Industria y Comercio

SUPERINTENDENCIA

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

(21) **EXPEDIENTE No.** 05-2056

(54) **TÍTULO** NUEVOS PIRAZOLOPIRIDINAS COMO INHIBIDORES DE QUINASA DEPENDIENTES DE CICLINAS

(51) **CLASIFICACIÓN INTERNACIONAL** A61K31/519; A61P25/28

(71) **SOLICITANTE** SCHERING CORPORATION Y PHARMACOPEIA DRUG DISCOVERY, INC

DOMICILIO

(74) **APODERADO** CARLOS R OLARTE

(22) **BOGOTÁ, D. C.,** MARZO 4, 2005

CSCSOC)5 (55)

(FORMA P 10)

OLARTERAISBECK

Industria y Comercio
SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Radicacion : 03d07316 00000000 Folios: 36
Fecha (AMD): 2003-09-04 17:26:23
Tramite : 911 PCT-PATENT 3/Y FASE NAL 411 PATENTES
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL 04-04-2005

(1) SOLICITUD DE:

[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 Delaware E.U.A.
Teléfono: _____ Fax: _____
E-mail: _____

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

(3) REPRESENTANTE APODERADO

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

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

(4) INVENTOR (ES) (72)

Nombre : VER PAGINA ADJUNTA
Dirección: VER PAGINA ADJUNTA
Nacionalidad o Domicilio: VER PAGINA ADJUNTA Ptos 3 y 4

(5) PCT (86)

Solicitud Internacional No. PCT/US2003/027555 Fecha 3 de Septiembre de 2003
Publicación Internacional No. WO 2004/022561 Fecha 18 de Marzo de 2004

(6) Título (54) NUEVOS PIRAZOLOPIRIMIDINAS COMO INHIBIDORES DE QUINASA DEPENDIENTES DE CICLINAS.

(7) Clasificación Internacional (51) C07D 487/04, A61K31/519 A61P25/28

(8) Prioridad SI [X] N [ ]

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
US	Septiembre 4, 2002	60/408,027
US	Octubre 29, 2002	60/421,959

(9) Comprobante de pago No. _____ **Fecha** _____

(10) **ANEX S**

- [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.
- [ ] Documento de cesión del interventor 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).
- [ ] Traducción del examen preliminar internacional efectuado por la IPEA.
- [ ] De ser el caso, copia del contrato de acceso.
- [ ] De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- [ ] De ser el caso, certificado de depósito del material biológico.
- [ ] Arte final 12 x 12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [ ] De ser el caso, modificaciones efectuadas a la solicitud internacional.
- [x] Otros. Búsqueda Internacional

(11) **FIGURA CARACTERÍSTICA:**

(12) Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE FIRMA: _____

C.C. 79.782.747 Btá T.P. 74.295

Inventors/Citizenship

GUZI, Timothy
Citizen of the United States
48 Red Road
Chatham, New Jersey 07928
United States of America

PARUCH, Kamil
Citizen of the Czech Republic
20 Third Avenue
Garwood, New Jersey 07027
United States of America

DWYER, Michael P.
Citizen of the United States
235 Katherine Street
Scotch Plains, New Jersey 07076
United States of America

DOLL, Ronald J.
Citizen of the United States
8 Concord Lane
Convent Station, New Jersey 07960
United States of America

GIRIJAVALLABHAN, Viyyoor Moopil
Citizen of the United States
10 Maplewood Drive
Parsippany, New Jersey 07054
United States of America

MALLAMS, Alan
Citizen of the United States
147 Kings Highway, RR3
Hackettstown, New Jersey 07840
United States of America

ALVAREZ, Carmen S.
Citizen of the United States
121 Walnut Street
Livingston, New Jersey 07039
United States of America

KEERTIKAR, Kartik M.
Citizen of India
24 Columbia Avenue
East Windsor, New Jersey 08520
United States of America

RIVERA, Jocelyn
Citizen of the United States
72 Regal Drive
Monmouth Junction, New Jersey 08852
United States of America

CHAN, Tin-Yau
Citizen of Hong Kong
26 Barlow Road
Edison, New Jersey 08817
United States of America

MADISON, Vincent
Citizen of the United States
12 Ronarm Drive
Mountain Lakes, New Jersey 07046
United States of America

FISCHMANN, Thierry O.
Citizen of the United States
2700 Sky Top Drive
Scotch Plains, New Jersey 07076
United States of America

Inventors/Citizenship

DILLARD, Lawrence W.
Citizen of the United States
278 Spring Hill Road
Skillman, New Jersey 08558
United States of America

TRAN, Vinh D.
Citizen of the United States
17374 Winemast Street
Fountain Valley, California 92708
United States of America

HE, Zhen Min
Citizen of the United States
5 Pennyroyal Court
Princeton, New Jersey 08540
United States of America

JAMES, Ray Anthony
Citizen of the United States
1036 Radcliffe Street
Bristol, Pennsylvania 19007
United States of America

PARK, Haengsoon
Citizen of the Republic of Korea
8910 Tamarron Drive
Plainsboro, New Jersey 08536
United States of America

PARADKAR, Vidyadhar M.
Citizen of the United States
3 Pine Ridge Drive
Somerville, New Jersey 08876
United States of America

HOBBS, Douglas Walsh
Citizen of the United States
1330 University Drive
Yardley, Pennsylvania 19067
United States of America

5

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05020016 00000000 Folios: 567
Fecha (AMD): 2005-03-04 17:26:23
Tramite : 011 PCI PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 05 - 16,637
FECHA : MARZO 4 DE 2005

05-20510

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
JOSE SANTOS	CONSIGNACION	BANCO POPULAR	050-00110-6	37061231	04/03/2005	443,000.00

***** 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	443,000.00
		TOTAL : $	443,000.00

SON: CUATROCIENTOS CUARENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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

APOSTILLA EN PODER DE REPRESENTACIÓN DE

SCHERING CORPORATION

APOSTILLA

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

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

CERTIFICADO

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

PODER DE REPRESENTACIÓN

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

CERTIFICADO NOTARIAL

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

Las certificaciones anteriores se basan en [illegible] 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

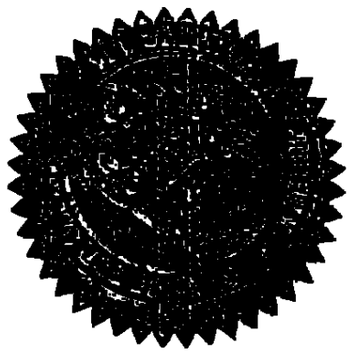
6. THE 29TH DAY OF AUGUST 2003

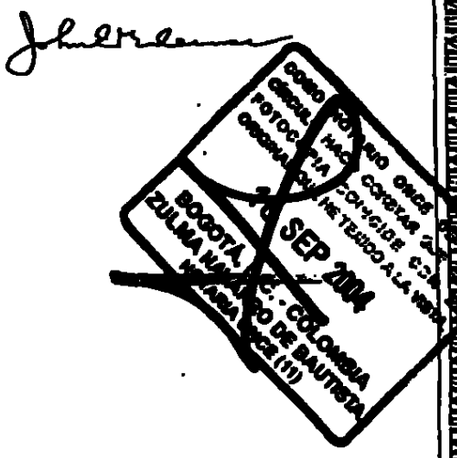
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A180345

9. SEAL/STAMP:

10. SIGNATURE





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

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

www.olarteraisbeck.com

Power of Attorney

The undersigned,
SCHERING CORPORATION

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

by means of these presents hereby grants to **Carlos R. Olarte and/or Ana Maria 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 Maria 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 Direc[illegible]

Date/Fecha: August 7, 2003

City,Country/Ciudad,Pais: Kenilworth, New Jersey, U.S.[illegible]

16 SEP 2004
BOGOTA, D.C. - COLOMBIA

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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

www.olarteraisbeck.com

Notarial Certification

On this date, August 7, 2003

The undersigned Notary Public certifies:

1. That Edward H. Mazer

of legal age and domiciled in 139 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

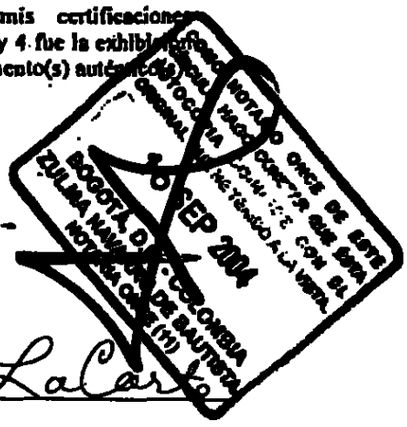
4. Que

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):



BLIC (Signature):

Marguerite La Corte

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

EL SUSCRITO NOTARIO ONCE (E) DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

03 NOV 2004

BOGOTA, D.C. - COLOMBIA
MONICA PALMA BAUTISTA NAVARRO
NOTARIA ONCE (11) E.

María del Pilar Iglesias
TRADUCTORA E
INTERPRETE OFICIAL
Resolución No. 819 Ministerio

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

COMO NOTARIA ONCE (E) DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
03 NOV 2004
BOGOTA, D.C. - COLOMBIA
MONICA ZULMA BAUTISTA NAVARRO
NOTARIA ONCE (11) E.

(12)

APOSTILLE

(CONVENTION DE LA HAYE DU 5 OCTOBRE 1961)

1. COUNTRY: UNITED STATES OF AMERICA

2. THIS PUBLIC DOCUMENT HAS BEEN SIGNED BY:
MELANIE J RICE

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

4. BEARS THE SEAL/STAMP OF:
MELANIE J RICE, NOTARY

CERTIFIED

5. AT TRENTON, NEW JERSEY

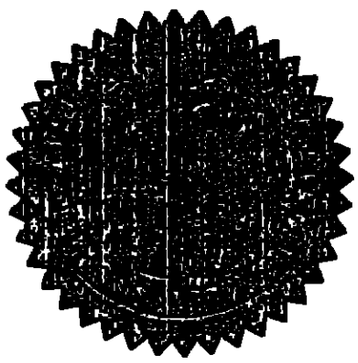
6. THE 25TH DAY OF OCTOBER 2004

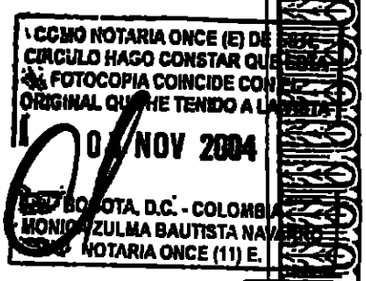
7. BY: John E McCormac, CPA, NEW JERSEY TREASURER

8. NO. A211395

9. SEAL/STAMP:

10. SIGNATURE





OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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

www.olarteraisbeck.com

Power of Attorney

The undersigned, [illegible] PHARMACOPEIA DRUG DISCOVERY, INC. domiciled in 3000 East Park Boulevard, Cranbury, New Jersey 08512-3516 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, [illegible] domiciliado en [illegible] 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: _____

Brian M. Posner, Vice President of Finance

Date/Fecha: 1 October 2004

City,Country/Ciudad,País: Cranbury, New Jersey, U.S.A.

COMO NOTARIA ONCE (E) DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
03 NOV 2004
BOGOTA, D.C. - COLOMBIA
MONICA ZULMA BAUTISTA NAVARRO
NOTARIA ONCE (11) E.

OLARTERAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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

www.olarteraisbeck.com

Notarial Certification

On this date,

The undersigned Notary Public certifies:

1. That

of legal age and domiciled in

signed the foregoing document.

2. That the grantor has executed the foregoing document as
of

3. That
having its principal place of business located in

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):

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): Melanie J. Rice 10/1/04

SEAL (optional)

MELANIE J. RICE
A Notary Public of New Jersey
My Commission Expires June 12, 2007

COMO NOTARIA ONCE (E) DE ESTE CIRCULO HAGO CONSTAR QUE ESTA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
03 NOV 2004
BOGOTA, D.C. - COLOMBIA
MONICA PALMA BAUTISTA NAVARRO
NOTARIA ONCE (11) E.

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
18 March 2004 (18.03.2004)

PCT

(10) International Publication Number
WO 2004/022561 A1

(51) International Patent Classification[7]: C07D 487/04, A61K 31/519 // (C07D 487/04, 239:00, 231:00)

(21) International Application Number:
PCT/US2003/027555

(22) International Filing Date:
3 September 2003 (03.09.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

60/408,027	4 September 2002 (04.09.2002)	US
60/421,959	29 October 2002 (29.10.2002)	US

(71) Applicants: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US). PHARMACOPEIA, INC. [US/US]; 3000 Eastpark Boulevard, Cranbury, NJ 08512 (US).

(72) Inventors: GUZI, Timothy, J.; 48 Red Road, Chatham, NJ 07928 (US). PARUCH, Kamil; 20 Third Avenue, Garwood, NJ 07027 (US). DWYER, Michael, P.; 235 Katherine Street, Scotch Plains, NJ 07076 (US). DOLL, Ronald, J.; 8 Concord Lane, Convent Station, NJ 07960 (US). GIRIJAVALLABHAN, Viyyoor, Moopil; 10 Maplewood Drive, Parsippany, NJ 07054 (US). MALLAMS, Alan; 147 Kings Highway, RR3, Hackettstown, NJ 07840 (US). ALVAREZ, Carmen, S.; 121 Walnut Street, Livingston, NJ 07039 (US). KEERTIKAR, Kartik, M.; 24 Columbia Avenue, East Windsor, NJ 08520 (US). RIVERA, Jocelyn; 72 Regal Drive, Monmouth Junction, NJ 08852 (US). CHAN, Tin-Yau; 26 Barlow Road, Edison, NJ 08817 (US). MADISON, Vincent; 12 Ronarm Drive, Mountain Lakes, NJ 07046 (US). FISCHMANN, Thierry, O.; 2700 Sky Top Drive, Scotch Plains, NJ 07076 (US). DILLARD, Lawrence, W.; 278 Spring Hill Road, Skillman, NJ 08558 (US). TRAN, Vinh, D.; 17374 Winemast Street, Fountain Valley, CA 92708 (US). HE, Zhen Min; 5 Pennyroyal Court, Princeton, NJ 08540 (US). JAMES, Ray, Anthony; 1036 Radcliffe Street, Bristol, PA 19007 (US). PARK, Haengsoon; 8910 Tamarron Drive, Plainsboro, NJ 08536 (US). PARADKAR, Vidyadhar, M.; 3 Pine Ridge Drive, Somerville, NJ 08876 (US). HOBBS, Douglas, Walsh; 1330 University Drive, Yardley, PA 19067 (US).

(74) Agent: KALYANARAMAN, Pulalyur, S.; Schering Corporation, Patent Department K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NI, NO, NZ, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
- *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*

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: 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 2004/022561 A1

PYRAZOLOPYRIMIDINES AS CYCLIN-DEPENDENT KINASE INHIBITORS

Field of the Invention

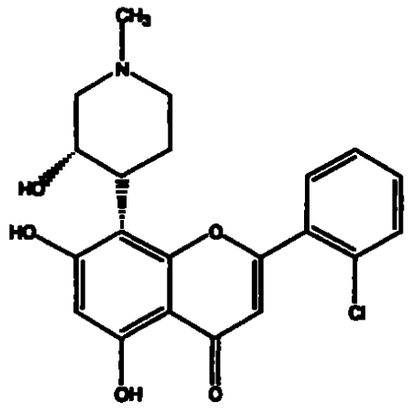
The present invention relates to pyrazolo[1,5-a]pyrimidine compounds useful as protein kinase inhibitors (such as for example, the inhibitors of the cyclin-dependent kinases, mitogen-activated protein kinase (MAPK/ERK), glycogen synthase kinase 3(GSK3beta) and the like), pharmaceutical compositions containing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

Background of the Invention

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

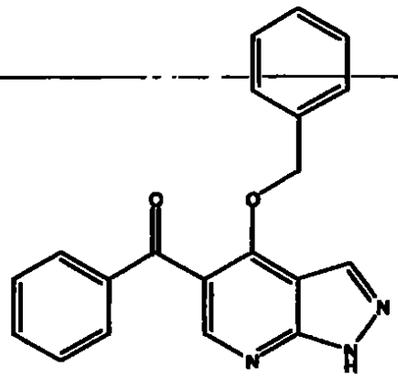
respond to insults or to proliferative signals, while the loss of proper checkpoint control in cancer cells contributes to tumorgenesis. The CDK2 pathway influences tumorgenesis at the level of tumor suppressor function (e.g. p52, RB, and p27) and oncogene activation (cyclin E). Many reports have demonstrated 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.

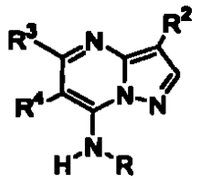
Pyrazolopyrimidines are known. For Example, WO92/18504, WO02/50079, WO95/35298, WO02/40485, EP94304104.6, EP0628559 (equivalent to US Patents 5,602,136, 5,602,137 and 5,571,813), U.S. 6,383,790, *Chem. Pharm. Bull.*, (1999) 47 928, *J. Med. Chem.*, (1977) 20, 296, *J. Med. Chem.*, (1976) 19 517 and *Chem.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

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

Summary of the Invention

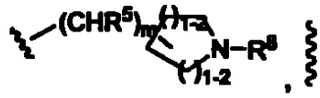
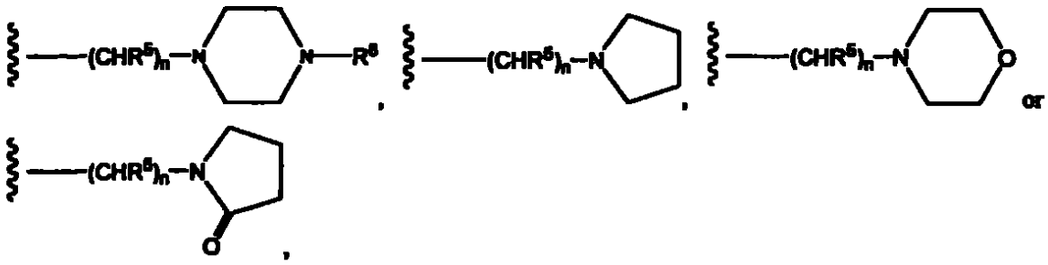
In its many embodiments, the present invention provides a novel class of pyrazolo[1,5-a]pyrimidine compounds as inhibitors of cyclin dependent kinases, methods of preparing such compounds, pharmaceutical compositions comprising one or more such compounds, methods of preparing pharmaceutical formulations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

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



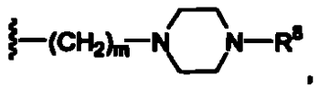
Formula III

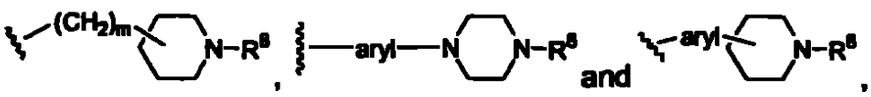
wherein:

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

wherein each of said alkyl, alkenyl, alkynyl, aryl, cycloalkyl, heterocyclyl, and heteroaryl can be unsubstituted or optionally substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, heterocyclylalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^{10}$, $-C(R^4R^5)_p-R^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^{10}$, $-SO_3H$, $-SR^{10}$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^5R^{10}$;

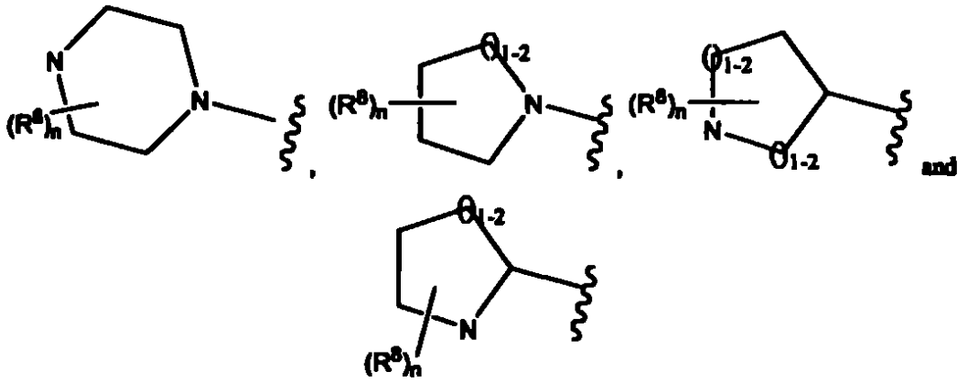
R^2 is selected from the group consisting of R^9, alkyl, alkenyl, alkynyl, CF_3, heterocyclyl, heterocyclylalkyl, halogen, haloalkyl, aryl, arylalkyl, heteroarylalkyl, alkynylalkyl, cycloalkyl, heteroaryl, alkyl substituted with 1-6 R^9 groups which can be the same or different and are independently 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, $-OCF_3$, $-(CR^4R^5)_pOR^5$, $-OR^5$, $-NR^5R^6$, $-(CR^4R^5)_pNR^5R^6$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ 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, $-OR^5$, $-NR^4R^5$, $-C(R^4R^5)_p-R^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)NR^4R^5$, $-C(O)R^5$, $-SO_3H$, $-SR^5$, $-S(O_2)R^7$, $-S(O_2)NR^4R^5$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^4R^5$;

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

R^7 is selected from the group consisting of alkyl, cycloalkyl, aryl, arylalkenyl, heteroaryl, arylalkyl, heteroarylalkyl, heteroarylalkenyl, and heterocyclyl, wherein each of said alkyl, cycloalkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally independently

substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^{10}$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^{10}$, $-C(O)R^5$, $-SR^{10}$, $-S(O_2)R^{10}$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^{10}$, $-N(R^5)C(O)R^{10}$ and $-N(R^5)C(O)NR^5R^{10}$;

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

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

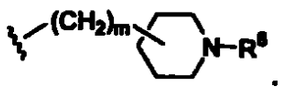
The compounds of Formula III can be useful as protein kinase inhibitors and can be useful in the treatment and prevention of proliferative diseases, for example, cancer, inflammation and arthritis. They may also be useful in the treatment of neurodegenerative diseases such Alzheimer's disease, cardiovascular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

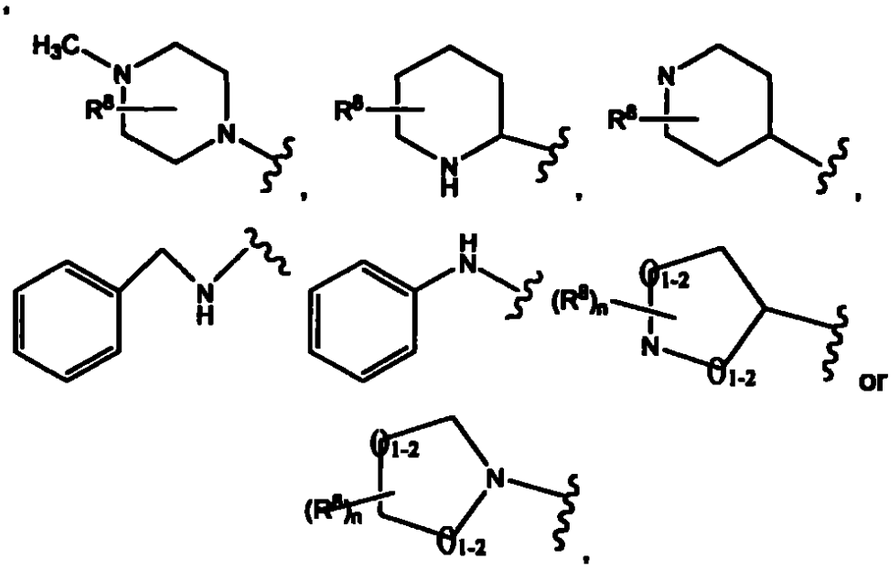
In another embodiment, R is $-(CHR^5)_n$-aryl, $-(CHR^5)_n$-heteroaryl,

$-(CHR^5)_n$-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.

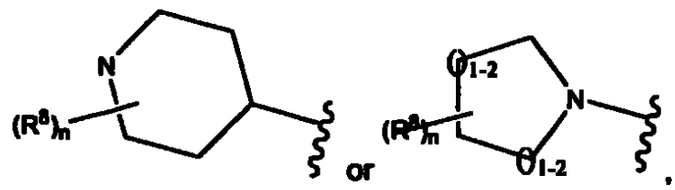
In another embodiment, n is 1 to 2.

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 the same or different, each moiety being independently selected from the group consisting of halogen, CF_3, lower alkyl, hydroxyalkyl, alkoxy, $-S(O_2)R^5$, and CN.

In an additional embodiment, R^4 is H.

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

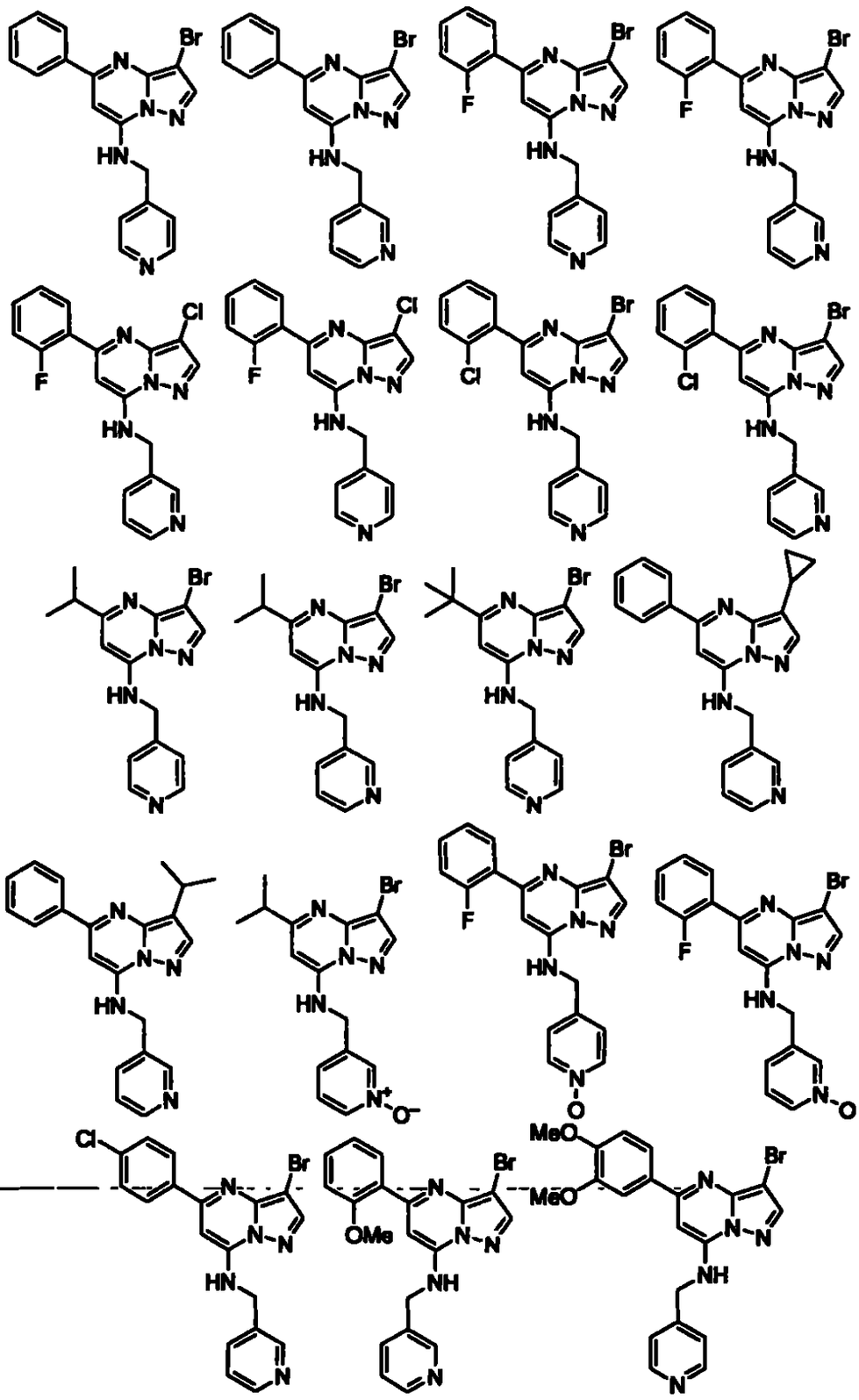
In an additional embodiment, R^8 is alkyl or hydroxyalkyl.

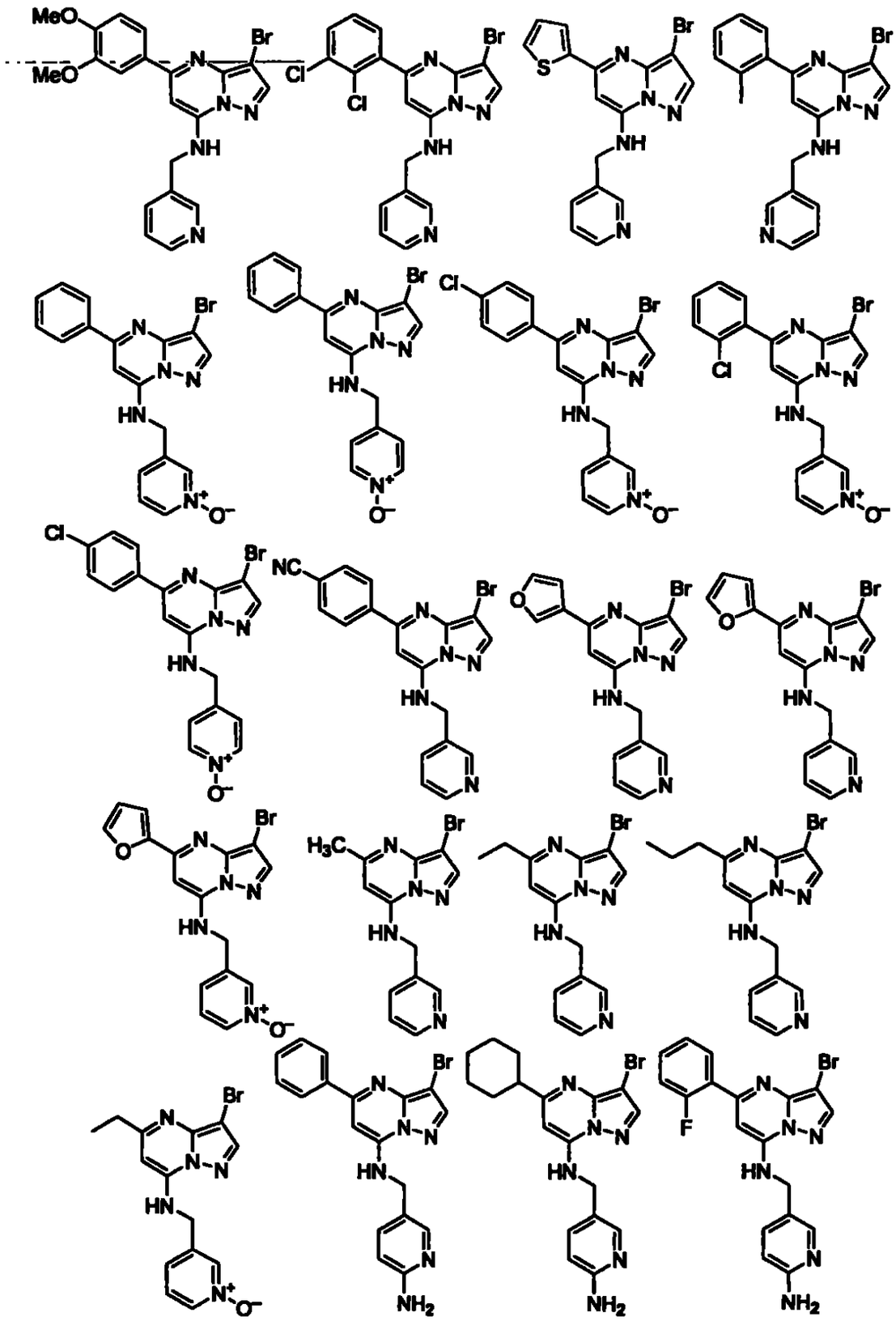
In an additional embodiment, n is 1.

In an additional embodiment, p is 1 or 2.

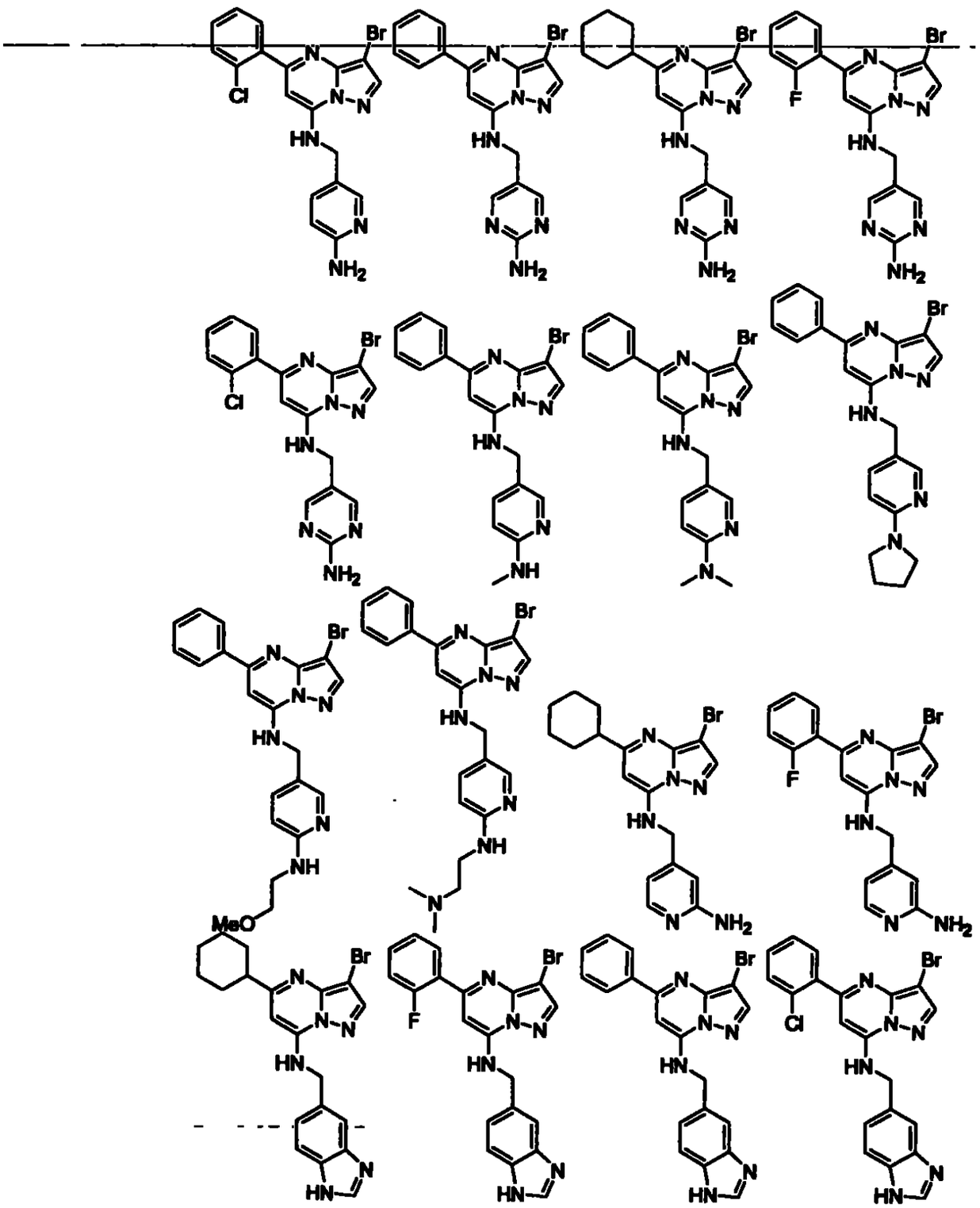
Another embodiment discloses the inventive compounds shown in Table 1, which exhibited CDK2 inhibitory activity of about 0.0001μM to > about 5 μM. The assay methods are described later (from page 333 onwards).

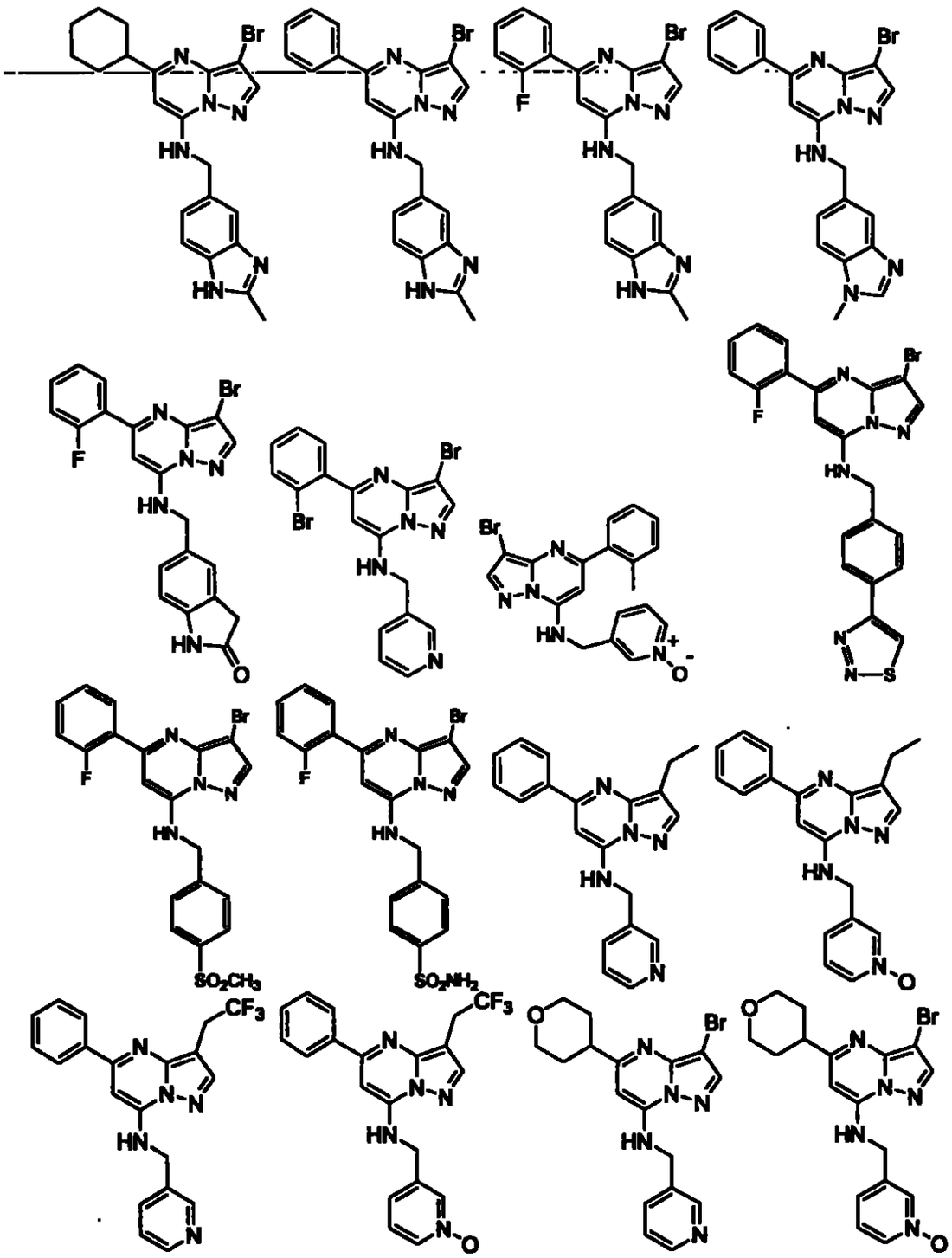
Table 1

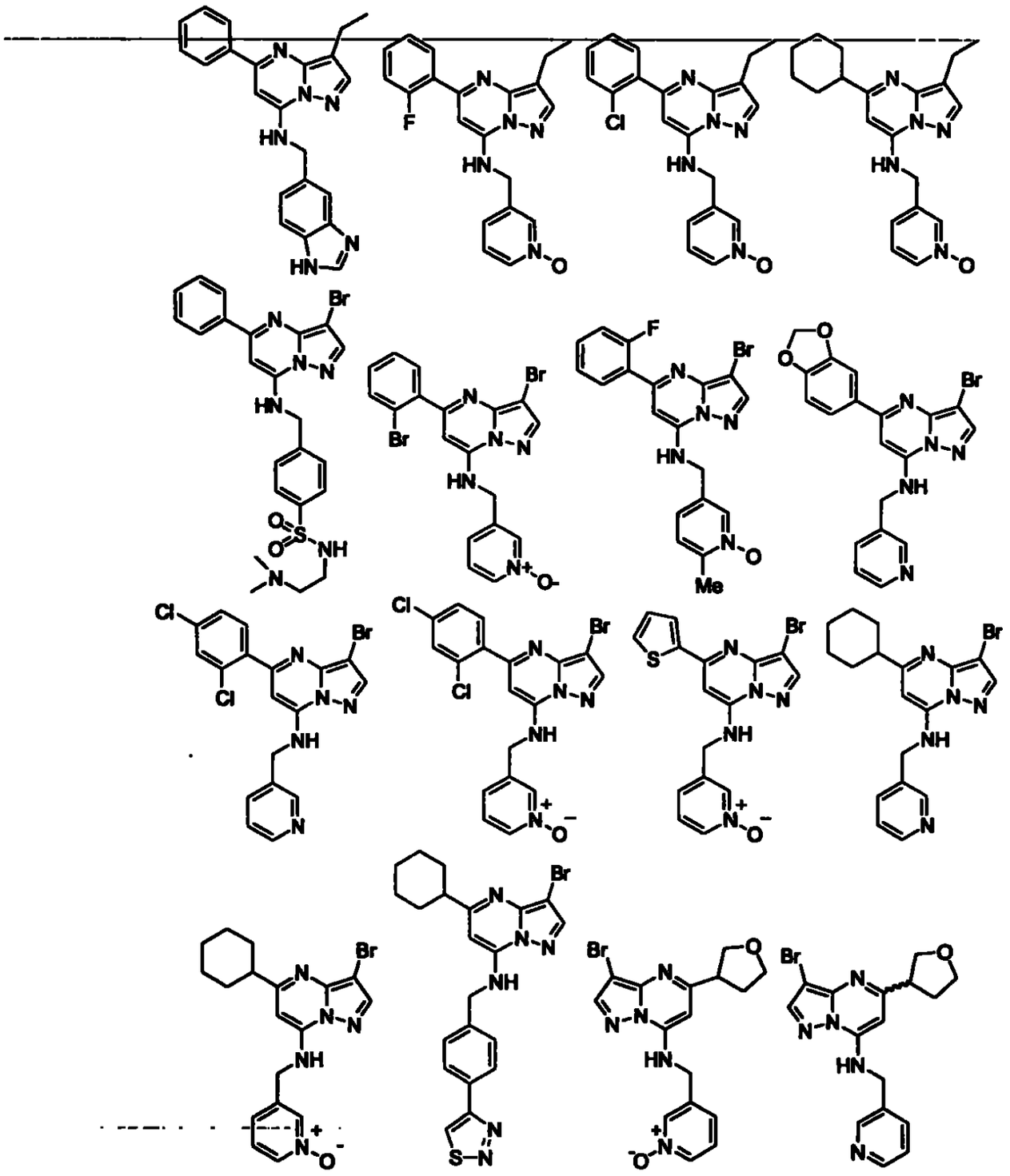


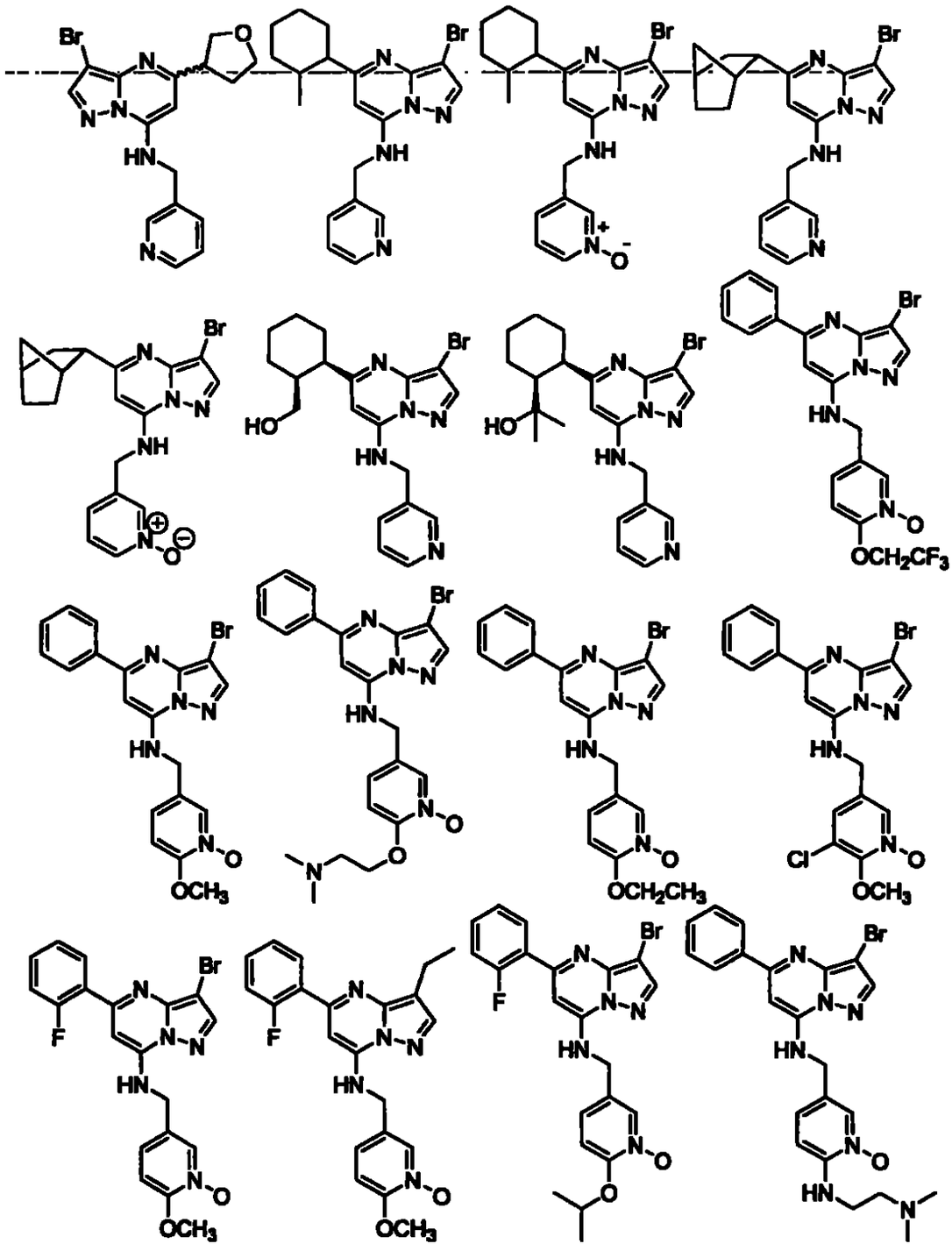


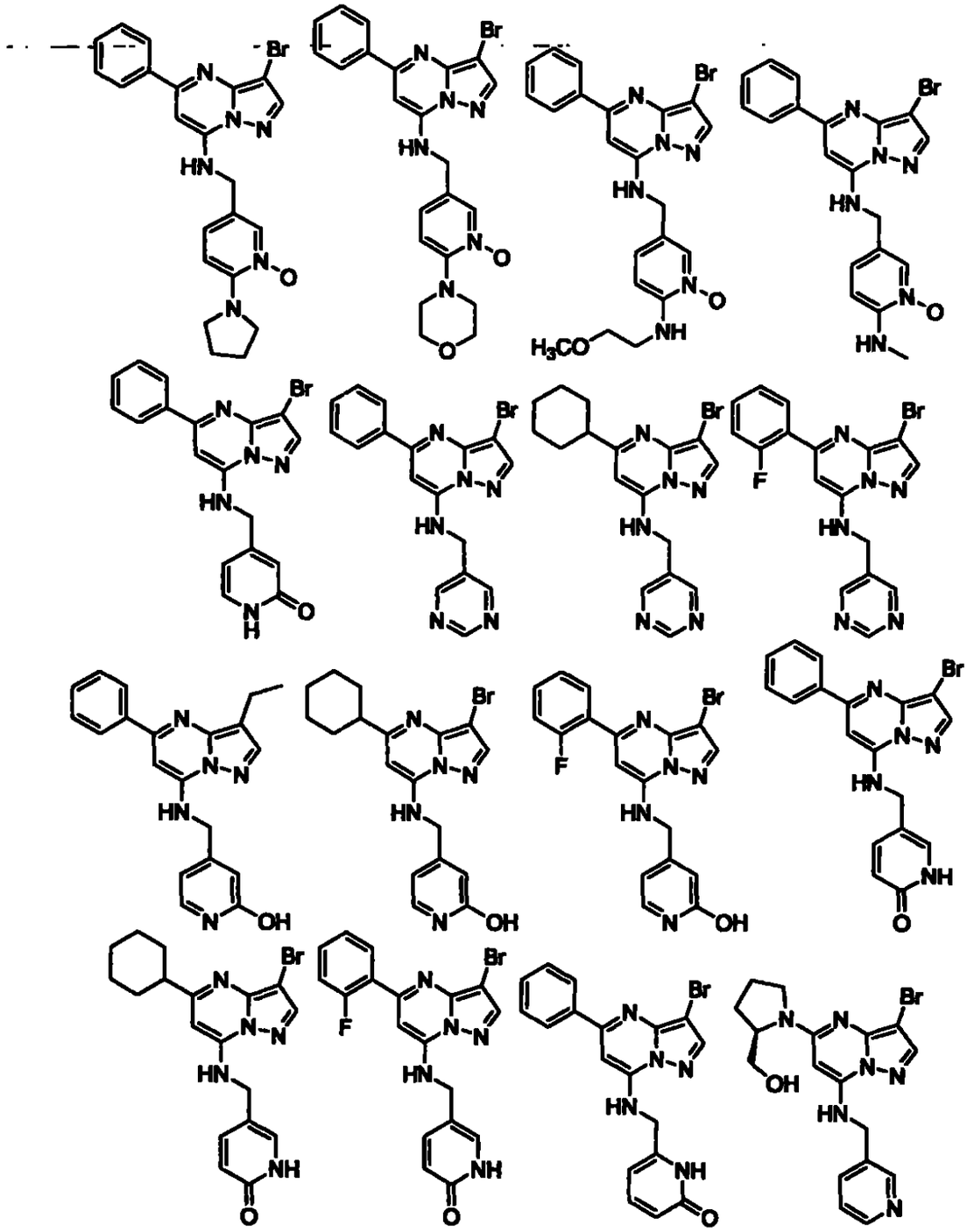
5

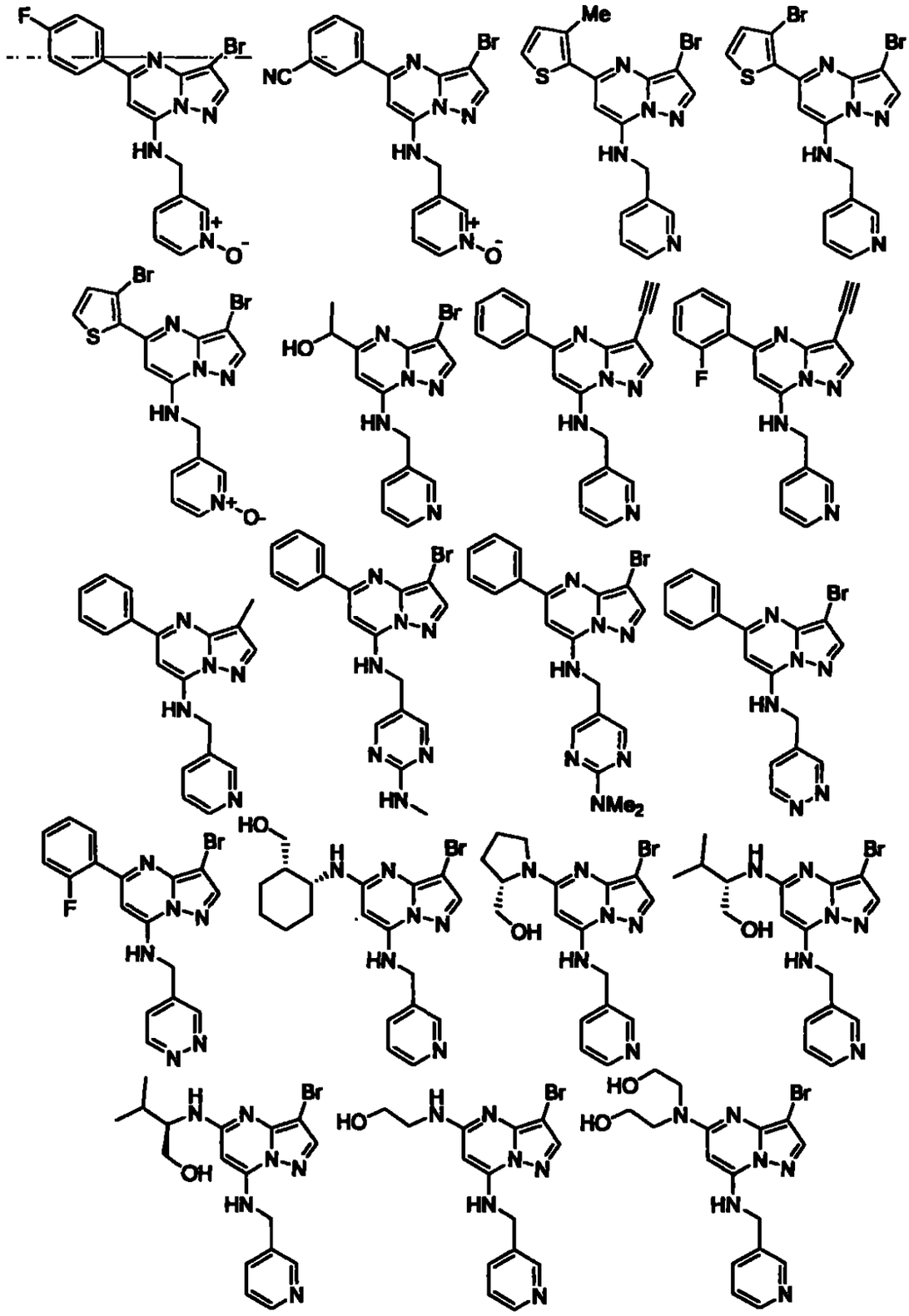




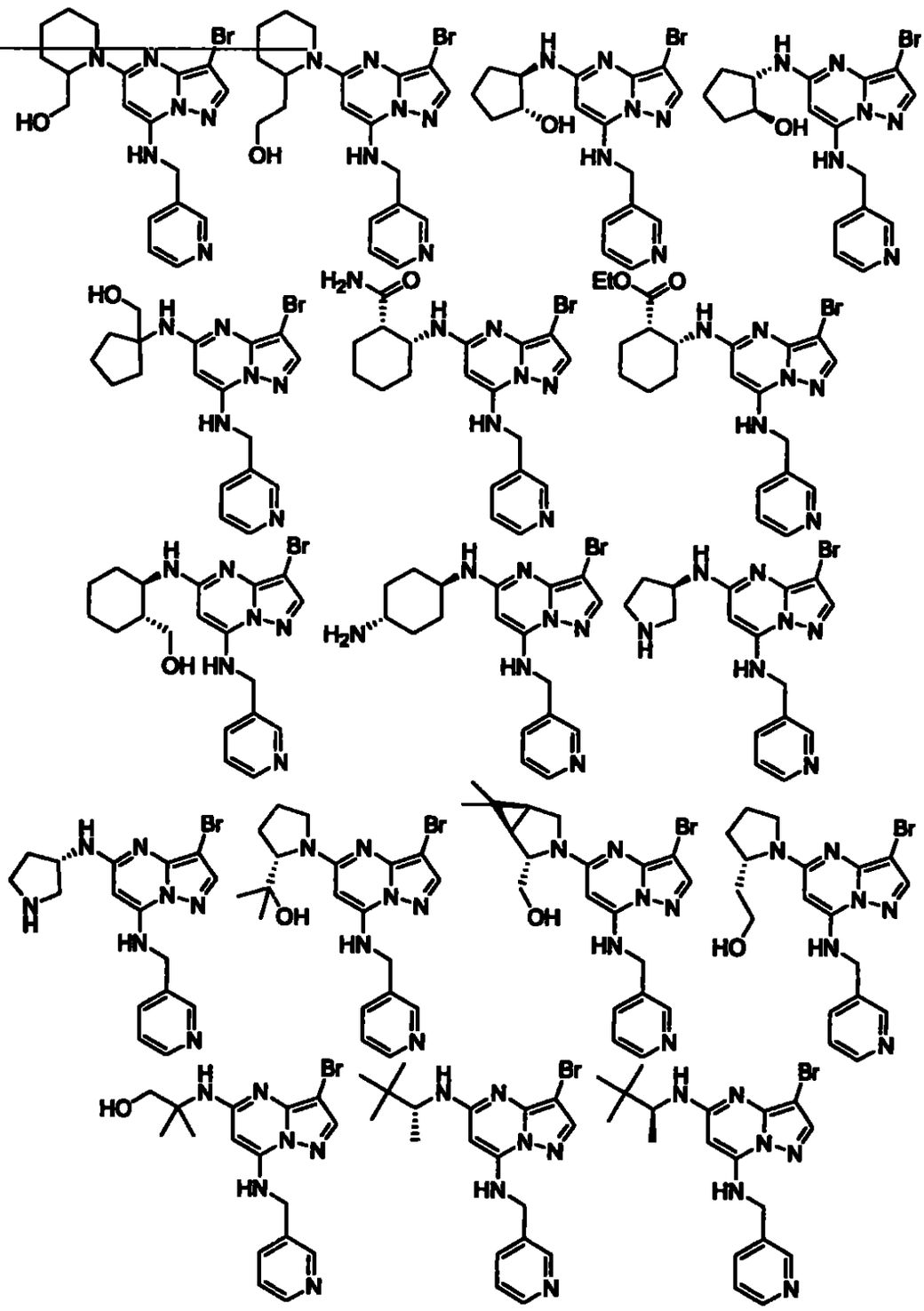




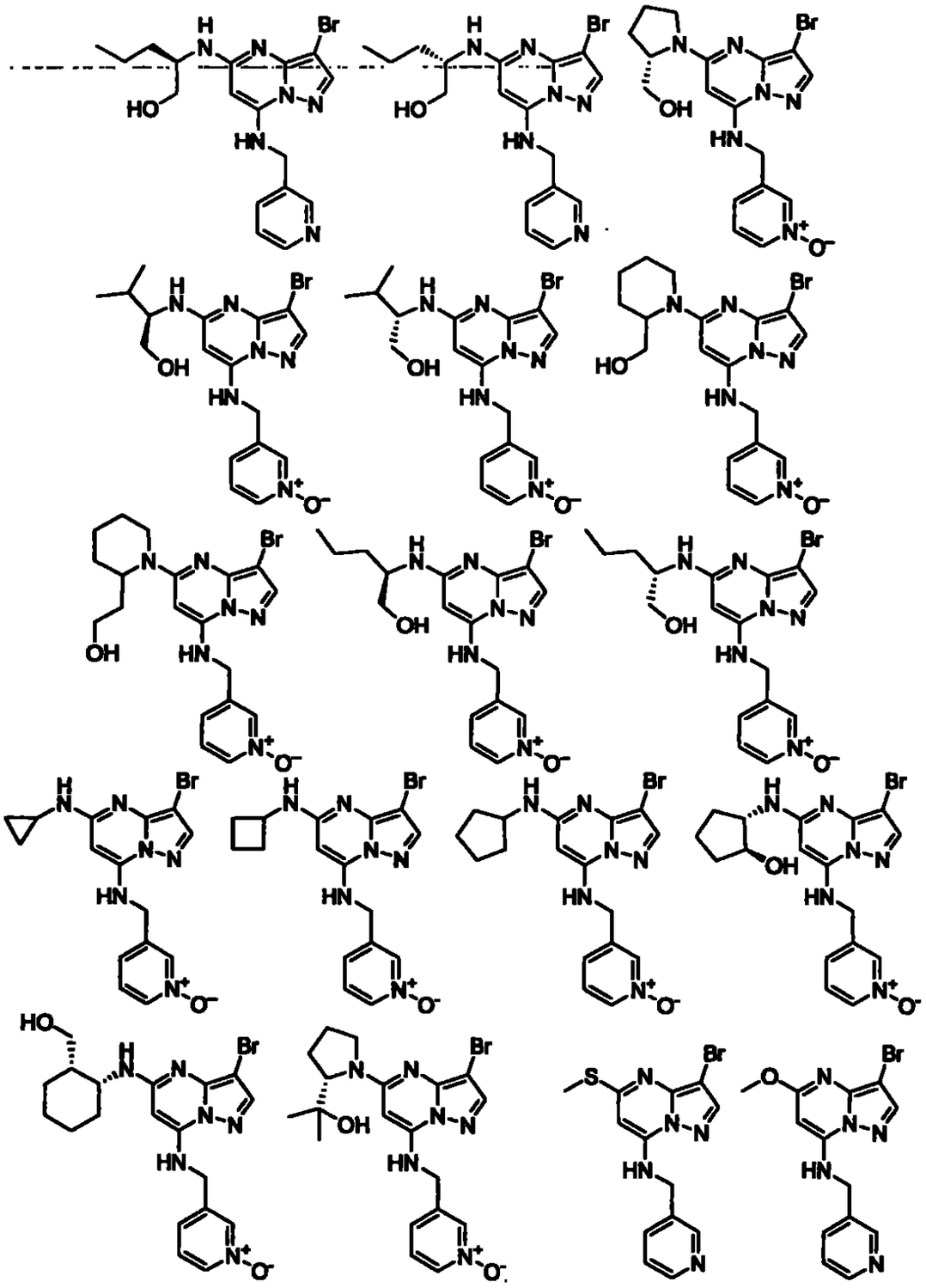


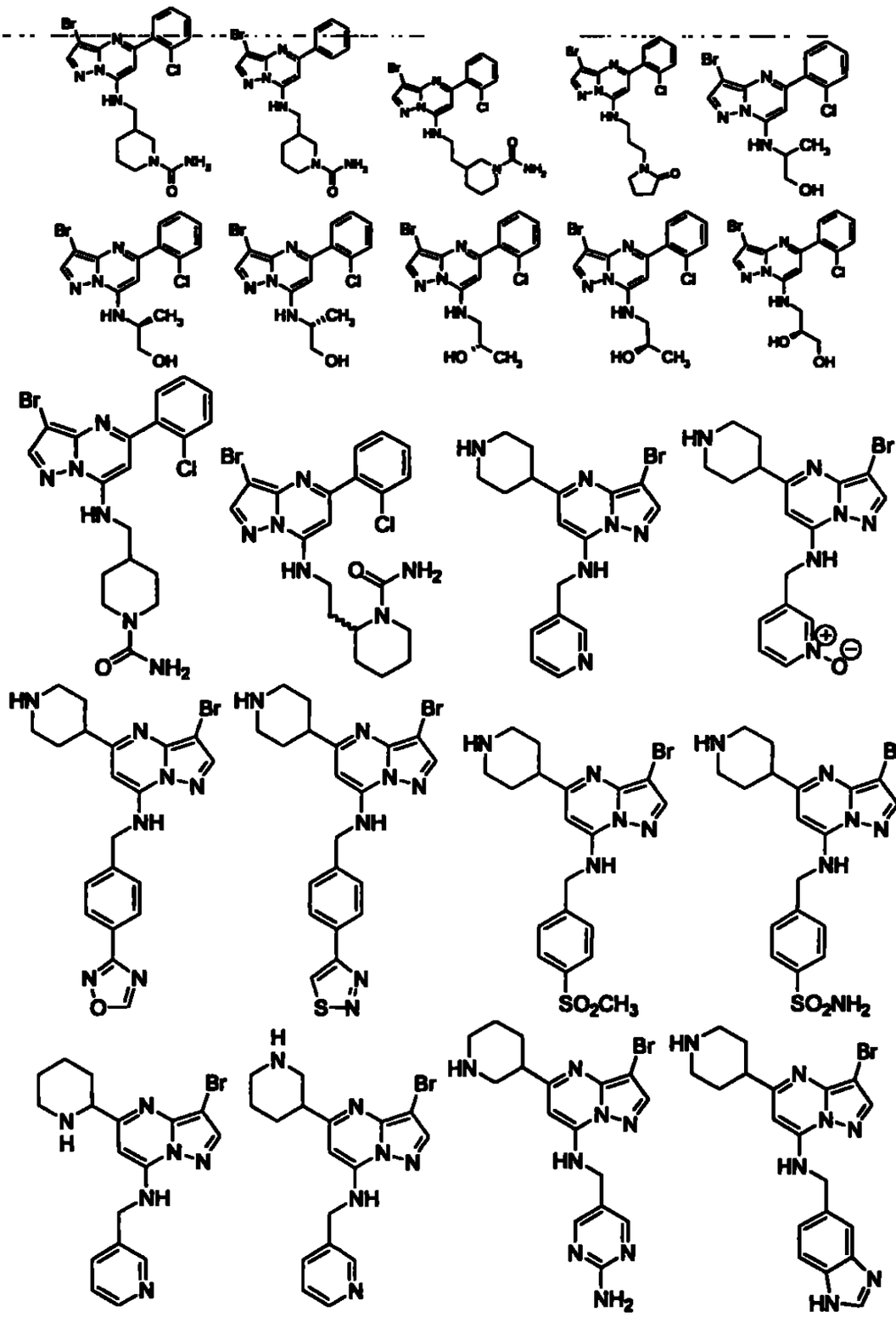


5

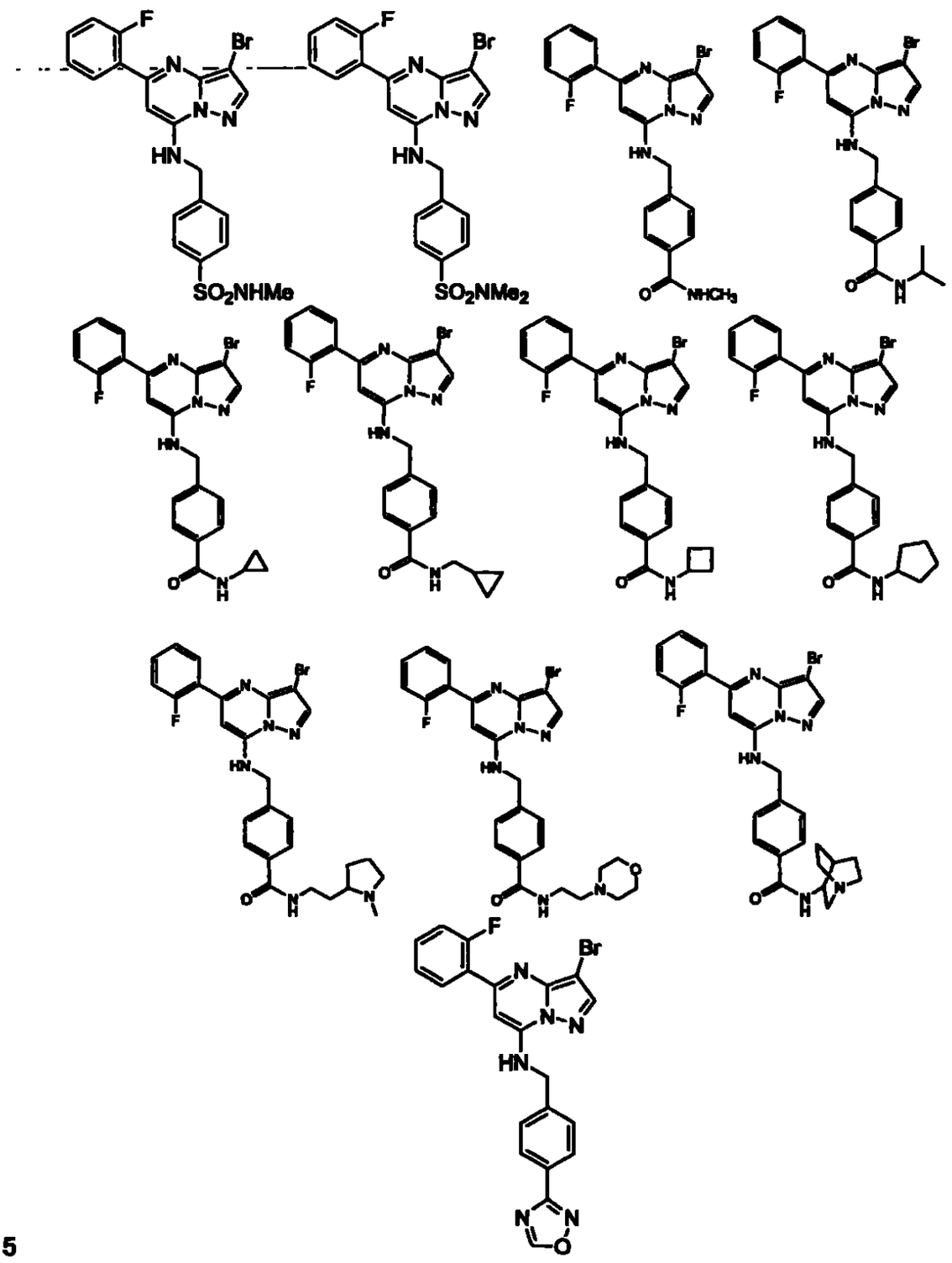


5

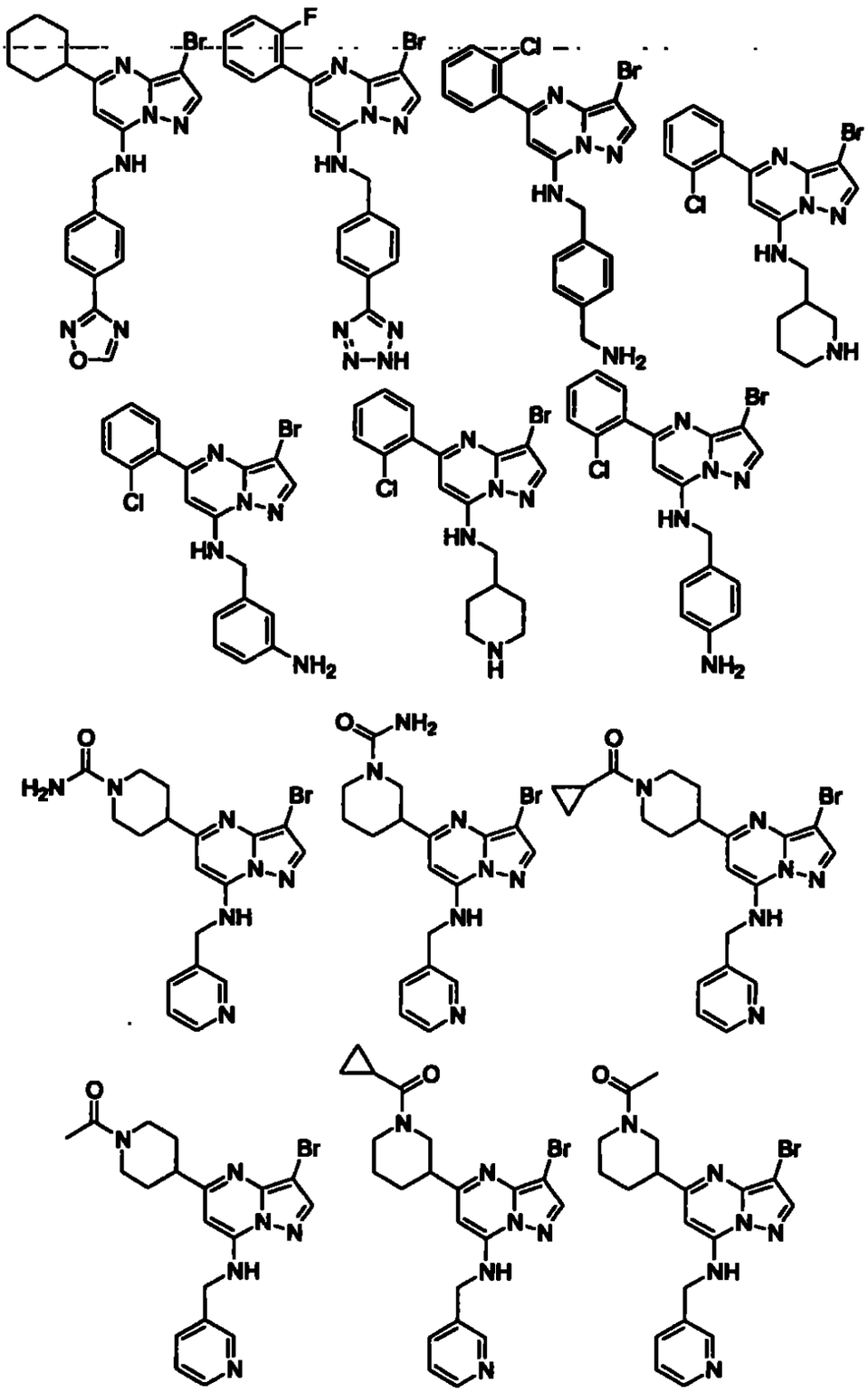




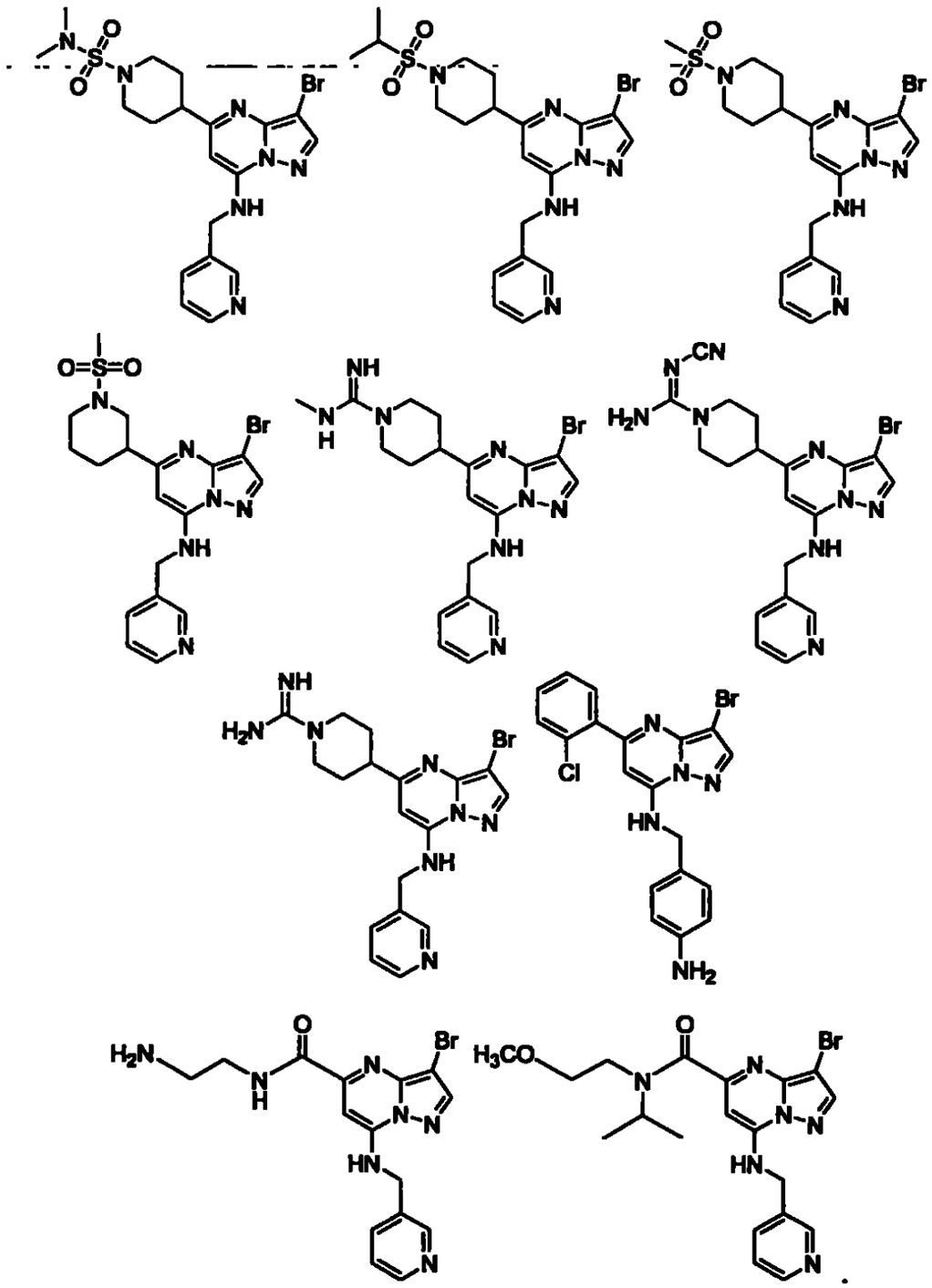
5



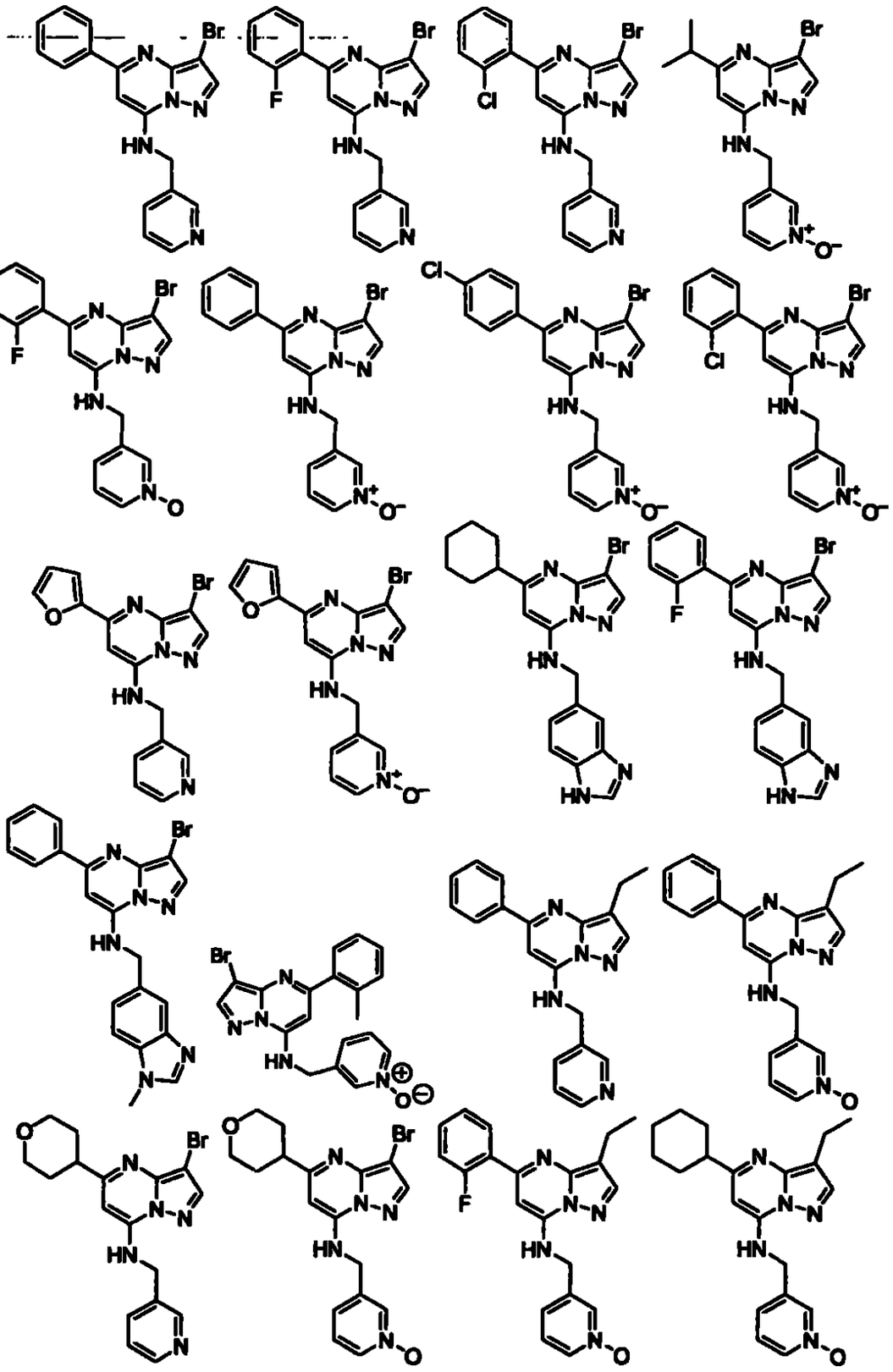
5



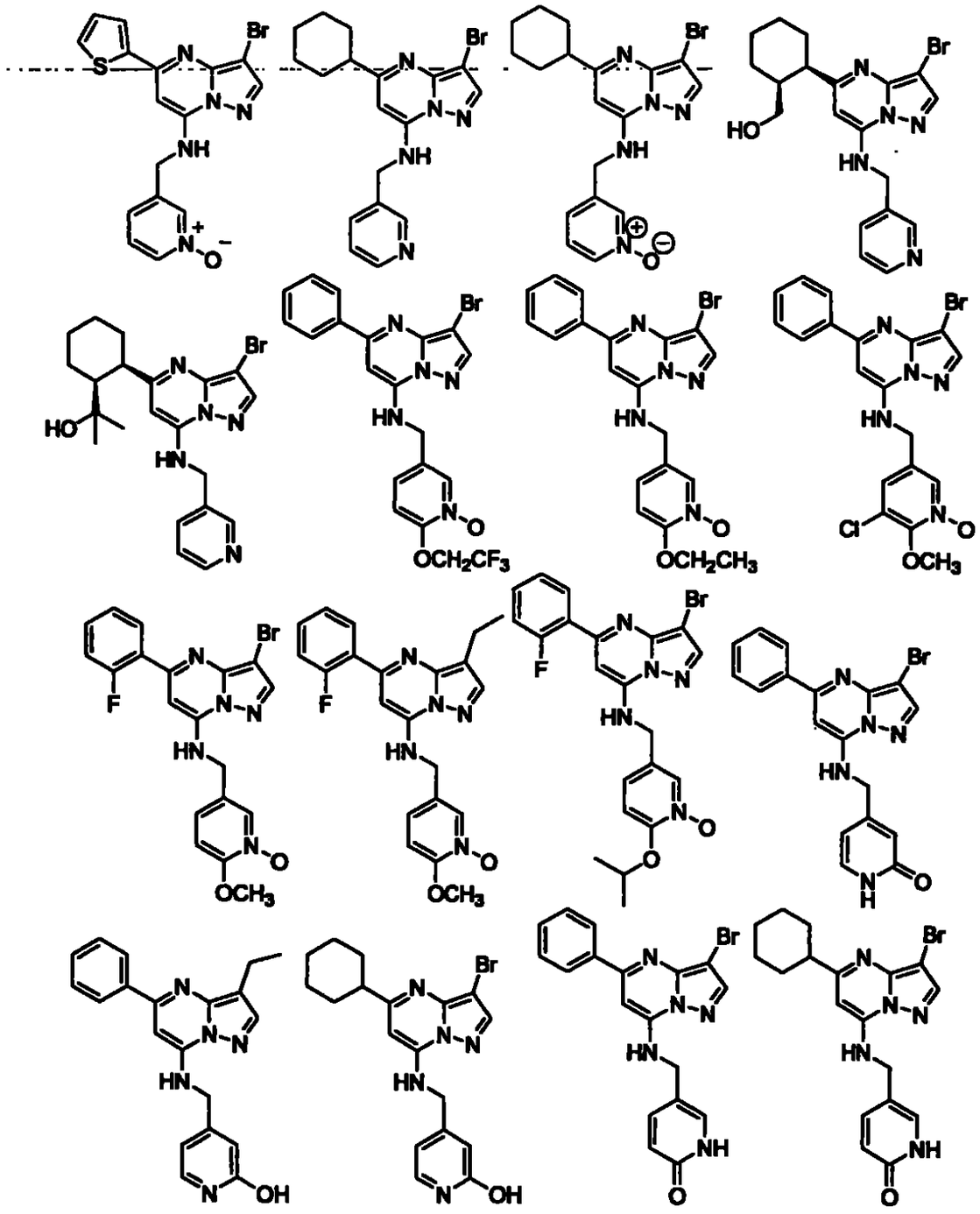
5

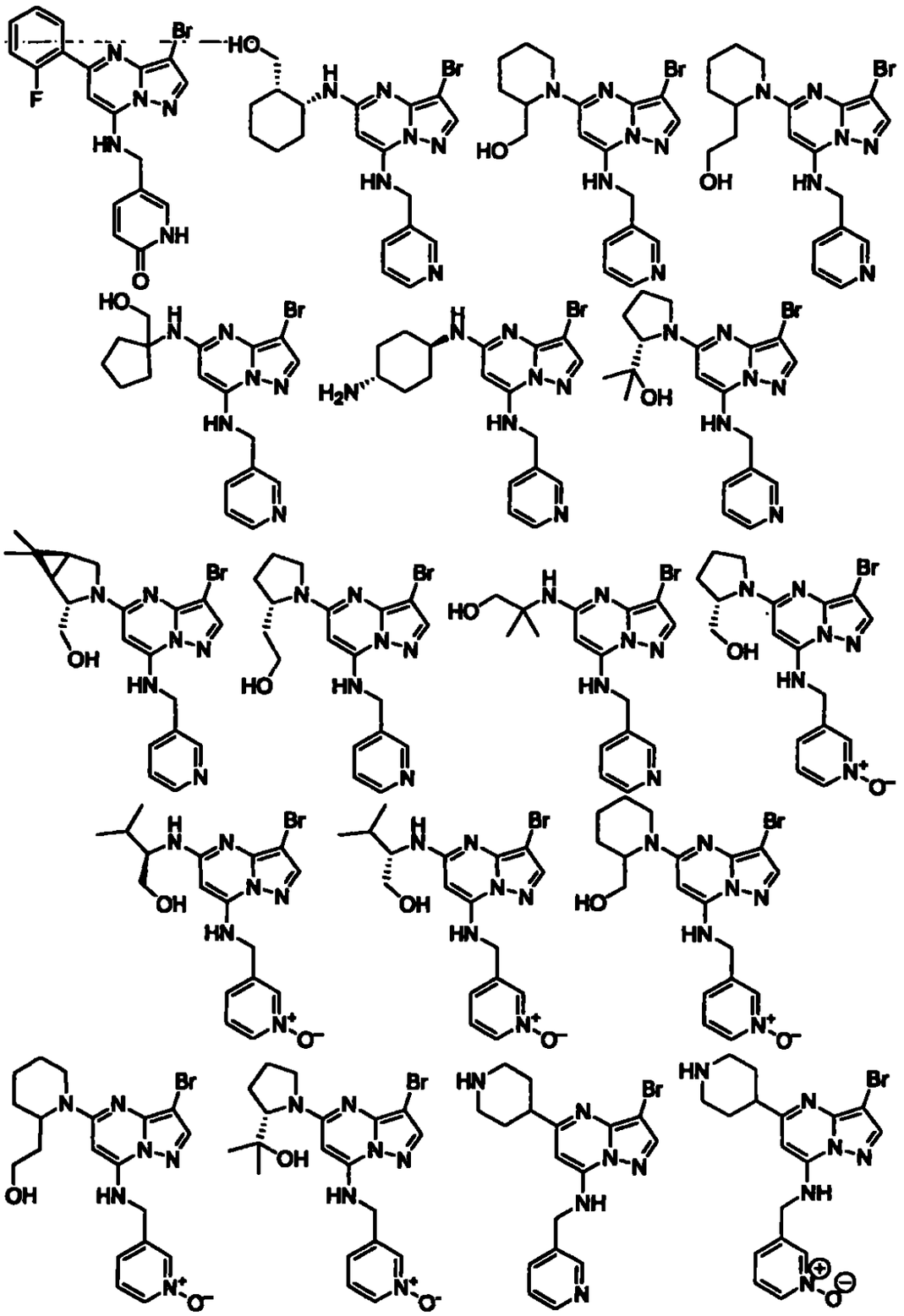


Another embodiment of the invention discloses the following compounds, which exhibited CDK2 inhibitory activity of about 0.0001μM to about 0.5μM:

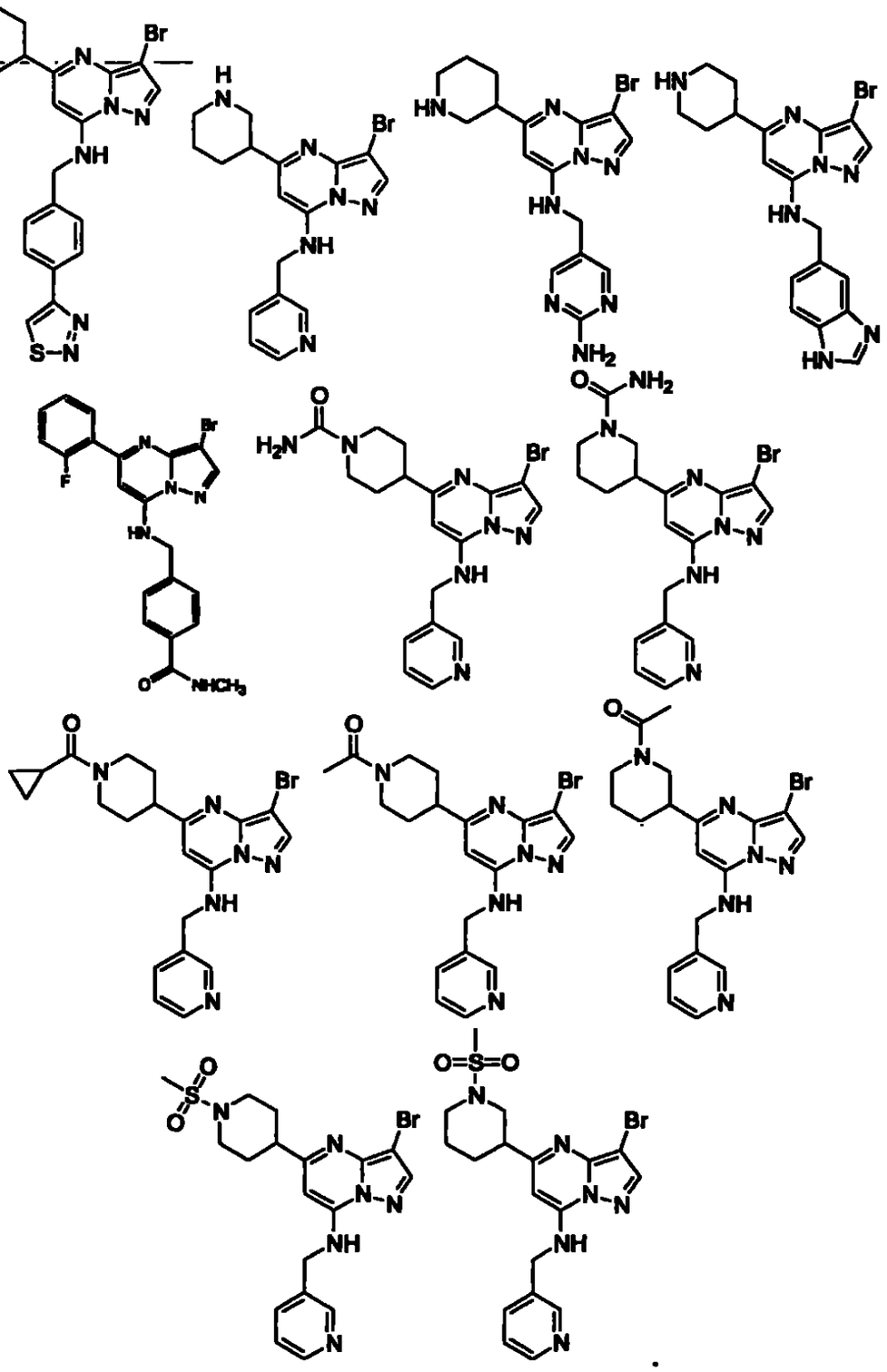


5

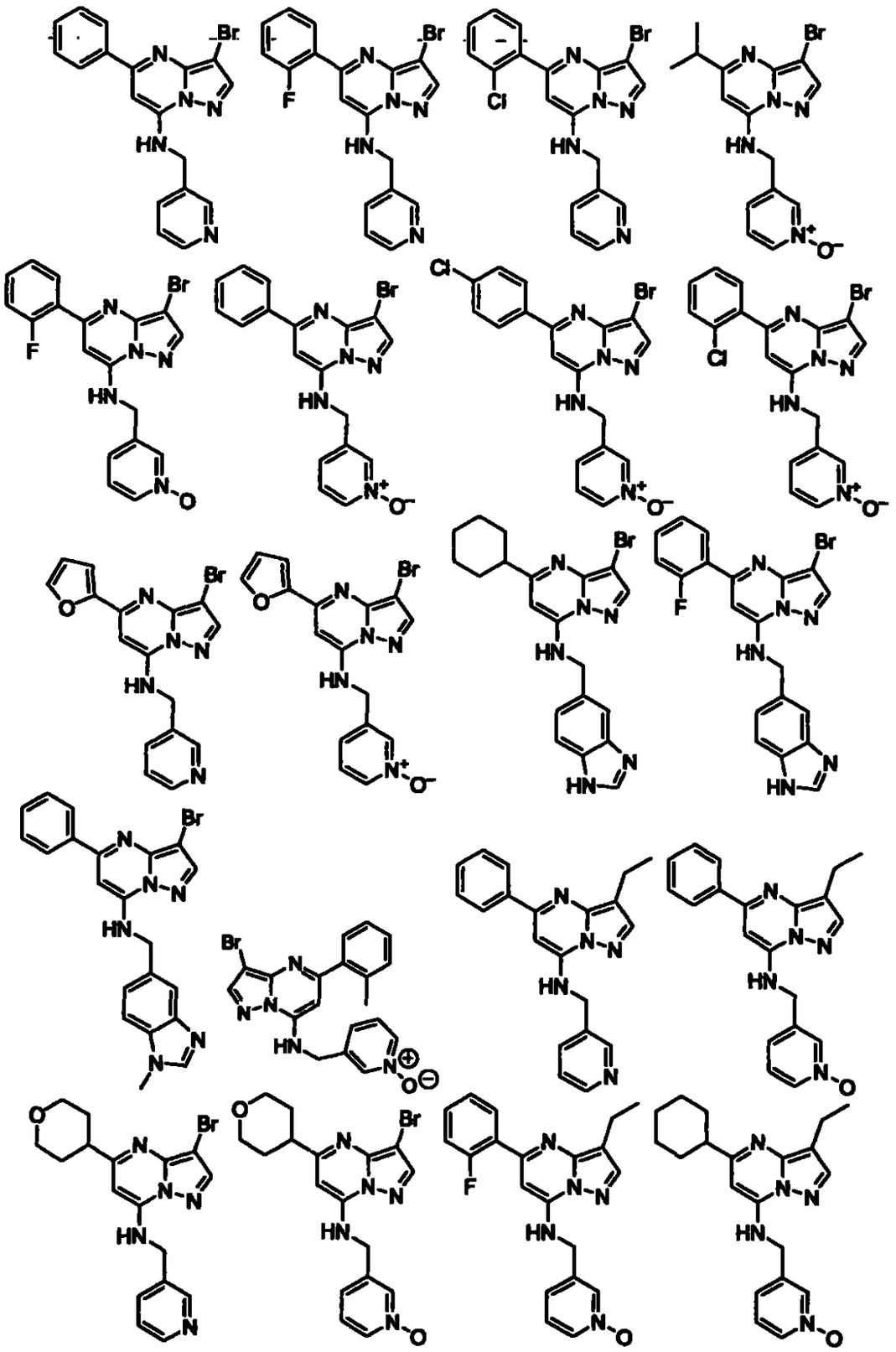


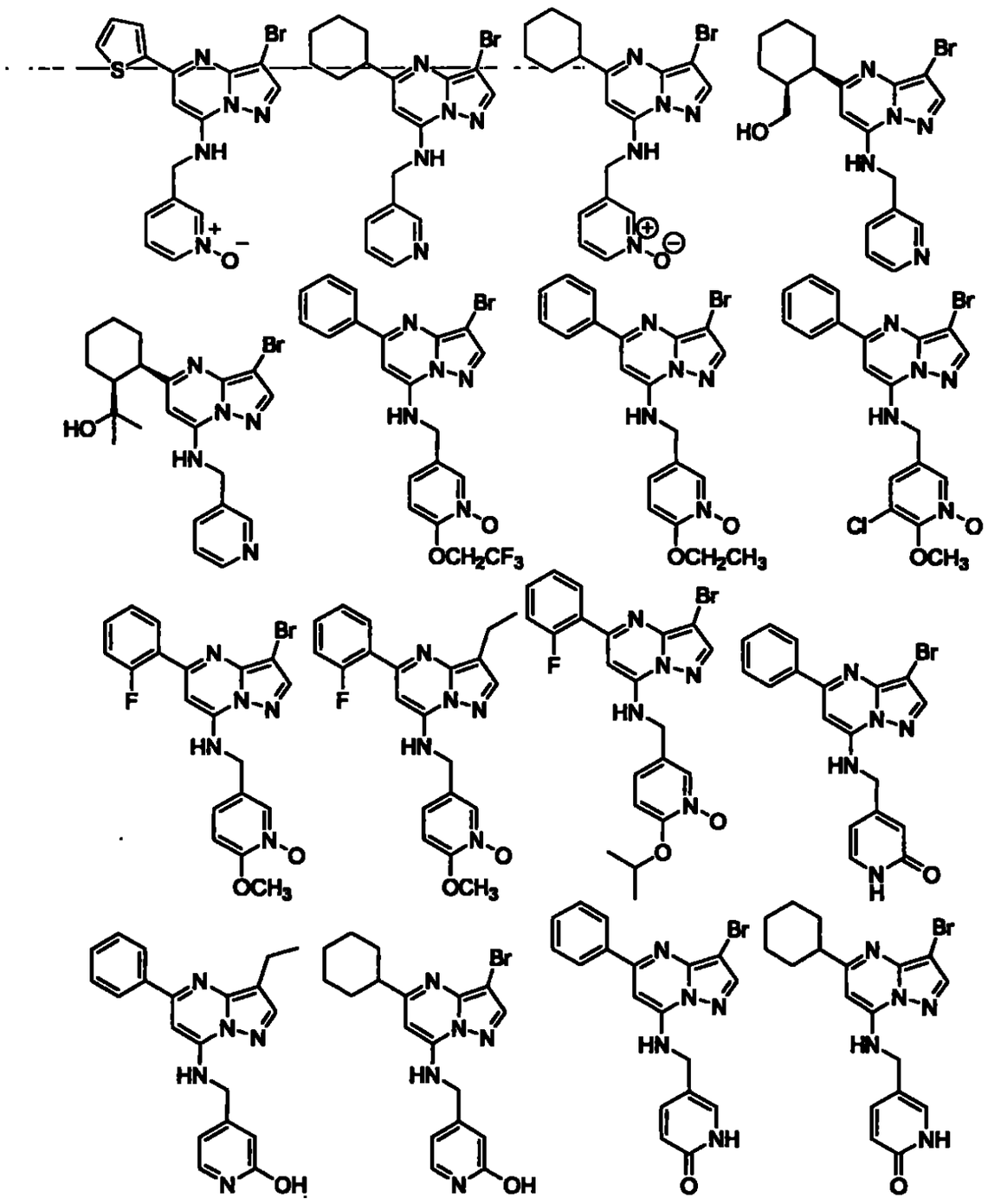


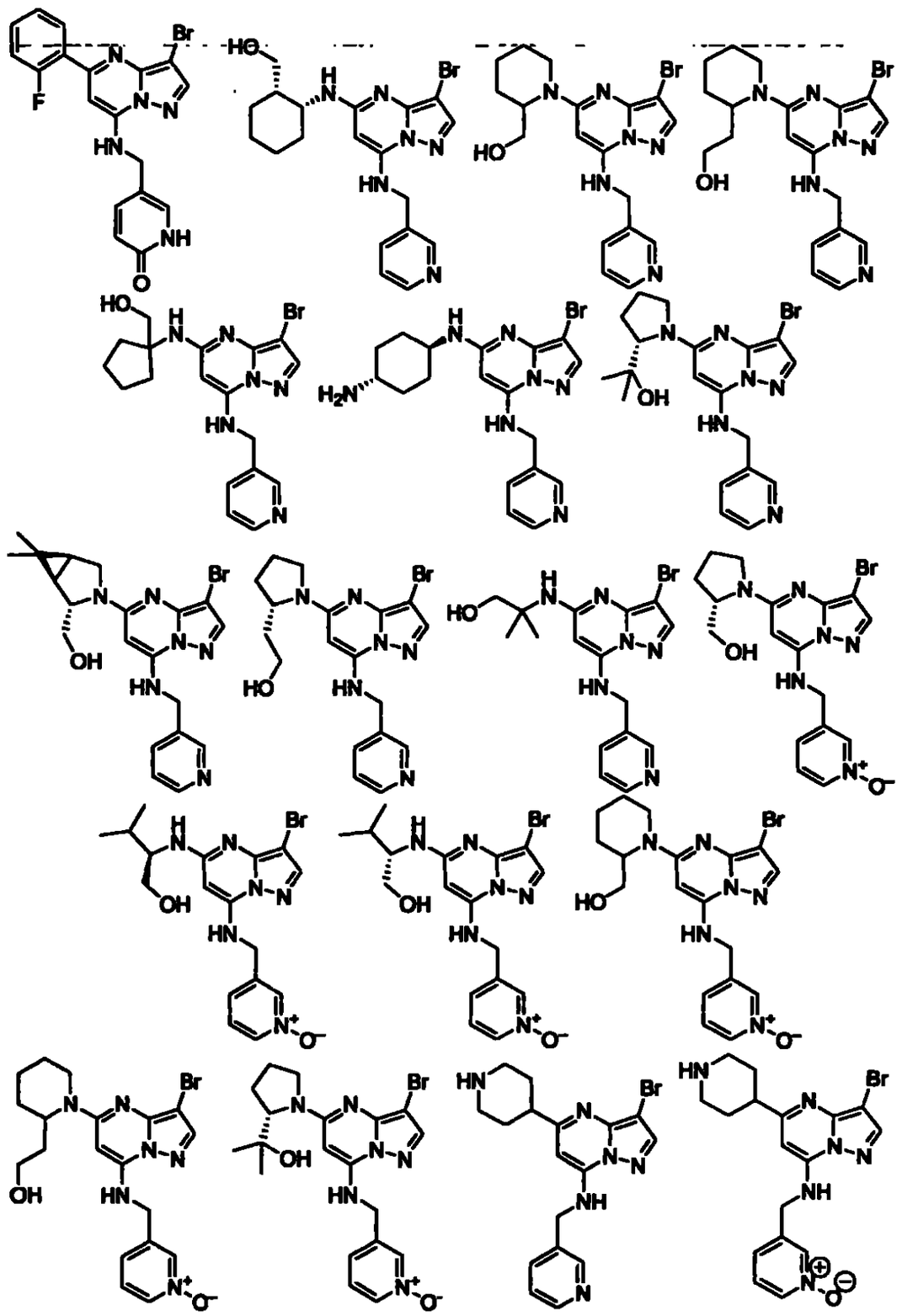
5

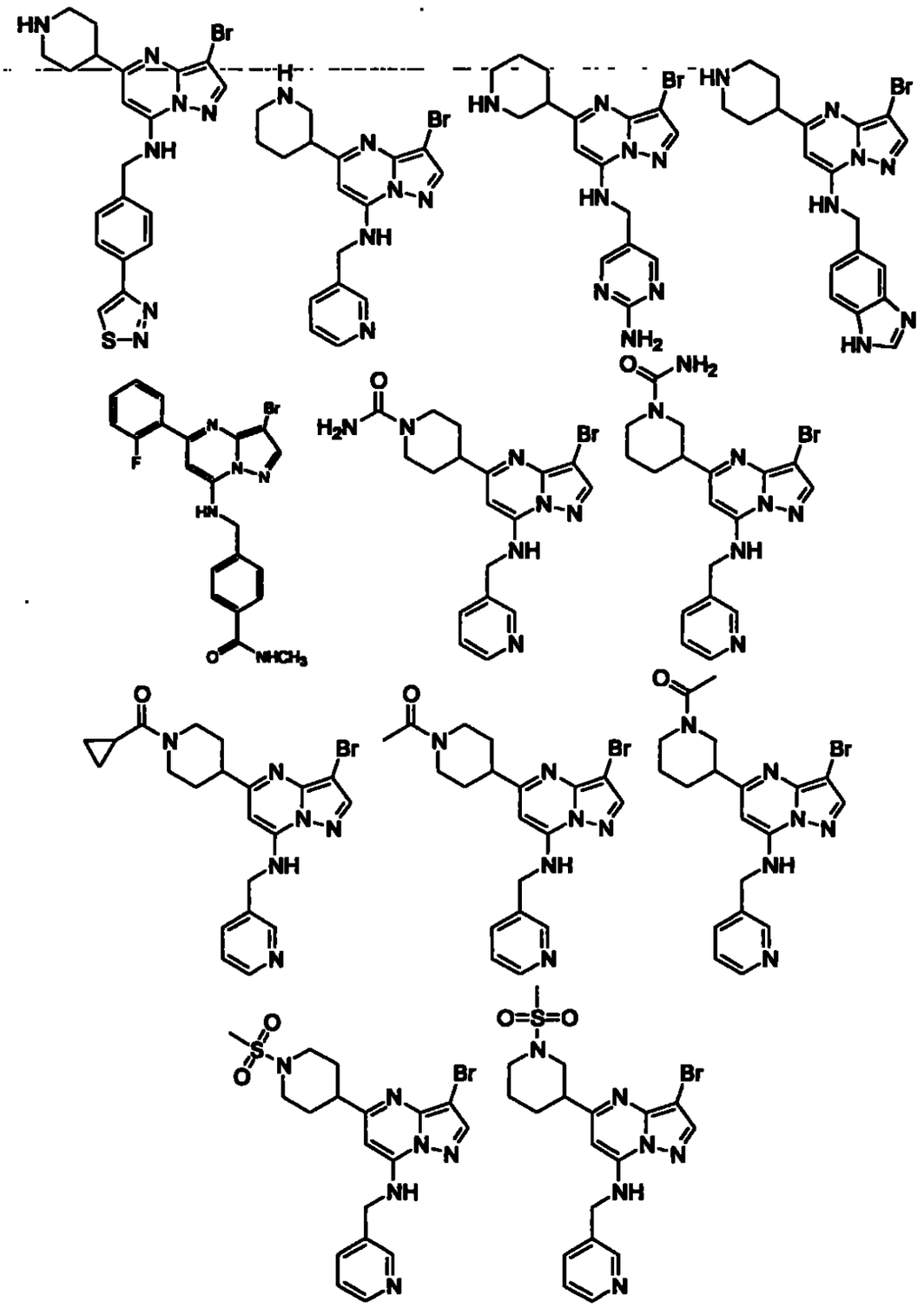


Another embodiment of the invention discloses the following compounds, which exhibited CDK2 inhibitory activity of about 0.0001μM to about 0.1μM:









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.

