicación Industrial (AI)	Si:	Reivindicaciones 1-31, 41-53
	No:	Reivindicaciones

2. Citas y explicaciones (Regla 70.7)

ver hoja separada.

Recuadro No. VI. Ciertos documentos citados

1. Ciertos documentos publicados (Regla 70.10)

y/o

2. Divulgaciones no escritas (Regla 70.9)

Ver hoja adjunta

REPORTE PRELIMINAR INTERNACIONAL SOBRE PATENTABILIDAD (HOJA ANEXA)

Solicitud Internacional No. PCT/US2005/003859

Re Punto III.

Ninguna formulación de opinión sobre la novedad, la actividad inventiva y la aplicación industrial

La reivindicaciones 32-40 relacionada con la materia considerada por esta Autoridad cubierta por las provisiones establecidas en la Regla 67.1 (iv) del PCT. Por lo tanto, no se formulará ninguna opinión con respecto a la aplicación industrial de la materia de estas reivindicaciones (Artículo 34(4)(a)(i) del PCT).

Las presentes reivindicaciones 1-2 se relacionan a un número sumamente grande de posible productos, consideras dentro del soporte del significado de Artículo 6 del PCT y revelan con el significado de Artículo 5 del PCT será encontrado, sin embargo, sólo para ver, la proporción pequeña de los productos reivindicados. En el presente caso, las reivindicaciones carecen de soporte, y la solicitud carece de novedad, para el significado de la búsqueda sobre todo el alcance reivindicado es imposible.
Sin embargo, la fase inicial de la búsqueda de las reivindicaciones 1-2, 4-9, 11-26 y 32-53 revelaron un número muy grande de documentos relevantes al problema de novedad. Muchos documentos fueron recuperados que es imposible determinar cuales partes de las reivindicaciones pueden decirse o definir la cual protección de la materia podría buscarse legitimamente (Artículo 6 del PCT).

En consecuencia, la búsqueda se ha llevado a cabo por esas partes de las reivindicaciones que parecen estar soportadas y reveladas, i.e. con una generalización razonable de los ejemplos en la descripción, nombrando partes relacionadas con compuestos como se definen en la reivindicación 3, método y composiciones de los mismos.

Se ha notado que el Examen Preliminar Internacional no se ha llevado a cabo en parte de la materia de las reivindicaciones 1-2, 4-9, 11-26, 32-53 que no se investigo (cf. Regla 66.1 e del PCT).

Re Punto V
Declaración razonada bajo la Regla 66.2 (a)(ii) con respecto a la novedad, nivel inventivo o aplicación industrial: anterioridades y explicaciones que soportan tal declaración

D1: WO 97/49378 A (L'OREAL; TERRANOVA, ERIC; FADLI, AZIZ; LAGRANGE, ALAIN) 31 de diciembre de 1997 (1997-12-31).

D2: US-A-6 107 305 (MISRA ET AL) 22 de Agosto 2000 (2000-08-22)

D3: WO 02/50079 A (SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES; PR) 27 de Junio de 2002 (2002-06-27)

D4: WO 2004/022561 A (SCHERING CORPORATION; PHARMACOPEIA, INC) 18 de Marzo de 2004 (2004-03-18)

D5: WO 2004/087707 A (VERNALIS LIMITED; PARRATT, MARTIN; BOWER, JUSTIN, FAIRFIELD; WILLIAMS) 14 de Octubre de 2004 (2004-10-14)

D6: WO 2004/022559 A (SCHERING CORPORATION; PHARMACOPEIA, INC) 18 de Marzo de 2004 (2004-03-18)

D7: WO 2004/076458 A (TEIJIN PHARMA LIMITED; KATAOKA, KENICHIRO; SUZUKI, NAOTAKA; KOSUGI, TO) 10 de Septiembre de 2004 (2004-09-10)

La presente solicitud revela derivados pirazolopirimidina (reivindicaciones 1-31, 43-53), métodos de tratamiento para administrar estos compuestos (reivindicaciones 32-40) y composiciones farmacéuticas de los mismos (reivindicaciones 41-42).