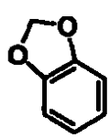
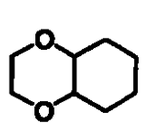
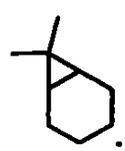
"Aralkyl" or "arylalkyl" means an aryl-alkyl- group in which the aryl and alkyl are as previously described. Preferred aralkyls comprise a lower alkyl group. Non-limiting examples of suitable aralkyl groups include benzyl, 2-phenethyl and naphthalenylmethyl. The bond to the parent moiety is through the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

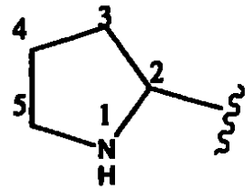
"Halogen" means fluorine, chlorine, bromine, or iodine. Preferred are fluorine, chlorine and bromine.

"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 Pharmaeuticals, 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..

Preferably, the pharmaceutical preparation is in a unit dosage form. In such form, the preparation is subdivided into suitably sized unit doses containing appropriate quantities of the active component, e.g., an effective amount to achieve the desired purpose.

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

The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage regimen for a particular situation is within the skill of the art. For convenience, the total daily dosage may be divided and administered in portions during the day as required.

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

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

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

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

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

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

Thin layer chromatography: TLC

dichloromethane: CH_2Cl_2

ethyl acetate: AcOEt or EtOAc

methanol: MeOH

trifluoroacetate: TFA

triethylamine: Et_3N or TEA

butoxycarbonyl: n-Boc or Boc

nuclear magnetic resonance spectroscopy: NMR

liquid chromatography mass spectrometry: LCMS

high resolution mass spectrometry: HRMS

milliliters: mL

millimoles: mmol

microliters: µl

grams: g

milligrams: mg

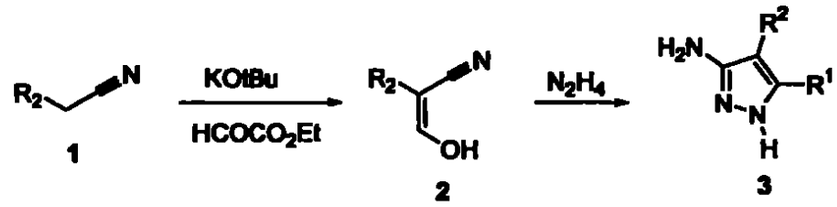
room temperature or rt (ambient): about 25°C.

dimethoxyethane: DME

EXAMPLES

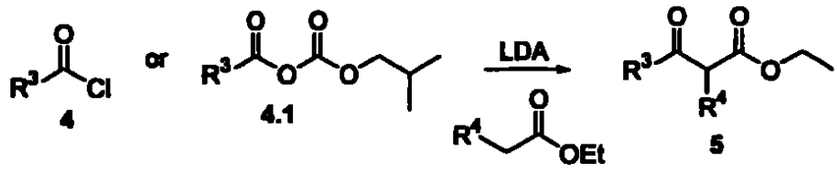
In general, the compounds described in this invention can be prepared through the general routes described below in Scheme 1. Treatment of the

Scheme 1



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.

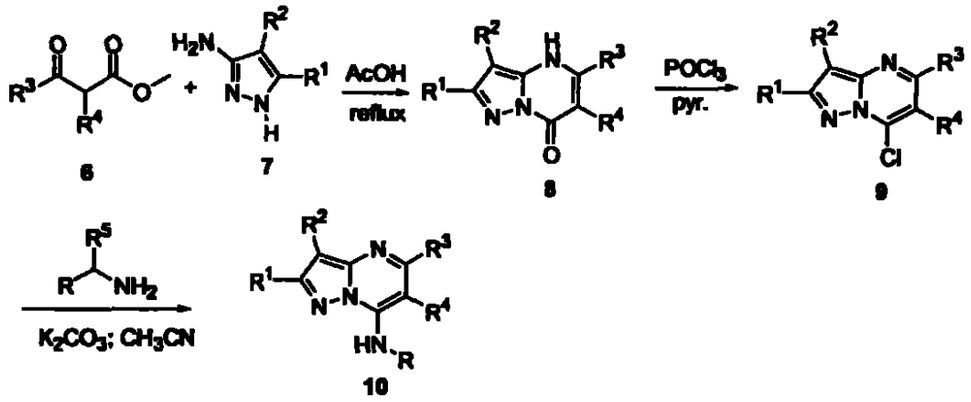
Scheme 2



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

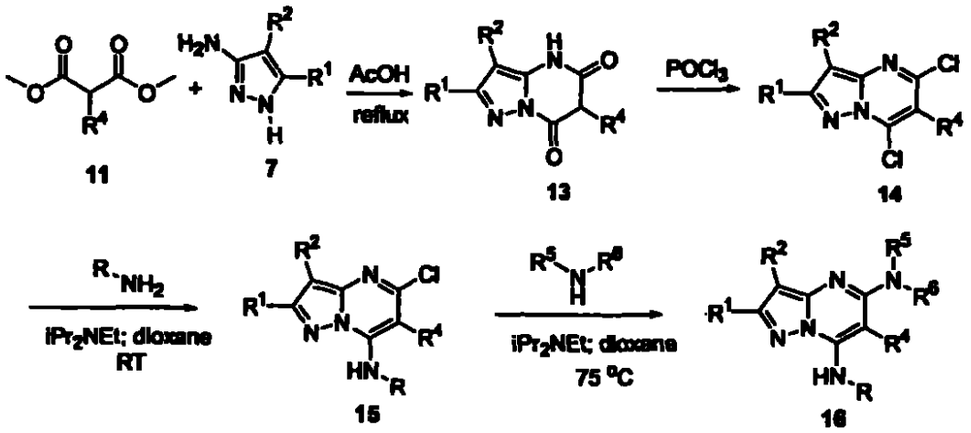


Condensation of compounds of type 7 with the appropriately functionalized malonate ester of type 11 gives rise to the pyridones 13 as shown in Scheme 4.

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.

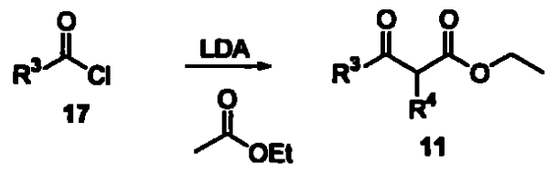
Incorporation of the N7-amino functionality can be accomplished through regioselective displacement of the chloride of compounds of type 14. Incorporation of the N5-amino functionality by addition of an appropriate amine at higher temperature.

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

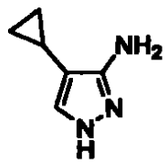


The chlorides of type 14 can be prepared by treatment of the pyridones 13 with $POCl_3$. When R^2 is equal to H, substitution in this position is possible on compounds of type 14 by electrophilic halogenation, acylation, and various other electrophilic aromatic substitutions.

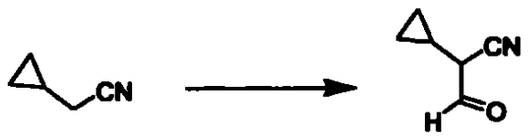
Incorporation of the N7-amino functionality can be accomplished through displacement of the chloride of compounds of type 15.

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.

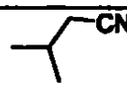
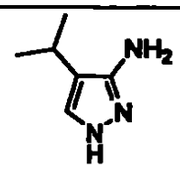
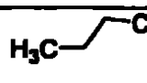
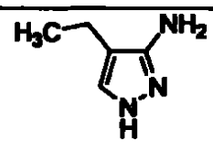
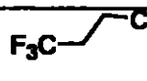
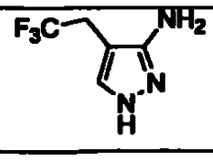
Step B:

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:

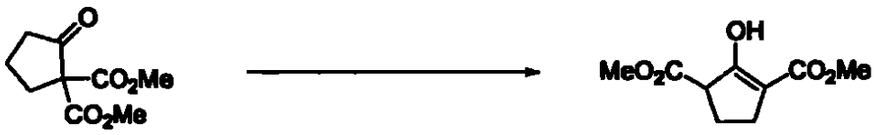
TABLE 2

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).

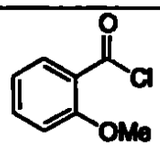
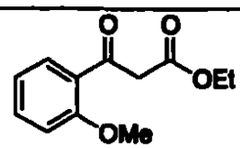
PREPARATIVE EXAMPLE 6:

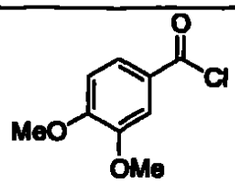
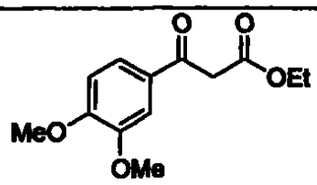
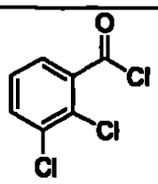
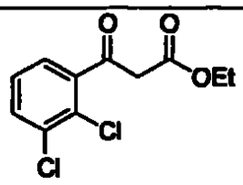
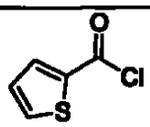
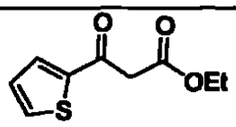
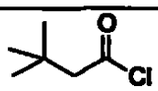
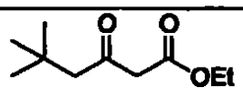
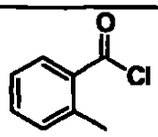
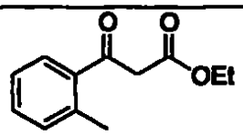
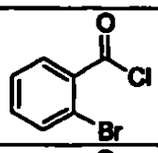
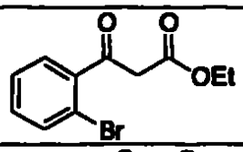
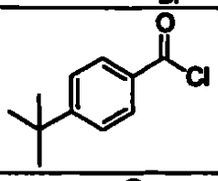
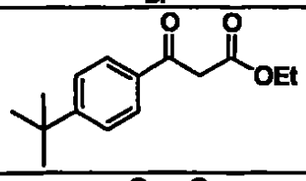
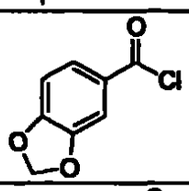
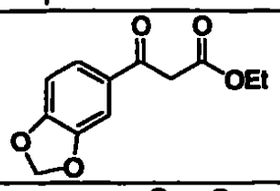
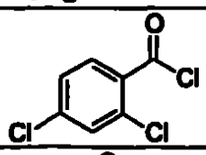
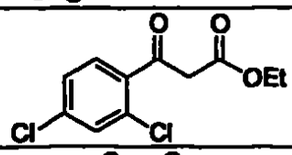
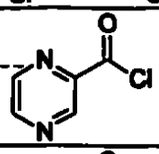
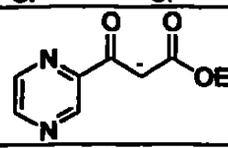
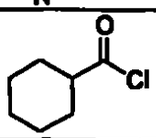
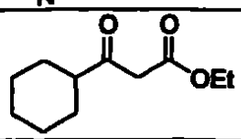
The reactions were done as outlined in (K. O. Olsen, *J. Org. Chem.*, (1987) 52, 4531 – 4536). Thus, to a stirred solution of lithium diisopropylamide in THF at -65 to –70 C was added freshly distilled ethyl acetate, dropwise. The resulting solution was stirred for 30 min and the acid chloride was added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

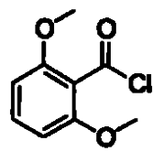
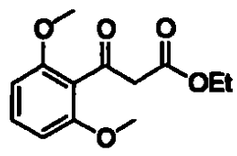
PREPARATIVE EXAMPLES 7-19:

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^+ = 262
17			Yield = 48 MH^+ = 195
18			Yield = 99 MH^+ =199

19			Yield=77% ^{1}H NMR ($CDCl_3$) δ 7.42(t, 1H), 6.68(d, 2H), 4.29(q, 2H), 3.97(d, 2H), 3.95(s, 3H), 1.38(t, 3H).

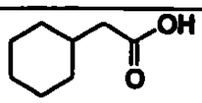
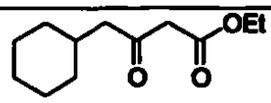
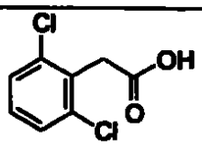
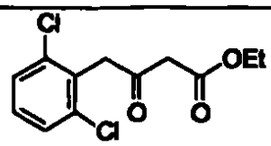
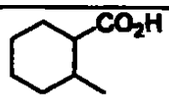
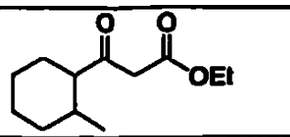
PREPARATIVE EXAMPLE 20:

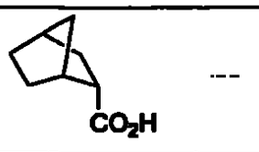
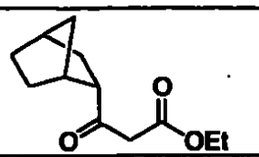
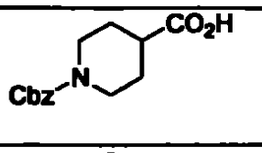
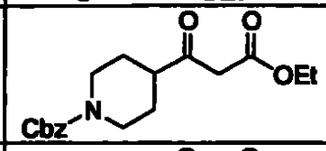
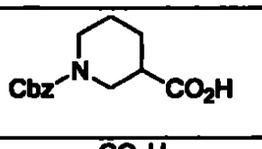
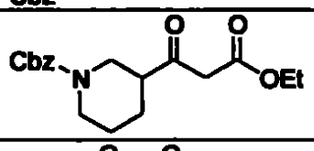
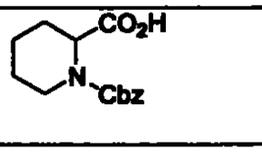
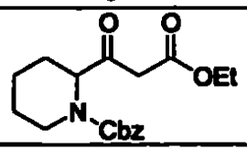
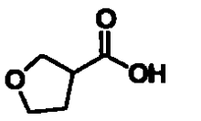
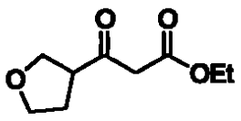
To a solution of the acid in THF was added Et_3N, followed by isobutyl chloroformate at –20 to –30°C. After the mixture was stirred for 30 min at –20 to –30°C, triethylamine hydrochloride was filtered off under argon, and the filtrate was added to the LDA-EtOAc reaction mixture (prepared as outlined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

PREPARATIVE EXAMPLES 21 - 28:

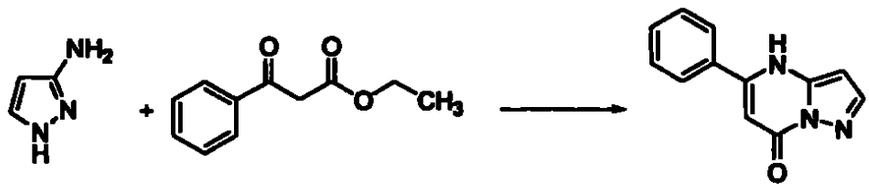
By essentially the same conditions set forth in Preparative Example 20 only substituting the carboxylic acid shown in Column 2 of Table 4, the compounds shown in Column 3 of Table 4 were prepared:

TABLE 4

Prep. Ex.	Column 2	Column 3	CMPD
21			Yield = 99% MH^+ = 213
22			Yield = 70% MH^+ = 275
23			Yield = quant MH^+ =213

24			Yield = quant MH$^+$ =211
25			Yield = 99 MH$^+$ = 334
26			Yield = 99 MH$^+$ = 334
27			Yield = 99 MH$^+$ = 334
28			Yield=77% ^{1}H NMR ($CDCl_3$) δ 4.21(q, 2H), 3.95(d, 2H), 3.93-3.79(m, 4H), 3.52(s, 2H), 2.65(m, 1H), 1.25(t, 3H), 1.23-1.2(m, 2H).

PREPARATIVE EXAMPLE 29:



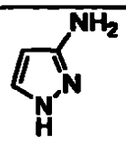
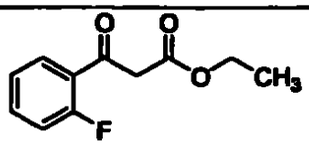
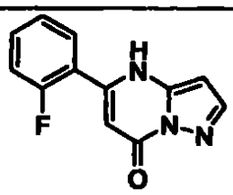
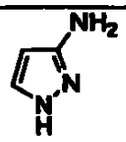
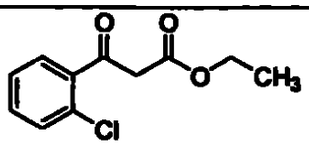
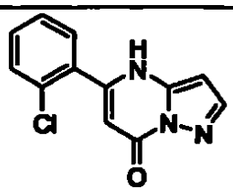
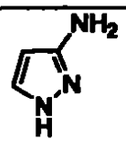
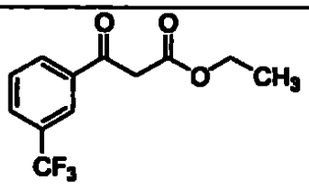
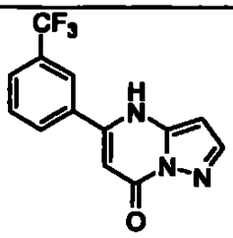
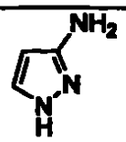
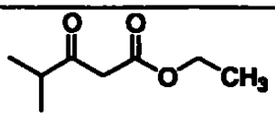
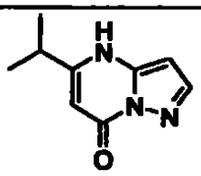
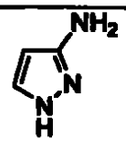
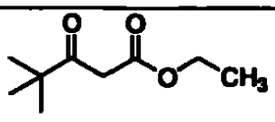
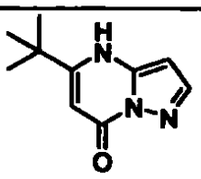
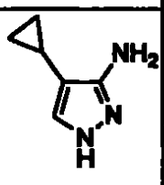
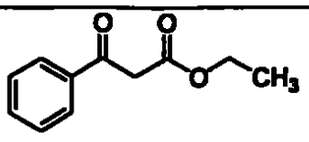
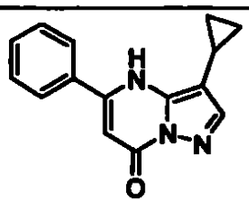
A solution of 3-aminopyrazole (2.0g, 24.07 mmol) and ethyl benzoylacetate (4.58 mL, 1.1 eq.) in AcOH (15 mL) was heated at reflux for 3 hours. The reaction mixture was cooled to room temperature and concentrated *in vacuo*. The resulting solid was diluted with EtOAc and filtered to give a white solid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

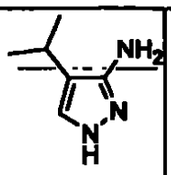
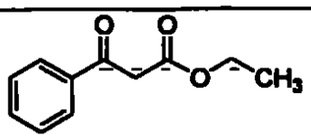
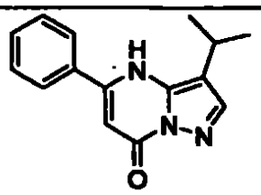
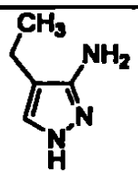
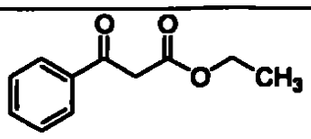
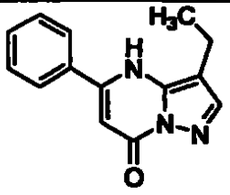
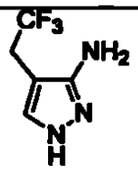
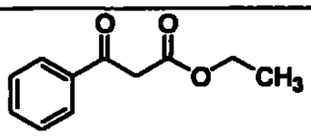
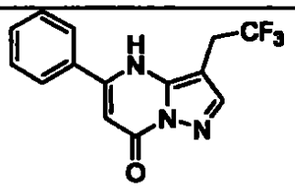
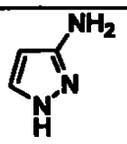
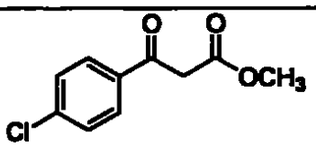
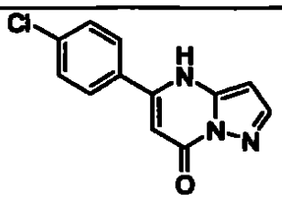
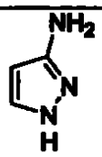
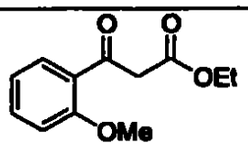
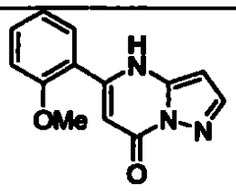
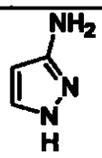
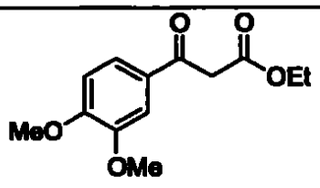
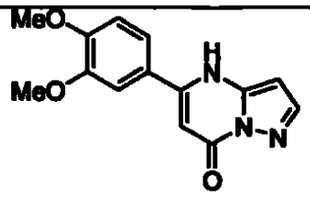
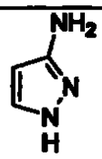
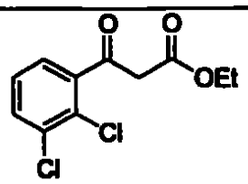
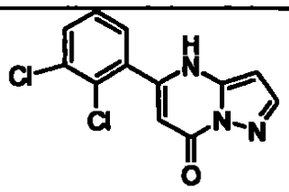
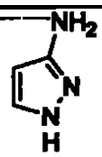
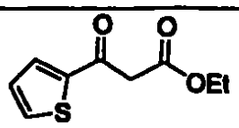
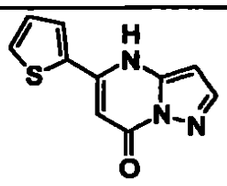
PREPARATIVE EXAMPLES 30-73:

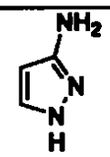
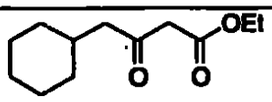
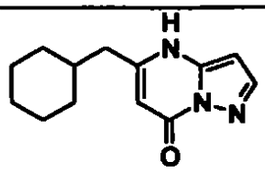
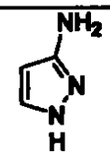
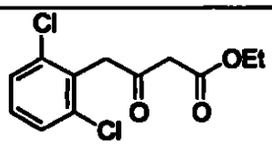
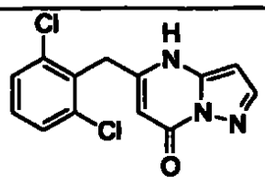
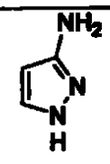
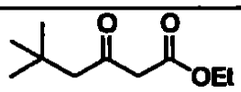
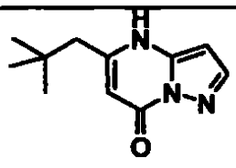
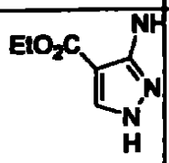
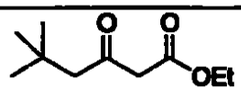
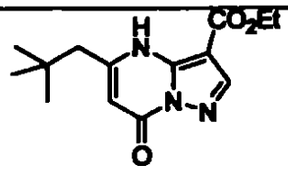
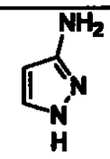
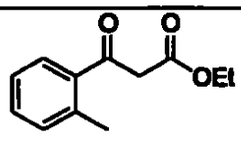
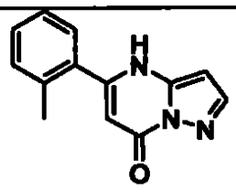
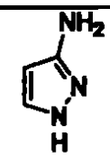
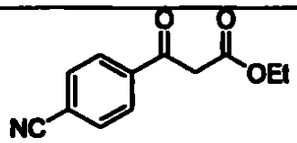
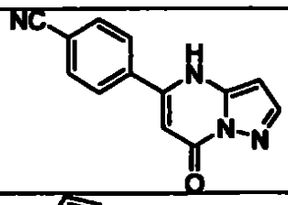
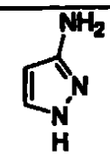
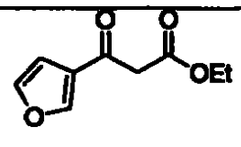
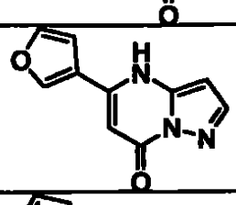
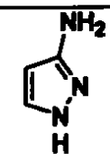
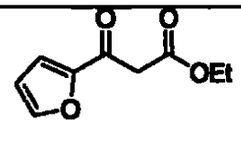
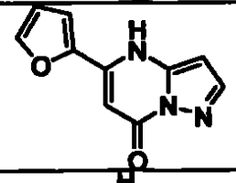
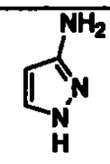
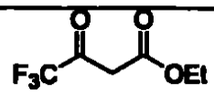
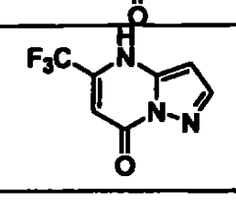
By essentially the same procedure set forth in Preparative Example 29 only substituting the aminopyrazole shown in Column 2 of Table 5 and the ester

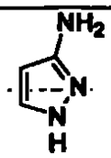
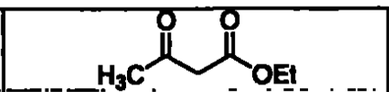
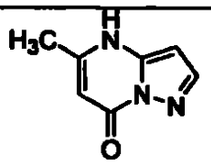
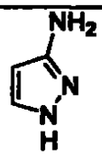
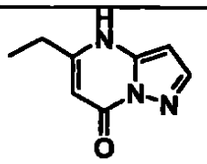
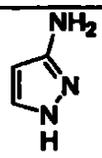
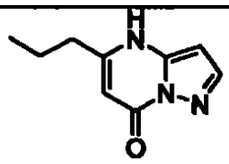
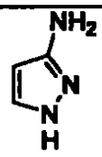
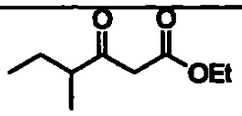
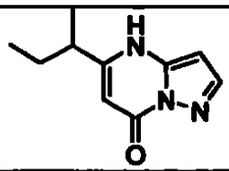
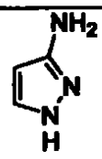
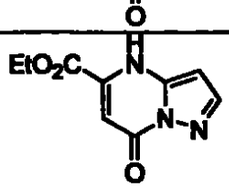
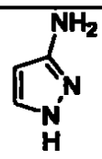
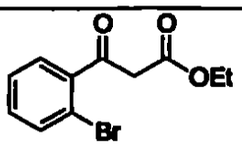
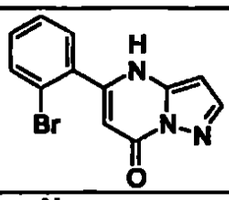
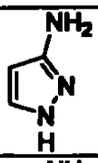
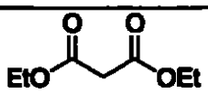
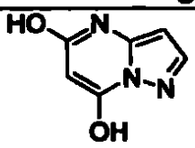
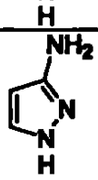
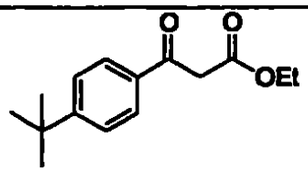
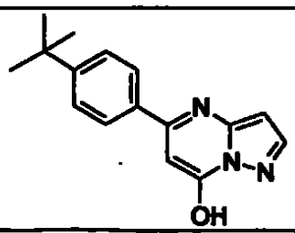
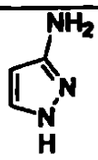
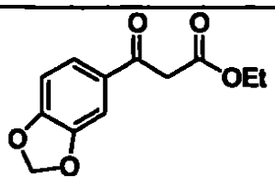
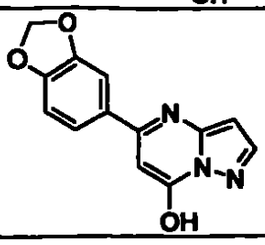
shown in Column 3 of Table 5, the compounds shown in Column 4 of Table 5 were prepared:

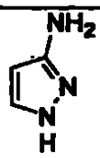
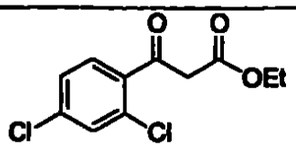
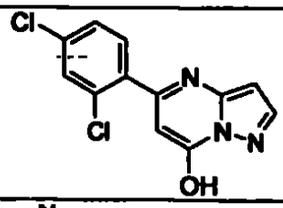
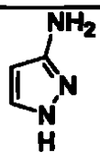
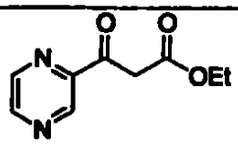
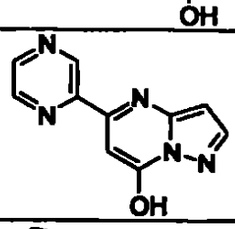
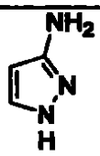
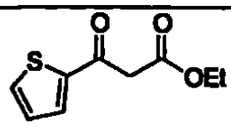
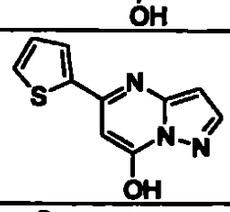
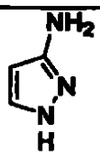
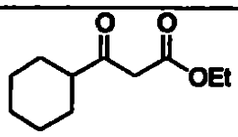
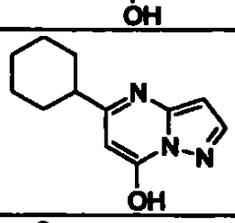
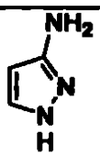
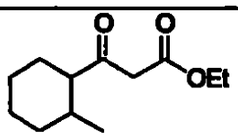
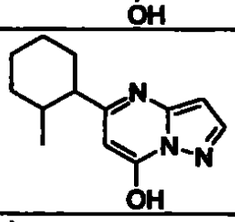
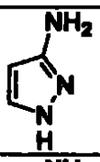
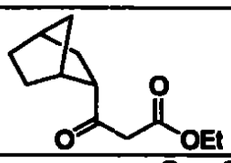
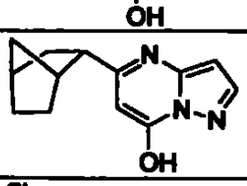
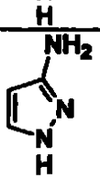
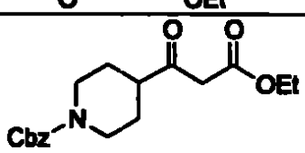
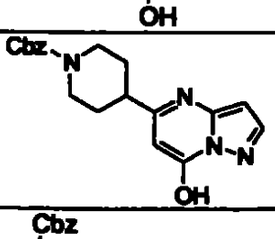
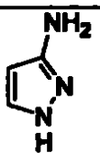
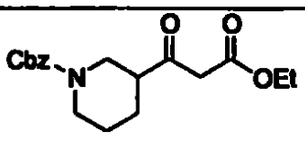
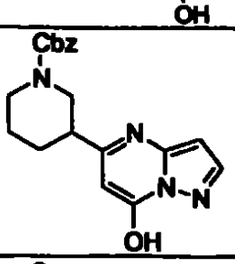
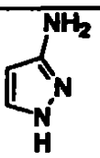
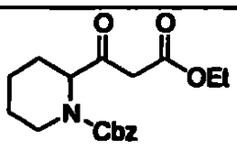
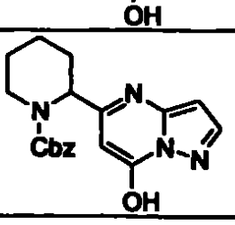
TABLE 5

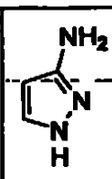
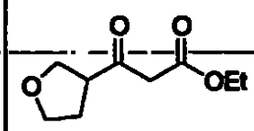
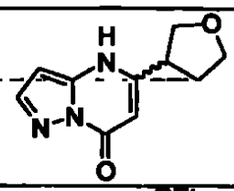
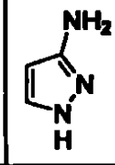
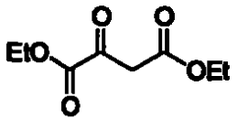
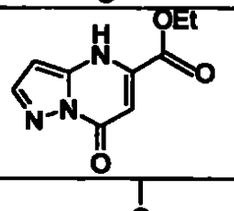
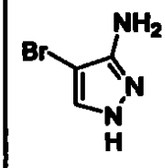
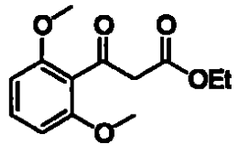
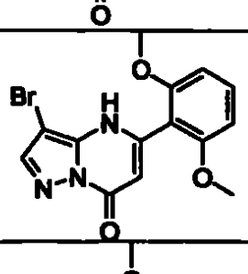
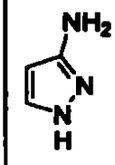
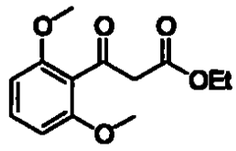
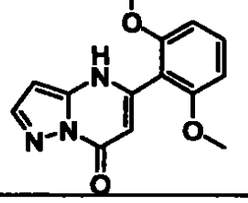
Prep. Ex.	Column 2	Column 3	Column 4	Column 5
30				
31				
32				
33				
34				
35				

36				
37				
37.10				
38				
39				
40				
41				
42				

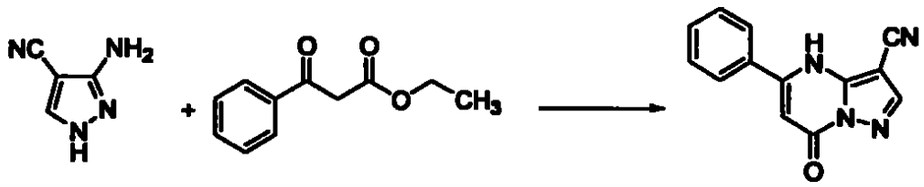
43				
44				
45				
46				
47				
48				
49				
50				
51				

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

61				Yield = 80 MH^+ = 280
62				Yield =72 MH^+ = 214
63				Yield = 51 MH^+ = 218
64				Yield = 82 MH^+ =218
65				Yield = 39 MH^+ =232
66				Yield = 30 MH^+ =230
67				Yield = 80 MH^+ =353
68				Yield = 49 MH^+ =353
69				Yield = 42 MH^+ =353

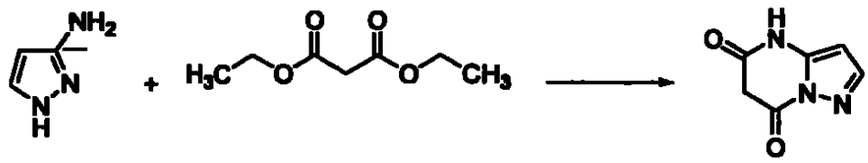
70				
71				
72				
73				

PREPARATIVE EXAMPLE 74:



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

PREPARATIVE EXAMPLE 75



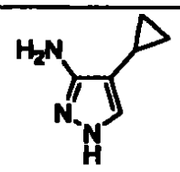
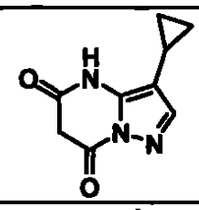
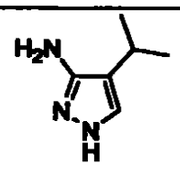
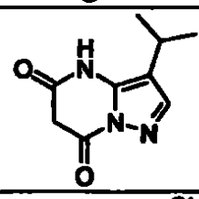
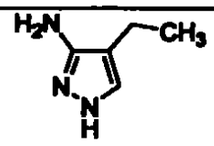
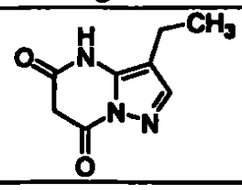
A procedure in US patent 3,907,799 was followed. Sodium (2.3 g, 2 eq.) was added to EtOH (150 mL) portionwise. When the sodium was completely

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

PREPARATIVE EXAMPLES 76-78:

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

TABLE 6

Prep. Ex.	Column 2	Column 3
76		
77		
78		

PREPARATIVE EXAMPLE 79:

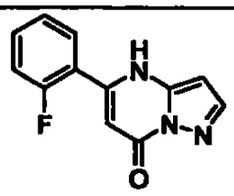
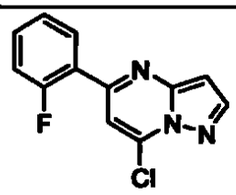
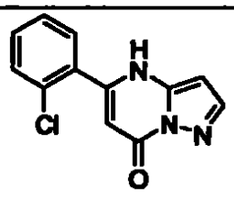
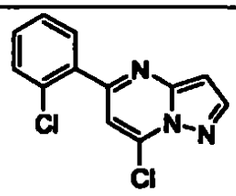
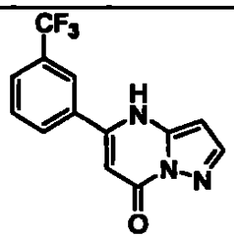
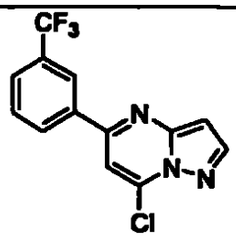
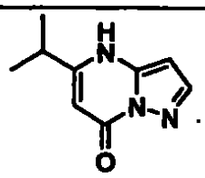
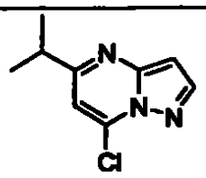
A solution of the compound prepared in Preparative Example 29 (1.0 g, 4.73 mmol) in $POCl_3$ (5 mL) and pyridine (0.25 mL) was stirred at room

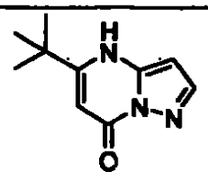
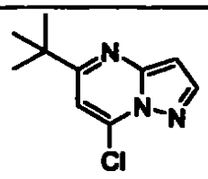
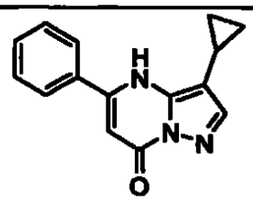
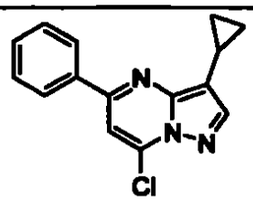
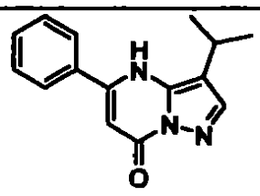
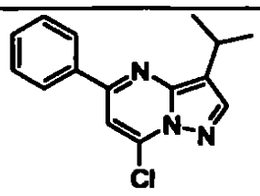
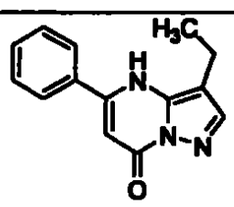
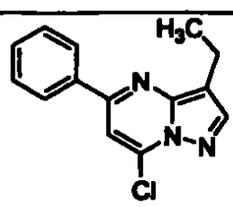
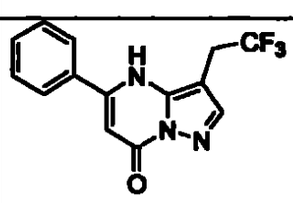
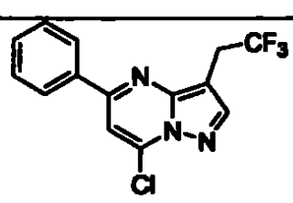
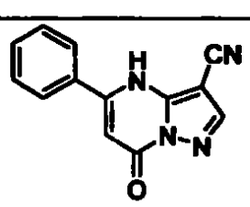
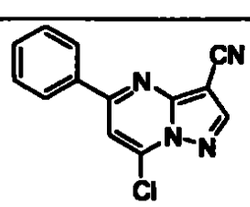
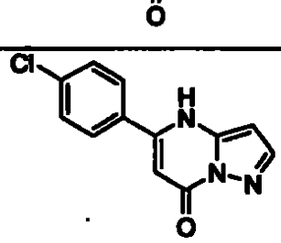
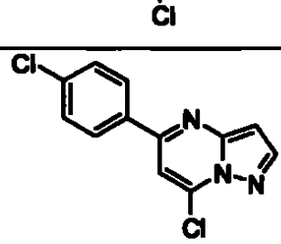
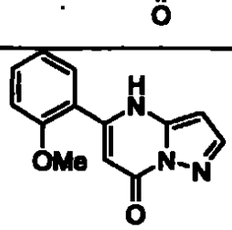
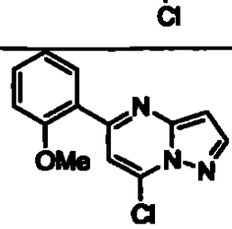
temperature 3 days. The resulting slurry was diluted with Et_2O, filtered, and the solid residue washed with Et_2O. The combined Et_2O washings were cooled to 0°C and treated with ice. When the vigorous reaction ceased, the resulting mixture was diluted with H_2O, separated, and the aqueous layer extracted with Et_2O. The combined organics were washed with H_2O and saturated NaCl, dried over Na_2SO_4, filtered, and concentrated to give a pale yellow solid (0.86 g, 79% yield). LCMS: MH^+=230.

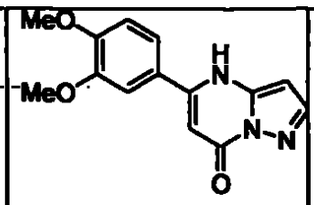
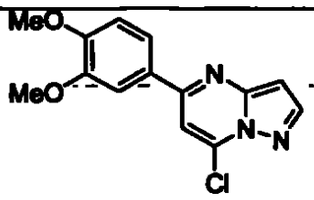
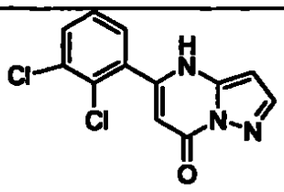
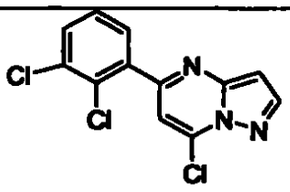
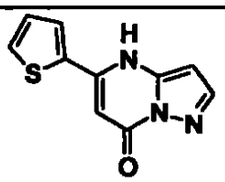
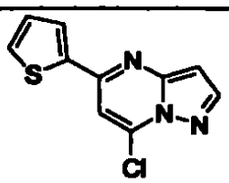
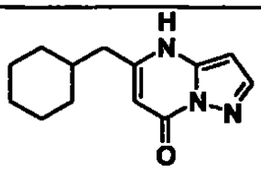
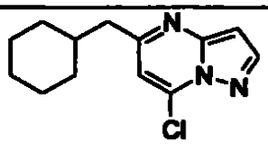
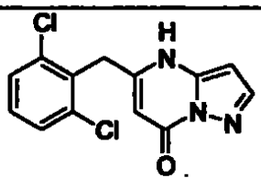
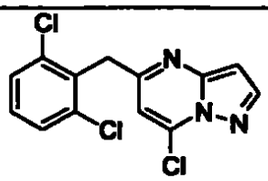
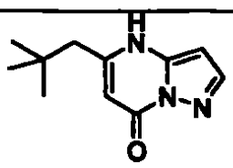
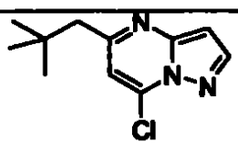
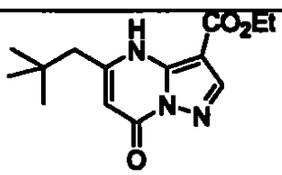
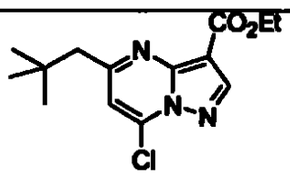
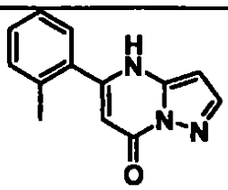
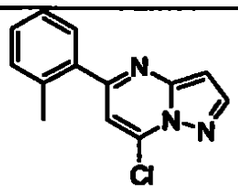
PREPARATIVE EXAMPLE 80-122:

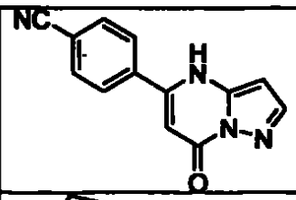
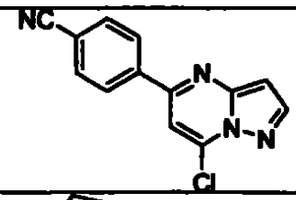
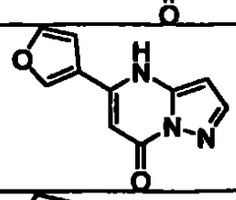
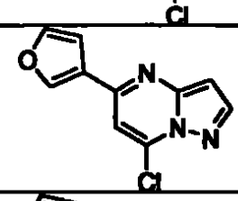
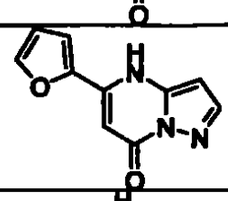
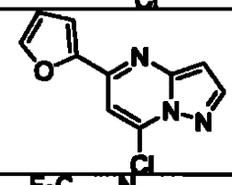
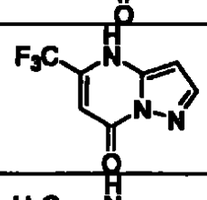
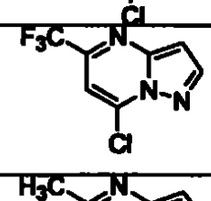
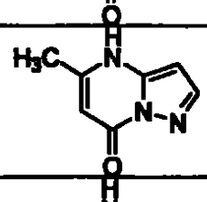
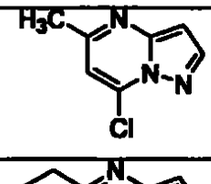
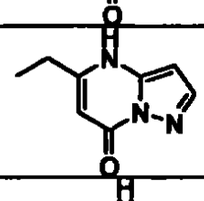
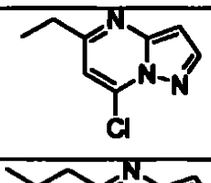
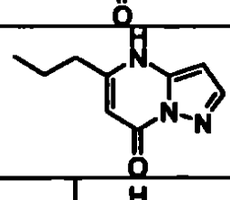
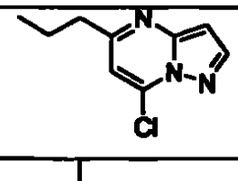
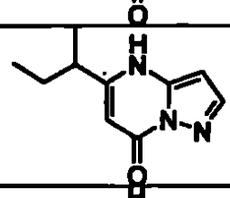
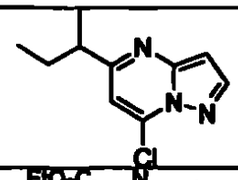
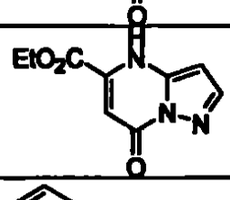
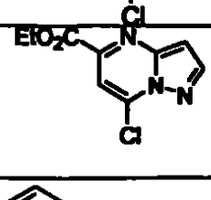
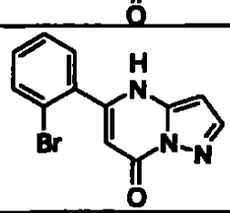
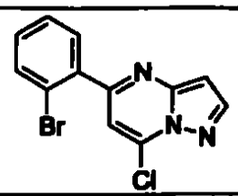
By essentially the same procedure set forth in Preparative Example 79, only substituting the compound shown in Column 2 of Table 7, the compounds shown in Column 3 of Table 7 were prepared:

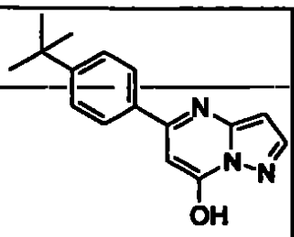
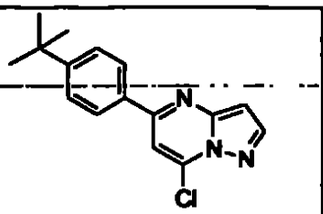
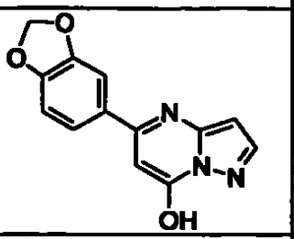
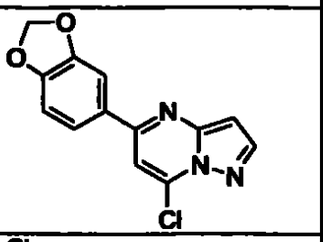
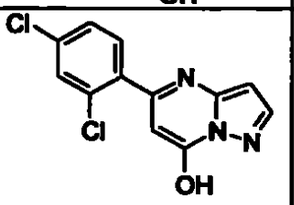
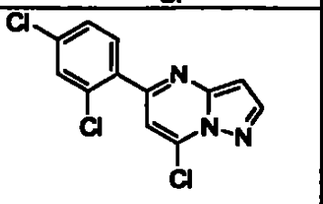
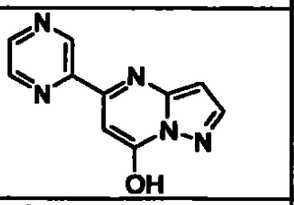
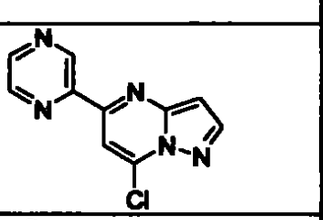
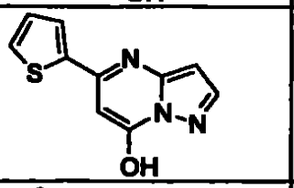
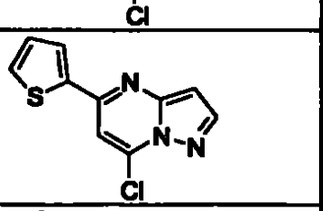
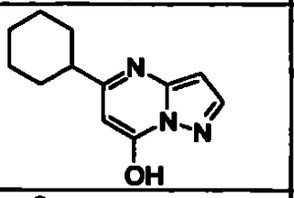
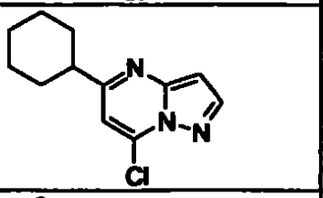
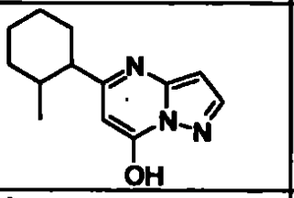
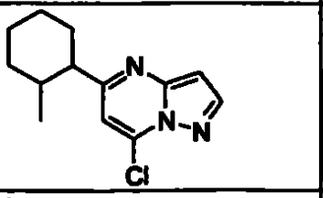
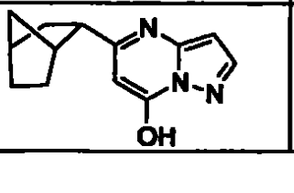
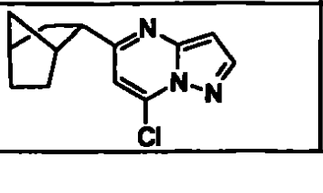
TABLE 7

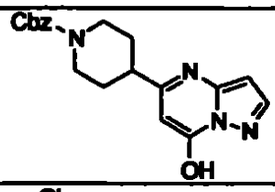
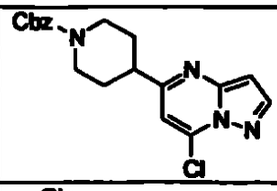
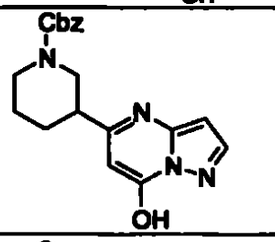
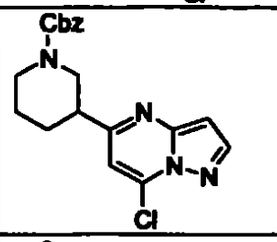
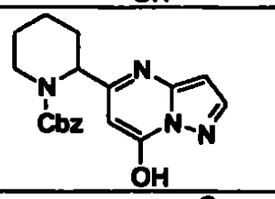
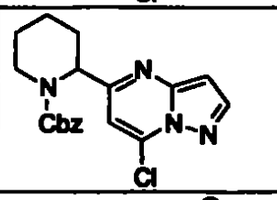
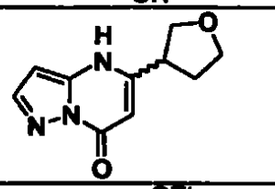
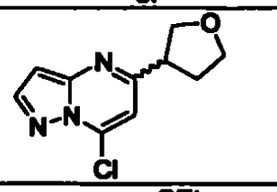
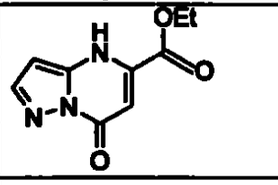
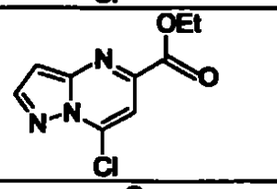
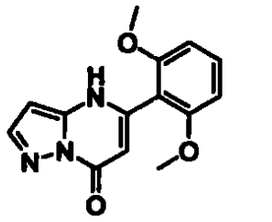
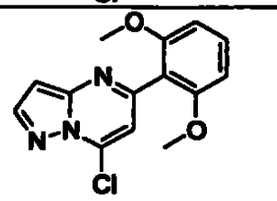
Prep. Ex.	Column 2	Column 3	CMPD
80			MS: MH^+=248
81			
82			MS: MH^+=298
83			MS: MH^+=196

84			MS: MH$^+$=210
85			
86			MS: MH$^+$=272
87			
87.10			
88			MS: MH$^+$=255
89			
90			Yield = 65% MS: MH$^+$ = 260

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

99			
100			
101			
102			
103			
104			
105			
106			
107			45% yield; MS: MH^+=226
108			MS: MH^+ = 308

109			Yield = quant MH^+ = 286
110			Yield = 50 MH^+ = 272
111			Yield = 85 MH^+ = 299
112			Yield = 97 MH^+ = 231
113			Yield = 45 MH^+ = 236
114			Yield = quant. MH^+ =236
115			Yield = 57 MH^+ =250
116			Yield = 89 MH^+ =248

117			Yield = 96 MH^+ =371
118			Yield = 99 MH^+ =371
119			Yield = 50 MH^+ =371
120			Yield=57% LCMS: MH^+=224
121			Yield=34% LCMS: MH^+=226
122			Yield=100% ^{1}H NMR ($CDCl_3$) δ 8.53(d, 1H), 7.66(t, 1H), 7.51(s, 1H), 7.45(d, 1H), 6.84(d, 2H).

PREPARATIVE EXAMPLE 123

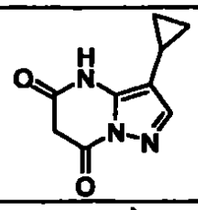
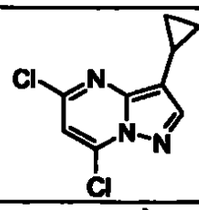
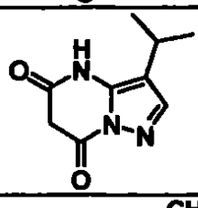
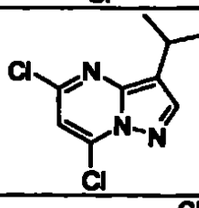
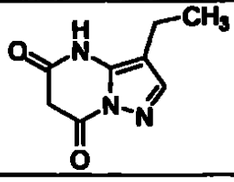
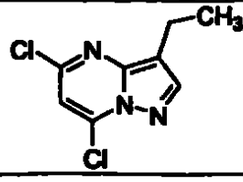
$POCl_3$ (62 mL) was cooled to 5 °C under nitrogen and dimethylaniline (11.4 g, 2.8 eq.) and the compound prepared in Preparative Example 75 (4.75 g,

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

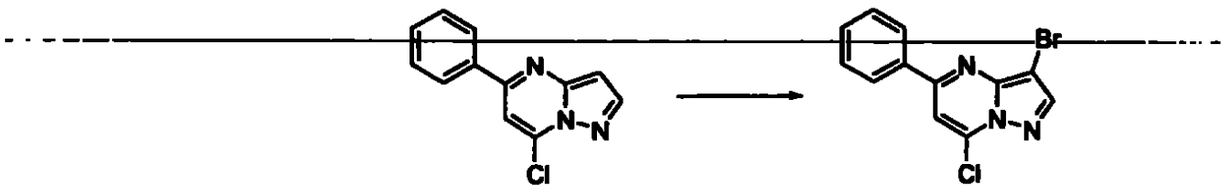
PREPARATIVE EXAMPLES 124-126

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

TABLE 8

Prep. Ex.	Column 2	Column 3
124		
125		
126		

PREPARATIVE EXAMPLE 127:

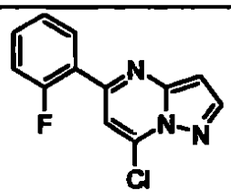
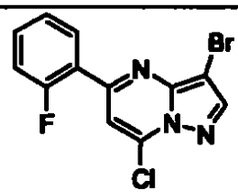
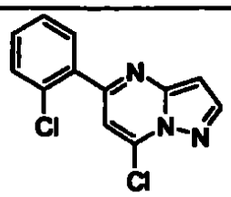
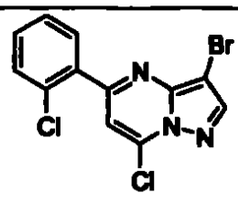
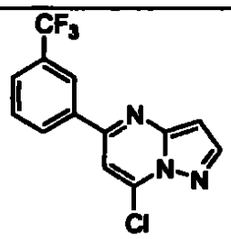
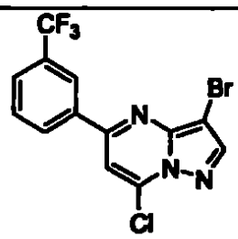


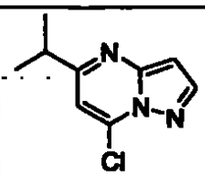
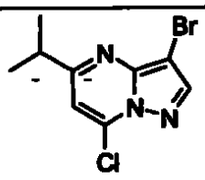
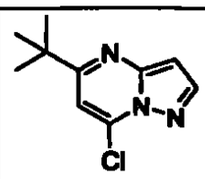
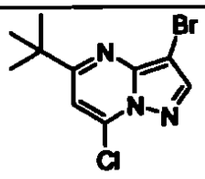
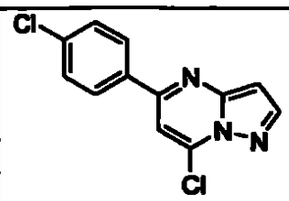
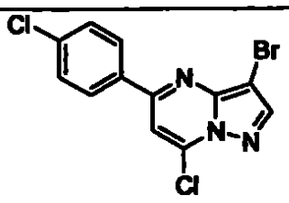
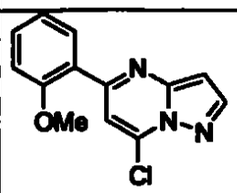
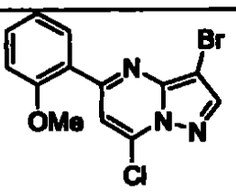
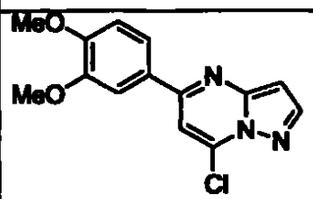
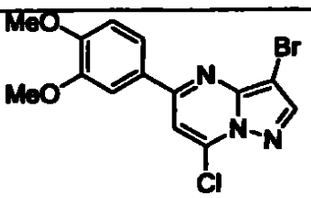
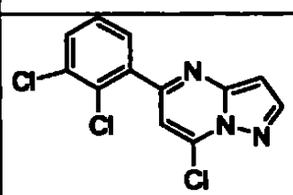
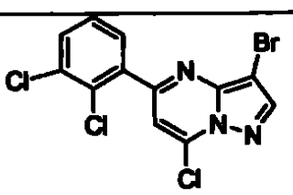
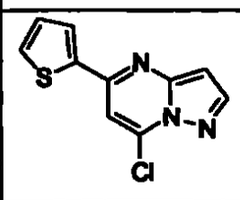
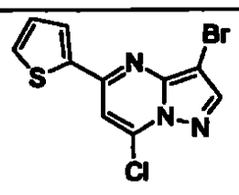
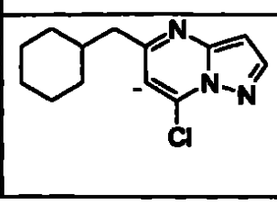
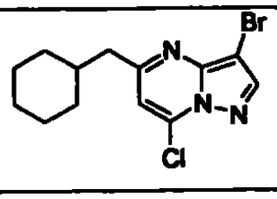
A solution of the compound prepared in Preparative Example 79 (0.10 g, 0.435 mmol) in CH_3CN (3 mL) was treated with NBS (0.085 g, 1.1 eq.). The reaction mixture was stirred at room temperature 1 hour and concentrated under reduced pressure. The crude product was purified by flash chromatography using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

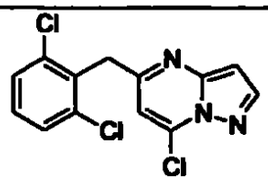
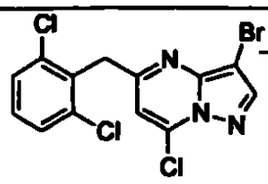
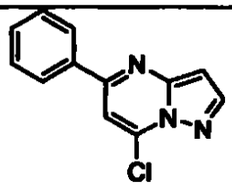
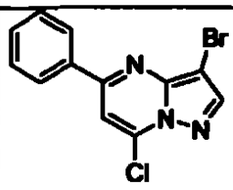
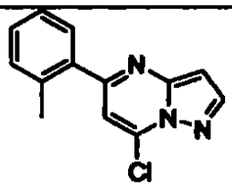
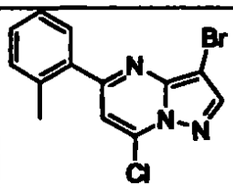
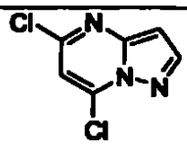
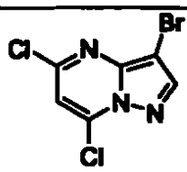
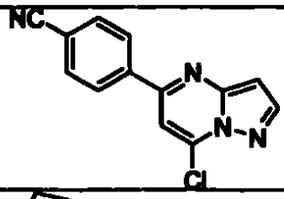
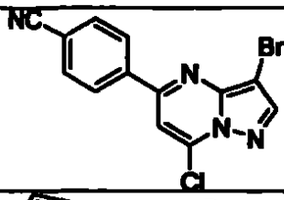
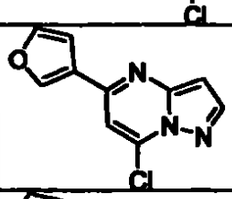
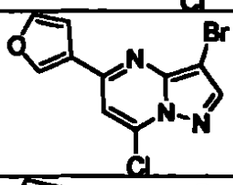
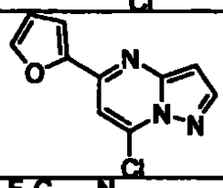
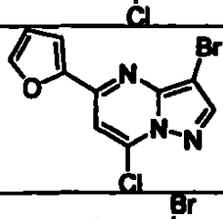
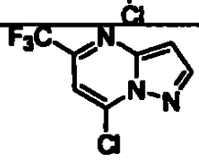
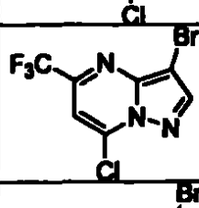
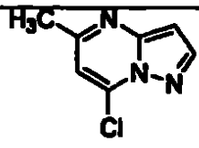
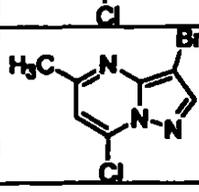
PREPARATIVE EXAMPLES 128-164:

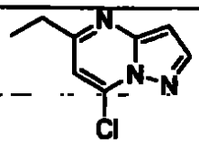
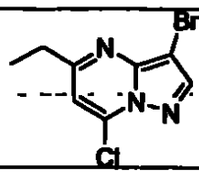
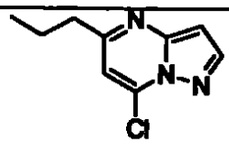
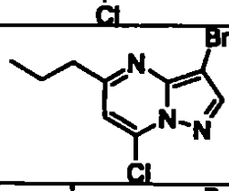
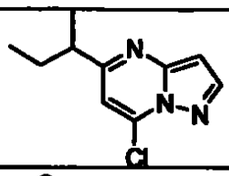
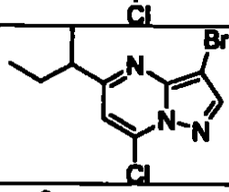
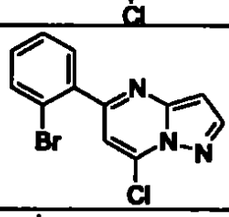
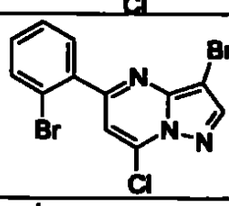
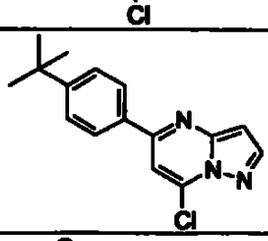
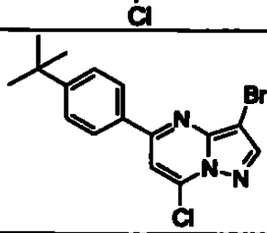
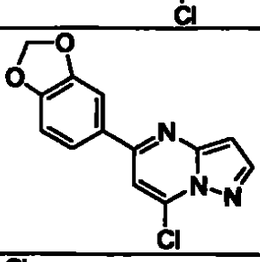
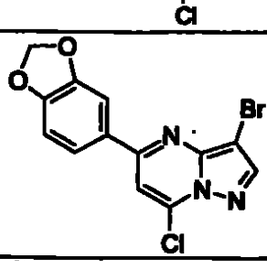
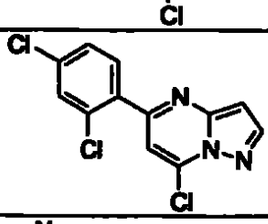
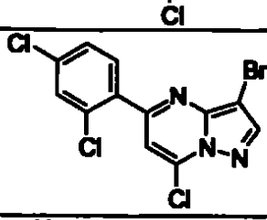
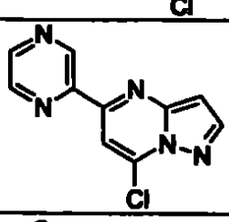
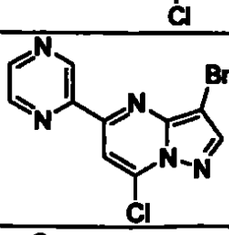
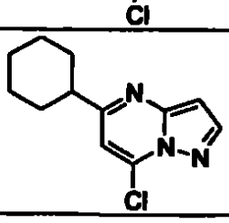
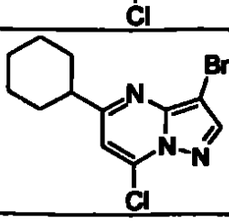
By essentially the same procedure set forth in Preparative Example 127 only substituting the compounds shown in Column 2 of Table 9, the compounds shown in Column 3 of Table 9 were prepared:

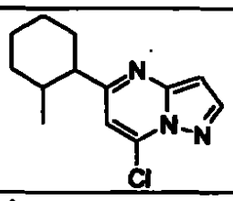
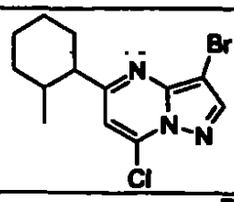
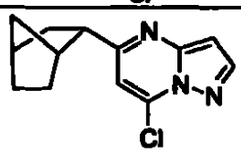
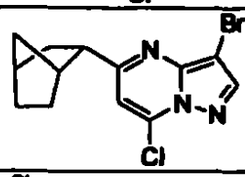
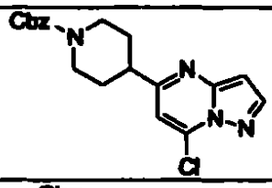
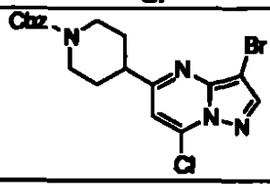
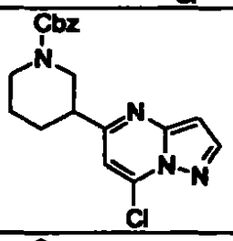
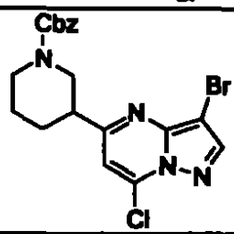
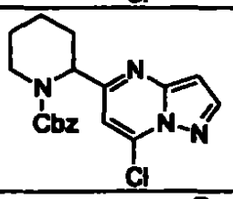
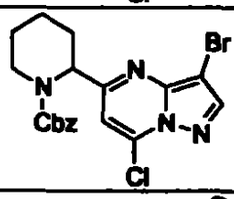
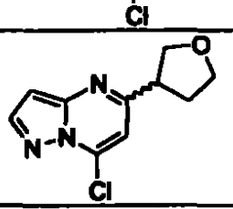
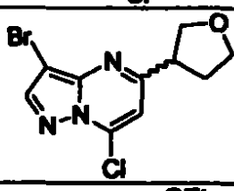
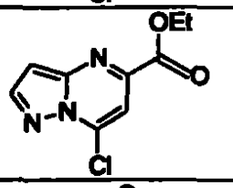
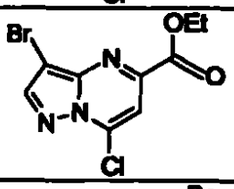
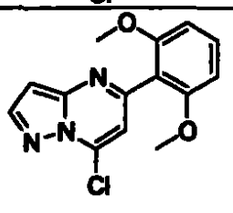
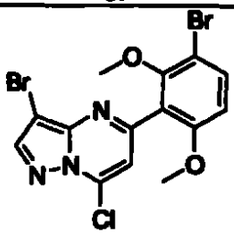
TABLE 9

Prep. Ex.	Column 2	Column 3	CMPD
128			MS: MH^+= 326
129			MS: MH^+= 342
130			MS: MH^+= 376

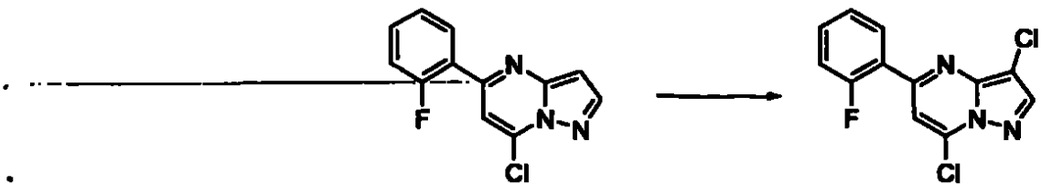
131			MS: MH^+=274
132			MS: MH^+=288
133			
134			Yield = 75% MS: MH^+ = 338
135			Yield = 52% MS: MH^+ = 368
136			Yield = 87% MS: MH^+ = 376
137			Yield = 100% MS: MH^+ = 316
138			Yield = 92% MS: MH^+ = 330

139			Yield = 82% MS: MH$^+$ = 395
140			Yield=88% MS: MH$^+$=308
141			Yield=100% MS: MH$^+$=322
142			MH$^+$=266
143			
144			
145			
146			
147			

148			
149			
150			
151			LCMS: MH^+ = 386
152			Yield = quant MH^+ = 364
153			Yield = quant MH^+ = 353
154			Yield = 95 MH^+ = 378
155			Yield = 77 MH^+ = 311
156			Yield =quant. MH^+ =314

157			Yield = 99 MH^+ =328
158			Yield = 98 MH^+ =326
159			Yield = 99 MH^+ =449
160			Yield = 95 MH^+ =449
161			Yield = 72 MH^+ =449
162			Yield=98% LCMS: MH^+=302
163			Yield=95% LCMS: MH^+=305
164			Yield=50% ^1H NMR ($CDCl_3$) δ 8.36(s, 1H), 7.72(d, 1H), 7.20(s, 1H), 6.82(d, 1H), 3.99(s, 3H), 3.90(s, 3H);

PREPARATIVE EXAMPLE 165:

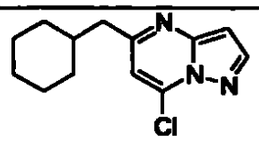
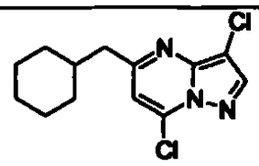
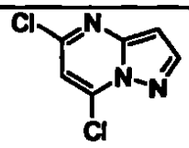
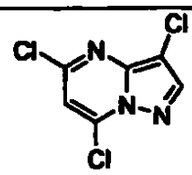


A solution of the compound prepared in Preparative Example 80 (0.3 g, 1.2 mmol) in CH_3CN (15 mL) was treated with NCS (0.18 g, 1.1 eq.) and the resulting solution heated to reflux 4 hours. Additional NCS (0.032 g, 0.2 eq.) added and the resulting solution was stirred at reflux overnight. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and the residue purified by flash chromatography using a 20% EtOAc in hexanes solution as eluent (0.28 g, 83% yield). LCMS: MH^+= 282.

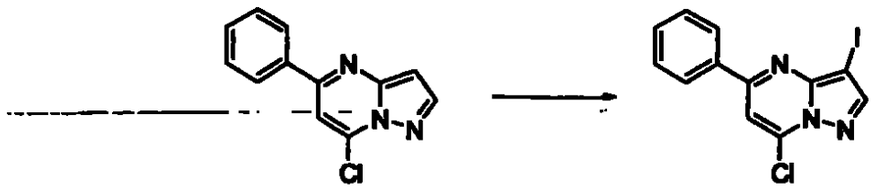
PREPARATIVE EXAMPLE 166-167:

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

TABLE 10

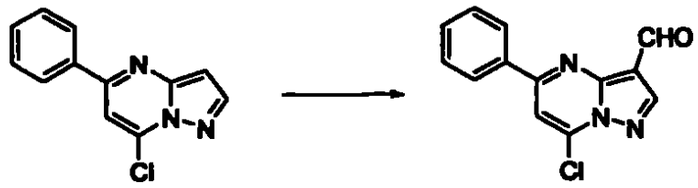
Prep. Ex.	Column 2	Column 3	CMPD
166			Yield = 82% LCMS: MH^+ = 286
167			

PREPARATIVE EXAMPLE 167.10:



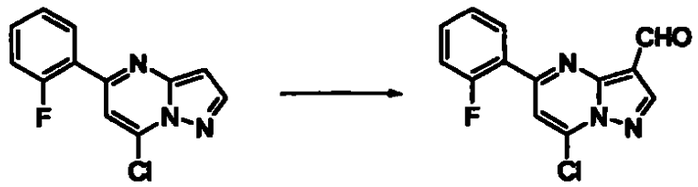
By essentially the same procedure set forth in Preparative Example 165 only substituting N-iodosuccinimide, the above compound was prepared.

PREPARATIVE EXAMPLE 168:



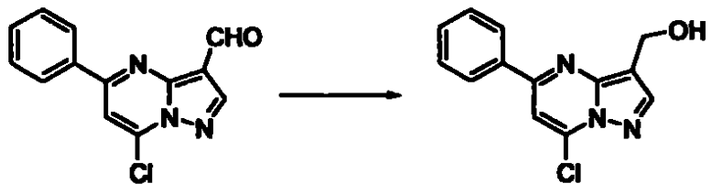
To a solution of the compound from Preparative Example 79 (1.0 g, 4.35 mmol) in DMF (6 mL) was added $POCl_3$ (1.24 mL, 3.05 eq.) and the resulting mixture was stirred at room temperature overnight. The reaction mixture was cooled to 0°C and the excess $POCl_3$ was quenched by the addition of ice. The resulting solution was neutralized with 1N NaOH, diluted with H_2O, and extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography using a 5% MeOH in CH_2Cl_2 solution as eluent (0.95 g, 85% yield). LCMS: MH^+=258.

PREPARATIVE EXAMPLE 169:



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

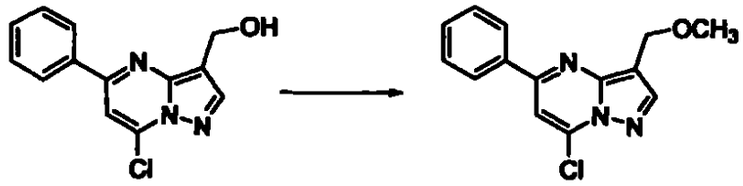
PREPARATIVE EXAMPLE 170:



To a solution of the product of Preparative Example 169 (0.25 g, 0.97 mmol) in THF was added $NaBH_4$ (0.041 g, 1.1 eq.) and the resulting solution was stirred at room temperature overnight. The reaction mixture was quenched

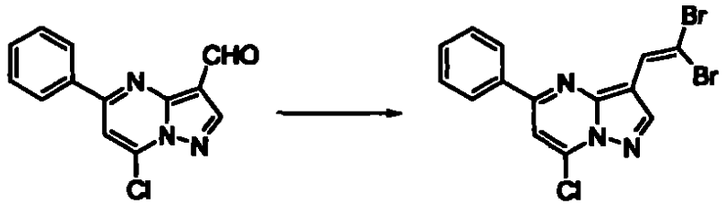
by the addition of H_2O and extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 60: 40 hexanes : EtOAc mix as eluent (0.17 g, 69% yield). MS: MH^+=260.

PREPARATIVE EXAMPLE 171:



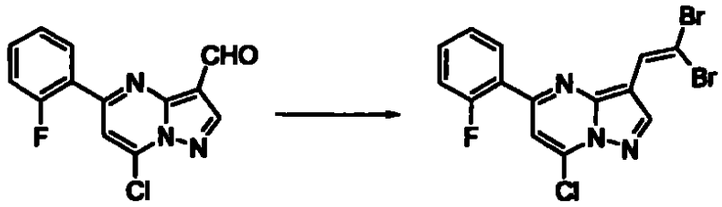
A solution of the compound prepared in Preparative Example 170 (0.12 g, 0.462 mmol), dimethyl sulfate (0.088 mL, 2.0 eq), 50% NaOH (0.26 mL) and catalytic Bu_4NBr in CH_2Cl_2 (4 mL) was stirred at room temperature overnight. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 30% EtOAc-in-hexanes solution as eluent (0.062 g, 48% yield).

PREPARATIVE EXAMPLE 172



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

PREPARATIVE EXAMPLE 173:



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

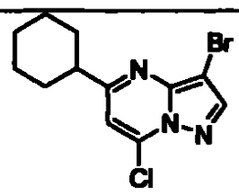
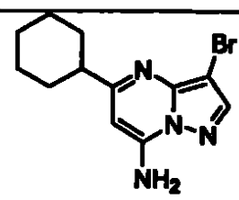
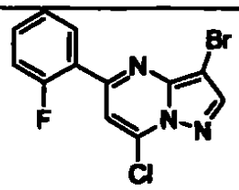
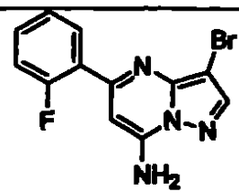
PREPARATIVE EXAMPLE 174:

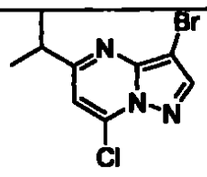
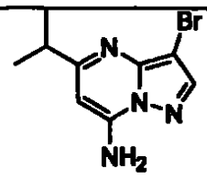
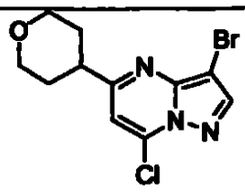
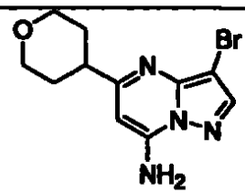
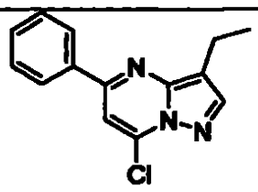
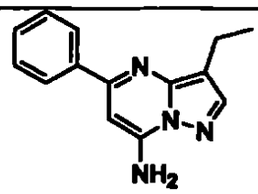
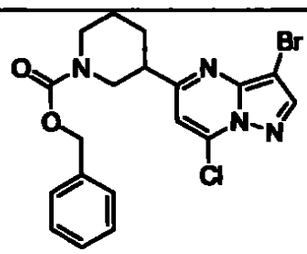
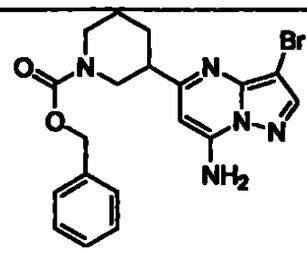
The compound prepared in Preparative Example 127 (3.08 g, 10.0 mmol), 2.0 M NH_3 in 2-propanol (50 mL, 100.0 mmol), and 37 % aqueous NH_3 (10.0 mL) were stirred in a closed pressure vessel at 50°C for 1 day. The solvent was evaporated and the crude product was purified by flash chromatography using 3:1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

PREPARATIVE EXAMPLES 175-180:

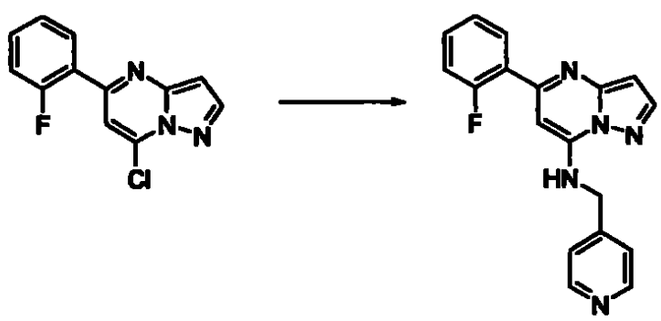
By essentially the same procedure set forth in Preparative Example 174 only substituting the compound shown in Column 2 of Table 11, the compounds shown in Column 3 of Table 11 were prepared.

TABLE 11

Prep. Ex.	Column 2	Column 3
175		
176		

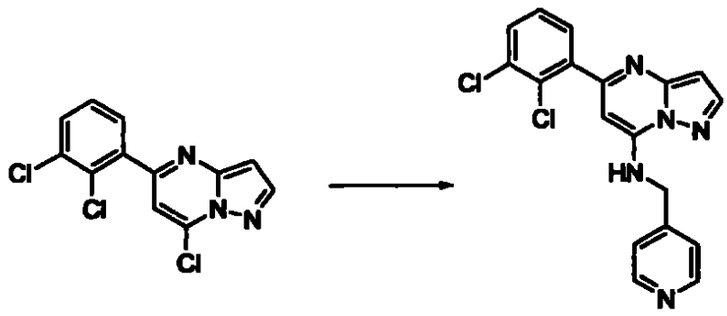
177		
178		
179		
180		

PREPARATIVE EXAMPLE 181:



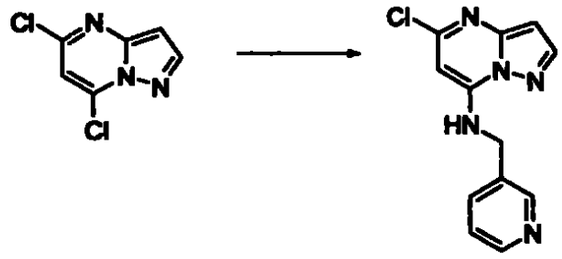
The compound prepared in Preparative Example 80 (0.3 g, 1.2 mmol), K_2CO_3 (0.33 g, 2 eq.), and 4-aminomethylpyridine (0.13 mL, 1.1 eq.) was heated to reflux overnight. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The residue was diluted with H_2O and extracted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

PREPARATIVE EXAMPLE 182:



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

PREPARATIVE EXAMPLE 183:



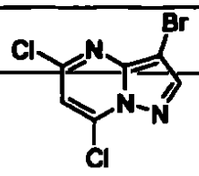
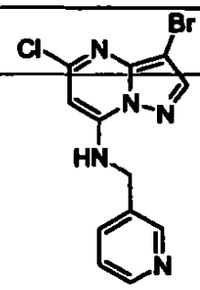
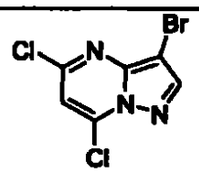
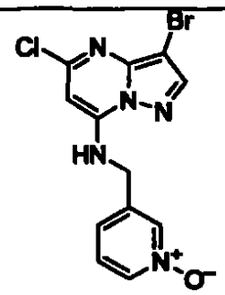
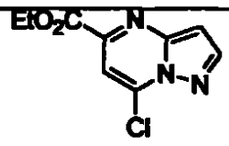
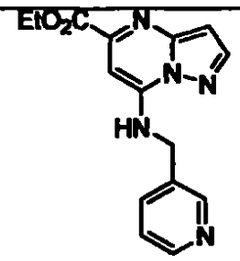
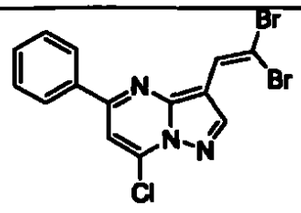
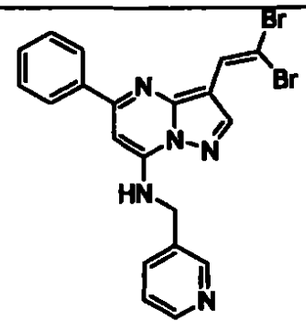
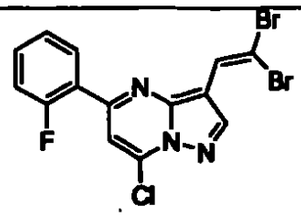
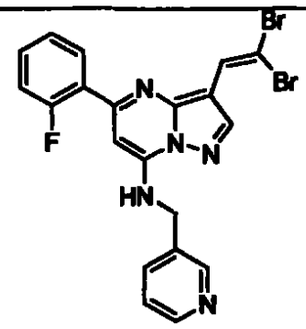
To a solution of the compound prepared in Preparative Example 123 (0.25 g, 1.3 mmol) in dioxane (5 mL) was added iPr_2NEt (0.47 mL, 2.0 eq.) and 3-aminomethylpyridine (0.15 ml, 1.1 eq.). The resulting solution was stirred at room temperature 72 hours. The reaction mixture was diluted with H_2O and extracted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

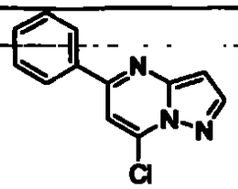
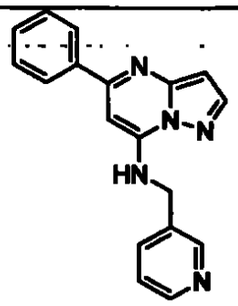
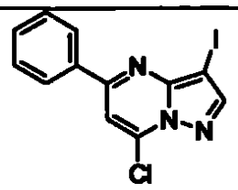
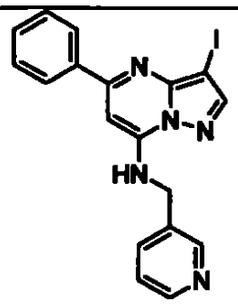
PREPARATIVE EXAMPLES 184-187:

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

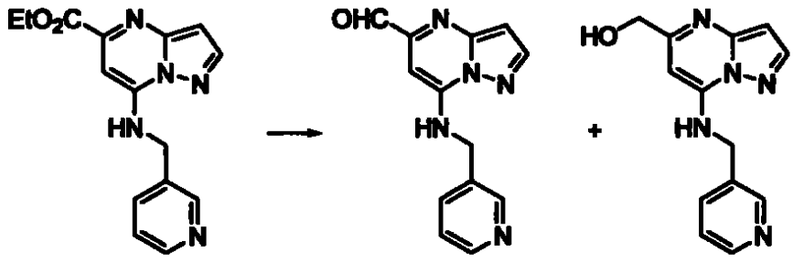
TABLE 12

Prep. Ex.	Column 2	Column 3

184		
184.1		
185		
186		
187		

187.1		
187.11		

PREPARATIVE EXAMPLE 188 and PREPARATIVE EXAMPLE 189:

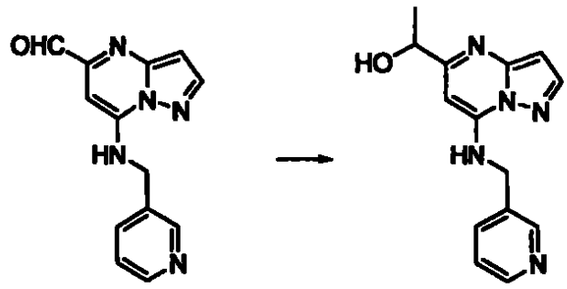


To a solution of the compound prepared in Preparative Example 185 (1.18 g, 3.98 mmol) in THF (35 mL) at -78 °C was added LAH (4.78 mL, 1M in Et_2O, 1.0 eq.) dropwise. The reaction mixture was stirred at -78 °C for 3 hours at which time additional LAH (2.0 mL, 1M in Et_2O, 0.42 eq.) was added dropwise.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

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

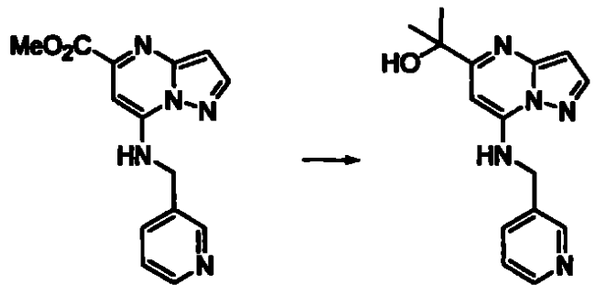
Preparative Example 189: (alcohol): 0.25 g, 24% yield. MS: MH^+ = 256.

PREPARATIVE EXAMPLE 190:



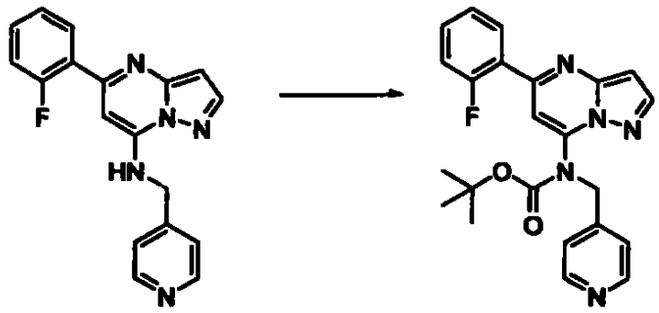
To a solution of the compound prepared in Preparative Example 188 (0.075 g, 0.30 mmol) in THF (2.0 mL) at 0 °C was added CH_3MgBr (0.3 mL, 3.0M solution in Et_2O, 3.0 eq.) dropwise. The resulting solution was stirred at 0 °C an additional 1.5 hours, warmed to room temperature, and stirred overnight.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

PREPARATIVE EXAMPLE 191:



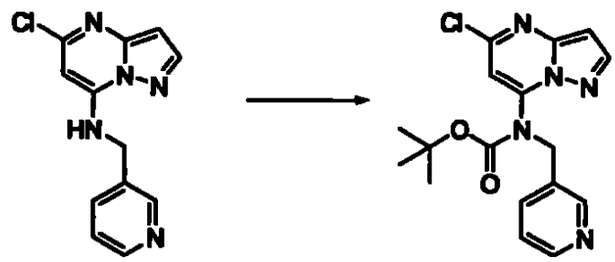
By essentially the same procedure set forth in Preparative Example 190 only substituting the compound prepared in Preparative Example 185 and using excess MeMgBr (5 eq.), the above compound was prepared.

PREPARATIVE EXAMPLE 192:



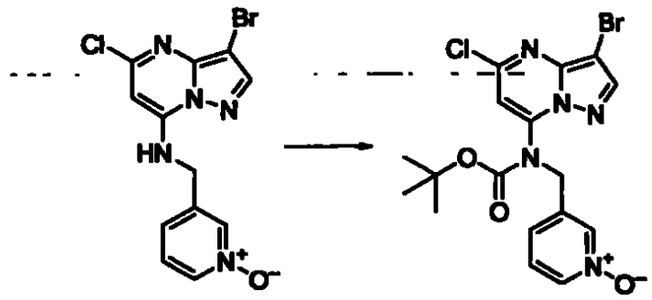
The compound prepared in Preparative Example 181 (0.29 g, 0.91 mmol), BOC_2O (0.22 g, 1.1 eq), and DMAP (0.13 g, 1.1 eq.) in dioxane (10 mL) was stirred at room temperature 3 days. Additional BOC_2O (0.10g, 0.5 eq.) was added and the reaction mixture was stirred 4 hours. The reaction mixture was concentrated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

PREPARATIVE EXAMPLE 193:



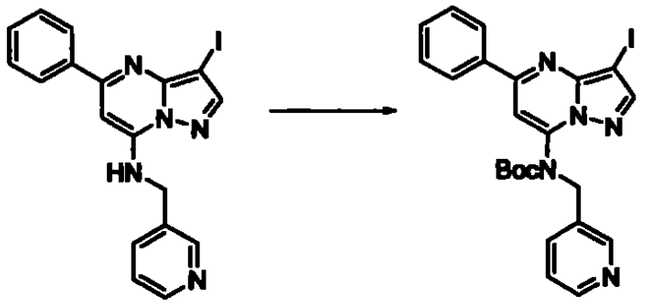
By essentially the same procedure set forth in Preparative Example 192 only substituting the compound prepared in Preparative Example 183, the above compound was prepared. MS: MH^+ = 360.

PREPARATIVE EXAMPLE 193.10:



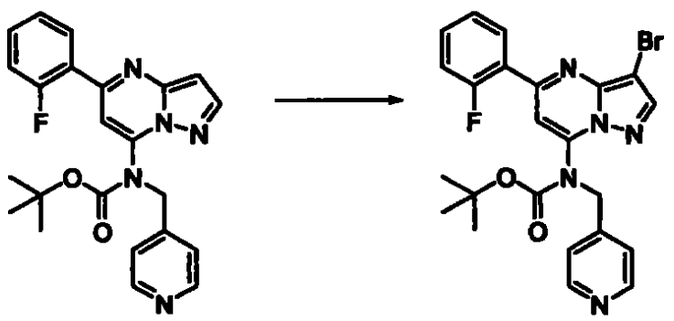
By essentially the same procedure set forth in Preparative Example 192 only substituting the compound prepared in Preparative Example 184.1, the above compound was prepared. MS: MH^+ = 454.

PREPARATIVE EXAMPLE 194:



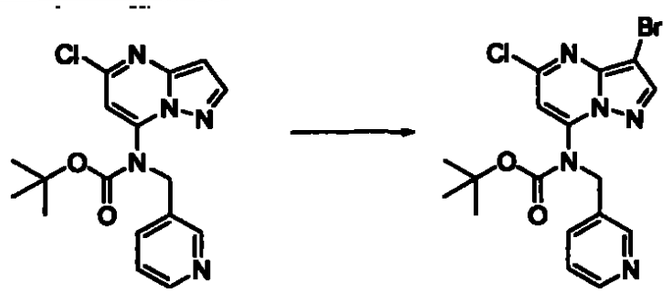
By essentially the same procedure set forth in Preparative Example 192 only substituting the above compound prepared in Preparative Example 187.11, the above compound was prepared (0.223 g, 88% yield). MS: MH^+ = 528.

PREPARATIVE EXAMPLE 195:



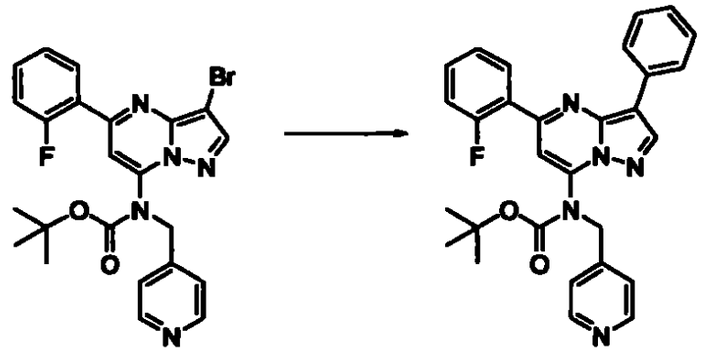
By essentially the same procedure set forth in Preparative Example 127 only substituting the compound prepared in Preparative Example 192, the above compound was prepared (0.38 g, 95% yield). LCMS: MH^+= 498.

PREPARATIVE EXAMPLE 196:



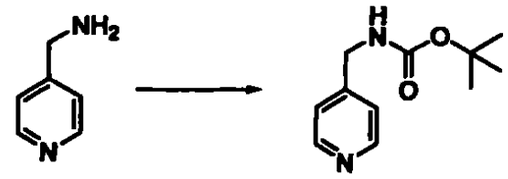
By essentially the same procedure set forth in Preparative Example 195, only substituting the compound prepared in Preparative Example 193, the above compound was prepared (0.3 g, 83% yield). MS: MH^+ = 438.

PREPARATIVE EXAMPLE 197:



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

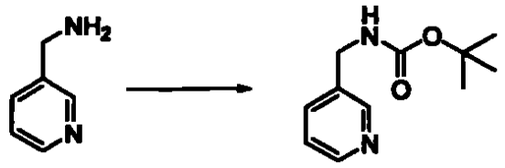
PREPARATIVE EXAMPLE 198:



To a solution of 4-aminomethylpyridine (1.41 mL, 13.87 mmol) in CH_2Cl_2 (50 mL) was added BOC_2O (3.3 g, 1.1 eq.) and TEA and the resulting solution

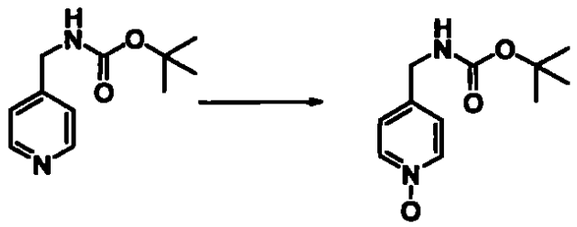
was stirred a room temperature 2 hours. The reaction mixture was diluted with H_2O (50 mL) and extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography using a 5% (10% NH_4OH in MeOH) solution in CH_2Cl_2 as eluent to give a yellow solid (2.62 g, 91% yield). LCMS: MH^+= 209.

PREPARATIVE EXAMPLE 199:



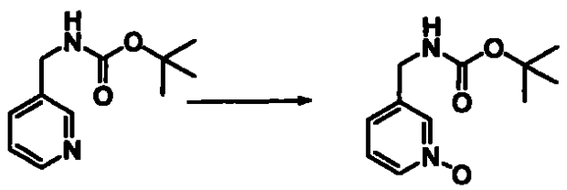
By essentially the same procedure set forth in Preparative Example 198 only substituting 3-aminomethylpyridine, the above compound was prepared as a yellow oil (2.66 g, 92% yield). LCMS: MH^+= 209.

PREPARATIVE EXAMPLE 200:



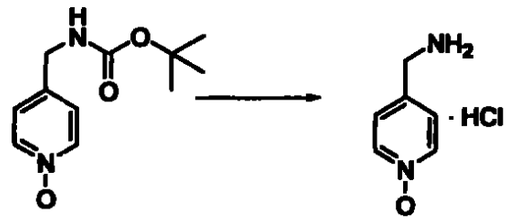
To a solution of the compound prepared in Preparative Example 198 (0.20 g, 0.96 mmol) in CH_2Cl_2 (5 mL) at 0°C was added *m*-CPBA (0.17 g, 1.0 eq) and the resulting solution stirred at 0°C 2 hours and stored at 4°C overnight at which time the reaction mixture was warmed to room temperature and stirred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

PREPARATIVE EXAMPLE 201:



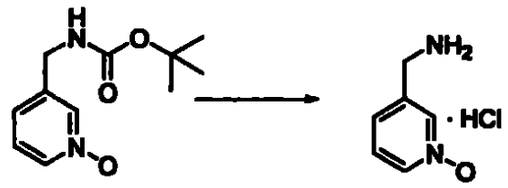
A solution of oxone (58.6 g) in H_2O (250 mL) was added dropwise to the compound prepared in Preparative Example 199 (27 g, 0.13 mol) and $NaHCO_3$ (21.8 g, 2.0 eq.) in MeOH (200 mL) and H_2O (250 mL). The resulting solution was stirred at room temperature overnight. The reaction mixture was diluted with CH2Cl2 (500 mL) and filtered. The layers were separated and the aqueous layer extracted with CH_2Cl_2. The combined organics were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give a white solid (21.0 g, 72% yield). MS: MH^+= 255.

PREPARATIVE EXAMPLE 202:



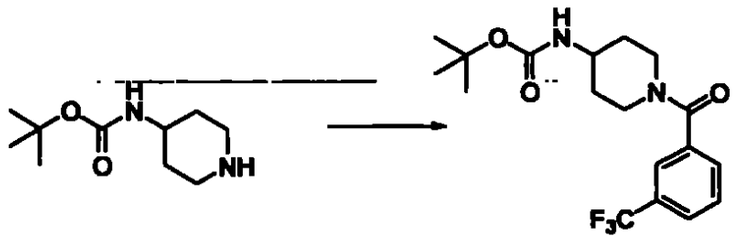
The compound prepared in Preparative Example 200 (0.29 g, 1.29 mmol) was stirred at room temperature in 4M HCl in dioxane (0.97 mL) 2 hours. The reaction mixture was concentrated *in vacuo* and used without further purification. LCMS: MH^+= 125.

PREPARATIVE EXAMPLE 203:



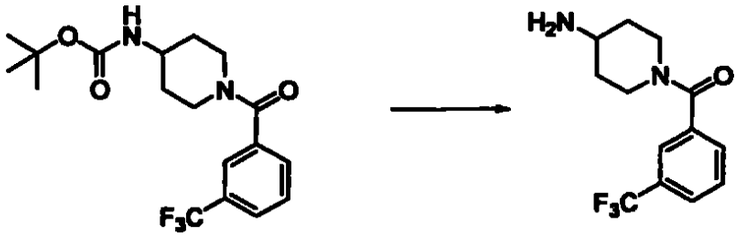
By essentially the same procedure set forth in Preparative Example 202 nly substituting the compound prepared in Preparative Example 201, the compound shown above was prepared. LCMS: MH^+= 125.

PREPARATIVE EXAMPLE 204:



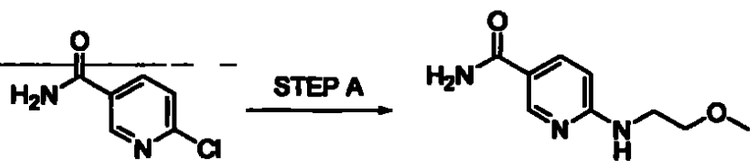
To 4-N-t-Butoxycarbonylaminopiperidine (0.8 g, 4.0 mmol) in CH_2Cl_2 (10 mL) at 0°C was added TEA (1.40 mL, 2.5 eq.) and 3-trifluoromethyl benzoyl chloride (1.05 g, 1.25 eq.). The resulting solution was stirred 15 minutes and warmed to room temperature and stirred 3 hours. The reaction mixture was diluted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

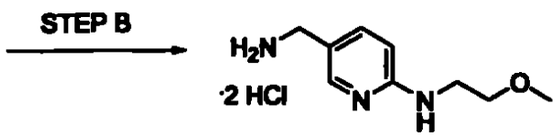
PREPARATIVE EXAMPLE 205:



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.

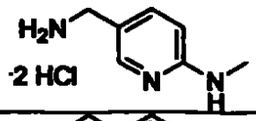
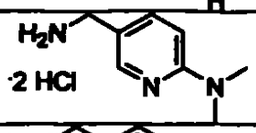
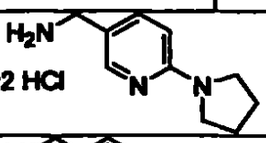
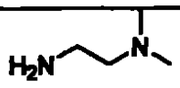
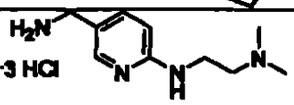
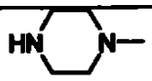
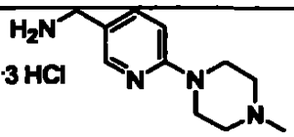
STEP B:

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.

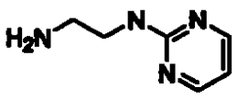
PREPARATIVE EXAMPLES 207-211:

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

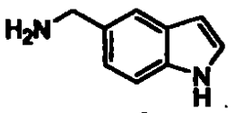
Prep.Ex.	Column 2 (Amine)	Column 3 (Amine)	CMPD M+H (free base)
207			M+H = 138
208			M+H = 152
209			M+H = 178
210			M+H = 195
211			M+H = 207

PREPARATIVE EXAMPLE 212:



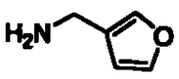
The above compound was prepared accordingly to the methods described in WO 91/18904.

PREPARATIVE EXAMPLE 213:



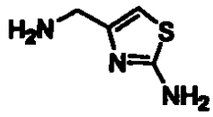
The above compound was prepared accordingly to the methods described in US 6,180,627 B1.

PREPARATIVE EXAMPLE 214:



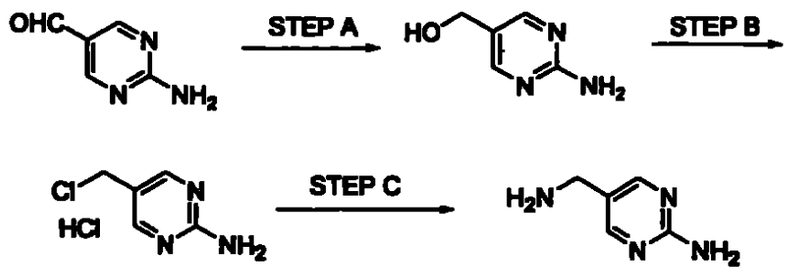
The known amine was prepared as described in *J. Med. Chem.* (2001), *44*, 4505-4508.

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.

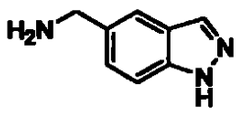
STEP B:

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:

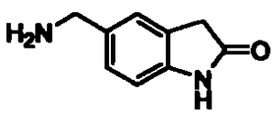
To a 15 mL pressure tube charged with a stir bar was added chloride (150 mg, 0.83 mmol) from Preparative Example 216, Step B followed by 7 M NH_3/MeOH (10 mL). The resulting solution was stirred for 48 h at rt where upon the mixture was concentrated under reduced pressure to afford a light yellow solid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

PREPARATIVE EXAMPLE 217:



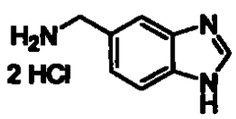
The above compound was prepared accordingly to methods described in WO 00/26210.

PREPARATIVE EXAMPLE 218:



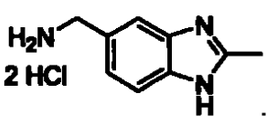
The above compound was prepared accordingly to methods described in WO 99/10325.

PREPARATIVE EXAMPLE 219:



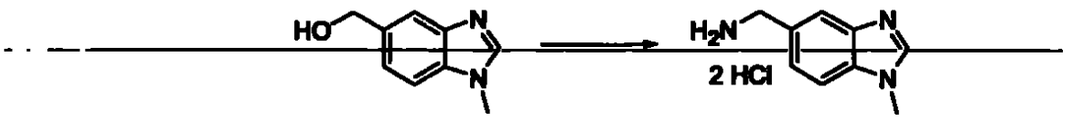
The known amine dihydrochloride was prepared according to methods described in WO 02/64211.

PREPARATIVE EXAMPLE 220:



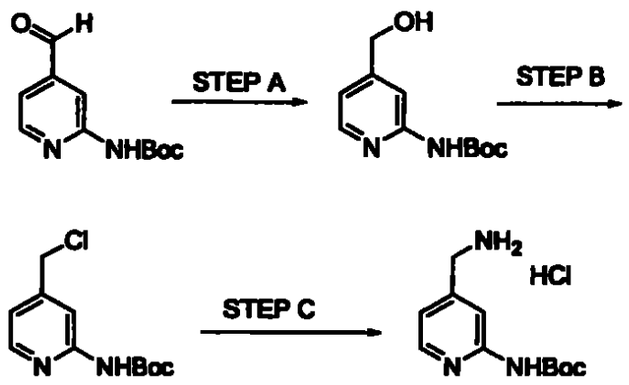
The above compound was prepared according to methods described in WO 02/64211.

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.

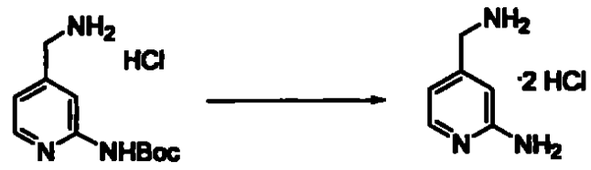
STEP B:

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:

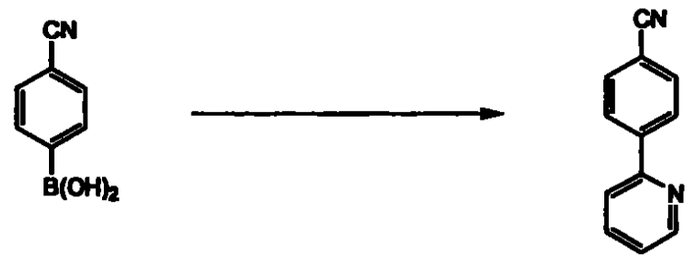
To a solution of crude chloride from Preparative Example 222, Step B (0.33 g, 1.36 mmol) in a pressure tube charged with 7M NH_3/MeOH (35 mL) and the mixture was stirred for 72 h. The mixture was concentrated under reduced pressure to afford 257 mg (85%) of a yellow semisolid. M+H (free base) = 224.

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:

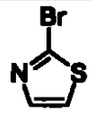
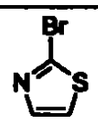
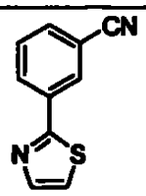
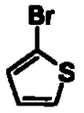
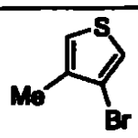
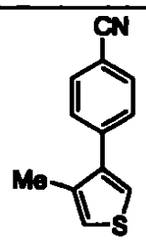


$Pd(PPh_3)_4$ (0.404 gm, 0.35 mmol) was added to a degassed solution of 4-cyanobenzene boronic acid (1.029 g, 7 mmol) and 2-bromopyridine (1.11 g, 7 mmol) in 75 mL acetonitrile. 0.4 M sodium carbonate solution (35 mL) was added to the reaction mixture and the resulting solution was refluxed at 90°C under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

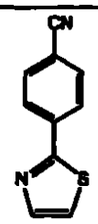
PREPARATIVE EXAMPLE 229:

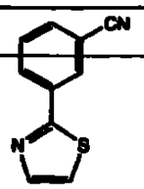
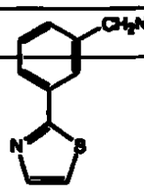
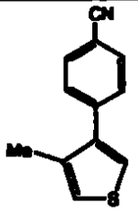
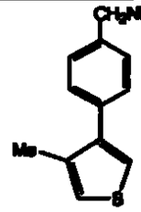
BH_3-THF solution (1 M, 24 mL, 5 eq) was added slowly to a stirring solution of 4-(2-pyridyl)-benzonitrile (0.85 g, 4.72 mmol) in anhydrous THF (25 mL) under Ar, and the resulting solution was refluxed for about 12 hr. The solution was cooled to 0°C using ice-water. Methanol (15 mL) was added drop-wise 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; ^{1}H NMR ($CDCl_3$) δ 8.85 (d, 1H), 8.7 (dd, 1H), 7.9 (dd, 1H), 7.75 (d, 2H), 7.7 (d, 2H), 7.4 (dd, 1H), 3.7 (t, 2H), 1.7 (t, 2H).

PREPARATIVE EXAMPLES 230-233:

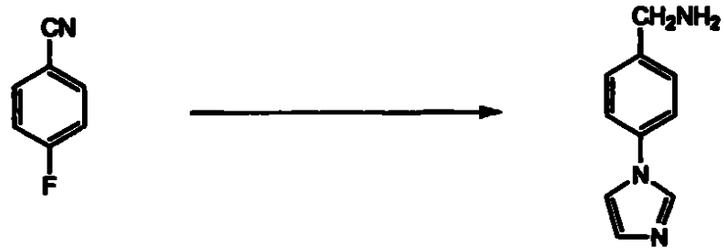
By following essentially the same procedure set forth in Preparative Example 229, compounds in column 3 of Table 15 were prepared.

Table 15

Prep. Ex.	Column 2	Column 3	Column 4
230			Yield = 60% LCMS: MH^+ = 191

231			Yield = 60% LCMS: MH^+ = 191
232			Yield = 70% LCMS: MH^+ = 190
233			Yield = 70% LCMS: MH^+ = 204

PREPARATIVE EXAMPLE 234:



Step A:

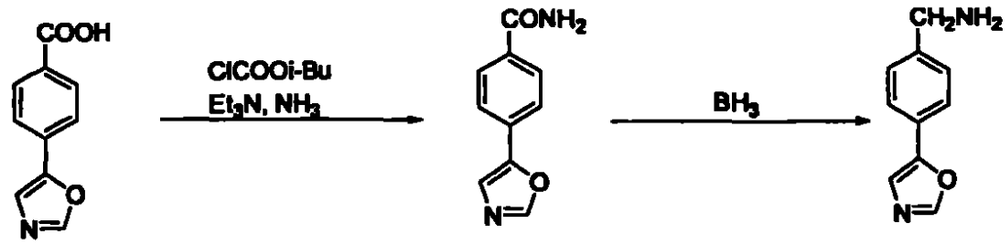
A mixture 4-fluorobenzonitrile (3 g, 25 mmol) and imidazolyl sodium (2.48 g, 27.5 mmol) in DMF (50 mL) was stirred at 80°C under Ar for 12 h. Progress of reaction was monitored by TLC. The reaction mixture was concentrated *in vacuo* and the residue was diluted with 50 mL water and stirred. The aqueous mixture was extracted with EtOAc (2 x 50 mL). Combined EtOAc extracts was dried over anhydrous MgSO4, concentrated, and the 4-(1-imidazolyl)-benzonitrile was isolated by column chromatography (3.6 g, 78%). LCMS: MH^+ = 170; ^1H NMR ($CDCl_3$) δ 8.0 (s, 1H), 7.5 (d, 2H), 7.4 (m, 3H), 7.3 (d, 1H)

Step B:

4-(1-imidazolyl)-benzonitrile (1g, 5.92 mmol) was dissolved in anhydrous THF (10 mL) and added drop-wise to a stirring solution of LAH –THF (1 M in THF, 18 mL) at room temperature. The reaction mixture was refluxed under Ar

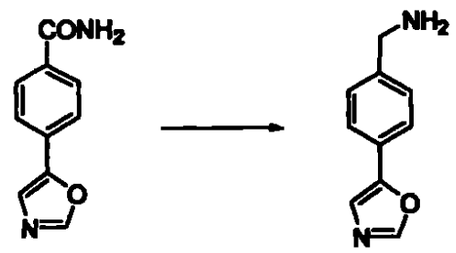
for 2 h and the progress was monitored by TLC. The mixture was cooled to 0°C and quenched by drop-wise addition of a saturated $Na_2SO_4 - H_2O$ solution. The mixture was stirred for 1 h and filtered to remove lithium salts. The filtrate was dried over anhydrous $MgSO_4$ and concentrated to obtain 4-(1-imidazolyl)-benzylamine (0.8 g, 80%). LCMS: MH^+ = 174.

PREPARATIVE EXAMPLE 235:



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

PREPARATIVE EXAMPLE 236:



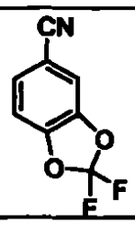
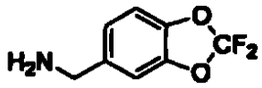
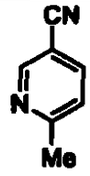
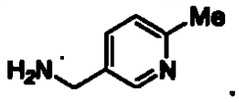
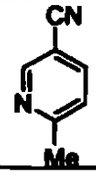
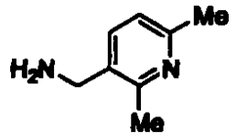
A suspension of 4-(5-oxazolyl)benzamide (500 mg, 2.657 mmol) in 10 mL of dry THF was cooled to 0 °C and 10 mL of 1 M BH_3.THF (10.00 mmol) was added. The contents were refluxed overnight and the excess borane was destroyed by dropwise addition of methanol. The solvent was evaporated and the residue was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

complex. After evaporation of the methanol, the residue was taken in water, basified to pH 10 and the product was extracted in to DCM. The DCM layer was dried (K_2CO_3) and the solvent was removed to provide 150 mg (32%) of 4-(5-oxazolyl)benzylamine: ^{1}H NMR ($CDCl_3$) δ 7.90 (s, 1H), 7.60 (d, 2H), 7.40 (d, 2H), 7.30 (s, 1H), 3.90 (s, 2H).

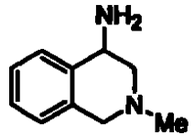
PREPARATIVE EXAMPLES 237-239:

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

Table 16

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

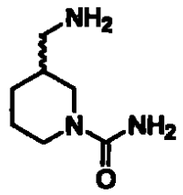
PREPARATIVE EXAMPLE 240



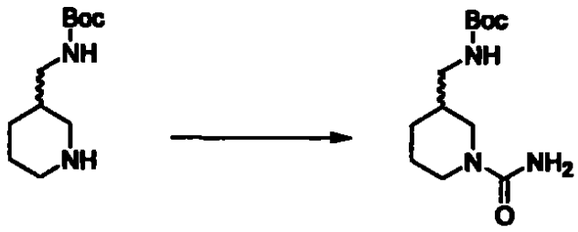
Prepared by the literature procedure (PCT Int. Appl, WO 0105783): ^{1}H NMR ($CDCl_3$) δ 7.35 (d, 1H), 7.24-7.10 (m, 2 H), 7.02 (d, 1H), 3.95 (t, 1H), 3.70 (d, 1H), 3.37 (d, 1H), 2.65 (m, 2H), 2.45 (s, 3H), 1.90 (bs, 2H)

PREPARATIVE EXAMPLE 241:

3-(AMINOMETHYL)PIPERIDINE-1-CARBOXAMIDE

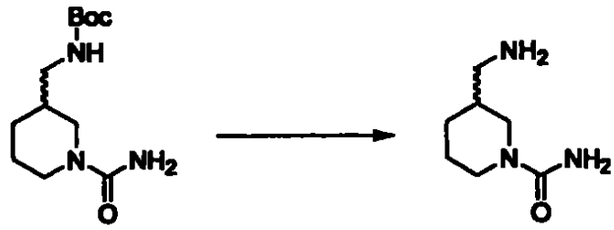


A. 3-(*tert*-BUTOXYCARBONYLAMINOMETHYL)PIPERIDINE-1-CARBOXAMIDE



3(R/S)-(*tert*-Butoxycarbonylaminomethyl)piperidine (3g, 14.0mmoles) was dissolved in anhydrous dichloromethane (50mL) and trimethylsilylisocyanate (9.68g, 11.4mL, 84.0mmoles) was added. The mixture was stirred under argon at 25°C for 68h. Additional trimethylsilylisocyanate (4.84g, 5.7mL, 42.0mmoles) was added and the mixture was stirred at 25°C for a total of 90h. The mixture was evaporated to dryness and chromatographed on a silica gel column (30x5cm) using 2% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give 3-(*tert*-butoxycarbonylaminomethyl)piperidine-1-carboxamide (3.05g, 85%): FABMS: m/z 258.1 (MH^+); HRFABMS: m/z 258.1816 (MH^+). Calcd. for $C_{12}H_{24}O_3N_3$: m/z 258.1818; δ_H ($CDCl_3$) 1.22 91H, m, CH_2), 1.42 (9H, s, -COOC(CH_3)$_3$), 1.48 (1H, m, CH_2), 1.67 (2H, m, CH_2), 1.78 (1H, m, CH), 2.80 (1H, m, CH_2), 2.99, 3H, m, CH_2), 3.59 (1H, m, $CH_2$0 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.

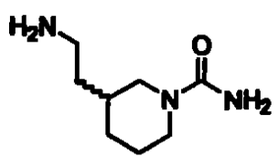
B. 3-(AMINOMETHYL)PIPERIDINE-1-CARBOXAMIDE



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, -$CH_2\underline{NH_2}$), 2.82 (1H, m, CH_2), 3.02 (1H, m, CH_2), 2.98 (2H, m, CH_2), 3.70 (1H, m, -$C\underline{H_2}NH_2$), 3.78 (1H, m, -$C\underline{H_2}NH_2$) and 5.24 ppm (1H, bs, NH); δ_C ($CDCl_3$ + drop CD_3OD) CH_2: 24.1, 28.6, 44.0, 44.8, 47.9; CH: 38.3; C: 159.0.

PREPARATIVE EXAMPLE 242:

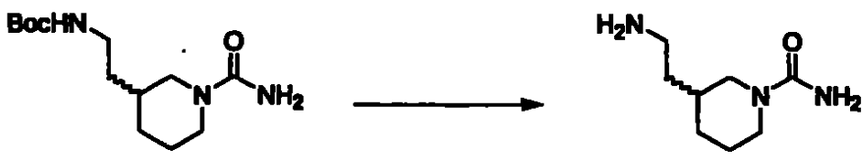
3-(2-AMINOETHYL)PIPERIDINE-1-CARBOXAMIDE



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

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

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

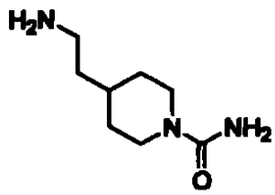


3-(2-*tert*-Butoxycarbonylaminoethyl)piperidine-1-carboxamide (392.7mg, 1.45mmoles) (prepared as described in Preparative Example 242, Step A above) was dissolved in methanol (7.5mL) and 10% conc. sulfuric acid in 1,4-dioxane

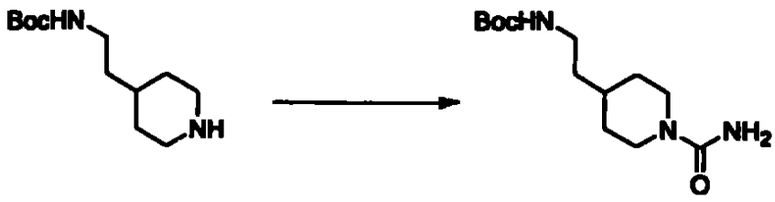
(19.5mL) was added. The mixture was stirred at 25°C for 1.25h. The mixture was diluted with methanol and BioRad AG1-X8 resin (OH^- form) was added until the pH was basic. The resin was filtered off, washed with methanol, evaporated to dryness and chromatographed on a silica gel column (30x2.5cm) using 15% (10% conc, ammonium hydroxide in methanol)-dichloromethane as the eluant to give 3-(2-aminoethyl)piperidine-1-carboxamide (233mg, 94%): FABMS: m/z 172.1 (MH^+); HRFABMS: m/z 172.1444(MH^+). Calcd for $C_8H_{18}N_3O$ requires: m/z 172.1450; δ_H ($CDCl_3$ + 3% CD_3OD) 1.14 (1H, m, CH_2), 1.40 (2H, m, CH_2), 1.49 (1H, m, CH), 1.58 (1H, m, CH_2), 1.69 (1H, m, CH_2), 1.85 (1H, m, CH_2), 2.55 (1H, m, CH_2), 2.67 (5H, m, CH_2/NH_2), 2.76 (1H, bm, CH_2), 2.84 (1H, m, CH_2) and 3.82 ppm (2H, m, $CONH_2$); δ_C ($CDCl_3$ + 3% CD_3OD) CH_2: 24.8, 30.9, 36.6, 38.9, 44.9, 50.0; CH: 33.4.

PREPARATIVE EXAMPLE 243:

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



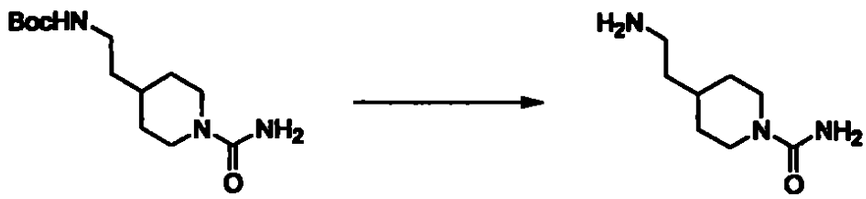
A. 4-(2-tert-BUTOXYCARBONYLAMINOETHYL)PIPERIDINE-1-CARBOXAMIDE



4-(2-*tert*-Butoxycarbonylaminoethyl)piperidine (500mg, 2.19mmoles) was dissolved in anhydrous dichloromethane (10mL) and trimethylsilylisocyanate (2.96mL, 21.9mmoles) was added. The mixture was stirred under argon at 25°C for 3.25h. The mixture was diluted with

dichloromethane and washed with saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$), filtered, evaporated to dryness and chromatographed on a silica gel column (15x5cm) using 5% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give 4-(2-*tert*-butoxycarbonylaminoethyl)piperidine-1-carboxamide (308.2mg, 52%): FABMS: m/z 272.0 (MH^+); HRFABMS: m/z 272.1965 (MH^+). Calcd. for $C_{13}H_{26}O_3N_3$: m/z 272.1974; δ_H ($CDCl_3$) 1.20 (2H, m, CH_2), 1.47 (9H, s, -$COOC(CH_3)_3$), 1.45-1.55 (3H, m, CH/CH_2), 1.75 (2H, m, CH_2), 2.82 (2H, m, CH_2), 3.19 (2H, m, CH_2), 3.96 (2H, m, CH_2), 4.64 (2H, m, CH_2) and 4.70 ppm (1H, bm, NH); δ_C ($CDCl_3$) CH_3: 28.5, 28.5, 28.5; CH_2: 31.8, 31.8, 36.7, 38.0, 44.5, 44.5; CH: 33.4; C: 79.2, 156.7, 158.1.

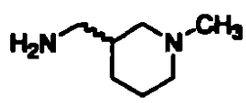
A. 3-(2-AMINOETHYL)PIPERIDINE-1-CARBOXAMIDE



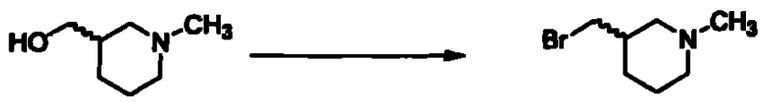
4-(2-*tert*-Butoxycarbonylaminoethyl)piperidine-1-carboxamide (283.3mg, 1.04mmoles) (prepared as described in Preparative Example 243, Step A above) was dissolved in methanol (5.4mL) and 10% conc. sulfuric acid in 1,4-dioxane (14.2mL) was added and the mixture was stirred at 25°C for 1.25h. The mixture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

PREPARATIVE EXAMPLE 244:

3-(AMINOMETHYL)-1-METHYLPIPERIDINE



A. 3-(BROMOMETHYL)-1-METHYLPIPERIDINE



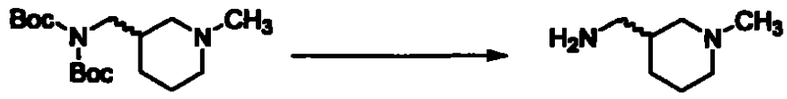
3-(Hydroxymethyl)-1-methylpiperidine (2g, 15.5mmoles) was dissolved in anhydrous acetonitrile (32mL) and anhydrous pyridine (2.02mL, 24.8mmoles) was added and the solution was cooled to 0°C. Dibromotriphenylphosphorane (8.49g, 20.2mmoles) was added at 0°C and the mixture was allowed to warm up to 25°C and was stirred for 94h. The mixture was evaporated to dryness and the residue was chromatographed on a silica gel column (30x5cm) using gradient elution with dichloromethane, 35% diethyl ether in dichloromethane and 5-10% methanol in dichloromethane as the eluant to give 3-(bromomethyl)-1-methylpiperidine (3.13g, 100%): FABMS: m/z 192.1 (MH^+); δ_H ($CDCl_3$) 1.52 (1H, m, CH_2), 1.99 (2H, m, CH_2), 2.43 (1H, m, CH_2), 2.75 (2H, m, CH_2), 2.82 (1H, m, CH), 2.86/2.88 (3H, s, NCH_3), 3.42/3.49 (2H, dd, -$C\underline{H_2}$Br) and 3.56 ppm (2H, m, CH_2); δ_C ($CDCl_3$) CH_3: 44.3; CH_2: 22.1, 26.6, 35.4, 54.8, 58.2; CH: 34.6.

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

3-(Bromomethyl)-1-methylpiperidine (1.5g, 7.81mmoles) (from Preparative Example 244, Step A above) and di-*tert*-butyliminodicarboxylate (1.697g, 7.81mmoles) were dissolved in anhydrous acetonitrile (25mL). Cesium carbonate (5.1g, 15.6mmoles) and lithium iodide (52mg, 0.391mmoles) were

added and the mixture was stirred at 70°C for 20h. The mixture was evaporated to dryness and the residue was partitioned between dichloromethane and saturated aqueous sodium bicarbonate. The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness. the residue was chromatographed on a silica gel column (30x5cm) using 3% methanol in dichloromethane as the eluant to give 3-(di-*tert*-butoxycarbonylamino)-1-methylpiperidine (1.331g, 52%): FABMS: m/z 329.2 (MH^+); HRFABMS: m/z 329.2438 (MH^+). Calcd. for $C_{17}H_{33}N_2O_4$: m/z 329.2440; δ_H ($CDCl_3$) 1.10 (1H, m, CH_2), 1.54 (18H, s, $-COOC(CH_3)_3$), 1.86 (2H, m, CH_2), 2.01 (1H, m, CH_2), 2.19 (1H m, CH), 2.34 (2H, bm, CH_2), 2.59 (3H, $-NCH_3$), 3.19 (2H, m, CH_2) and 3.52/3.52 ppm (2H, $-CH_2N-$); δ_C ($CDCl_3$) CH_3: 28.5, 28.5, 28.5, 28.5, 28.5, 28.5, 47.2; CH_2: 25.4, 28.3, 50.4, 56.8, 60.8; CH: 37.2; C: 83.0, 83.0,153.5, 153.5.

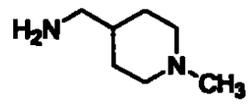
A. 3-(AMINOMETHYL)-1-METHYLPIPERIDINE



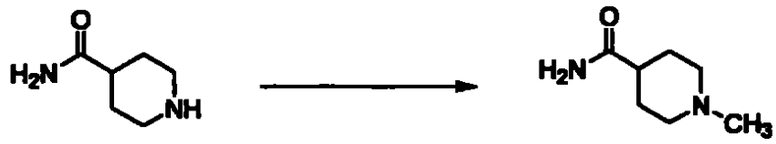
3-(Di-*tert*-butoxycarbonylamino)-1-methylpiperidine (500mg, 1.52mmoles) (from Preparative Example 244, Step B above) was dissolved in methanol (7.5mL) and 10% (v/v) conc. sulfuric acid in 1,4-dioxane (19.75mL) was added. The solution was stirred at 25°C for 0.5h. Methanol (300mL) was added, followed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

PREPARATIVE EXAMPLE 245:

4-(AMINOMETHYL)-1-METHYLPIPERIDINE

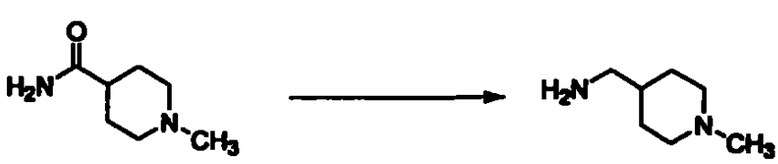


A. 1-METHYLISONIPECOTAMIDE



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

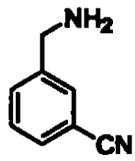
B. 4-(AMINOMETHYL)-1-METHYLPIPERIDINE



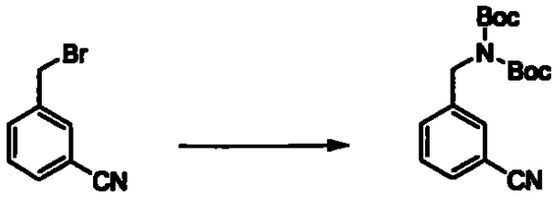
1-Methylisonipecotamide (6.75g, 47.5mmoles) (prepared as described in Preparative Example 245, Step A above) was dissolved in anhydrous THF (350mL) and the resulting mixture was added in portions to a stirred slurry of lithium aluminum hydride (1.8g, 47.5mmoles) in anhydrous THF (100mL) at 0°C under nitrogen. The mixture was stirred at 0°C for 30min and then heated at 66°C for 25h under nitrogen. Distilled water (1.88mL) was added dropwise to the stirred mixture at 0°C, followed by 20% aqueous sodium hydroxide (1.42mL) and then distilled water (6.75mL) and the mixture was stirred for 15min. The mixture was filtered and the solids were washed with THF and dichloromethane. The combined filtrates were evaporated to dryness and chromatographed on a silica gel column (30x5cm) using 15%-20% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give 4-(aminomethyl)-1-methylpiperidine (0.678g, 11%): FABMS: m/z 129.1 (MH^+); HRFABMS: m/z 129.1389 (MH^+). Calcd. for $C_7H_{17}N_2$: m/z 129.1392; δ_H (d_6-DMSO): 2.08ppm (3H, s, $-NCH_3$); δ_C (d_6-DMSO): CH_3: under DMSO peaks; CH_2: 29.6, 29.6, 46.7, 55.2, 55.2; CH: 46.2.

PREPARATIVE EXAMPLE 246:

3-(AMINOMETHYL)BENZONITRILE



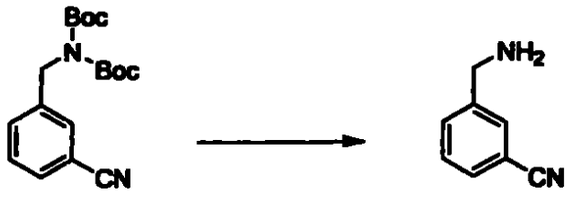
A. 3-(Di-*tert*-BUTOXYCARBONYLAMINO)BENZONITRILE



3-(Bromomethyl)benzonitrile (5g, 25.5mmoles) and di-tert-butyliminodicarboxylate (5.54g, 25.5mmoles) were dissolved in anhydrous THF

(50mL) and cesium carbonate (16.62g, 25.5mmoles) and lithium iodide (170.5mg, 1.275mmoles) were added. The mixture was stirred at 70°C for 22h and the reaction was worked up as described in Preparative Example 89, Step B above. The residue was chromatographed on a silica gel column (60x5cm) using 5% ethyl acetate in hexane as the eluant to give 3-(di-*tert*-butoxycarbonylamino)benzonitrile (7.39g, 87%): FABMS: m/z 333.2 (MH^+); HRFABMS: m/z 333.1815 (MH^+); Calcd. for $C_{18}H_{25}N_2O_4$: m/z 333.1814; δ_H ($CDCl_3$) 1.52 (18H, s, -COOC(CH_3)$_3$), 4.84 (2H, s, CH_2), 7.48 (1H, m, Ar-H), 7.60 (2H, m, Ar-H) and 7.65 ppm (1H, m, Ar-H); δ_C ($CDCl_3$) CH_3: 28.1, 28.1, 28.1, 28.1, 28.1, 28.1; CH_2: 48.4; CH: 129.2, 131.0, 131.0, 131.9; C: 83.2, 83.2, 112.5, 118.8, 140.1, 152.5, 152.5.

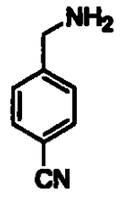
B. 3-(AMINOMETHYL)BENZONITRILE



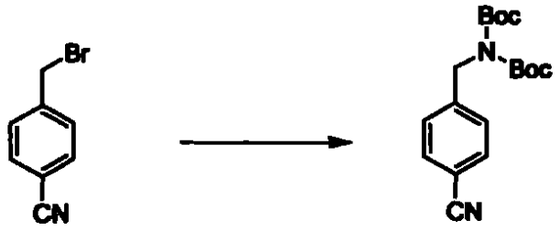
3-(Di-*tert*-butoxycarbonylamino)benzonitrile (2g, 6.0mmoles) (prepared as described in Preparative Example 246, Step A above) was dissolved in methanol (30mL) and 10%(v/v) (10% conc. sulfuric acid in 1,4-dioxane) (79mL) was added. The solution was stirred at 25°C for 0.25h and worked up as described in Preparative Example 89, Step C above). The residue was chromatographed on a silica gel column (15x5cm) using 3% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give the title compound (651.4mg, 82%): FABMS: m/z 133.1 (MH^+); HRFABMS: m/z 133.0762 (MH^+). Calcd. for $C_8H_9N_2$: m/z 133.0766 ; δ_H ($CDCl_3$) 2.57 (2H, s, -CH_2NH_2), 3.92 (2H, s, -CH_2NH_2). 7.46 (1H, m, Ar-H), 7.57 (2H, m, Ar-H) and 7.64 ppm (1H, m, Ar-H); δ_C ($CDCl_3$) CH_2: 45.2; CH: 129.4, 130.7, 130.7, 131.8; C: 112.4, 118.8, 143.8.

PREPARATIVE EXAMPLE 247:

4-(AMINOMETHYL)BENZONITRILE

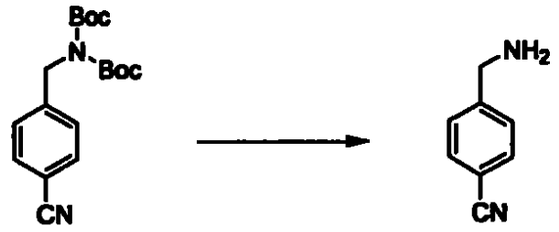


A. 3-(Di-*tert*-BUTOXYCARBONYLAMINOMETHYL)BENZONITRILE



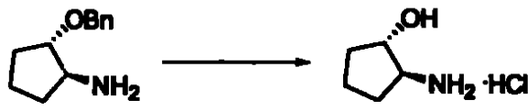
4-(Bromomethyl)benzonitrile (5g, 25.5mmoles) and di-tert-butyliminodicarboxylate (5.54g, 25.5mmoles) were dissolved in anhydrous THF (50mL) and cesium carbonate (16.62g, 25.5mmoles) and lithium iodide (170.5mg, 1.275mmoles) were added. The mixture was stirred at 70°C for 23h and the reaction was worked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

B. 4-(AMINOMETHYL)BENZONITRILE



4-(Di-*tert*-butoxycarbonylaminomethyl)benzonitrile (2g, 6.0mmoles) (prepared as described in Preparative Example 247, Step A above) was dissolved in TFA (4mL) and the solution was stirred at 25°C for 0.25h. The reaction mixture was diluted with dichloromethane and extracted with 1N sodium hydroxide. The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness. The residue was chromatographed on a silica gel column (15x5cm) using 3% (10% conc. ammonium hydroxide in methanol)-dichloromethane as the eluant to give 4-(aminomethyl)benzonitrile (108mg, 68%): FABMS: m/z 133.1 (MH^+); HRFABMS: m/z133.0764 (MH^+). Calcd. for $C_8H_9N_2$: m/z 133.0766; δ_H ($CDCl_3$) 2.04 (2H, s, $-CH_2N\underline{H}_2$), 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

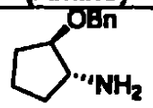
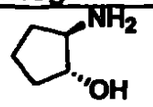
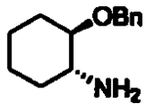
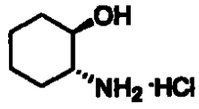
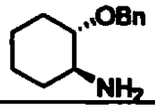
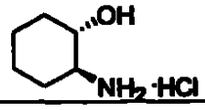


To a solution of (1*S*,2*S*)-2-benzyloxycyclopentyl amine (1.5 g, 7.84 mmol) in MeOH (50 mL) at rt was added 10 % Pd/C (50% wet, 1.0 g) followed by dropwise addition of conc. HCl (0.7 mL). The mixture was stirred under a balloon of H_2 for 14 h and the catalyst was filtered off thru a pad of Celite.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

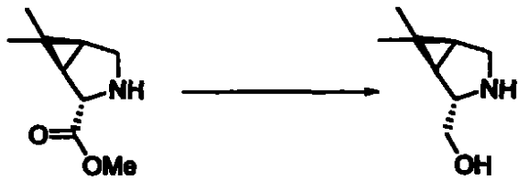
PREPARATIVE EXAMPLES 249-251

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

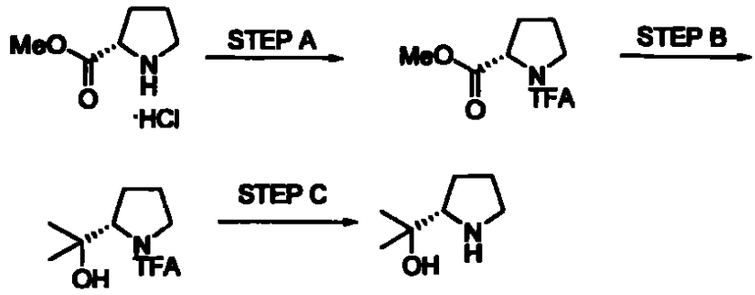
Ex.	Column 2 (Amine)	Column 3 (Cleavage method)	CMPD M+H
249			M+H = 102 (free base)
250			M+H = 116 (free base)
251			M+H = 116 (free base)

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 (85%) of a yellow/orange solid. M+H = 142.

PREPARATIVE EXAMPLE 253



STEP A:

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

STEP B:

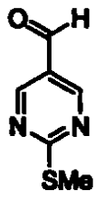
To a solution of the compound prepared in Preparative Example 253, Step A (0.68 g, 3.0 mmol) in THF (20 mL) at 0 °C was added MeMgI (5.1 mL, 3.0M in Et_2O) dropwise over 10 min. The resulting solution was stirred for 16 h at rt whereupon the mixture was quenched by addition of sat. aq. NH_4Cl. The mixture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

STEP C:

To a solution of the compound prepared in Preparative Example 253, Step B (0.68 g, 3.0 mmol) in MeOH (5 mL) was added a solution of KOH (0.68 g, 12.1 mmol) in MeOH (5 mL). The mixture was stirred at reflux for 12h and rt for 72h whereupon the mixture was concentrated to dryness. The crude residue

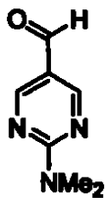
was suspended in EtOAc (50 mL) and was stirred vigorously for 30 min and was filtered. This procedure was repeated 2X more and the resultant filtrate was concentrated under reduced pressure to afford 128 mg (33%) of a maroon/orange oil. M+H = 130. This material was used without purification in the subsequent coupling step.

PREPARATIVE EXAMPLE 254:



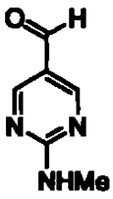
The aldehyde was prepared according to the procedure of Gupton (*J. Heterocyclic Chem.* (1991), *28*, 1281).

PREPARATIVE EXAMPLE 255



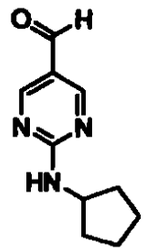
Using the aldehyde from Preparative Example 254, the procedure of Gupton (*J. Heterocyclic Chem.* (1991), *28*, 1281) was employed to prepare the title aldehyde.

PREPARATIVE EXAMPLE 256



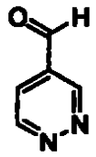
The title aldehyde was prepared according to the procedure of Ragan et. al *Synlett* (2000), *8*, 1172-1174.

PREPARATIVE EXAMPLE 257



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

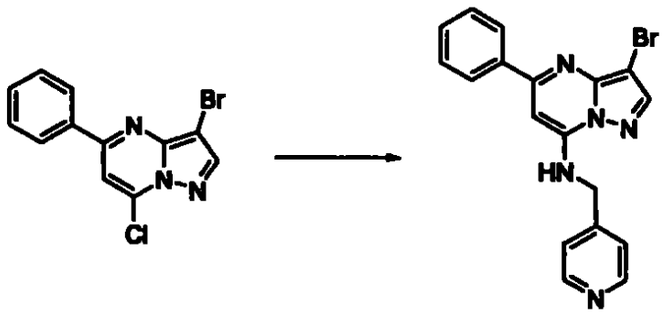
PREPARATIVE EXAMPLE 258



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

EXAMPLES

EXAMPLE 1:

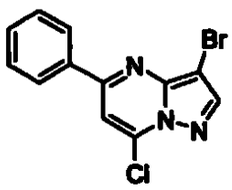
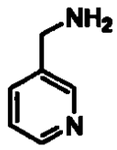
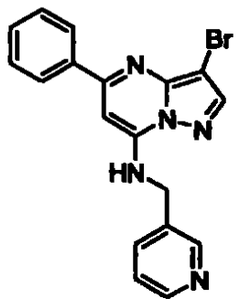
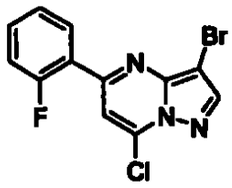
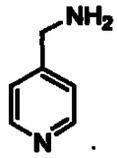
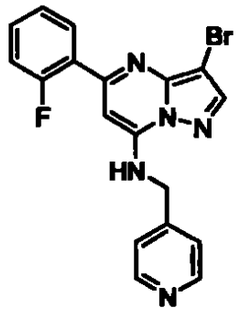
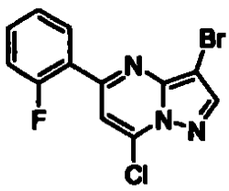
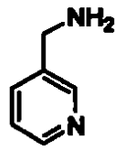
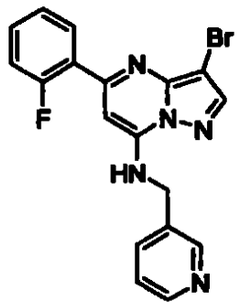


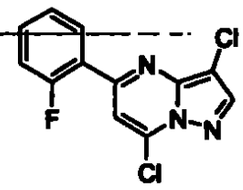
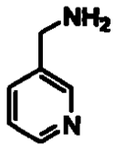
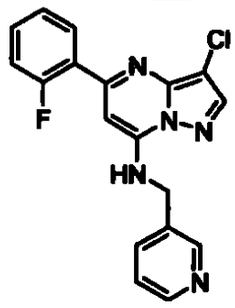
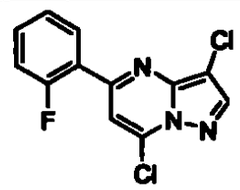
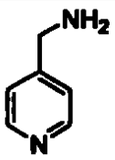
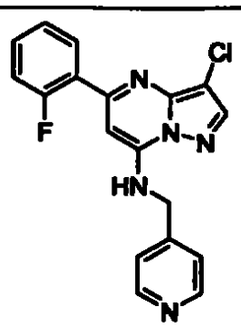
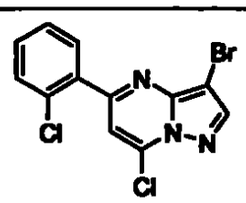
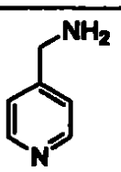
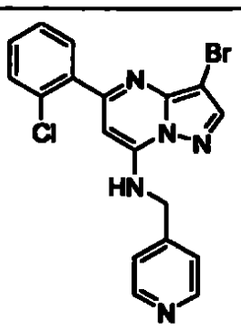
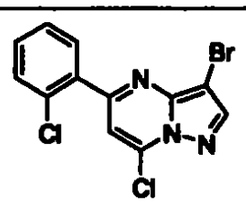
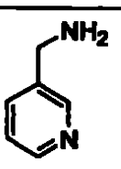
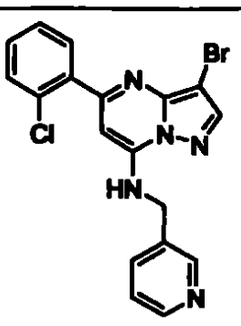
A solution of the product from Preparative Example 127 (0.27 g, 0.875 mmol), 4-aminomethylpyridine (0.12 g, 1.3 eq.), and K_2CO_3 (0.24 g, 2 eq.) in CH_3CN (5 mL) was stirred at room temperature 48 hours. The reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organics were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

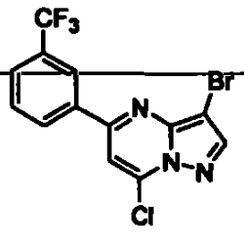
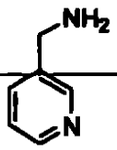
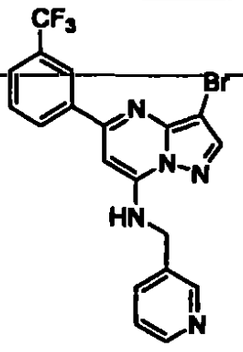
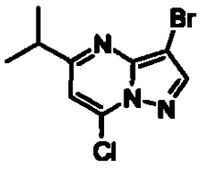
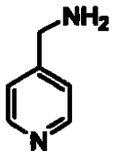
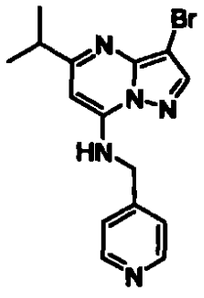
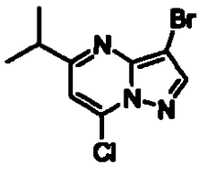
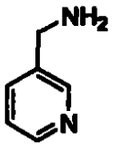
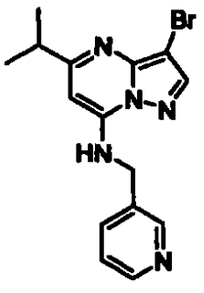
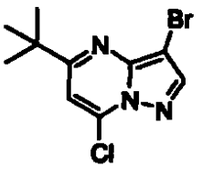
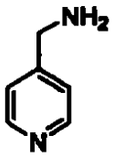
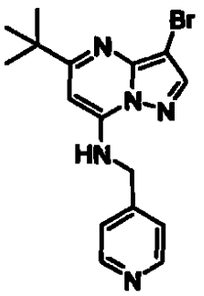
EXAMPLES 2-210:

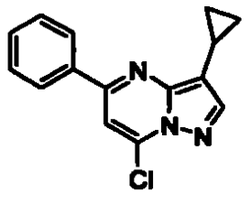
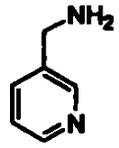
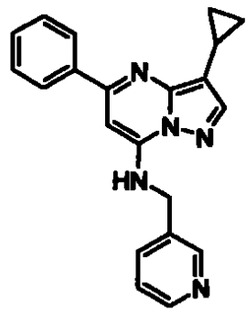
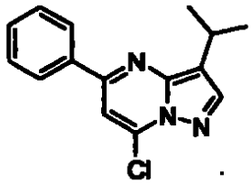
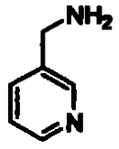
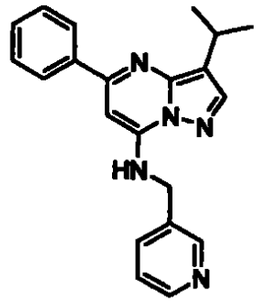
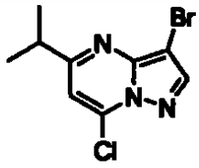
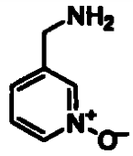
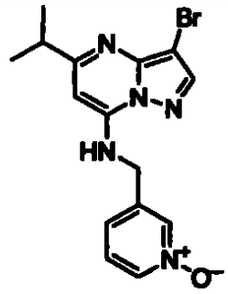
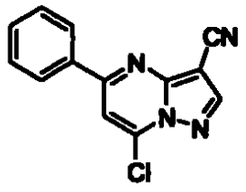
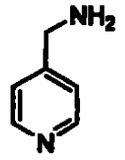
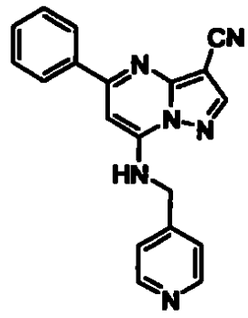
By following essentially the same procedure set forth in Example 1 only substituting the chlorides shown in Column 2 of Table 18 and the amines shown in Column 3 of Table 18, the compounds in Column 4 of Table 18 were prepared:

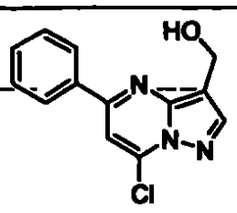
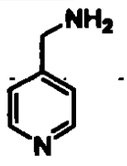
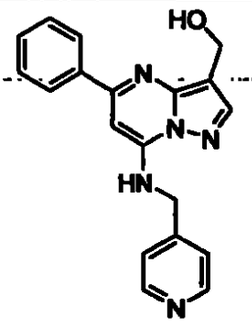
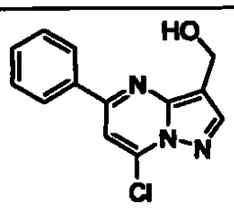
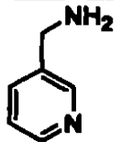
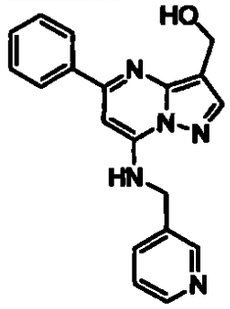
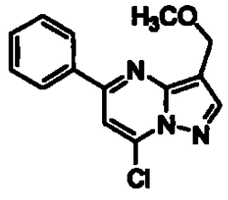
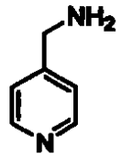
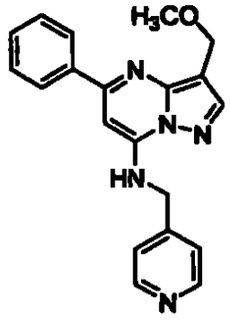
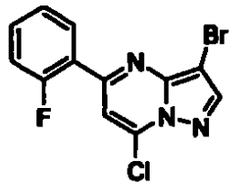
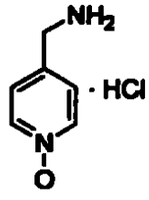
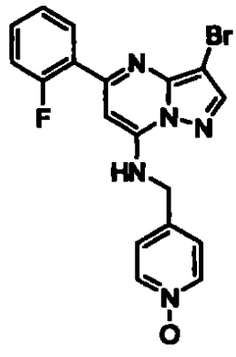
TABLE 18

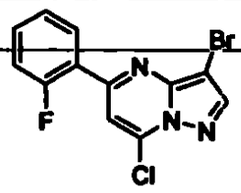
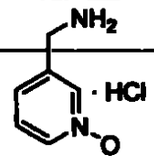
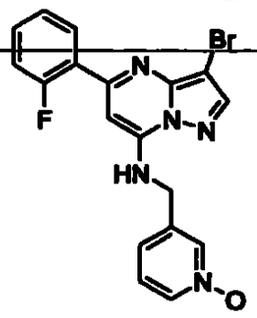
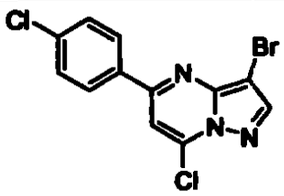
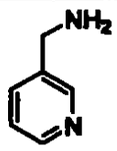
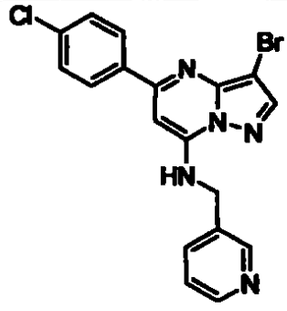
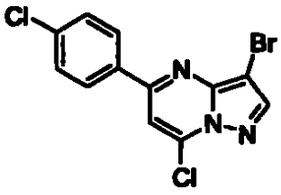
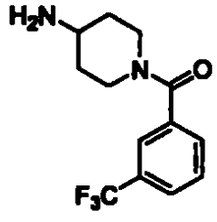
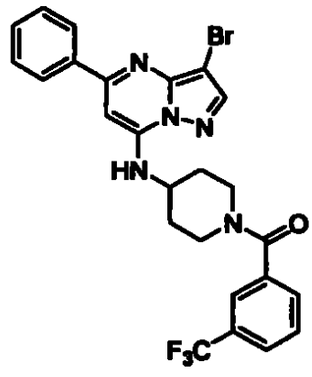
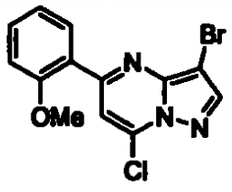
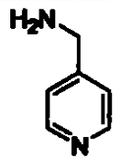
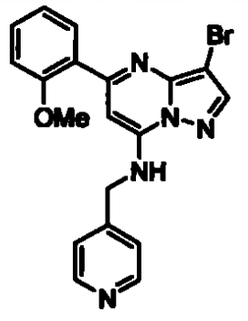
Ex.	Column 2	Column 3	Column 4	Data
2				LCMS: MH^+= 380; mp=175-176°C
3				LCMS: MH^+= 398; mp= 156-157°C
4				LCMS: MH^+= 398; mp= 45-49°C

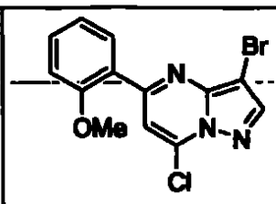
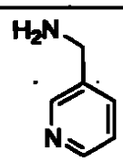
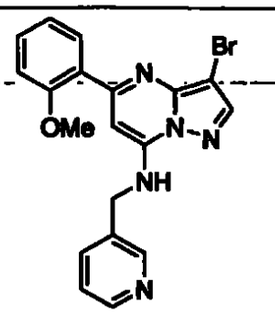
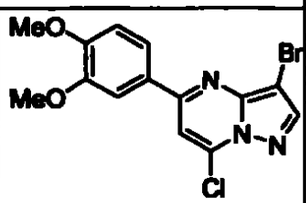
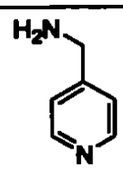
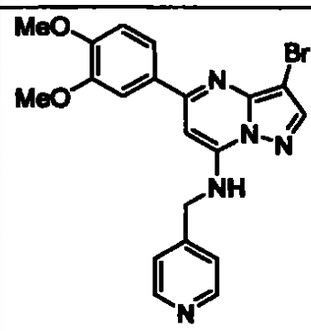
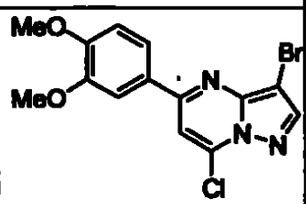
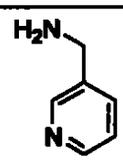
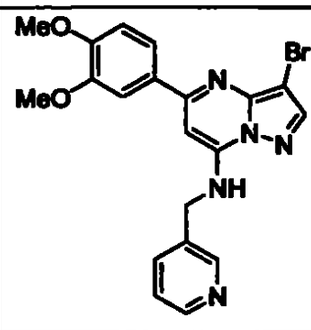
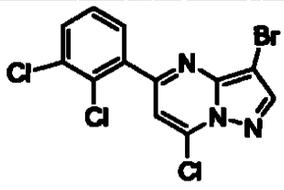
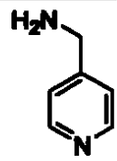
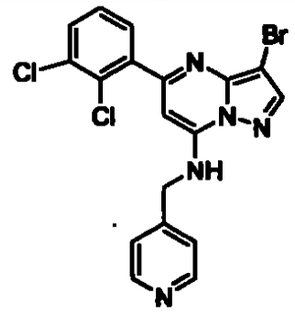
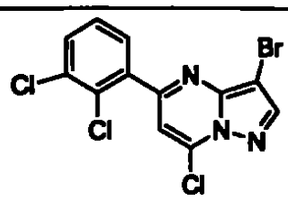
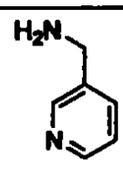
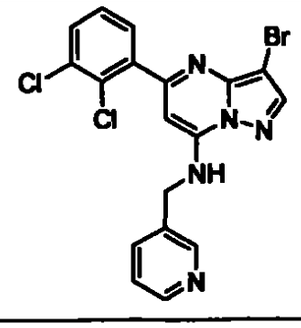
5				LCMS: MH^+= 354; mp= 43-46°C
6				LCMS: MH^+= 354; mp= 149-150°C
7				LCMS: MH^+= 414; mp= 86-92°C
8				LCMS: MH^+= 414; mp= 185-186°C

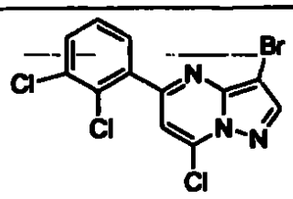
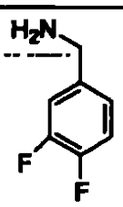
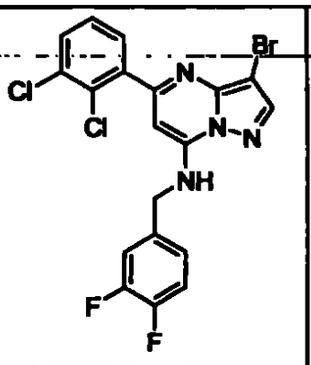
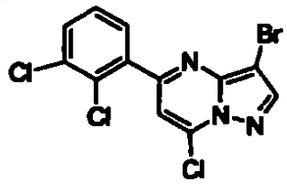
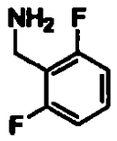
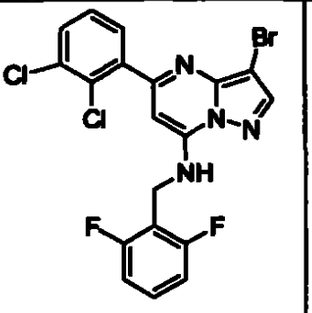
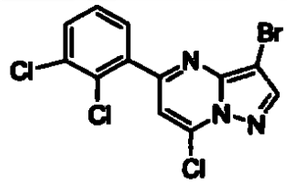
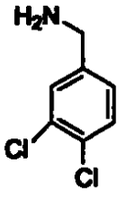
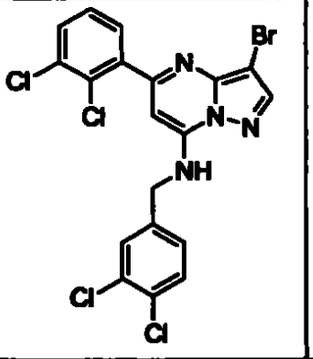
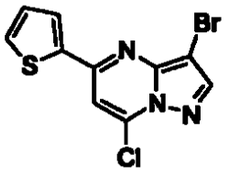
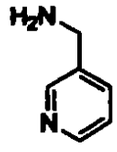
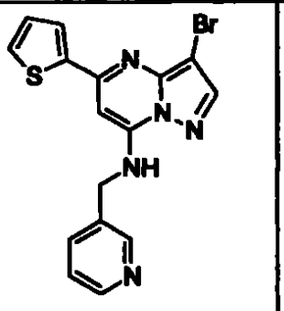
9				LCMS: MH$^+$= 448; mp= 167-168°C
10				LCMS: MH$^+$= 346; mp= 57-58°C
11				LCMS: MH$^+$= 347; mp=122.9-125.3 °C
12				LCMS: MH$^+$= 360; mp= 127-128°C

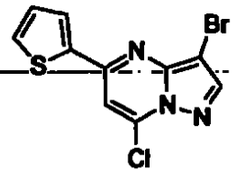
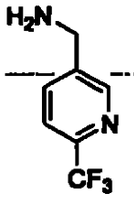
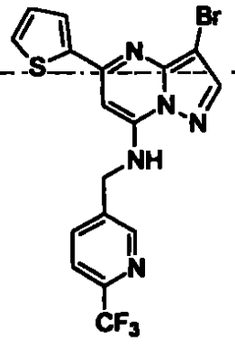
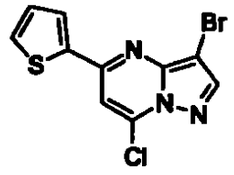
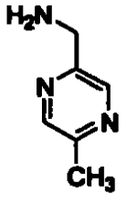
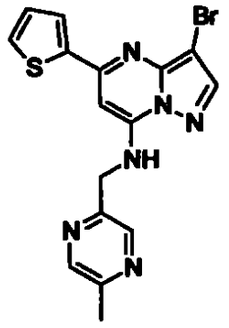
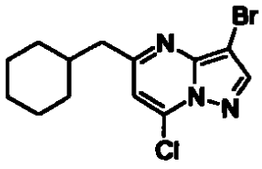
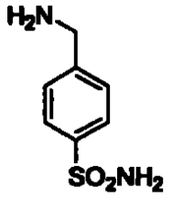
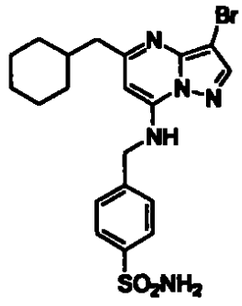
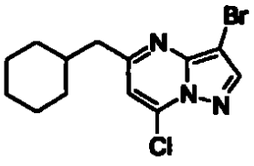
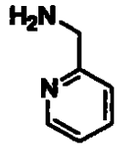
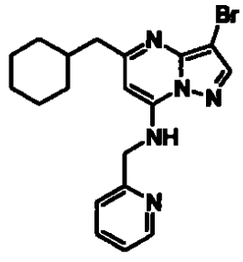
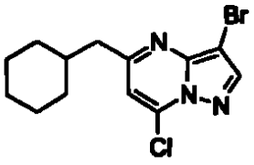
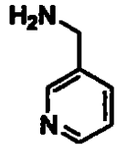
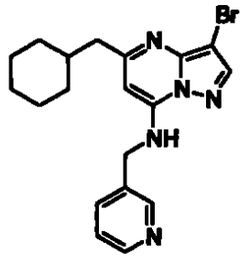
13				LCMS: MH^+= 342; mp= 133-135°C
14				LCMS: MH^+= 344; mp= 152-155°C
15				LCMS: MH^+= 362; mp= 164-167°C
16				LCMS: MH^+= 327; mp= 146-155°C

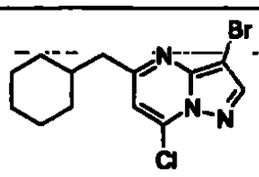
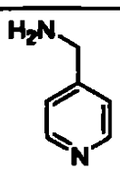
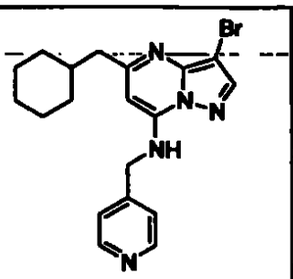
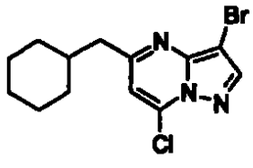
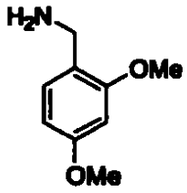
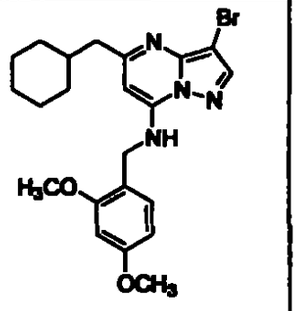
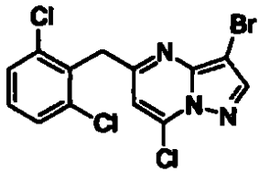
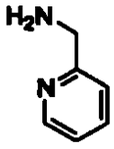
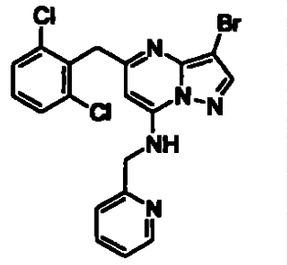
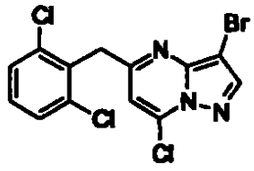
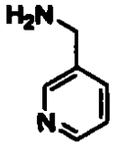
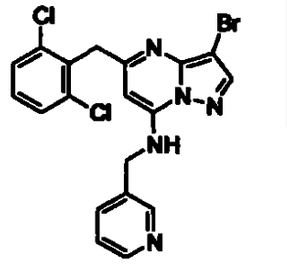
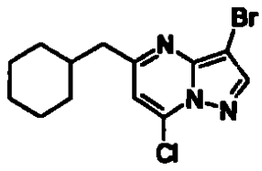
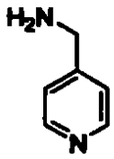
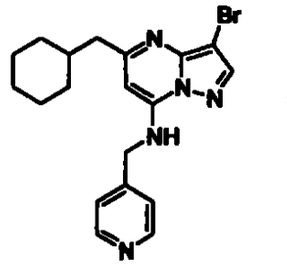
17				LCMS: MH^+= 332; mp= 71-82°C
17.1				MS: MH^+ = 332.
18				LCMS: MH^+= 346; mp= 58-65°C
19				LCMS: MH^+= 414; mp= 211-213°C

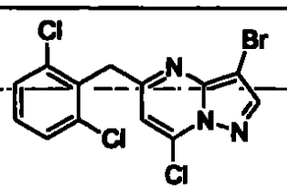
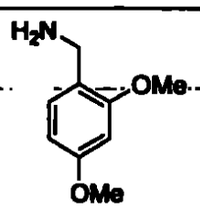
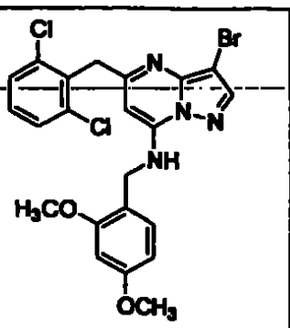
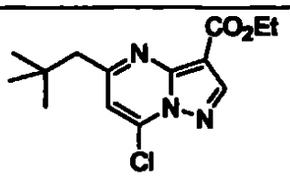
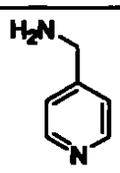
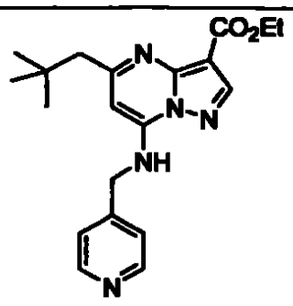
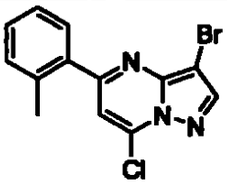
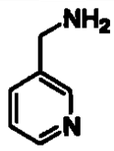
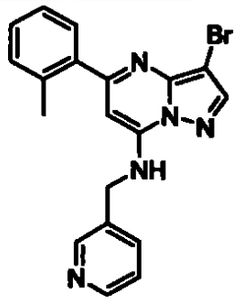
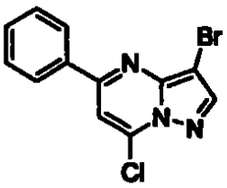
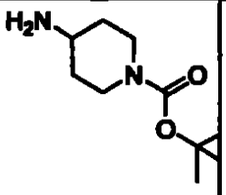
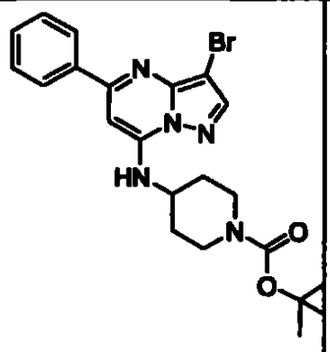
20				LCMS: MH^+= 414; mp= 194-197°C
21				MS: MH^+ = 414 m.p. 211 – 216°C
22				LCMS: MH^+= 544; mp= 104-107°C
23				Yield = 83% LCMS: MH^+ = 410.

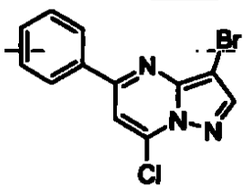
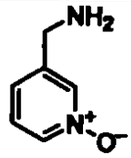
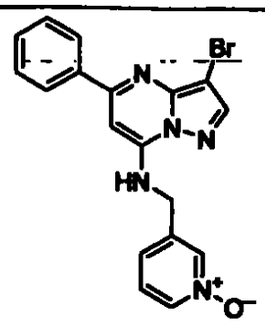
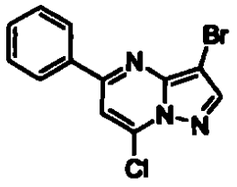
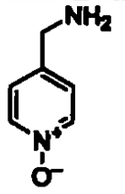
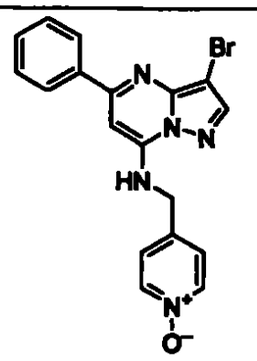
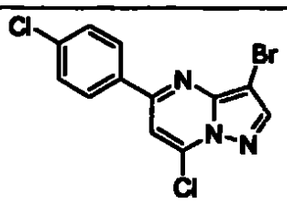
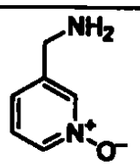
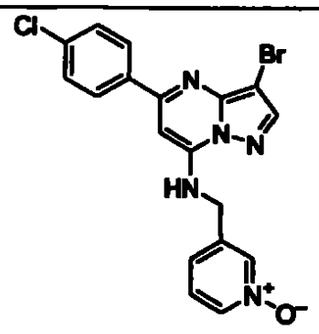
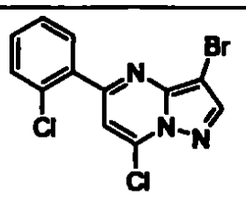
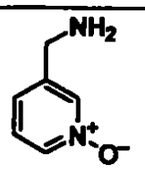
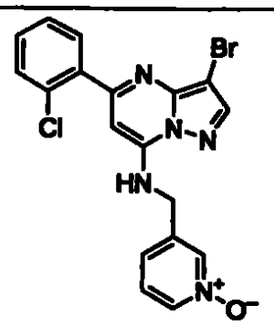
24				Yield = 84% LCMS: MH^+ = 410.
25				Yield = 96% LCMS: MH^+ = 440.
26				Yield = 99% LCMS: MH^+ = 440.
27				Yield = 89% LCMS: MH^+ = 448.
28				Yield = 78% LCMS: MH^+ = 448.

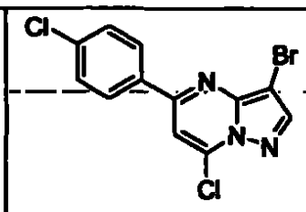
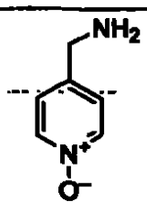
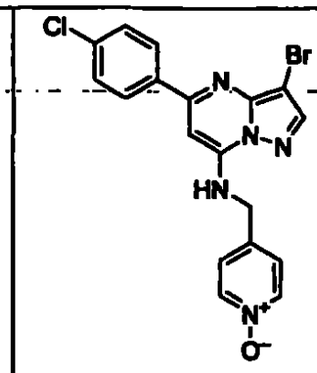
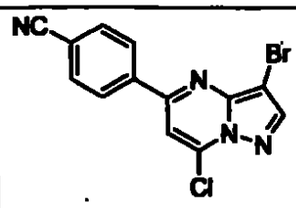
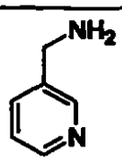
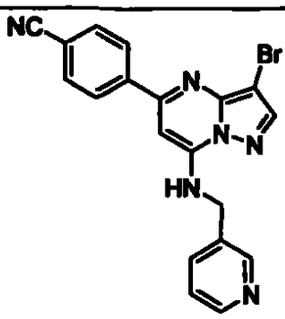
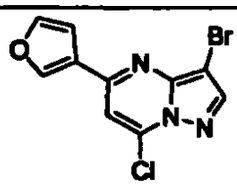
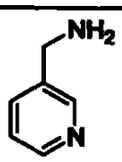
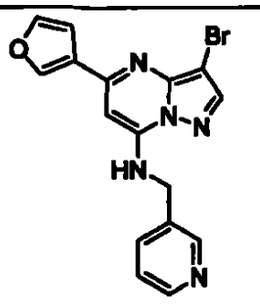
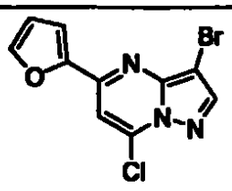
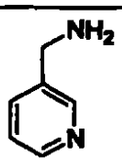
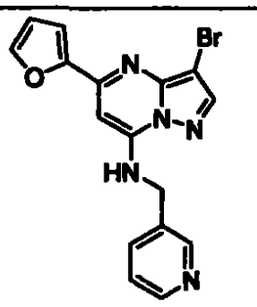
30				Yield = 96% LCMS: MH^+ = 483.
31				Yield = 35% LCMS: MH^+ = 483.
32				Yield = 77% LCMS: MH^+ = 515.
33				Yield = 100% m.p. 179°C LCMS: MH^+ = 388

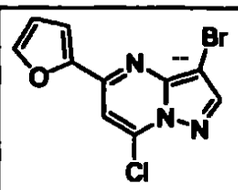
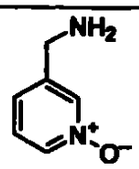
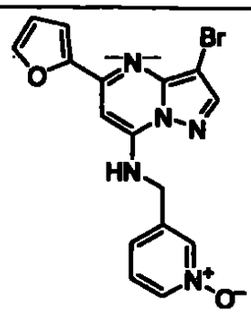
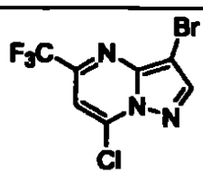
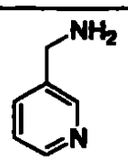
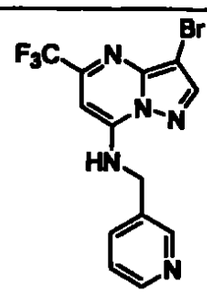
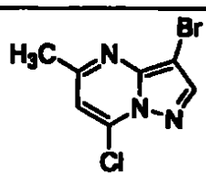
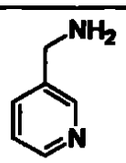
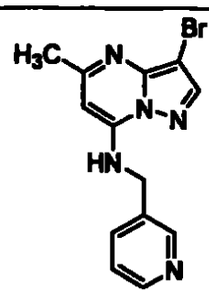
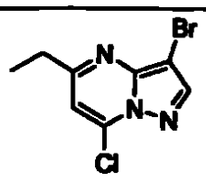
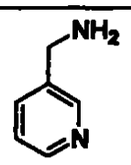
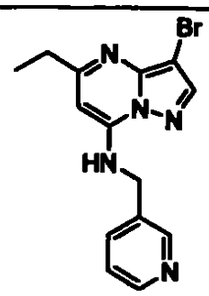
34				Yield = 99% m.p. 186°C LCMS: MH^+ = 456
35				Yield = 98% m.p. 181°C LCMS: MH^+ = 401
36				Yield = 63% m.p. 192°C LCMS: MH^+ = 480
37				Yield = 75% m.p. 126 – 127°C LCMS: MH^+ = 400
38				Yield = 94% m.p. 132 -133°C LCMS: MH^+ = 400

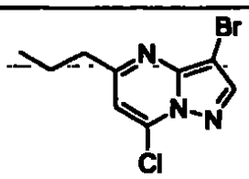
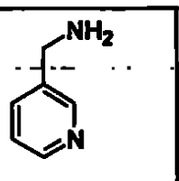
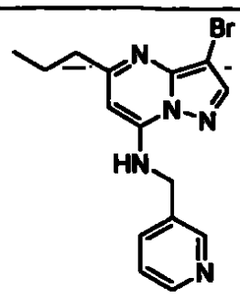
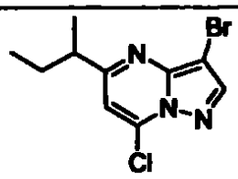
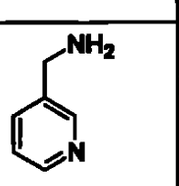
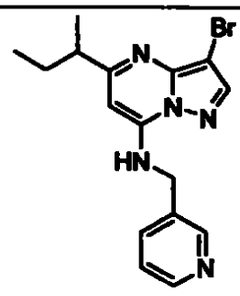
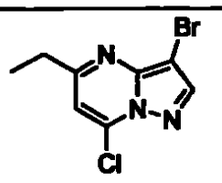
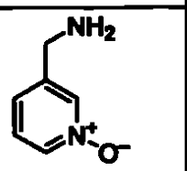
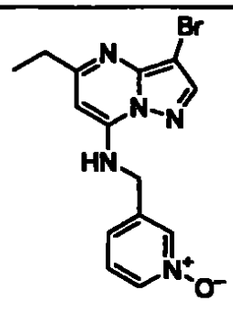
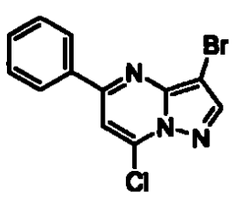
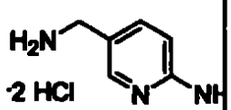
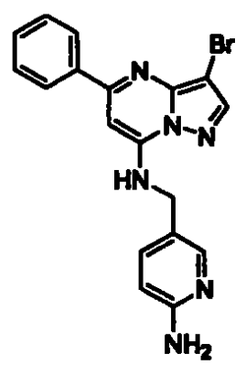
39				Yield = 95% m.p. 121 – 122°C LCMS: MH⁺ = 400
40				Yield = 98% LCMS: MH⁺ = 460
41				Yield = 87% m.p. 170 - 171°C LCMS: MH⁺ = 464
42				Yield = 84% m.p. 216 -217°C LCMS: MH⁺ = 464
43				Yield = 96% m.p. 214°C LCMS: MH⁺ = 464

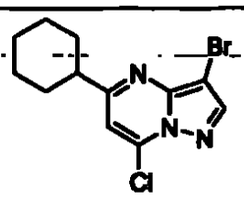
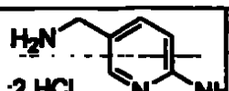
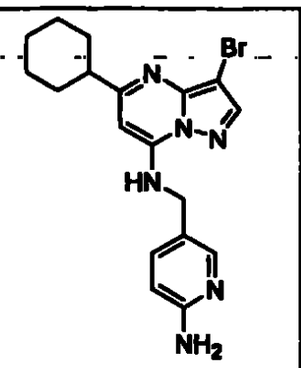
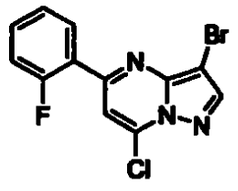
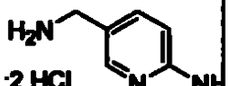
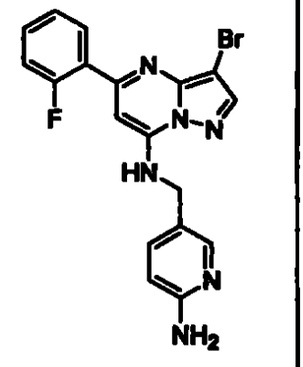
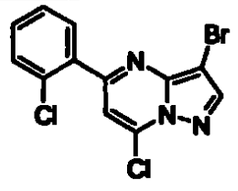
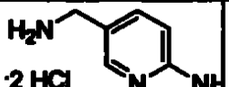
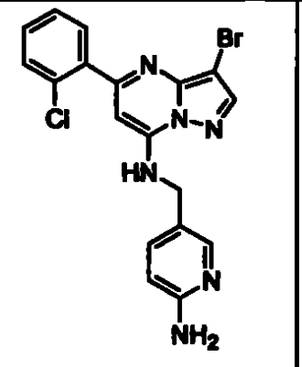
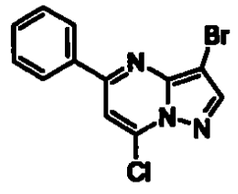
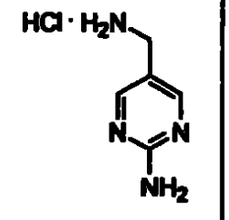
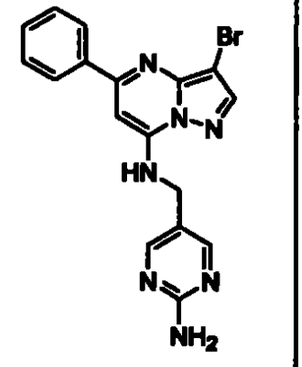
44				Yield = 95% m.p. 158°C LCMS: MH^+ = 522
45				Yield=90 % LCMS: MH^+= 278
46				Yield=100%; LCMS: MH^+=394
47				LCMS: MH+ = 473 m.p. 84 - 87°C

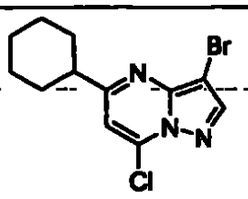
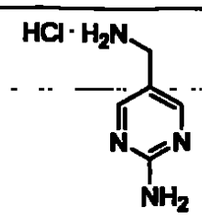
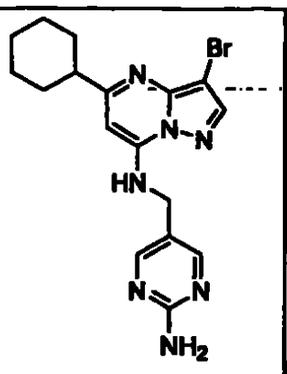
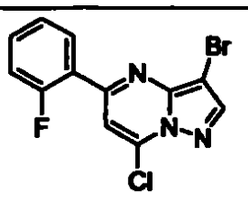
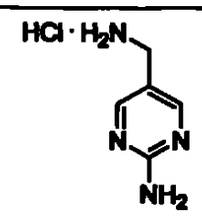
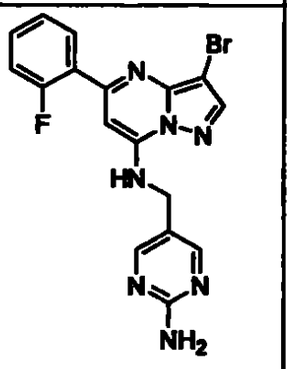
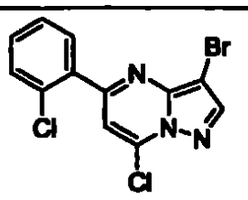
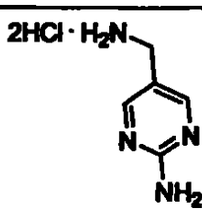
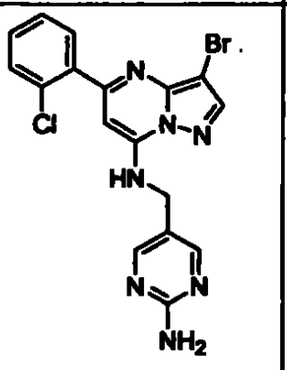
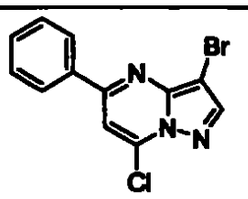
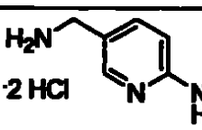
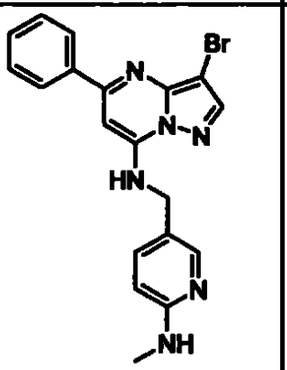
48				MS: MH^+ = 396 m.p. 91.5 – 93.3°C
49				MS: MH^+ = 396 m.p. 196 – 199°C
50				MS: MH^+ = 430 m.p. 242 – 244°C
51				MS: MH^+ = 430 m.p. 218°C

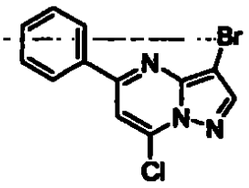
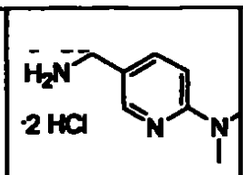
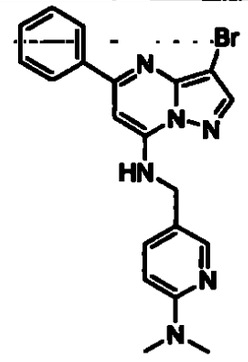
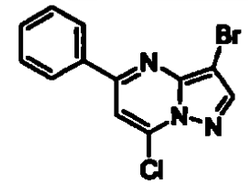
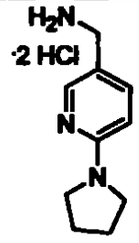
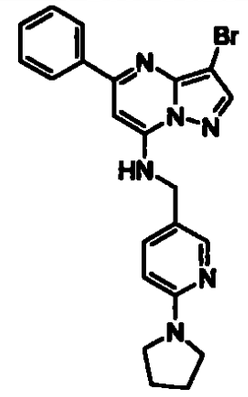
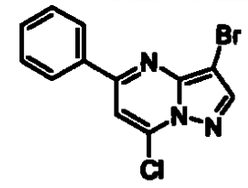
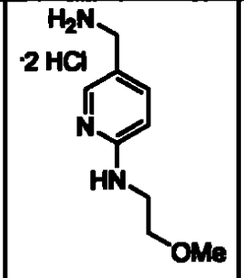
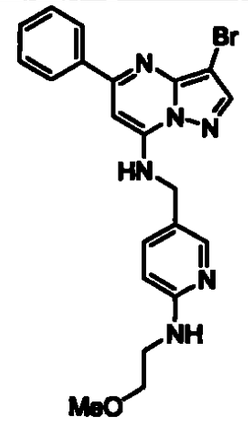
52				MS: MH$^+$ = 430 m.p. 230 – 233°C
54				MS: MH$^+$ = 405 m.p. 185 – 188°C
55				MS: MH$^+$ = 370 m.p. 229 – 232°C
56				MS: MH$^+$ = 370 m.p. 85 – 90°C

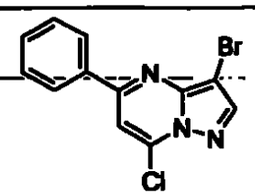
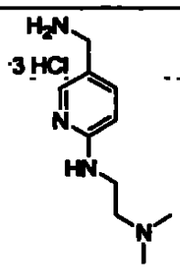
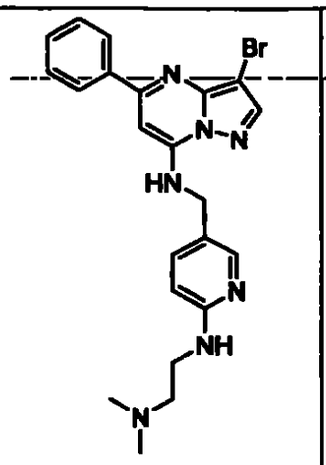
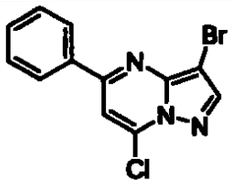
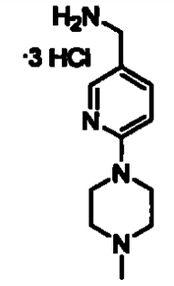
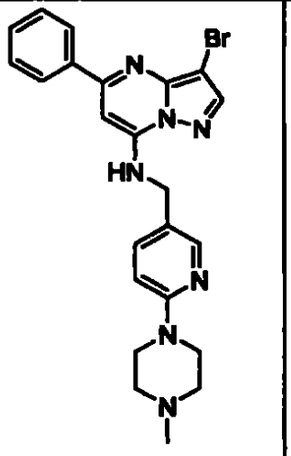
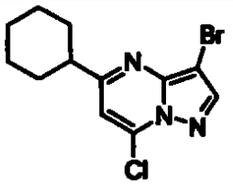
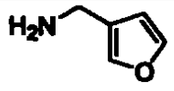
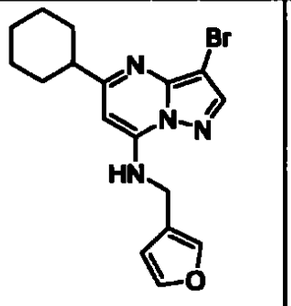
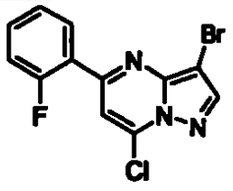
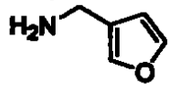
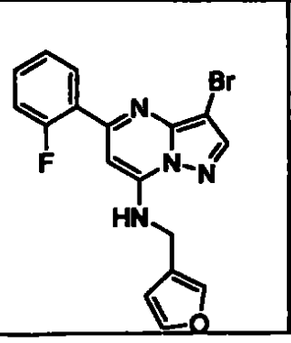
57				MS: MH^+ = 386 m.p. 227 – 230°C
58				MS: MH^+ = 372 m.p. 212 – 215°C
59				MS: MH^+ = 318 m.p. 169 – 171°C
60				MS: MH^+ = 332 m.p. 170 – 173°C

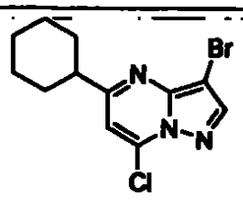
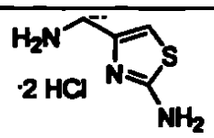
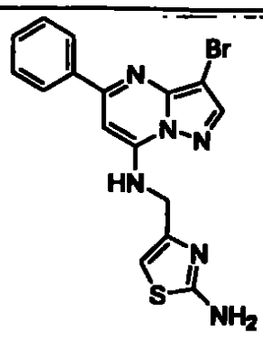
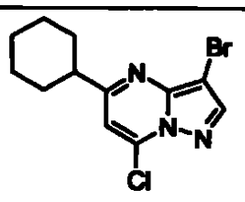
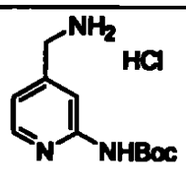
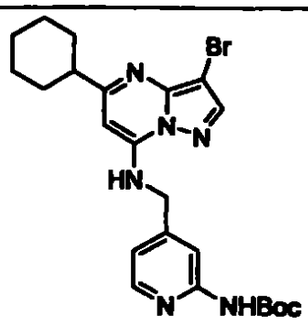
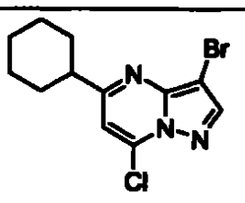
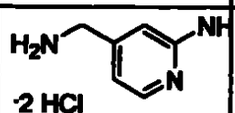
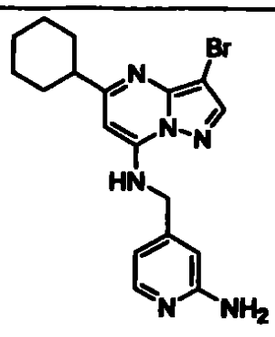
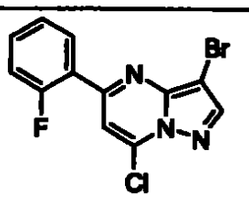
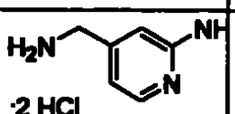
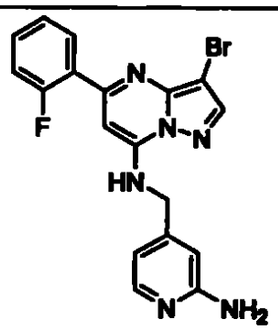
61				MS: MH^+ = 346 m.p. 156 – 159°C
62				MS: MH^+ = 360 m.p. 114 – 116°C
63				MS: MH^+ = 348 m.p. 197 – 200°C
64				1. mp = 230-232 2. M+H = 396

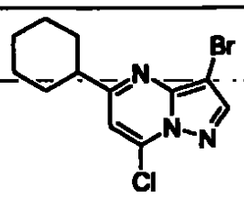
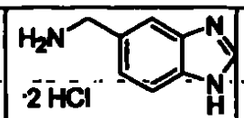
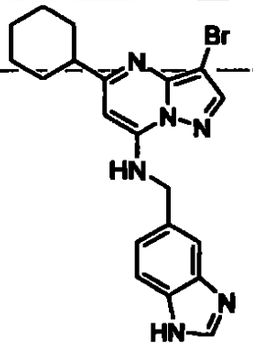
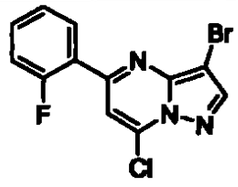
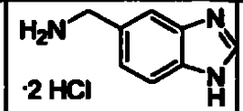
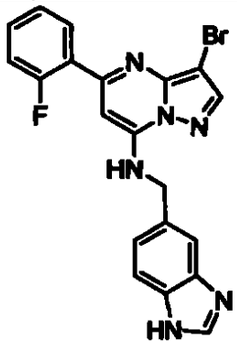
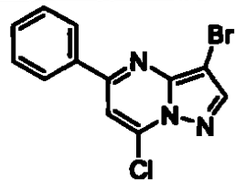
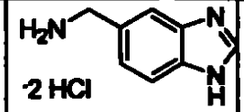
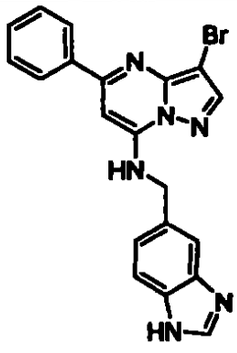
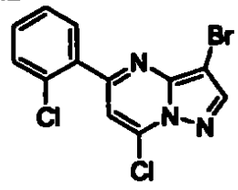
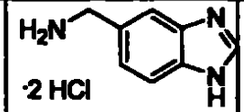
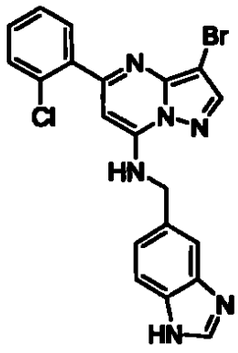
65				1. mp = 205-207 2. M+H = 402
66				1. mp = 220-223 2. M+H = 414
67				1. mp = 191-193 2. M+H = 431
68				1. mp = 235-237 2. M+H = 397

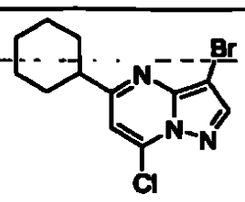
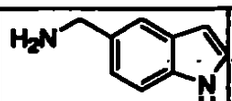
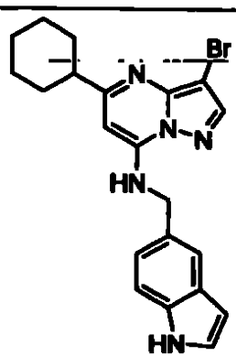
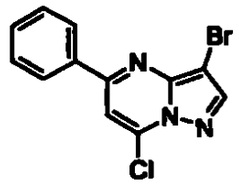
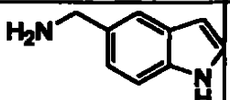
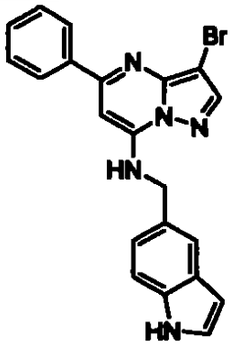
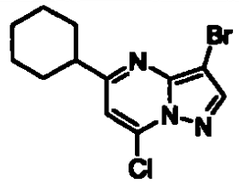
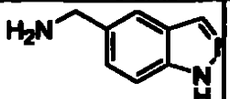
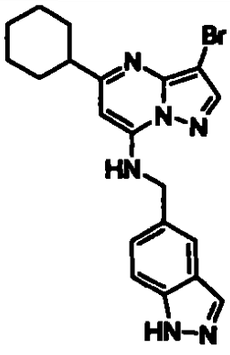
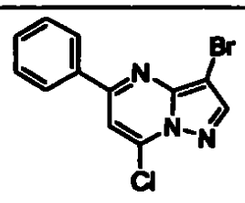
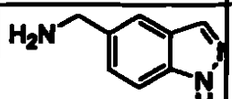
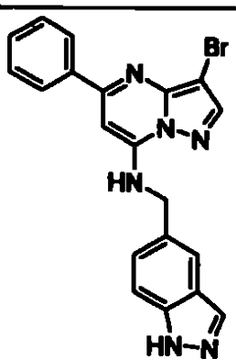
69				1. mp = ≥250 2. M+H = 403
70				1. mp = 230-232 2. M+H = 415
71				1. mp = 235-238 2. M+H = 431
72				1. mp = 186-188 2. M+H = 410

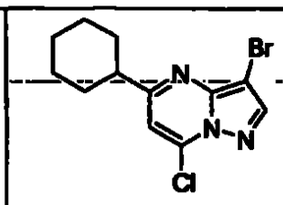
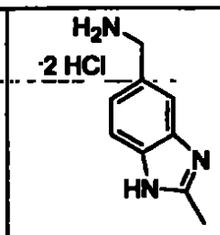
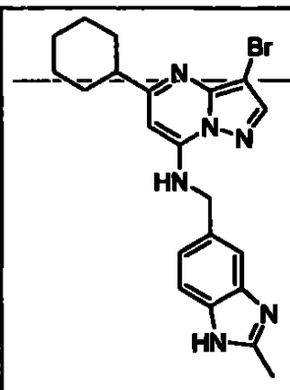
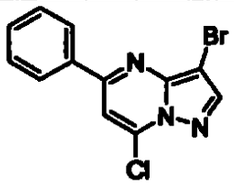
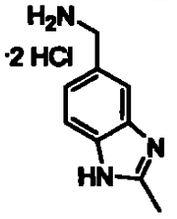
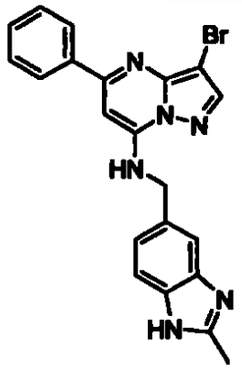
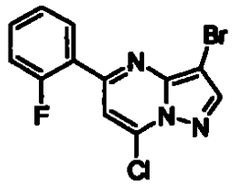
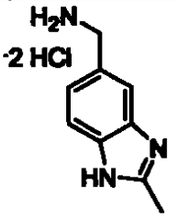
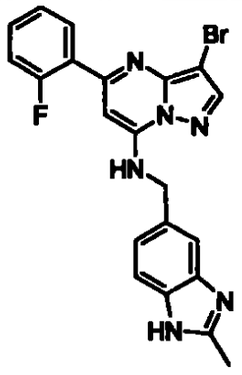
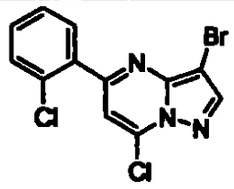
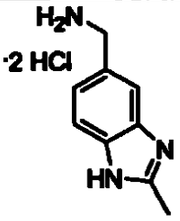
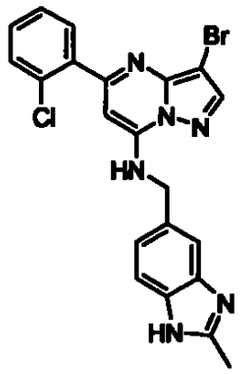
73				1. mp = 136-138 2. M+H = 424
74				1. mp = 192-195 2. M+H = 450
75				1. mp = 88-90 2. M+H = 454

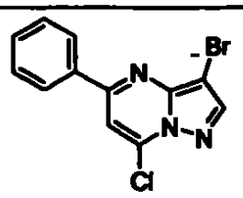
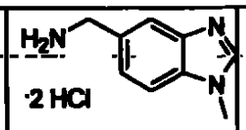
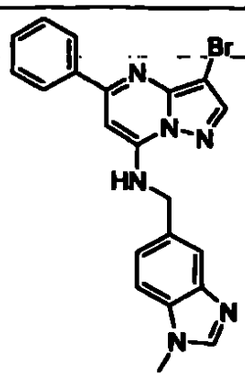
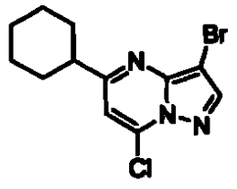
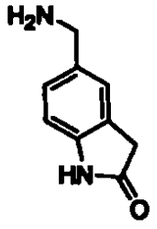
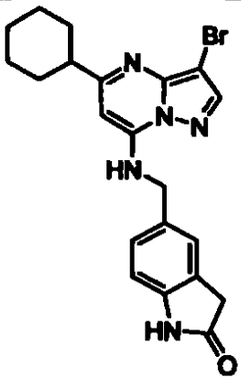
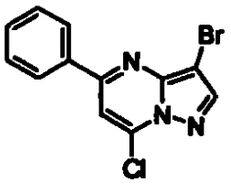
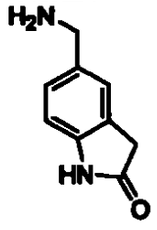
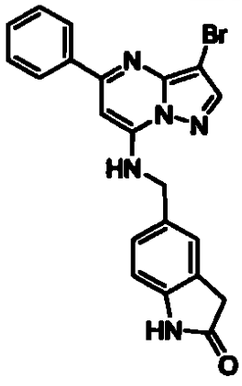
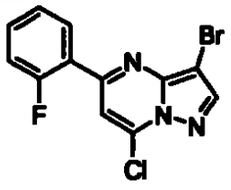
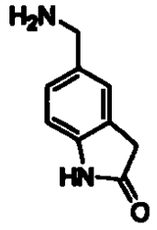
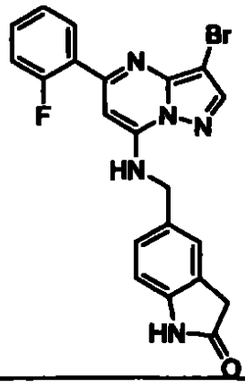
76				1. mp = 230-232 2. M+H = 467
77				1. mp = 131-133 2. M+H = 479
78				1. mp = 85-88 2. M+H = 376
79				1. mp = 131-133 2. M+H = 388