Para la evaluación de las reivindicaciones 32-40 de la presente, sobre la pregunta si son industrialmente aplicables, no existen criterios unificados en los Estados pertenecientes al PCT. La patentabilidad también puede depender de la formulación de las reivindicaciones. La EPO, por ejemplo, no reconoce como industrialmente aplicable aquella materia que reivindique el uso de un compuesto en tratamiento médico, pero permite, sin embargo, reivindicar sobre un compuesto conocido para primero uso en tratamiento médico y el uso de tal compuesto en la manufactura de un medicamento para un nuevo tratamiento médico.

Los siguientes comentarios con relación a la novedad y nivel inventivo de las reivindicaciones 1-2, 4-9, 11-26, 32-53 solo se refieren a la materia de las mismas la cual actualmente es buscada (Artículo 17(2) del PCT), i.e. esa parte de las reivindicaciones se refieren a compuestos pirazolopirimidina en los cuales los sustituyentes son como se definen en la reivindicación 3, métodos y composiciones de los mismos.

D1: releva pirazolo [1,5-a] derivados de pirimidina para el uso en los tintes para el pelo.
El título compuesto de acuerdo con ex. 4 del documento D1 es un compuesto representativo revelado en el presente caso y por consiguiente perjudicial para la novedad de la materia de las reivindicaciones 1-3, 5-7, 10, 19, 41 y 43 (Artículo 33(2) del PCT).

Los compuestos que son bio-isosters de pirazolo [1,5-a] pirimidina y convenientes como inhibidores CDK son conocidos del documento D2 (pirazolopiridinas) y documento D3 (pirazolotroazinas).

Puede considerarse el arte previo anterior a ambos documentos D2 y D3.

El problema bajo la presente solicitud era proporcionar compuestos heterobiciclicos que es conveniente como inhibidores CDK.

El problema se ha resuelto por los compuestos revelados, que pueden ser vistos en la descripción.

Los compuestos de acuerdo con el presente caso son representativos de una clase de sustancias que nunca han sido sugeridos como inhibidores CDK. Como ninguno de los documentos D2 y D3 hace pensar en un intercambio de los átomos del anillo bioisosterico del compuesto revelado en la presente solicitud no puede ser considerado obvio por una persona experta en el arte.

Un nivel inventivo en esencia del Artículo 33(3) del PCT pueden por lo tanto ser reconocidos por la materia de las reivindicaciones 4, 8-9, 11-18, 20-40, 42 y 44-53.

Otras objeciones:

Contrario a los requerimientos de la Regla 5.1 (a)(ii) del PCT, el fondo relevante del arte revelado en el documento D1-D3 no está mencionado en la descripción, ni esos documentos están identificados allí.

El término relativo "bajo" usado en el producto de las reivindicaciones es ambiguo e incierto y deja al lector en la duda acerca del significado de las características técnicas a que se refiere, quedando allí la definición de la materia de dichas reivindicaciones incierta (Articulo 6 del PCT).

La reivindicación 42 debería referirse a la reivindicación 39, y no a la reivindicación 41 (Art. 6 del PCT).

El termino "compuesto 2" empleado en la reivindicación 3 debería ser reemplazado por "compuesto de la reivindicación 2".

Re Punto VI
Ciertos documentos citados

Debe señalarse que los documentos D4-D7 revelan compuestos que son representativos de los compuestos de acuerdo con el producto reivindicado del presente caso que no excluye la materia de la misma por las provisiones (es, en este respecto, notó que, si un termino tal

gusta "aril" ó "aralquil" es empleado en una condición, el termino de todas formas solo designa el radical no sustituido, i.e. "aril" puede presentar fenil, pero no e.g. un grupo 4-bromofenil) y por consiguiente será relevante en un eventual examen en fase europea.