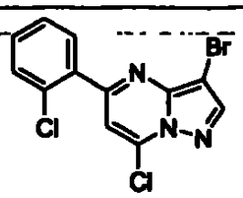
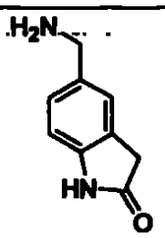
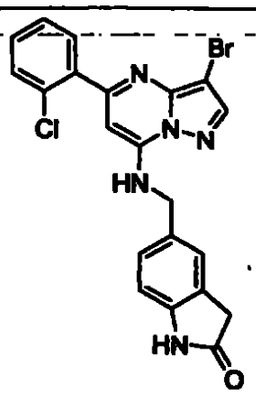
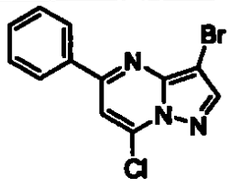
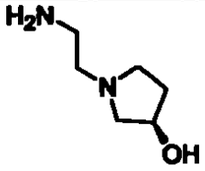
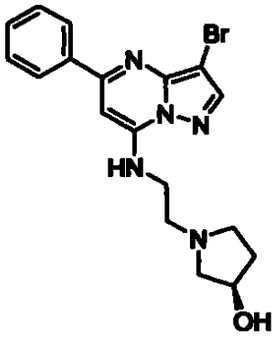
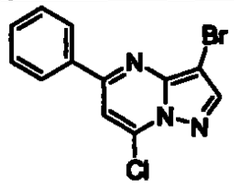
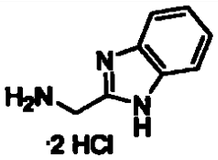
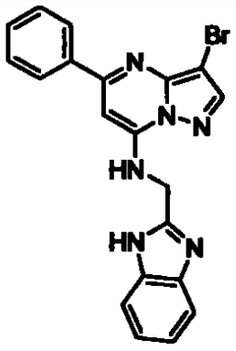
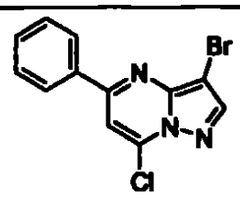
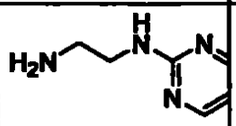
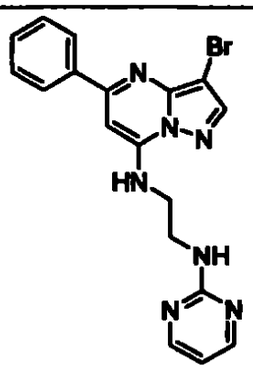
80				1. mp = 206-208 2. M+H = 408
81				1. mp = 108-110 2. M+H = 502
82				1. mp = 83-85 2. M+H = 402
83				1. mp = 220 2. M+H = 414

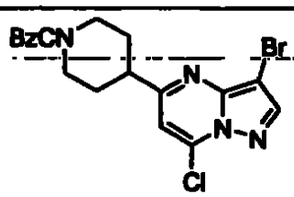
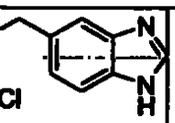
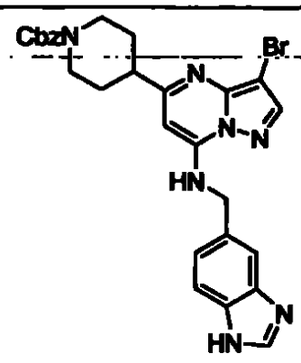
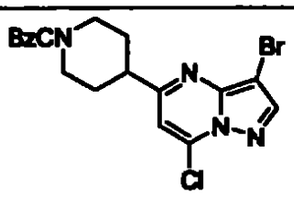
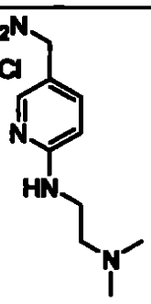
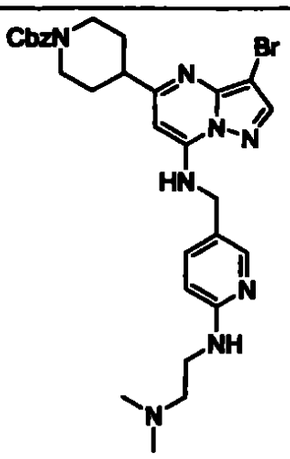
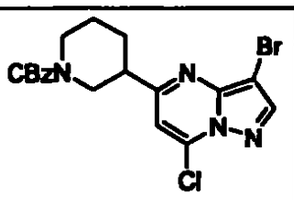
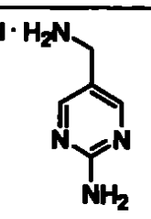
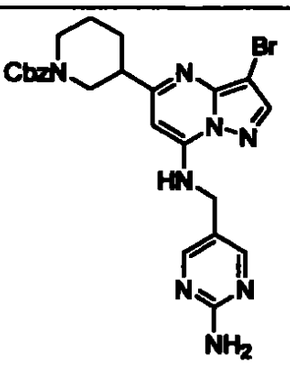
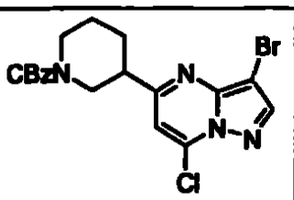
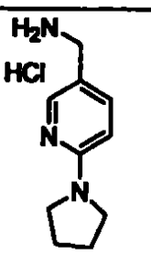
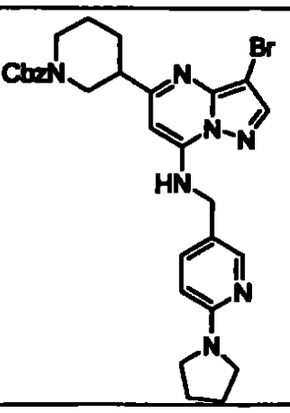
84		 ·2 HCl		1. mp = 154-156 2. M+H = 426
85		 ·2 HCl		1. mp = 152-153 2. M+H = 438
86		 ·2 HCl		1. mp = 159-161 2. M+H = 420
87		 ·2 HCl		1. mp = >220 2. M+H = 455

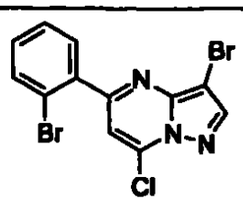
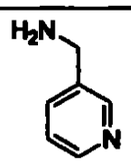
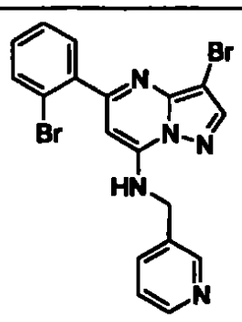
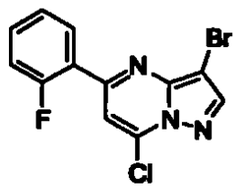
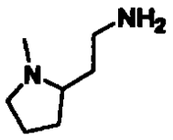
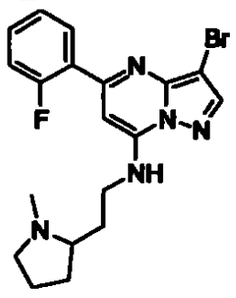
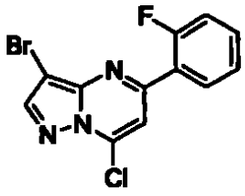
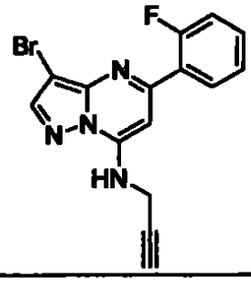
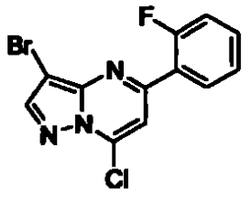
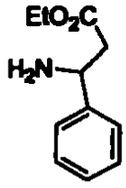
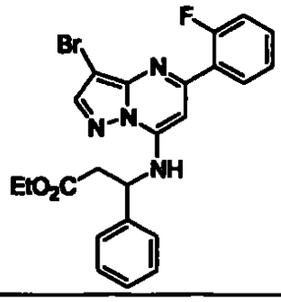
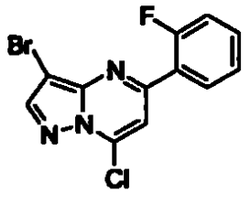
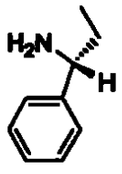
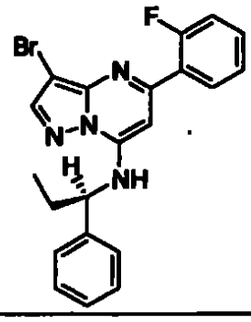
88				1. mp = 223-225 2. M+H = 425
89				1. mp = 199-201 2. M+H = 419
90				1. mp = 184-186 2. M+H = 426
91				1. mp = 196-198 2. M+H = 420

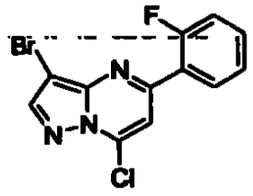
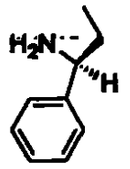
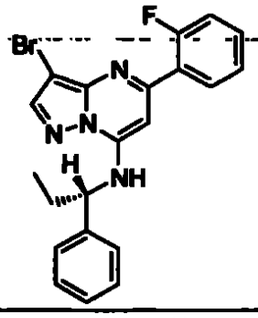
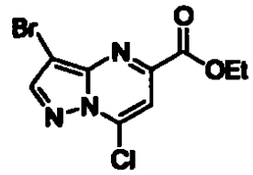
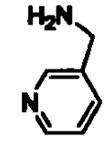
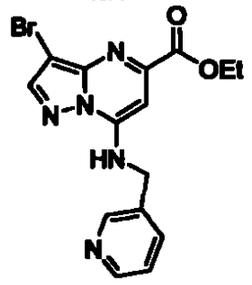
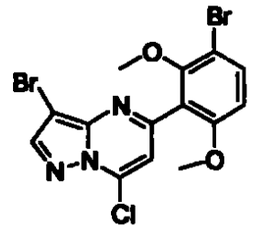
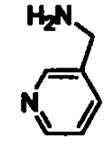
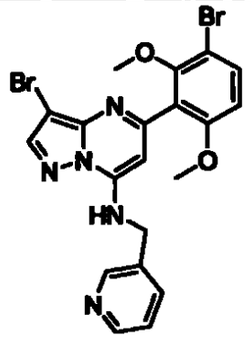
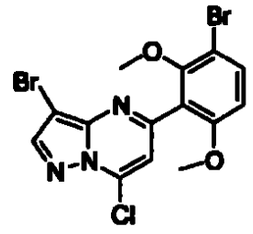
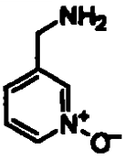
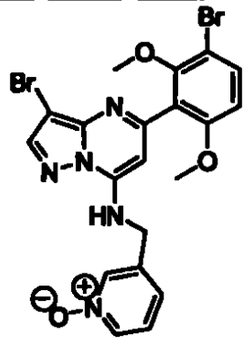
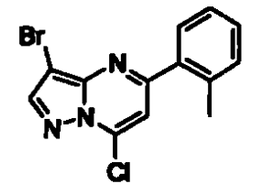
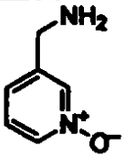
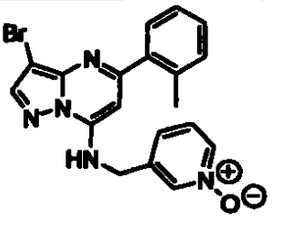
92				1. mp = 156-159 2. M+H = 440
93				1. mp = 173-176 2. M+H = 434
94				1. mp = 173-175 2. M+H = 452
95				1. mp = 174-176 2. M+H = 469

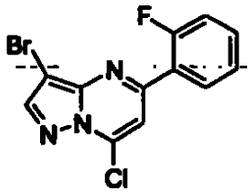
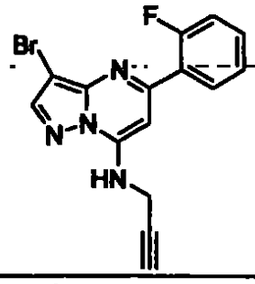
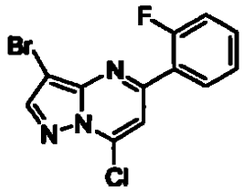
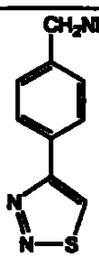
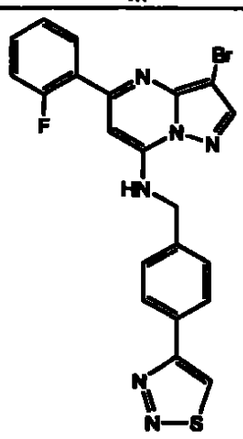
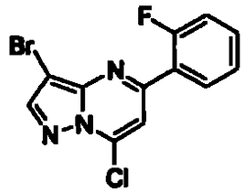
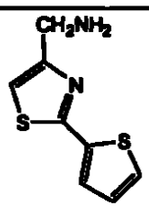
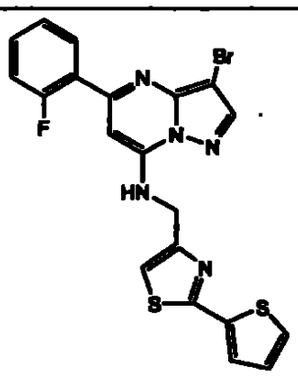
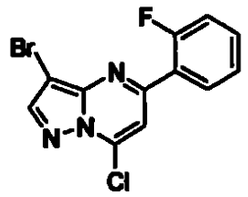
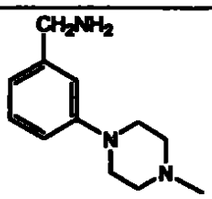
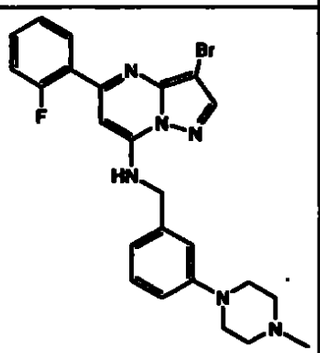
96				1. mp = 230-234 2. M+H = 434
97				1. mp = 191-193 2. M+H = 441
98				1. mp = 202-205 2. M+H = 434
99				1. mp = 209-212 2. M+H = 453

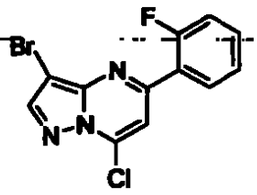
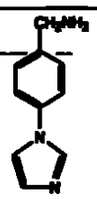
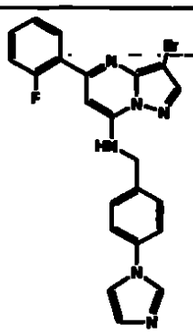
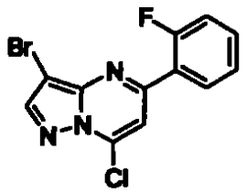
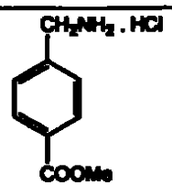
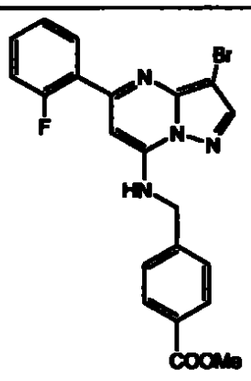
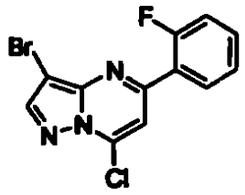
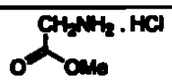
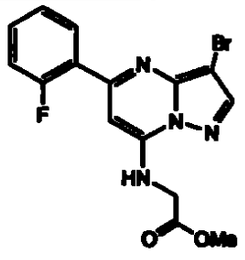
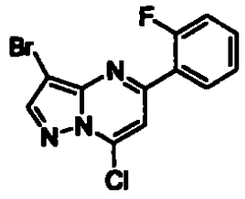
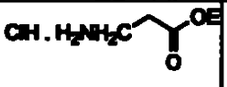
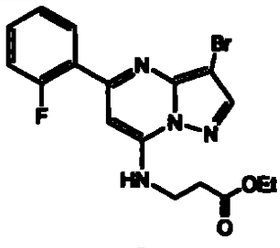
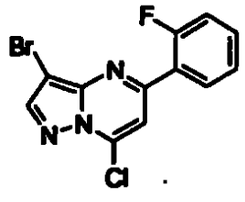
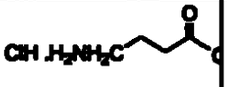
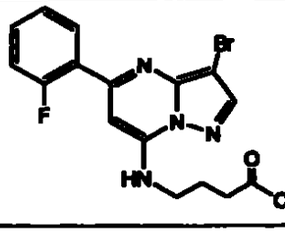
100				1. mp = 219-221 2. M+H = 469
101				1. mp = 64-66 2. M+H = 403
102				1. mp = 168-170 2. M+H = 420
103				1. mp = 213-216 2. M+H = 411

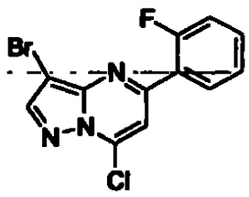
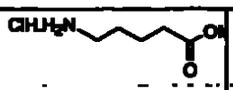
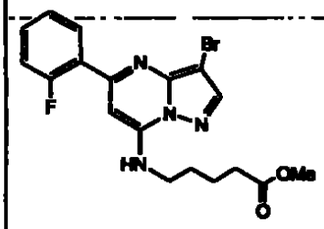
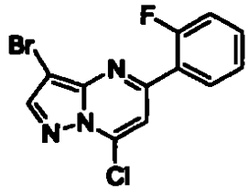
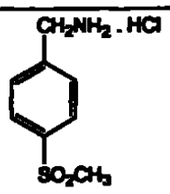
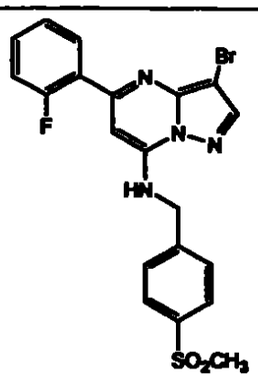
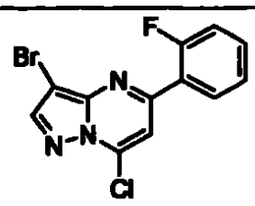
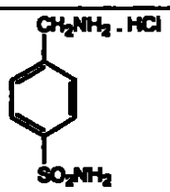
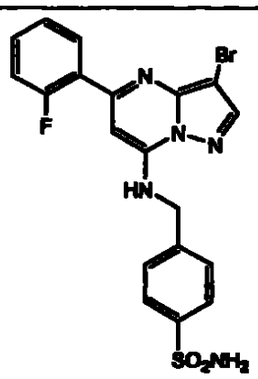
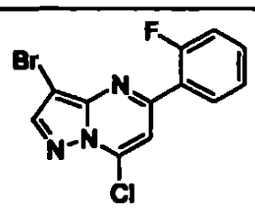
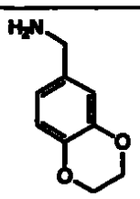
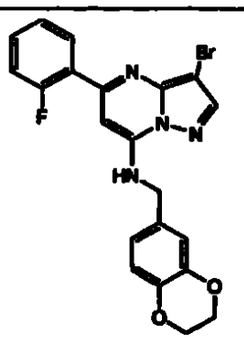
104				1. mp = 98-100 2. M+H = 561
105				1. mp 70-72 2. M+H = 606
106				1. mp 168-170 2. M+H = 538
107				1. mp 189-191 2. M+H = 592

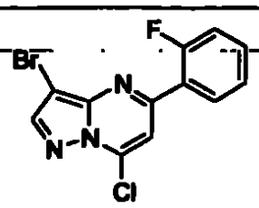
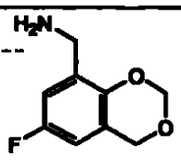
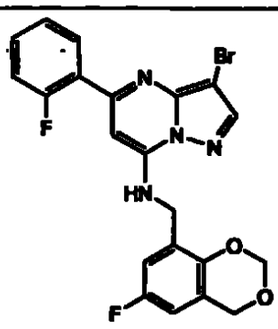
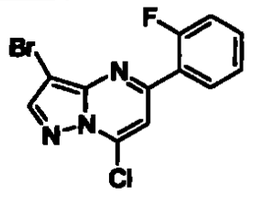
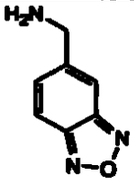
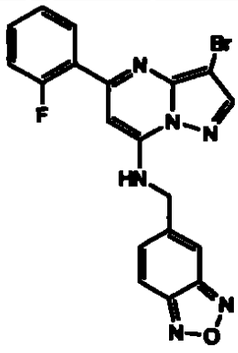
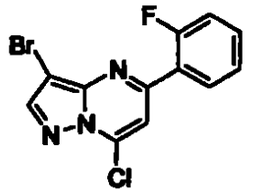
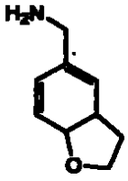
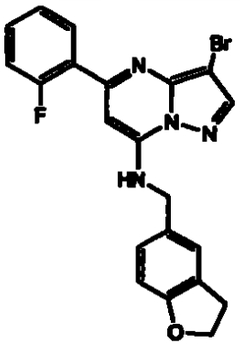
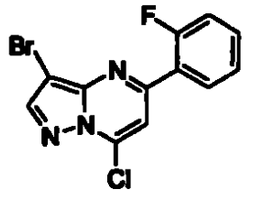
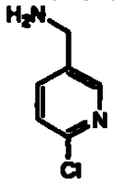
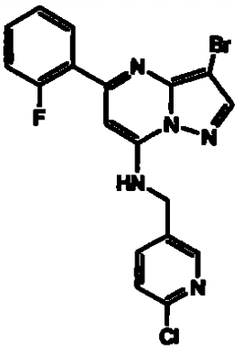
108				LCMS: MH^+ = 458;
109				Yield = 89 LCMS: MH^+ = 418 m. p. = 131-132 °C
110				Yield=95% LCMS: MH^+= 347
111				Yield=91% 3H); LCMS: MH^+= 484
112				Yield=87% LCMS: MH^+= 427

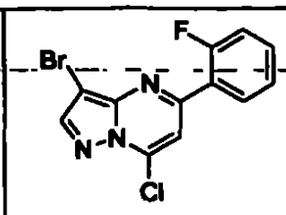
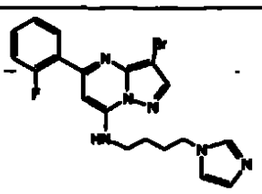
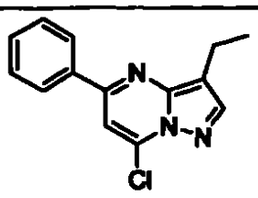
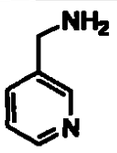
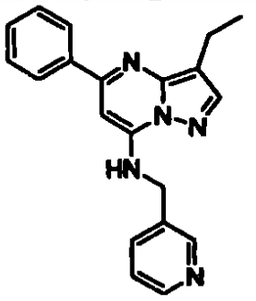
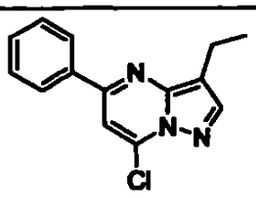
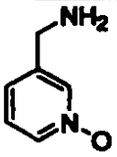
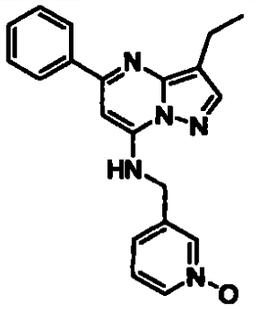
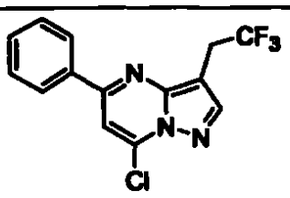
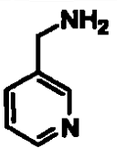
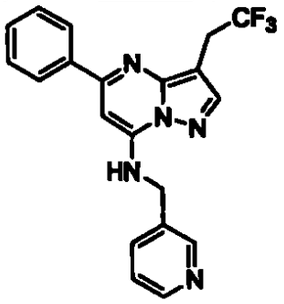
113				Yield=80% LCMS: MH$^+$= 427
114				Yield=91% LCMS: MH$^+$= 378
115				Yield=92% , 3H); LCMS: MH$^+$=520
116				Yield=98% LCMS: MH$^+$=536
117				Yield=82% LCMS: MH$^+$=410

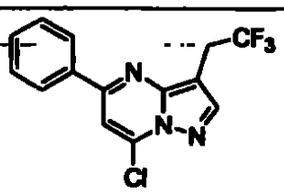
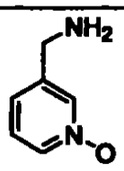
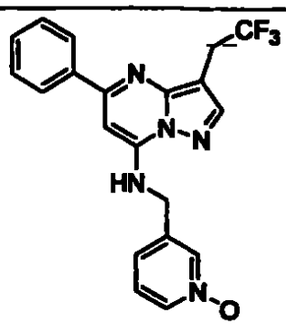
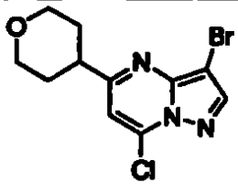
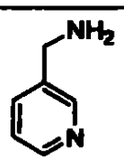
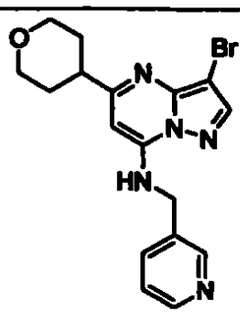
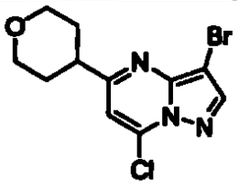
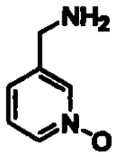
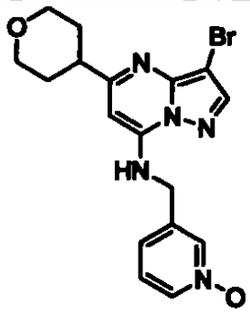
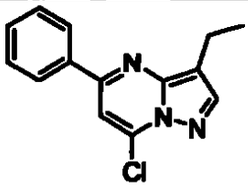
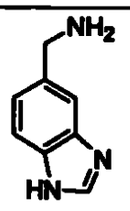
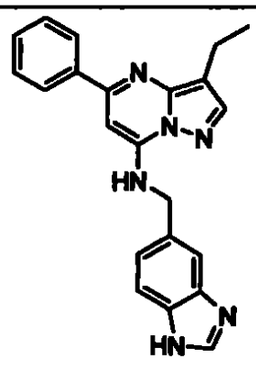
118				Yield=95% LCMS: MH^+= 347
121				Yield = 65% LCMS: MH^+ = 481.02
126				Yield=71% MH^+ = 486
127				Yield=71% MH^+ = 495.1

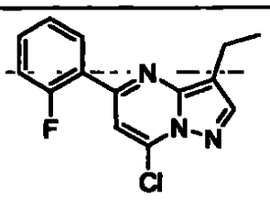
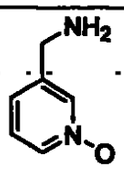
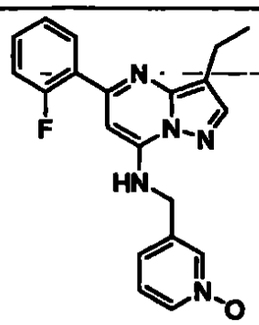
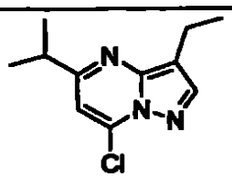
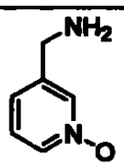
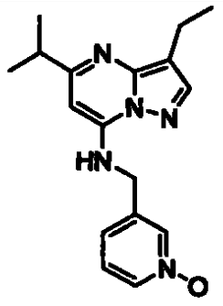
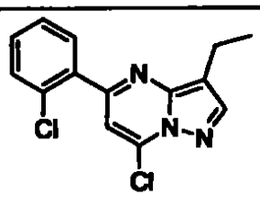
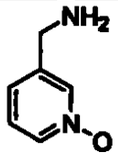
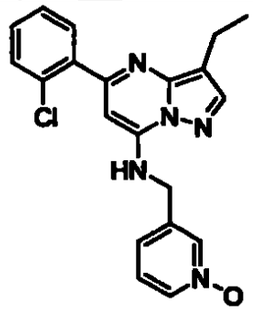
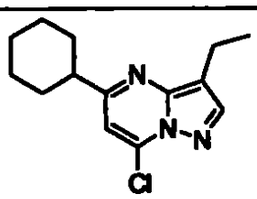
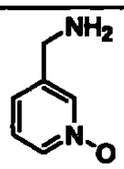
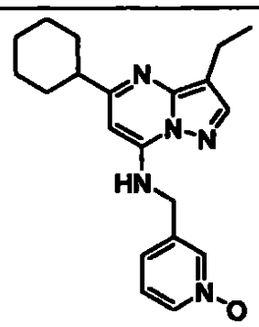
128				Yield=55% MH$^+$ = 463
129				Yield = 77% LCMS: MH$^+$ = 455
130				^{1}H NMR (Yield = 75% LCMS: MH$^+$ = 379
131				Yield = 75% LCMS: MH$^+$ = 407
132				Yield = 75% LCMS: MH$^+$ = 421

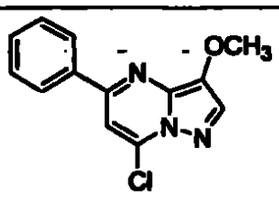
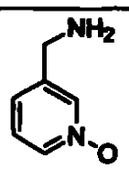
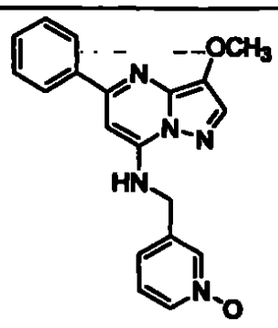
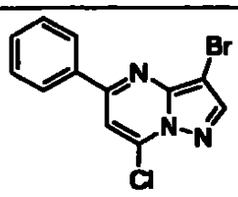
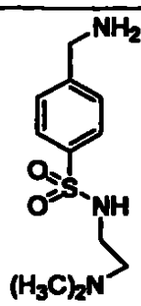
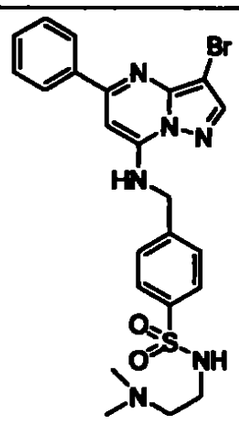
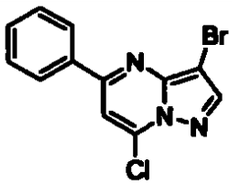
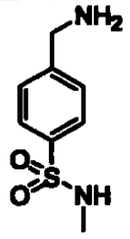
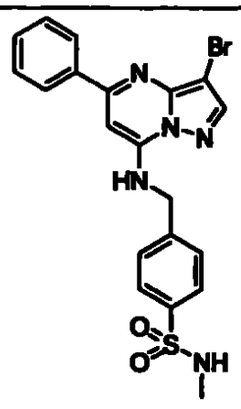
133				Yield = 70% LCMS: MH^+ = 421
134				Yield = 78% LCMS: MH^+ = 475
135				Yield = 75% LCMS: MH^+ = 476
136				Yield = 65% LCMS: MH^+ = 455

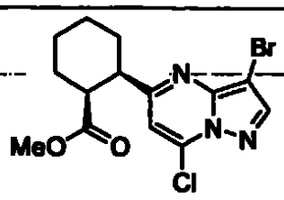
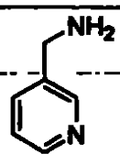
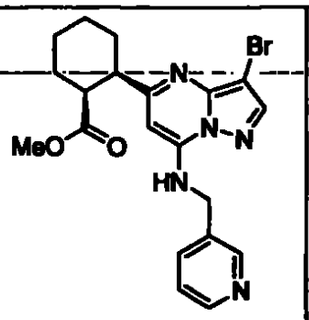
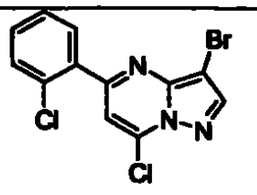
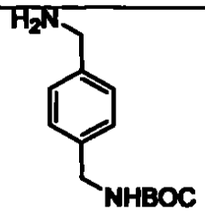
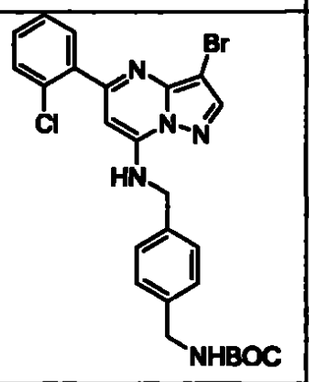
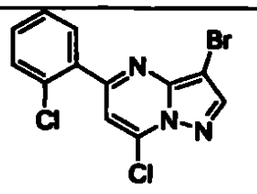
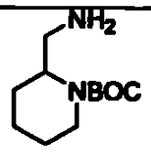
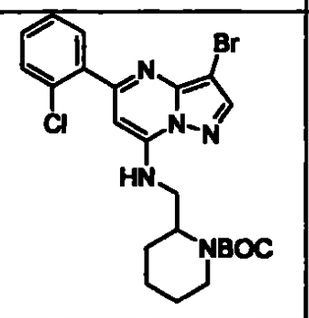
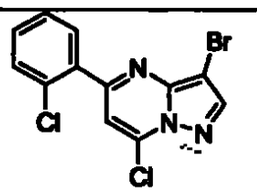
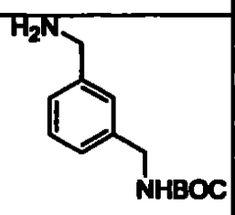
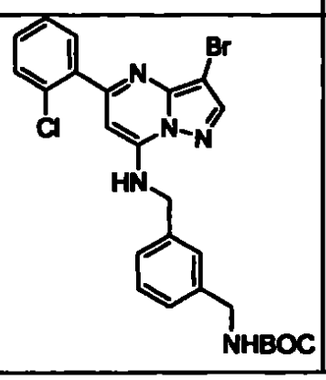
137				Yield = 55% LCMS: MH^+ = 473)
138				Yield = 60% LCMS: MH^+ = 439
139				Yield = 65% LCMS: MH^+ = 441
140				Yield = 80% LCMS: MH^+ = 432

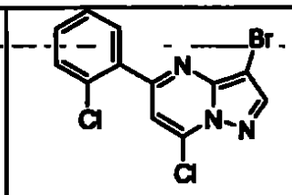
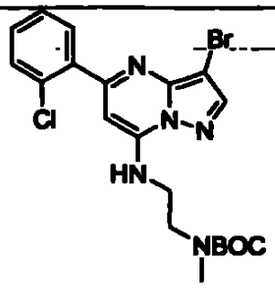
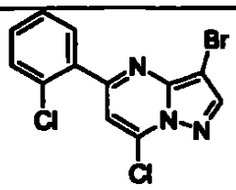
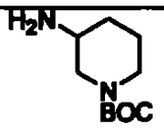
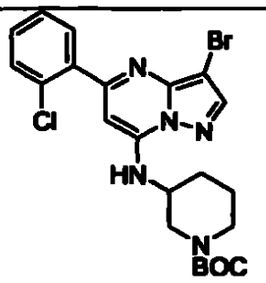
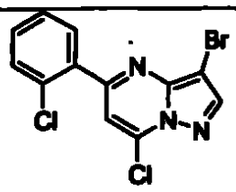
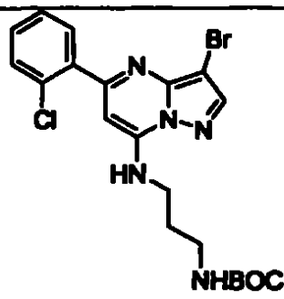
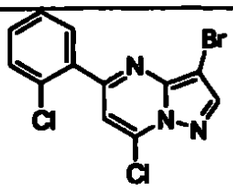
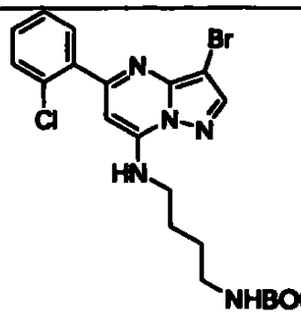
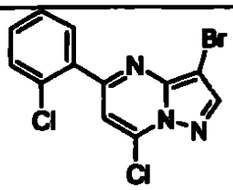
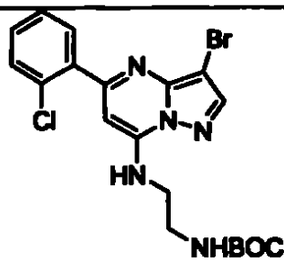
141				Yield = 60% LCMS: MH^+ = 429
142				LCMS: MH^+=330 ; mp=109-111°C
143				LCMS: MH^+=346 ; mp=186-188°C
144				LCMS: MH^+=384 ; mp=148-150°C

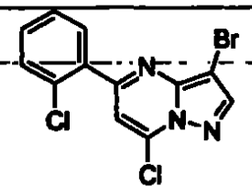
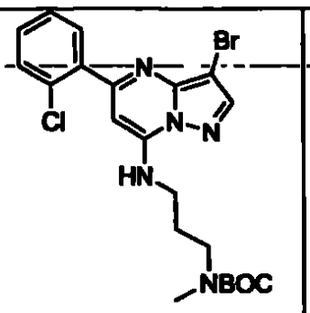
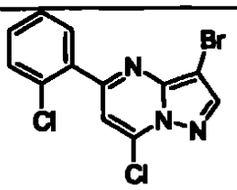
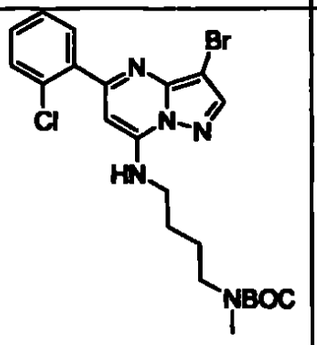
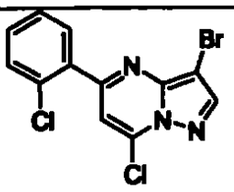
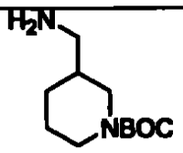
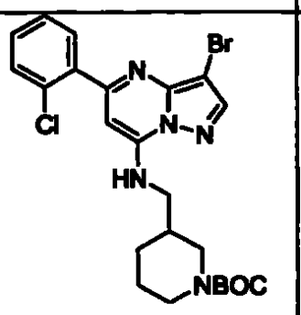
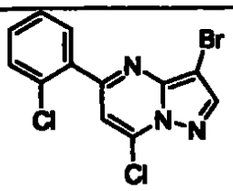
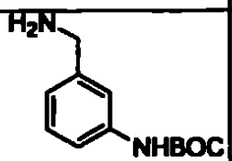
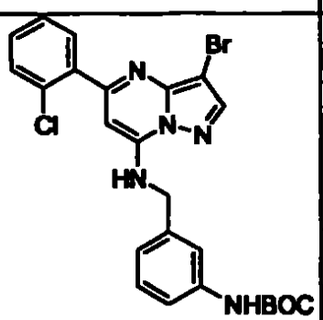
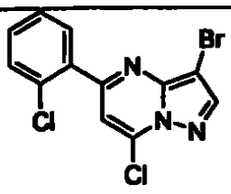
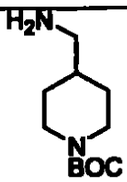
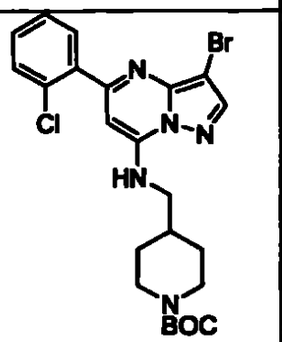
145				LCMS: MH$^+$=400; mp=186-188°C
146				LCMS: M2H$^+$=390; mp=192-194°C
147				LCMS: M$^+$=404; mp=220-222°C
148				LCMS: MH$^+$=389; mp>230° C

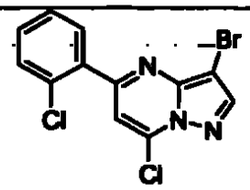
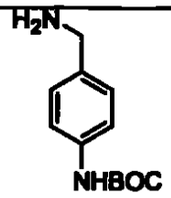
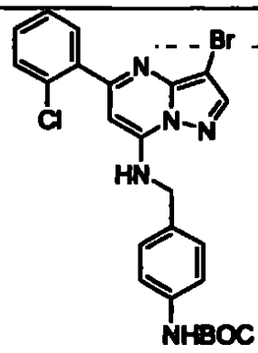
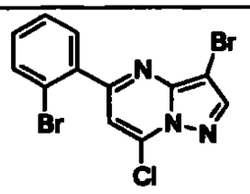
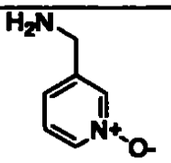
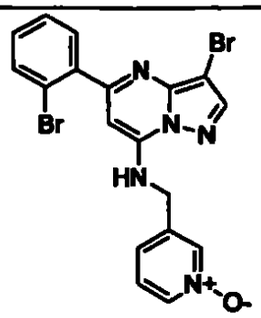
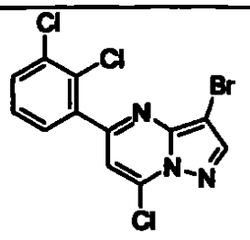
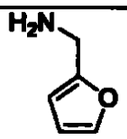
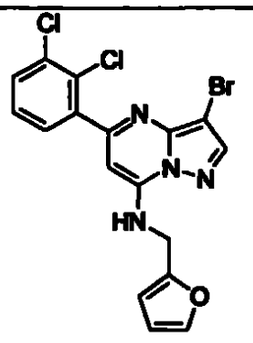
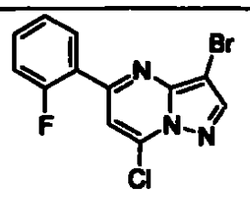
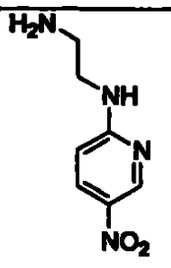
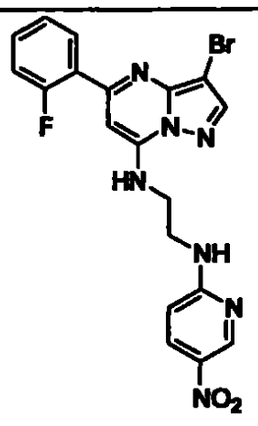
149				LCMS: MH^+=364 ; mp=186-188°C
150				LCMS: MH^+=312 ; mp=138-140°C
151				LCMS: M^+=380; mp=172-174°C
152				LCMS: MH^+=352 ; mp=201-203°C

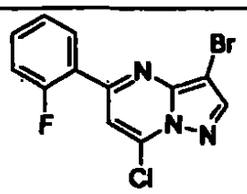
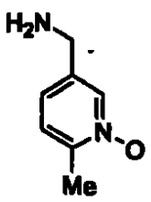
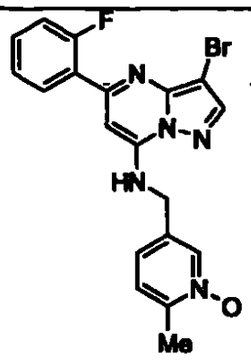
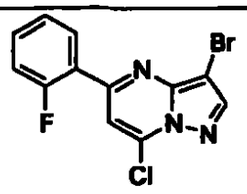
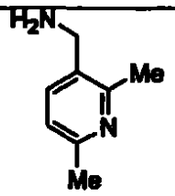
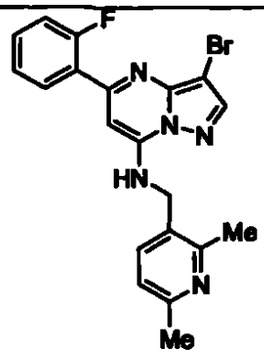
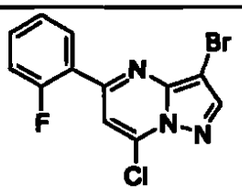
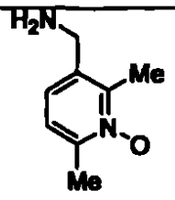
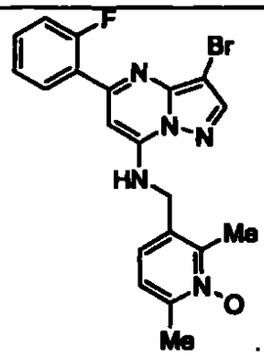
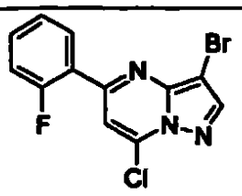
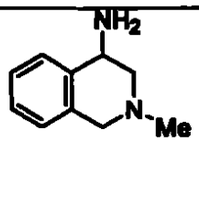
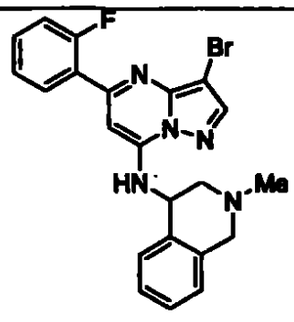
153				LCMS: MH$^+$=348; mp=166-168°C
154				LCMS: M2H$^+$=531; mp=78-80°C
155				LCMS: M2H$^+$=474; mp=161-163°C

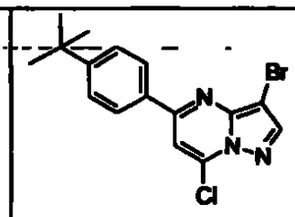
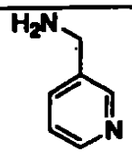
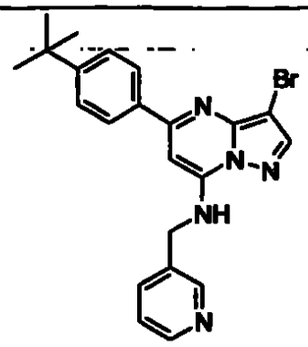
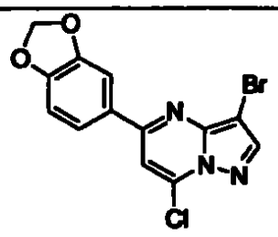
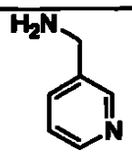
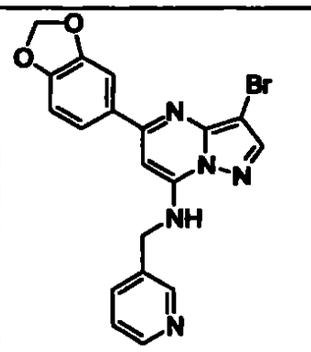
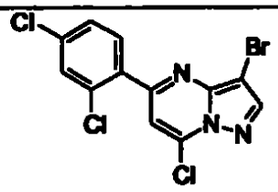
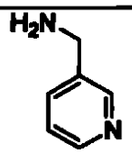
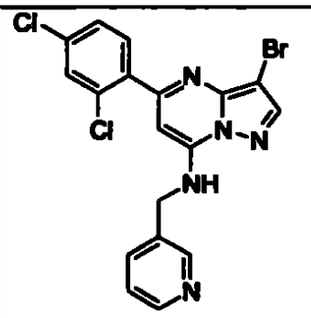
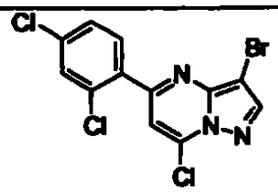
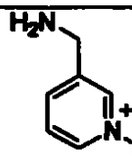
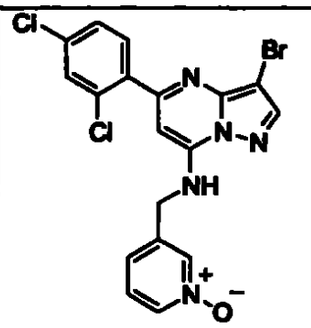
156				LCMS: M⁺=444; mp=48-51°C
157				MH⁺ = 542.1
158				MH⁺ = 520.1
159				MH⁺ = 542.1

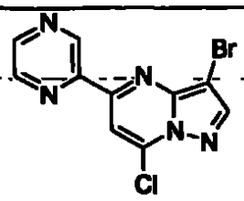
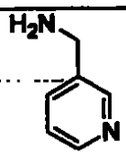
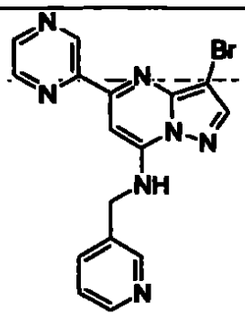
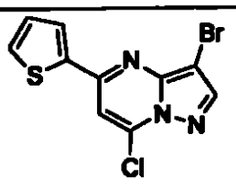
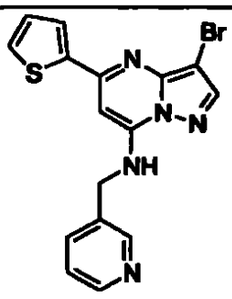
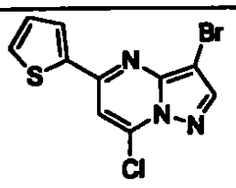
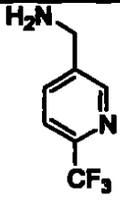
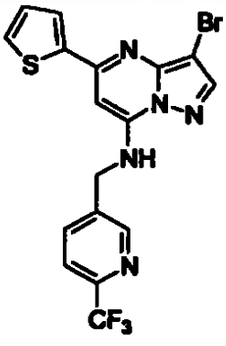
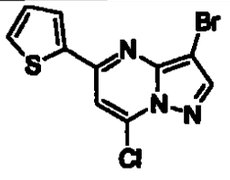
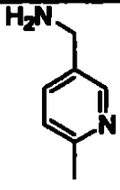
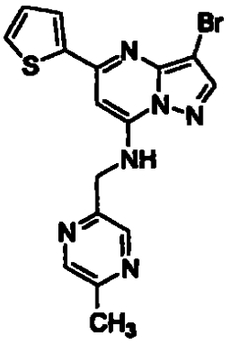
160				MH^+ = 480.1
161				MH^+ = 506.1
162				MH^+ = 480.1
163				MH^+ = 494.1
164				MH^+ = 466.1

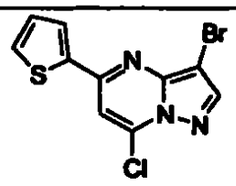
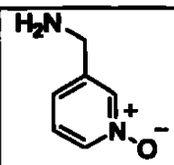
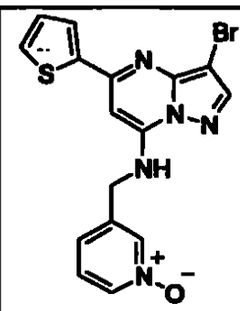
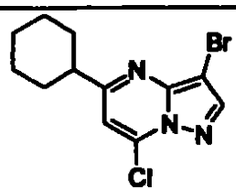
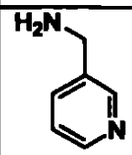
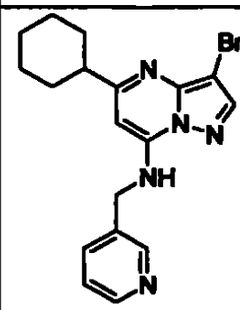
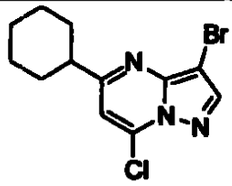
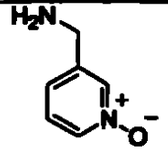
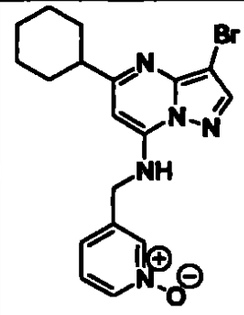
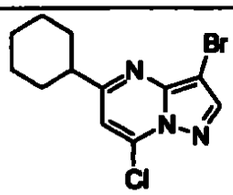
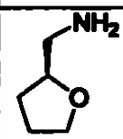
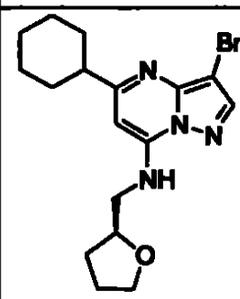
165				MH^+ = 494.1
166				MH^+ = 508.1
167				MH^+ = 520.1
168				MH^+ = 528.1
169				MH^+ = 520.1

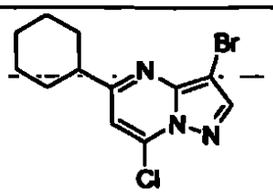
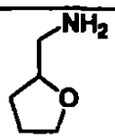
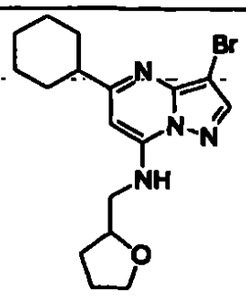
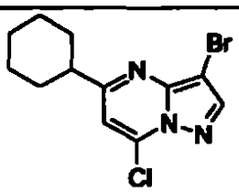
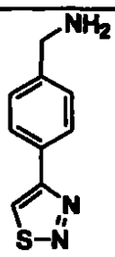
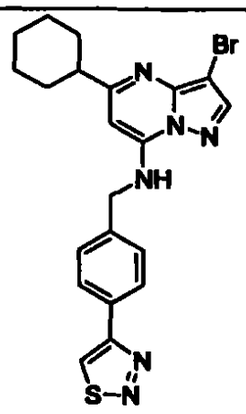
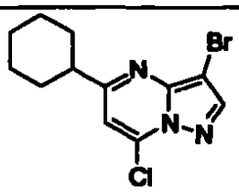
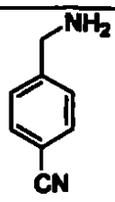
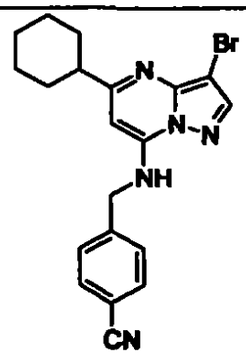
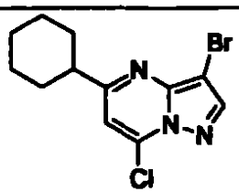
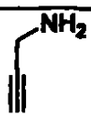
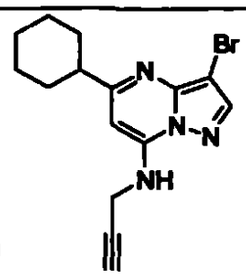
170				MH^+ = 528:1
171				LCMS: MH^+ = 474;
172				LCMS: MH^+ = 437;
173				LCMS: MH^+ = 472;

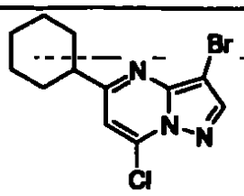
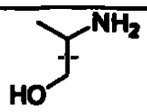
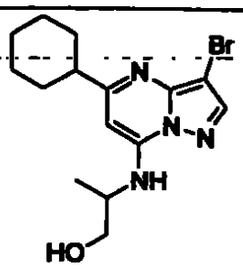
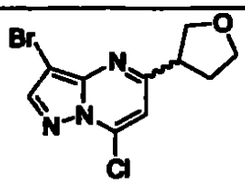
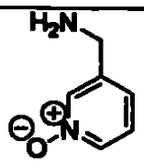
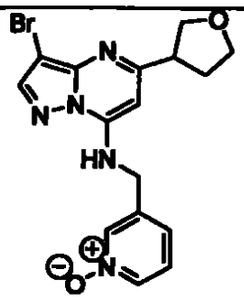
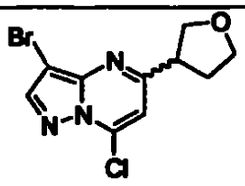
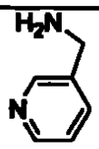
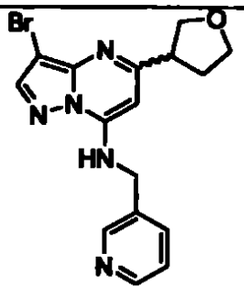
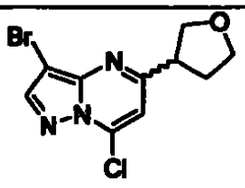
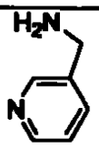
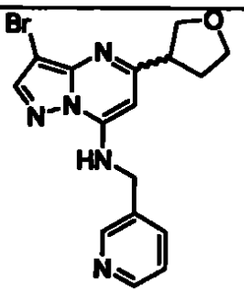
174				LCMS: MH$^+$ = 428.1
175				LCMS: MH$^+$ = 426.2
176				LCMS: MH$^+$ = 442.0
177				LCMS: MH$^+$ = 452.0

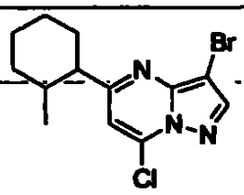
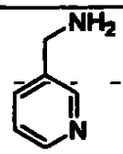
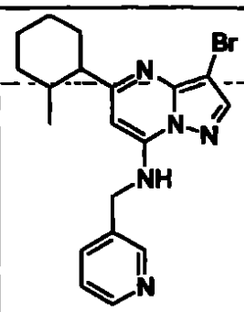
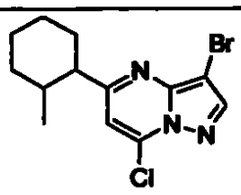
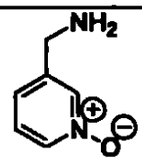
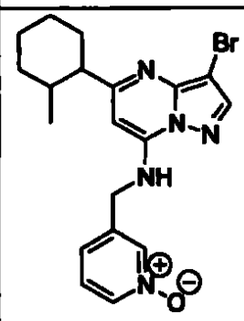
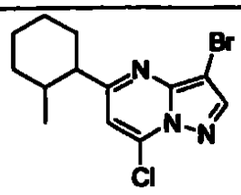
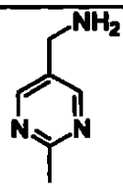
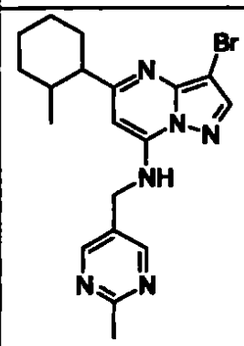
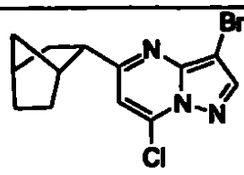
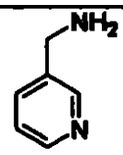
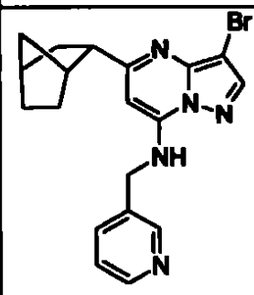
178				Yield = 90 MH^+ =436 m. pt. = 89.1 °C
179				MH^+ =424 m. pt. = 188.2 °C
180				MH^+ =448 m. pt. = 211.3 °C
181				Yield = quant. MH^+ = 464

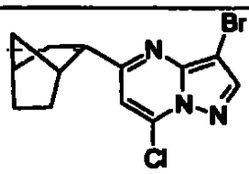
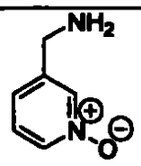
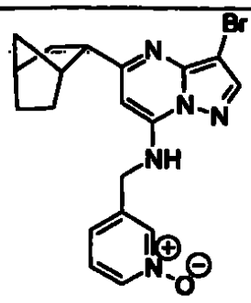
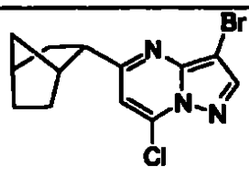
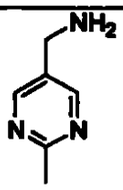
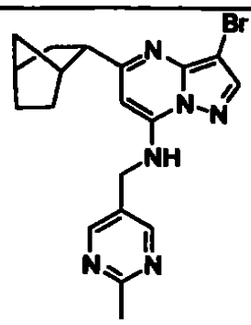
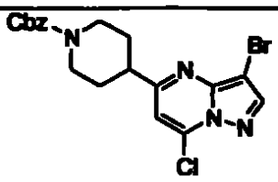
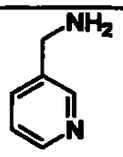
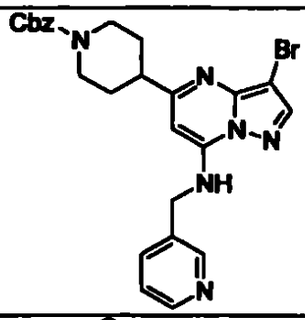
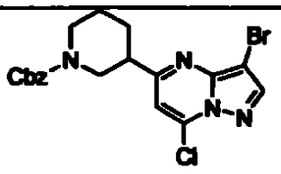
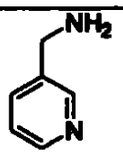
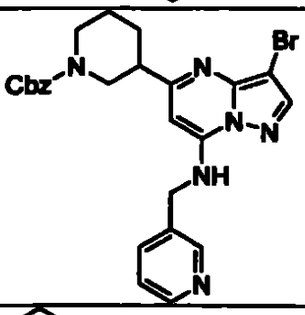
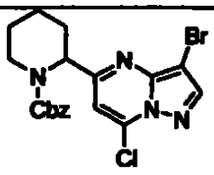
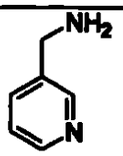
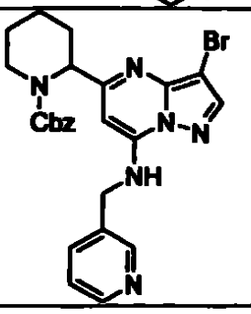
182				MH^+ = 382 m. pt. = 185.8 °C
183				MH^+ = 387 m. pt. = 181 – 182 °C
184				MH^+ = 453
185				MH^+ = 401 m. pt. = 178.3 °C

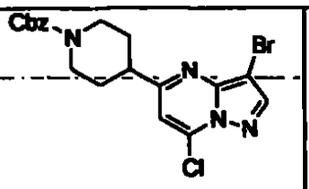
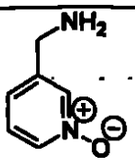
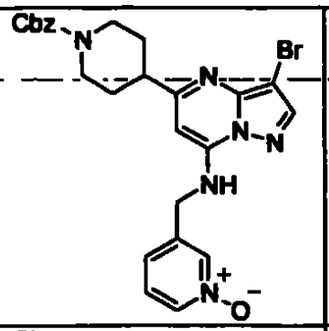
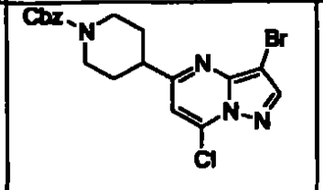
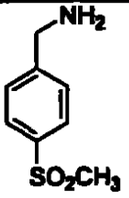
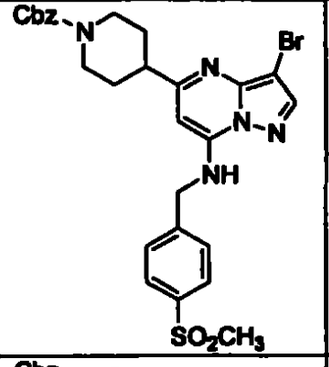
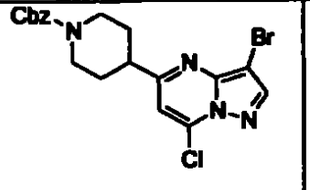
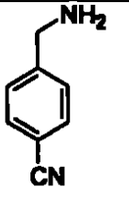
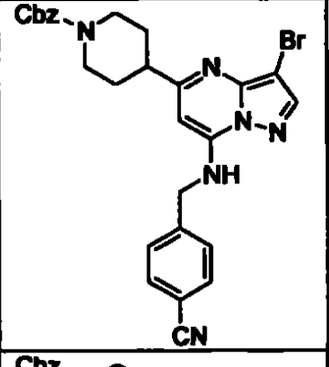
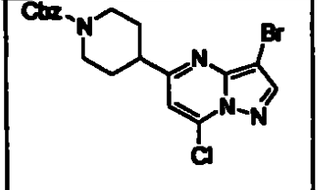
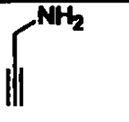
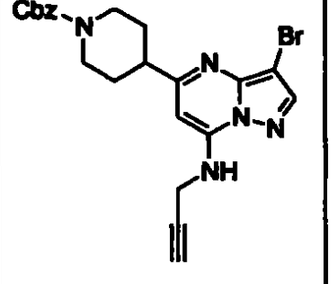
186				MH^+ = 402
187				Yield = 91 MH^+ = 386 m. pt. = 148.3 °C
188				Yield = 65 MH^+ = 402 m. pt. = 174.5 °C
189				MH^+ = 379 m. pt. = 82 – 83 °C

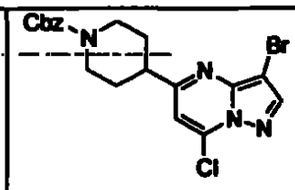
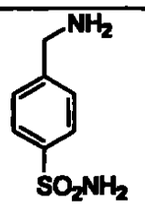
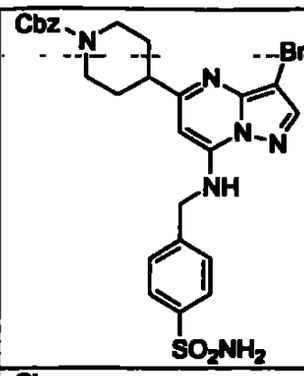
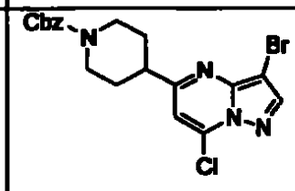
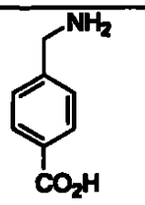
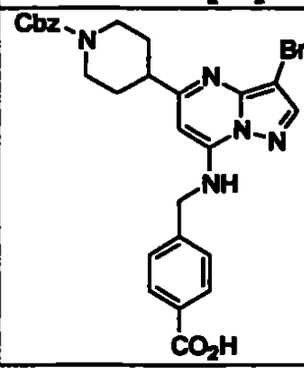
190				MH^+ = 379 m. pt. = 50.7 °C
191				Yield = 89 MH^+ = 469 m. pt. = 186.7°C
192				Yield = 93 MH^+ = 410 m. pt. = 86.7°C
193				Yield = 76 MH^+ = 333 m. pt. = 120.3°C

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

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

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

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

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

Additional data for select examples given below.

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

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

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

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

Example 27: ^{1}H NMR ($CDCl_3$) δ 8.75 (d, J = 4.5 Hz, 2H), 8.19 (s, 1H), 7.63 (d, J = 7.8 Hz, 2H), 7.44-7.40 (m, 3H), 7.07 (m, 1H), 6.26 (s, 1H), 4.83 (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).

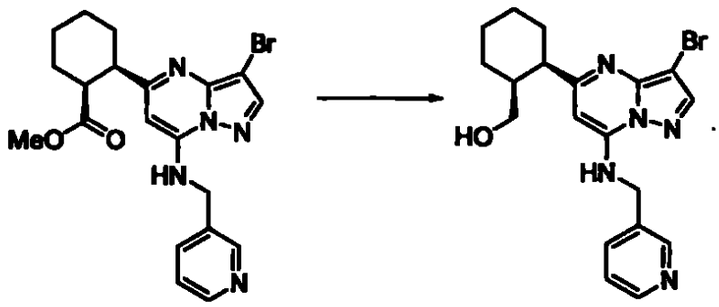
Example 197: ^{1}H NMR (CD_3OD) δ 8.73(d, 1H), 8.58(q, 1H), 8.12(s, 1H), 8.00(d, 1H), 7.54(q, 1H), 6.19(s, 1H), 4.86(s, 2H), 4.22-4.08(m, 2H), 4.03-3.93(m, 2H), 3.63(m, 1H), 2.50-2.39(m, 1H), 2.32-2.21(m, 1H).

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).

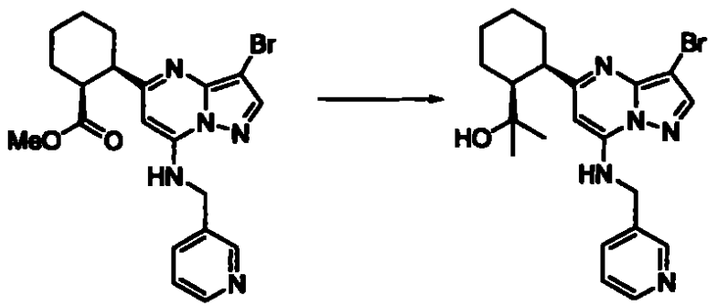
Example 203: ^{1}H NMR (300MHz, $CDCl_3$) □□8.10 (s, 1H), 8.08 (s, 1H), 6.27 (s, 2H), 4.95 (s, 2H), 3.00 – 2.90 (dd, 2H), 2.60 (m, 2H), 2.48 (br s, 1H), 2.39 (s, 3h), 2.25 m, 1H), 1.95 – 1.70 (m, 3H).

EXAMPLE 211:



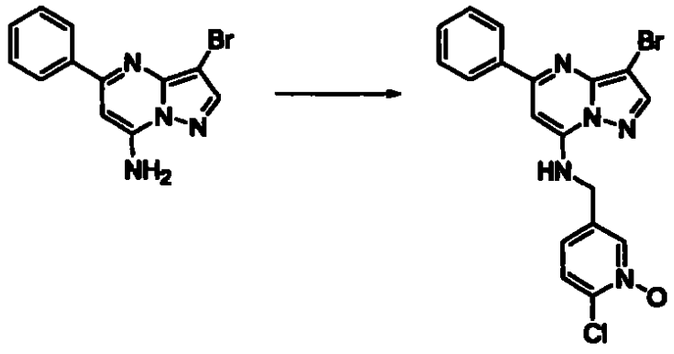
To a solution of the compound prepared in Example 156 (100 mg, 0.23 mmol) in dry THF (4 mL) was added $LiAlH_4$ (1.0 M in THF, 0.110 mL, 0.110 mmol) at 0°C under N_2. The mixture was stirred at 0°C for 1hr, warmed to 25°C, then additional $LiAlH_4$ (1.0 M in THF, 0.400 mL) was added, the mixture was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



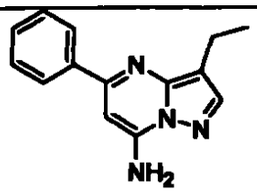
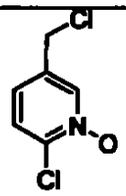
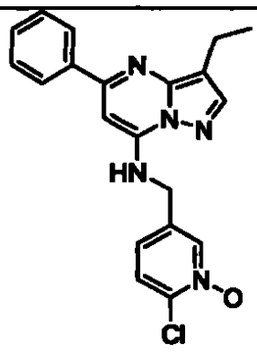
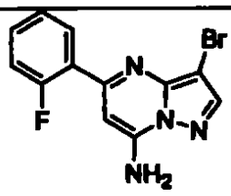
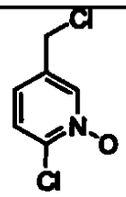
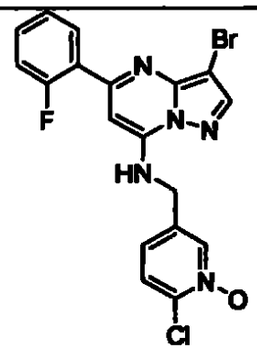
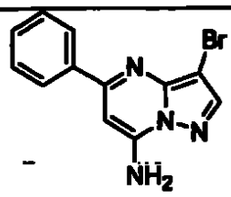
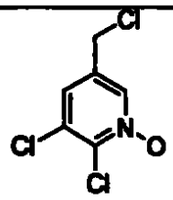
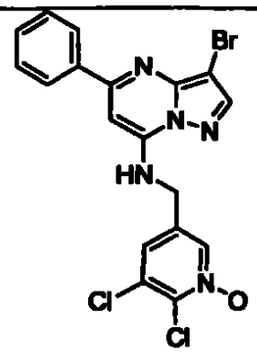
Anhydrous DMF (40 mL) was added under N_2 to the compound prepared in Preparative Example 174 (2.50 g, 8.65 mmol) and 60 % NaH in mineral oil (346 mg, 8.65 mmol). The mixture was stirred at 25°C for 1 hr, then 2-chloro-5-chloromethylpyridine N-oxide (1.54 g, 8.65 mmol) in anhydrous DMF (20 mL) was added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

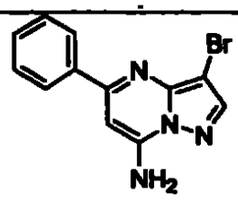
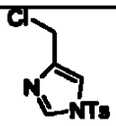
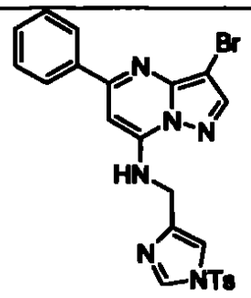
30:1 CH_2Cl_2:MeOH as eluent. So obtained solid was triturated by 50 mL of 1:1 EtOAc: hexane. Pale yellow solid (1.25 g, 34%) was obtained. LCMS: MH^+=432. Mp=224-226 °C.

EXAMPLES 214-217:

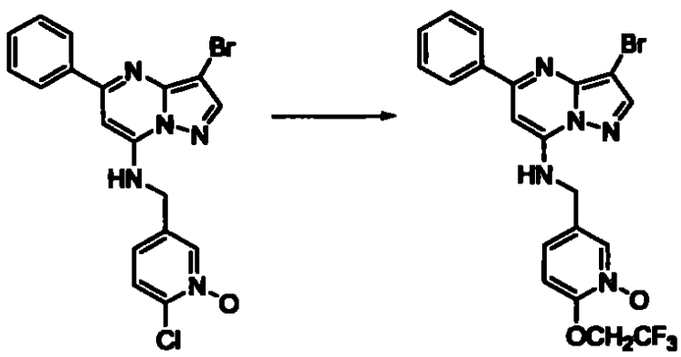
By essentially the same procedure set forth in Example 213 combining the compounds shown in Column 2 of Table 19 with compounds in Column 3 of Table 19, the compounds shown in Column 3 of Table 19 were prepared.

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^+=466; mp=126-128°C

217				LCMS: M^+=523

EXAMPLE 218:



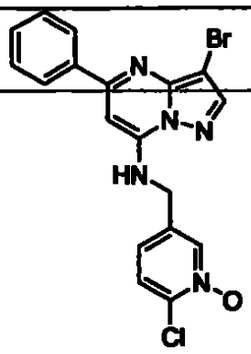
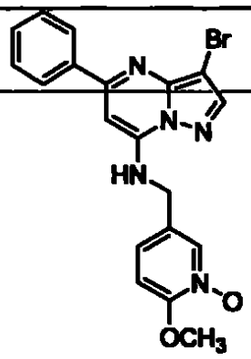
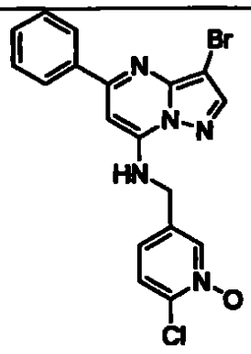
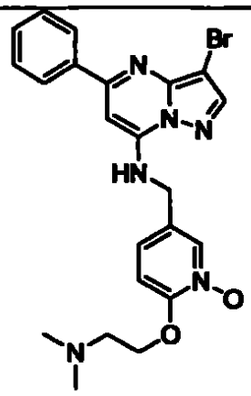
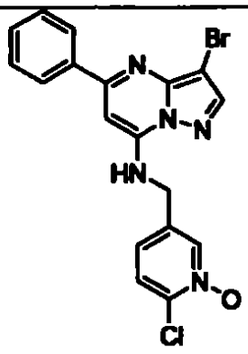
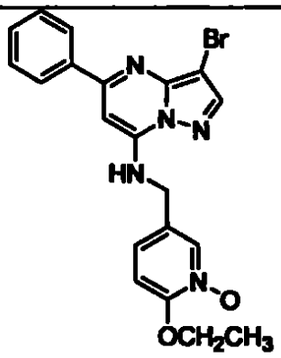
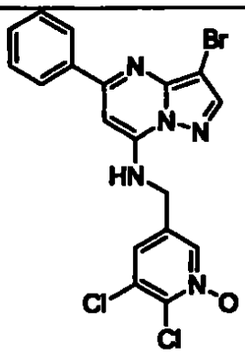
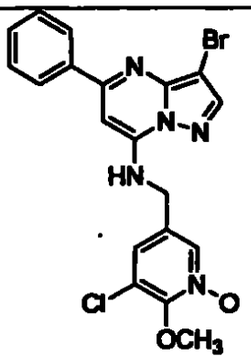
CF_3CH_2OH (3.0 mL) was added under N_2 to 60% NaH in mineral oil (40 mg, 1.0 mmol), the mixture was stirred for 20 min, then the product prepared in Example 213 (50 mg, 0.12 mmol) was added. The mixture was refluxed for 20 hr, the solvent was evaporated, and the residue was purified by flash chromatography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

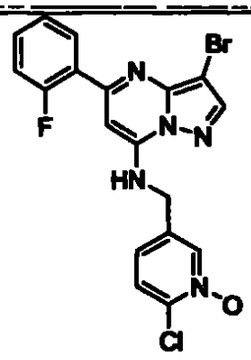
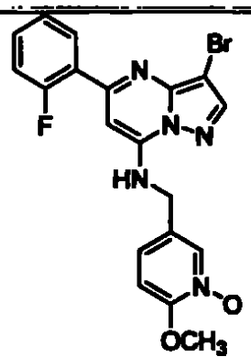
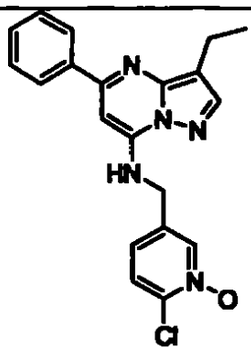
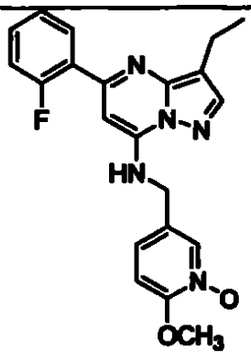
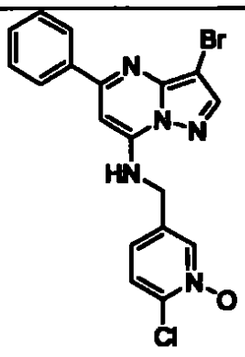
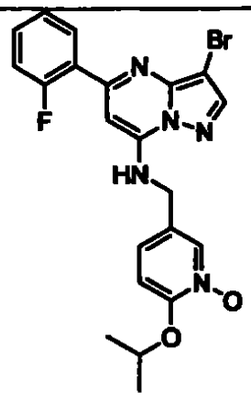
EXAMPLES 219-225:

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

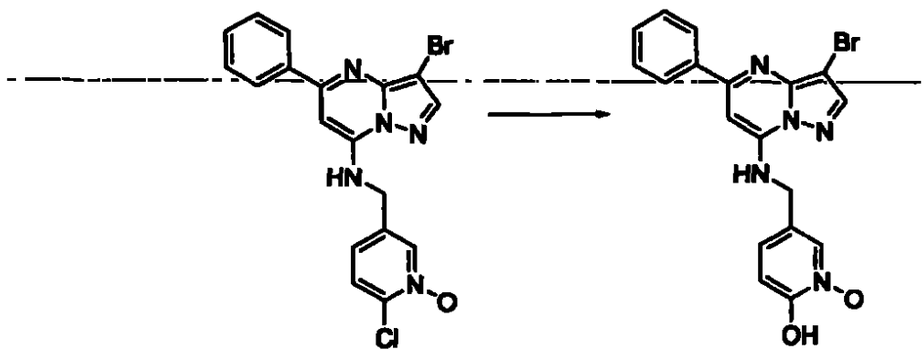
TABLE 20

Ex.	Column 1	Column 2	Data

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

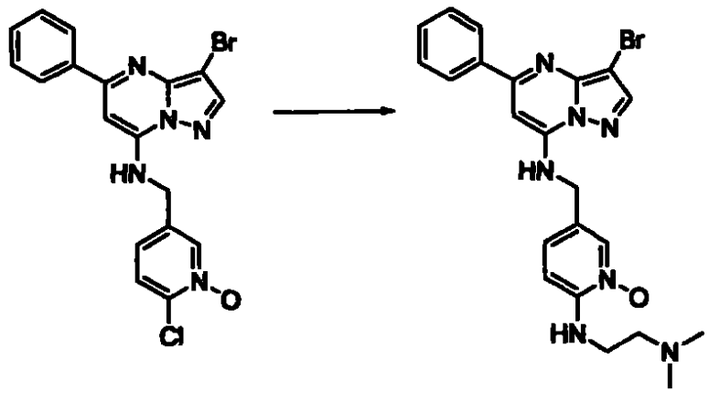
223			LCMS: MH^+=444; mp=112-114°C
224			LCMS: M^+=376; mp=°C
225			LCMS: MH^+=; mp=°C

EXAMPLE 226:



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

EXAMPLE 227:



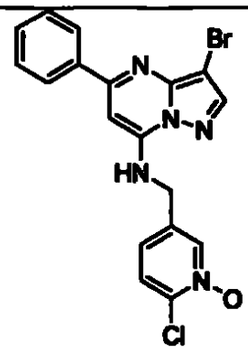
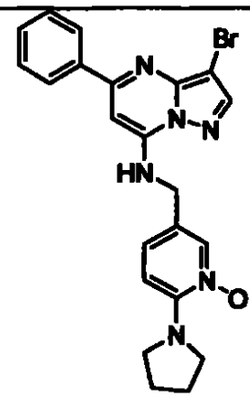
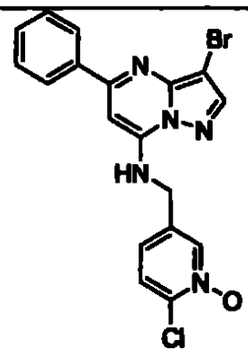
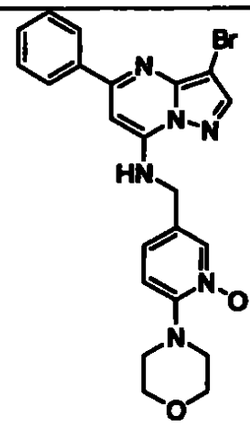
A mixture of the product prepared in Example 213 (129 mg, 0.30 mmol), N,N-dimethylethylenediamine (0.165 mL, 1.50 mmol), and diisopropylethylamine (0.10 mL) in anhydrous N-methylpyrrolidinone (1.0 mL) was stirred at 100°C for

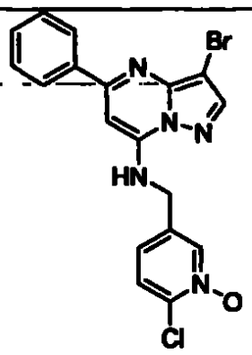
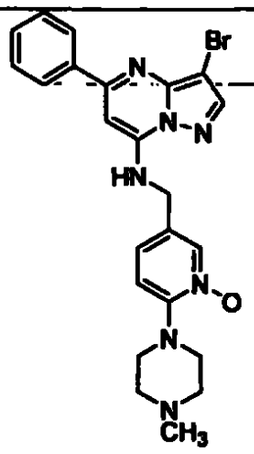
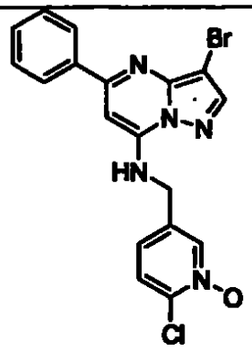
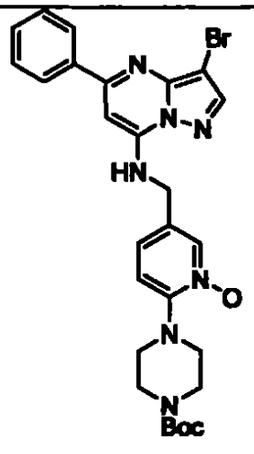
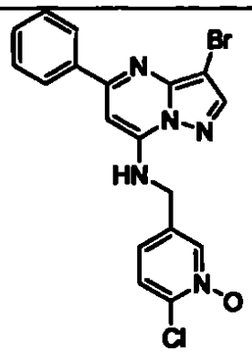
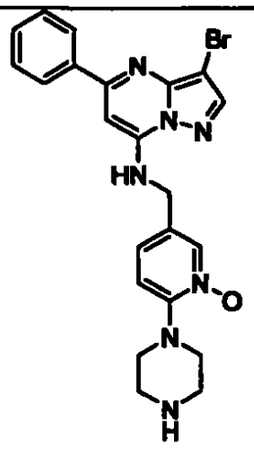
24 hr. The solvent was evaporated, and the residue was purified by flash chromatography using 20:1 CH_2Cl_2: 7N NH_3 in MeOH as eluent to yield pale yellow solid (110 mg, 76%). LCMS: M^+=482. Mp=76-78 °C.

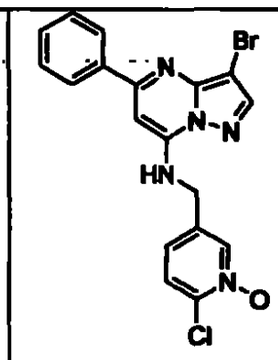
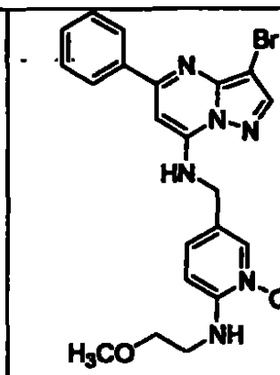
EXAMPLES 228-233:

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

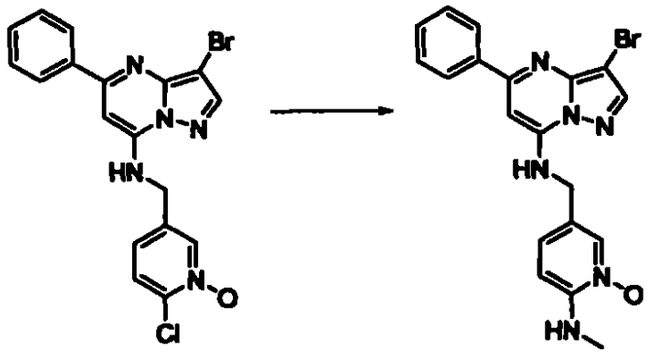
TABLE 21

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

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

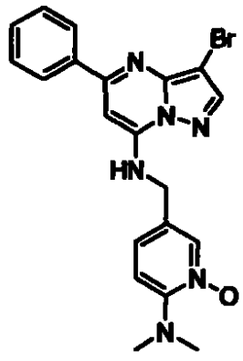
233			LCMS: $M2H^+$=471 ; mp=88-90°C

EXAMPLE 234:



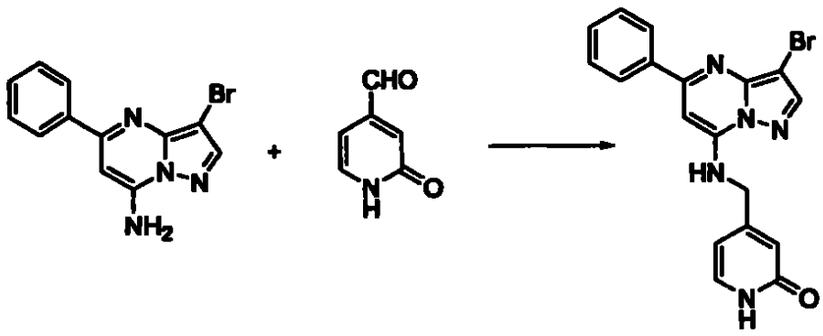
A mixture of the product prepared in Example 213 (80 mg, 0.19 mmol) and 2.0 M methylamine in THF was stirred in a closed pressure vessel at 50°C for 72 hr. The solvent was evaporated, and the residue was purified by flash chromatography using 10:1 CH_2Cl_2: MeOH as eluent to yield pale yellow solid (40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

EXAMPLE 235:



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

EXAMPLE 236:



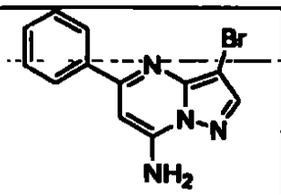
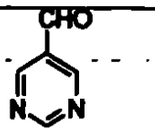
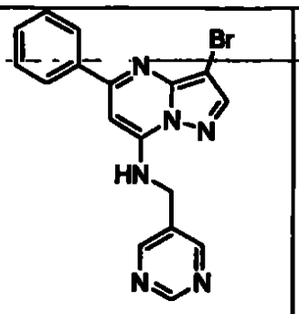
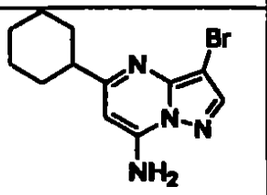
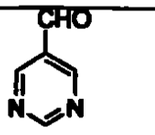
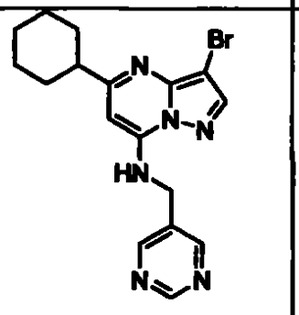
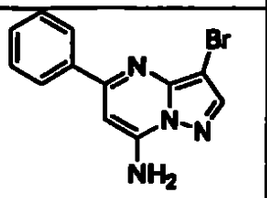
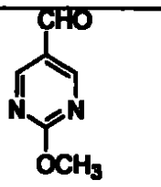
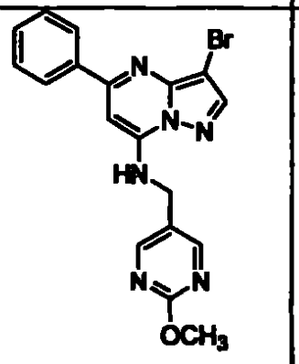
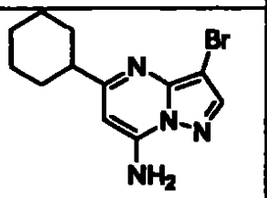
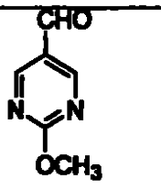
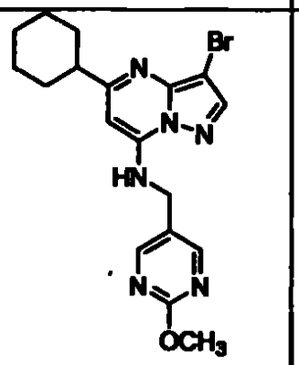
The compound prepared in Preparative Example 174 (140 mg, 0.48 mmol) and the aldehyde (71 mg, 0.58 mmol) were stirred in anhydrous THF (4 mL) at 50°C under N_2. $Ti(OiPr)_4$ (0.574 mL, 1.92 mmol) was added, the mixture was stirred at 50°C.3 hr, and cooled to 25°C. $NaBH_3CN$ (181 mg, 2.88 mmol) was added,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

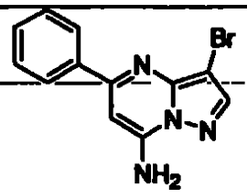
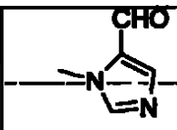
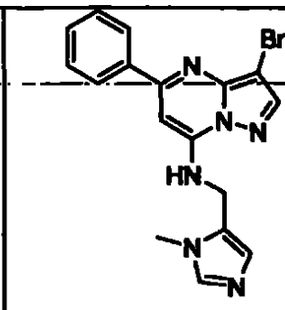
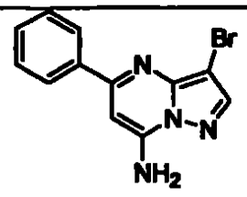
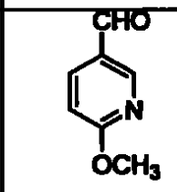
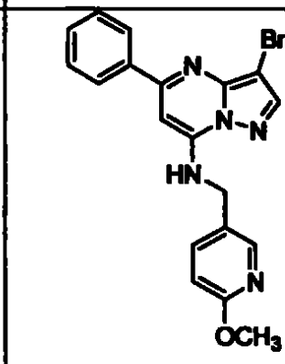
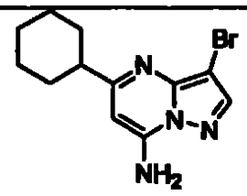
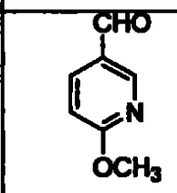
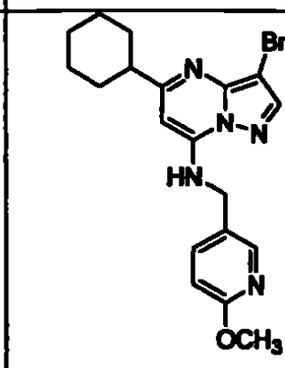
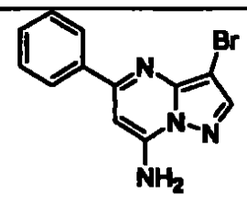
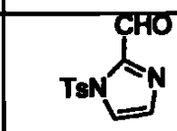
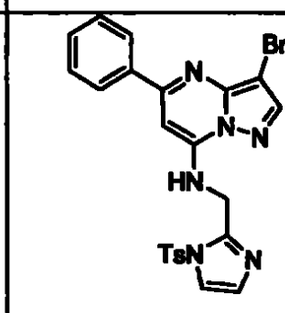
EXAMPLES 237-256:

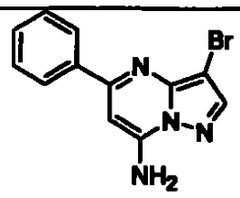
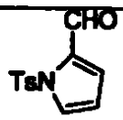
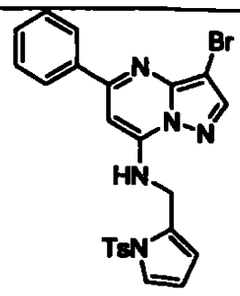
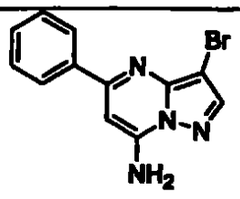
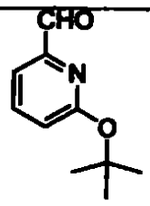
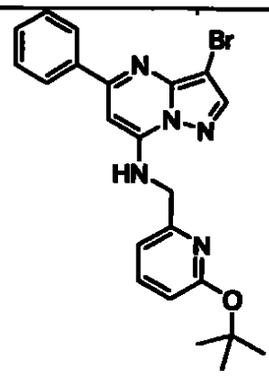
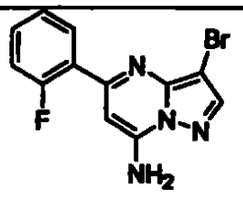
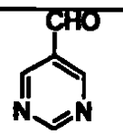
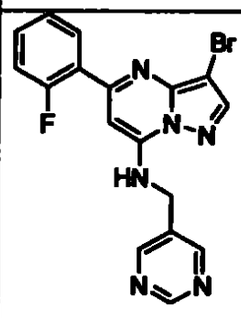
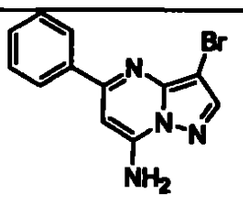
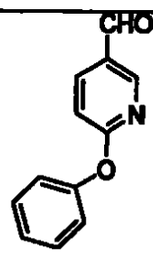
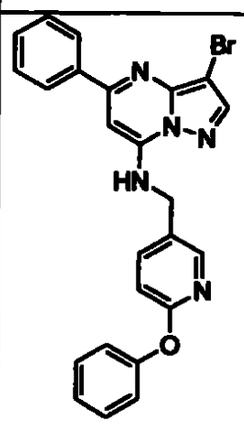
By essentially the same procedure set forth in Example 236 combining the compounds shown in Column 2 and 3 of Table 22, the compounds shown in Column 4 of Table 22 were prepared.

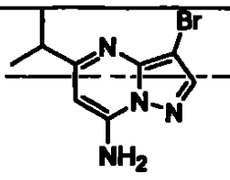
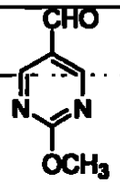
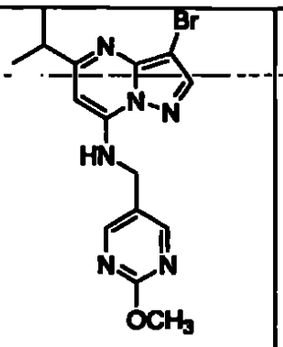
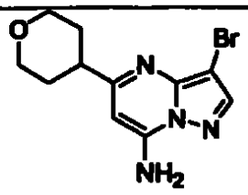
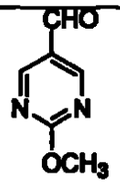
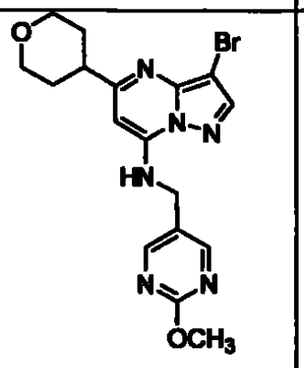
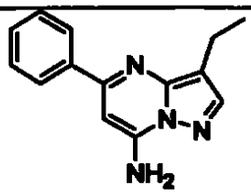
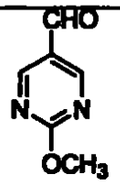
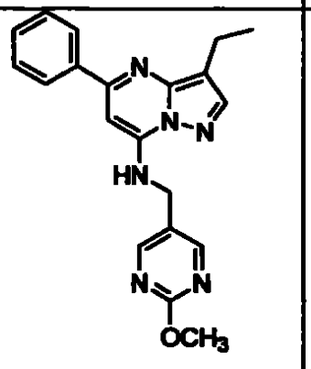
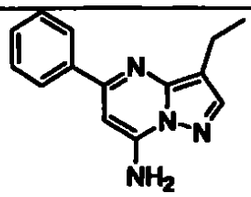
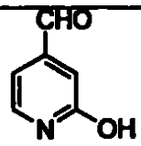
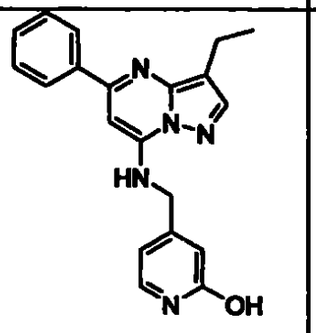
TABLE 22

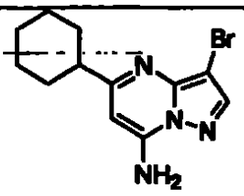
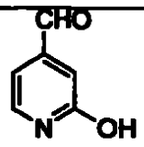
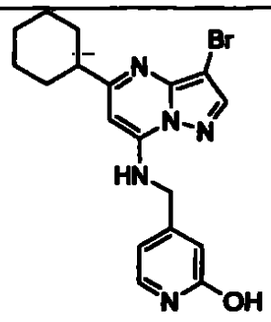
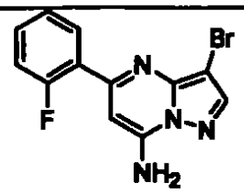
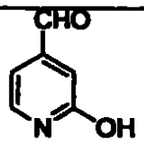
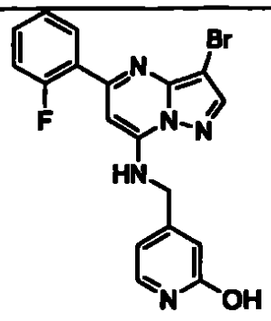
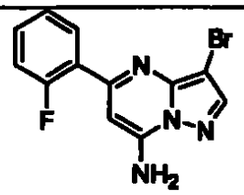
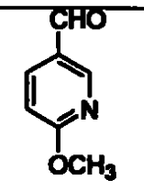
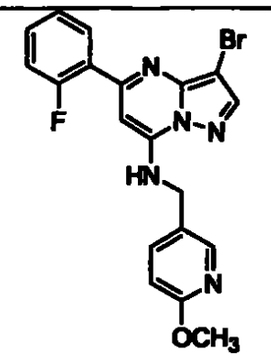
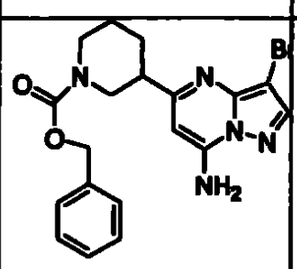
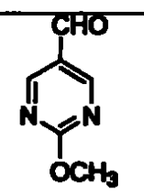
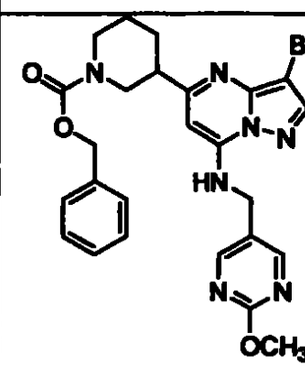
Ex.	Column 2	Column 3	Column 4	Data

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

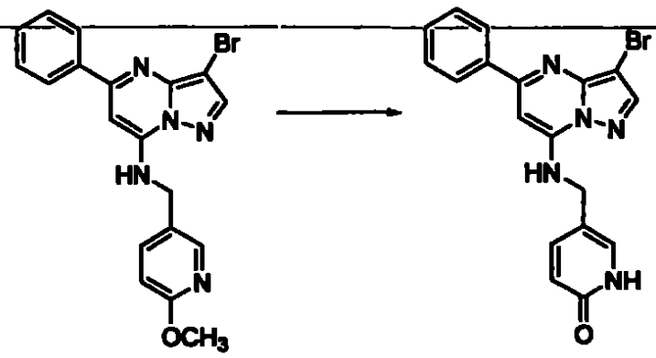
241				LCMS: $M2H^+$=385; mp=214-216°C
242				LCMS: MH^+=; mp=°C
243				LCMS: M^+=416; mp=80-82°C
244				

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

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

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

EXAMPLE 257:

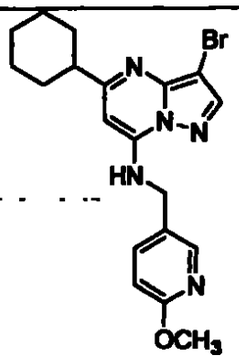
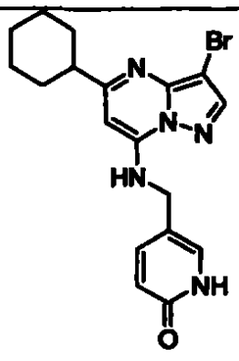


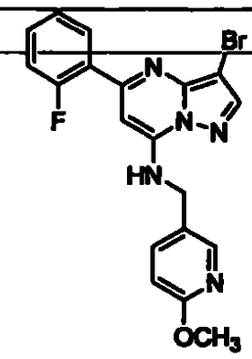
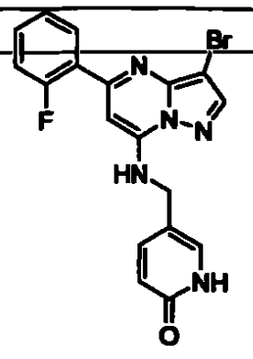
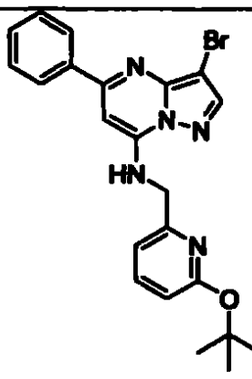
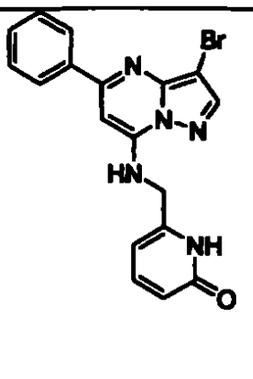
A mixture of the compound prepared in Example 242 (100 mg, 0.24 mmol), conc. aqueous HCl (1.0 mL) and acetic acid (2.0 mL) were stirred at 100°C under N_2 for 2 hr, then poured onto Na_2CO_3 (15 g), and extracted with 1:1 acetone:CH_2Cl_2 (3 x 30 mL). Combined extracts were filtered, and the solvent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

EXAMPLES 258-260:

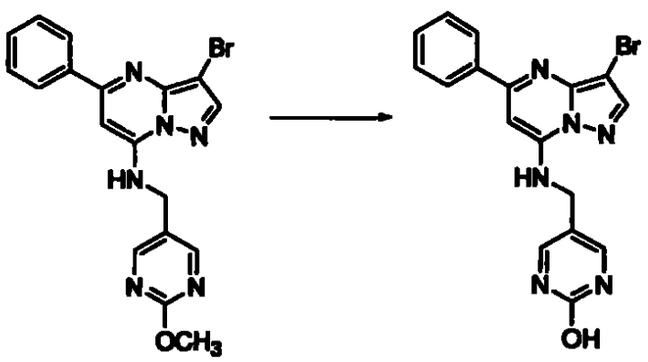
By essentially the same procedure set forth in Example 257 starting from the compounds shown in Column 1 of Table 23, the compounds shown in Column 2 of Table 23 were prepared.

TABLE 23

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

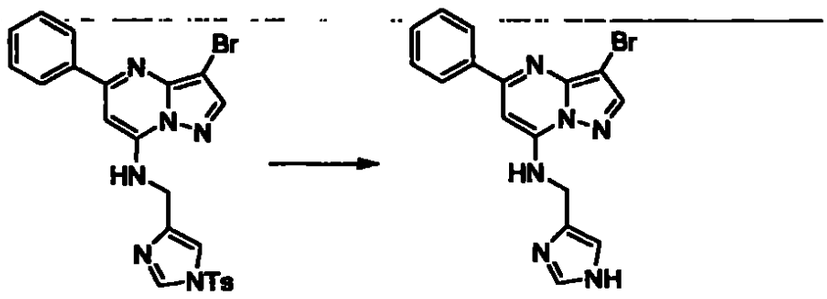
259			LCMS: MH^+=416; mp=215-216°C
260			LCMS: $M2H^+$=398 ; mp>230°C

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:

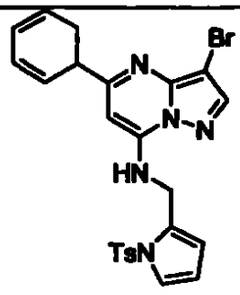
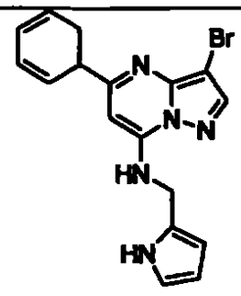


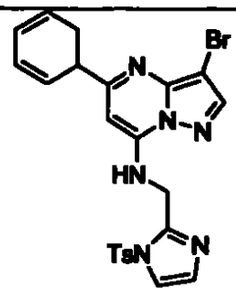
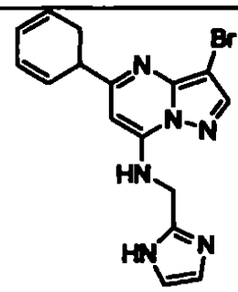
A mixture of the product prepared in Example 217 (40 mg, 0.077 mmol) and 5.0 M aqueous NaOH (0.8 mL) in MeOH (3.0 mL) was refluxed under N_2 for 1 hr. $NaHCO_3$ (700 mg) was added, the solvent evaporated, and the residue was purified by flash chromatography using 10:1:0.1 CH_2Cl_2: MeOH: conc. NH_4OH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

EXAMPLES 263-264:

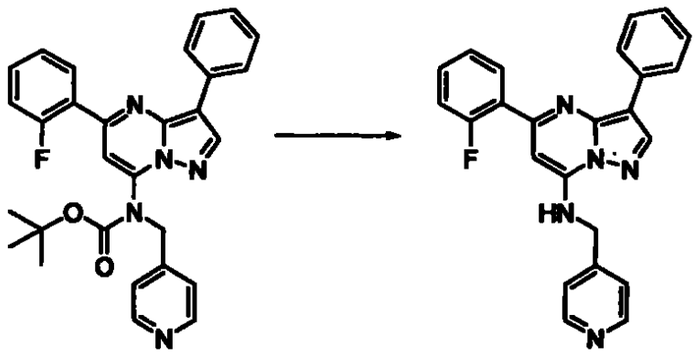
By essentially the same procedure set forth in Example 262 starting from the compounds shown in Column 1 of Table 24, the compounds shown in Column 2 of Table 24 were prepared.

TABLE 24

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

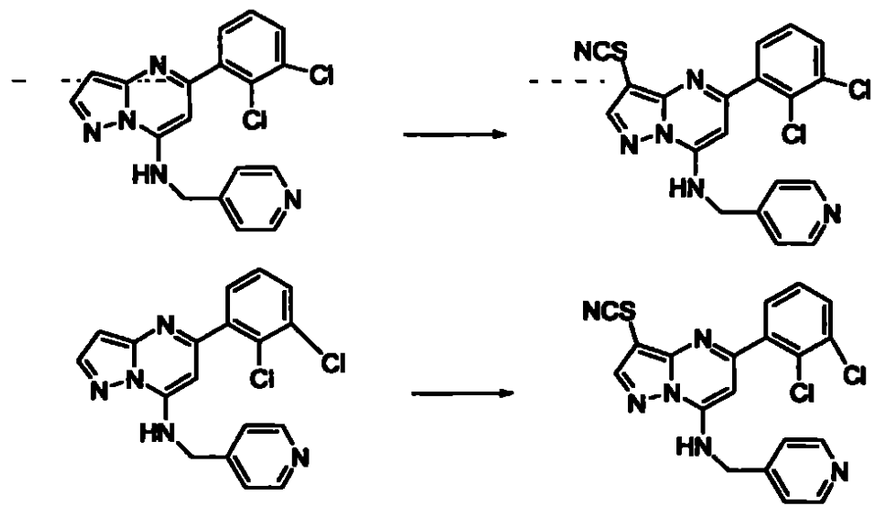
264			LCMS: $M2H^+$=371 ; mp=180-182°C

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:



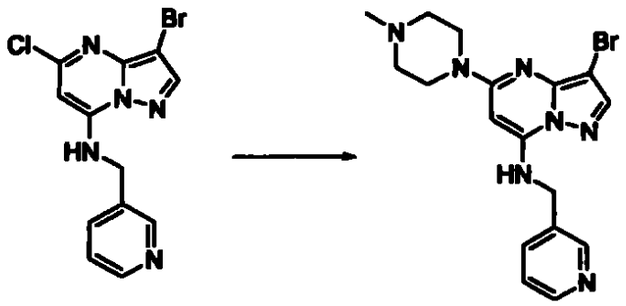
A solution of the compound prepared in Preparative Example 182 (26 mg, 0.070 mmol) and potassium thiocyanate (13 mg, 0.14 mmol) in MeOH (1 mL) was cooled in a cold water bath. To it was added a solution of bromine (22 mg, 0.14mmol) in MeOH (0.7 mL) dropwise. The resulting reaction mixture was stirred 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:



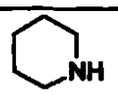
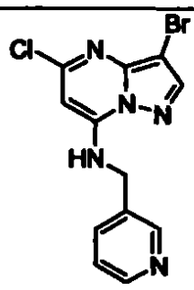
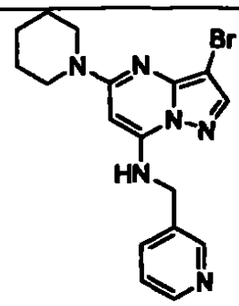
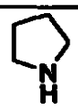
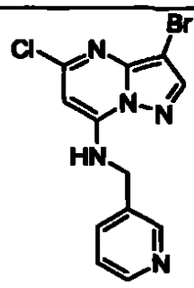
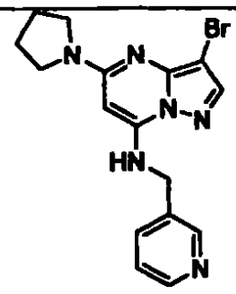
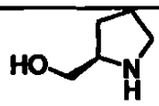
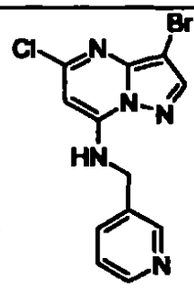
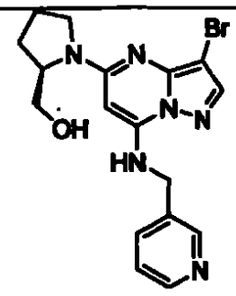
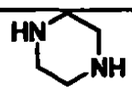
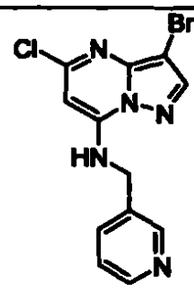
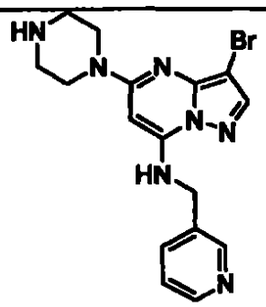
A solution of the compound from Preparative Example 184 (0.05 g, 0.15 mmol), N-methylpiperazine (20 μL, 1.2 eq.) and iPr_2Et (52 μL, 2.0 eq.) in dioxane (1 mL) was heated to 70 °C overnight. The reaction mixture was cooled to room temperature and diluted with H_2O and saturated $NaHCO_3$. The resulting 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.)

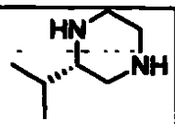
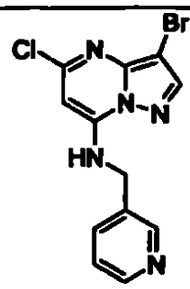
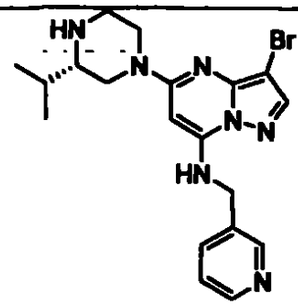
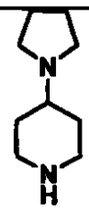
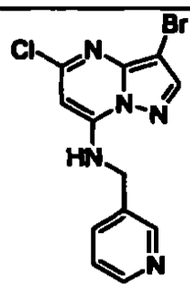
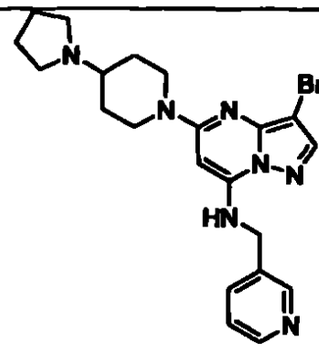
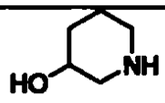
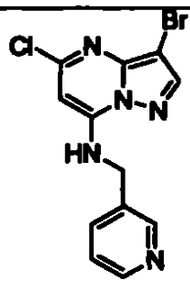
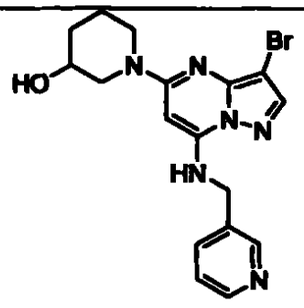
EXAMPLES 269-275:

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

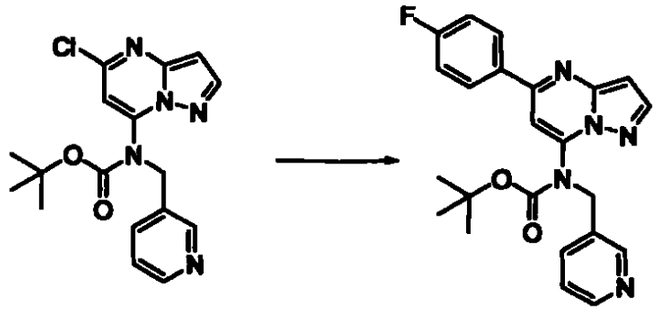
Ex.	Column 2	Column 3	Column 4	CMPD

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

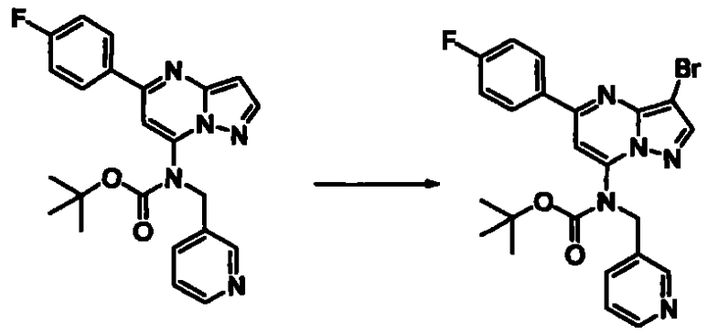
EXAMPLE 276:

Step A:



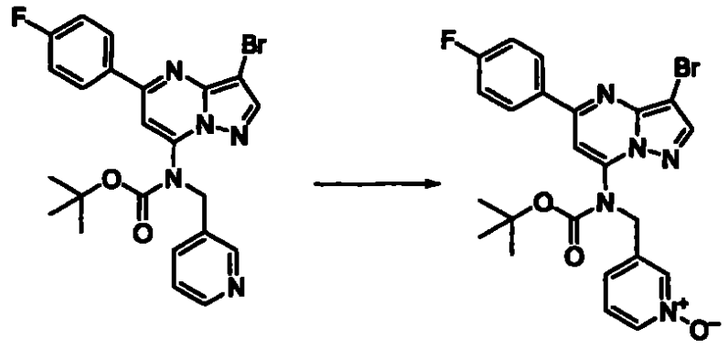
4-Fluorophenyl magnesium bromide (0.68 mL, 1.2 eq.) was added to the compound prepared in Preparative Example 193 (0.20 g, 0.55 mmol) and $PdCl_2(dppf)_2$ (0.037 g, 10 mol%) in THF and the resulting solution was stirred at room temperature 72 hours. The reaction mixture was dilute with saturated NH_4Cl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



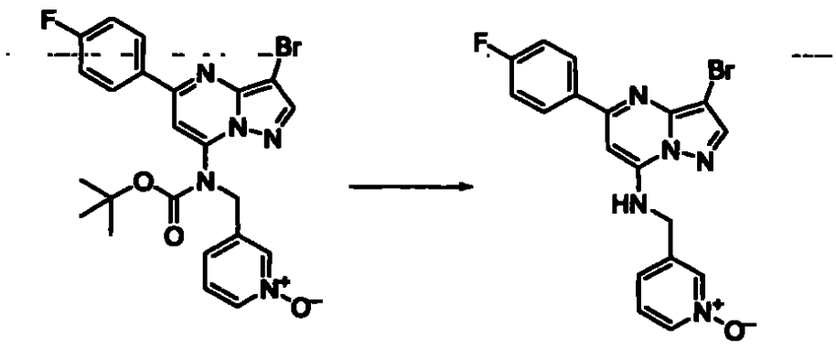
By essentially the same procedure set forth in Preparative Example 127 only substituting the compound prepared in Example 276, Step A, the above compound was prepared (0.17 g, 94% yield).

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).

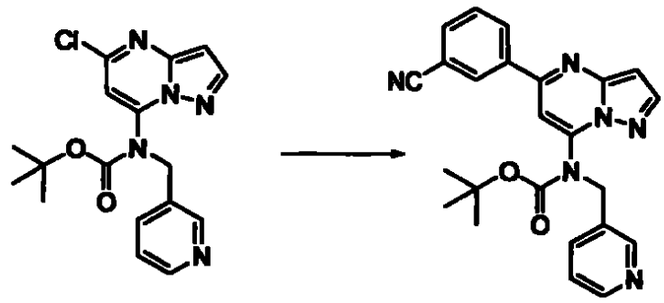
Step D:



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, 62% yield). MS: MH^+ = 414; mp = 110-115 °C.

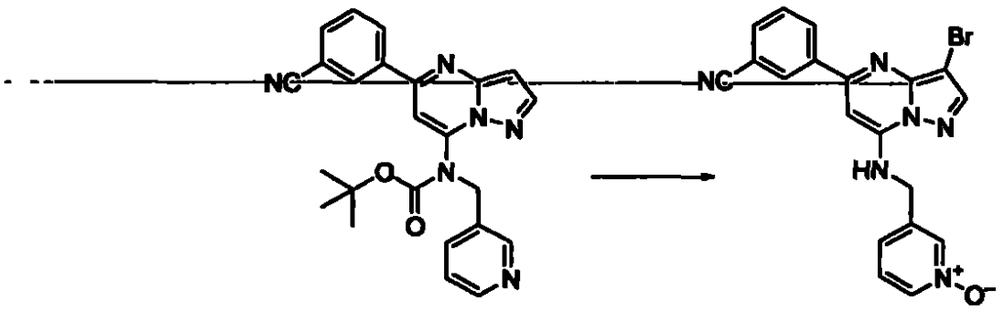
EXAMPLE 277:

Step A:



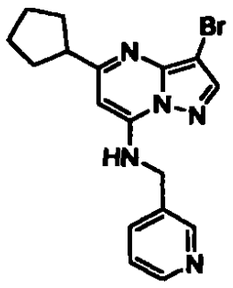
$Pd(PPh_3)_4$ (0.065 g, 10 mol%) was added to 3-cyanophenyl zinc iodide (2.2 mL, 0.5 M solution in THF, 2 eq.) and the compound prepared in Preparative Example 193 (0.2 g, 0.56 mmol) in DMF (2.0 mL) and the resulting solution heated to 80 °C g for 144 hours. The reaction mixture was cooled to room temperature,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

Step B through Step D:



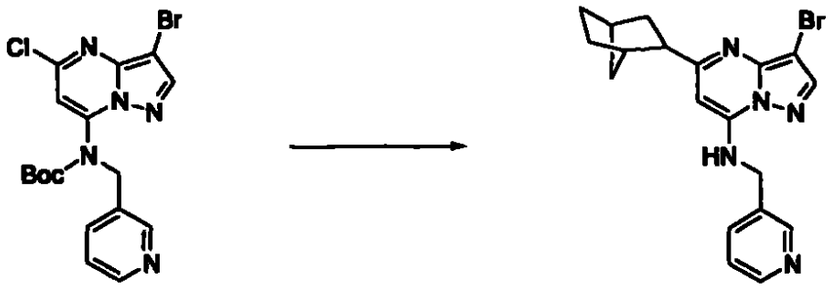
By essentially the same procedures set forth in Example 276, Step B through Step D, the above compound was prepared (0.023 g, 53% yield). MS: MH^+ = 421; mp = 230 °C (dec.)

EXAMPLE 278:



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

EXAMPLE 279:



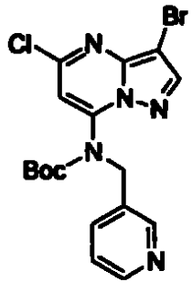
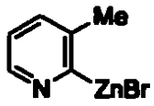
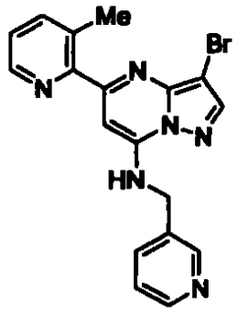
The palladium-catalyzed zinc cross-coupling reaction was carried out in a manner similar to the procedure described in *J. Org. Chem.* (1999), 453. A solution of the chloropyrazolopyrimidine (200 mg, 0.458 mmol), $Pd(PPh_3)_4$ (53

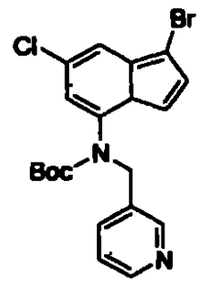
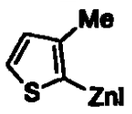
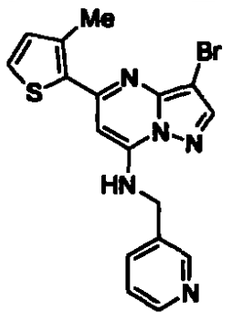
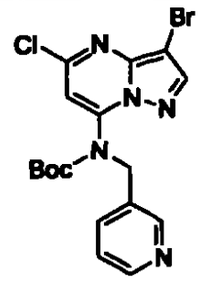
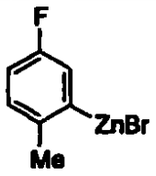
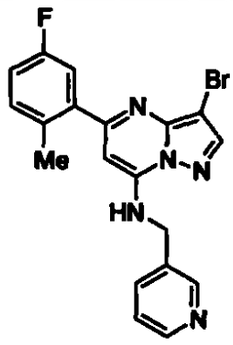
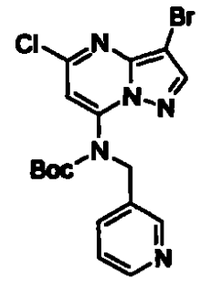
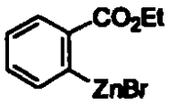
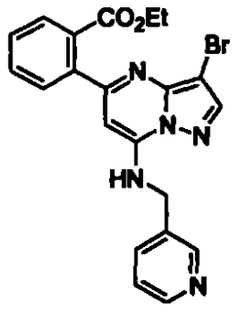
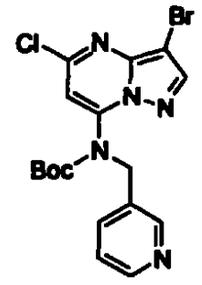
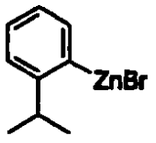
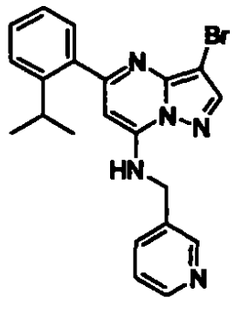
mg, 0.046 mmol), and *exo*-2-norbonylzinc bromide (0.5 M in THF, 0.95 mL, 0.47 mmol) in DMF (2 mL) was refluxed at 100°C (oil bath temp.) overnight. The reaction mixture was quenched with half-saturated NH_4Cl and extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under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

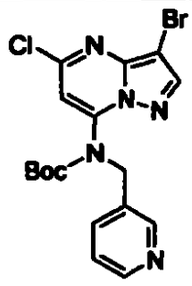
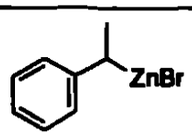
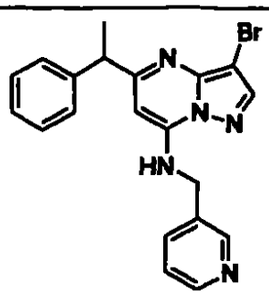
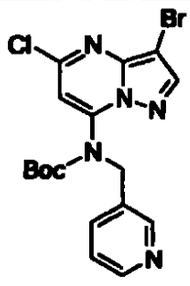
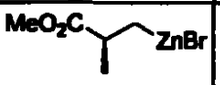
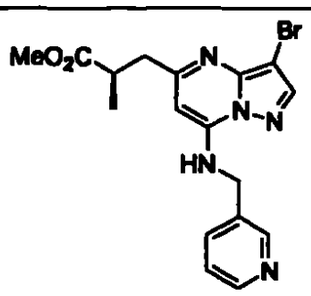
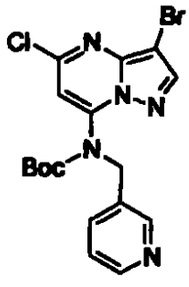
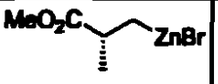
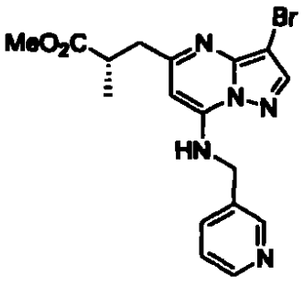
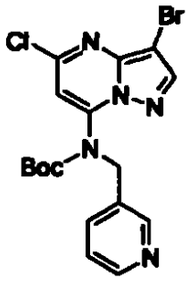
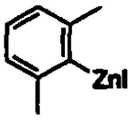
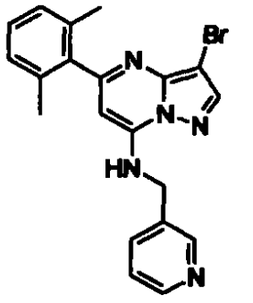
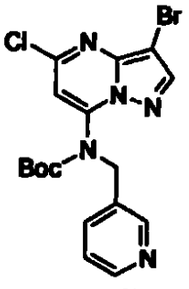
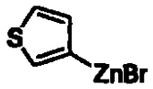
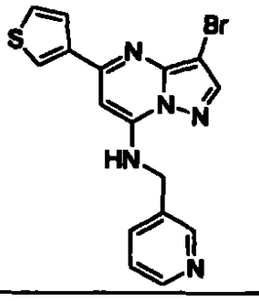
EXAMPLES 280-294:

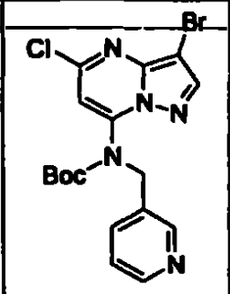
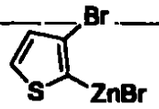
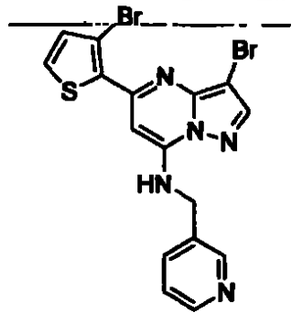
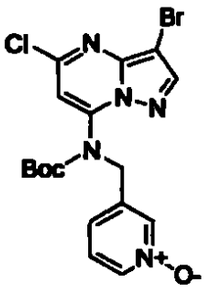
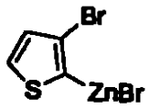
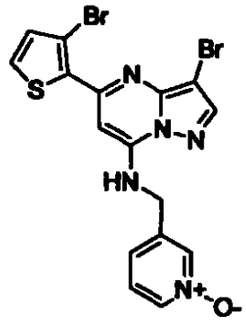
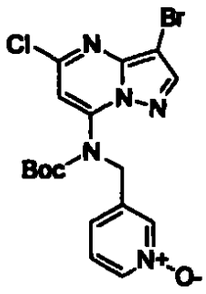
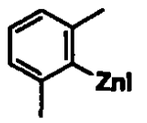
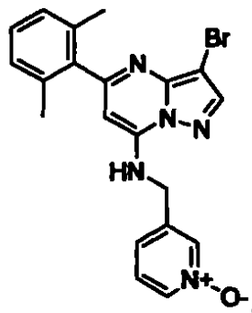
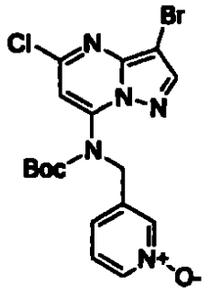
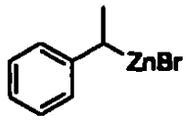
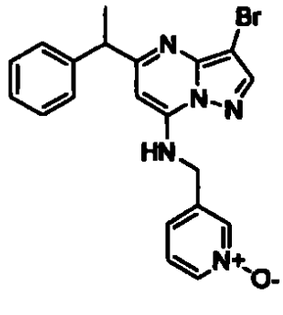
By following essentially the same procedure set forth in Example 279 only substituting the chlorides shown in Column 2 of Table 26 and the organozinc reagents shown in Column 3 of Table 26, the compounds in Column 4 of Table 26 were prepared:

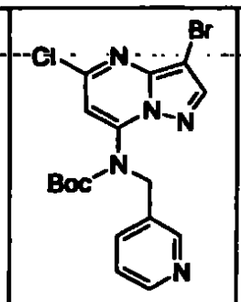
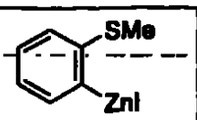
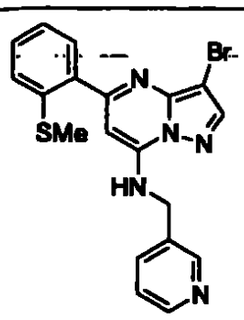
Table 26

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

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

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

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

294				LCMS: MH^+ = 426

Additional data for select compounds is shown below.

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

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

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

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

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

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

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

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

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

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

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

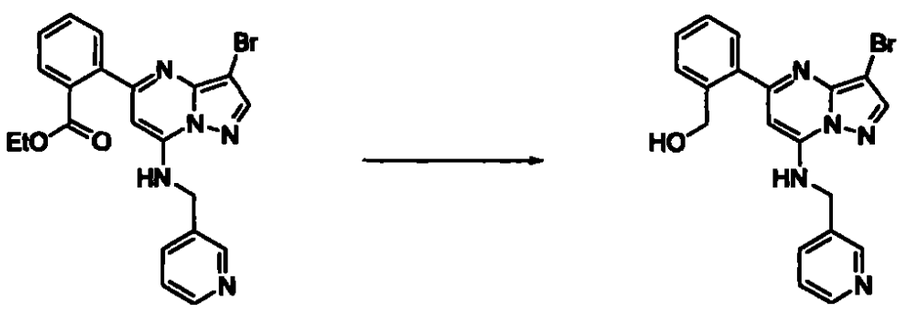
EXAMPLE 291: ^{1}H NMR (DMSO-d_6) δ 9.12 (s, 1H), 8.40 (s, 1H), 8.33 (s, 1H), 8.13 (m, 1H), 7.82 (d, J = 5.1 Hz, 1H), 7.40-7.39 (m, 2H), 7.22 (d, J = 5.1 Hz, 1H), 6.86 (s, 1H), 4.86 (s, 2H).

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

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

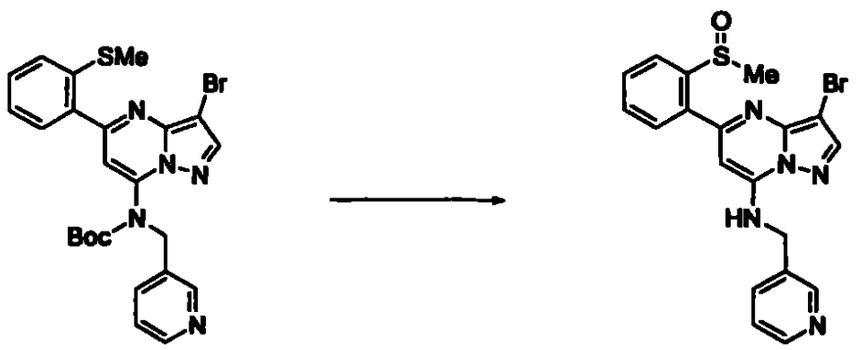
EXAMPLE 294: ^{1}H NMR ($CDCl_3$) δ 8.67 (s, 1H), 8.59 (d, J = 4.8 Hz, 1H), 8.01 (s, 1H), 7.71 (m, 1H), 7.52 (dd, J = 7.8, 1.8 Hz, 1H), 7.40-7.19 (m, 4H), 6.78 (t, J = 6.0 Hz, 1H), 6.32 (s, 1H), 4.67 (d, J = 6.0 Hz, 2H), 2.38 (s, 3H).

EXAMPLE 295:



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

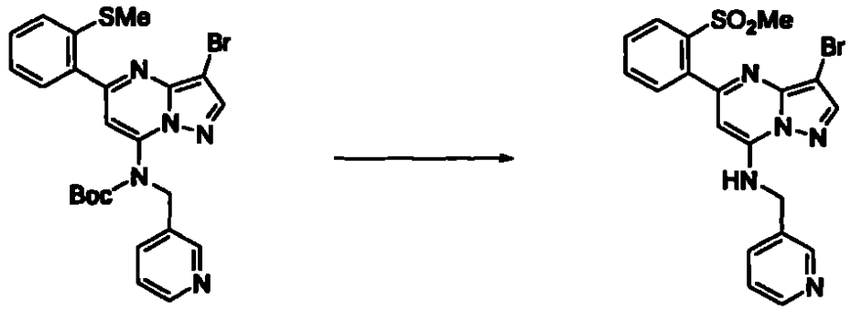
EXAMPLE 296:



To a solution of the *N*-Boc-protected compound prepared in Example 294 (45 mg, 0.085 mmol) in CH_2Cl_2 (4 mL) at –50°C was added *m*-CPBA (18 mg, 0.10 mmol). After stirring for 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

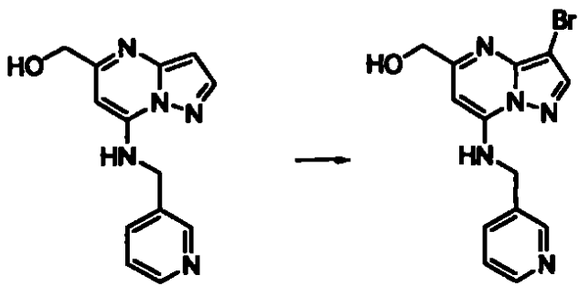
extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by preparative thin-layer chromatography using a 5% MeOH in EtOAc solution as eluent (26 mg, 89% yield). LCMS: MH^+ = 442; ^1H NMR ($CDCl_3$) δ 8.71 (s, 1H), 8.64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

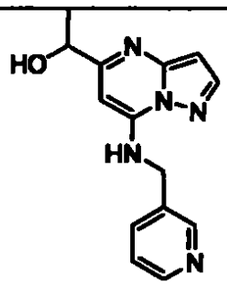
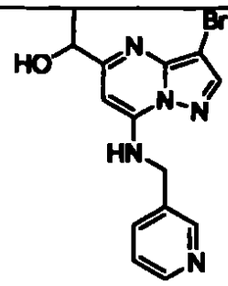
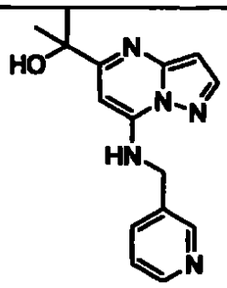
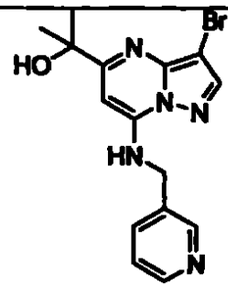


By essentially the same procedure set forth in Preparative Example 127 only substituting the compound prepared in Preparative Example 189, the above compound was prepared. MS: MH^+ = 334; mp = 170-173 °C.

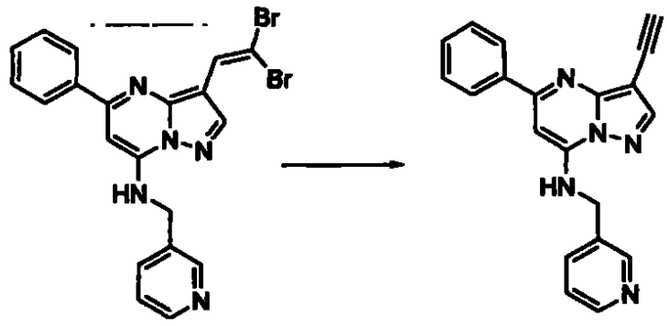
Examples 299-300:

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

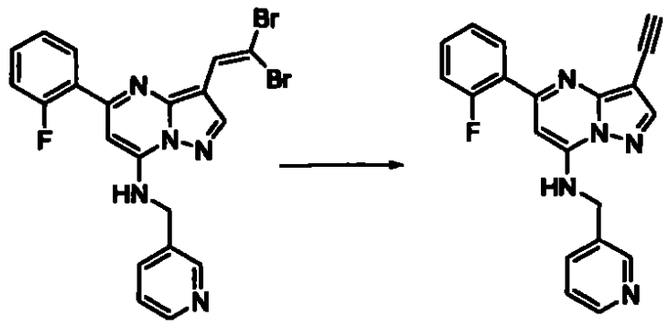
Ex.	Column 2	Column 3	CMPD
299			MS: MH^+ = 348 m.p. = 73 – 83 °C
300			MS: MH^+ = 362 m.p. = 165 – 175 °C

EXAMPLE 301:



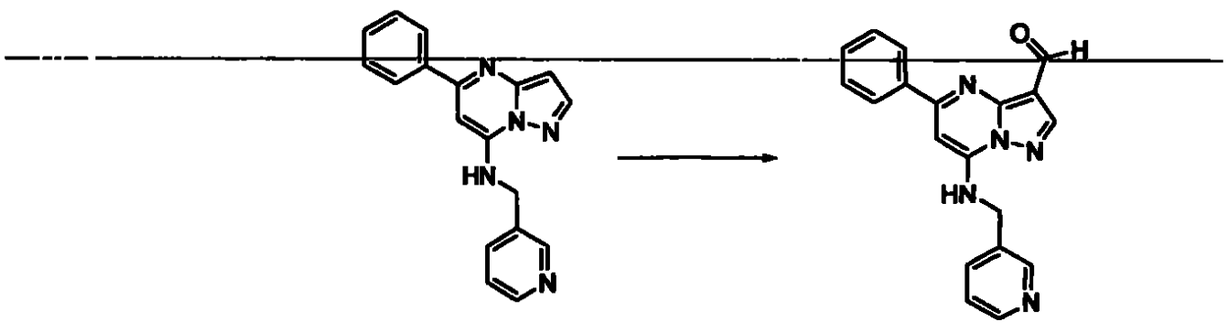
To a solution of the compound prepared in Preparative Example 186 (0.1 g, 0.21 mmol) in THF (4.0 mL) at -78 °C was added nBuLi (0.57 mL, 2.16M in hexanes, 5.0 eq.) at -78 °C. The reaction mixture was stirred 2 hours at -78 °C, quenched with H_2O, warmed to room temperature, and extracted with EtOAc.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



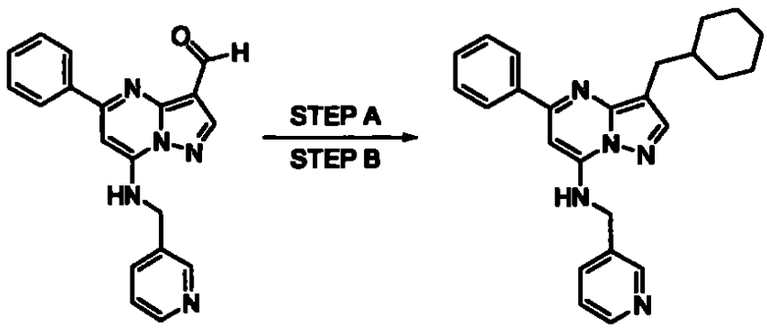
By essentially the same procedure set forth in Example 301 only substituting the compound from Preparative Example 187, the above compound was prepared (0.049 g, 68% yield).MS: MH^+ = 344; mp = 69-71 °C.

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.

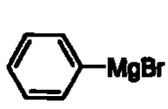
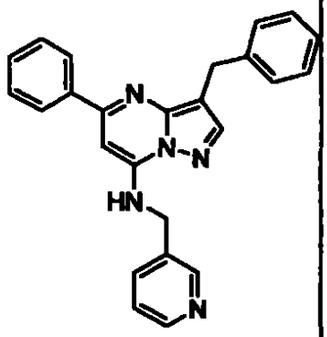
STEP B:

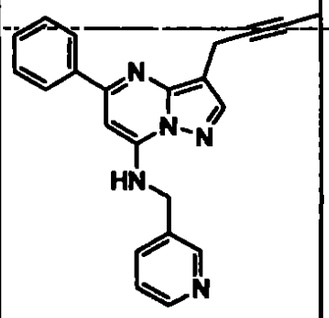
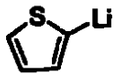
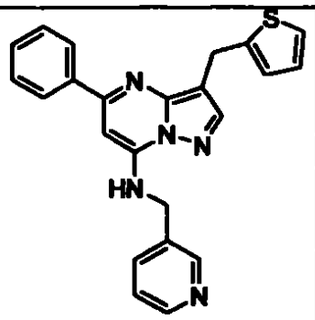
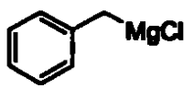
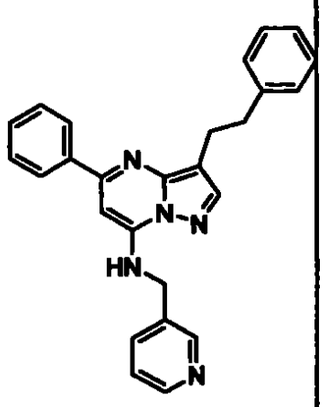
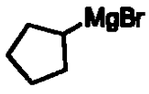
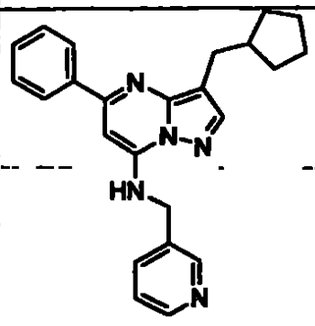
To a solution of alcohol (53 mg, 0.13 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C was added Et_3SiH (24 µL, 0.15 mmol) followed by TFA (24 µL, 0.30 mmol). The mixture was stirred for 2 h at 0 °C and rt for 2 h whereupon additional portions of Et_3SiH (24 µL, 0.15 mmol) and TFA (24 µL, 0.30 mmol) were added and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

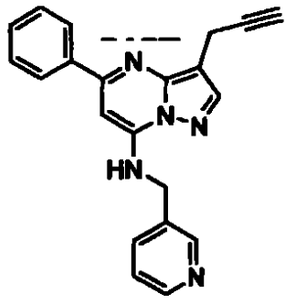
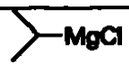
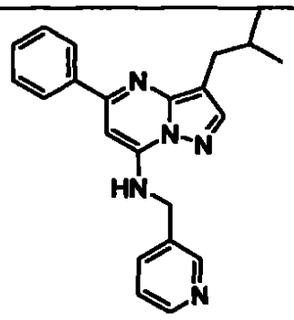
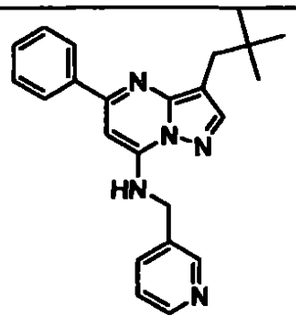
EXAMPLES 305-312:

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:

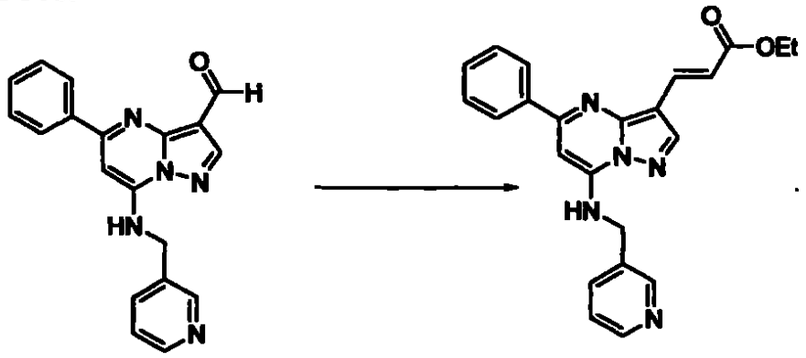
TABLE 28

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

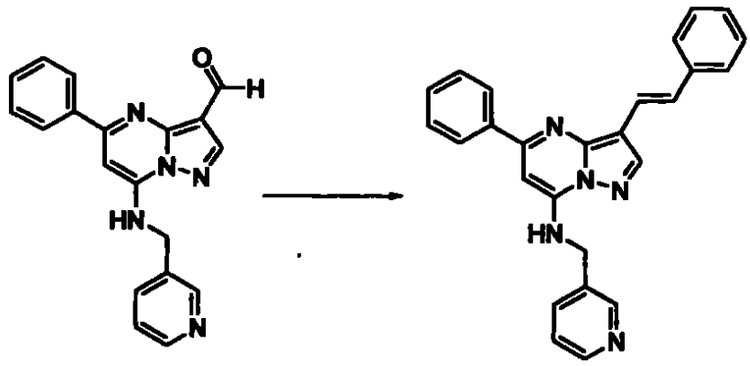
EXAMPLE 313:



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

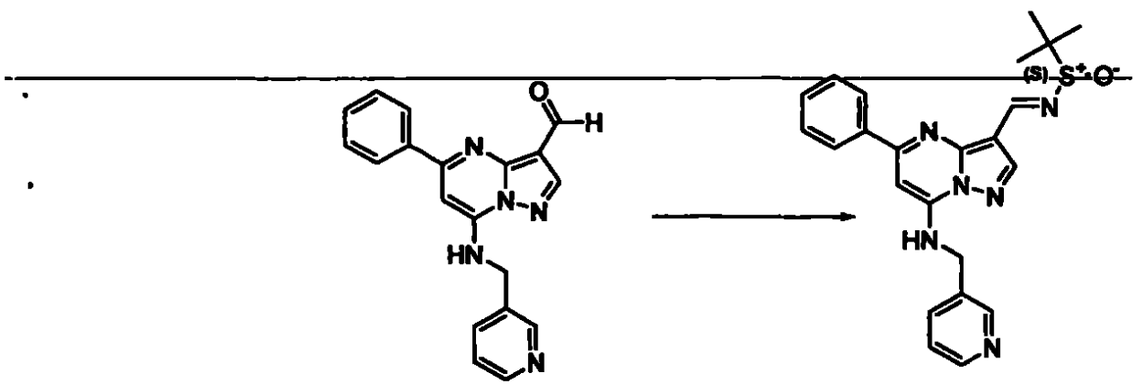
(0.12 g, 0.33 mmol) in one portion. The mixture was heated at reflux for 24h, cooled to rt, and concentrated under reduced pressure. The mixture was diluted CH_2Cl_2 (5 mL), brine (2 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 4 mL). The organic layers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



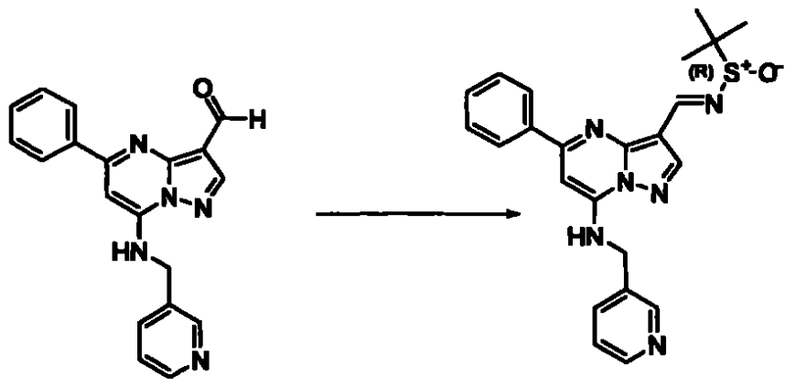
To a mixture of benzyltriphenylphosphonium bromide (0.59 g, 1.37 mmol) in THF (3 mL) was added NaH (55 mg, 1.37 mmol) and the mixture was stirred for 30 min. The aldehyde (0.15 g, 0.46 mmol) from Example 303 was added in a single portion and the mixture was heated at reflux for 36h. The mixture was cooled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



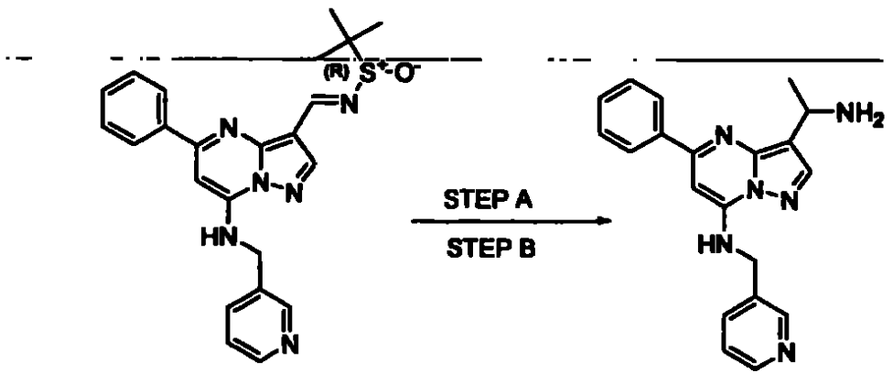
To a solution of aldehyde (0.20 g, 0.60 mmol) from Example 303 in THF (3 mL) was added Ti (i-OPr)$_4$ (0.36 mL, 1.21 mmol) dropwise followed by addition of (*S*)-(-)-2-methyl-2-propanesulfinamide (74 mg, 0.61 mmol). The resulting mixture was stirred for 18h at reflux, cooled to rt, and quenched with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



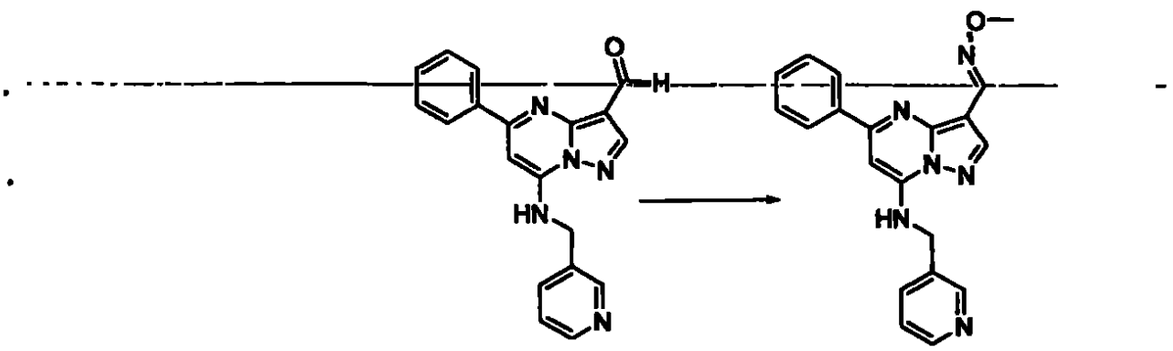
STEP A:

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:

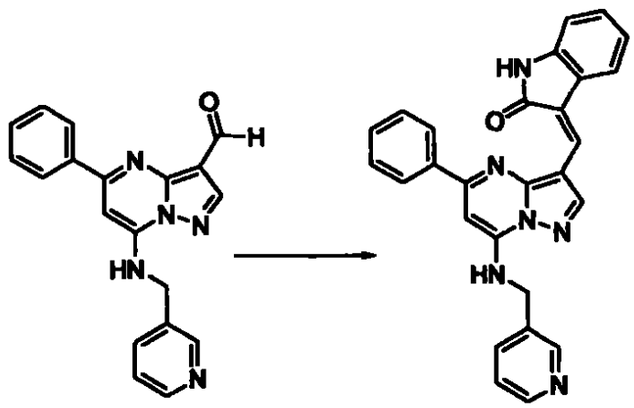
The crude material from Step A (30 mg, 0.067 mmol) in MeOH (2 mL) was added conc. HCl (2 mL). The mixture was stirred at rt for 12h and the mixture was concentrated to dryness. The crude material was partitioned between CH_2Cl_2 (3 mL) and sat. aq. $NaHCO_3$ (2 mL) and the layers were separated. The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

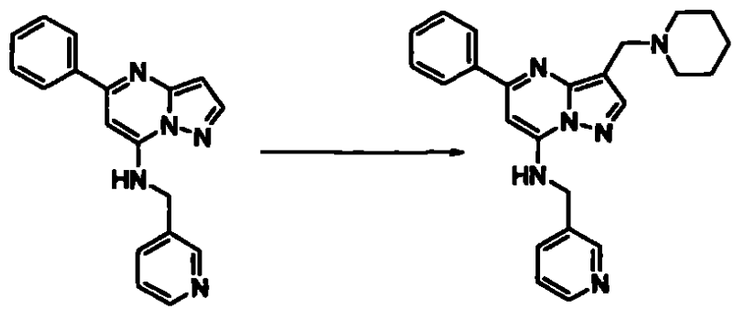
EXAMPLE 319:



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:

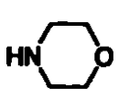


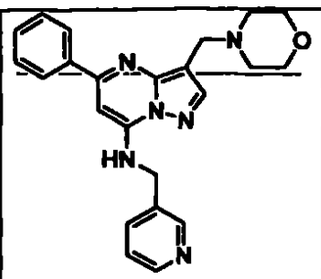
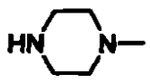
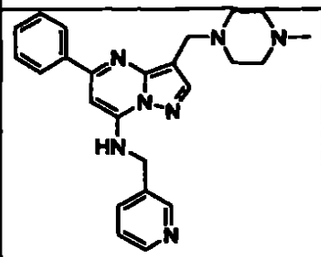
To a solution of 3-H analog (106 mg, 0.35 mmol) from Preparative Example 187.10 in AcOH (2 mL) was added 37% aqueous formaldehyde (1.5 ml; 1.40 mmol) followed by piperidine (100 µL; 0.37 mmol). The resulting mixture was stirred at rt for 24h and the AcOH was removed under reduced pressure. The mixture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

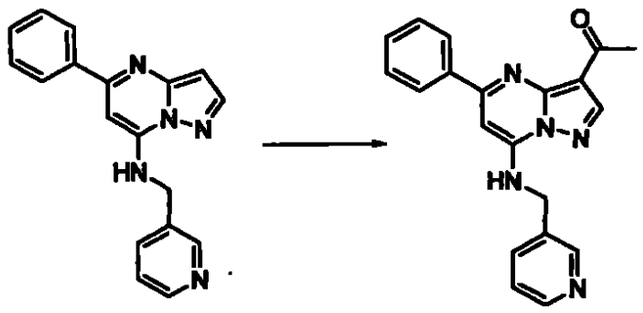
By essentially the same procedure set forth in Example 320 only substituting the amines in Column 2 of Table 29 and employing the 3-H adduct from Preparative Example 187.10, the compounds in Column 3 of Table 29 were prepared:

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

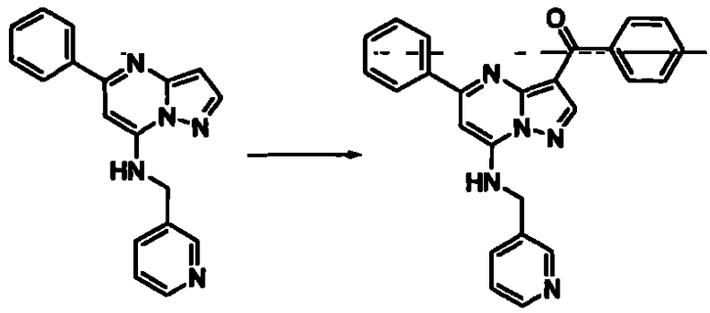
			
322			1. mp = 102-104 2. M+H = 414

EXAMPLE 323:



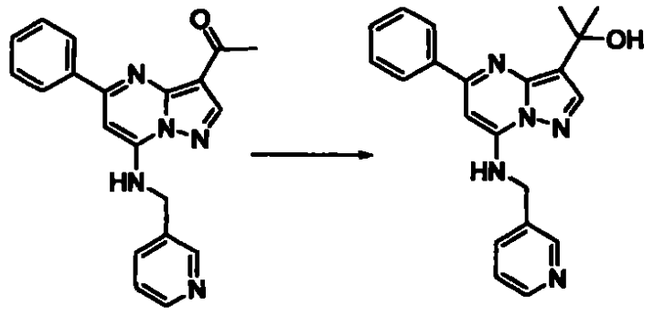
To a solution of 3-H analog (113 mg, 0.38 mmol) from Preparative Example 187.10 in CH_2Cl_2 (5 mL) at rt was added $AlCl_3$ (215 mg, 1.61 mmol) followed by AcCl (100 mL, 1.40 mmol). The mixture was heated at reflux for 12h and was cooled to rt. The mixture was treated sequentially with 3M HCl (3 mL)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



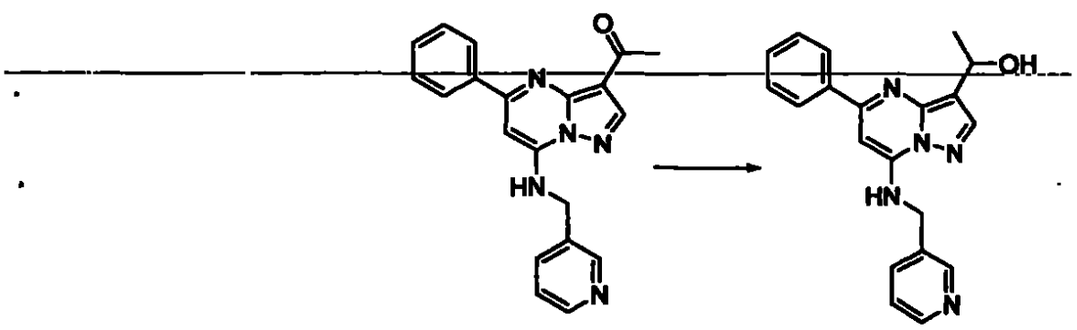
Utilizing the method described in Example 323, except employing benzoyl chloride, the title compound was prepared in 61% yield as a white solid. mp 172-175 °C; M+H = 406.

EXAMPLE 325:



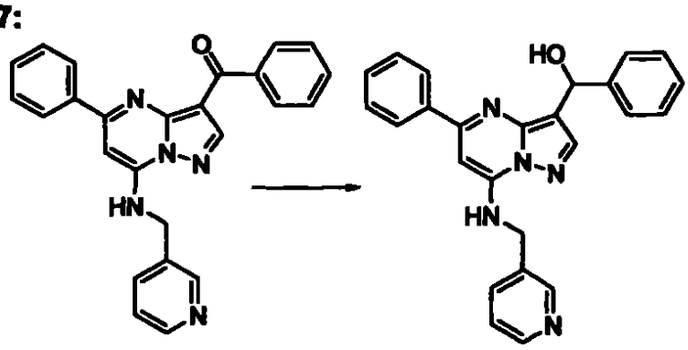
To a solution of ketone (100 mg, 0.29 mmol) from Example 323 in CH_2Cl_2 (2.5 mL) at 0 °C was added MeMgBr (0.35 mL, 3.0M in Et_2O) dropwise. The resulting mixture was stirred for 18h at rt and was carefully quenched by addition of sat. aq. NH_4Cl (2 mL) and CH_2Cl_2 (2 mL) were added. The layers were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



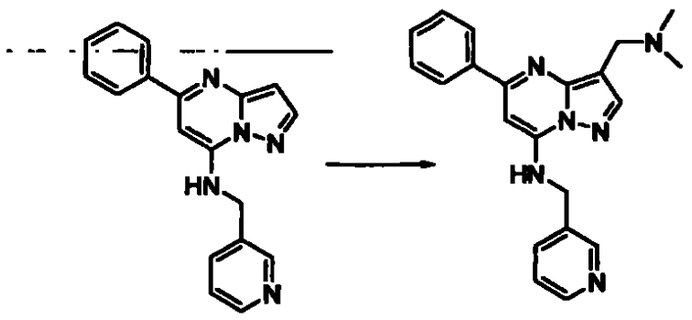
To a solution of ketone (84 mg, 0.24 mmol) from Example 323 in MeOH/THF (1:1; 2 mL total) at 0 °C was added $NaBH_4$ (12 mg, 0.30 mmol) in one portion. The resulting mixture was stirred for 18h at rt whereupon and additional portion of $NaBH_4$ (12 mg, 0.30 mmol) was added. The mixture was stirred for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



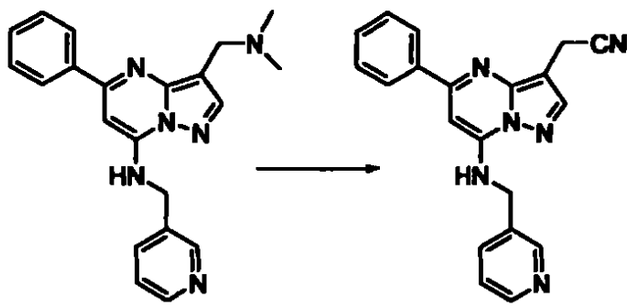
Using the same procedure as outlined in Example 326, the ketone (84 mg, 0.21 mmol) was converted to 53 mg (62%) as a light yellow solid. mp 78-80 °C; M+H = 408.

EXAMPLE 328:



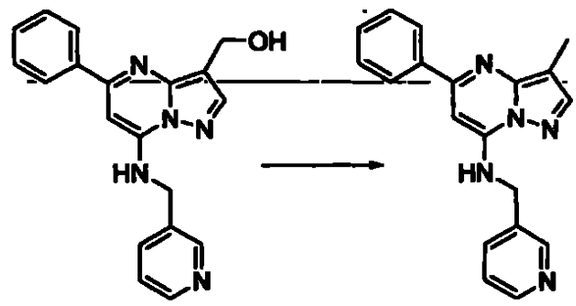
To a solution of 3-H adduct (1.3 g, 4.31 mmol) from Preparative Example 187.10 in CH_2Cl_2 (50 mL) was added Eschenmoser's salt (0.79 g, 4.31 mmol) followed by dropwise addition of TFA (0.56 mL, 7.33 mmol). The mixture was stirred at rt for 48 h and was diluted with CH_2Cl_2 (250 mL). The organic layer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



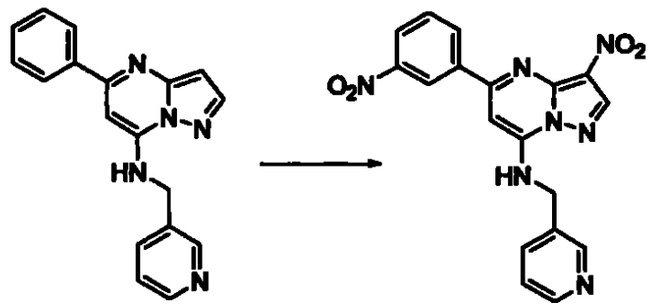
To a solution of tertiary amine adduct (100 mg, 0.28 mmol) from Example 328 in 50% aq. DMF (5 mL) in a pressure tube was added KCN (0.15 g, 2.32 mmol). The tube was capped and heated at 100 °C for 96h. The mixture was cooled to rt and was diluted with EtOAc (25 mL). The organic layer was washed with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

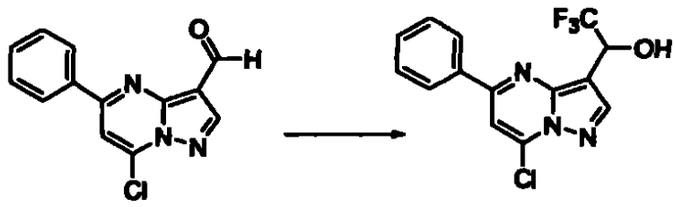


To a solution of 3-H adduct (90 mg, 0.30 mmol) from Preparative Example 187.10 in conc. H_2SO_4 (2 mL) at 0 °C was added fuming HNO_3 (30 µL, 0.72 mmol) dropwise. The resulting mixture was stirred for 1 h at 0 °C whereupon ice

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

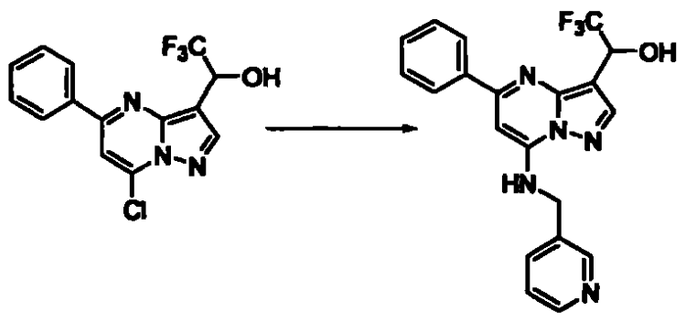
EXAMPLE 332:

Step A:



To a solution of aldehyde (0.10 g, 0.39 mmol) from Preparative Example 168 in THF (2.5 mL) at 0 °C was added CF_3TMS (64 mL, 0.43 mmol) followed by CsF (10 mg). The resulting mixture was stirred for 2 h at 0 °C and 2h at rt. 1M HCl (5 mL) was added and the mixture was diluted with CH_2Cl_2 (10 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL), and the organic layers were combined. The organic layer was washed with brine (1 x 10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 127 mg (99%) of a yellow semisolid. M+H =328. The crude product was carried on without further purification.

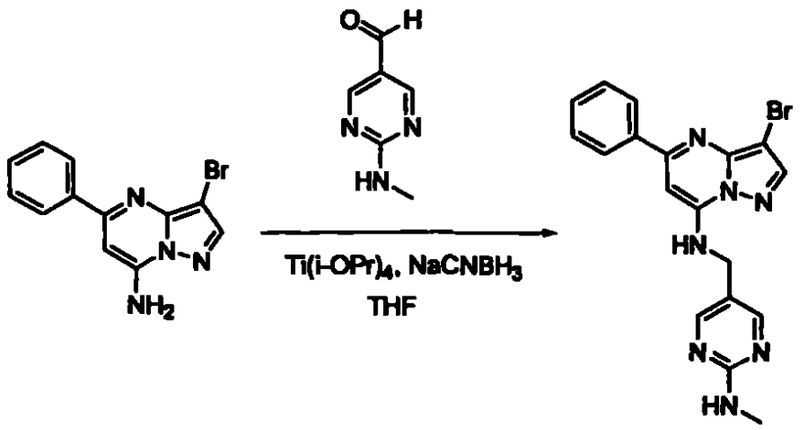
Step B:



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

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

EXAMPLE 333:



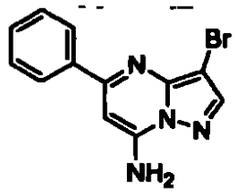
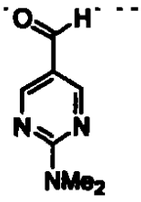
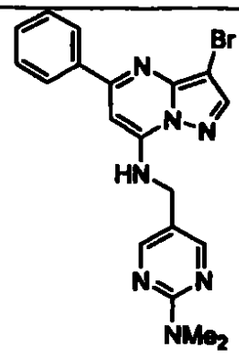
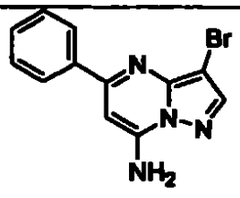
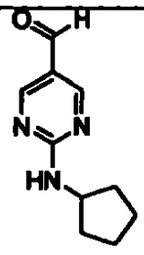
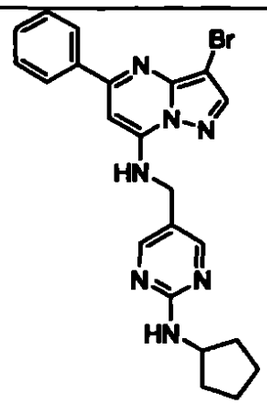
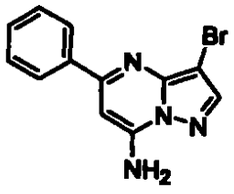
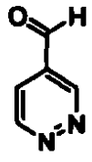
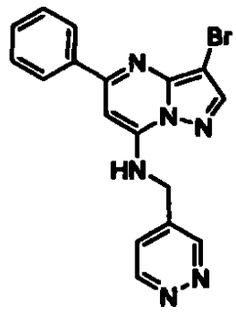
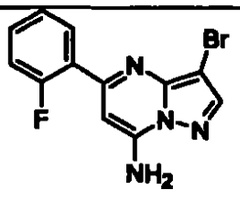
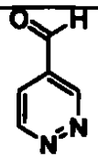
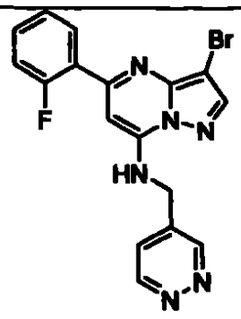
To a solution of aniline (200 mg, 0.69 mmol) from Preparative Example 174 in THF (6 mL) at rt was added aldehyde (114 mg, 0.83 mmol) from Preparative Example 256 followed by dropwise addition of Ti(*i*-OPr)$_4$ (0.82 mL, 2.77 mmol). The mixture was stirred at reflux for 4 h and was cooled to rt. $NaCNBH_3$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

EXAMPLES 334-337:

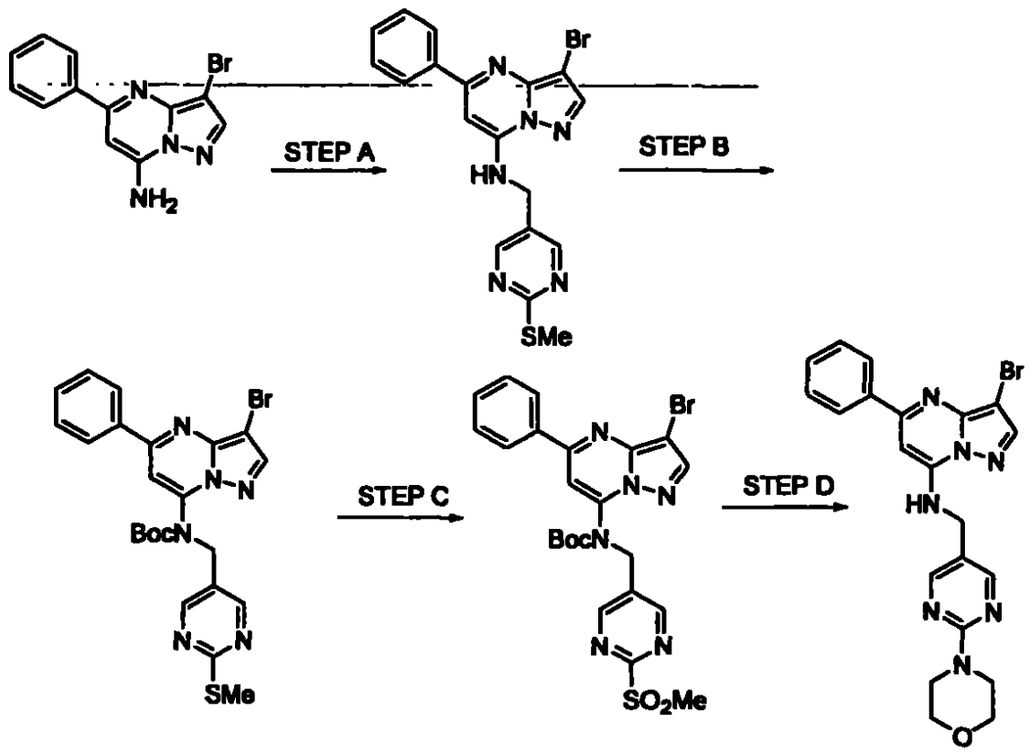
By essentially the same procedure set forth in Example 333 only by utilizing the anilines shown in Column 2 of Table 30 and the aldehydes shown in Column 3 of Table 30, the compounds in Column 4 of Table 30 were prepared:

TABLE 30

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

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

EXAMPLE 338:



STEP A:

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

STEP B:

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

STEP C:

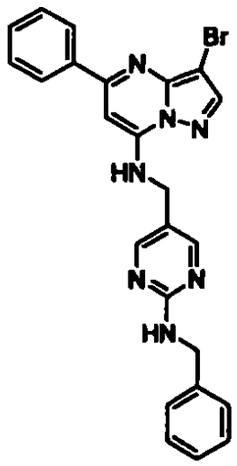
To a solution of thiomethyl derivative from Example 338, Step B (41 mg, 0.078 mmol) in CH_2Cl_2 (2 mL) was added MCPBA (33 mg, 0.19 mmol) in one portion. The resulting mixture was stirred for 3h at rt and the mixture was diluted

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

STEP D:

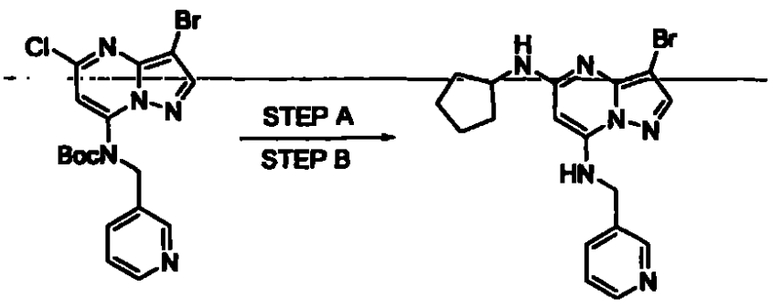
To a flask charged with sulfone from Example 338, Step C (75 mg, 0.13 mmol) and a stir bar was added morpholine (2 ml; 22 mmol). The mixture was heated at reflux for 12h, cooled to rt, and concentrated to dryness under high vacuum. The crude product was purified by preparative thin-layer chromatography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

EXAMPLE 339:



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

EXAMPLE 340:



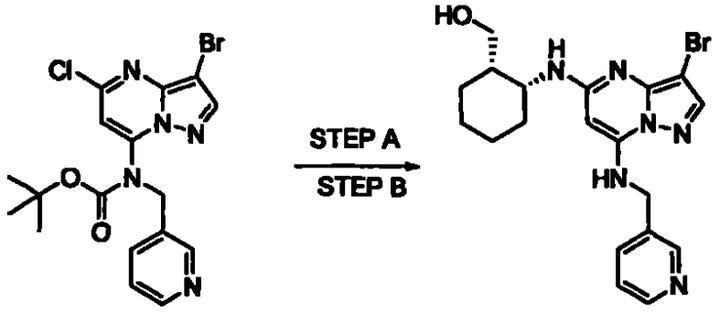
STEP A:

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

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

To a solution of the compound prepared in Example 340, Step A (135 mg, 0.28 mmol) in CH_2Cl_2 (2 mL) at rt was added TFA (0.54 mL, 7.0 mmol) dropwise. The resulting solution was stirred for 18 h at rt and was concentrated under reduced pressure. The crude material was redissolved in CH_2Cl_2 (5 mL) and the organic layer was sequentially washed with sat. aq. $NaHCO_3$ (2 x 2 mL) and brine (1 x 2 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude material was purified by preparative thin-layer chromatography (8 x 1000 µM) eluting with CH_2Cl_2/MeOH (20:1) to afford 105 mg (97%) of white solid. mp 120-122 °C; M+H = 389.

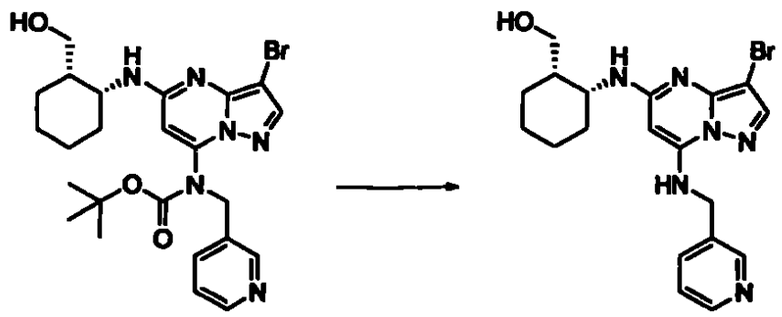
EXAMPLE 341:



Step A:

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

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

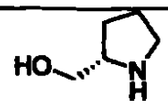
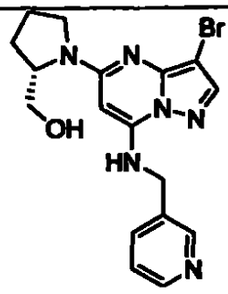
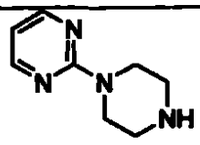
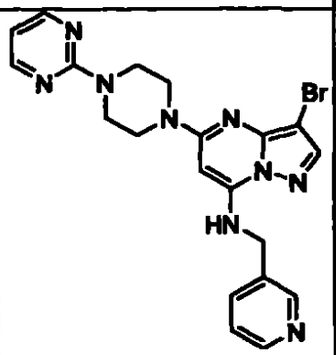
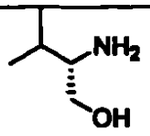
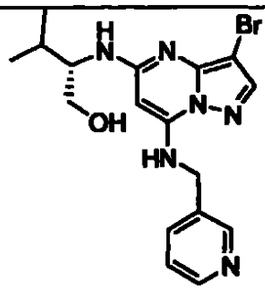
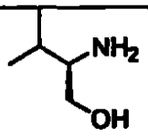
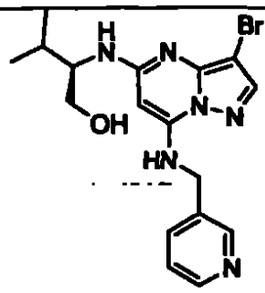


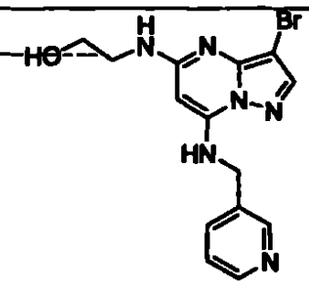
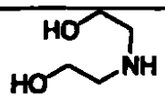
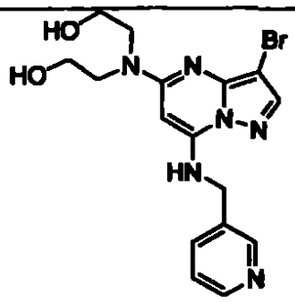
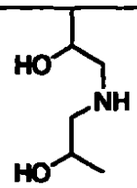
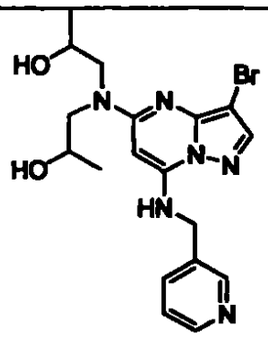
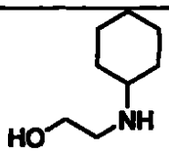
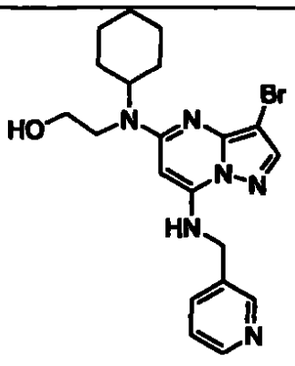
To a mixture of the compound prepared in Example 341, Step A (0.14 g, 0.26 mmol) in EtOH : H_2O (3 mL, 2 : 1) was added KOH (0.29 g, 20 eq.) in one portion. The resulting solution was stirred at reflux 14 hours, cooled to room temperature, and concentrated under reduced pressure. The residue was taken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

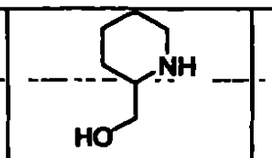
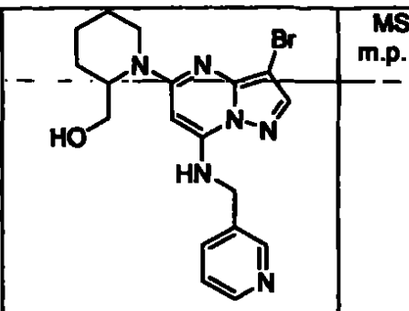
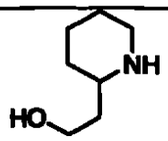
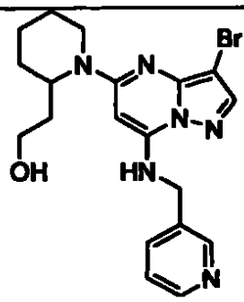
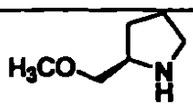
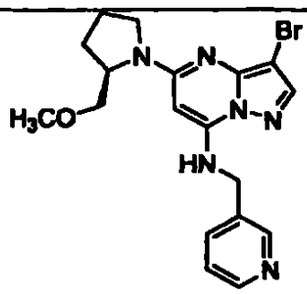
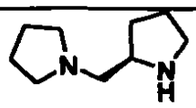
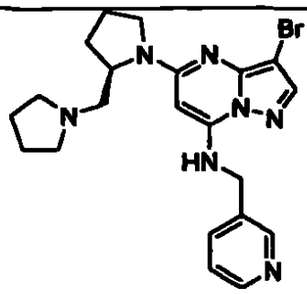
EXAMPLES 342-397:

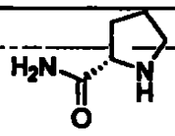
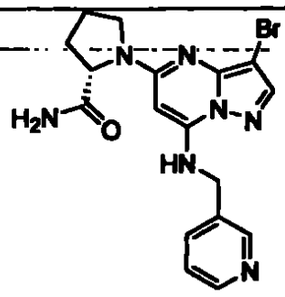
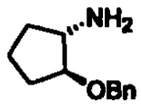
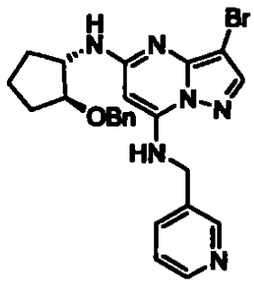
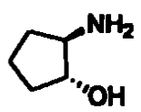
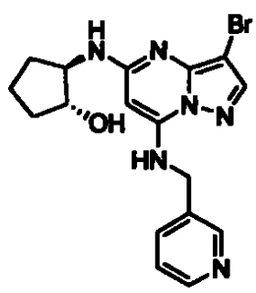
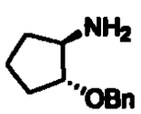
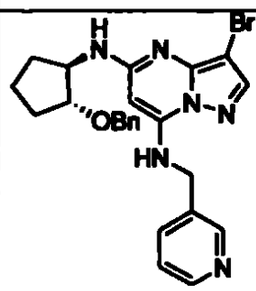
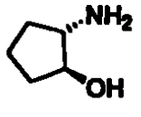
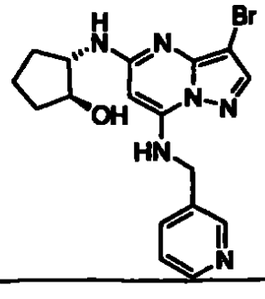
By essentially the same procedure set forth in Example 340 only substituting the chlorides in Column 2 of Table 31 and removing the t-butoxycarbonyl protecting group by the method shown in Column 3 of Table 31, the compounds shown in Column 4 of Table 31 were prepared.

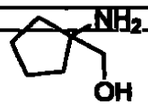
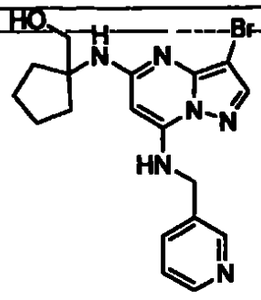
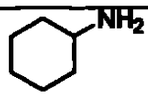
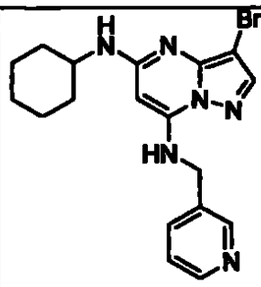
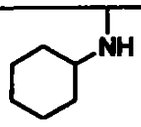
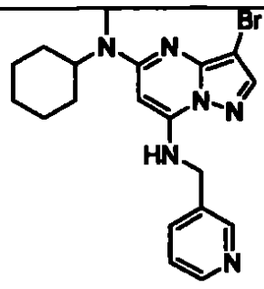
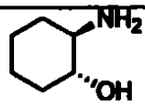
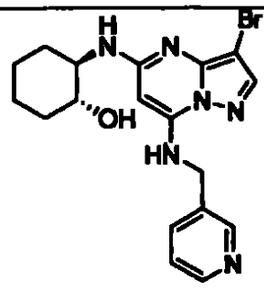
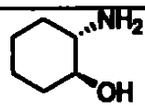
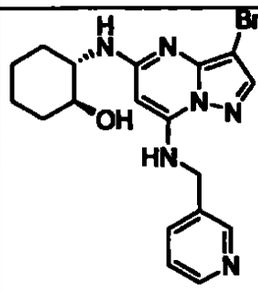
Table 31

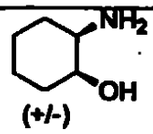
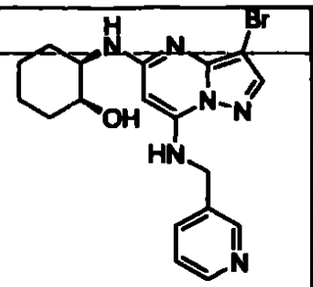
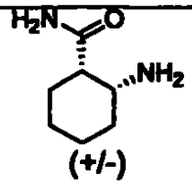
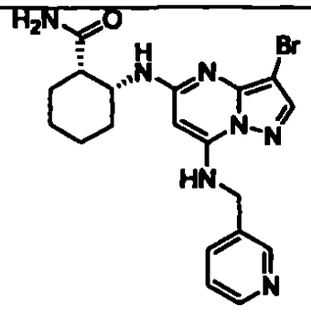
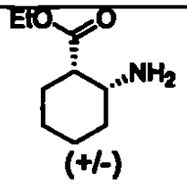
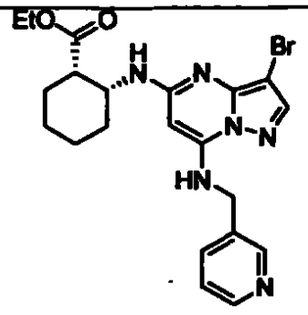
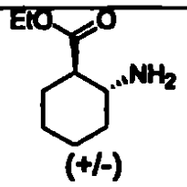
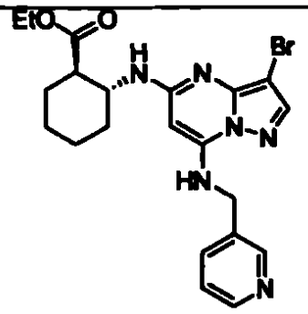
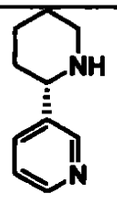
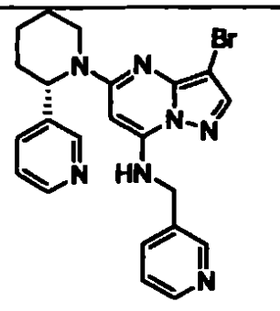
Ex.	Column 2	Column 3	Column 4	CMPD
342		HCl		MS: MH$^+$ = 403 m.p. 151 – 157 °C
343		HCl		MS: MH$^+$ = 466 m.p. 212 – 217 °C
344		HCl		MS: MH$^+$ = 405 m.p. 53 – 58 °C
345		HCl		MS: MH$^+$ = 405 m.p. 63 – 69 °C

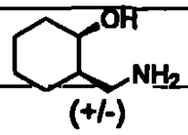
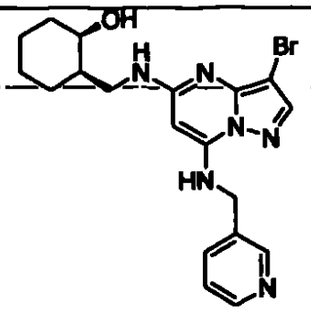
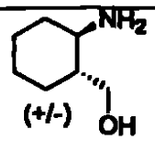
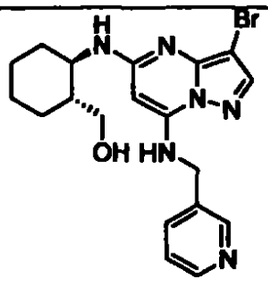
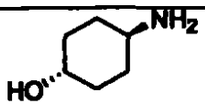
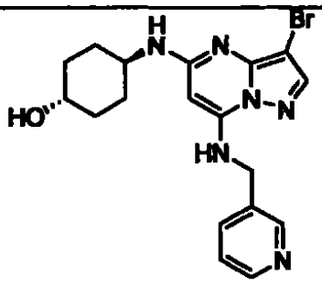
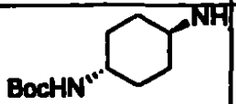
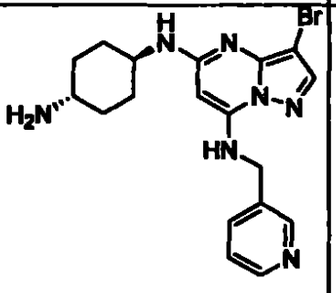
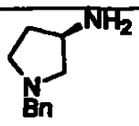
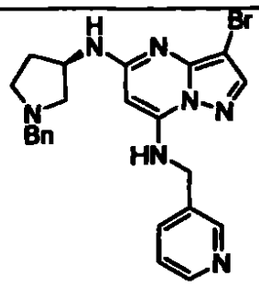
346		HCl		MS: MH$^+$ = 363 m.p. 170 – 171 °C
347		HCl		MS: MH$^+$ = 407 m.p. 148 – 151 °C
348		HCl		MS: MH$^+$ = 435 m.p. 56 – 59 °C
349		HCl		MS: MH$^+$ = 445 m.p. 66 – 68 °C

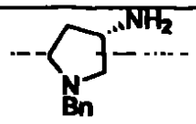
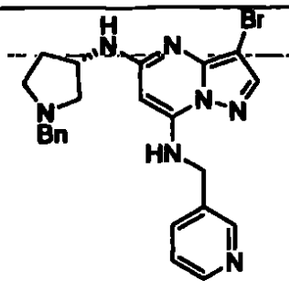
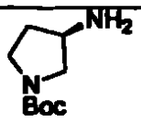
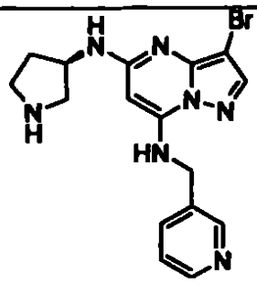
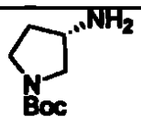
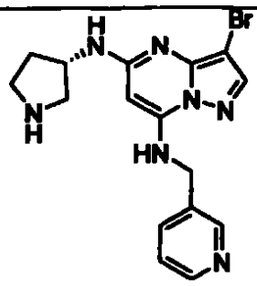
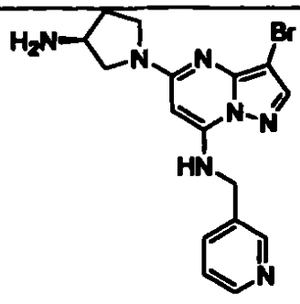
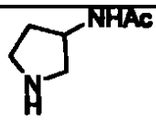
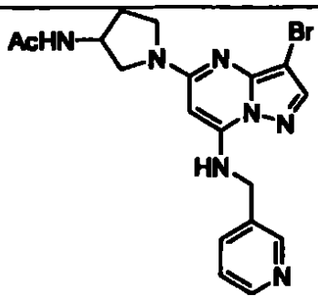
350		KOH		MS: MH$^+$ = 417 m.p. 149 – 151 °C
351		KOH		MS: MH$^+$ = 431 m.p. 111 – 114 °C
352		KOH		MS: MH$^+$ = 417 m.p. 53 – 58 °C
353		KOH		MS: MH$^+$ = 456 m.p. 186 – 189 °C

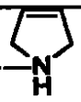
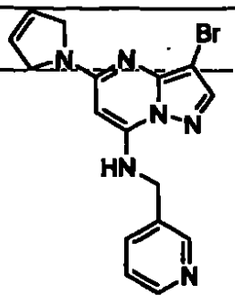
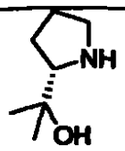
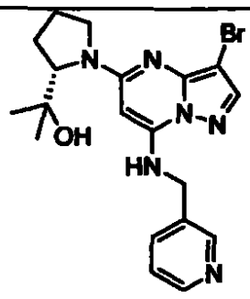
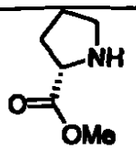
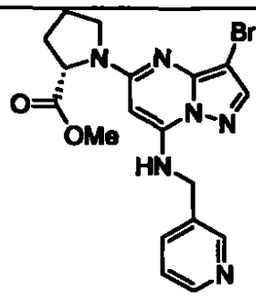
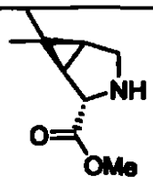
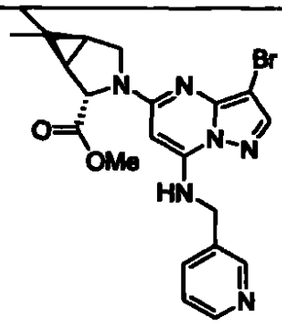
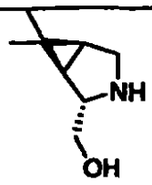
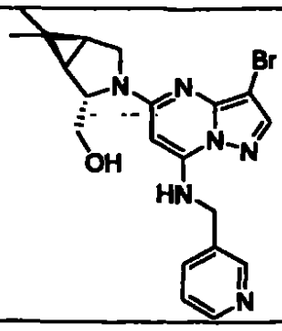
354		KOH		MS: MH$^+$ = 416 m.p. 210 – 213 °C
355		TFA		1. mp = 68-70 2. M+H = 494
356		KOH		1. mp = 181-183 2. M+H = 404
357		TFA		1. mp = 69-71 2. M+H = 494
358		KOH		1. mp = 182-184 2. M+H = 404

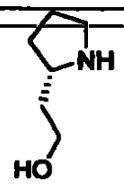
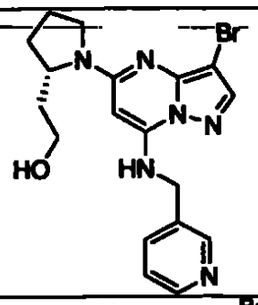
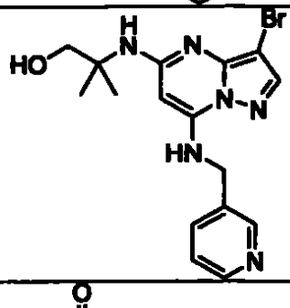
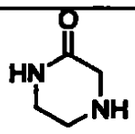
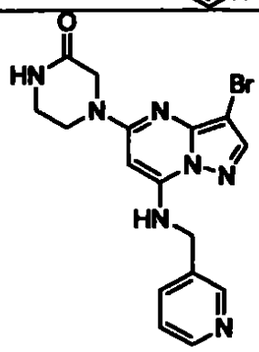
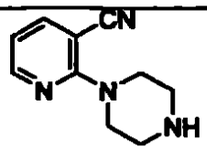
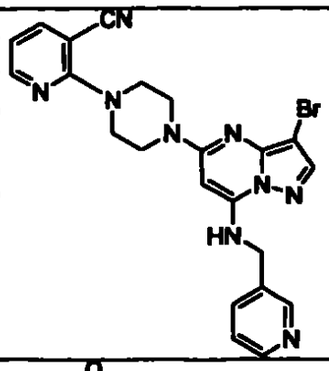
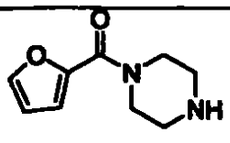
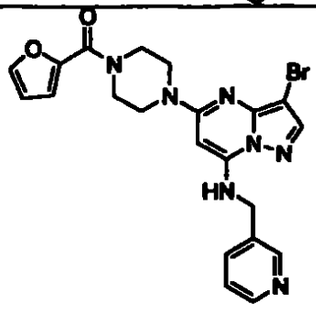
359		KOH		1. mp = 202-204 2. M+H = 418
360		TFA		1. mp = 160-162 2. M+H = 402
361		TFA		1. mp = 151-153 2. M+H = 416
362		KOH		1. mp = 140-143 2. M+H = 418
363		KOH		1. mp = 139-142 2. M+H = 418

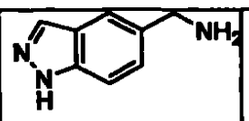
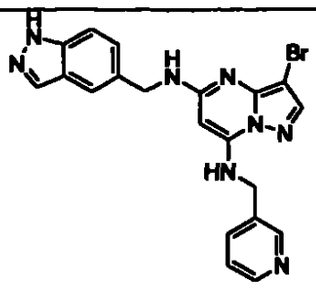
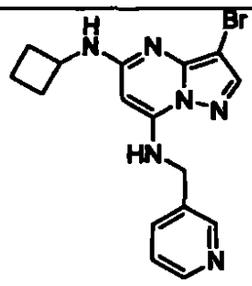
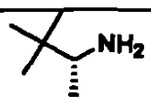
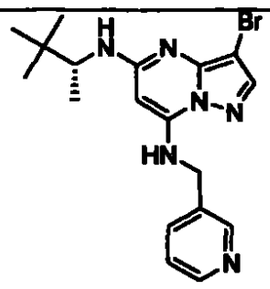
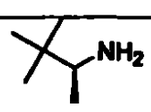
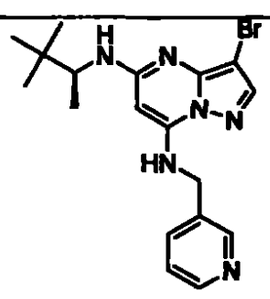
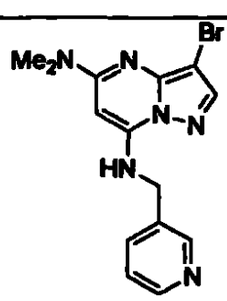
364		KOH		1. mp = 115-117 2. M+H = 418
366		TFA		1. mp = 102-104 2. M+H = 445
367		TFA		1. mp = 118-120 2. M+H = 474
368		TFA		1. mp = 106-108 2. M+H = 474
369		TFA		1. mp = 160-161 2. M+H = 464

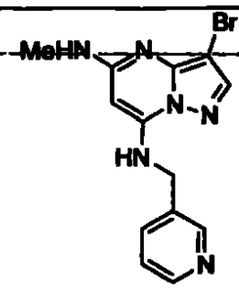
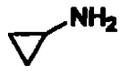
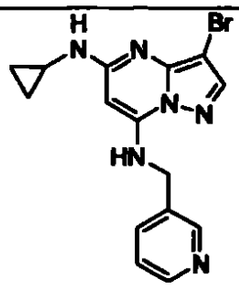
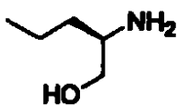
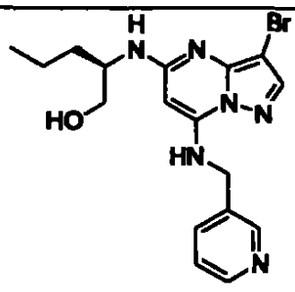
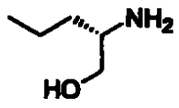
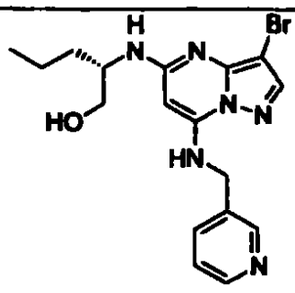
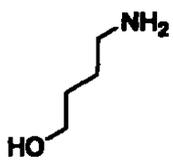
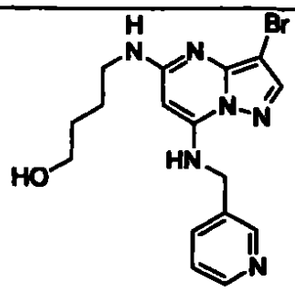
370		TFA		1. mp = 93-95 2. M+H = 432
371		KOH		1. mp = 108-110 2. M+H = 432
372		KOH		1. mp = 180-182 2. M+H = 418
373		TFA		1. mp = 169-170 2. M+H = 417
374		TFA		1. mp = 77-79 2. M+H = 479

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

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

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

388		TFA		1. mp = 167-169 2. M+H = 450
389		TFA		1. mp = 90-92 2. M+H = 374
390		TFA		1. mp = 113-115 2. M+H = 404
391		TFA		1. mp = 114-116 2. M+H = 404
392	$HNMe_2$	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).

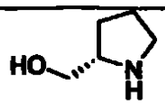
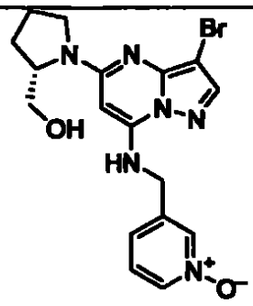
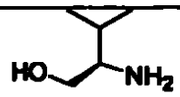
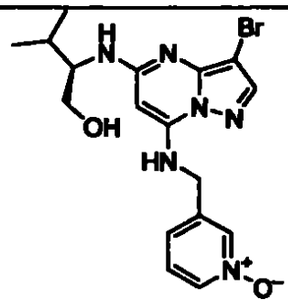
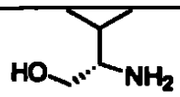
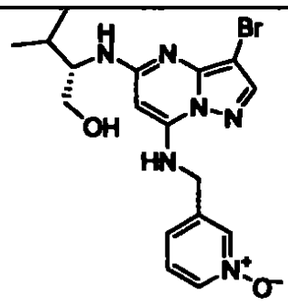
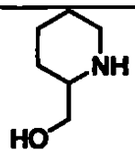
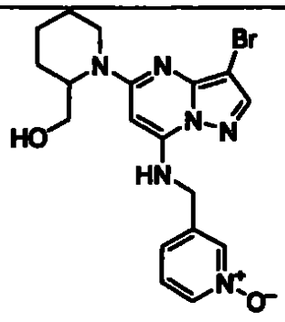
Example 396: ^{1}H NMR ($CDCl_3$) δ 8.60 (s, 1H), 8.56 (d, J = 4.2 Hz, 1H), 7.73 (s, 1H), 7.66 (m, 1H), 7.31 (dd, J = 7.8, 4.8 Hz, 1H), 6.51 (t, J = 6.0 Hz, 1H), 5.05 (s, 1H), 4.86 (d, J = 6.6 Hz, 1H), 4.50 (d, J = 6.0 Hz, 2H), 3.94 (m, 1H), 3.78 (dd, J = 11.1, 2.4 Hz, 1H), 3.57 (dd, J = 11.1, 7.2 Hz,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

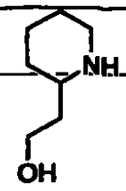
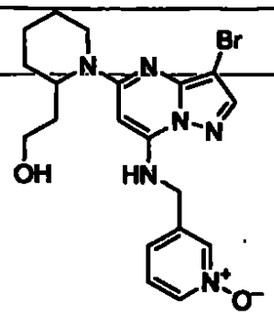
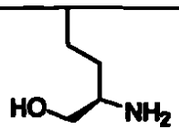
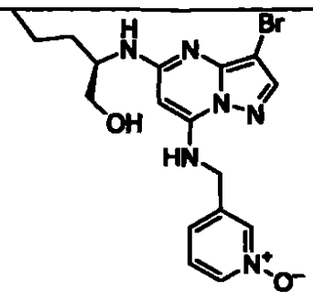
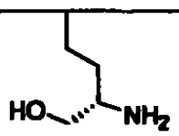
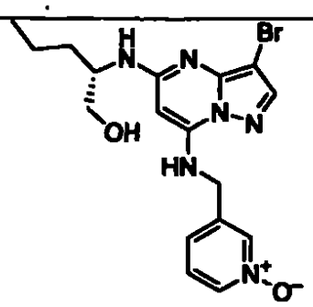
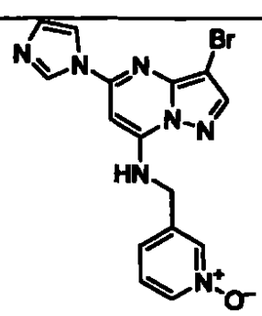
Example 397: ^{1}H NMR ($CDCl_3$) δ 8.65 (s, 1H), 8.59 (d, J = 4.5 Hz, 1H), 7.75 (s, 1H), 7.69 (m, 1H), 7.31 (m, 1H), 6.43 (t, J = 6.0 Hz, 1H), 5.06 (s, 1H), 4.88 (m, 1H), 4.55 (d, J = 6.0 Hz, 2H), 3.70 (m, 2H), 3.38 (m, 2H), 1.79-1.61 (m, 4H).