PATENT COOPERATION TREATY

PATENT DEPARTMENT
RECEIVED
JUN 13 2006

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

KALYANARAMAN, Palaiyur S.
SCHERING CORPORATION
Patent Department K-6-1 1990
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530
ETATS-UNIS D'AMERIQUE

Computer Review
Date/Entry Date
PA
Attny

☐ FILE ☐ CHECK (PCE Rule 71.1)

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

Date of mailing (day/month/year)	09.06.2006
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
OC01617K1	

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US2005/003859	08.02.2005	11.02.2004

Applicant
SCHERING CORPORATION

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Ulrich, J Tel. +49 89 2399-8048

Form PCT/IPEA/416 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference OC01617K1	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/US2005/003859	International filing date *(day/month/year)* 08.02.2005	Priority date *(day/month/year)* 11.02.2004

International Patent Classification (IPC) or national classification and IPC
INV. C07D487/04 A61K31/495 A61P35/00

Applicant
SCHERING CORPORATION

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07.09.2005	09.06.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Fritz, M Telephone No. +49 89 2399-

Form PCT/IPEA/409 (Cover Sheet) (April 2005)

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No. PCT/US2005/003859

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-594 **as originally filed**

   Claims, Numbers

   1-53 **as originally filed**

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 32-40

because:

☒ the said international application, or the said claims Nos. 32-40 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☒ See separate sheet for further details

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	4,8-9,11-18,20-40,42,44-53
	No:	Claims	1-3,5-7,10,19,41,43
Inventive step (IS)	Yes:	Claims	4,8-9,11-18,20-40,42,44-53
	No:	Claims	1-3,5-7,10,19,41,43
Industrial applicability (IA)	Yes:	Claims	1-31,41-53
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item III

N n-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 32-40 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with re-spect to the industrial applicability of the subject-matter of these claims (Art. 34(4)(a)(i) PCT).

Present claims 1-2 relate to an extremely large number of possible products, whereas support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the products claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible.
Moreover the initial phase of the search of claims 1-2, 4-9, 11-26 and 32-53 revealed a very large number of documents relevant to the issue of novelty. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT).

Consequently, the search has been carried out for those parts of the claims which ap-pear to be supported and disclosed, i.e. within a reasonable generalisation of the ex-amples in the description, namely those parts relating to the compounds as defined in claim 3, methods and compositions thereof.

It is noted that an International Preliminary Examination is not carried out on that part of subject-matter of claims 1-2, 4-9, 11-26, 32-53 which was not searched (cf. Rule 66.1 e) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

D1: WO 97/49378 A (L'OREAL; TERRANOVA, ERIC; FADLI, AZIZ; LAGRANGE, ALAIN) 31 December 1997 (1997-12-31)

D2: US-A-6 107 305 (MISRA ET AL) 22 August 2000 (2000-08-22)
D3: WO 02/50079 A (SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES ; PR) 27 June 2002 (2002-06-27)
D4: WO 2004/022561 A (SCHERING CORPORATION; PHARMACOPEIA, INC) 18 March 2004 (2004-03-18)
D5: WO 2004/087707 A (VERNALIS LIMITED; PARRATT, MARTIN; BOWER, JUSTIN, FAIRFIELD; WILLIAMS) 14 October 2004 (2004-10-14)
D6: WO 2004/022559 A (SCHERING CORPORATION; PHARMACOPEIA, INC) 18 March 2004 (2004-03-18)
D7: WO 2004/076458 A (TEIJIN PHARMA LIMITED; KATAOKA, KENICHIRO; SUZUKI, NAOTAKA; KOSUGI, TO) 10 September 2004 (2004-09-10)

The present application discloses pyrazolopyrimidine derivatives (claims 1-31,43-53), methods of treatment by administering these compounds (claims 32-40) and pharmaceutical compositions thereof (claims 41-42).

For the assessment of the present claims 32-40 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentabi-lity can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

The following comments with regard to novelty and inventive step of claims 1-2, 4-9, 11-26, 32-53 only refer to the subject-matter thereof which was actually searched (Article 17(2) PCT), i.e. that part of claims referring to the pyrazolopyrimidine compounds in which the substituents are those as defined in claim 3, methods and compositions the-reof.

D1 discloses pyrazolo[1,5-a]pyrimidine derivatives to be used in hair dyes.
The title compound according to ex. 4 of D1 is a representative of the compounds disclosed in the present case and therefore detrimental for the novelty of the subject-mat-ter of claims 1-3,5-7,10,19,41 and 43 (Article 33(2) PCT).