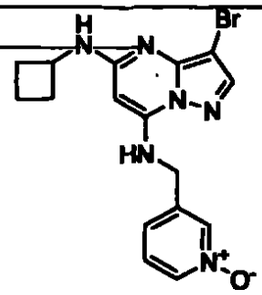
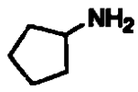
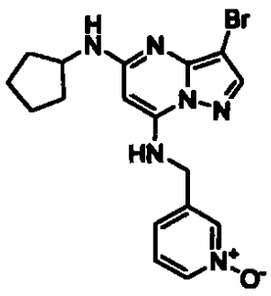
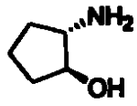
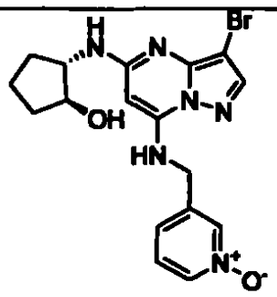
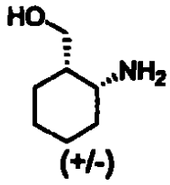
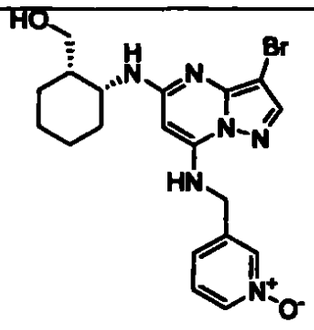
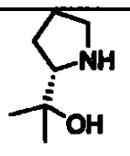
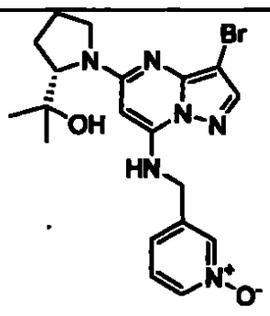
EXAMPLES 398-416:

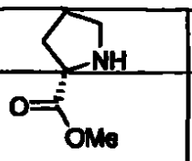
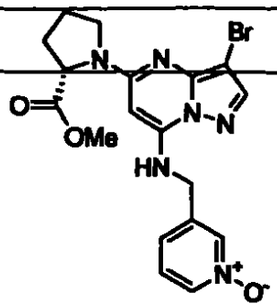
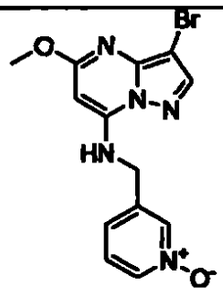
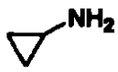
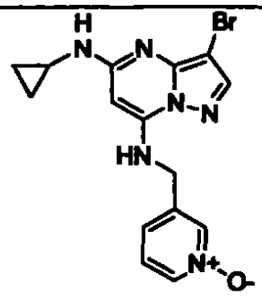
By essentially the same conditions set forth in Example 341, Steps A and B only substituting the compound prepared in Preparative Example 193.10, the compounds in Column 4 of Table 32 were prepared.

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

Additional data for select examples shown below:

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

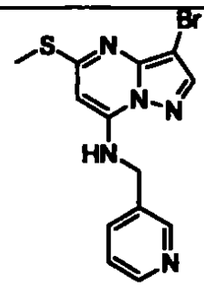
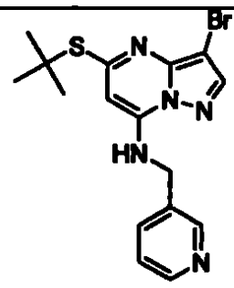
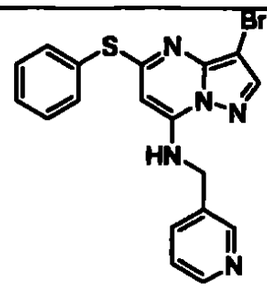
Example 403: ^{1}H NMR (DMSO-d_6+$CDCl_3$) δ 8.08 (s, 1H), 7.90 (d, J = 6.3 Hz, 1H), 7.49 (s, 1H), 7.34 (t, J = 6.3 Hz, 1H), 7.16-7.09 (m, 2H), 5.65 (d, J = 6.6 Hz, 1H), 4.97 (s, 1H), 4.90 (s, 1H), 4.29 (d, J = 6.3 Hz, 2H), 3.70 (m, 1H), 3.46 (m, 1H), 3.34 (m, 1H), 1.35-1.17 (m, 4H), 0.71 (t, J = 7.2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

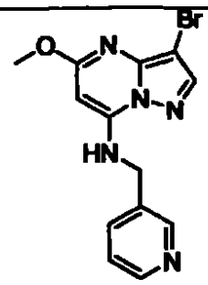
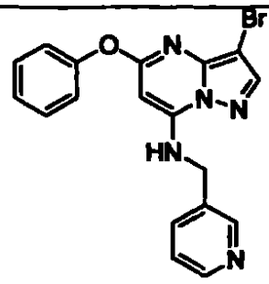
Example 404: ^{1}H NMR (DMSO-d_6) δ 8.21 (s, 1H), 8.12 (d, J = 6.6 Hz, 1H), 8.06 (m, 1H), 7.86 (s, 1H), 7.38 (t, J = 7.8 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 6.73 (d, J = 8.7 Hz, 1H), 5.28 (s, 1H), 4.70 (t, J = 5.1 Hz, 1H), 4.41 (d, J = 6.6 Hz, 2H), 4.00 (s, 1H), 3.39 (m, 1H), 1.53 (m, 1H), 1.36-1.25 (m,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

EXAMPLES 417—421:

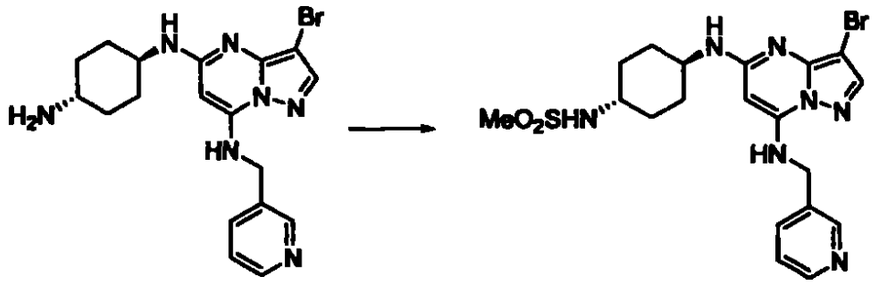
By the procedure set forth in *Chem. Pharm. Bull.* **1999, *47*, 928-938.** utilizing the oxygen or sulfur nucleophiles shown in Column 2 as described of Table 33 and by employing the cleavage method listed in Column 3 of Table 33, the compounds in Column 4 of Table 33 were prepared:

TABLE 33

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

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

EXAMPLE 422:

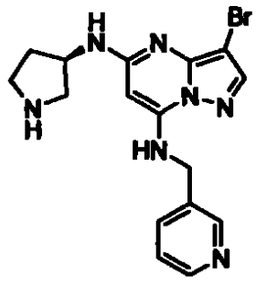
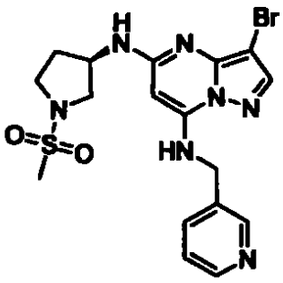
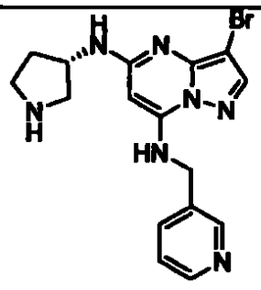
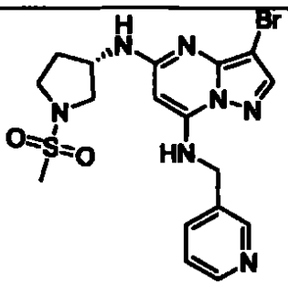


To a solution of amino compound (18 mg, 0.043 mmol) from Example 373 in CH_2Cl_2 (1 mL) at rt was added DIPEA (10 μL, 0.056 mmol) followed by $MeSO_2Cl$ (4 mL, 0.052 mmol). The mixture was stirred at rt for 12 h and was diluted with CH_2Cl_2 (2 mL) and sat. aq. $NaHCO_3$ (2 mL). The layers were separated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

EXAMPLES 423-424:

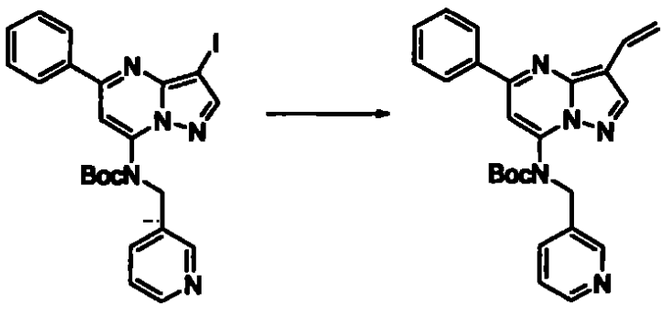
Utilizing the procedure outlined in Example 422, the amino compounds (Column 2) were converted to the corresponding methylsulfonamides (Column 3) in Table 34.

TABLE 34

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

EXAMPLE 425:

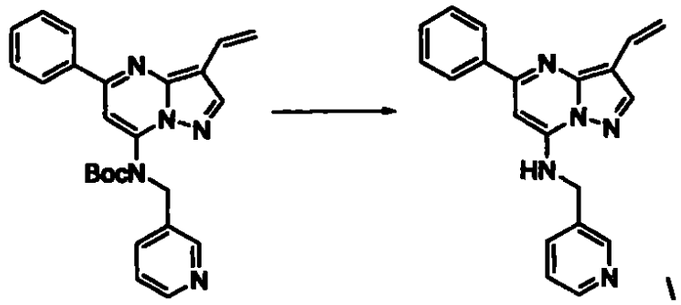
STEP A:



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

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

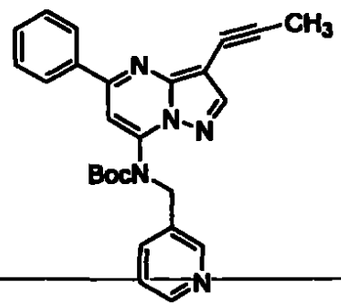
STEP B:



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

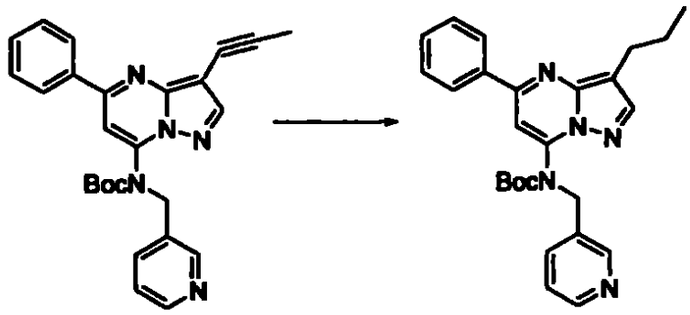
EXAMPLE 426:

STEP A:



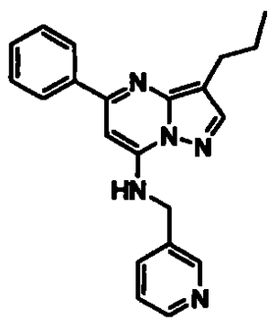
By essentially the same procedure set forth in Example 425, Step A only using tributylmethylethynyltin, the compound shown above was prepared.

STEP B:



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

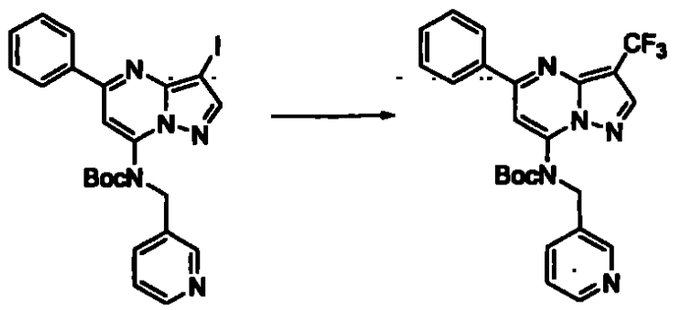
STEP C:



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

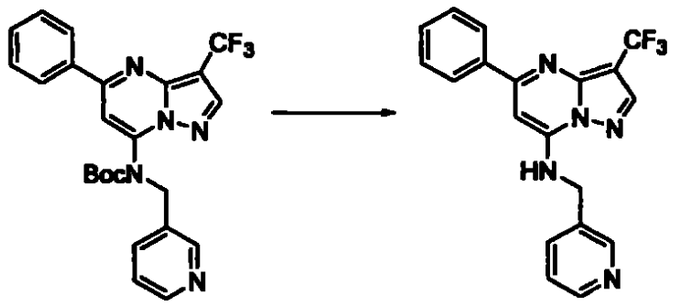
EXAMPLE 427:

STEP A:



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

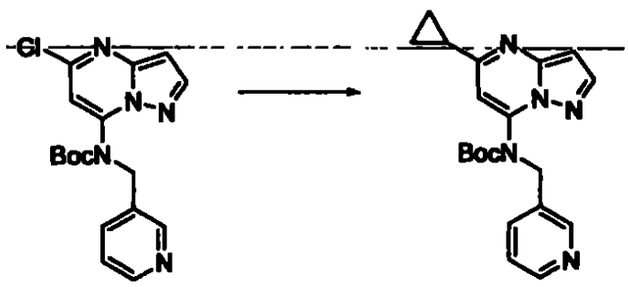
STEP B:



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

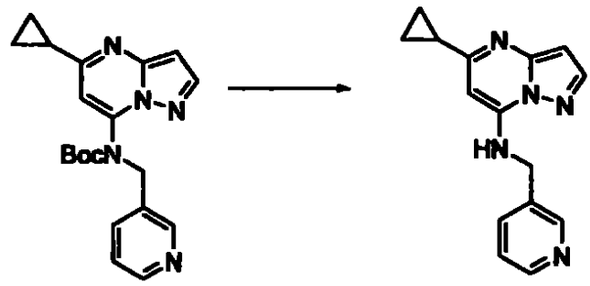
EXAMPLE 428:

STEP A:



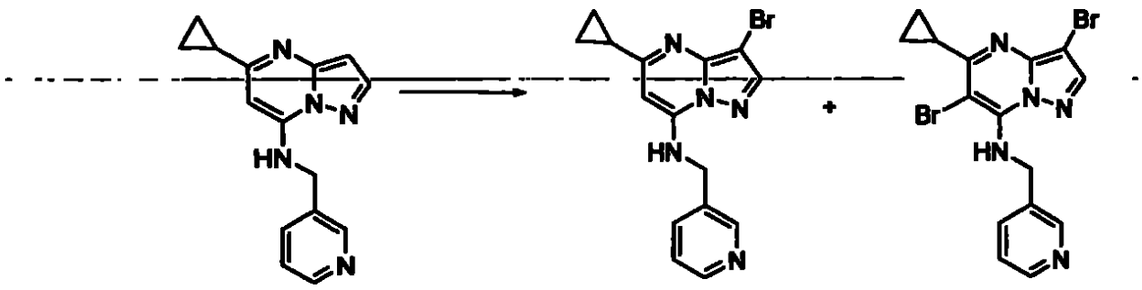
A mixture of the compound prepared in Preparative Example 193 (100 mg, 0.28 mmol), tetracyclopropyltin (91 mg, 0.32 mmol), Pd_2dba_3 (8.0 mg, 0.009 mmol) and $Pd(Pt\text{-}Bu_3)_2$ (9.0 mg, 0.017 mmol) in anhydrous dioxane (3 mL) was refluxed under N_2 for 27 hr. The solvent was evaporated and the residue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

STEP B:



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

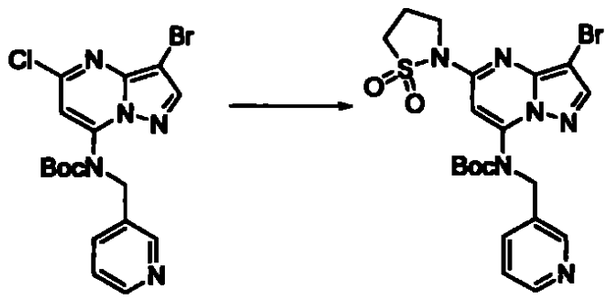
STEP C:



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

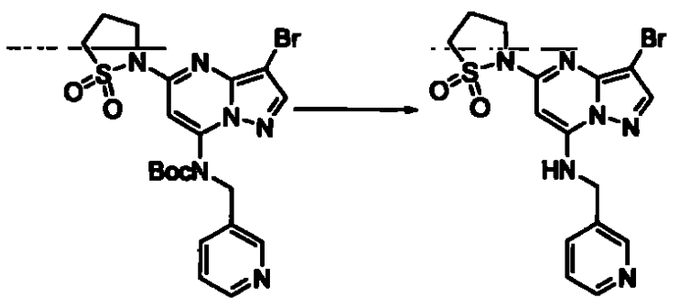
EXAMPLE 429:

STEP A:



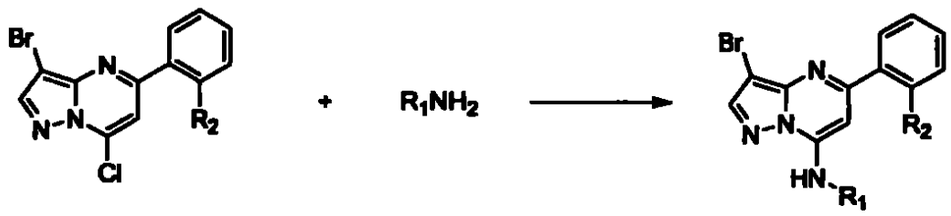
1,3-propanesultam (72 mg, 0.60 mmol) in anhydrous DMF (3 mL) was added under N_2 to 60 % NaH in mineral oil (36 mg, 0.90 mmol). The mixture was stirred for 20 min, then the compound prepared in Preparative Example 196 (200 mg, 0.46 mmol) was added. The mixture was stirred at 100°C for 30 min, the solvent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

STEP B:



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

EXAMPLE 430:

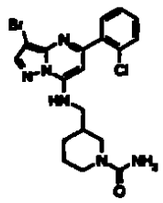
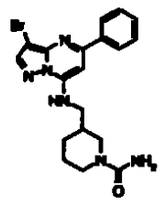
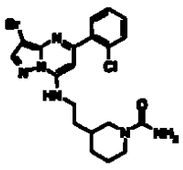
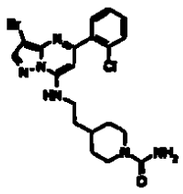
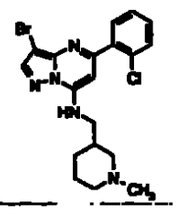


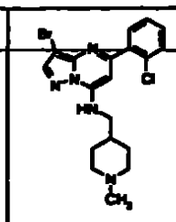
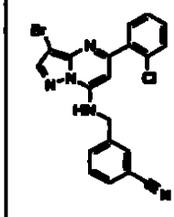
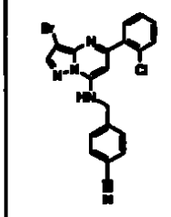
Where: R_2=H, or Cl

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

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

TABLE 35

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

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

Additional physical data for the compounds are given below:

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

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

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

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

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

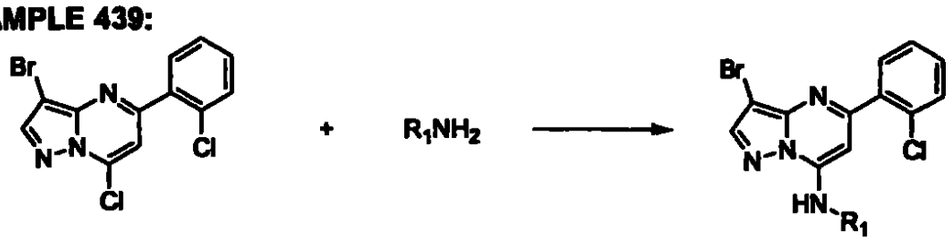
EXAMPLE 435: Reactants: 3-Bromo-7-chloro-5-phenylpyrazolo[1,5-a]pyrimidine (174mg, 0.507mmoles) (prepared as described in Preparative Example 129) and 3-(aminomethyl)-1-methylpiperidine (65mg, 0.507mmoles) (prepared as described in Preparative Example 244 above); diisopropyl ethylamine (0.178mL, 1.014mmoles);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

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

EXAMPLE 437: Reactants: 3-Bromo-7-chloro-5-phenylpyrazolo[1,5-a]pyrimidine (191mg, 0.557mmoles) (prepared as described in Preparative Example 129); 3-(aminomethyl)benzonitrile (88.3mg, 0.668mmoles) (prepared as described in Preparative Example 246 above); diisopropyl ethylamine (0.192mL, 1.114mmoles); anhydrous 1,4-dioxane (4.5mL). Physical data: HRFABMS: m/z 438.0125 (MH^+). Calcd. for $C_{19}H_{12}N_5BrCl$: m/z 438.0121; δ_H ($CDCl_3$) 4.76 (2H, d, -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.

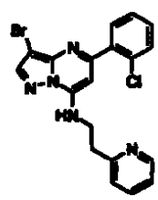
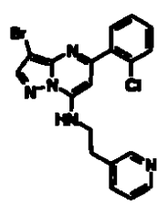
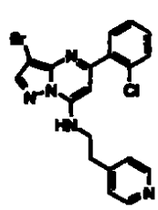
EXAMPLE 439:

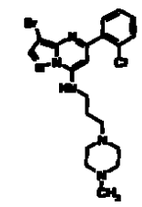
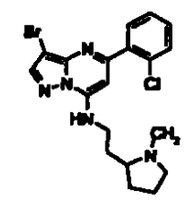
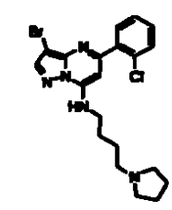
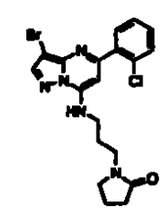
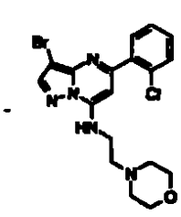


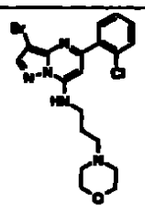
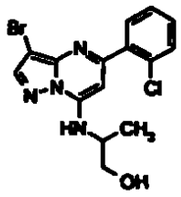
3-Bromo-7-chloro-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidine (50mg, 0.146mmoles) (prepared as described in Preparative Example 129) was dissolved in anhydrous 1,4-dioxane (5mL) in a GeneVac Technologies carousel reaction tube. PS-diisopropyl ethylamine resin (161mg, 0.5828mmoles) was

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, $C_5H_4NC\underline{H_2}CH_2NH$-), 3.94 (2H, ddd, $C_5H_4NCH_2C\underline{H_2}NH$-), 6.40 (1H, s, H_6), 7.22-7.29 (3H, m, Ar-H), 7.38-7.44 (2H, m, Ar-H), 7.51 (1H, m, Ar-H), 7.68 (1H, ddd, Ar-H), 7.73 (1H, Ar-H), 8.18 (1H, s, H_2) and 8.68ppm (1H, NH); δ_C ($CDCl_3$) CH_2: 36.4, 41.5; CH: 87.3, 122.1, 123.6, 127.1, 130.1, 130.1, 131.6, 137.0, 143.8, 149.5; C: 83.1, 132.1, 138.9, 145.7, 146.3, 158.0, 158.1.

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

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

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

EXAMPLE 443: Physical properties: HRFABMS: m/z 463.1003 (MH^+). Calcd. for $C_{20}H_{25}N_6BrCl$: m/z 463.1013; δ_H ($CDCl_3$) 1.98 (2H, m, $=NCH_2C\underline{H_2}CH_2NH$-), 2.43 (3H, s, NCH_3), 2.67 (2H, m, $=NC\underline{H_2}CH_2CH_2NH$-), 2.70 (8H, piperazine CH_2), 3.58 (2H, m, $=NCH_2CH_2C\underline{H_2}NH$-), 6.32 (1H, s, H_6), 7.37-7.43 (2H, m, Ar-H), 7.50 (1H, m, Ar-H), 7.73 (1H, m, Ar-H), 8.06 (1H, s, H_2) and 8.60ppm (1H, m, NH); δ_C ($CDCl_3$) CH_3: 46.1; CH_2: 24.1, 42.8, 53.3, 54.6, 54.6, 57.5, 57.5; CH: 87.1, 127.0, 130.0, 130.1, 131.5, 143.4; C: 82.7, 132.1, 139.2, 145.7, 146.7, 158.0.

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

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

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

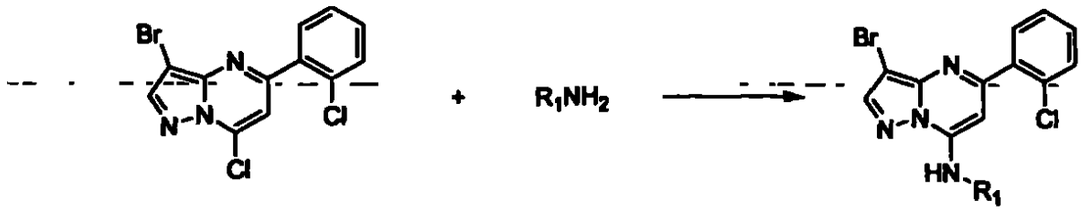
(1H, s, H_2); δ_C ($CDCl_3$) CH_2: 18.0, 26.3, 30.8, 39.2, 39.9, 47.5; CH: 87.0, 127.1, 130.1, 130.1, 131.6, 144.1; C: 82.9, 132.1, 138.9, 145.6, 146.2, 157.9, 176.2.

EXAMPLE 447: Physical properties: HRFABMS: m/z 436.0532 (MH^+). Calcd. for $C_{18}H_{20}N_5OBrCl$: m/z 436.0540; δ_H ($CDCl_3$) 2.60 (4H, bm, -N($C\underline{H}_2CH_2$)$_2$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.

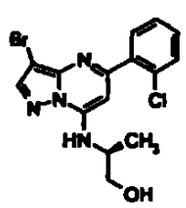
EXAMPLE 449: Physical properties: HRFABMS: m/z 381.0114 (MH^+). Calcd. for $C_{15}H_{15}N_4OBrCl$: m/z 381.0118; δ_H ($CDCl_3$) 1.39 (3H, d, CHC$\underline{H}_3$), 2.76 (1H, bm, -OH), 3.71 (1H, m, =CHC$\underline{H}_2$OH), 3.81 (1H, m, =CHC$\underline{H}_2$OH), 3.88 (1H, m, =C$\underline{H}CH_2$OH), 6.38 (1H, s, H_6), 7.38 (2H, m, Ar-H), 7.48 (1H, m, Ar-H), 7.68 (1H, m, Ar-H) and 8.02 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 16.9; CH_2: 65.0; CH: 50.0, 88.0, 127.1, 130.1, 130.3, 131.4, 143.8; C: 83.0, 132.0, 138.5, 145.6, 146.0, 158.2.

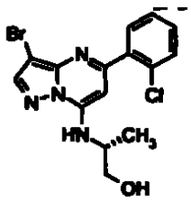
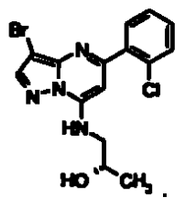
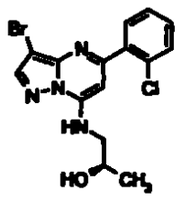
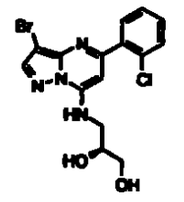
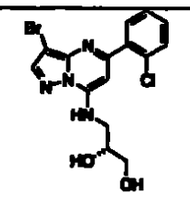
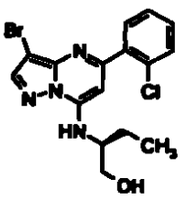
EXAMPLE 450:

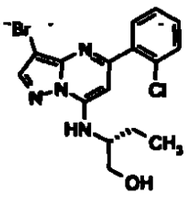
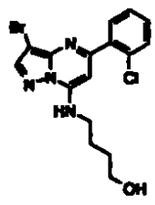


3-Bromo-7-chloro-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidine (50mg, 0.146mmoles) (prepared as described in Preparative Example 129) was dissolved in anhydrous 1,4-dioxane (5mL) in a GeneVac Technologies carousel reaction tube. PS-diisopropyl ethylamine resin (161mg, 0.5828mmoles) was added to each tube.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

TABLE 37

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

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

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

Additional physical data for the compounds are given below:

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

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

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

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

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

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

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

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

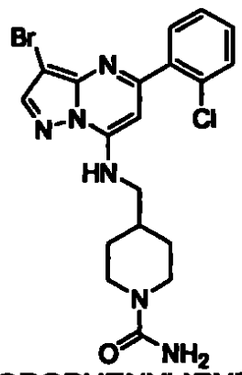
EXAMPLE 458: Physical properties: HRFABMS: m/z 395.0274 (MH^+). Calcd. for $C_{16}H_{17}N_4OBrCl$: m/z 395.0274; $[\alpha]_D^{25°C}$ +27.5° (c= 0.25, MeOH); δ_H ($CDCl_3$) 1.05

(3H, dd, CH_3), 1.76 (1H, m, CH_2), 1.85 (1H, m, CH_2), 2.28 (1H, bs, $CH_2O\underline{H}$), 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.

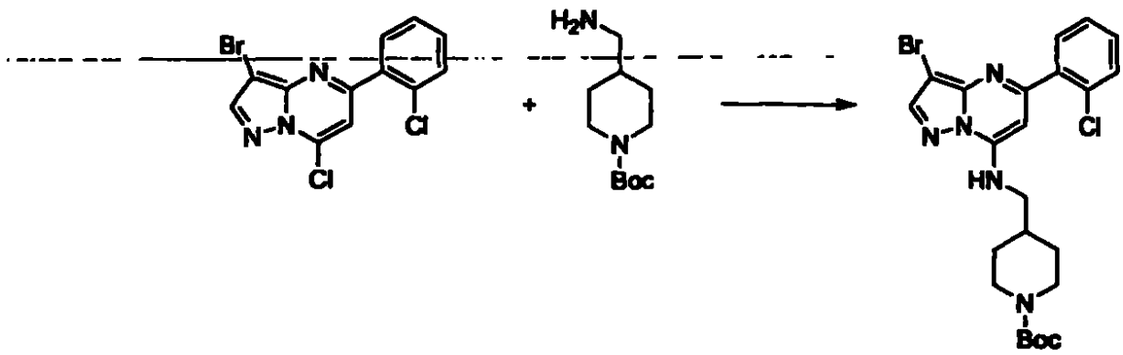
EXAMPLE 459: Physical properties: HRFABMS: m/z 395.0264 (MH^+). Calcd. for $C_{16}H_{17}N_4OBrCl$: m/z 395.0274; δ_H ($CDCl_3$) 1.77 (2H, m, $-NHCH_2CH_2C\underline{H_2}CH_2OH$), 1.90 (1H, bm, $-NHCH_2CH_2CH_2CH_2O\underline{H}$), 1.93 (2H, m, $-NHCH_2C\underline{H_2}CH_2CH_2OH$), 3.54 (2H, m, $-NHC\underline{H_2}CH_2CH_2CH_2OH$),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

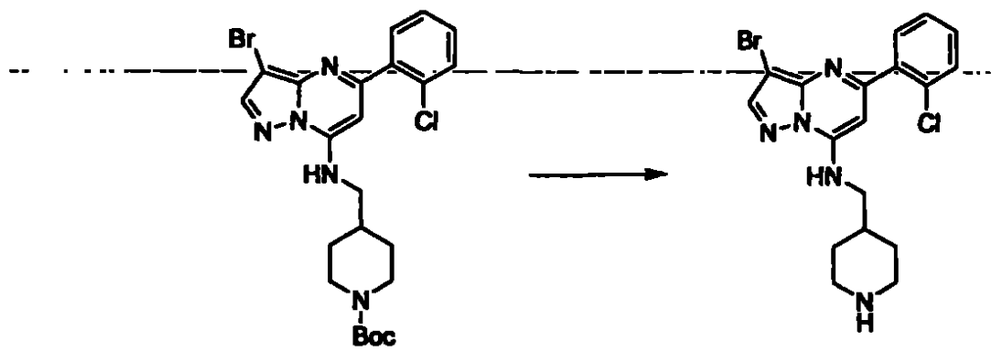


A. 4-{[3-BROMO-5-(2-CHLOROPHENYL)PYRAZOLO[1,5-a]PYRIMIDIN-7-YLAMINO]METHYL}PIPERIDINE-1-CARBOXYLIC ACID *tert*-BUTYL ESTER:



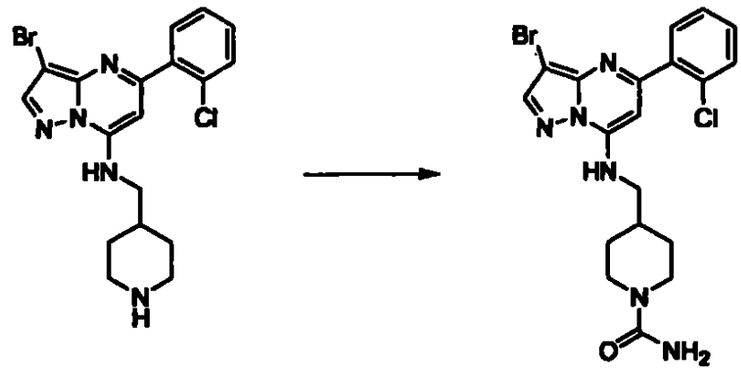
3-Bromo-7-chloro-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidine (300mg, 0.875mmoles) (prepared as described in Preparative Example 129) was dissolved in anhydrous 1,4-dioxane (6.8mL). 4-(aminomethyl)piperidine-1-carboxylic acid *tert*-butyl ester (225mg, 1.05mmoles) and diisopropyl ethylamine (0.3055mL, 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_6), 6.55 (1H, m, NH), 7.42 (2H, m, Ar-H), 7.52 (1H, m, Ar-H), 7.76 (1H, m, Ar-H) and 8.07 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 28.5, 28.5, 28.5; CH_2: 29.1, 29.1, 43.5, 43.5, 47.9; CH: 36.3, 87.5, 127.2, 130.2, 130.3, 131.6, 143.9; C: 79.7, 83.3, 132.1, 138.6, 145.4, 146.3, 154.7, 158.1.

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



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

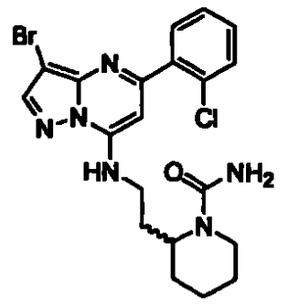
C. 4-{[3-BROMO-5-(2-CHLOROPHENYL)PYRAZOLO[1,5-a]PYRIMIDIN-7-YLAMINO]METHYL}PIPERIDINE-1-CARBOXYLIC ACID AMIDE:



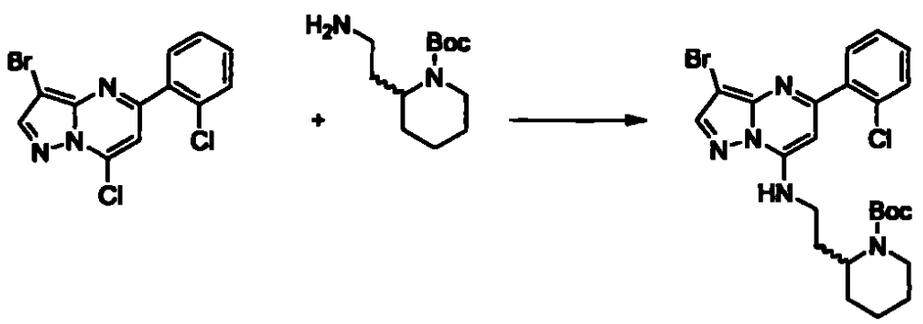
[3-Bromo-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidin-7-yl]piperidin-4-ylmethylamine (57mg, 0.136mmoles) (prepared as described in Example 460, Step B above) was dissolved in anhydrous dichloromethane (1.2mL) and trimethylsilylisocyanate (0.091mL, 0.679mmoles) was added. The mixture was stirred at 25°C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

EXAMPLE 461:

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



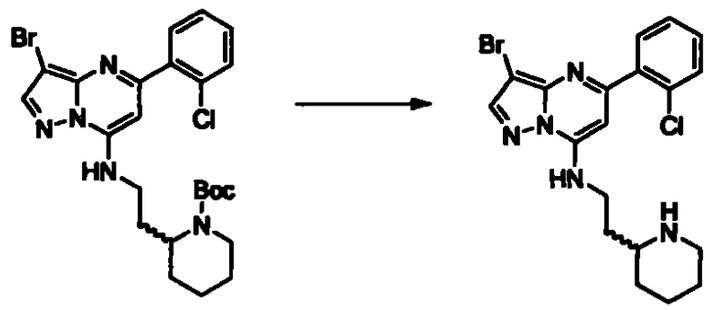
A. 2-{2-[3-BROMO-5-(2-CHLOROPHENYL)PYRAZOLO[1,5-a]PYRIMIDIN-7-YLAMINO]ETHYL}PIPERIDINE-1-CARBOXYLIC ACID *tert*-BUTYL ESTER:



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

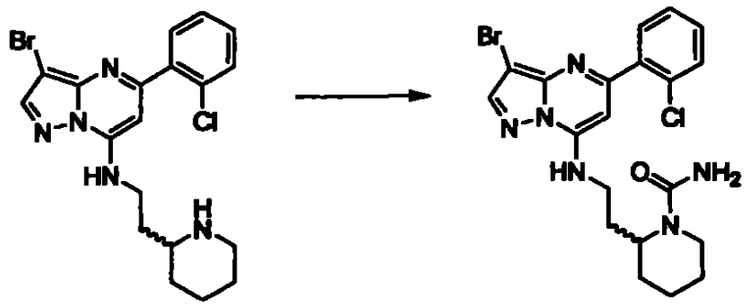
7.51 (1H, m, Ar-H), 7.76 (1H, m, Ar-H) and 8.08 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 28.5, 28.5, 28.5; CH_2: 19.2, 25.5, 29.2, 29.2, 39.2, 67.1; CH: ~47.4, 87.1, 127.1, 130.1, 130.1, 131.6, 143.9; C: 80.0, 83.0, 132.1, 138.9, 145.7, 146.2, 158.0.

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



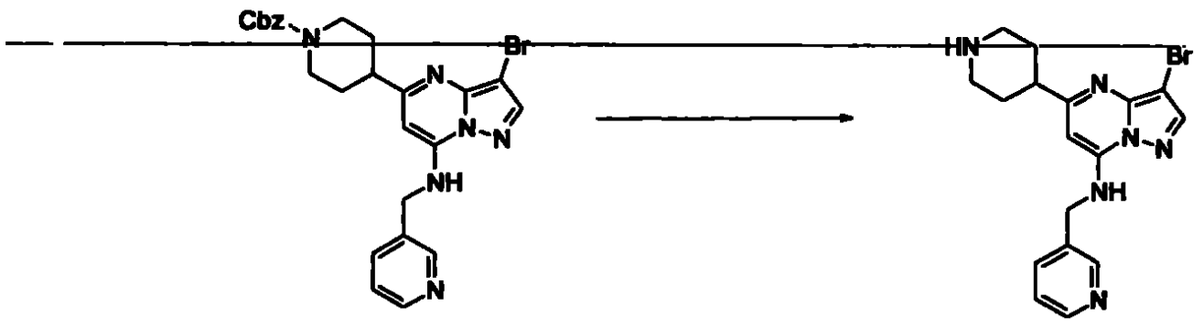
2-{[3-Bromo-5-(2-chlorophenyl)pyrazolo[1,5-a]pyrimidin-7-ylamino]ethyl}piperidine-1-carboxylic acid *tert*-butyl ester (465mg, 0.869mmoles) (prepared as described in Example 461, Step A above) was dissolved in methanol (4.5mL) and 10% (v/v) conc. sulfuric acid in 1,4-dioxane (11.76mL) was added. The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

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



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

EXAMPLE 462:

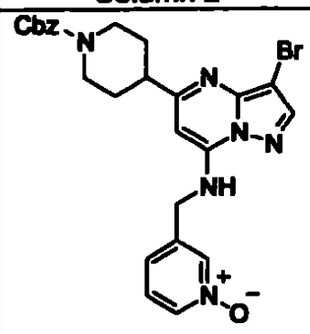
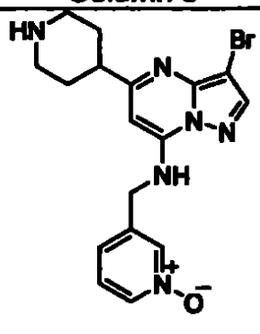


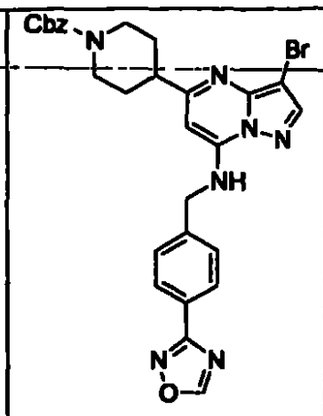
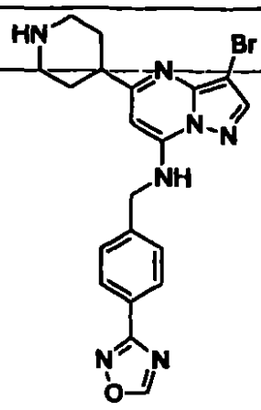
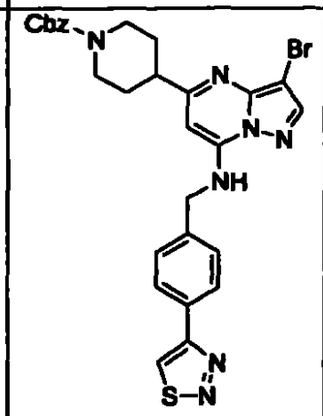
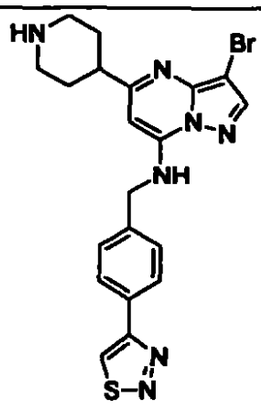
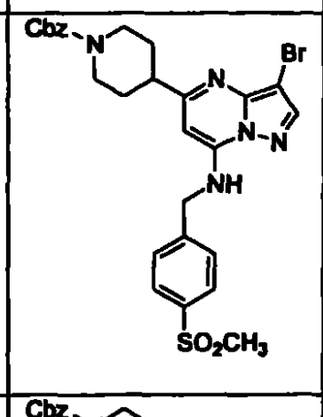
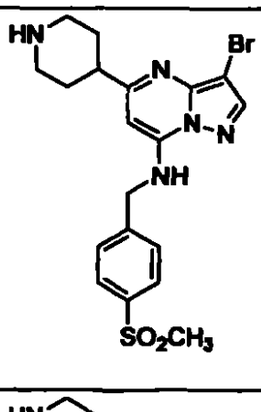
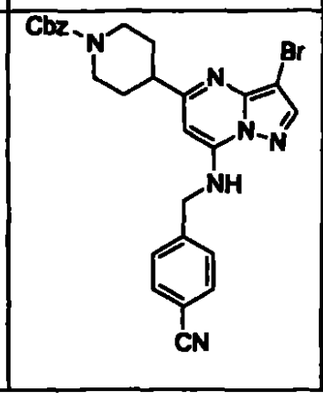
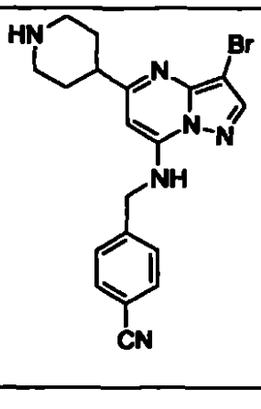
To a solution of the compound prepared in Example 204 (1.11 g, 2.12 mmol) in anhydrous acetonitrile (20 mL) was added TMSI (1.70 g, 8.52 mmol), dropwise at ambient temperature. After 10 minutes the acetonitrile was removed *in vacuo*. The resulting yellow foam was treated with 2 N HCl solution (7 mL)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

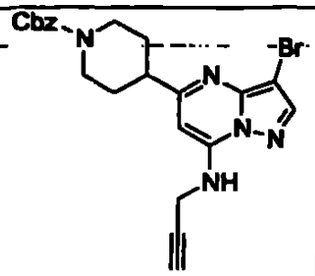
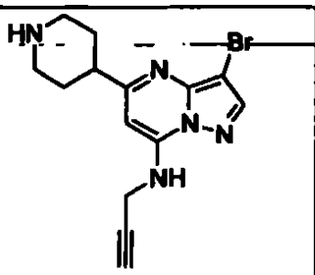
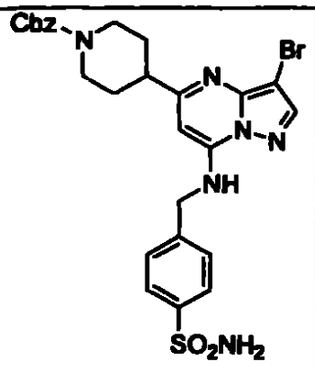
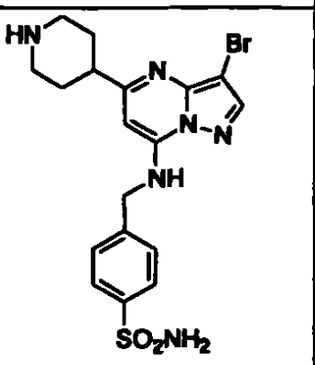
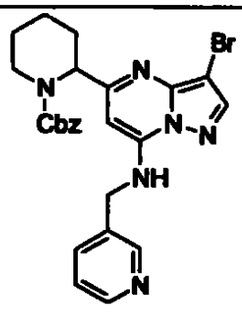
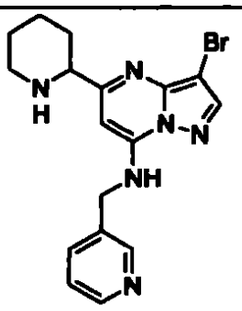
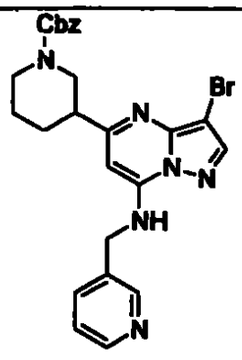
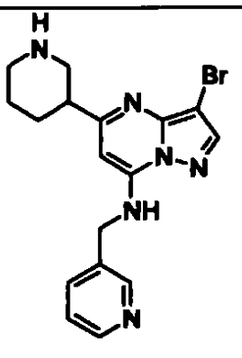
EXAMPLES 463-472:

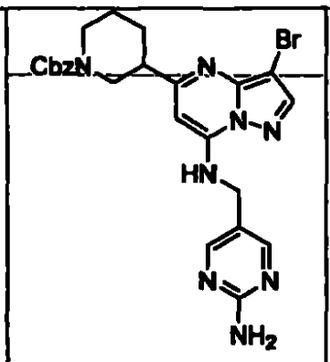
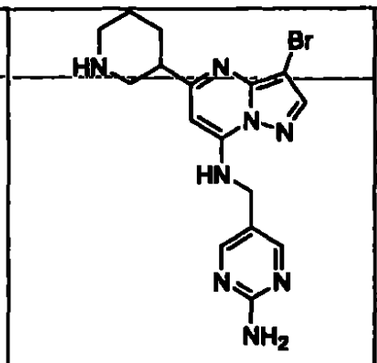
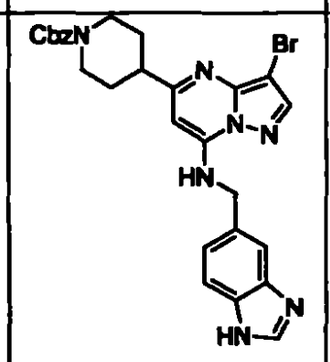
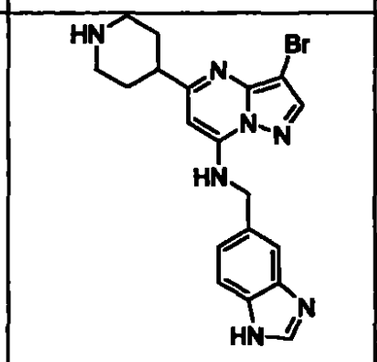
By essentially the same procedure set forth in Example 462 only substituting the compounds shown in Column 2 of Table 38, the compounds shown in Column 3 of Table 38 were prepared.

TABLE 38

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

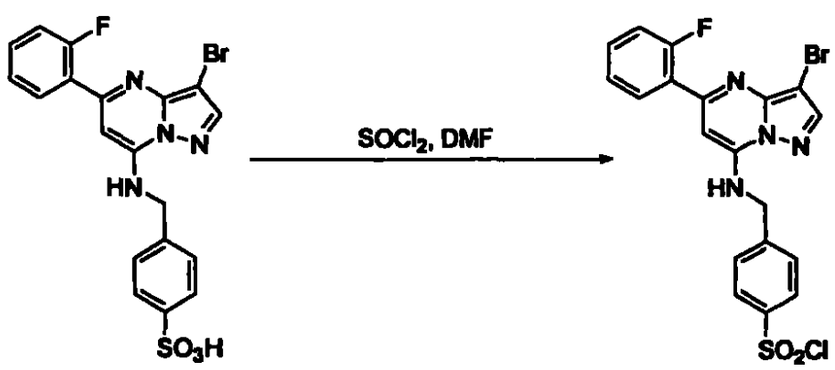
464			MH^+ = 454 m. p. = 175.4 °C
465			Yield = 87 MH^+ = 470 m. p. = 220 °C m. pt (hydrochloride salt) = 164.3 °C
466			MH^+ = 464 m. p. = 206 °C
467			MH^+ = 411 m. p. = 169.5 °C

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

472			1. mp = 230-232 2. M+H = 396
472 .10			1. mp = 157-160 2. M+H = 427

EXAMPLE 473:

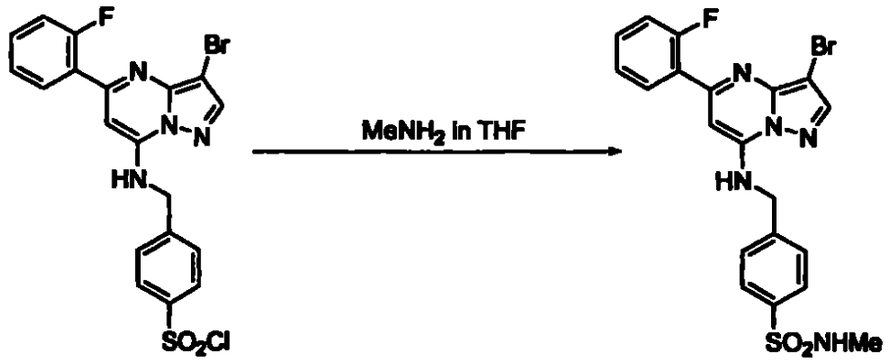
Step A:



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

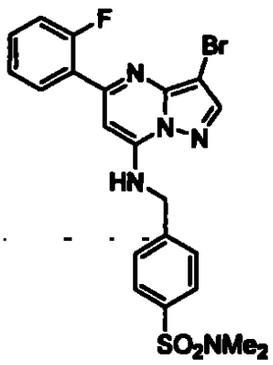
step without further purification. ^{1}H NMR ($CDCl_3$) δ 8.20-8.10 (m,1H), 8.10-7.95 (m, 3H), 7.65 (d, 2H), 7.45-7.35 (m, 1H), 7.35-7.20 (m, 1H), 7.15-7.05 (m, 1H), 6.95 (t, 1H), 4.85 (d, 2H).

Step B:



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

EXAMPLE 474:

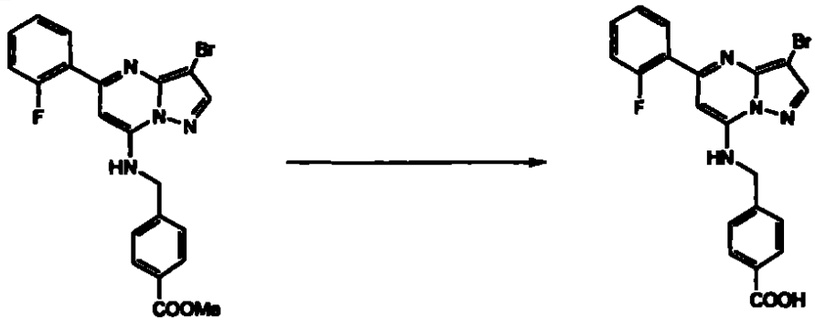


By essentially the same procedure set forth in Example 473, only substituting dimethylamine, the above compound was prepared. ^{1}H NMR ($CDCl_3$)

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

LCMS: MH^+ = 504.2

EXAMPLE 475:

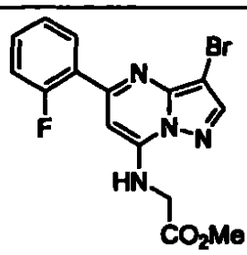
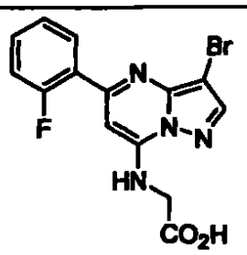


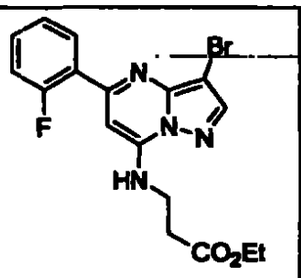
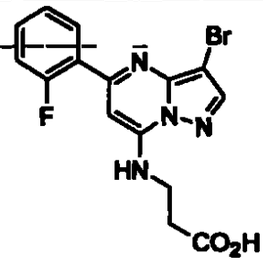
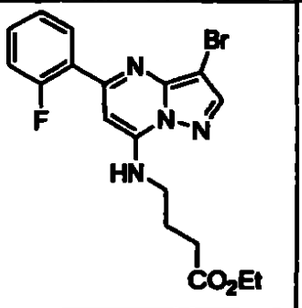
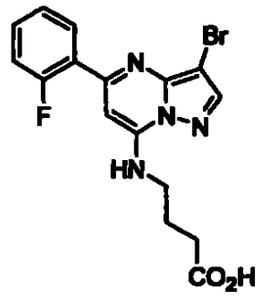
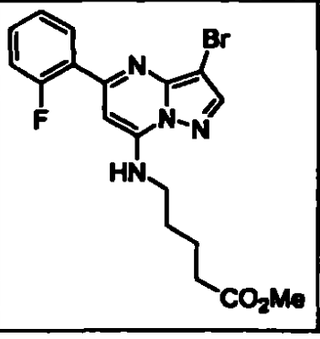
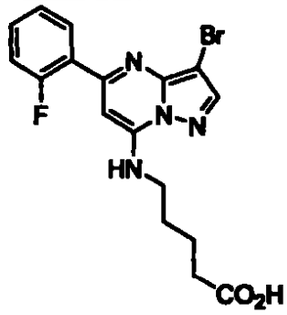
A mixture of the compound prepared in Example 129 (300 mg, 0.66 mmol), NaOH (5 g), CH_3OH –H_2O (100 mL, 90:10) was stirred at 25 C for about 15 h. Progress of hydrolysis was checked by TLC. Reaction mixture was concentrated to remove methanol. The concentrate was diluted with 50 mL water, and extracted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

Example 476-479:

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

Table 39

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

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

+

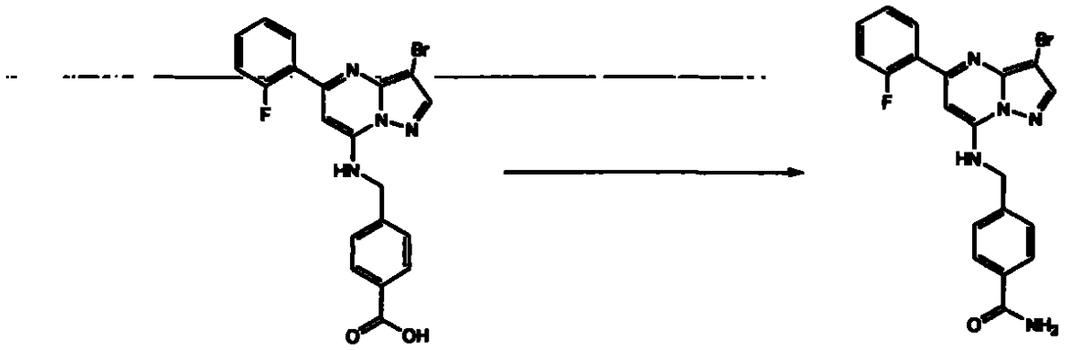
Additional data for select examples shown below:

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

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

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

EXAMPLE 480:

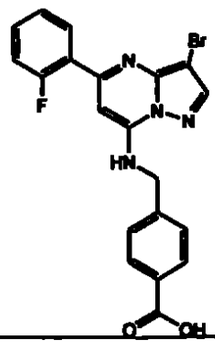
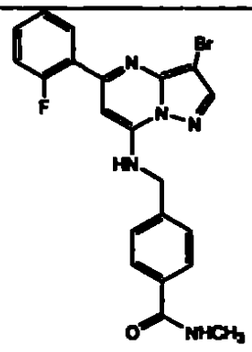


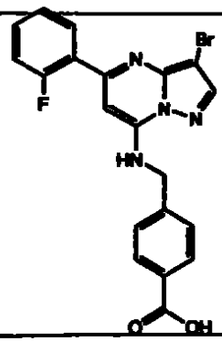
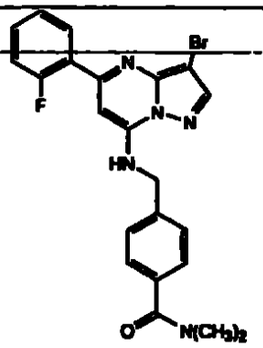
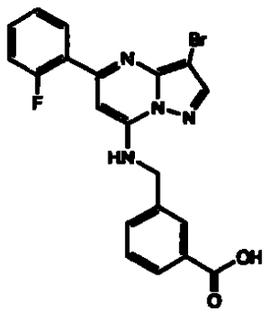
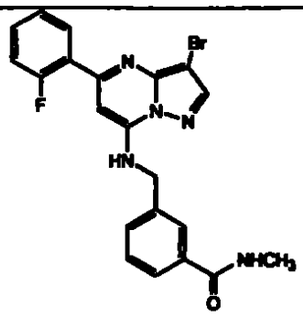
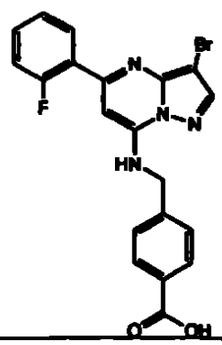
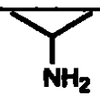
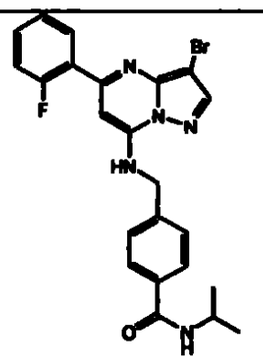
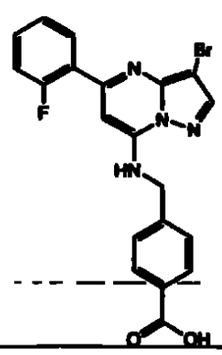
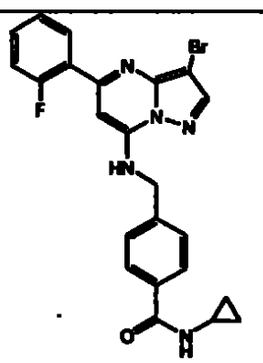
A mixture of the acid from Example 475 (85mg, 0.193 mmol) and Et_3N (20 mg, 0.193 mmol) in THF (20 mL) was stirred at 25 C for 15 min. Isobutyryl chl roformate (28mg, 0.205 mmol) was added to the reaction mixture and stirred for 10 min followed by addition of NH4OH solution (0.5 mL). The reaction mixture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

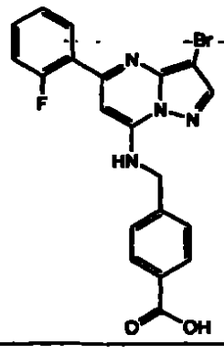
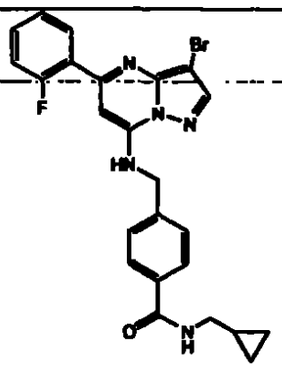
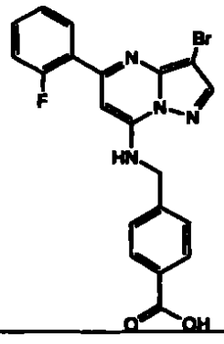
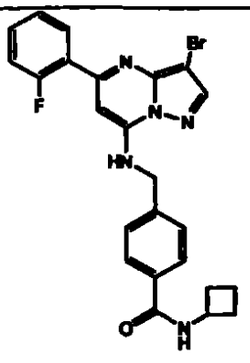
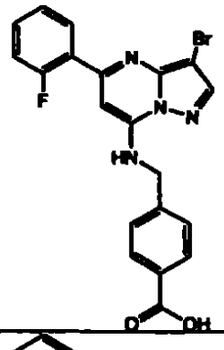
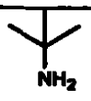
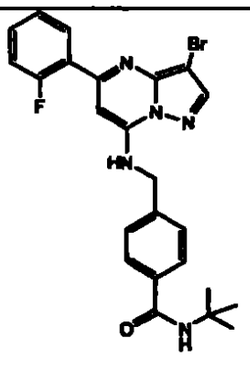
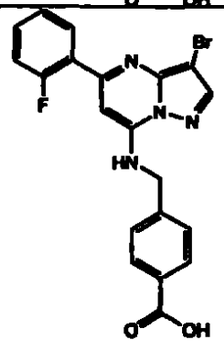
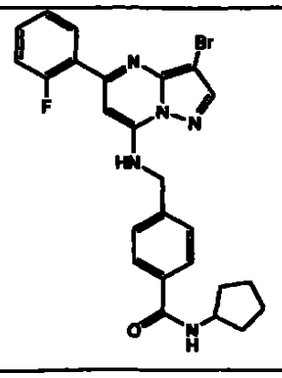
EXAMPLES 481-509:

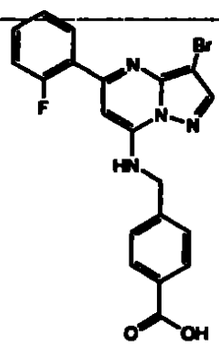
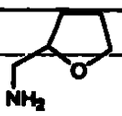
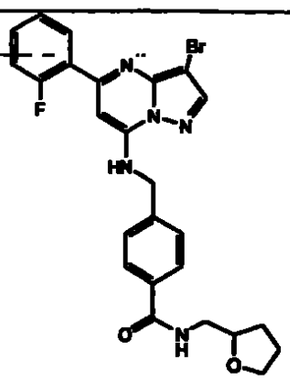
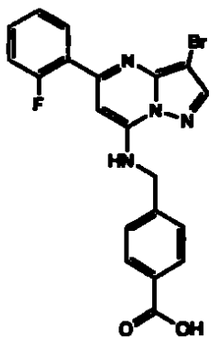
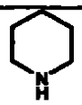
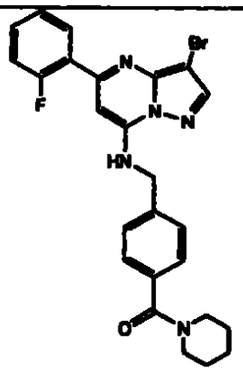
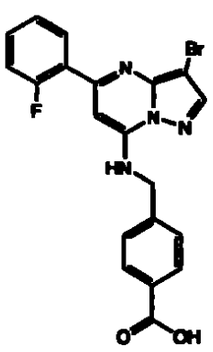
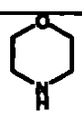
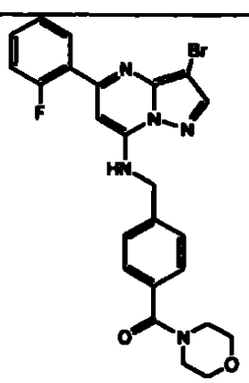
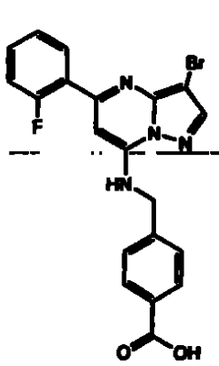
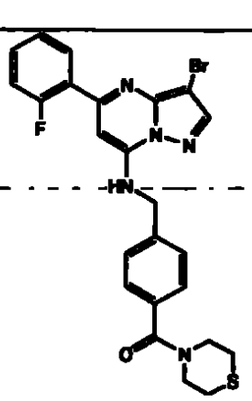
By essentially the same procedure set forth in Example 480 only substituting the carboxylic acid shown in Column 2 of Table 40 and the amine shown in Column 3 of Table 40, the compounds shown in Column 4 of Table 40 were prepared.

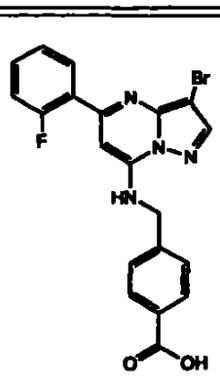
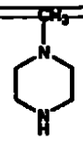
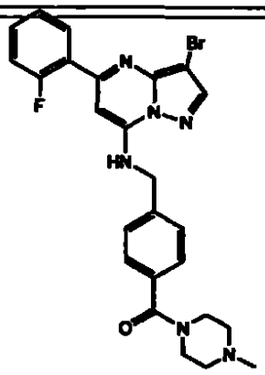
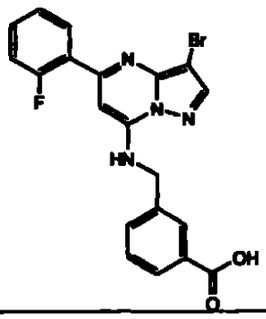
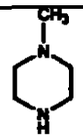
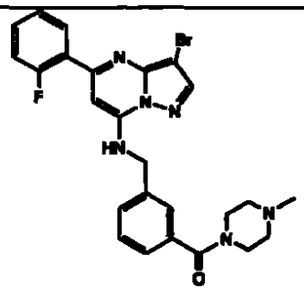
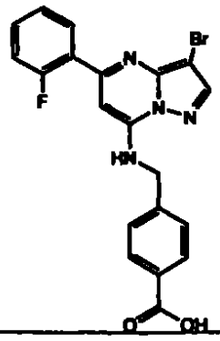
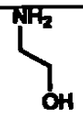
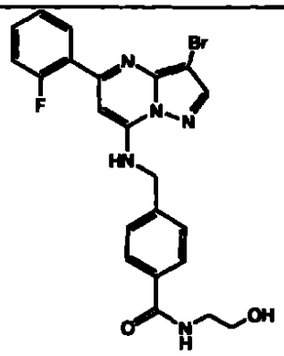
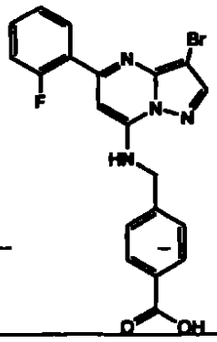
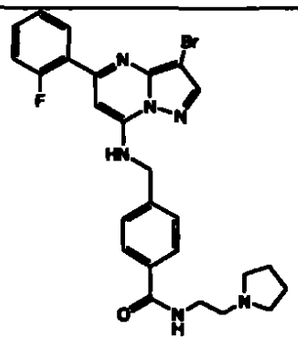
Table 40

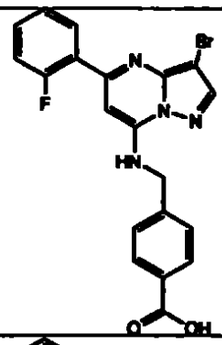
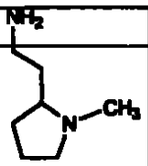
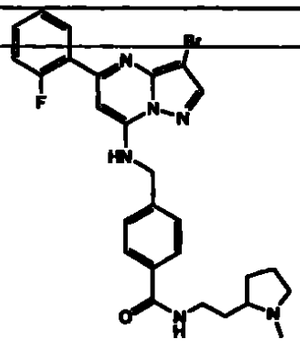
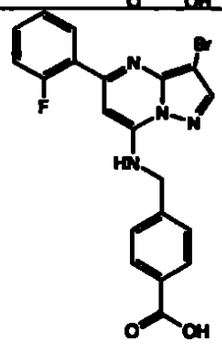
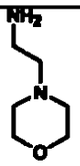
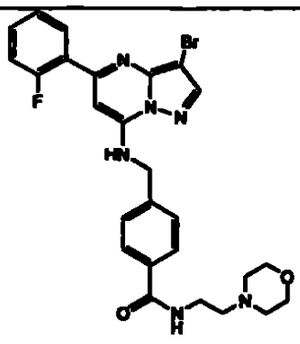
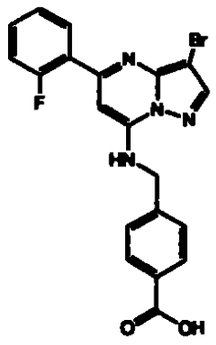
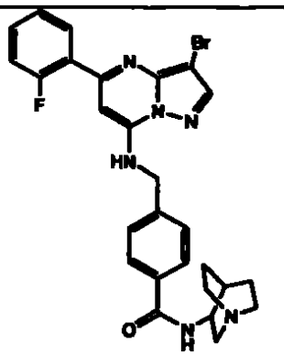
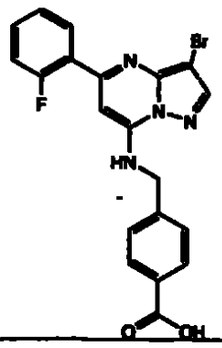
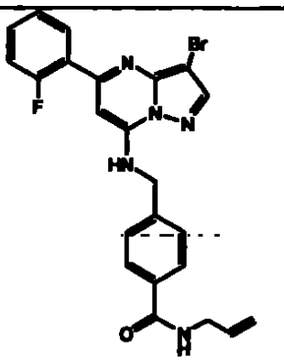
Ex.	Column 2	Column 3	Column 4	CMPD
481		CH_3NH_2		Yield = 88% LCMS: MH^+ = 454

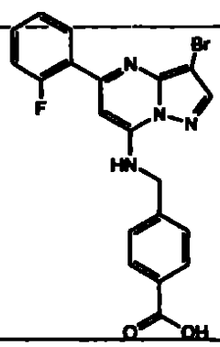
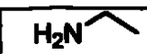
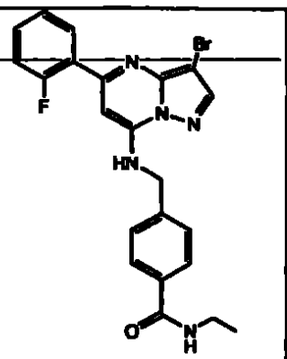
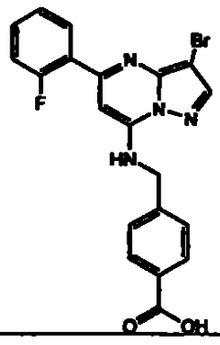
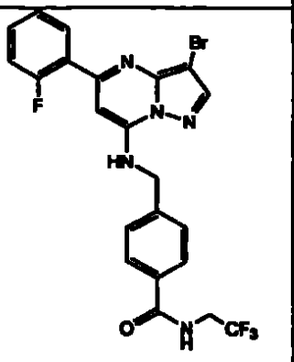
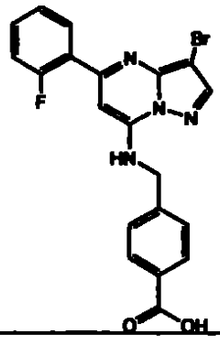
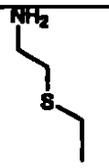
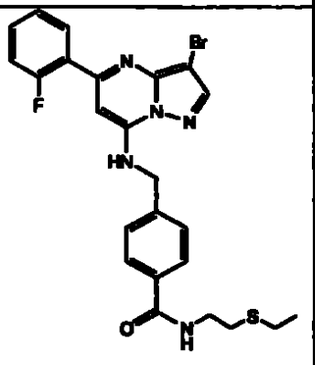
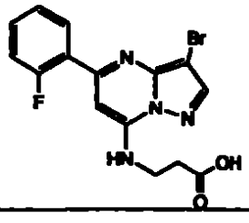
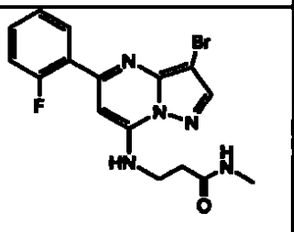
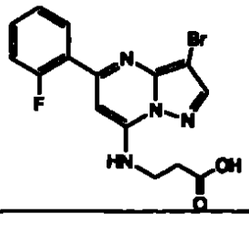
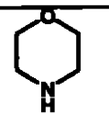
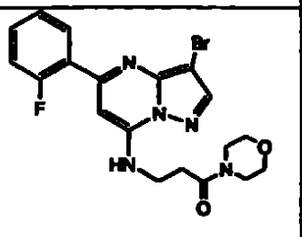
482		$(CH_3)_2NH$		Yield=80 % LCMS MH^+ = 468
483		CH_3NH_2		Yield=70 % LCMS MH^+ = 454.
484				Yield=75 % LCMS MH^+ = 482.1
485				Yield=71 % LCMS MH^+ = 480.1

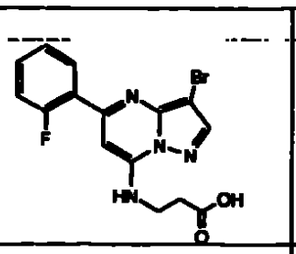
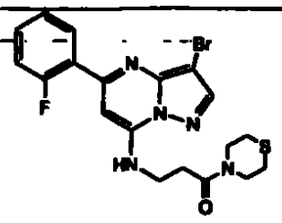
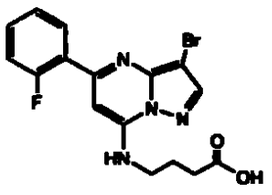
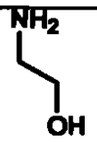
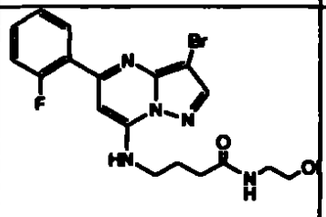
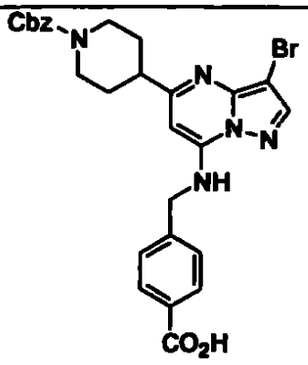
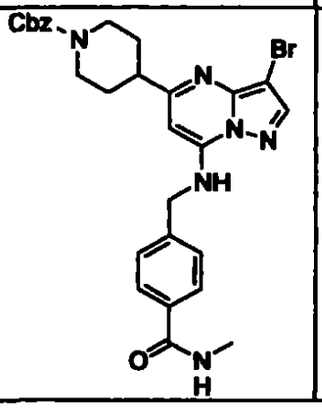
486				Yield=75 % LCMS MH$^+$ = 494.1
487				Yield=75 % MH$^+$ = 494.1
488				Yield=75 % MH$^+$ = 496.1
489				Yield=75 % LCMS MH$^+$ = 508.1

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

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

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

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

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

Additional data for select examples given below:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

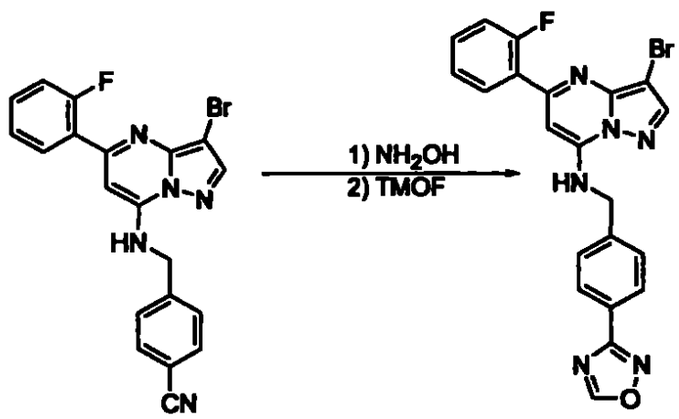
Example 505: ^{1}H NMR ($CDCl_3$) δ 8.15 (dt, 1H), 8.0 (s, 1H), 7.4 (m, 1H), 7.25 (dd, 1H), 7.15 (dd, 1H), 7.0 (t, 1H), 6.5 (s, 1H), 3.8 (m, 2H), 2.7 (t, 2H), 3.0 (d, 3H).

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

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

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

EXAMPLE 509:

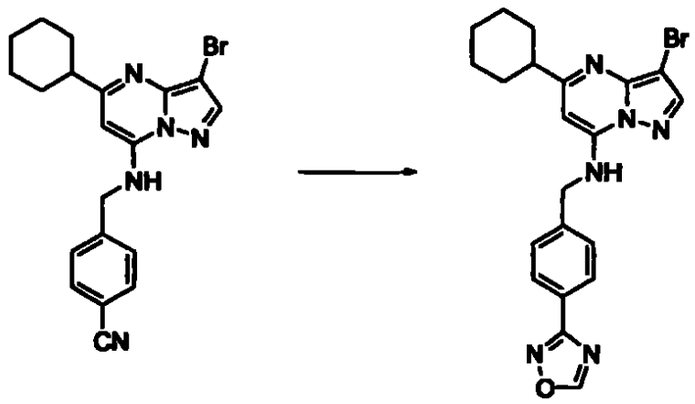


A solution of NaOH (59 mg, 1.47 mmol) in 1 mL of water was added to a suspension of $NH_2OH.HCl$ (102 mg, 1.47 mmol) in 10 mL of methanol at 0 °C. After 5 min, the compound prepared in Example 210.10 (208 mg, 0.49 mmol) was added and the reaction mixture was refluxed overnight. The solvent was removed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

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

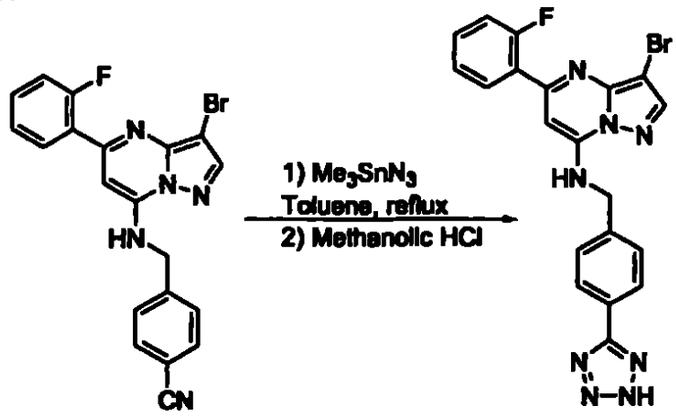
LCMS: MH^+ = 465.2

Example 510:



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

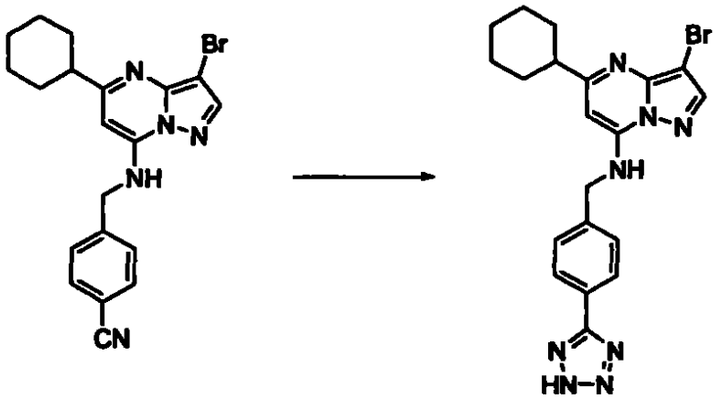
EXAMPLE 511:



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

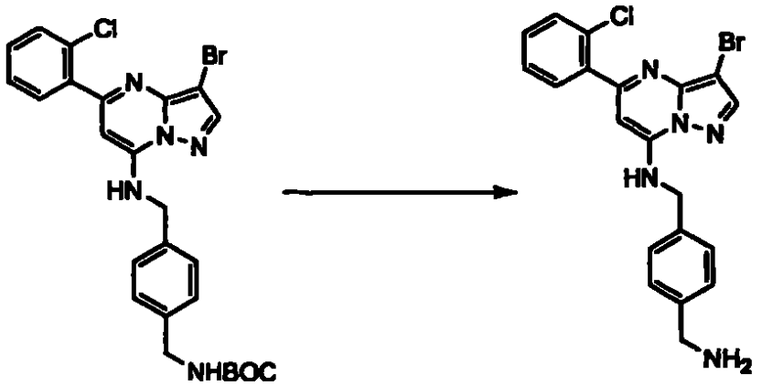
extracted into EtOAc. Evaporation of the EtOAc layer after drying (Na_2SO_4) provided the residue which was purified by chromatography (silica; DCM:MeOH (98:2→95:5)) to yield 50 mg (19%) of the pure tetrazole. ^1H NMR (CD_3OD) δ 8.10 (s, 1H), 8.00 (d, J = 9 Hz, 2H), 7.90 (t, J = 7 Hz, 1H), 7.65 (d, J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

EXAMPLE 512:



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

EXAMPLE 513:



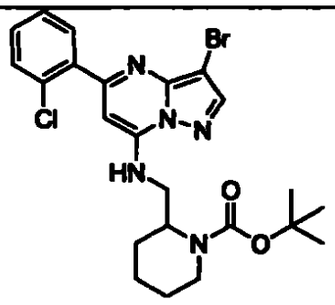
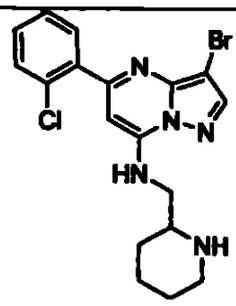
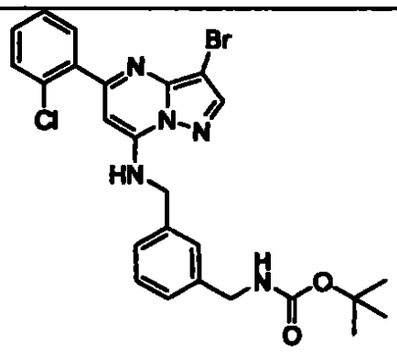
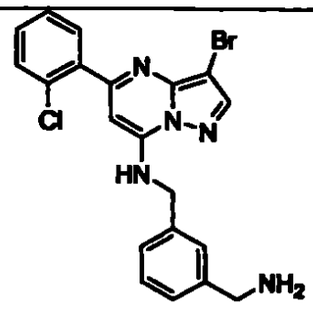
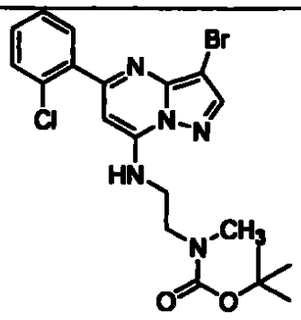
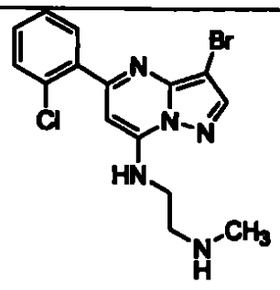
The compound prepared in Example 157 was dissolved in dioxane (30 mL) and a HCl-dioxane solution (4 M, 30 mL) was added. The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was evaporated under reduced pressure and ethyl acetate (200 mL) was added. The organic

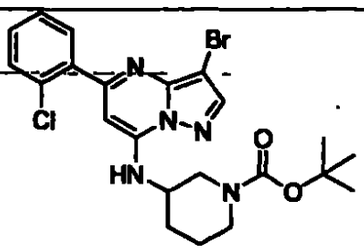
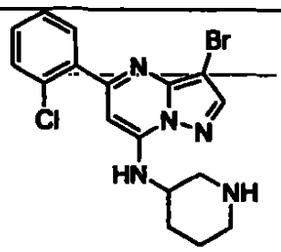
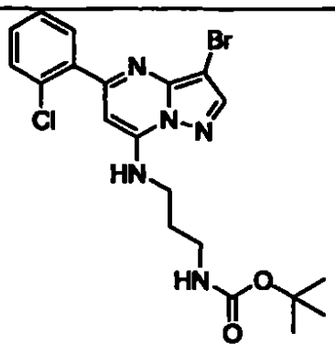
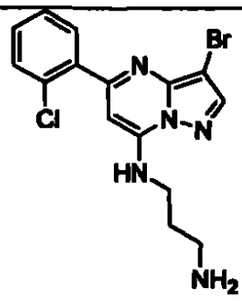
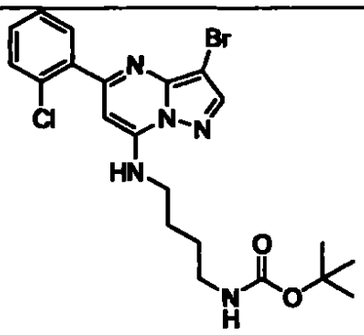
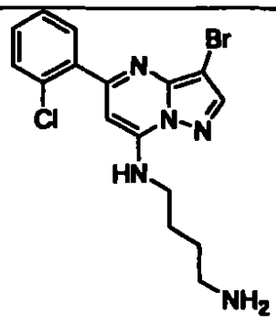
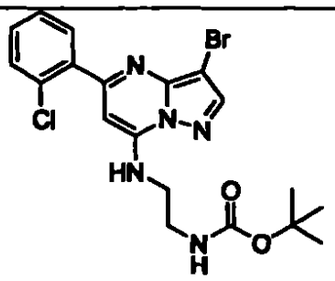
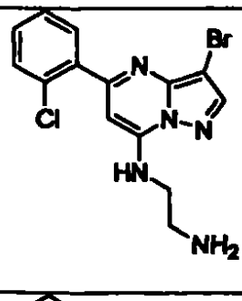
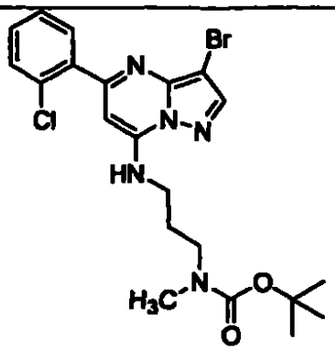
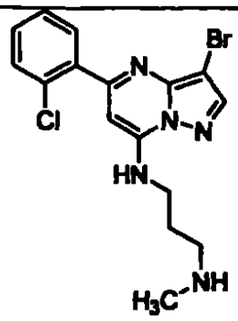
solution was washed with 1 N sodium hydroxide followed by saturated brine. The organic layer was dried over anhydrous sodium sulfate and evaporated under reduced pressure. MH^+ = 442.1

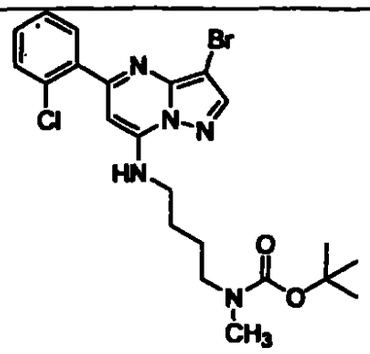
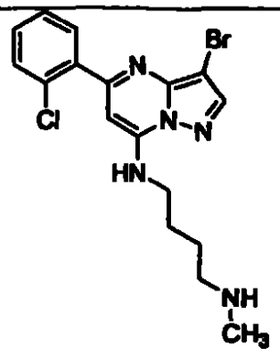
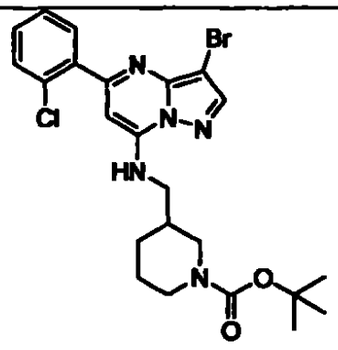
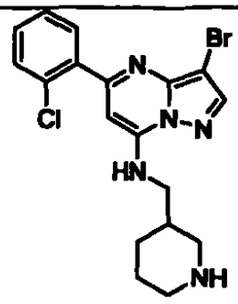
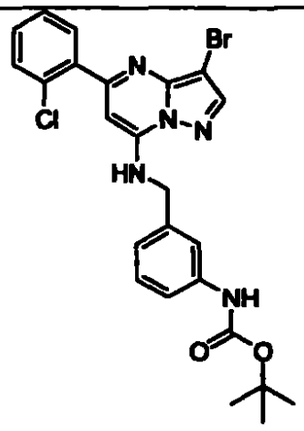
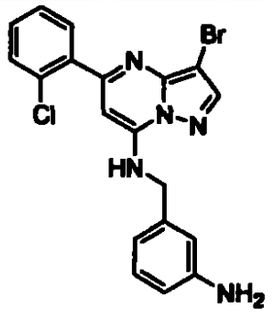
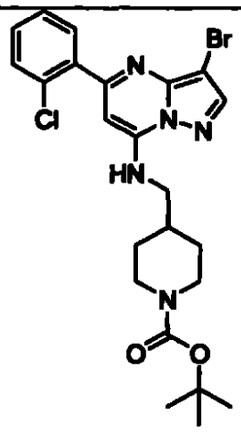
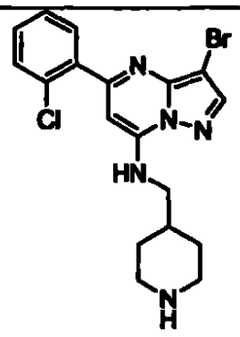
EXAMPLE 514-526:

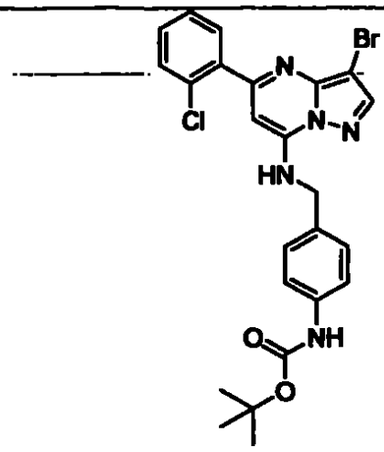
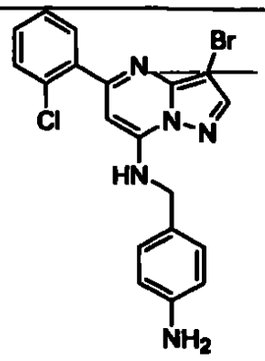
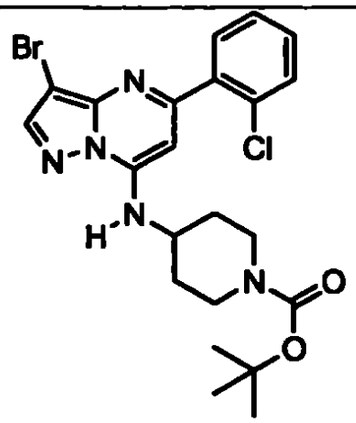
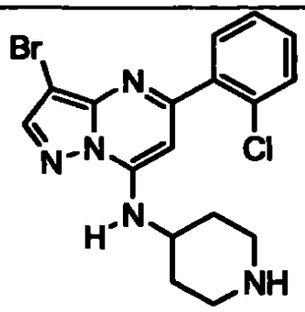
By essentially the same procedure set forth in Example 513, only substituting the compounds shown in Column 2 of Table 41, the compounds shown in Column 3 of Table 41 were prepared.

TABLE 41

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

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

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

526			MH^+ = 428.1
526.10			

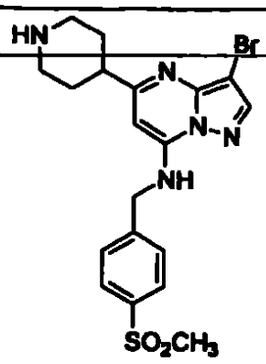
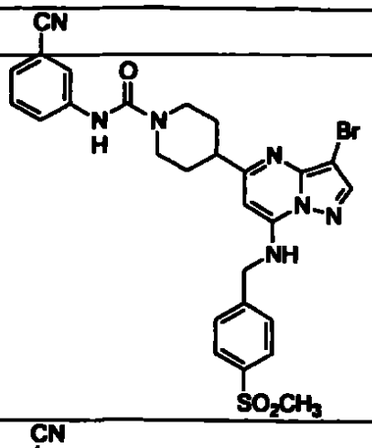
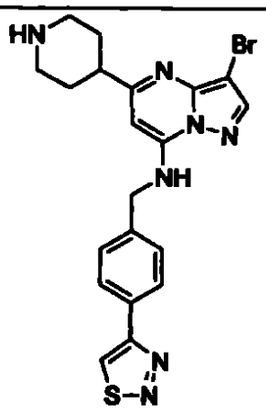
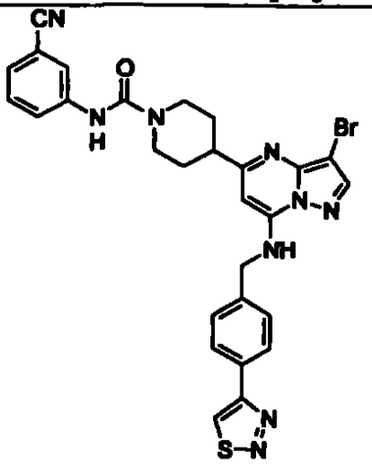
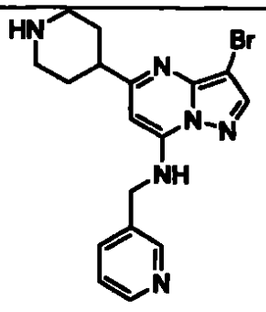
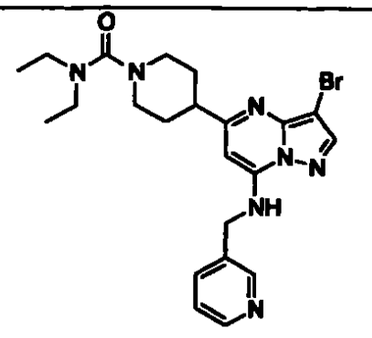
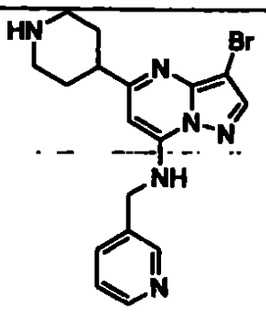
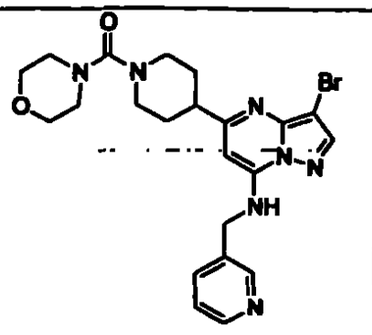
EXAMPLES 528-564:

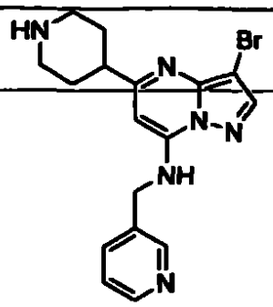
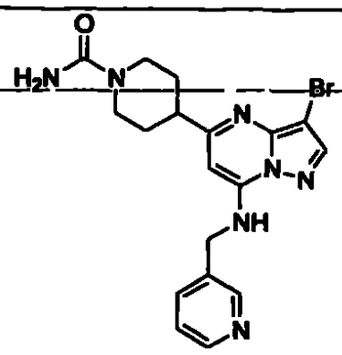
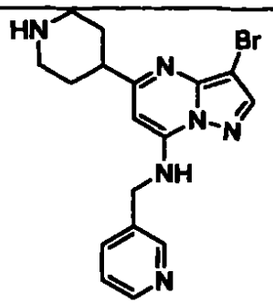
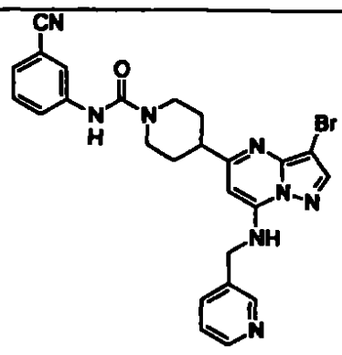
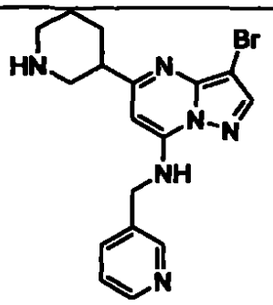
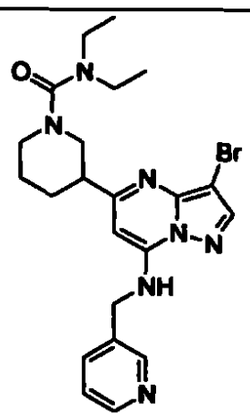
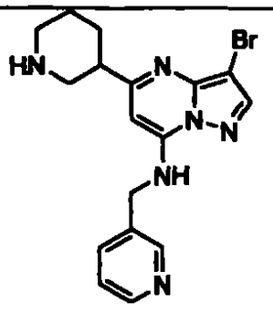
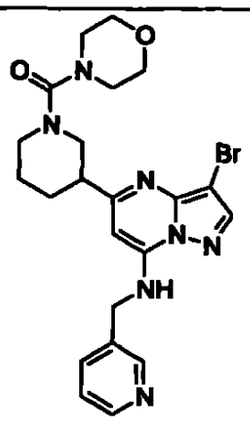
General procedure for 5-piperidinyl parallel library formation:

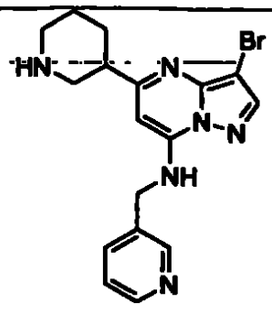
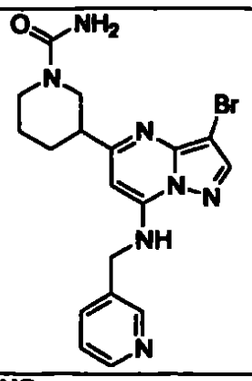
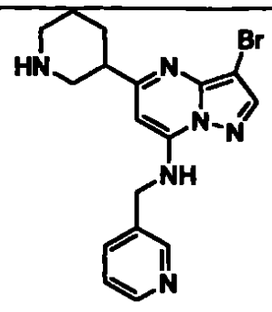
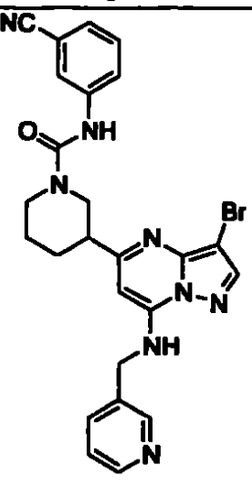
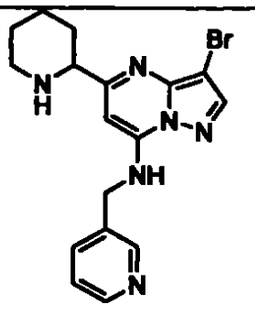
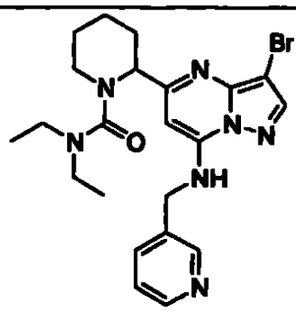
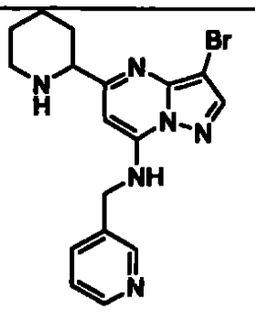
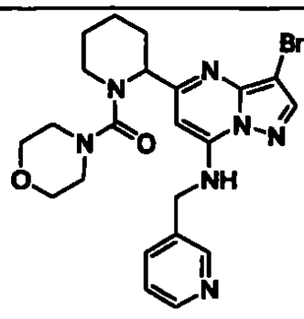
To a mixture of the starting material (80 mg, 0.21 mmol) shown in Column 2 of Table 42 in anhydrous CH_2Cl_2 (1.5 mL) was added DIPEA (75 μL, 0.42 mmol) and the appropriate capping reagent (1.1 equiv., 0.23 mmol). After 1 to 2 h, the reaction mixture was applied to 1000 micron preparatory TLC plate and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

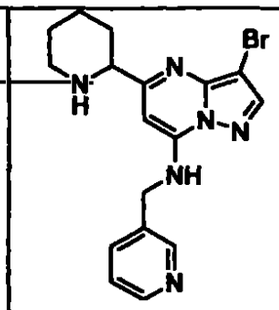
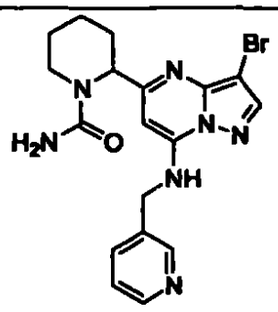
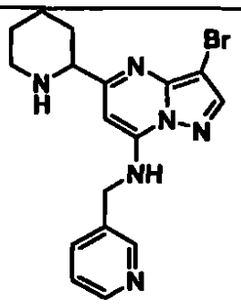
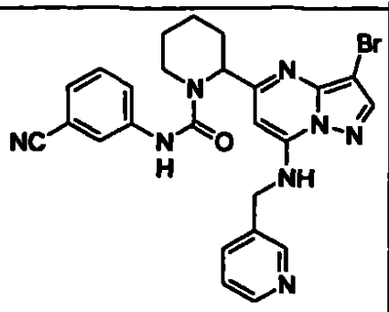
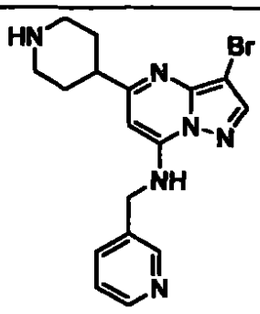
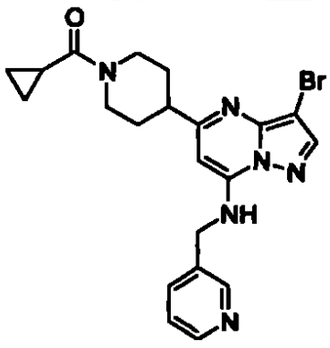
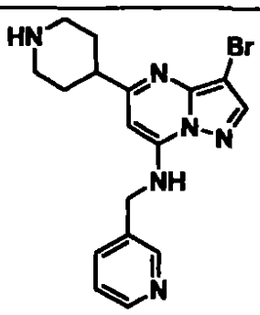
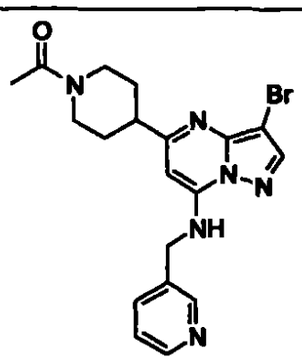
TABLE 42

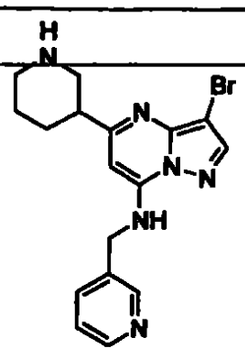
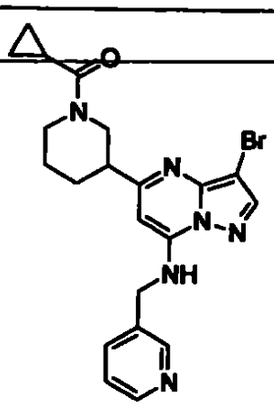
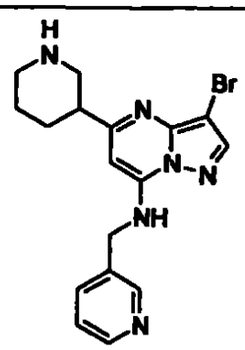
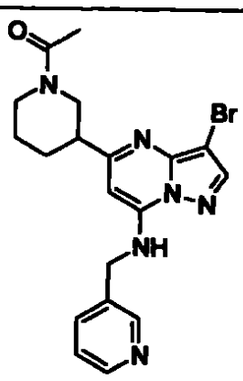
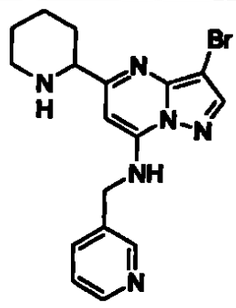
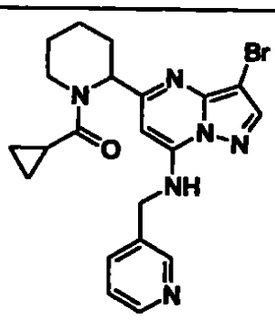
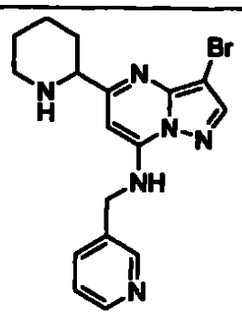
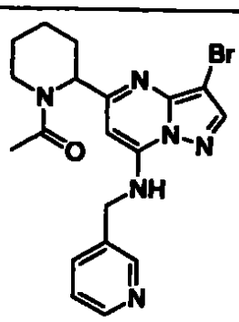
Ex.	Column 2	Column 3	CMPD

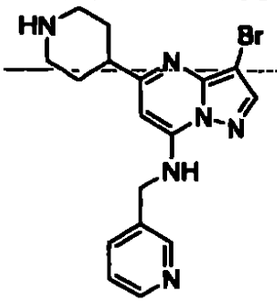
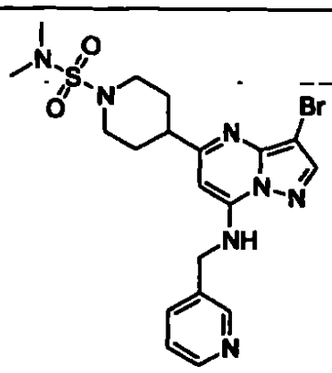
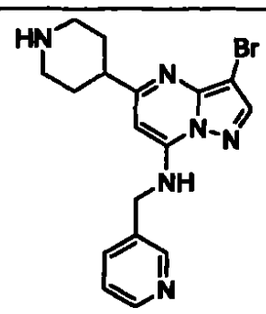
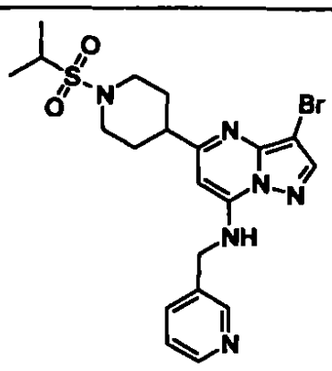
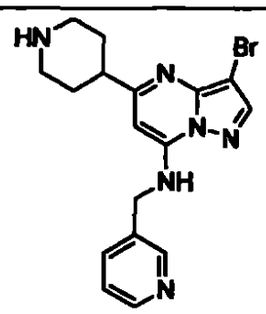
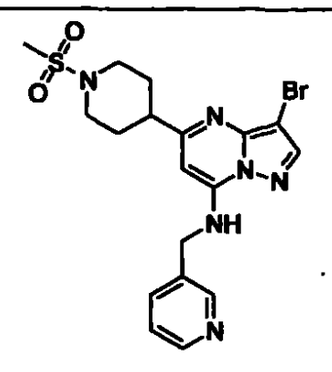
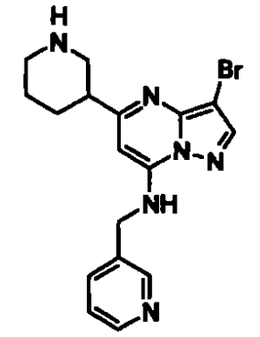
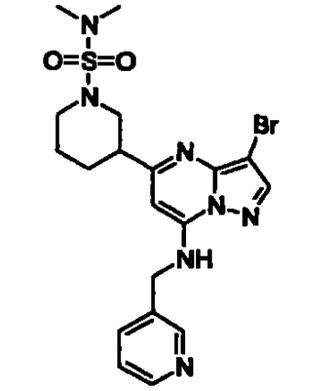
528			MH^+ = 608 m. p. = 230.1 °C
529			Yield = 82 MH^+ = 614 m. p. = 235.4 °C
530			MH^+ = 486 m. p. = 60.5 °C
531			MH^+ = 500 m. p. = 113.6 °C

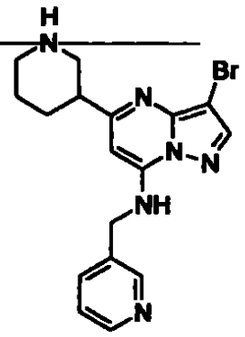
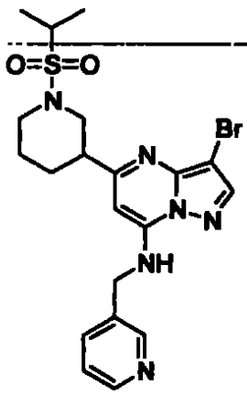
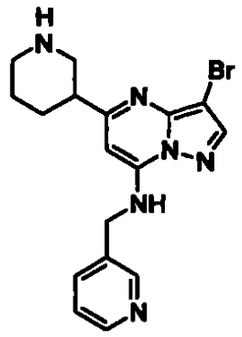
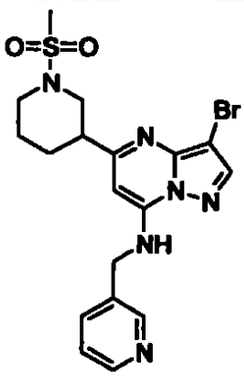
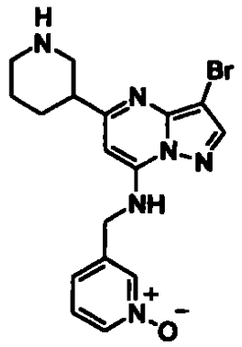
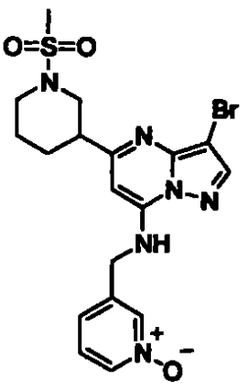
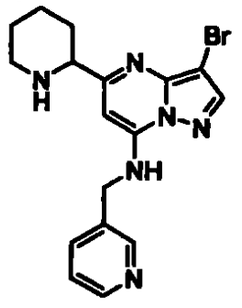
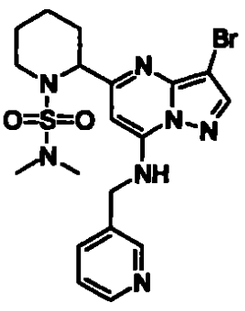
532			MH^+ = 430 m. p. = 158.3 – 159.2 °C
533			MH^+ = 531 m. p. =105.9 °C
534			MH^+ = 486
535			MH^+ = 500

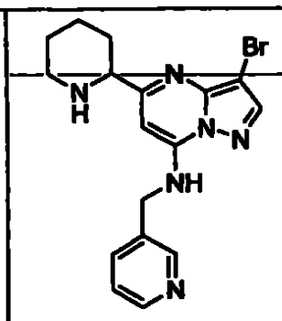
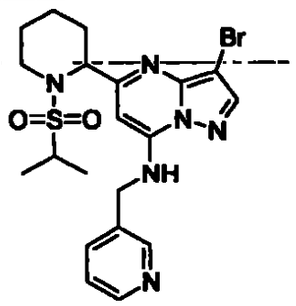
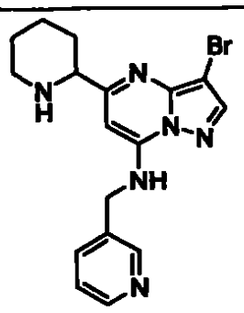
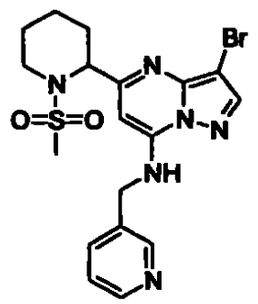
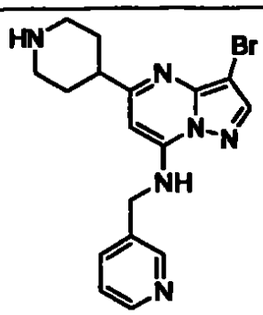
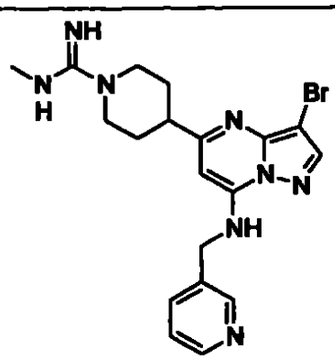
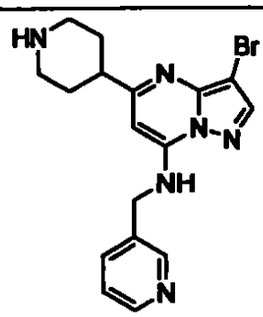
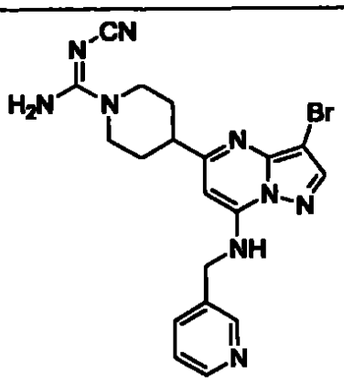
536			MH^+ = 430
537			MH^+ = 531
538			MH^+ = 486 m. p. = 69.6 °C
539			MH^+ = 500 m. p. = 82.3 °C

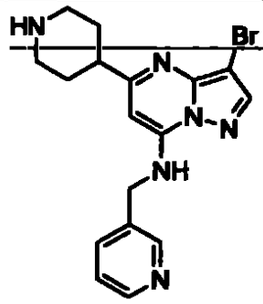
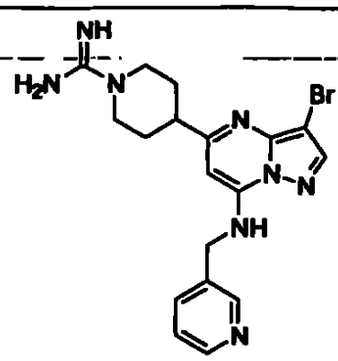
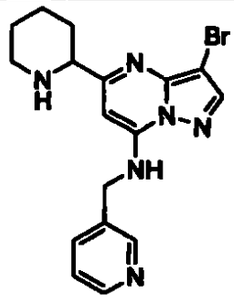
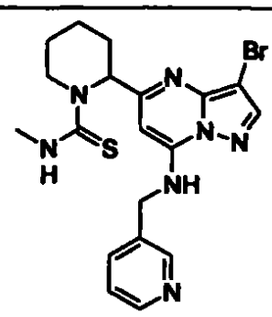
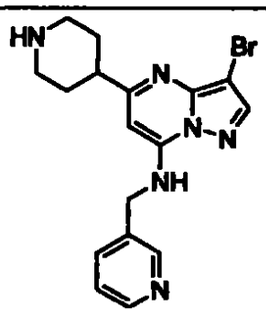
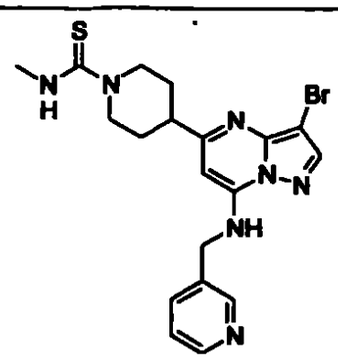
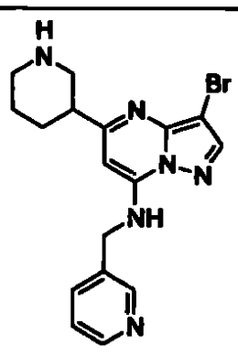
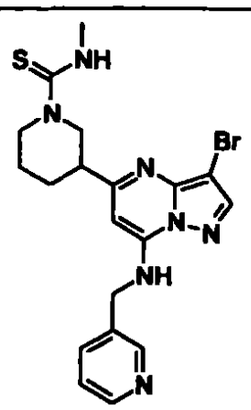
540			MH^+ = 430 m. p. = 223.6 °C
541			MH^+ = 531 m. p. = 118.1 °C
542			MH^+ = 455 m. p. = 109 – 110 °C
543			MH^+ = 429 m. p. = 111.5 °C

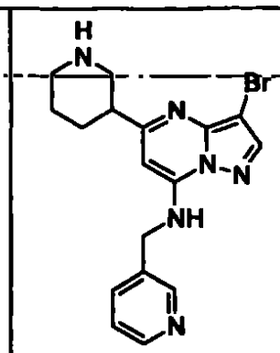
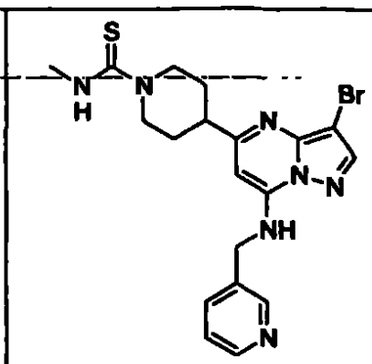
544			MH$^+$ = 455
545			MH$^+$ = 429
546			MH$^+$ = 455 m. p. =80.1 °C
547			MH$^+$ = 429 m. p. = 64.7 °C

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

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

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

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

564			MH^+ = 460 m. p. = 95.4 °C

Additional data for select examples given below.