Compounds which are bioisosteres of pyrazolo[1,5-a]pyrimidine and suitable as CDK inhibitors are known from D2 (pyrazolopyridines) and D3 (pyrazolotriazines).

As closest prior art may be regarded both D2 and D3.

The problem underlying the present application was to provide further heterobicyclic compounds which are suitable as CDK-inhibitors.

This problem has been solved by the compounds disclosed, as can be seen in the description.

The compounds according to the present case are representatives of a class of substances which have never been suggested as CDK inhibitors. As none of D2 and D3 suggests a bioisosteric exchange of the ring atoms the compounds disclosed in the present application cannot be considered obvious for the man skilled in the art.

An inventive step in the sense of Article 33(3) PCT can therefore be acknowledged for the subject-matter of claims 4, 8-9,11-18,20-40, 42 and 44-53.

Further objections:

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclo-sed in the documents D1-D3 is not mentioned in the description, nor are these docu-ments identified therein.

The relative term "lower" used in the product claims is vague and unclear and leaves the reader in doubt as to the meaning of the technical features to which it refers, there-by rendering the definition of the subject-matter of said claims unclear (Article 6 PCT).

Claim 42 should refer to claim 39, not to claim 41 (Art,. 6 PCT).

The term "compound 2" employed in claim 3 should be replaced by "compound of claim 2".

Re Item VI
Certain documents cited

It should be pointed out that the documents D4-D7 disclose compounds which are representatives of the compounds according to the product claims of the present case that are not excluded from the subject-matter thereof by the provisos (it is, in this respect, noted that, if a term such like "aryl" or "aralkyl" is employed in a proviso, this term at any rate designates only the unsubstituted moieties, i.e. "aryl" may represent phenyl, but not e.g. a 4-bromophenyl group) and therefore will be relevant in an eventual euro-pean stage of examination.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATI N TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
25 August 2005 (25.08.2005)

PCT

(10) International Publication Number
WO 2005/077954 A3

(51) International Patent Classification[7]: C07D 487/04, A61K 31/495, A61P 35/00

(21) International Application Number: PCT/US2005/003859

(22) International Filing Date: 8 February 2005 (08.02.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/776,988 11 February 2004 (11.02.2004) US

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(74) Agent: KALYANARAMAN, Palaiyur S.; SCHERING 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, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, 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, 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)) for all designations*

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

(88) Date of publication of the international search report:
13 October 2005

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: PYRAZOLOPYRIMIDINE-DERIVATIVES AS CYCLIN DEPENDENT KINASE INHIBITORS

(57) Abstract: In its many embodiments, the present invention provides 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 2005/077954 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/003859

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/495 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97/49378 A (L'OREAL; TERRANOVA, ERIC; FADLI, AZIZ; LAGRANGE, ALAIN) 31 December 1997 (1997-12-31) Ex. 4, title cpd.	1-3,5-7, 10,19, 41,43
A	US 6 107 305 A (MISRA ET AL) 22 August 2000 (2000-08-22) the whole document	1-53
A	WO 02/50079 A (SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES ; PR) 27 June 2002 (2002-06-27) the whole document	1-53
P,X	WO 2004/022561 A (SCHERING CORPORATION; PHARMACOPEIA, INC) 18 March 2004 (2004-03-18) Examples	1-53

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 July 2005	29/07/2005

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2005/003859

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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P,X	WO 2004/076458 A (TEIJIN PHARMA LIMITED; KATAOKA, KENICHIRO; SUZUKI, NAOTAKA; KOSUGI, TO) 10 September 2004 (2004-09-10) Examples	1-53

Form PCT/ISA/210 (continuation of second sheet) (January 2004)

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WO 2004076458	A	10-09-2004	WO	2004076458 A1	10-09-2004

Form PCT/ISA/210 (patent family annex) (January 2004)

INTERNATIONAL SEARCH REPORT

Intern[illegible] Application No
PCT/US2005/003859

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Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
EXTRACTO PARA PUBLICACIÓN
SOLICITUD DE PATENTE DE INVENCIÓN PCT

(21) N° de solicitud:	(51) Int Cl: C07D 487/04, A61K 31/495, A61P 35/00
22) Fecha de solicitud:	(71)Solicitante(s) SCHERING CORPORATION y PHARMACOPEIA DRUG DISCOVERY INC.
(30) Prioridad (31) *No. Prioridad* 32) *Fecha* (33) *País* 10/776.988 11/02/04 US	(72) Inventor(es) VER PAGINA ADJUNTA
	(74) Apoderado: J. IAN RAISBECK
(85) Fecha límite inicio fase nacional: (86) Datos relativos a la presentación de la solicitud PCT Fecha de presentación de la solicitud: *08/02/05* No. de solicitud *PCT/US2005/003859*	(87) Publicación internacional Fecha: *25/08/05* N° publicación: *WO 2005/077954*

(54) Título: **PIRAZOLOPIRIMIDINAS NOVEDOSAS COMO INHIBIDORES DE QUINASA CICLINA-DEPENDIENTES.**

Resumen - Reivindicación(es):

En sus numerosas realizaciones, la presente invención provee una clase novedosa de compuestos derivados de pirazolo[1,5-a] pirimidina como inhibidores de quinasas ciclina-dependientes, métodos para preparar tales compuestos, composiciones farmacéuticas que contienen uno o más de tales compuestos, métodos para preparar formulaciones farmacéuticas que comprenden uno o más de tales compuestos y métodos de tratamiento, prevención, inhibición o alivio de una o más enfermedades asociadas con las CDKs usando tales compuestos o composiciones farmacéuticas.

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Industria y Comercio
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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-078330- -00000-0000
Fec: 2006-08-09 17:30:53 Dep: 2020 INUECREACIONES
Tra: 11 PATENTEVII
Exp: 379 FAGENACIONALII
Act: 411 PRESENTACION Folios: 1004

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

11/09/06

(3) **SOLICITUD DE:**

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

[ ] Capítulo I. [X] Capítulo II.

(4) **SOLICITANTE (71)**

Nombre: SCHERING CORPORATION y PHARMACOPEIA DRUG DISCOVERY, INC.
Dirección: 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530, y 3000 Eastpark Boulevard, Cranbury, NJ 08512 E.U.A.
Nacionalidad o Domicilio: ESTADOUNIDENSE
Lugar de Constitución: Kenilworth y Cranbury E.U.A.
Teléfono: _____ Fax: _____
E-mail: _____

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

(5) **REPRESENTANTE O APODERADO**

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E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN
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C.E. [ ] Otro [ ]
Cual _____
Número 79.376.996 Btá
TP 135.799

(6) **INVENTOR (ES) (72)**

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

(8) **PCT (86)**
Solicitud Internacional No. PCT/US2005/003859 Fecha Febrero 8, 2005
Publicación Internacional No. WO 2005/077954 Fecha Agosto 25, 2005

(9) **Título (54): PIRAZOLOPIRIMIDINAS NOVEDOSAS COMO INHIBIDORES DE QUINASA CICLINA-DEPENDIENTES**

(7) **Clasificación Internacional (51)** C07D 487/04, A61K 31/495, A61P 35/00

(10) **Prioridad**
SI [X] N [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Febrero 11, 2004	10/776.988

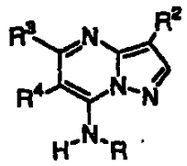
Comprobante de pago No. 06 - 58,177 **Fecha** Agosto 1, 2006

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REIVINDICACIONES

ndo así especialmente descrito y determinado la naturaleza de la presente ión y la forma como la misma ha de ser llevada a la práctica, se declara icar como de propiedad y derecho exclusivo.