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

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

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

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

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

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

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

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

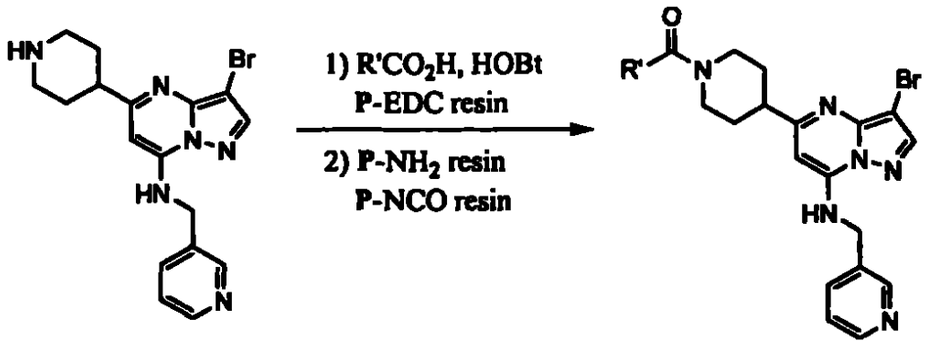
Example 552: ^{1}H NMR (300MHz, $CDCl_3$) δ 8.67 (s, 1H), 8.62 – 8.59 (d, 1H), 7.95 (s, 1H), 7.74 – 7.69 (d, 1H), 7.36 – 7.31 (dd, 1H), 6.67 – 6.60 (t, 1H), 5.98 (s, 1H), 4.67 – 4.63 (d, 2H), 3.92 – 3.86 (m, 1H), 3.85 – 3.75 (m, 1H), 3.40 – 3.30 (dd, 1H), 3.27 – 3.16 (m, 1H), 3.10 – 2.86 (m, 2H), 2.10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

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

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

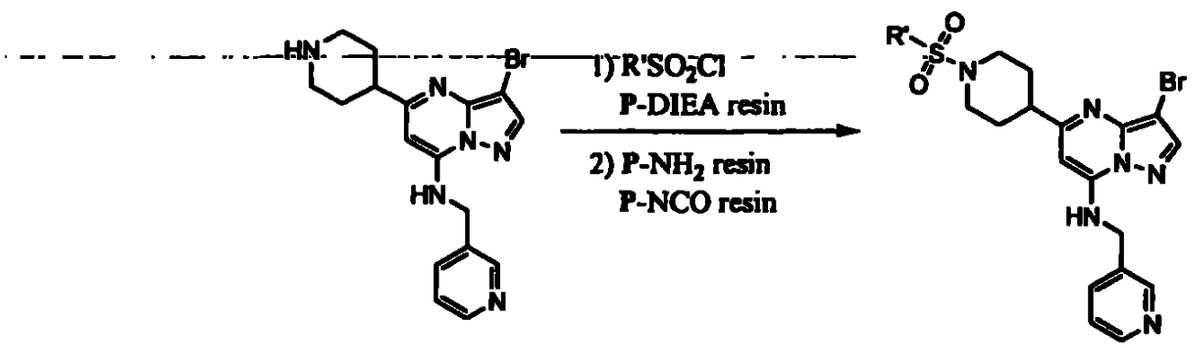
Example 563: ^{1}H NMR (300MHz, $CDCl_3$) δ 8.66 (s, 1H), 8.62 – 8.58 (d, 1H), 7.96 (s, 1H), 7.73 – 7.68 (d, 1H), 7.36 – 7.30 (dd, 1H), 6.96 – 6.86 (br s, 1H), 6.79 – 6.74 (t, 1H), 6.00 (s, 1H), 4.67 – 4.64 (d, 2H), 4.37 – 4.30 (dd, 1H), 4.22 – 4.13 (m, 1H), 3.97 – 3.86 (dd, 1H), 3.73 – 3.64 (m, 1H),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

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



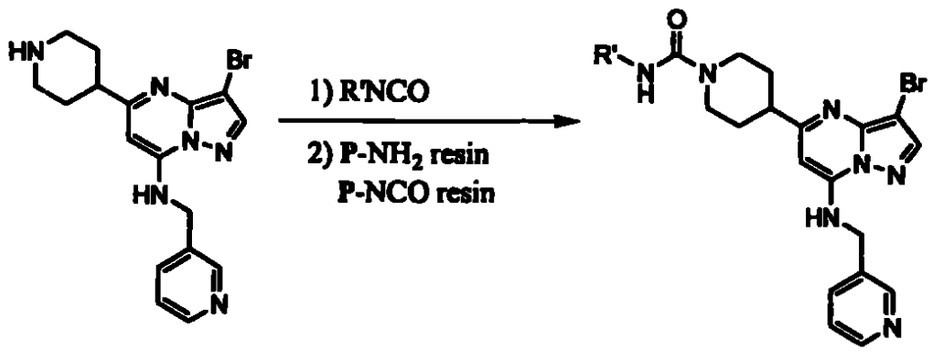
Parallel synthesis was conducted in polypropylene 96-well reaction blocks with removable top seal and fixed bottom seal. Each reaction well was fitted with a 20 micron polypropylene bottom frit and the maximum volume was 3 mL. Collection block was not fitted with bottom frit. To each reaction well was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

GENERAL PROCEDURE 2: Procedure for the sulfonamide formation parallel synthesis



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

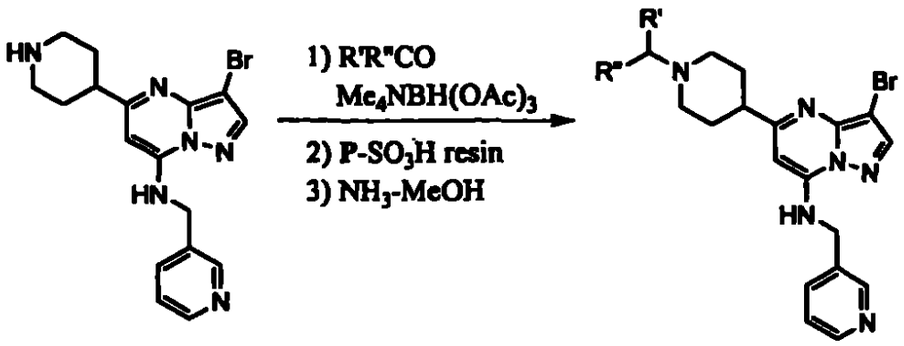
GENERAL PROCEDURE 3: Procedure for the urea formation parallel synthesis



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

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

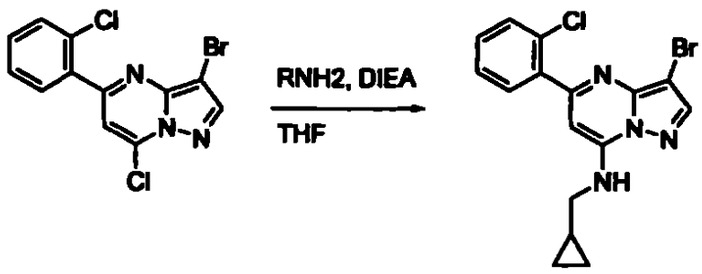
GENERAL PROCEDURE 4: Procedure for the reductive alkylation parallel synthesis



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

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

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

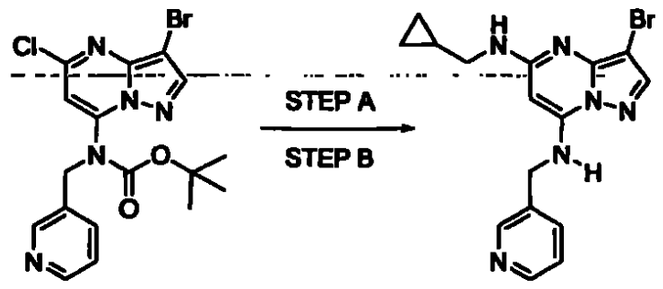


To 3-bromo-7-chloro-5-(2-chloro-phenyl)-pyrazolo[1,5-a]pyrimidine (9.0 mg, 0.03 mmol) in tetrahydrofuran were added di-*iso*-propylethylamine (12 µL, 0.07), followed by cyclopropylmethylamine (70 µL, .07 mmol; 1M solution in DMF). The reaction mixture was heated to 70 °C for 36 h and then cooled to rt.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

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

General protocols:

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



STEP A:

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

STEP B(acidic):

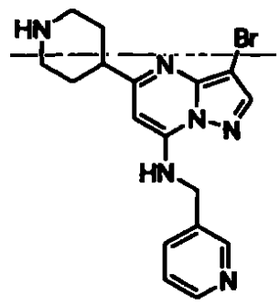
The product from STEP A was taken up in 35% TFA/DCM and agitated for 4 h followed by concentration under high vacuum. The residue was treated with 10% HCl(aq) in MeOH agitated for 2 h and then concentrated to give the desired product. . observed m/z 375.21.

STEP B(basic):

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

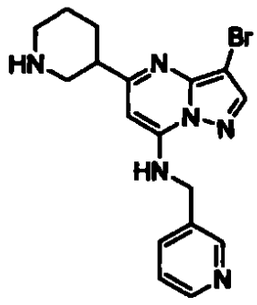
EXAMPLE 565:

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



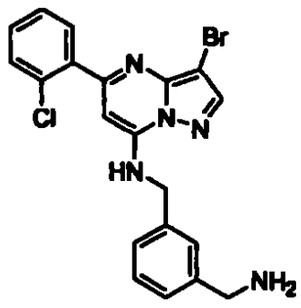
EXAMPLE 566:

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



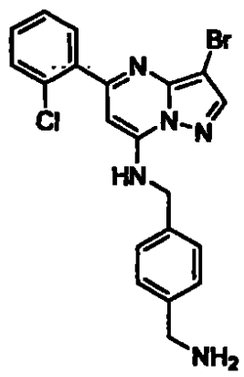
EXAMPLE 567:

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



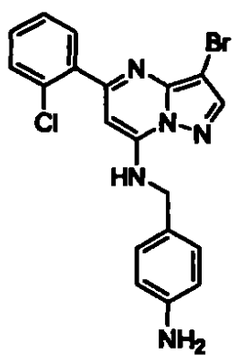
EXAMPLE 568:

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



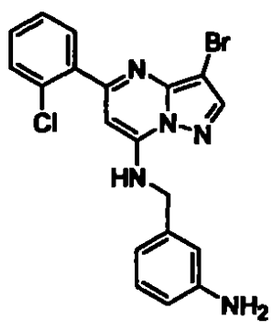
EXAMPLE 569:

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



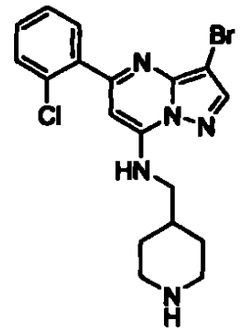
EXAMPLE 570:

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



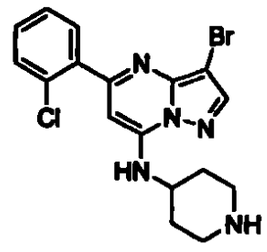
EXAMPLE 571:

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



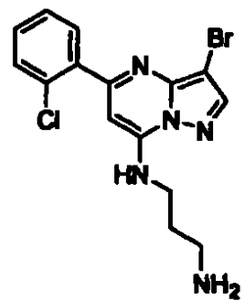
EXAMPLE 572:

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



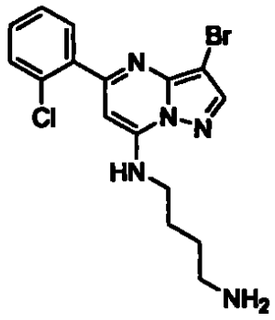
EXAMPLE 573:

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



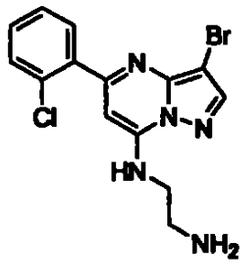
EXAMPLE 574:

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



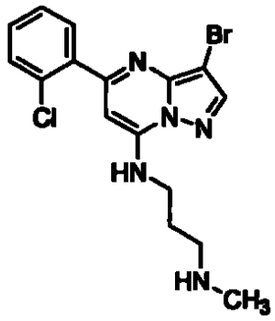
EXAMPLE 575:

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



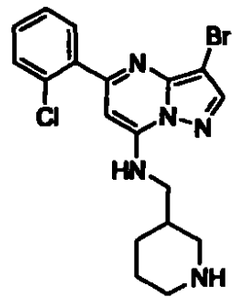
EXAMPLE 576:

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



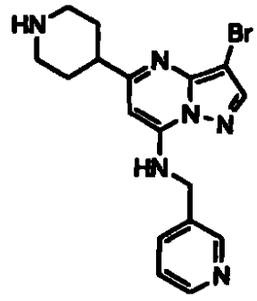
EXAMPLE 577:

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



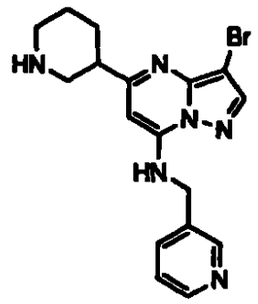
EXAMPLE 578:

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



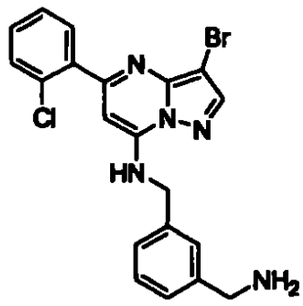
EXAMPLE 579:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 471 shown below, the compounds shown in Table 57 with the observed m/z were prepared.



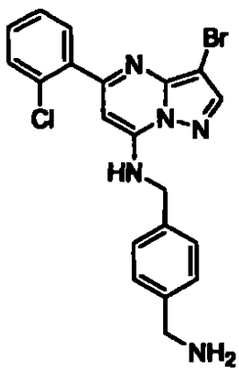
EXAMPLE 580:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 515 shown below, the compounds shown in Table 58 with the observed m/z were prepared.



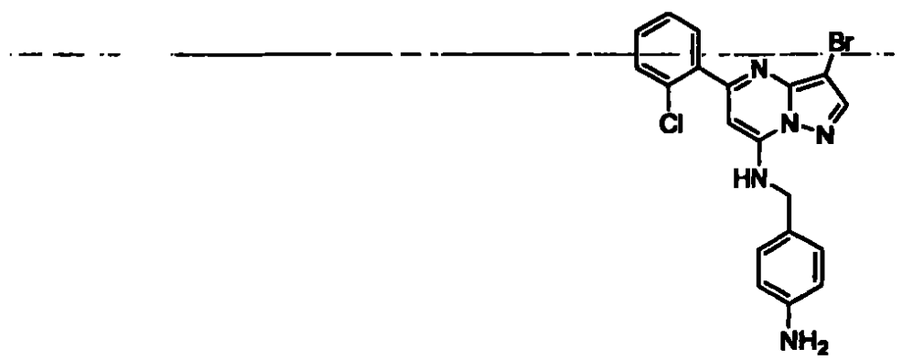
EXAMPLE 581:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 513 shown below, the compounds shown in Table 59 with the observed m/z were prepared.



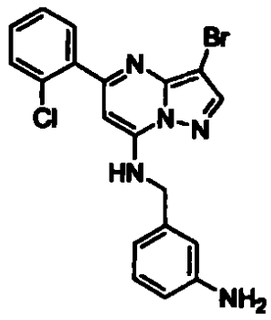
EXAMPLE 582:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 513 shown below, the compounds shown in Table 60 with the observed m/z were prepared.



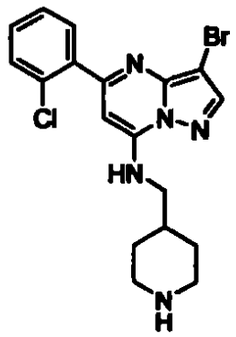
EXAMPLE 583:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 524 shown below, the compounds shown in Table 61 with the observed m/z were prepared.



EXAMPLE 584:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 525 shown below, the compounds shown in Table 62 with the observed m/z were prepared.

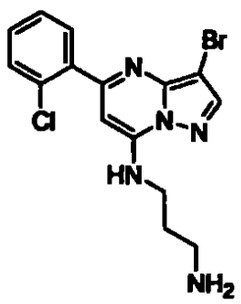


EXAMPLE 585:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 526.10 shown below, the compounds shown in Table 63 with the observed m/z were prepared.

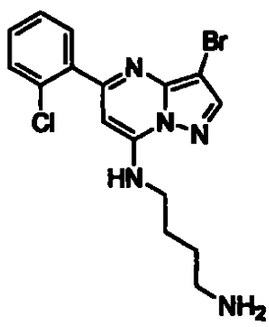
EXAMPLE 586:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 518 shown below, the compounds shown in Table 64 with the observed m/z were prepared.



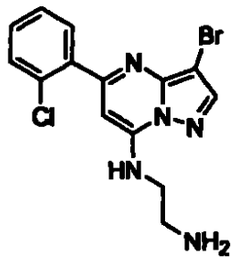
EXAMPLE 587:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 519 shown below, the compounds shown in Table 65 with the observed m/z were prepared.



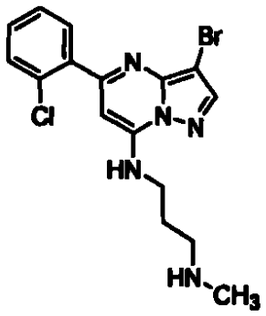
EXAMPLE 588:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 520 shown below, the compounds shown in Table 67 with the observed m/z were prepared.



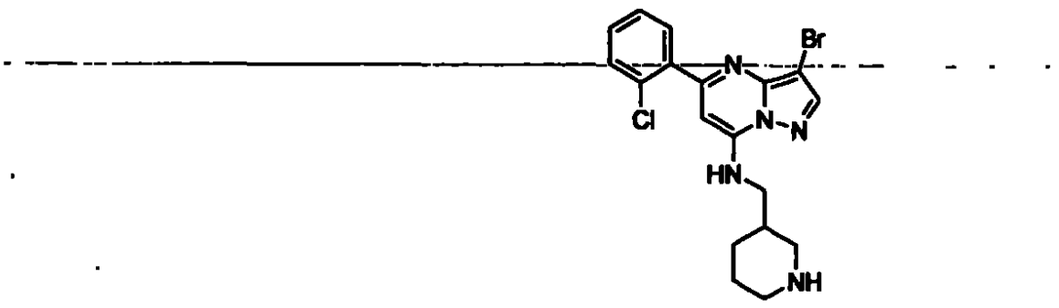
EXAMPLE 589:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 521 shown below, the compounds shown in Table 68 with the observed m/z were prepared.



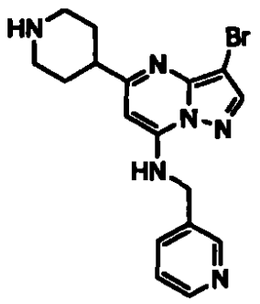
EXAMPLE 590:

By utilizing the procedure set forth in General Procedure 2 and the compound from Example 523 shown below, the compounds shown in Table 69 with the observed m/z were prepared.



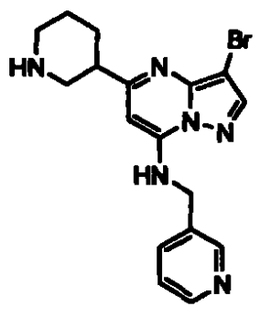
EXAMPLE 591:

By utilizing the procedure set forth in General Procedure 3 and the compound from Example 462 shown below, the compounds shown in Table 70 with the observed m/z were prepared.



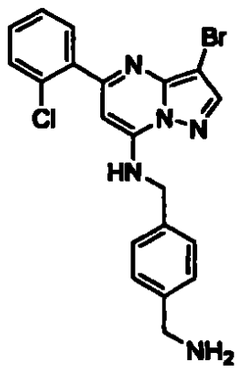
EXAMPLE 592:

By utilizing the procedure set forth in General Procedure 3 and the compound from Example 471 shown below, the compounds shown in Table 71 with the observed m/z were prepared.



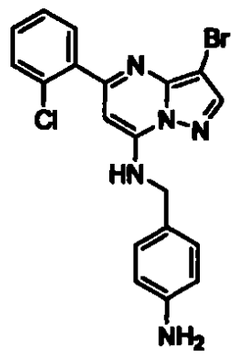
EXAMPLE 593:

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



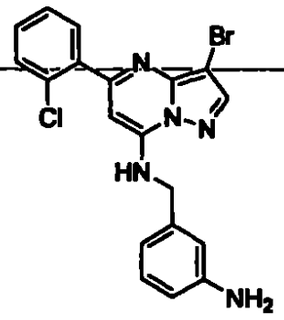
EXAMPLE 594:

By utilizing the procedure set forth in General Procedure 3 and the compound from Example 524 shown below, the compounds shown in Table 73 with the observed m/z were prepared.



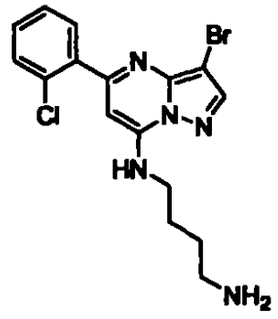
EXAMPLE 595:

By utilizing the procedure set forth in General Procedure 3 and the compound from Example 524 shown below, the compounds shown in Table 74 with the observed m/z were prepared.



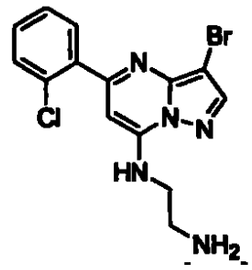
EXAMPLE 596:

By utilizing the procedure set forth in General Procedure 3 and the compound from Example 519 shown below, the compounds shown in Table 75 with the observed m/z were prepared.



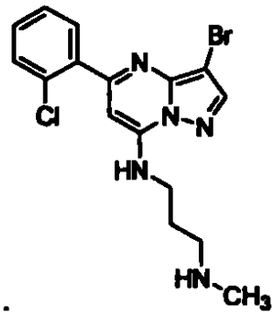
EXAMPLE 597:

By utilizing the procedure set forth in General Procedure 3 and the compound from Example 520 shown below, the compounds shown in Table 76 with the observed m/z were prepared.



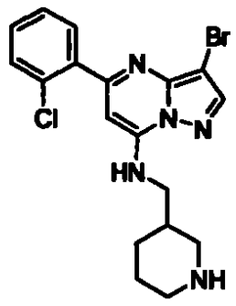
EXAMPLE 598:

By utilizing the procedure set forth in General Procedure 3 and the compound from Example 521 shown below, the compounds shown in Table 77 with the observed m/z were prepared.



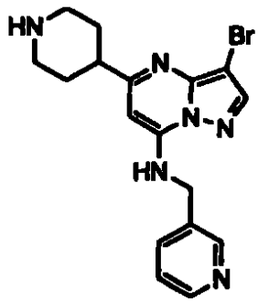
EXAMPLE 599:

By utilizing the procedure set forth in General Procedure 3 and the compound from Example 523 shown below, the compounds shown in Table 78 with the observed m/z were prepared.



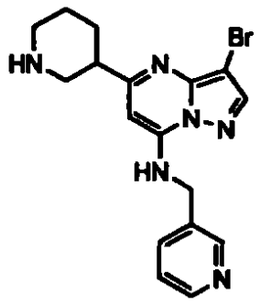
EXAMPLE 600:

By utilizing the procedure set forth in General Procedure 4 and the compound from Example 462 shown below, the compounds shown in Table 79 with the observed m/z were prepared.



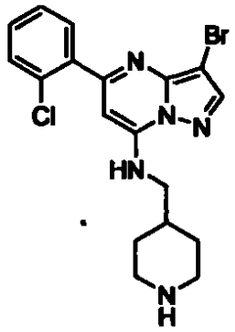
EXAMPLE 601:

By utilizing the procedure set forth in General Procedure 4 and the compound from Example 471 shown below, the compounds shown in Table 80 with the observed m/z were prepared.



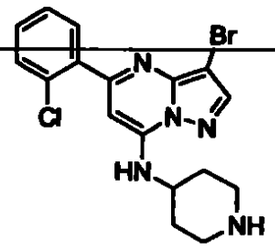
EXAMPLE 602:

By utilizing the procedure set forth in General Procedure 4 and the compound from Example 525 shown below, the compounds shown in Table 81 with the observed m/z were prepared.



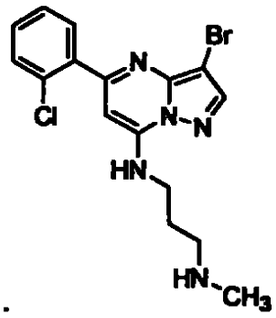
EXAMPLE 603:

By utilizing the procedure set forth in General Procedure 4 and the compound from Example 526.10 shown below, the compounds shown in Table 82 with the observed m/z were prepared.



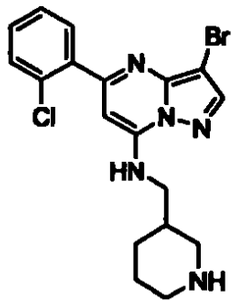
EXAMPLE 604:

By utilizing the procedure set forth in General Procedure 4 and the compound from Example 521 shown below, the compounds shown in Table 83 with the observed m/z were prepared.



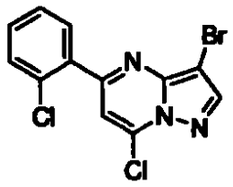
EXAMPLE 605:

By utilizing the procedure set forth in General Procedure 4 and the compound from Example 523 shown below, the compounds shown in Table 84 with the observed m/z were prepared.



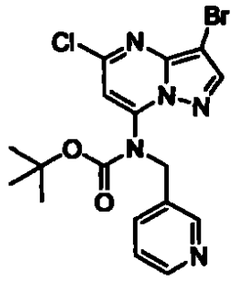
EXAMPLE 606:

By utilizing the procedure set forth in General Procedure 5 and the compound from Preparative Example 81 shown below, the compounds shown in Table 85 with the observed m/z were prepared.



EXAMPLE 607:

By utilizing the procedure set forth in General Procedure 6 and the compound from Preparative Example 196, the compounds shown in Table 86 with the observed m/z were prepared.



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

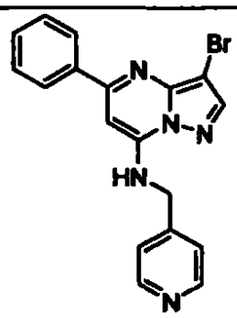
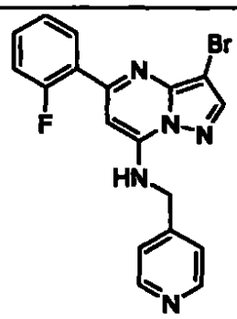
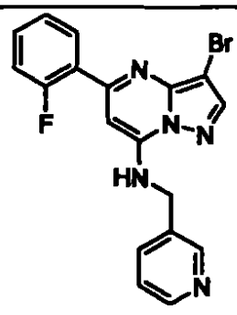
minutes and the supernatant retained. 5ml of anti-GluTAG beads (for one liter of SF9 cells) were then used to capture cyclin-CDK2 complexes. Bound beads were washed three times in lysis buffer. Proteins were competitively eluted with lysis buffer containing 100-200ug/mL of the GluTAG peptide. Eluate 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.

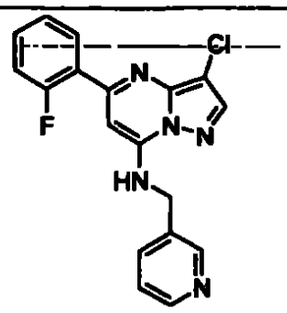
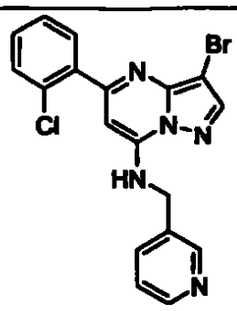
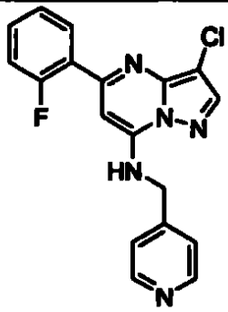
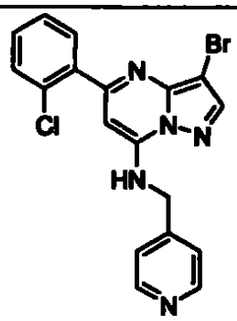
IN VITRO KINASE ASSAY: CDK2 kinase assays (either cyclin A or E-dependent) were performed in low protein binding 96-well plates (Corning Inc, Corning, New York). Enzyme was diluted to a final concentration of 50 ug/ml in kinase buffer containing 50mM Tris pH 8.0, 10mM $MgCl_2$, 1mM DTT, and 0.1mM sodium 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 uM in kinase buffer. Compounds were diluted in 10%DMSO to desirable concentrations. For each kinase reaction, 20 ul of the 50 ug/ml enzyme solution (1 ug of enzyme) and 20 ul of the 1 uM substrate solution were mixed, then combined with 10 ul of diluted compound in each well for testing. The kinase reaction was started by addition of 50 ul of 4 uM ATP and 1 uCi 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 ul 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).

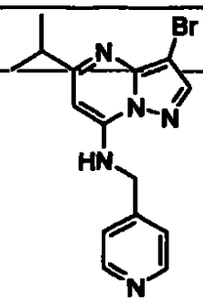
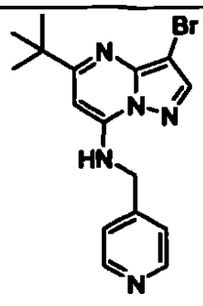
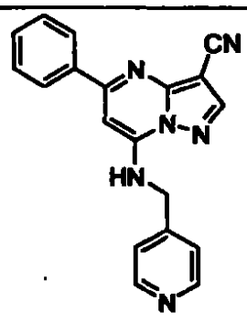
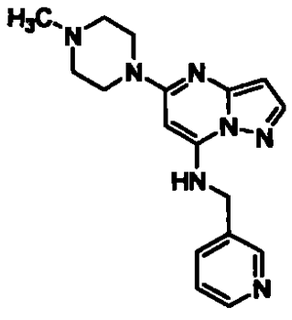
IC_{50} DETERMINATION: Dose-response curves were plotted from inhibition data generated, each in duplicate, from 8 point serial dilutions of inhibitory

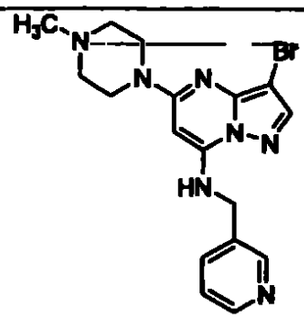
compounds. Concentration of compound was plotted against % kinase activity, calculated by CPM of treated samples divided by CPM of untreated samples. To generate IC_{50} values, the dose-response curves were then fitted to a standard sigmoidal curve and IC_{50} values were derived by nonlinear regression 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

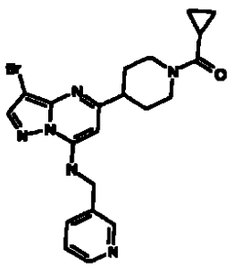
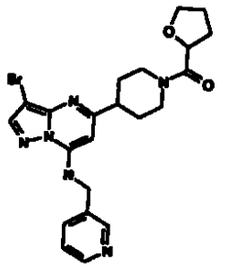
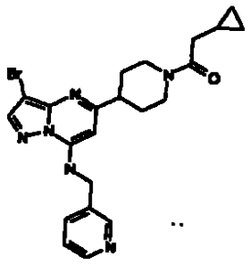
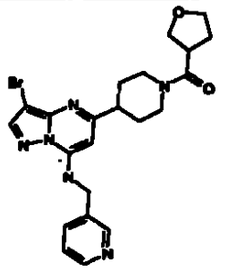
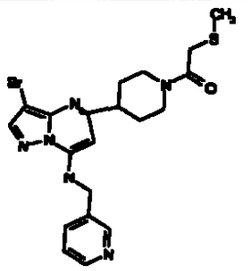
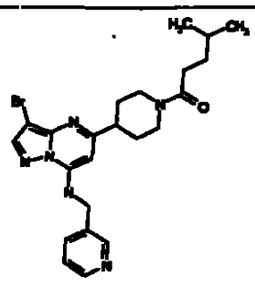
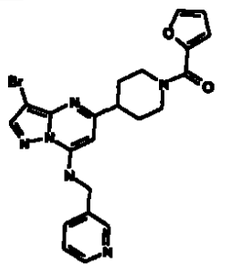
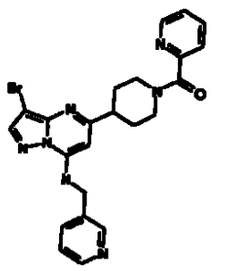
	10	0.042
	12	0.17
	16	0.62
	1	5.6

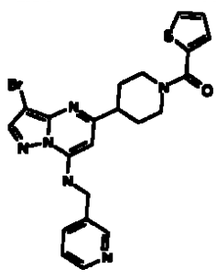
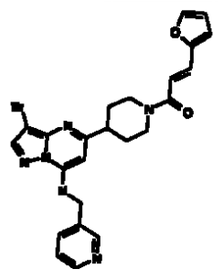
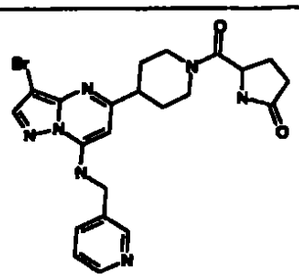
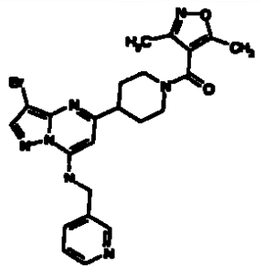
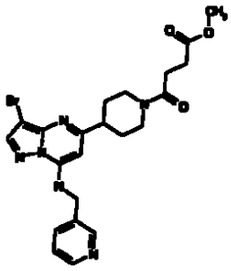
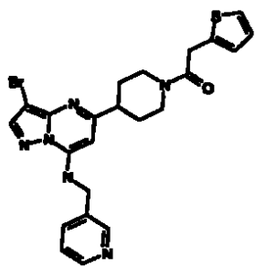
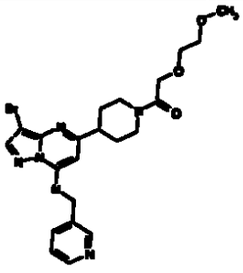
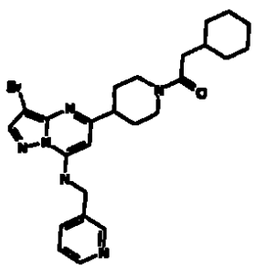
	3	0.14

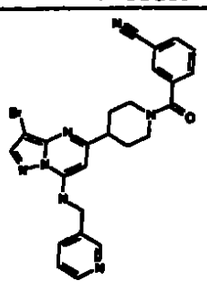
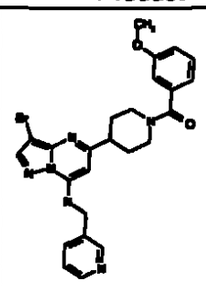
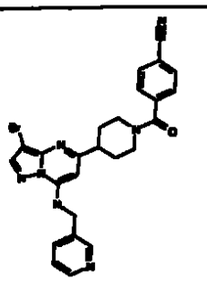
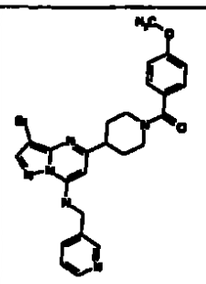
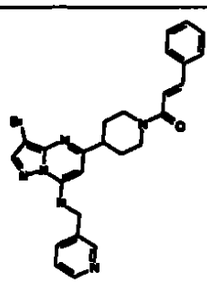
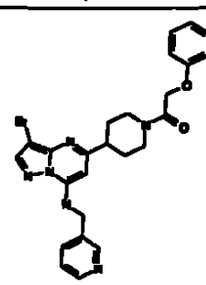
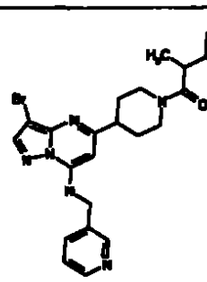
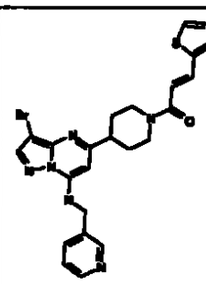
As demonstrated above by the assay values, the compounds of the present invention exhibit excellent CDK inhibitory properties.

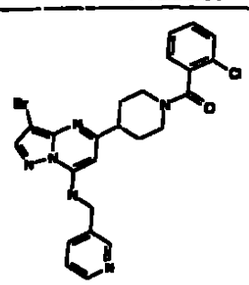
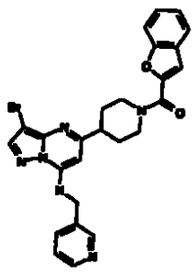
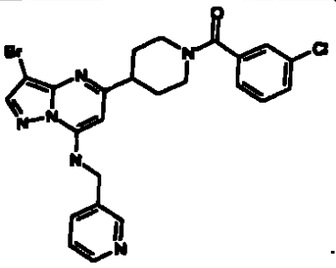
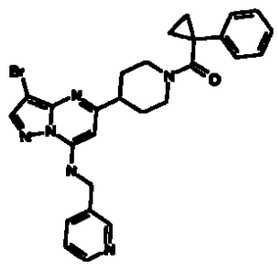
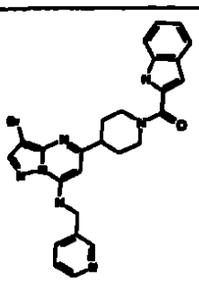
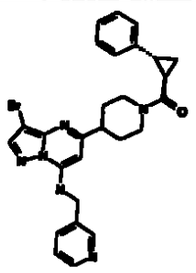
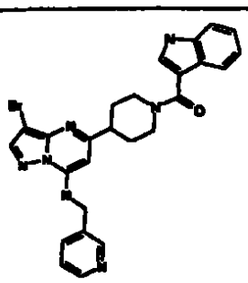
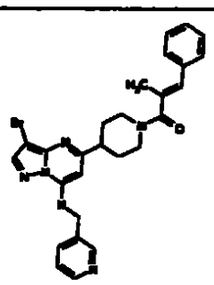
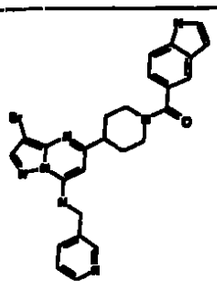
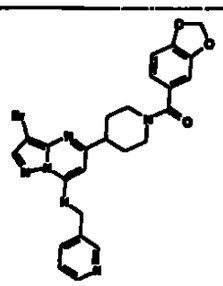
While the present invention has been described with in conjunction with the specific embodiments set forth above, many alternatives, modifications and other variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall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

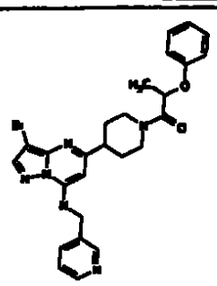
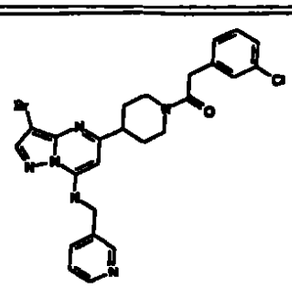
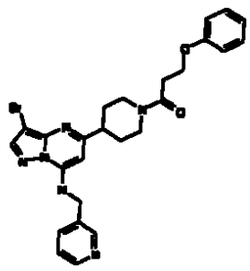
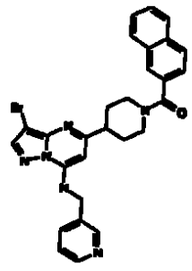
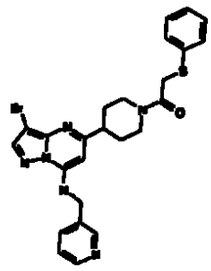
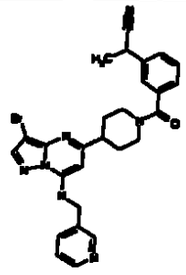
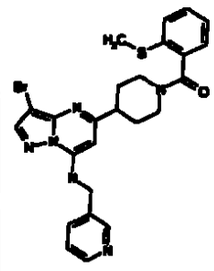
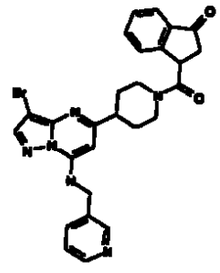
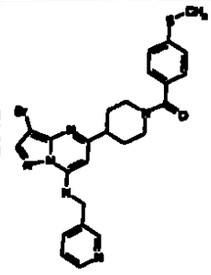
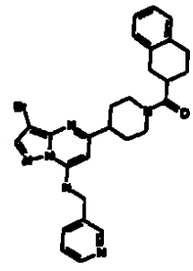
TABLE 43

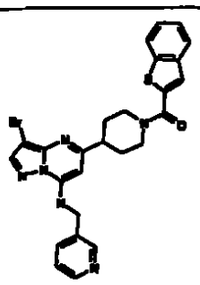
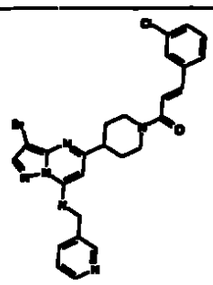
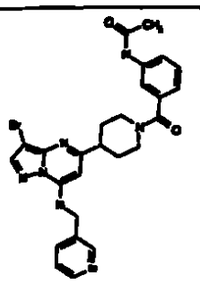
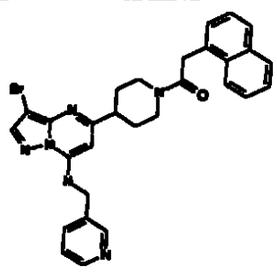
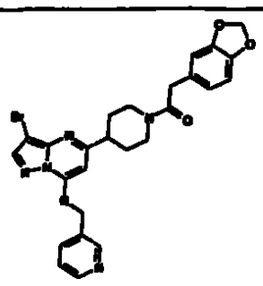
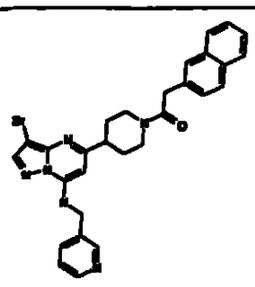
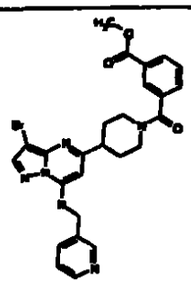
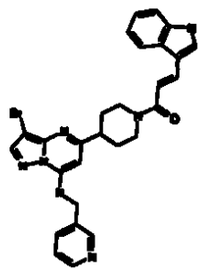
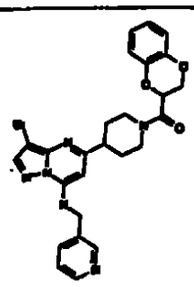
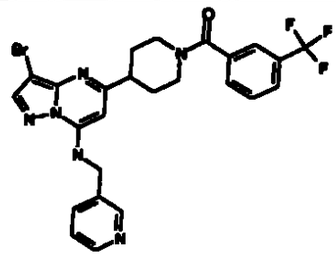
Ex.	Compound	m/z	Ex.	Compound	m/z
4301		457.25	4305		487.27
4302		471.26	4306		487.27
4303		477.26	4307		487.27
4304		483.27	4308		494.27

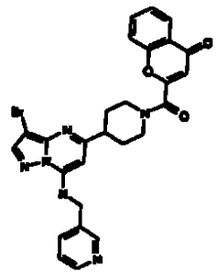
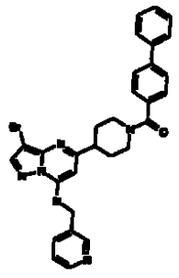
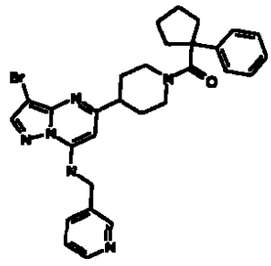
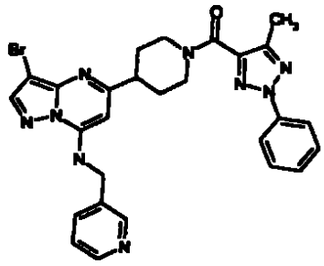
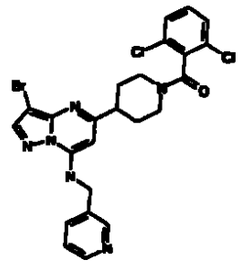
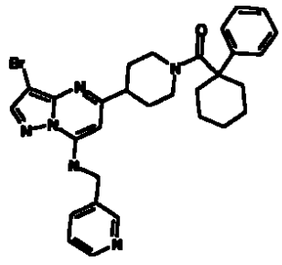
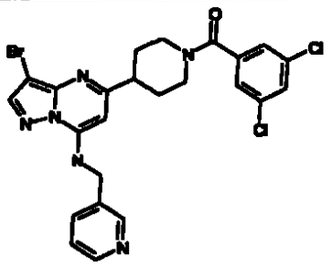
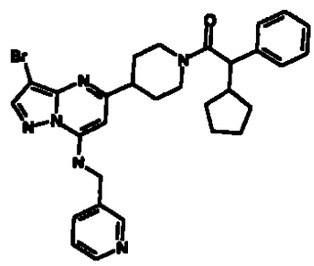
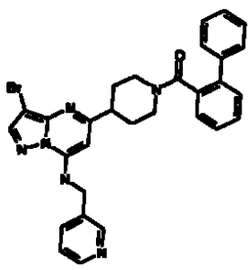
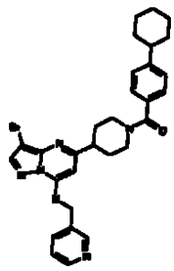
Ex.	Product	m/z	Ex.	Product	m/z
4309		498.27	4313		509.28
4310		500.27	4314		512.28
4311		503.28	4315		513.28
4312		505.28	4316		513.28

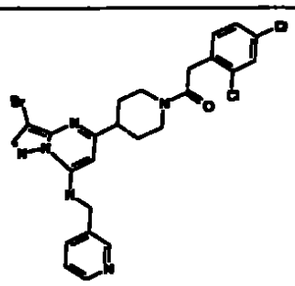
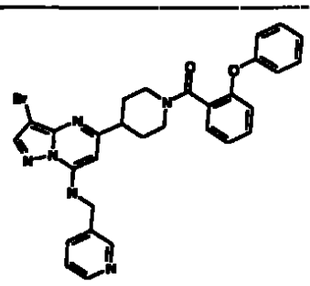
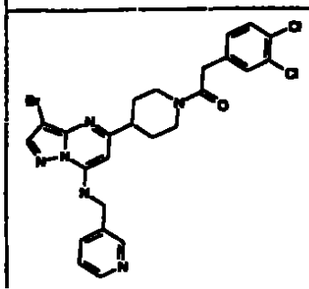
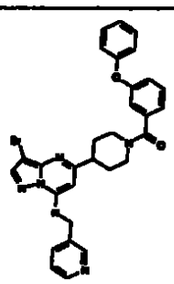
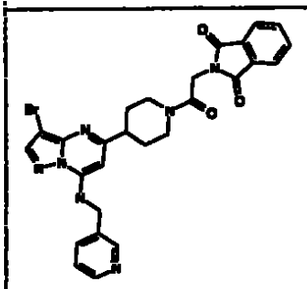
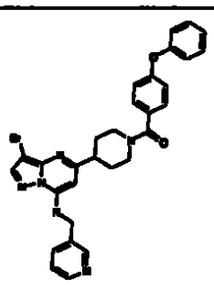
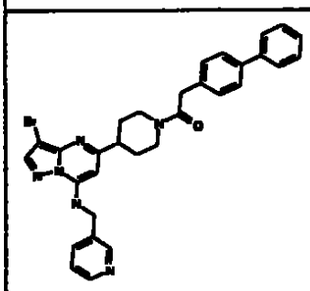
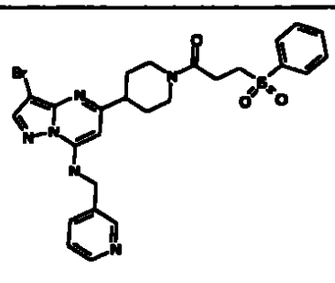
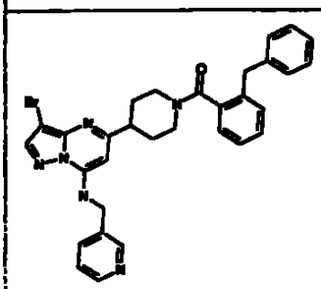
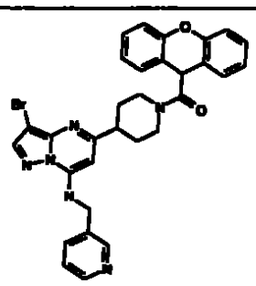
Ex.	Product	m/z	Ex.	Product	m/z
4317		518.28	4321		523.29
4318		518.28	4322		523.29
4319		519.29	4323		523.29
4320		521.29	4324		525.29

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. 546.3
	1. 4338 2. 539.3		1. 4343 2. 547.3
	1. 4339 2. 539.3		1. 4344 2. 547.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4345 2. 549.3		1. 4350 2. 553.3
	1. 4346 2. 550.3		1. 4351 2. 557.31
	1. 4347 2. 551.3		1. 4352 2. 557.31
	1. 4348 2. 551.3		1. 4353 2. 558.31
	1. 4349 2. 551.3		1. 4354 2. 561.31

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4355 2. 561.31		1. 4360 2. 569.31
	1. 4356 2. 561.31		1. 4361 2. 574.32
	1. 4357 2. 561.31		1. 4362 2. 573.32
	1. 4358 2. 561.31		1. 4363 2. 573.32
	1. 4359 2. 569.31		1. 4364 2. 575.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4365 2. 575.32		1. 43700 2. 585.32
	1. 43666 2. 575.32		1. 4371 2. 583.32
	1. 4367 2. 574.32		1. 4372 2. 585.32
	1. 43688 2. 583.32		1. 4373 2. 585.32
	1. 4369 2. 583.32		1. 4374 2. 597.33

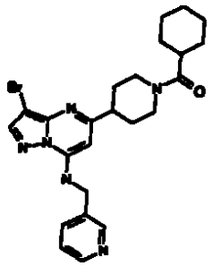
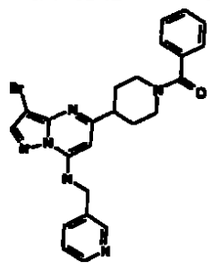
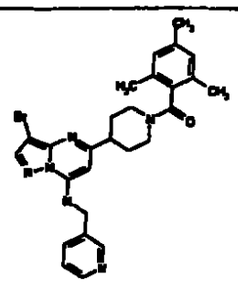
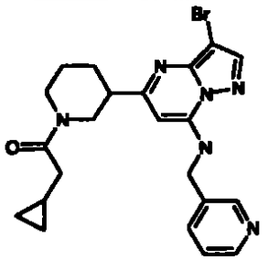
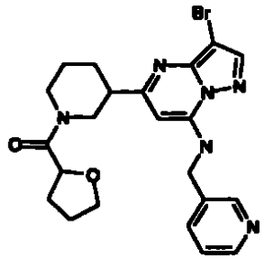
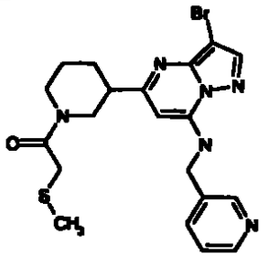
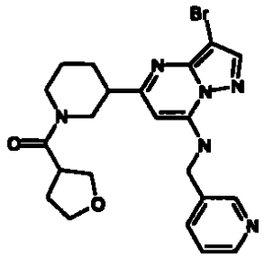
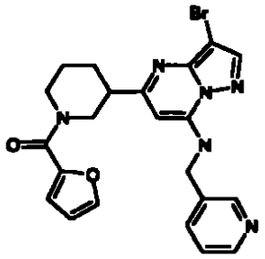
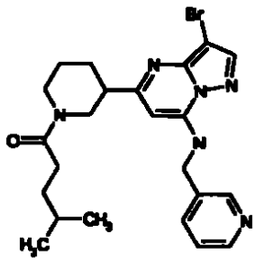
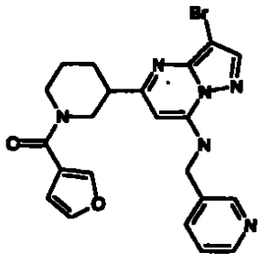
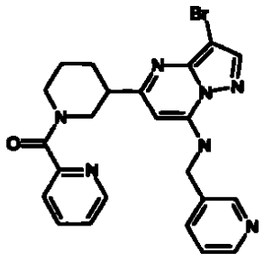
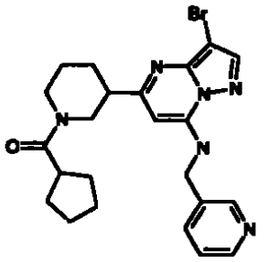
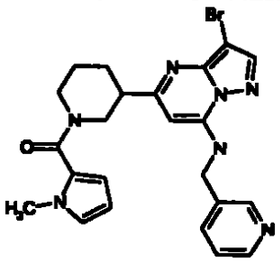
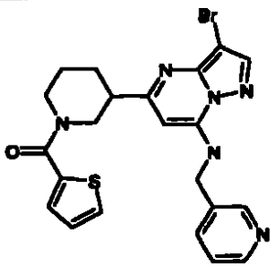
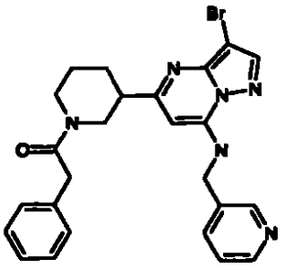
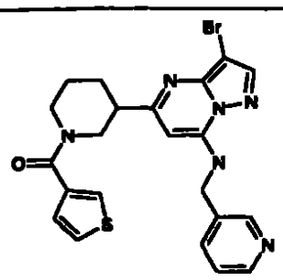
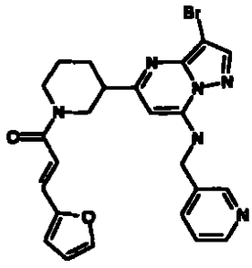
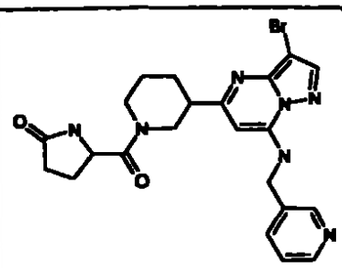
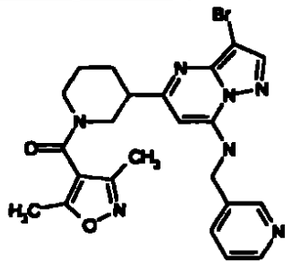
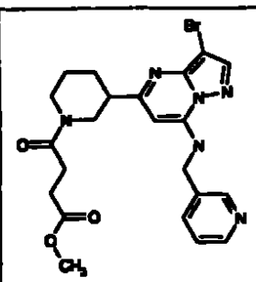
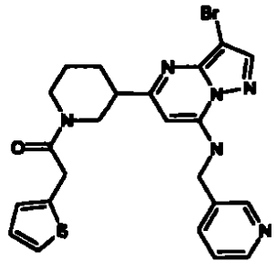
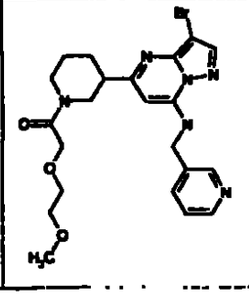
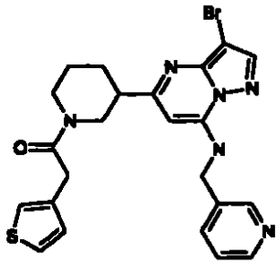
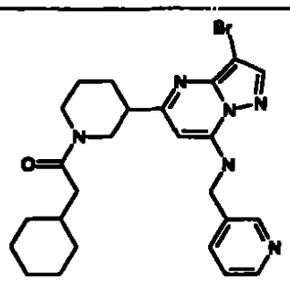
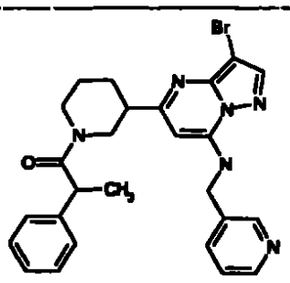
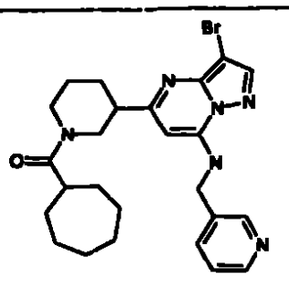
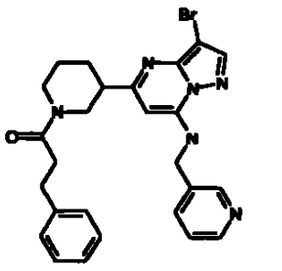
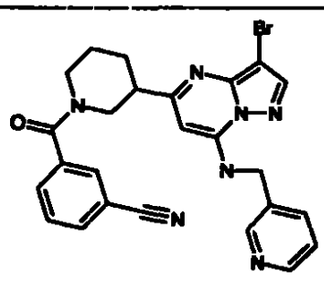
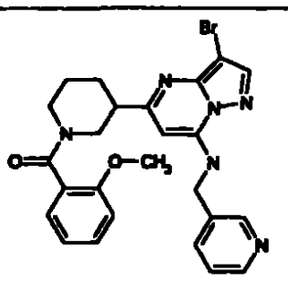
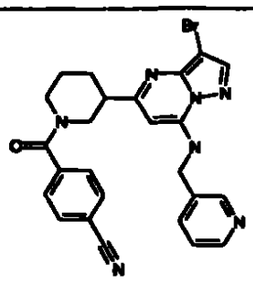
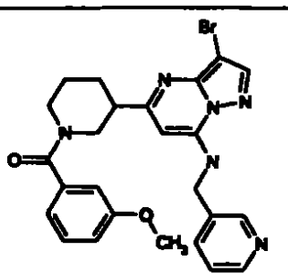
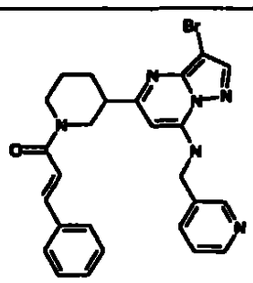
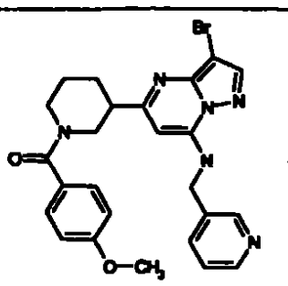
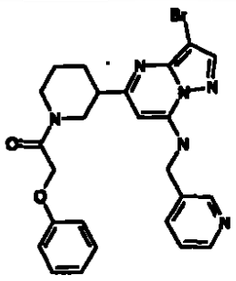
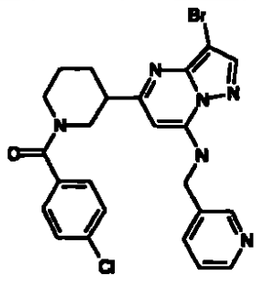
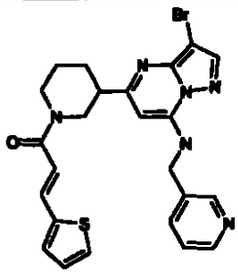
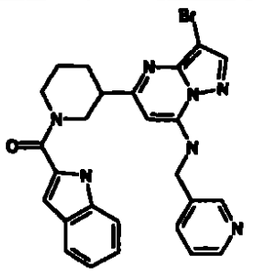
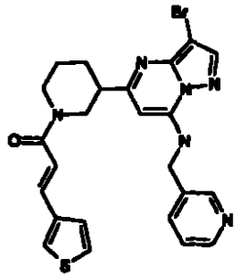
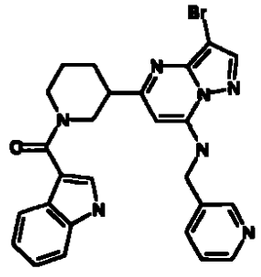
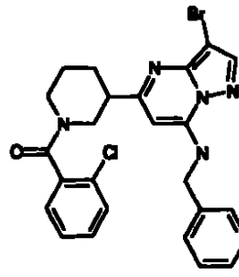
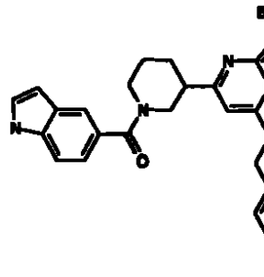
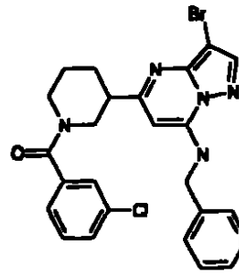
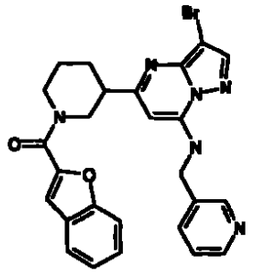
Product	1. Ex. 2. m/z
	1. 4375 2. 499.27
	1. 4376 2. 493.27
	1. 4377 2. 535.29

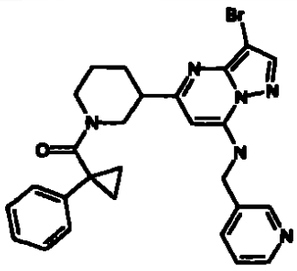
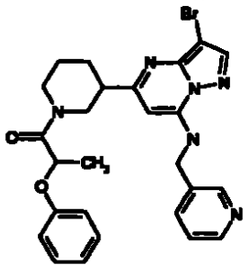
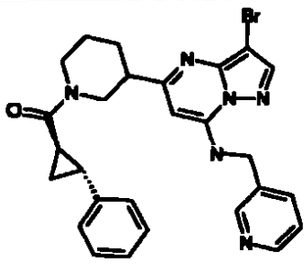
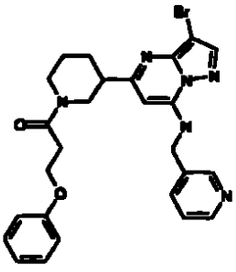
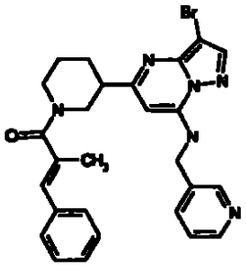
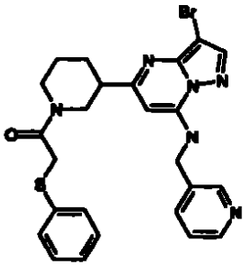
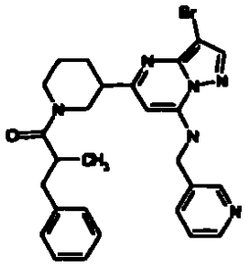
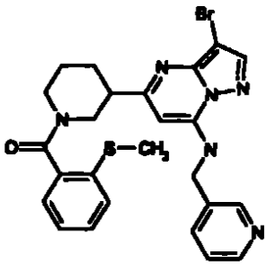
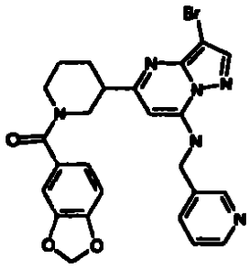
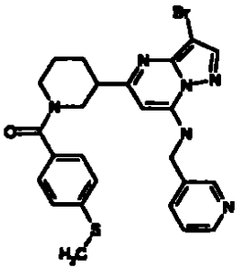
TABLE 44

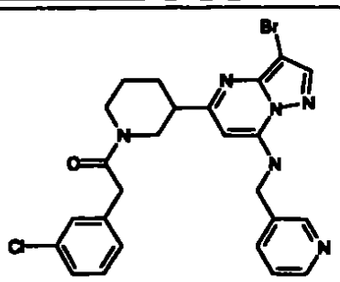
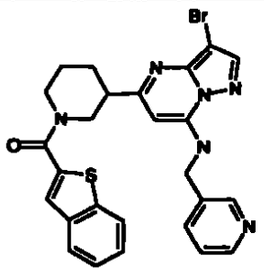
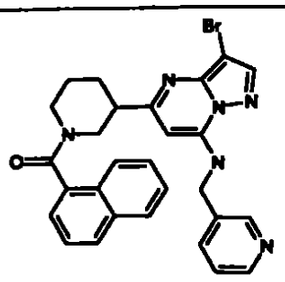
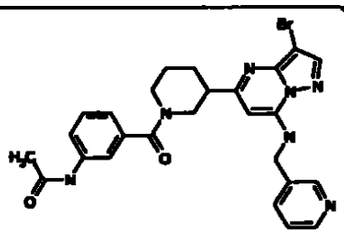
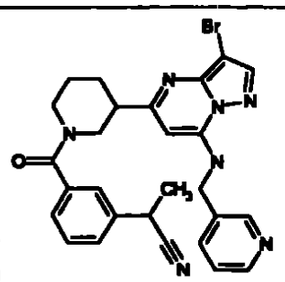
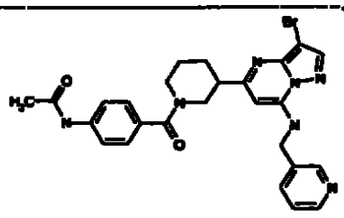
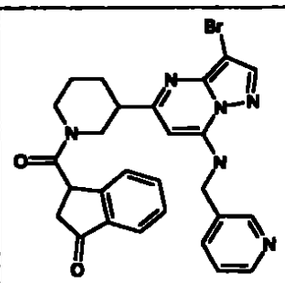
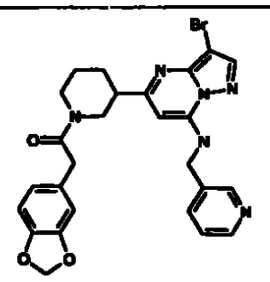
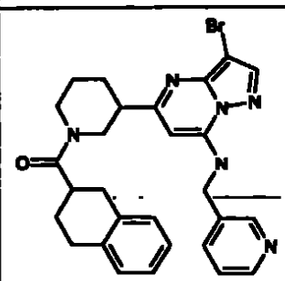
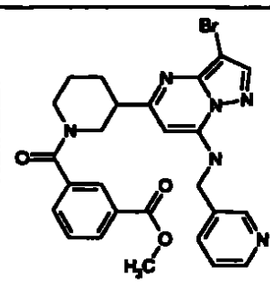
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4401 2. 471.3		1. 4406 2. 487.27
	1. 4402 2. 475.26		1. 4407 2. 487.27
	1. 4403 2. 483.27		1. 4408 2. 487.27
	1. 4404 2. 481.26		1. 4409 2. 494.3
	1. 4405 2. 485.27		1. 4410 2. 496.27

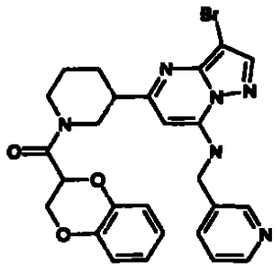
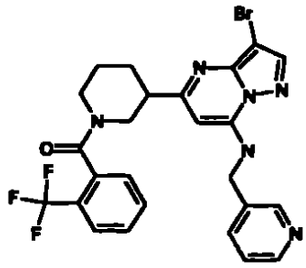
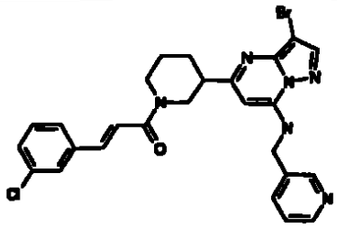
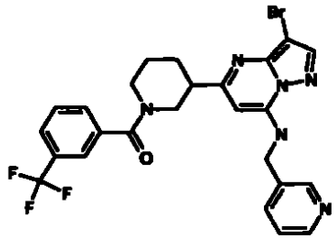
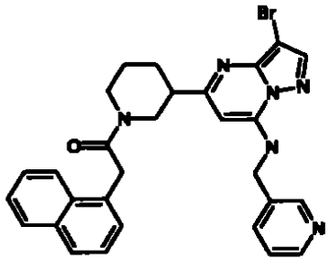
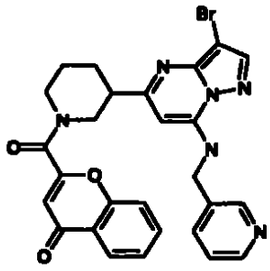
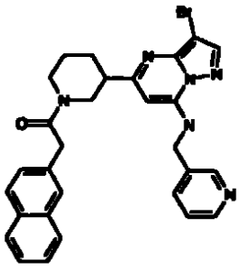
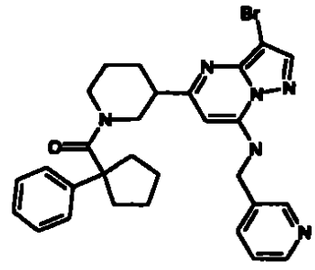
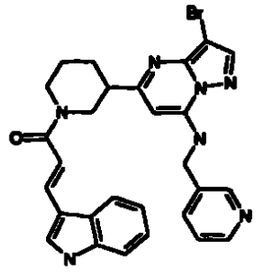
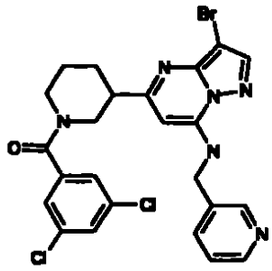
Product	1. Ex 2. m/z	Product	1. Ex. 2. m/z
	1. 4411 2. 499.27		1. 4416 2. 507.28
	2. 4412 2. 499.27		1. 4417 2. 509.3
	1. 4413 2. 500.27		1. 4418 2. 512.28
	1. 4414 2. 503.28		1. 4419 2. 513.28
	1. 4415 2. 505.28		1. 4420 2. 513.28

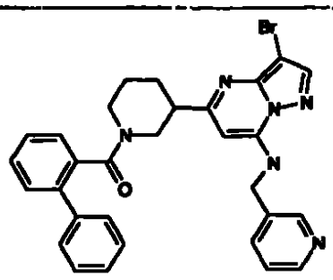
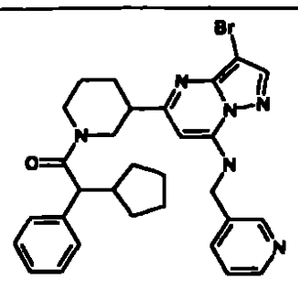
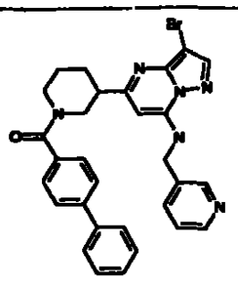
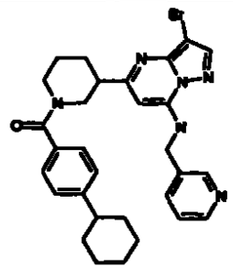
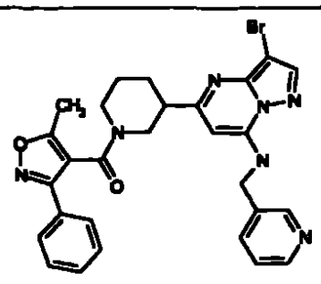
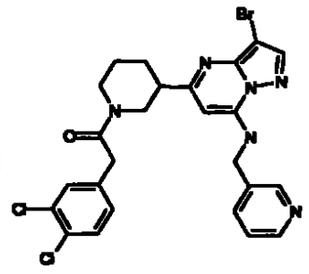
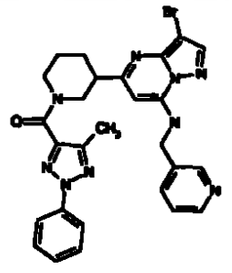
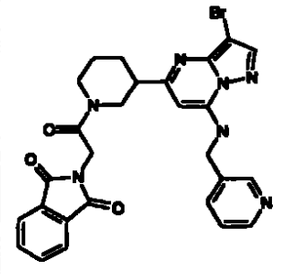
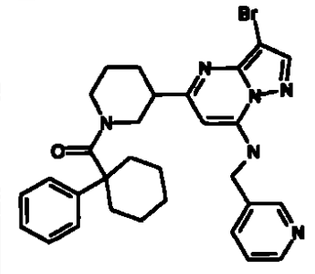
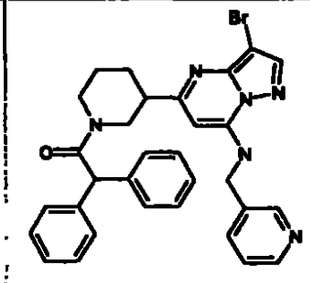
Product	1. x. 2. m/z	Product	1. Ex. 2. m/z
	1. 4421 2. 513.28		1. 4426 2. 521.29
	1. 4422 2. 513.28		1. 4428 2. 521.29
	1. 4423 2. 518.28		1. 4428 2. 523.29
	1. 4424 2. 518.28		1. 4429 2. 523.29
	1. 4425 2. 519.3		1. 4430 2.523.29

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. 533.28		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
	1. 4474 2. 572.31		1. 4479 2. 576.32
	1. 4475 2. 575.32		1. 4480 2. 583.32

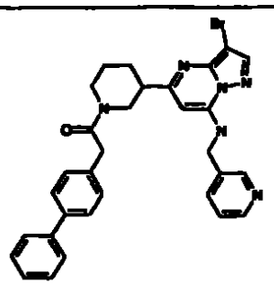
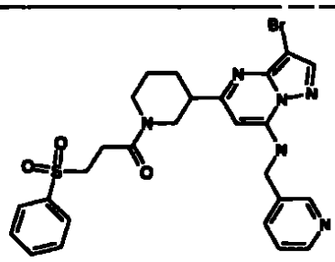
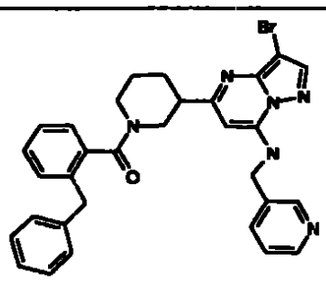
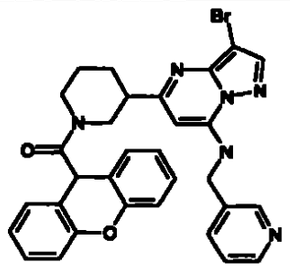
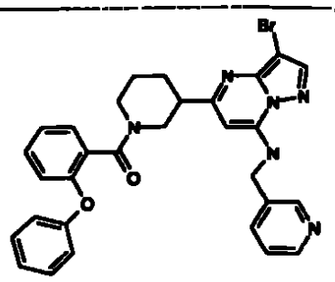
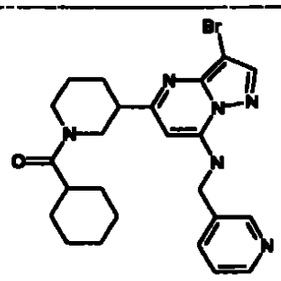
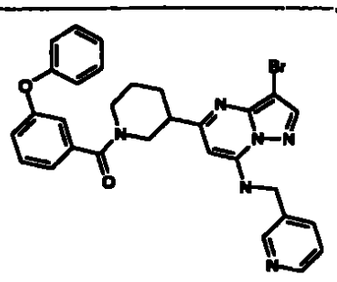
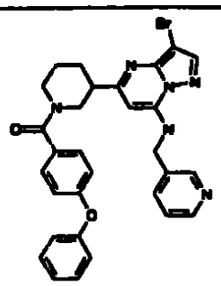
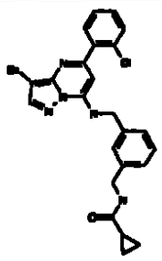
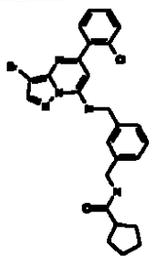
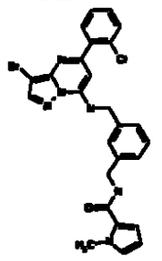
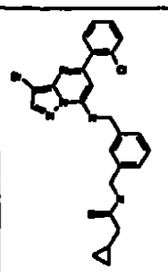
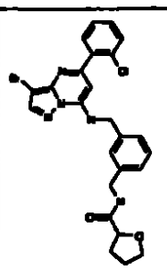
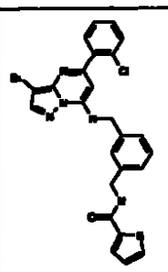
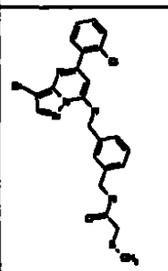
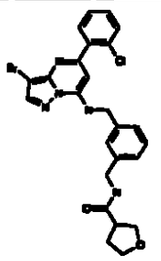
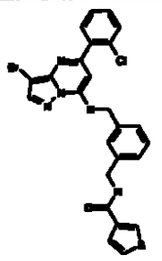
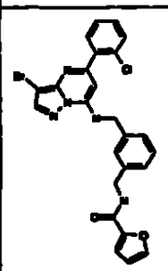
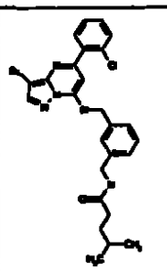
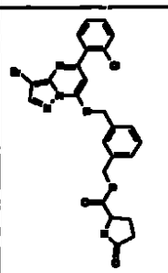
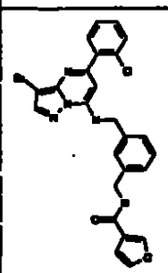
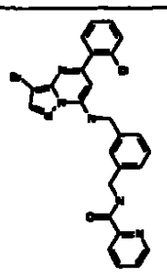
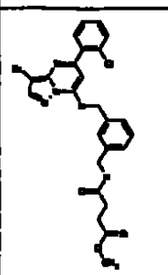
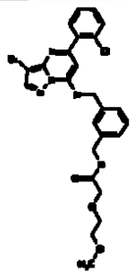
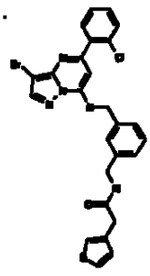
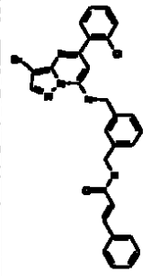
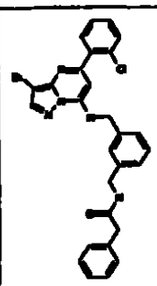
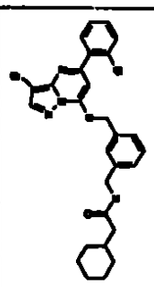
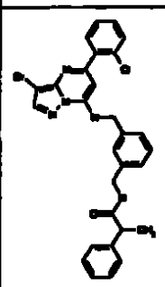
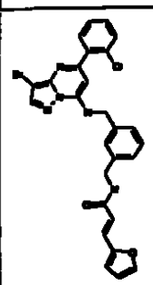
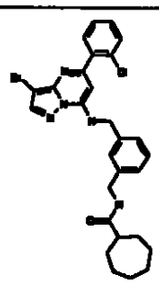
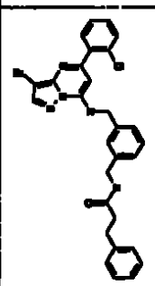
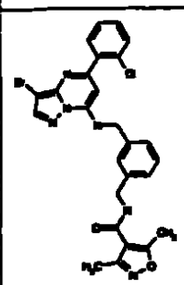
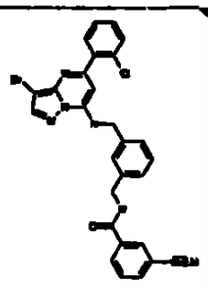
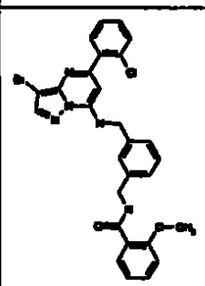
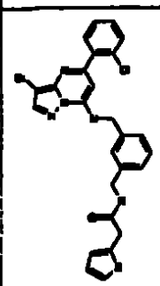
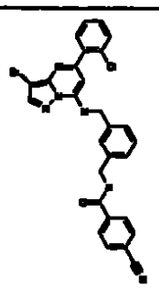
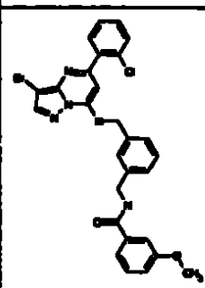
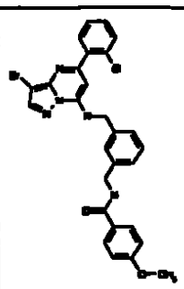
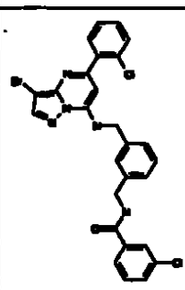
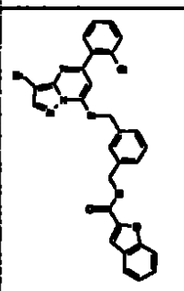
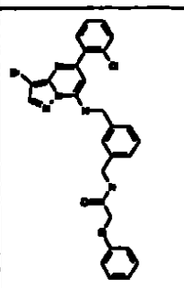
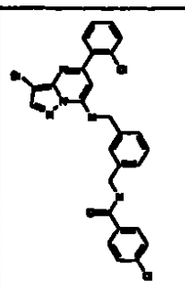
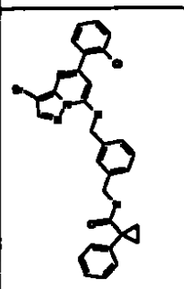
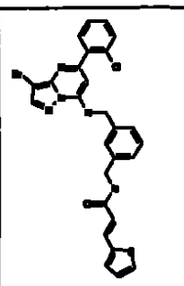
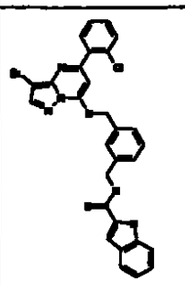
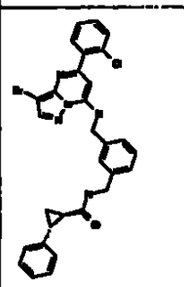
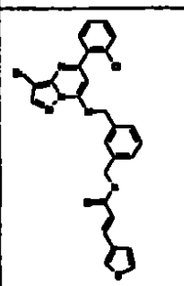
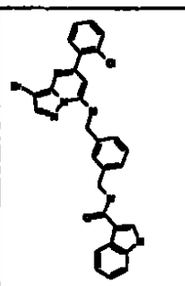
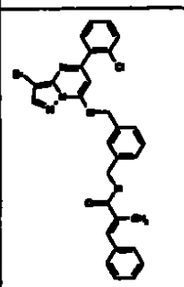
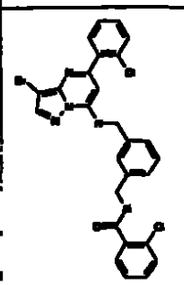
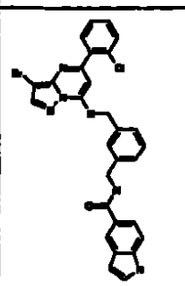
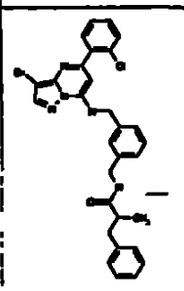
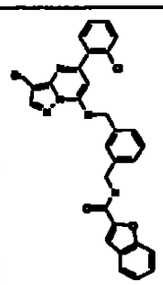
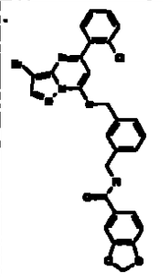
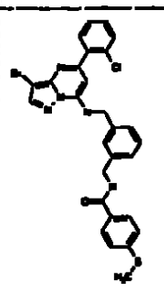
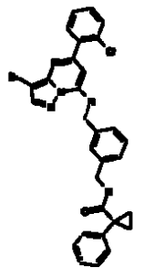
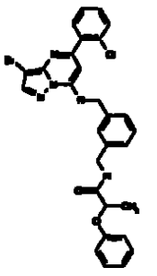
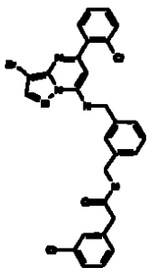
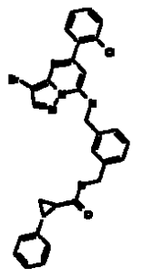
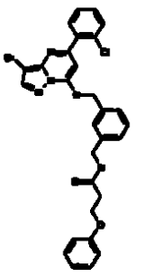
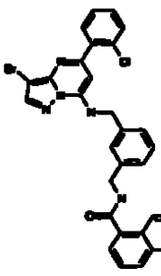
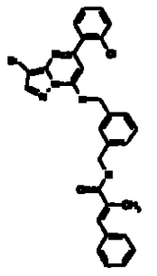
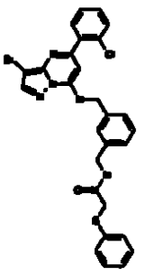
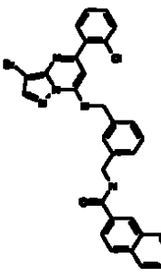
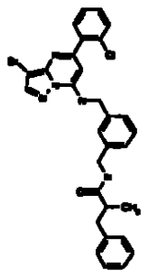
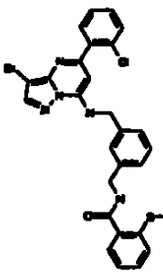
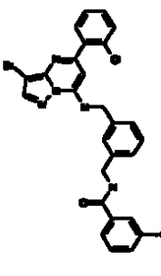
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4481 2. 583.32		1. 4486 2. 585.32
	1. 4482 2. 583.32		1. 4487 2. 597.33
	1. 4483 2. 585.32		1. 4488 2. 499.27
	1. 4484 2. 585.32		
	1. 4485 2. 585.3		

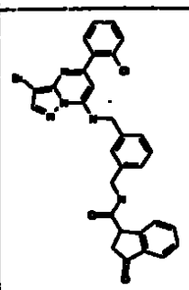
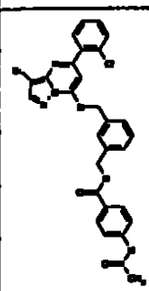
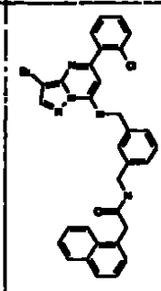
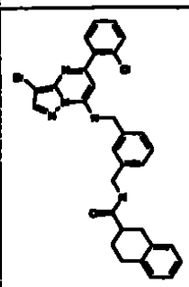
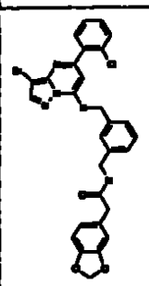
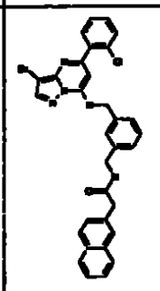
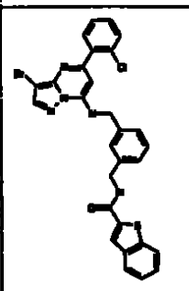
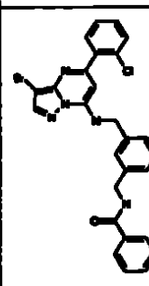
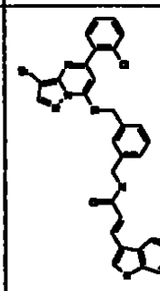
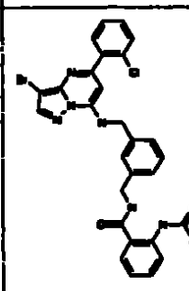
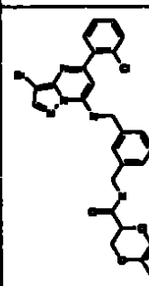
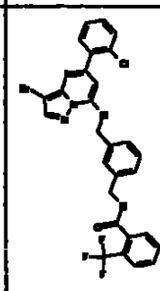
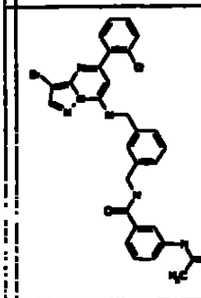
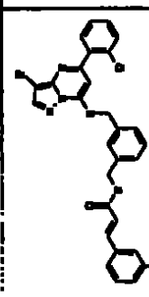
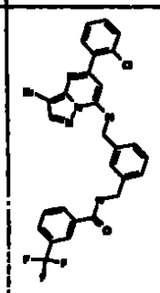
TABLE 45

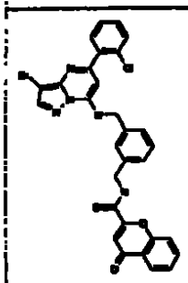
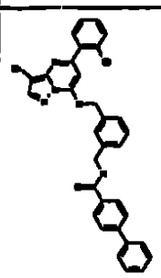
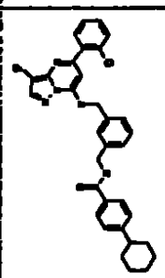
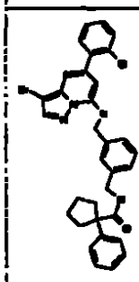
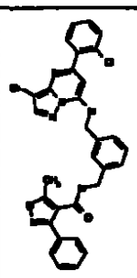
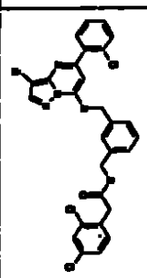
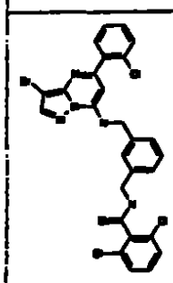
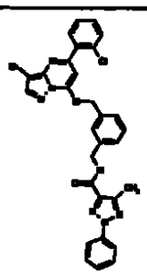
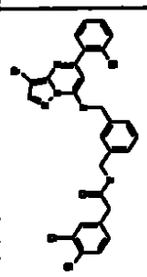
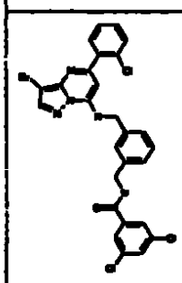
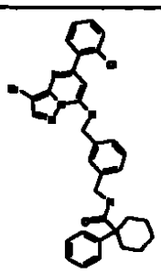
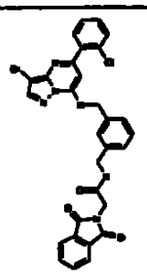
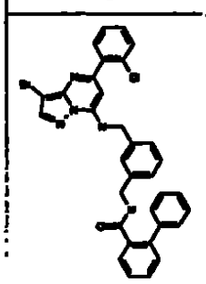
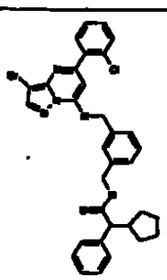
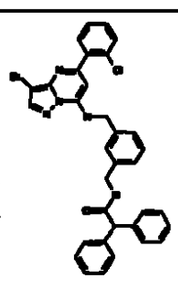
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4501 2. 512.28		1. 4506 2. 540.3		1. 4511 2. 551.3
	1. 4502 2. 526.29		1. 4507 2. 542.3		1. 4512 2. 554.3
	1. 4503 2. 532.29		1. 4508 2. 542.3		1. 4513 2. 554.3
	1. 4504 2. 538.3		1. 4509 2. 542.3		1. 4514. 2. 555.31
	1. 4505 2. 538.3		1. 4510 2. 549.3		1. 4515 2. 558.31

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4516 2. 560.31		1. 4521 2. 568.31		1. 4526 2. 574.32
	1. 4517 2. 562.31		1. 4522 2. 568.31		1. 4527 2. 576.32
	1. 4518 2. 564.31		1. 4523 2. 568.31		1. 4528 2. 576.32
	1. 4519 2. 567.31		1. 4524 2. 573.32		1. 4529 2. 578.32
	1. 4520 2. 568.31		1. 4525 2. 573.32		1. 4530 2. 578.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4531 2. 578.32		1. 4536 2. 582.32		1. 4541 2. 588.32
	1. 4532 2. 578.32		1. 4537 2. 582.32		1. 4542 2. 588.32
	1. 4533 2. 580.32		1. 4538 2. 587.32		1. 4543 2. 588.32
	1. 4534 2. 580.32		1. 4539 2. 587.32		1. 4544 2. 588.32
	1. 4535 2. 582.32		1. 4540 2. 587.32		1. 4545 2. 590.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4546 2. 588.32		1. 4551 2. 592.33		1. 4556 2. 593.33
	1. 4547 2. 588.32		1. 4552 2. 592.33		1. 4557 2. 596.33
	1. 4548 2. 588.32		1. 4553 2. 592.33		1. 4558 2. 596.33
	1. 4549 2. 588.32		1. 4554 2. 594.33		1. 4559 2. 598.33
	1. 4550 2. 590.32		1. 4555 2. 594.33		1. 4560 2. 601.33

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4561 2. 602.33		1. 4665 2. 605.33		1. 4571 2. 612.34
	1. 4562 2. 602.33		1. 4567 2. 606.33		1. 4572 2. 612.34
	1. 4563 2. 604.33		1. 4568 2. 606.33		1. 4573 2. 613.34
	1. 4564 2. 603.3		1. 4569 2. 606.33		1. 4574 2. 616.34
	1. 4565 2. 605.33		1. 4570 2. 608.33		1. 4575 2. 616.34

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4576 2. 616.34		1. 4581 2. 624.34		1. 4586 2. 630.35
	1. 4577 2. 616.34		1. 4582 2. 629.35		1. 4587 2. 630.35
	1. 4578 2. 616.34		1. 4583 2. 629.35		1. 4588 2. 630.35
	1. 4579 2. 616.34		1. 4584 2. 630.35		1. 4589 2. 631.35
	1. 4580 2. 624.34		1. 4585 2. 630.35		1. 4590 2. 638.35

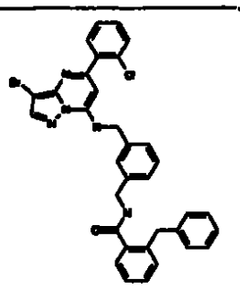
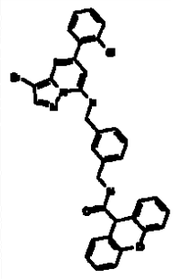
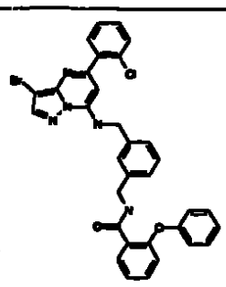
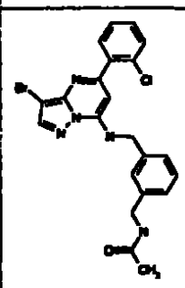
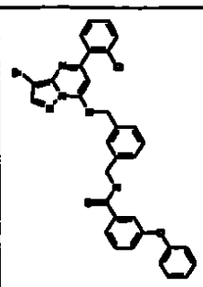
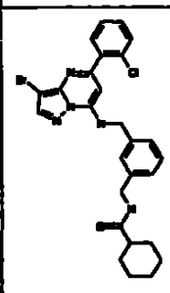
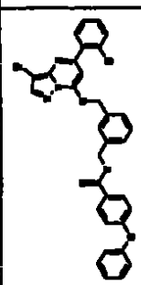
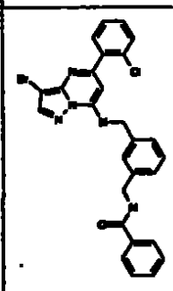
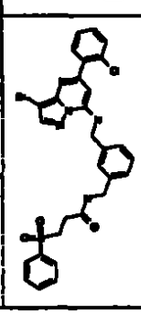
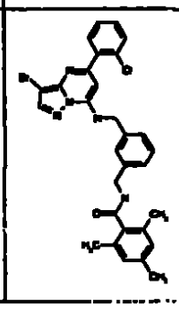
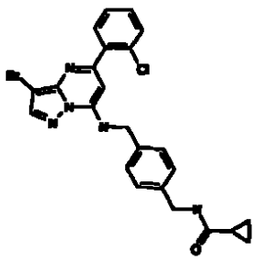
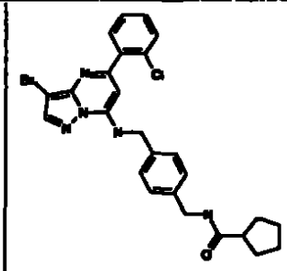
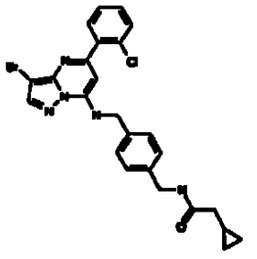
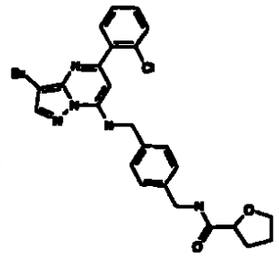
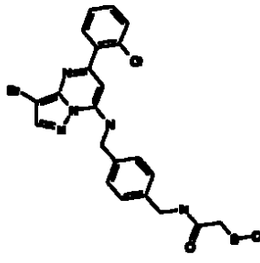
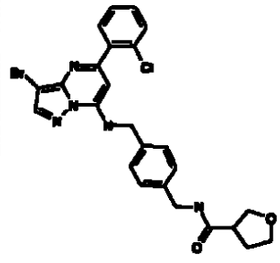
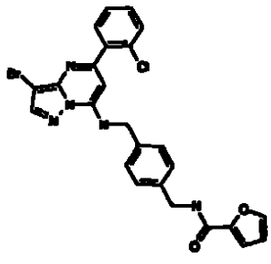
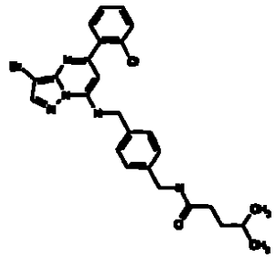
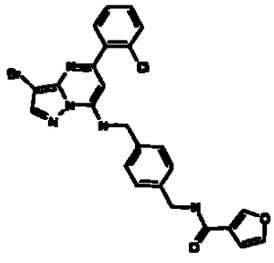
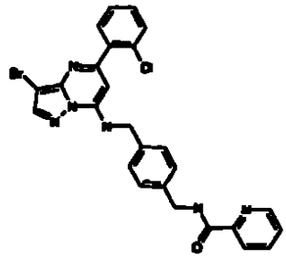
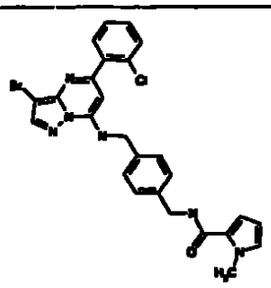
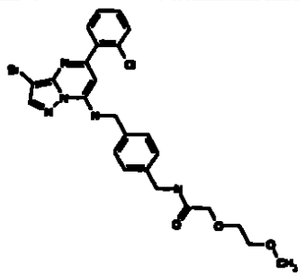
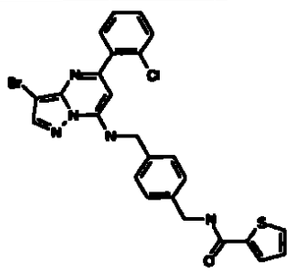
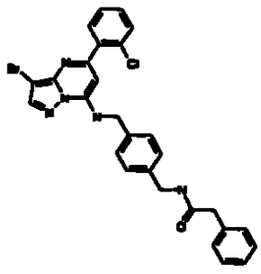
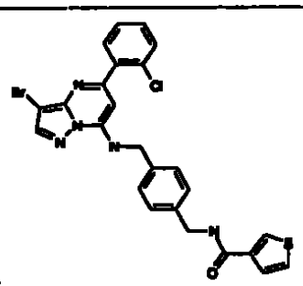
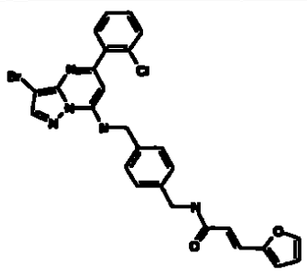
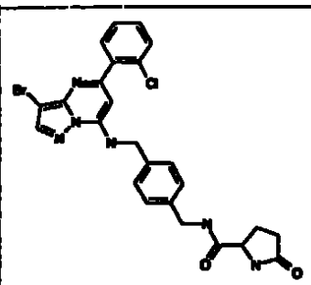
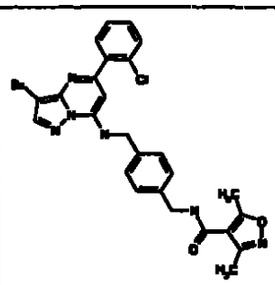
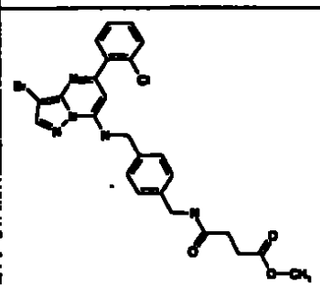
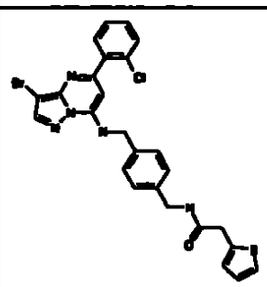
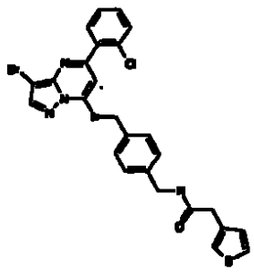
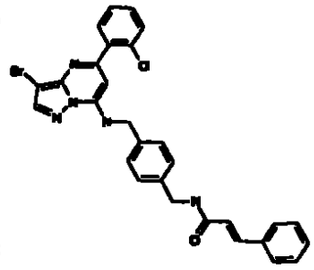
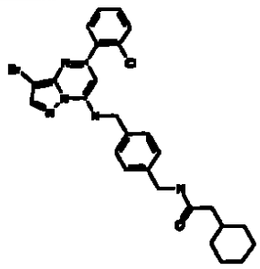
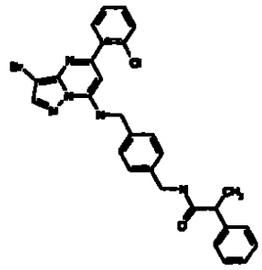
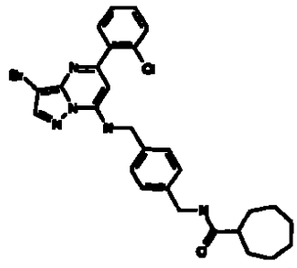
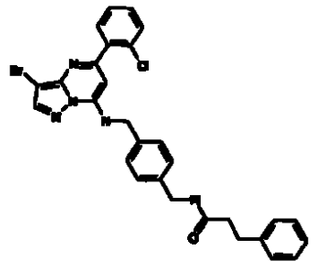
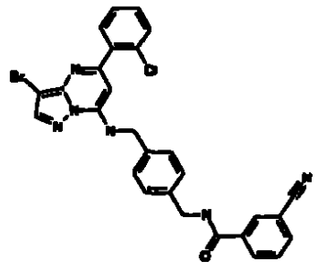
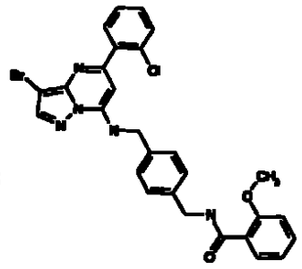
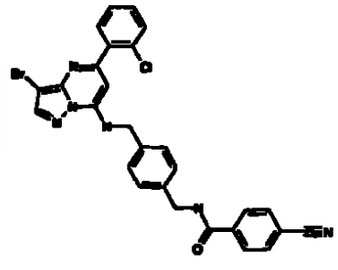
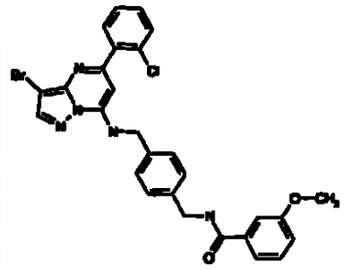
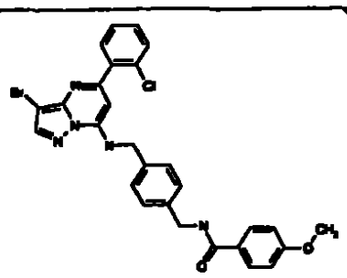
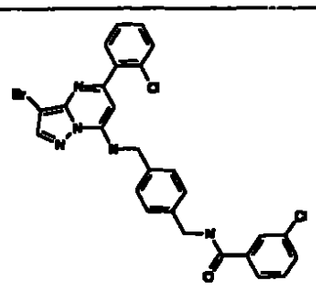
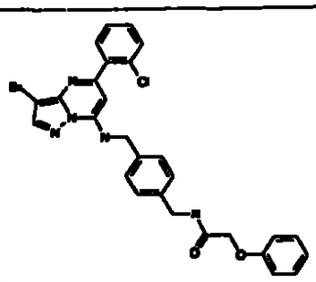
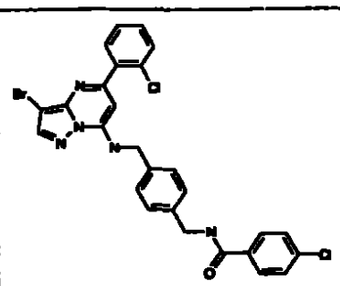
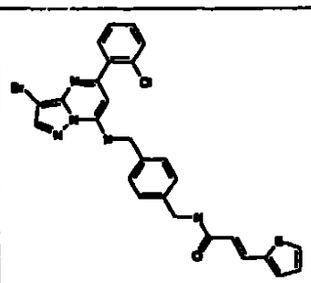
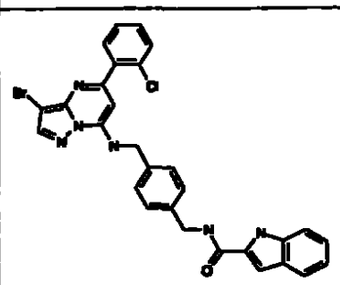
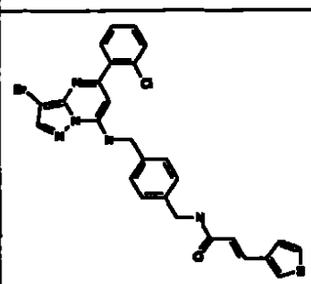
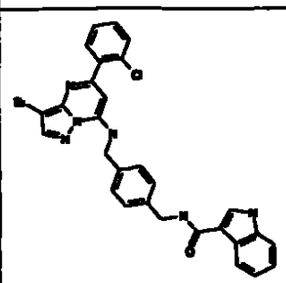
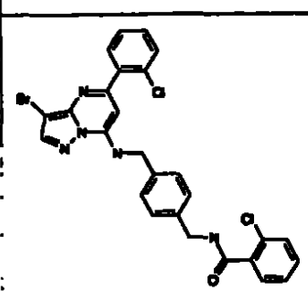
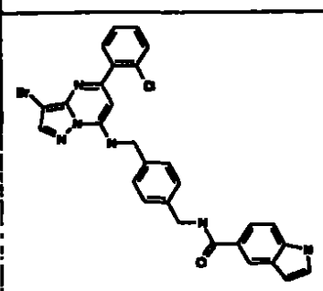
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4591 2. 638.35		1. 4596 2. 652.36
	1. 4592 2. 640.35		1. 4597 2. 486.27
	1. 4593 2. 640.35		1. 4598 2. 554.3
	1. 4594 2. 640.35		1. 4599 2. 548.3
	1. 4595 2. 640.35		1. 45100 2.