Un compuesto representado mediante la fórmula estructural:

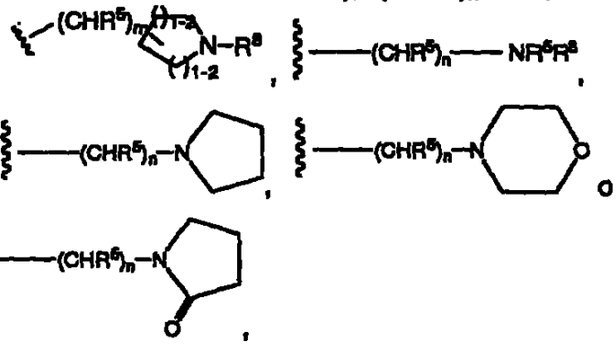


sal aceptable para uso farmacéutico o solvato de dicho compuesto,

ual:

R es H, alquilo, alquenilo, alquinilo, arilalquilo, arilalquenilo, cicloalquilo, lquilalquilo, alquenilalquilo, alquinilalquilo, heterociclilo, heterociclilalquilo, oarilalquilo (incluyendo el N-óxido de dicho heteroarilo), -$(CHR^5)_n$-arilo,

-$(CHR^5)_n$-heteroarilo,

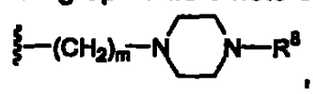


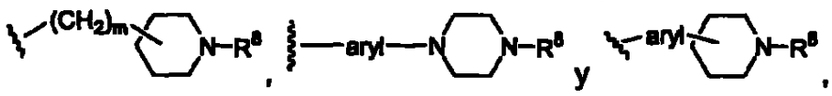
de cada uno de dichos alquilo, alquenilo, alquinilo, arilo, cicloalquilo, erociclilo y heteroarilo puede ser no sustituido o sustituido opcionalmente con ó o más restos que pueden ser iguales o diferentes, seleccionándose cada ó independientemente del grupo que consiste en halógeno, alquilo, arilo, oalquilo, heterociclilalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^{10}$, $-C(R^4R^5)_p-R^9$, $R^5)$Boc, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^{10}$, $-SO_3H$, $-SR^{10}$, $(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^{10}$;

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1005 1007

R^2 se selecciona del grupo que consiste en R^9, alquilo, alquenilo, alquinilo, heterociclilo, heterociclilalquilo, halógeno, haloalquilo, arilo, arilalquilo, arilalquilo, alquinilalquilo, cicloalquilo, heteroarilo, alquilo sustituido con 1-6 R^9 que pueden ser iguales o diferentes y se seleccionan independientemente del listado de R^9 que se muestra a continuación, arilo tituido con 1-3 grupos arilo o heteroarilo que pueden ser iguales o diferentes y seleccionan independientemente de grupos fenilo, piridilo, tiofenilo, furanilo y , arilo fusionado con un grupo arilo o heteroarilo, heteroarilo sustituido con grupos arilo o heteroarilo que pueden ser iguales o diferentes y se cionan independientemente de grupos fenilo, piridilo, tiofenilo, furanilo y ó, heteroarilo fusionado con un grupo arilo o heteroarilo,





de uno o más de los arilo y/o uno o más de los heteroarilo en las definiciones donadas anteriormente para R^2 puede ser no sustituido o sustituido onalmente con uno o más restos que pueden ser iguales o diferentes, cionándose cada resto independientemente del grupo que consiste en geno, -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, lo, arilo y OCF_3;

R^3 se selecciona del grupo que consiste en H, halógeno, $-NR^5R^6$, $-OR^6$, , $-C(O)N(R^5R^6)$, alquilo, alquinilo, cicloalquilo, arilo, arilalquilo, heterociclilo, rociclilalquilo, heteroarilo y heteroarilalquilo,

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 06-078330- -00000-0000
Fec: 2006-08-09 17:38:59 Dep: 2020 NUECREACIONES
Tra: 11 PATENTES
Eve: 370 FASENACIONALII
Act 411 PRESENTACION Folios: 1004

REQUISITOS MINIMOS PARA ADMISION 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 [ ]

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
RAISBECK J. IAN

REFERENCIA	Radicación No.	06 78330
	Solicitud internacional	US2005/003859
	Fecha inicio fase nacional	11/09/2006
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	11704

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 las copias de los documentos en que constan las cesiones del derecho a la patente del inventor a los solicitantes o a sus causantes. (Art. 26-k) Decisión 486.

2. La solicitud no contiene el poder debidamente otorgado por la sociedad PHARMACOPEIA DRUG DISCOVERY, INC., con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior, requerimiento fue notificado por fijación en lista de
fecha 19 OCT. 2006
aalvarado