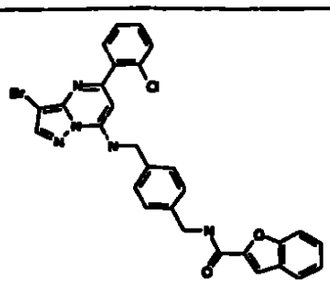
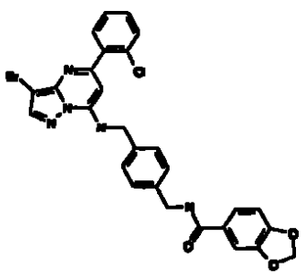
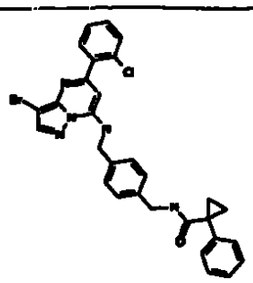
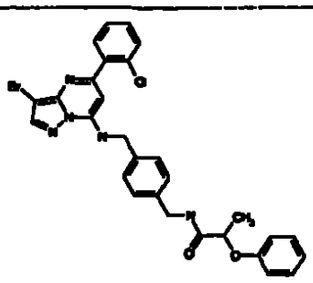
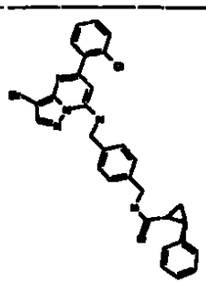
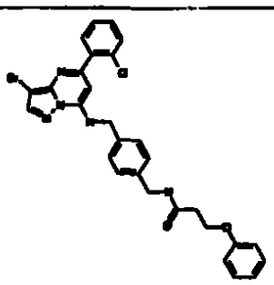
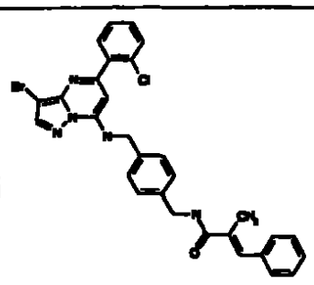
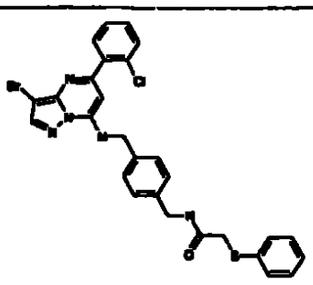
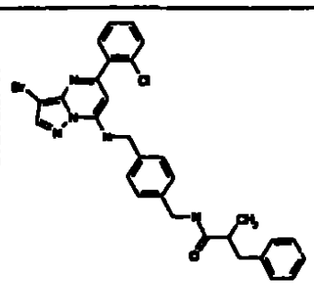
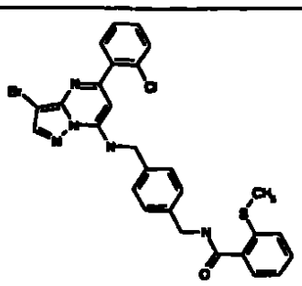
TABLE 46

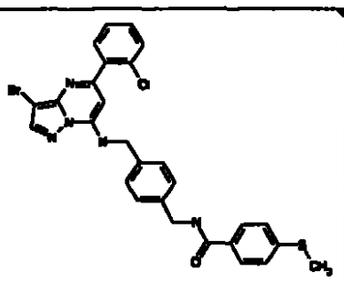
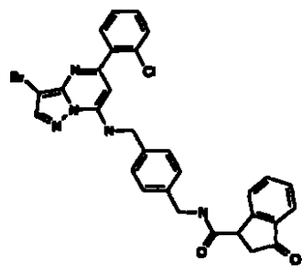
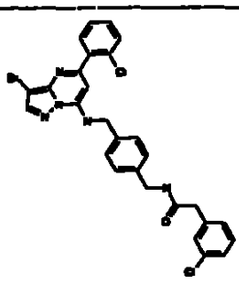
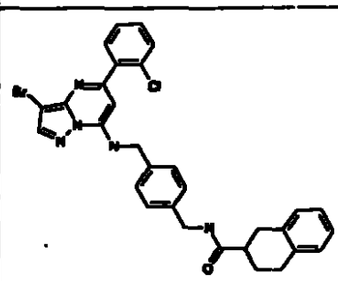
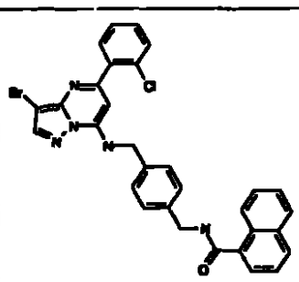
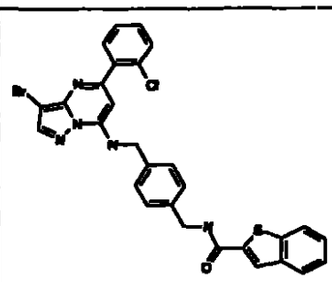
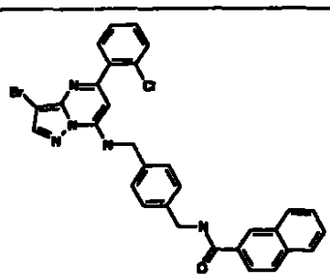
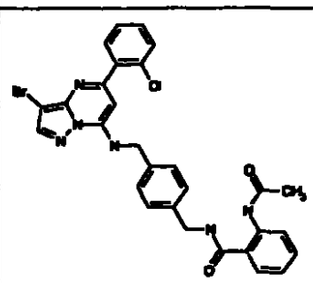
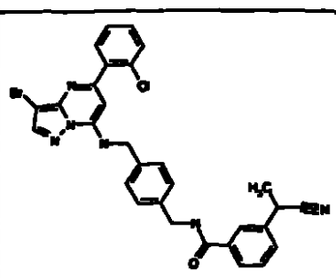
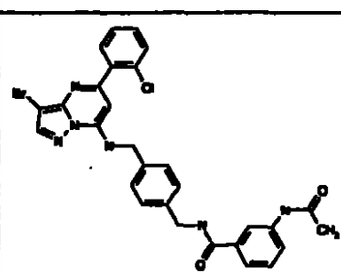
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4601 2. 512.28		1. 4606 2. 540.3
	1. 4602 2. 526.29		1. 4607 2. 542.3
	1. 4603 2. 532.29		1. 4608 2. 542.3
	1. 4604 2. 536.3		1. 4609 2. 542.3
	1. 4605 2. 536.3		1. 4610 2. 547.3

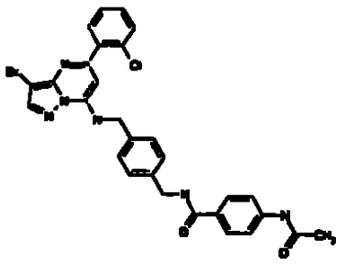
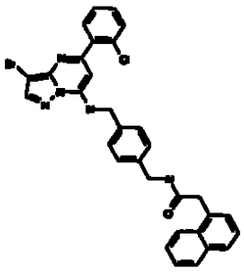
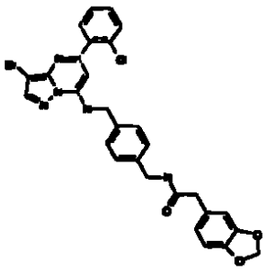
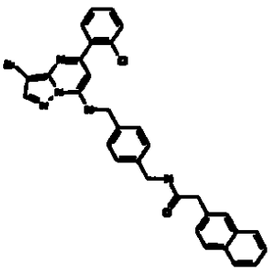
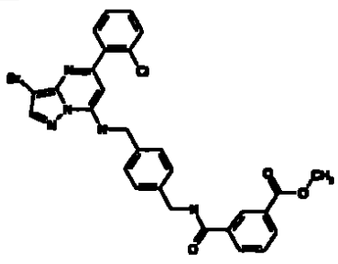
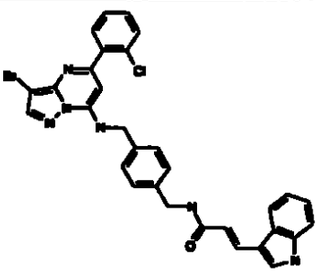
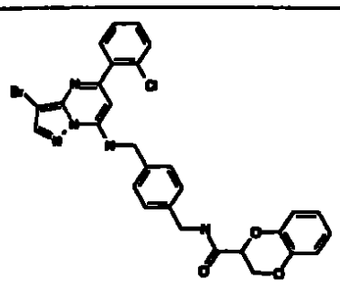
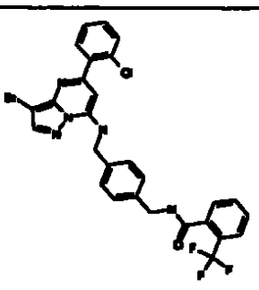
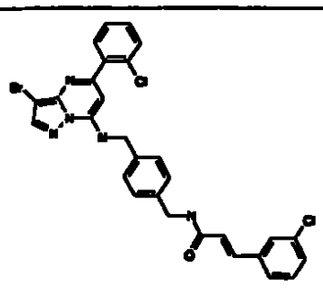
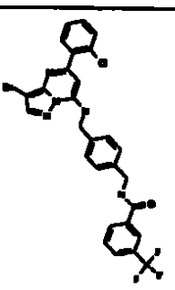
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4611 2. 551.3		1. 4616 2. 560.31
	1. 4612 2. 552.3		1. 4617 2. 562.31
	1. 4613 2. 552.3		1. 4618 2. 562.3
	1. 4614 2. 555.31		1. 4619 2. 567.31
	1. 4615 2. 558.31		1. 4620 2. 568.31

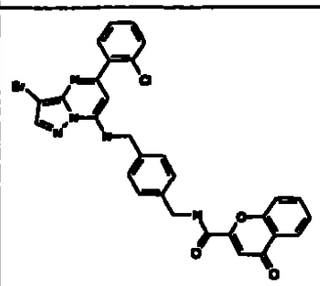
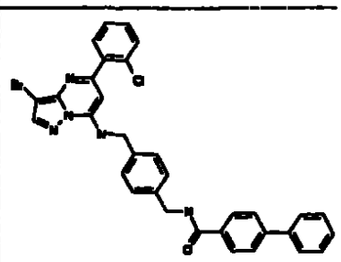
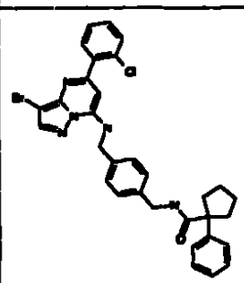
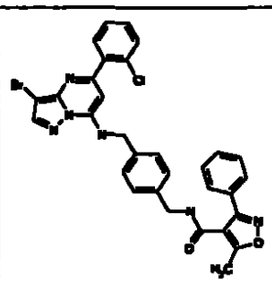
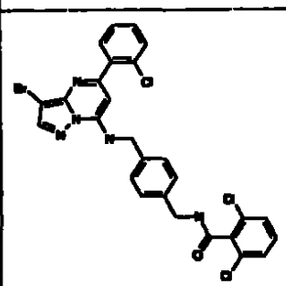
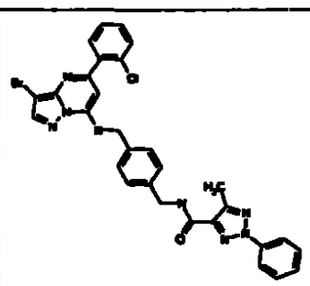
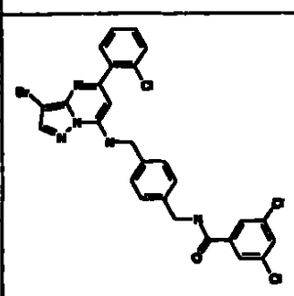
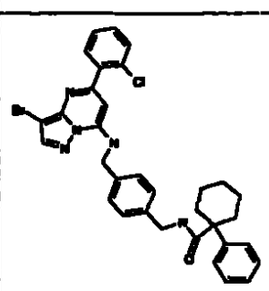
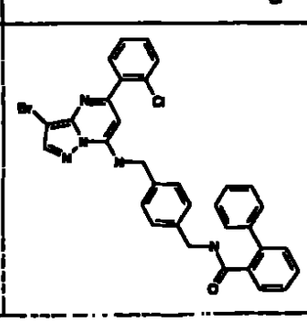
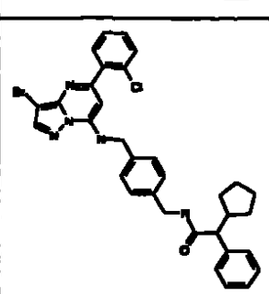
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4621 2. 568.31		1. 4626 2. 574.32
	1. 4622 2. 568.31		1. 4627 2. 576.32
	1. 4623 2. 568.31		1. 4628 2. 576.32
	1. 4624 2. 573.32		1. 4629 2. 578.32
	1. 4625 2. 573.32		1. 4630 2. 578.32

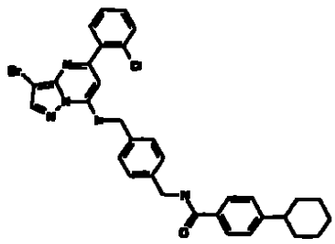
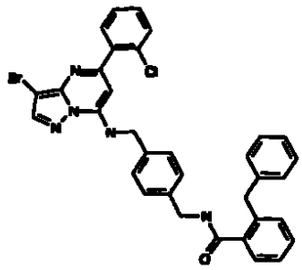
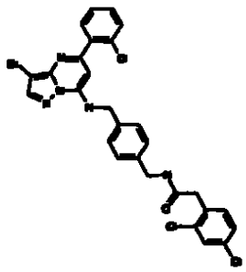
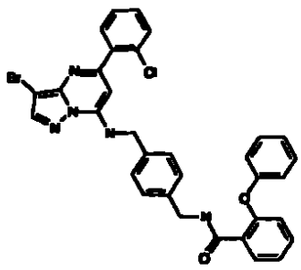
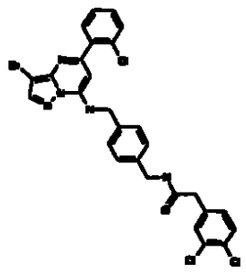
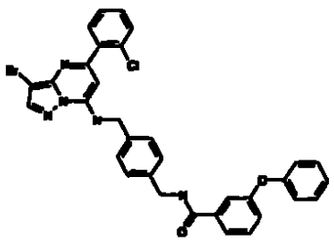
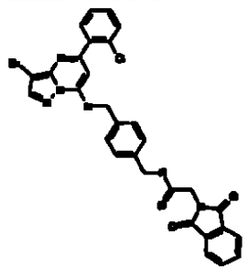
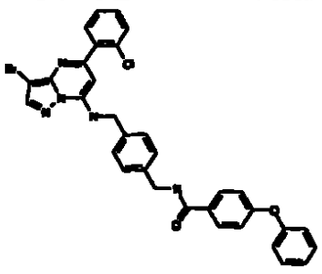
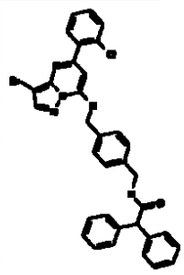
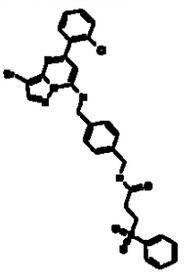
Product	1. Ex. 2. m/x	Product	1. Ex. 2. m/z
	1. 4631 2. 578.32		1. 4636 2. 582.32
	1. 4632 2. 578.32		1. 4637 2. 582.32
	1. 4633 2. 580.32		1. 4638 2. 587.32
	1. 4634 2. 580.32		1. 4639 2. 585.3
	1. 4635 2. 582.32		1. 4640 2. 585.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4641 2. 588.32		1. 4646 2. 592.33
	1. 4642 2. 588.32		1. 4647 2. 592.33
	1. 4643 2. 588.32		1. 4648 2. 592.33
	1. 4644 2,. 588.32		1. 4649 2.
	1. 4645 2. 590.32		1. 4650 2. 594.33

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4651 2. 594.33		1. 4656 2. 602.33
	1. 4652 2. 596.33		1. 4657 2. 602.33
	1. 4653 2. 596.3		1. 4658 2. 604.33
	1. 4654 2. 598.33		1. 4659 2. 603.3
	1. 4655 2. 601.33		1. 4660 2. 605.33

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4661 2. 605.33		1. 4666 2. 612.34
	1. 4662 2. 606.33		1. 4667 2. 612.34
	1. 4663 2. 606.33		1. 4668 2. 613.34
	1. 4664 2. 606.33		1. 4669 2. 616.34
	1. 4665 2. 608.33		1. 4670 2. 616.34

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4671 2. 616.34		1. 4676 2. 624.34
	1. 4672 2. 616.34		1. 4677 2. 629.35
	1. 4673 2. 616.34		1. 4678 2. 629.35
	1. 4674 2. 616.34		1. 4679 2. 630.35
	1. 4675 2. 624.34		1. 4680 2. 630.35

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4681 2. 630.35		1. 4686 2. 638.35
	1. 4682 2. 630.35		1. 4687 2. 640.35
	1. 4683 2. 630.35		1. 4688 2. 640.35
	1. 4684 2. 631.35		4689 2.
	1. 4685 2. 638.35		1. 4690 2. 640.35

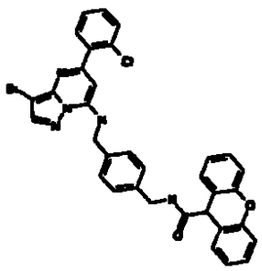
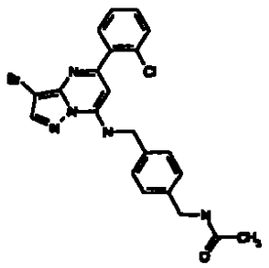
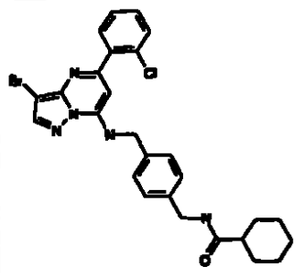
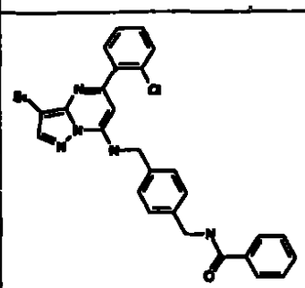
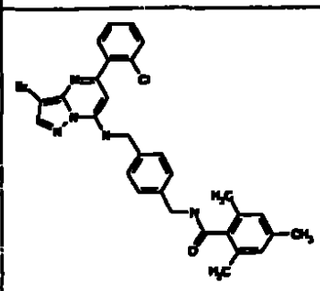
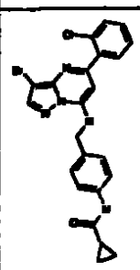
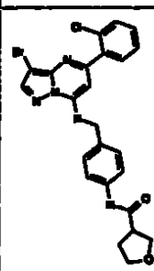
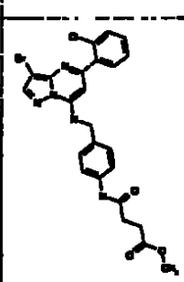
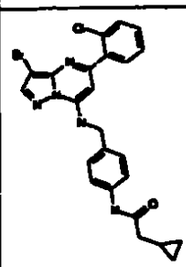
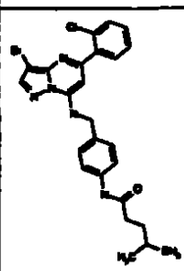
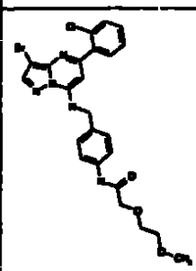
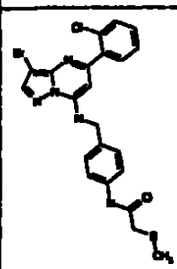
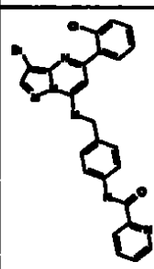
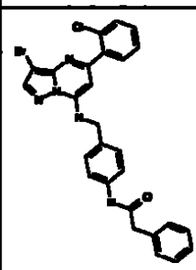
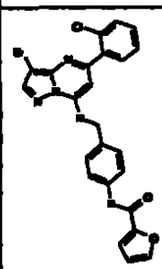
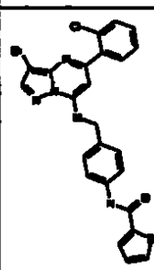
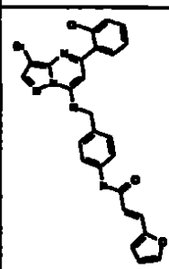
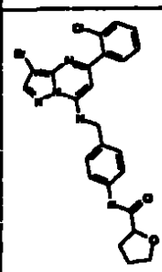
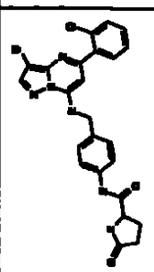
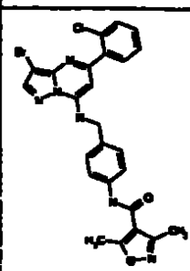
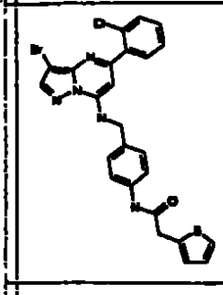
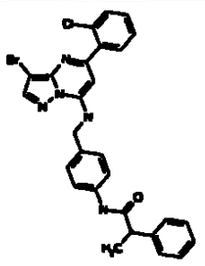
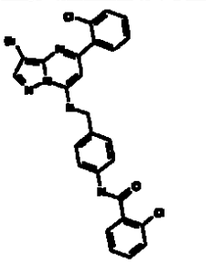
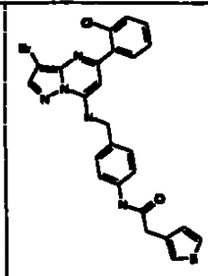
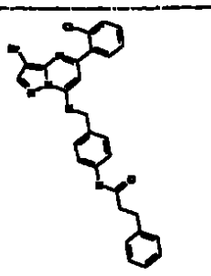
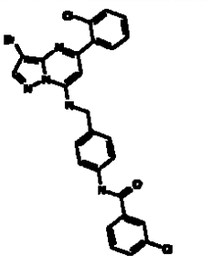
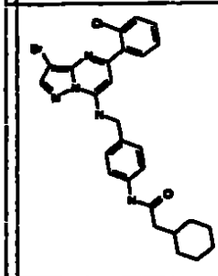
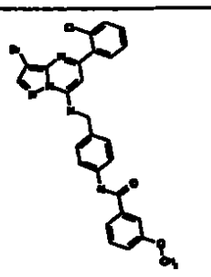
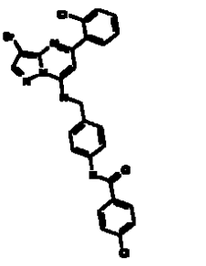
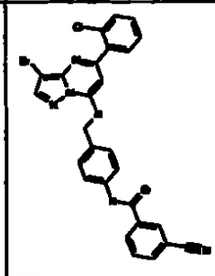
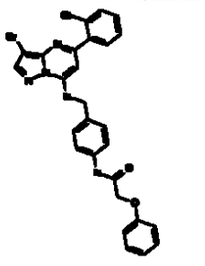
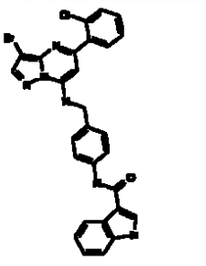
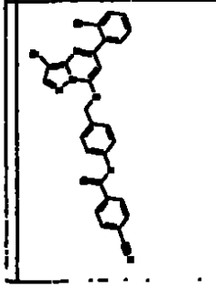
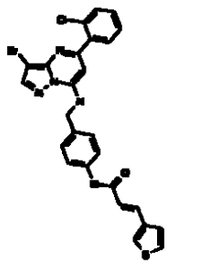
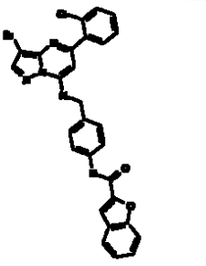
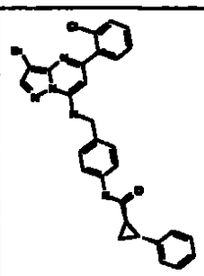
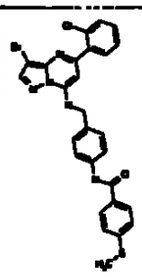
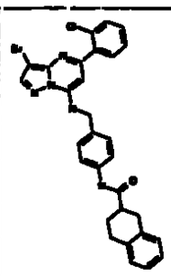
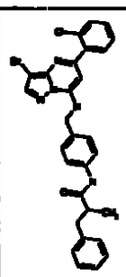
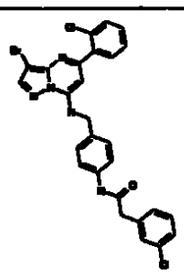
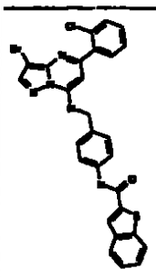
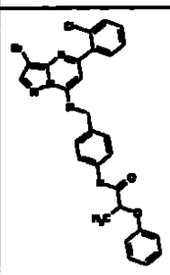
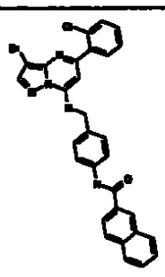
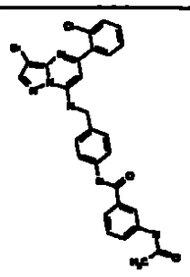
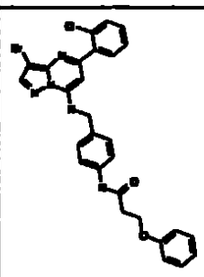
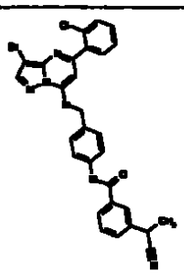
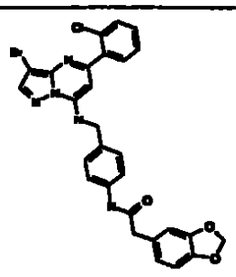
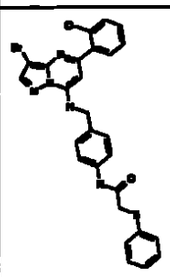
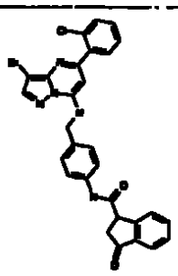
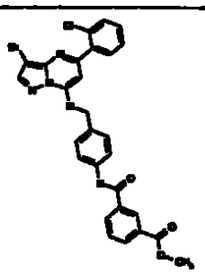
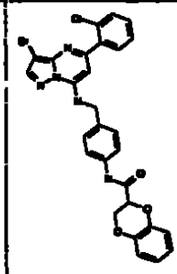
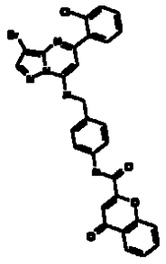
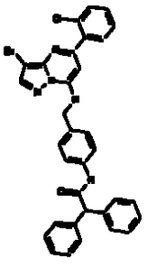
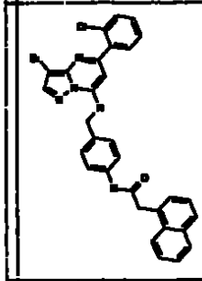
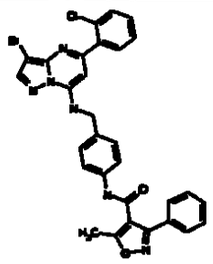
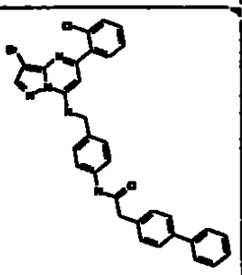
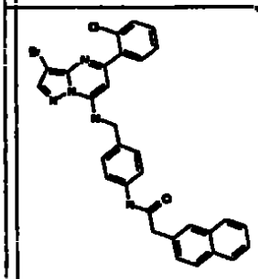
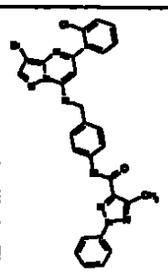
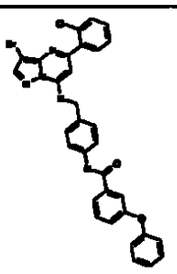
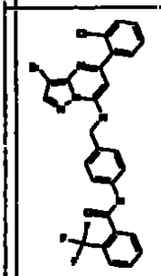
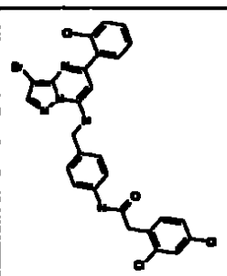
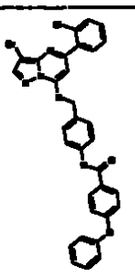
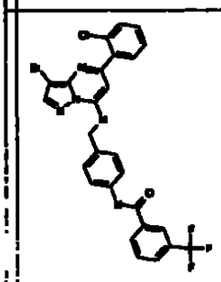
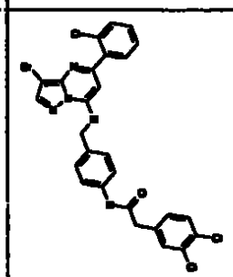
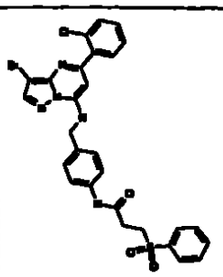
Product	1. Ex. 2. m/z
	1. 4691 2. 652.36
	1. 4692 2. 484.3
	1. 4693 2. 554.3
	1. 4694 2. 548.3
	1. 4695 2. 590.32

TABLE 47

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4701 2. 498.27		1. 4706 2. 528.29		1. 4711 2. 544.3
	1. 4702 2. 512.28		1. 4707 2. 528.29		1. 4712 2. 546.3
	1. 4703 2. 518.28		1. 4708 2. 535.29		1. 4713 2. 548.3
	1. 4704 2. 524.29		1. 4709 2. 540.3		1. 4714 2. 550.3
	1. 4705 2. 528.29		1. 4710 2. 541.3		1. 4715 2. 553.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4716 2. 554.3		1. 4721 2. 562.31		1. 4726 2. 568.31
	1. 4717 2. 554.3		1. 4722 2. 562.31		1. 4727 2. 568.31
	1. 4718 2. 554.3		1. 4723. 2 564.31		1. 4728 2. 568.31
	1. 4719 2. 559.31		1. 4724 2. 564.31		1. 4729 2. 573.32
	1. 4720 2. 559.31		1. 4725 2. 566.31		1. 4730 2. 574.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4731 2. 574.32		1. 4736 2. 580.32		1. 4741 2. 588.32
	1. 4732 2. 576.32		1. 4737 2. 582.32		1. 47 2. 590.62
	1. 4733 2. 578.32		1. 4738 2. 584.32		1. 4743 2. 591.33
	1. 4734 2. 578.32		1. 4739 2. 585.32		1. 4744 2. 592.
	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

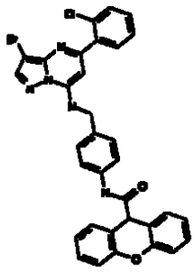
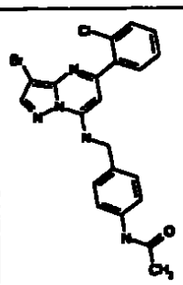
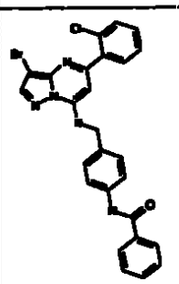
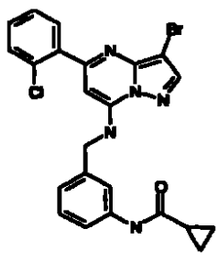
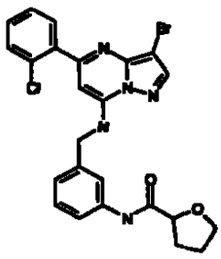
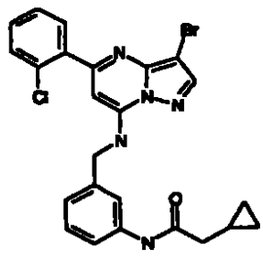
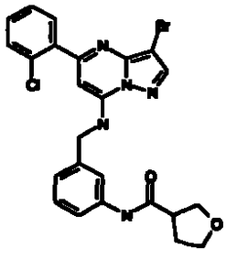
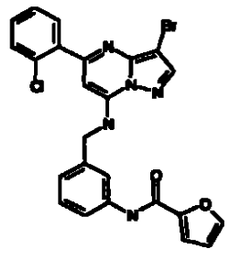
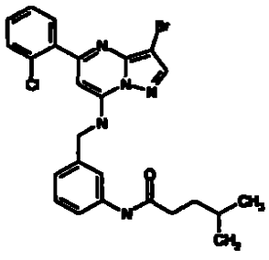
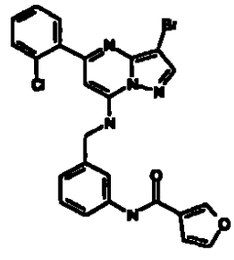
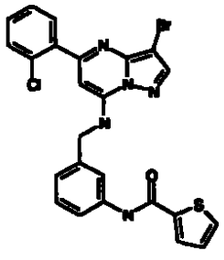
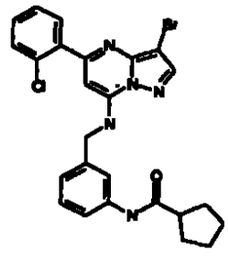
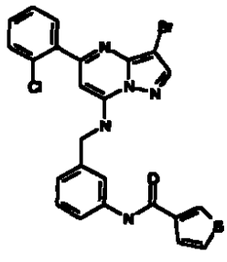
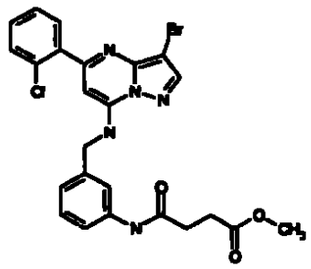
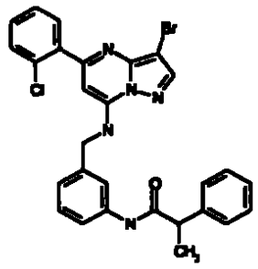
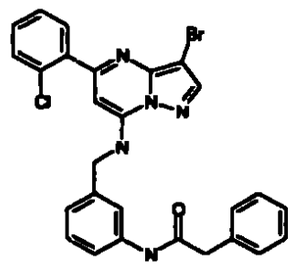
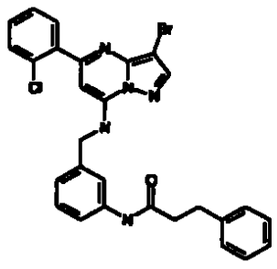
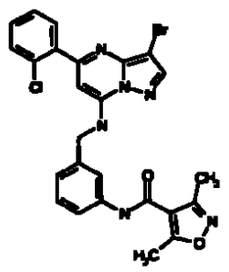
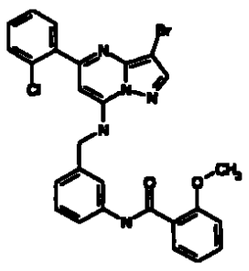
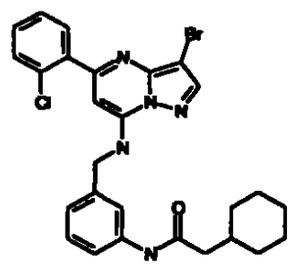
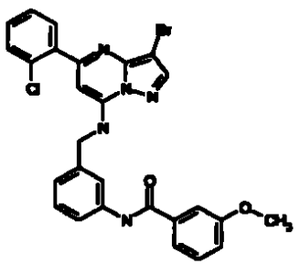
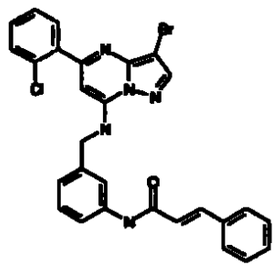
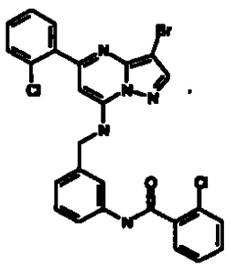
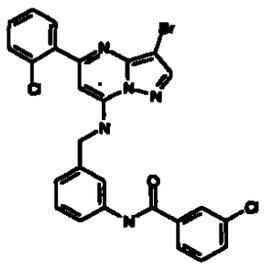
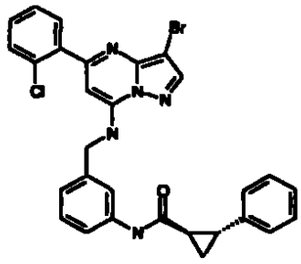
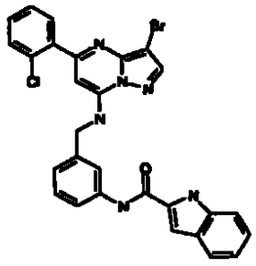
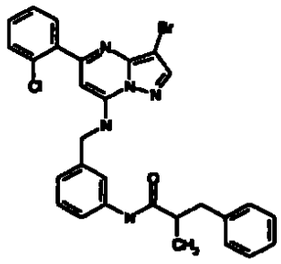
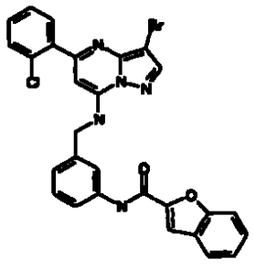
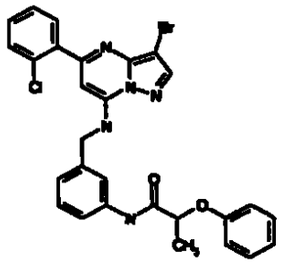
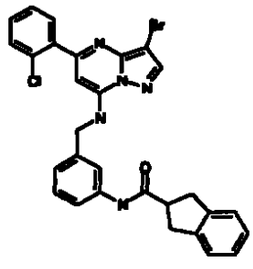
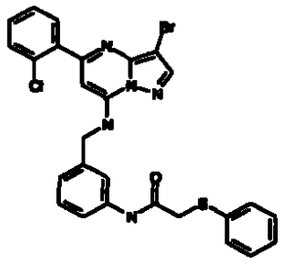
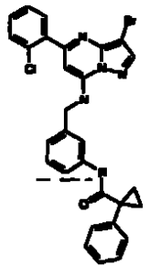
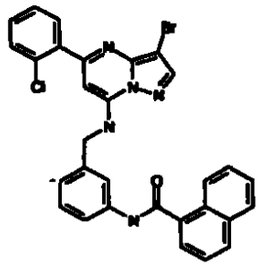
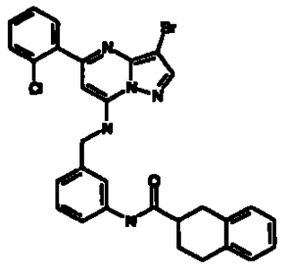
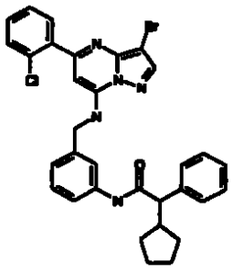
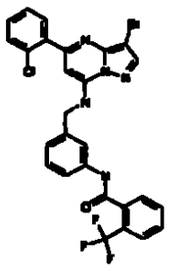
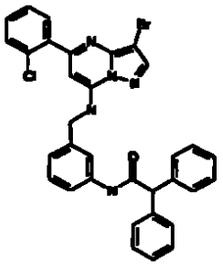
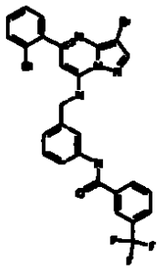
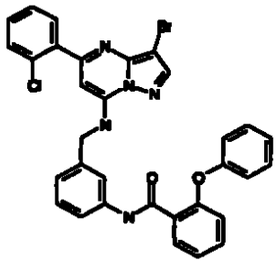
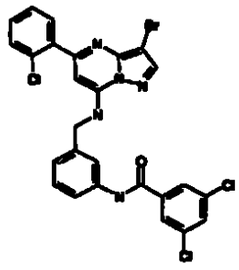
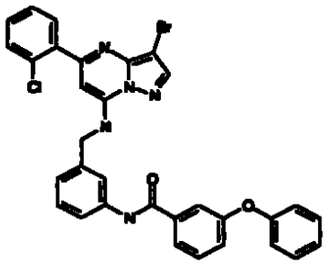
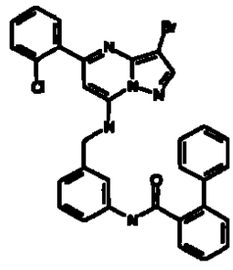
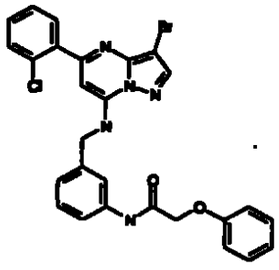
Product	1. Ex. 2. m/z
	1. 4761 2. 638.35
	1. 4762 2. 472.26
	1. 4763 2. 534.29

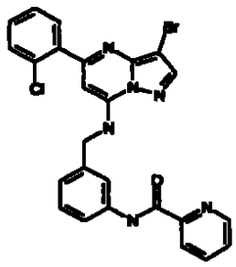
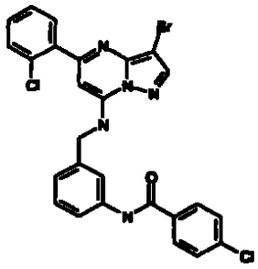
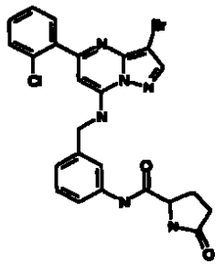
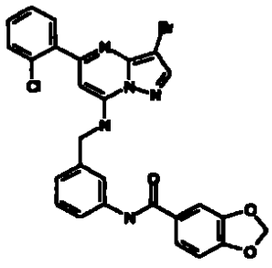
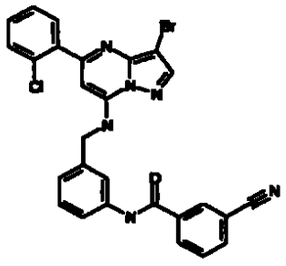
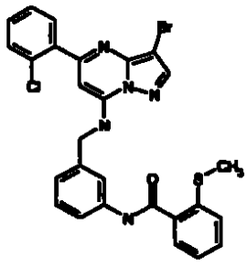
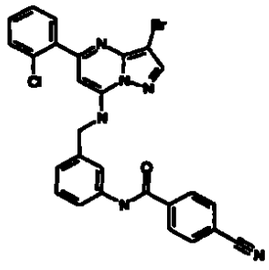
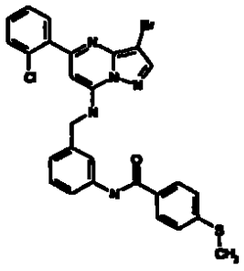
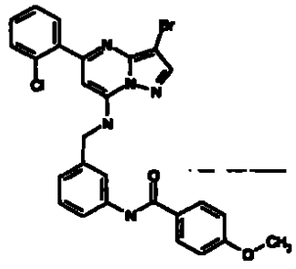
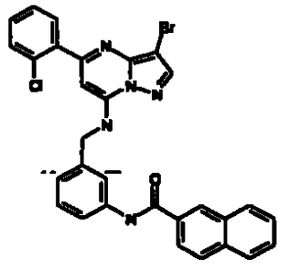
TABLE 48

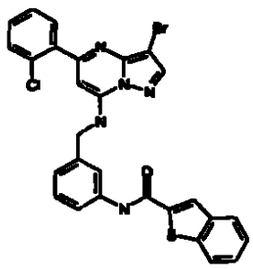
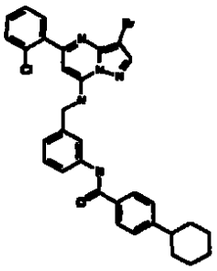
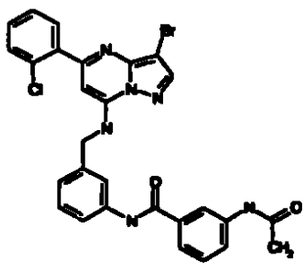
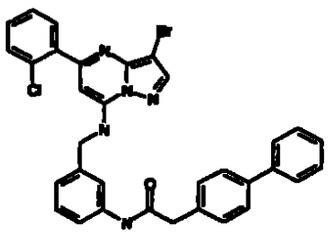
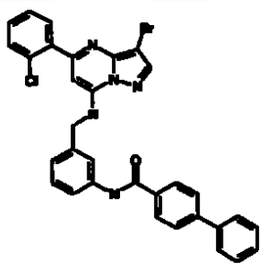
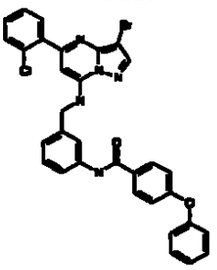
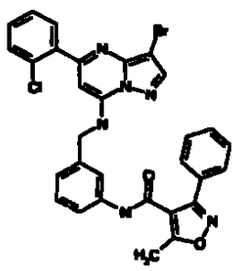
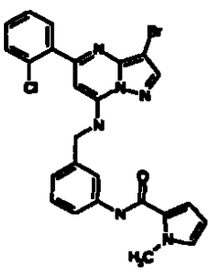
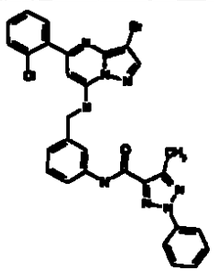
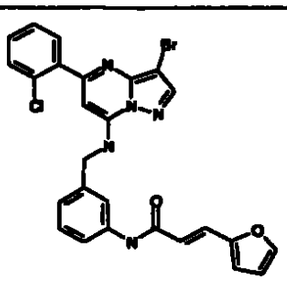
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4801 2. 498.27		1.4806 2. 528.29
	1. 4802 2. 512.28		1.. 4807 2. 528.29
	1. 4803 2. 524.29		1. 4808 2. 528.29
	1. 4804 2. 524.29		1. 4809 2. 540.3
	1. 4805 2. 526.29		1. 4810 2. 540.3

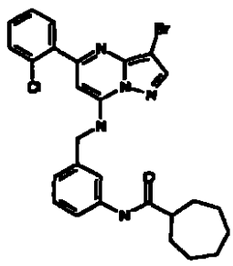
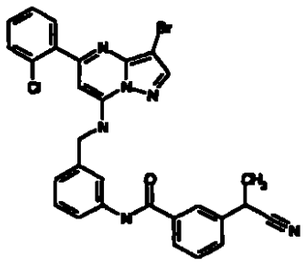
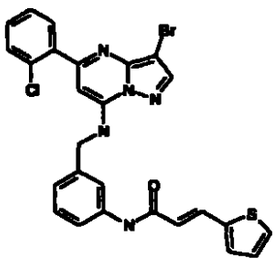
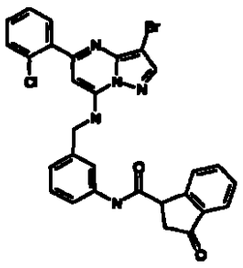
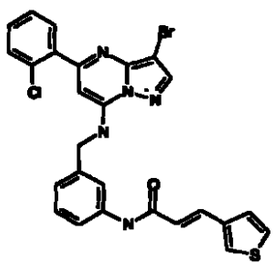
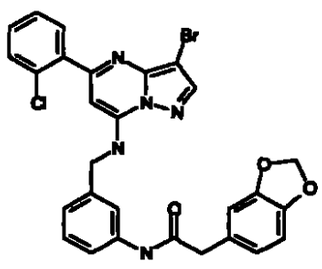
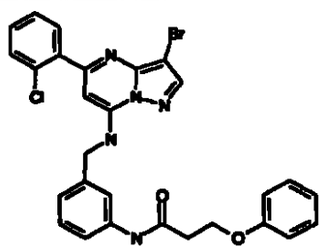
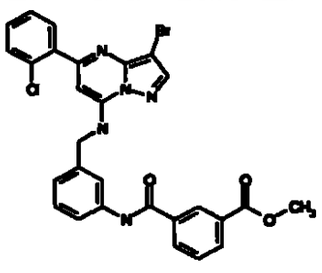
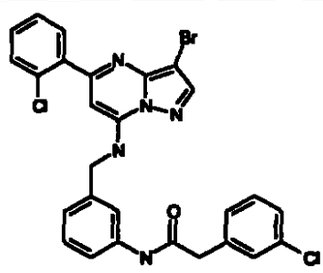
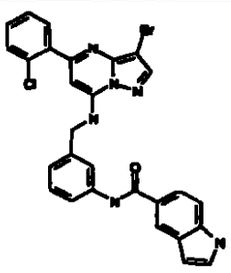
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4811 2. 544.3		1. 4816 2. 562.31
	1. 4812 2. 548.3		1. 4817 2. 562.31
	1. 4813 2. 553.3		1. 4818 2. 564.31
	1. 4814 2. 554.3		1. 4819 2. 564.31
	1. 4815 2. 560.31		1. 4820 2. 568.31

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4821 2. 568.31		1. 4826 2. 574.32
	1. 4822 2. 573.32		1. 4828 2. 576.32
	1. 4821 2. 574.32		1. 4829 2. 578.32
	1. 4824 2. 574.32		1. 4829 2. 580.32
	1. 4825 2. 574.32		1. 4830 2. 584.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4831 2. 588.32		1. 4836 2. 616.34
	1. 4832 2. 602.33		1. 4837 2. 624.34
	1. 4833 2. 602.33		1. 4838 2. 626.34
	1. 4834 2. 602.33		1. 4839 2. 626.34
	1. 4835 2. 610.34		1. 4840 2. 564.31

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4841 2. 535.29		1. 4846 2. 568.31
	1. 4842 2. 541.3		1. 4847 2. 578.32
	1. 4843 2. 559.31		1. 4848 2. 580.32
	1. 4844 2. 559.31		1. 4849 2. 580.32
	1. 4845 2. 564.31		1. 4850 2. 584.32

Product	1. Ex. 2. m/z		Product	1. Ex. 2. m/z
	1. 4851 2. 590.32			1. 4856 2. 616.34
	1. 4852 2. 591.33			1. 4857 2. 624.34
	1. 4853 2. 610.34			1. 4858 2. 626.34
	1. 4854 2. 615.34			1. 4859 2. 537.3
	1. 4855 2. 615.34			1. 4860 2. 550.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4861 2. 554.3		1. 4866 2. 587.32
	1. 4862 2. 566.31		1. 4867 2. 588.32
	1. 4863 2. 566.31		1. 4868 2. 592.33
	1. 4864 2. 578.32		1. 4869 2. 592.33
	1. 4865 2. 582.32		1. 4870 2. 573.32

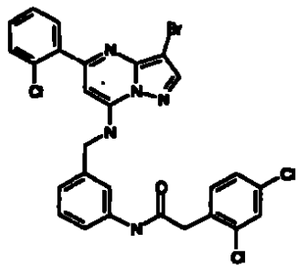
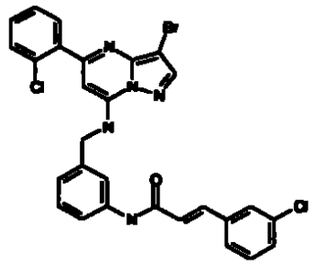
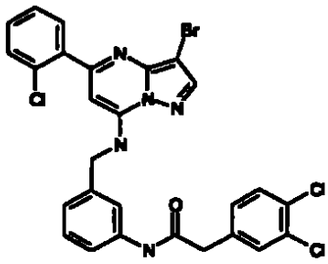
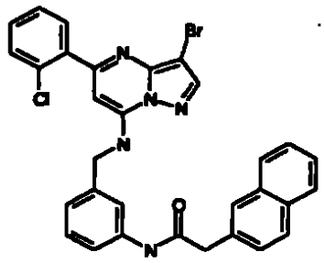
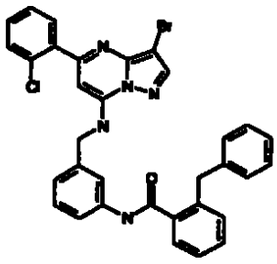
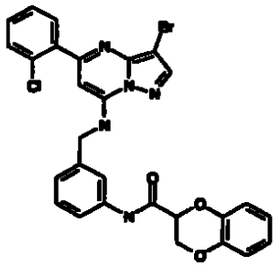
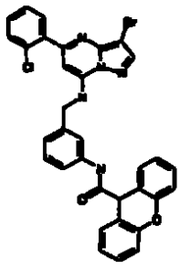
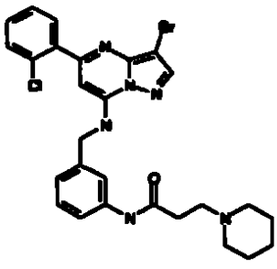
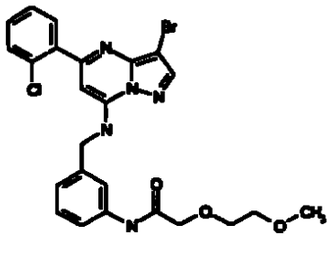
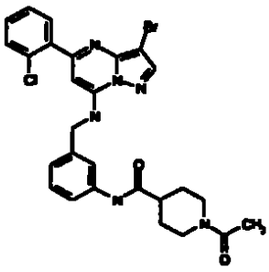
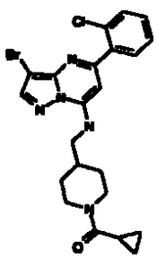
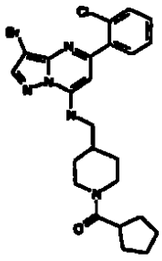
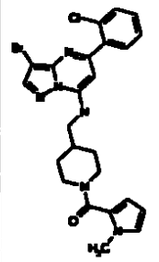
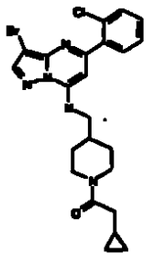
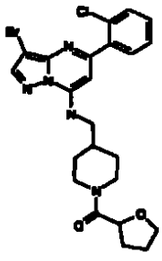
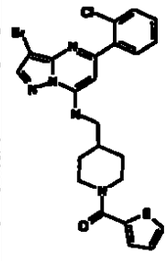
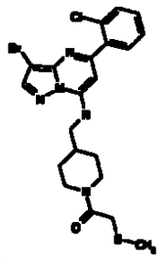
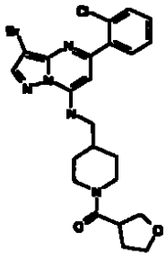
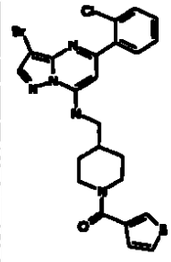
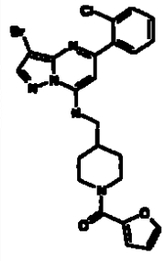
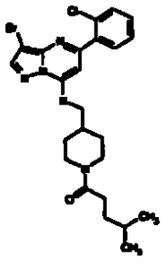
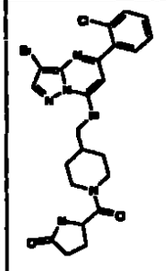
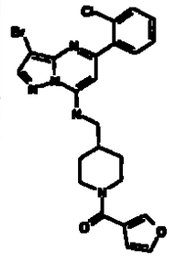
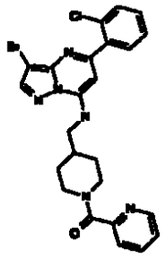
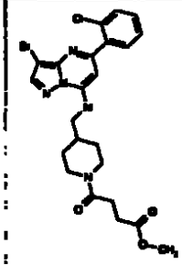
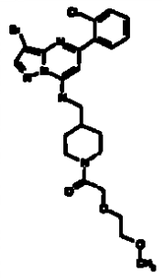
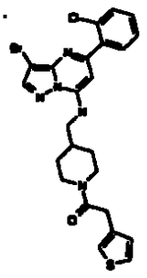
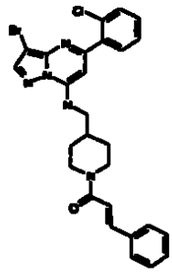
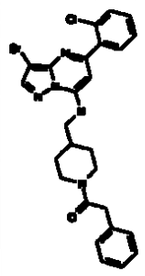
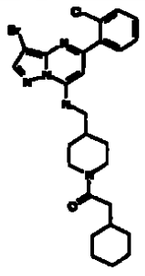
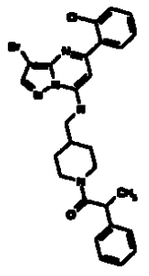
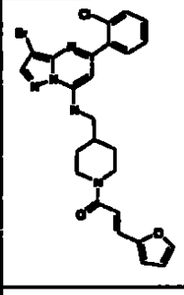
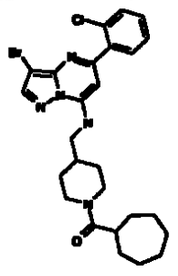
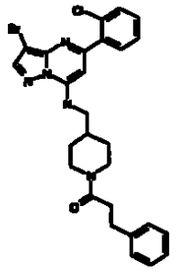
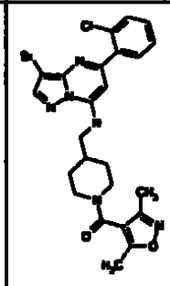
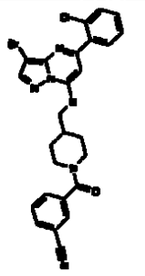
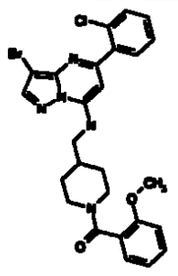
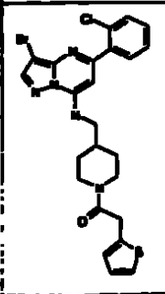
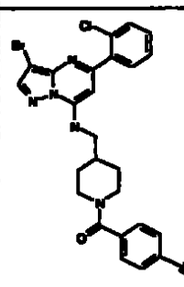
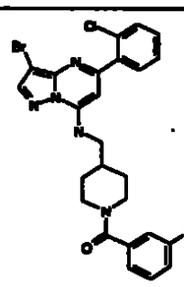
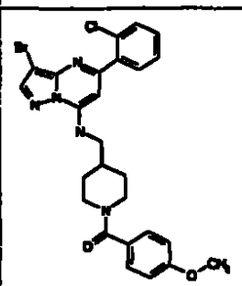
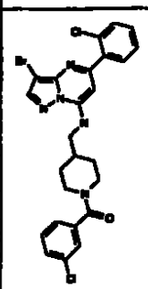
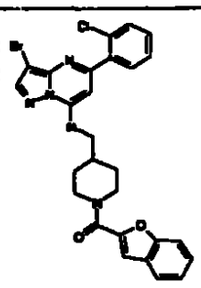
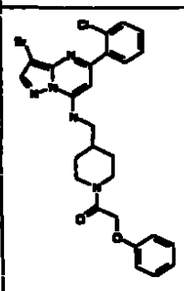
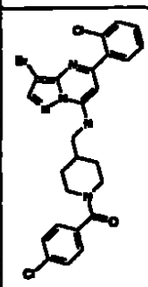
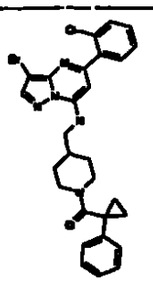
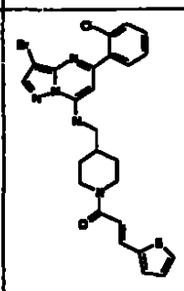
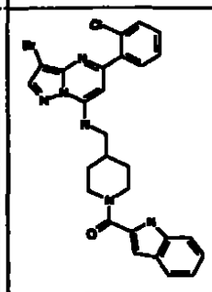
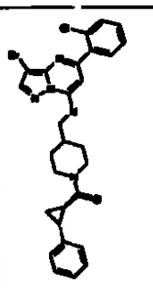
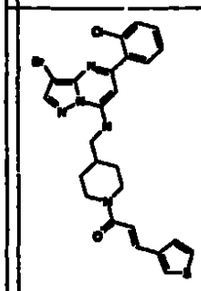
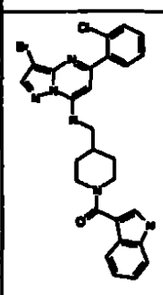
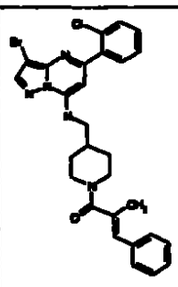
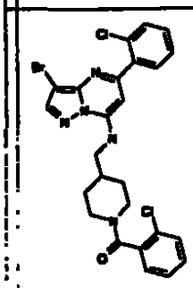
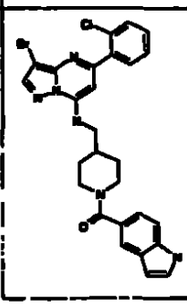
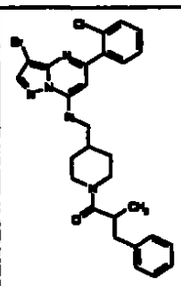
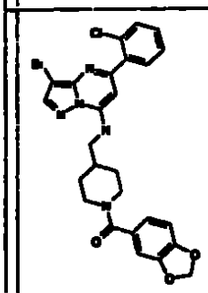
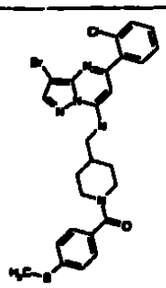
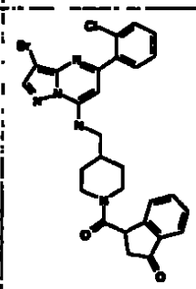
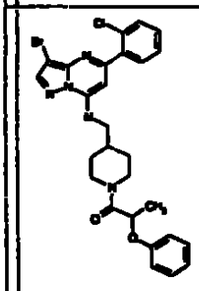
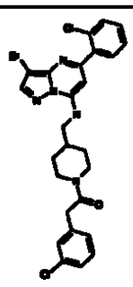
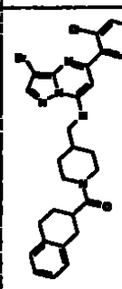
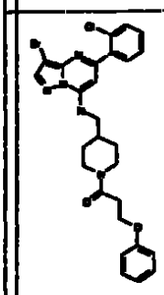
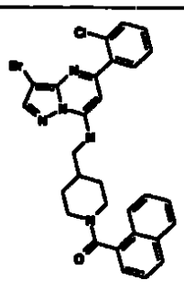
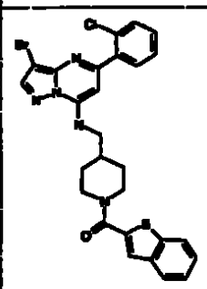
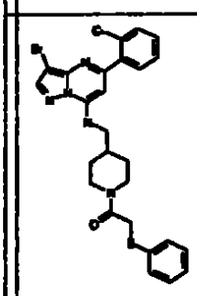
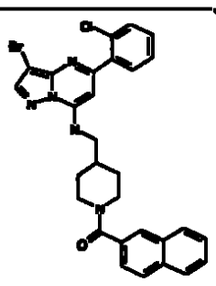
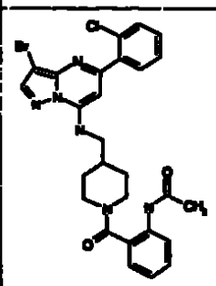
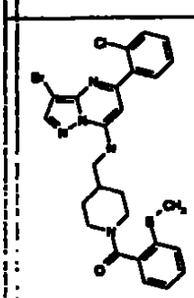
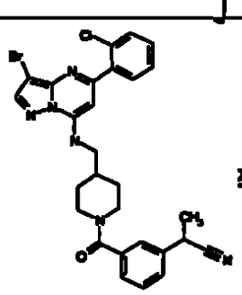
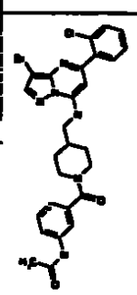
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4871 2. 616.34		1. 4876 2. 594.33
	1. 4872 2. 616.34		1. 4877 2. 598.33
	1. 4873 2. 624.34		1. 4878 2. 592.33
	1. 4874 2. 638.35		1. 4879 2. 569.31
	1. 4875 2. 546.3		1. 4880 2. 583.32

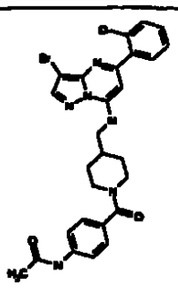
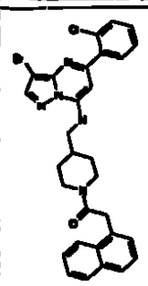
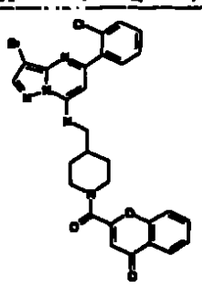
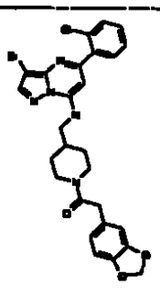
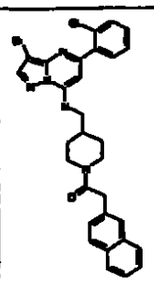
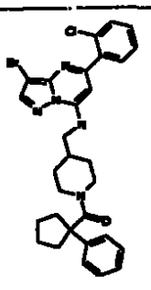
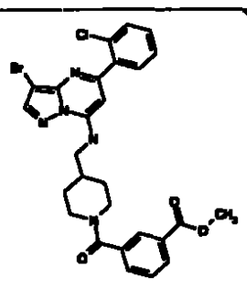
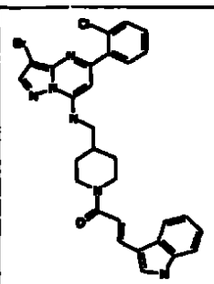
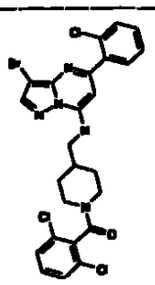
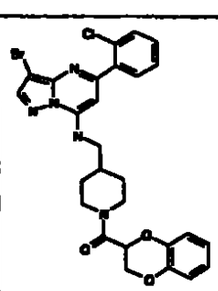
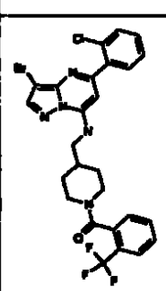
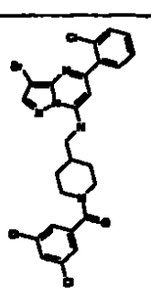
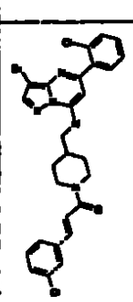
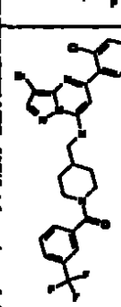
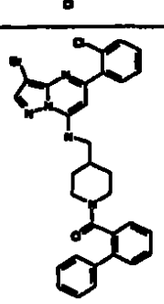
TABLE 49

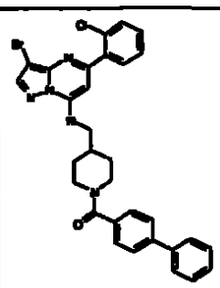
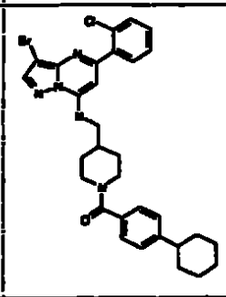
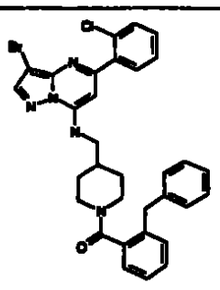
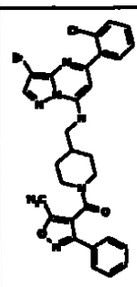
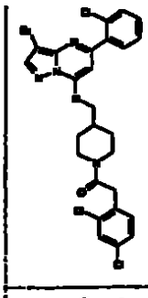
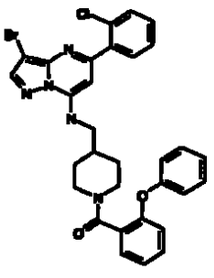
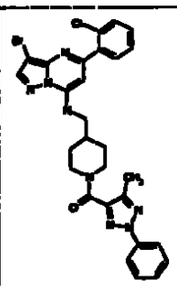
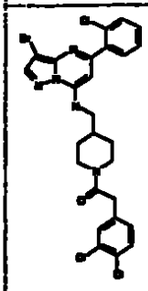
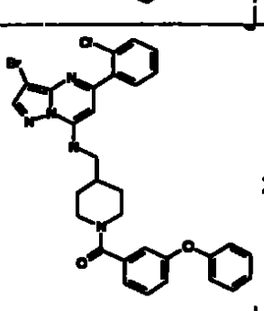
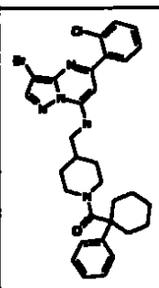
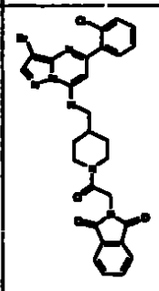
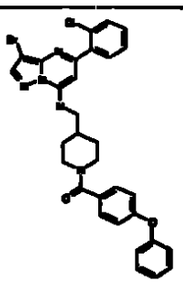
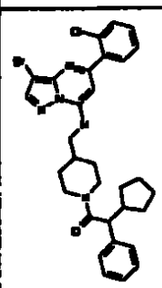
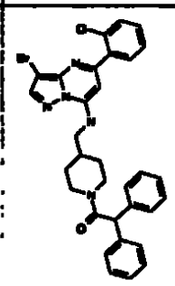
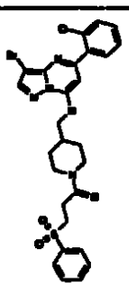
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4901 2. 490.27		1. 4906 2. 518.28		1. 4911 2. 529.29
	1. 4902 2. 504.28		1. 4907 2. 520.29		1. 4912 2. 532.29
	1. 4903 2. 510.28		1. 4908 2. 520.29		1. 4913 2. 532.29
	1. 4904 2. 516.28		1. 4909 2. 520.29		1. 4914 2. 533.29
	1. 4905 2. 516.28		1: 4910 2. 527.29		1. 4915 2. 536.29

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 4916 2. 538.3		1. 4921 2. 546.3		1. 4926 2. 552.3
	1. 4917 2 .540.3		1. 4922 2. 546.3		1. 4927 2. 554.3
	1. 4918 2. 542.3		1. 4923 2. 546.3		1. 4928 2. 554.3
	1. 4919 2. 545.3		1. 4924 2. 551.3		1. 4929 2. 556.31
	1. 4920 2. 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
	1. 4980 2. 608.33		1. 4985 2. 616.34		1. 4990 2. 618.34

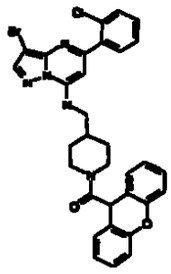
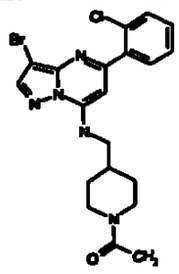
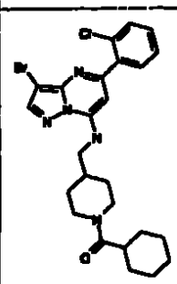
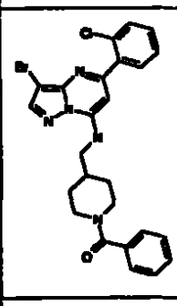
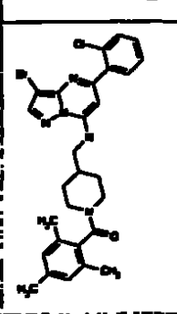
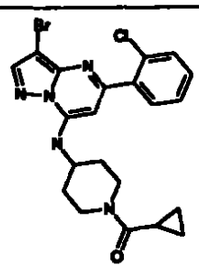
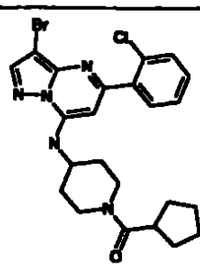
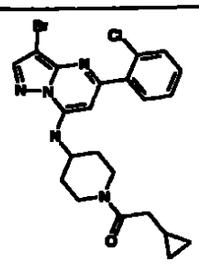
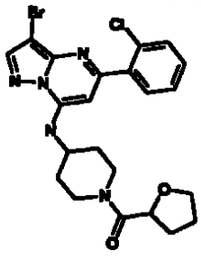
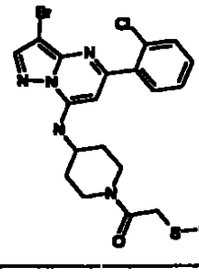
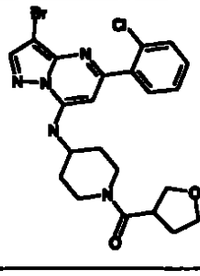
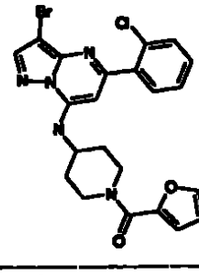
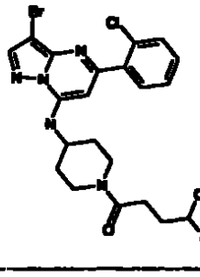
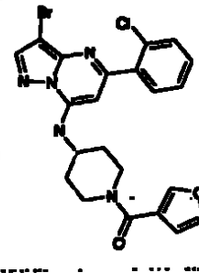
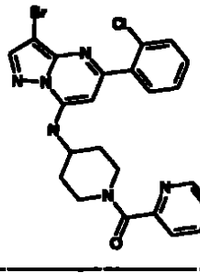
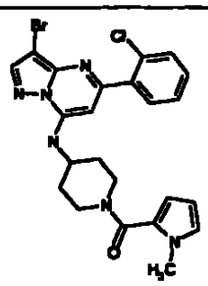
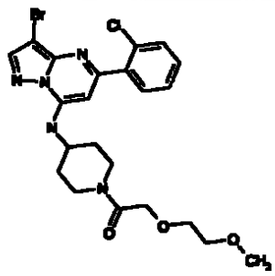
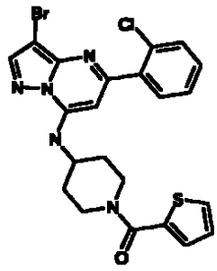
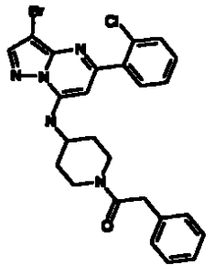
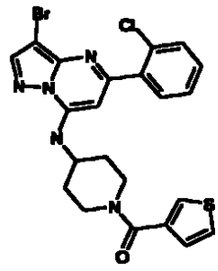
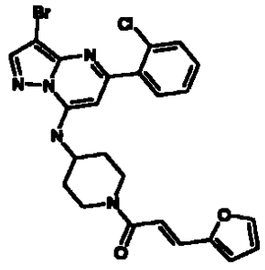
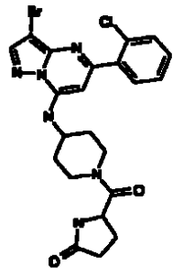
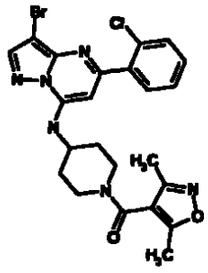
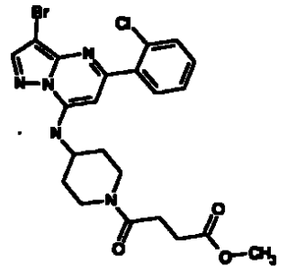
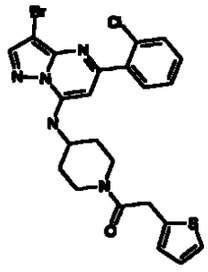
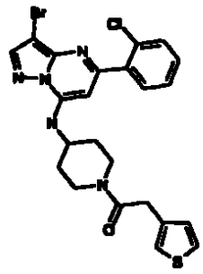
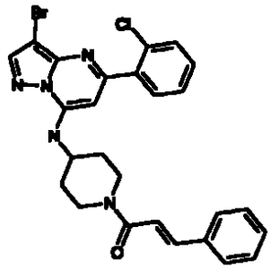
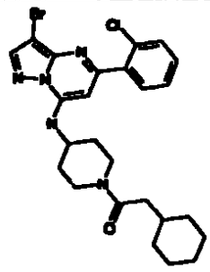
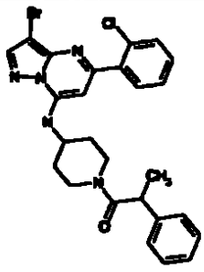
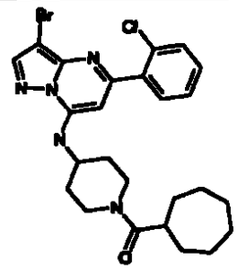
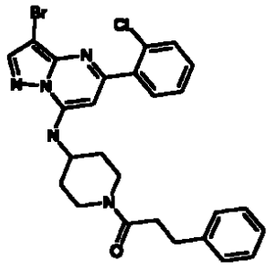
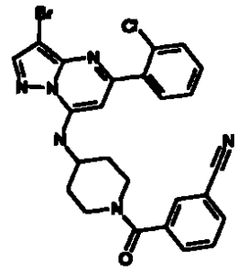
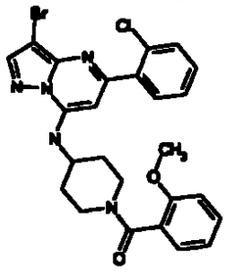
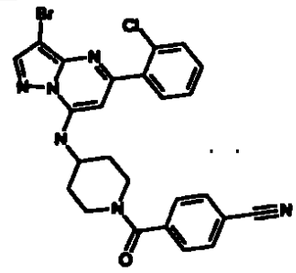
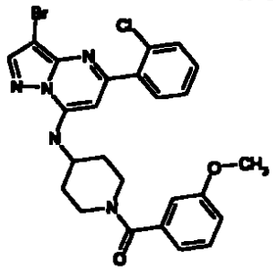
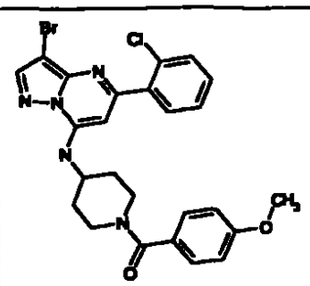
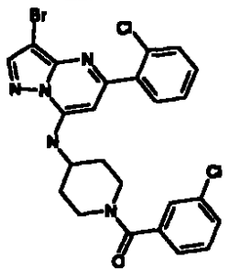
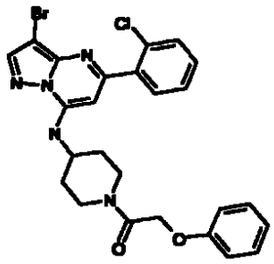
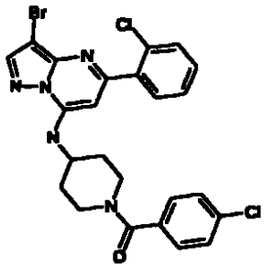
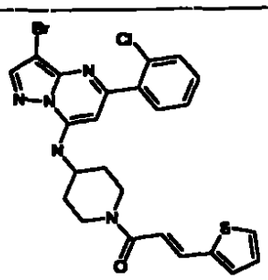
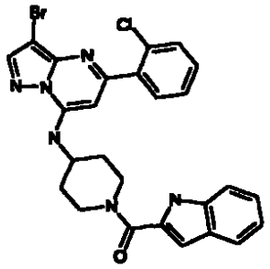
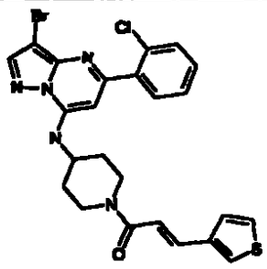
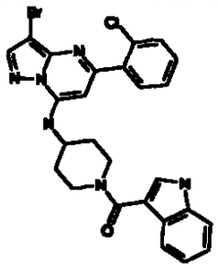
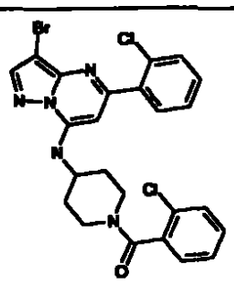
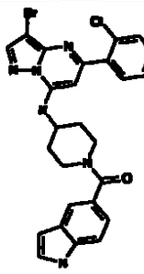
Product	1. Ex. 2. m/z
	1. 4991 2. 630.35
	1. 4992 2. 464.26
	1. 4993 2. 532.29
	1. 4994 2. 526.29
	1. 4995 2. 568.31

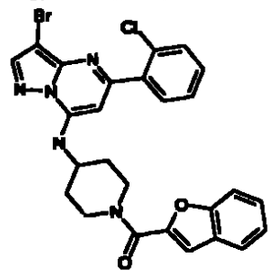
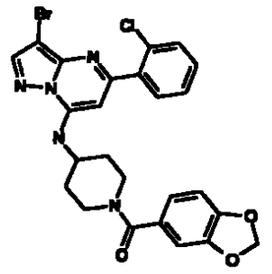
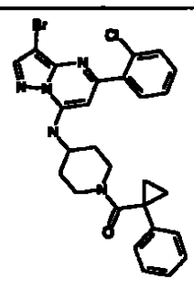
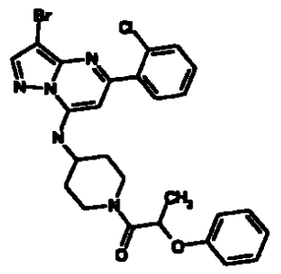
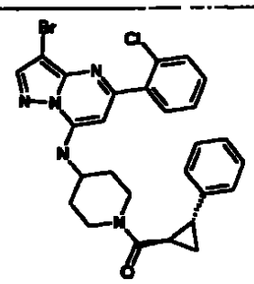
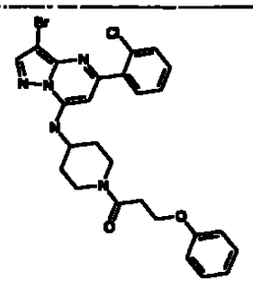
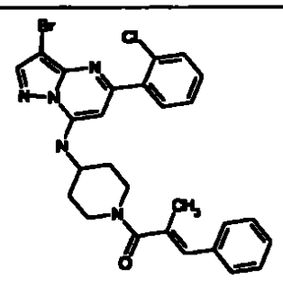
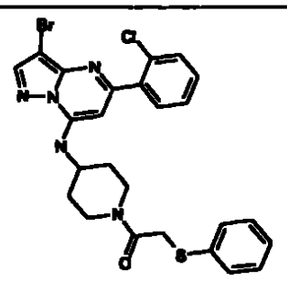
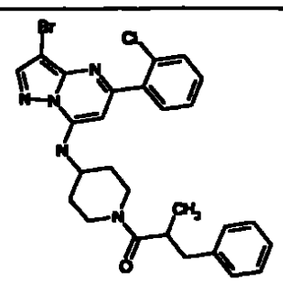
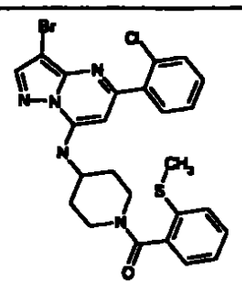
TABLE 50

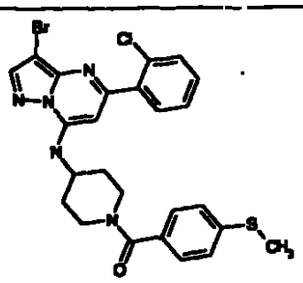
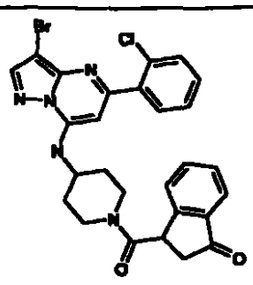
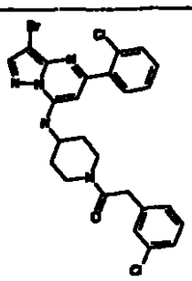
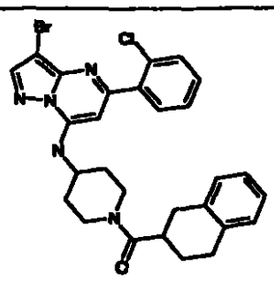
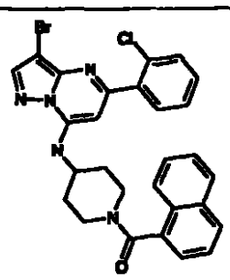
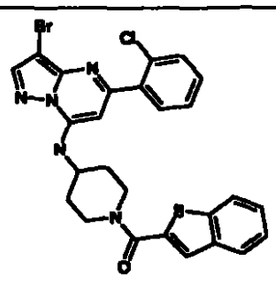
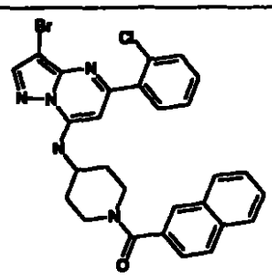
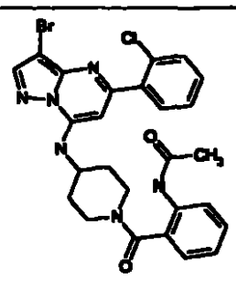
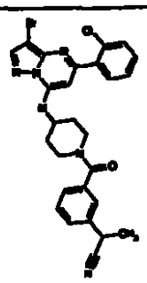
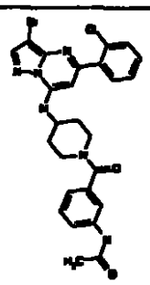
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5001 2.476.26		1. 5006 2. 504.28
	1. 5002 2. 490.27		1. 5007 2. 506.28
	1. 5003 2. 496.27		1. 5008 2. 506.28
	1. 5004 2. 502.28		1. 5009 2. 506.28
	1. 5005 2. 502.28		1. 5010 2. 513.28

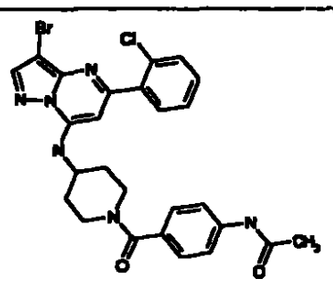
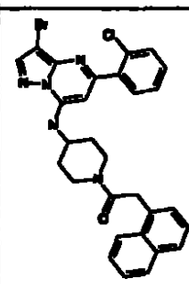
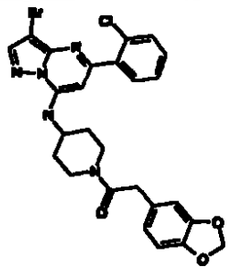
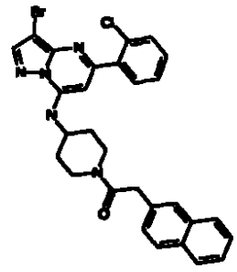
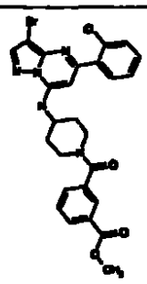
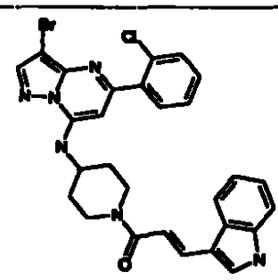
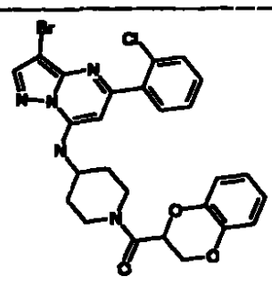
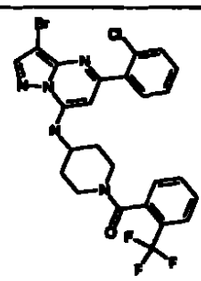
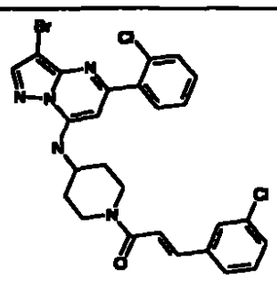
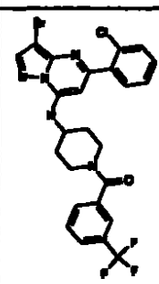
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5011 2. 515.28		1. 5016 2. 524.29
	1. 5012 2. 518.28		1. 5017 2. 526.29
	1. 5013 2. 518.28		1. 5018 2. 528.29
	1. 5014 2. 519.29		1. 5019 2. 531.29
	1. 5015 2. 522.29		1. 5020 2. 532.29

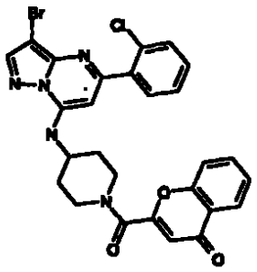
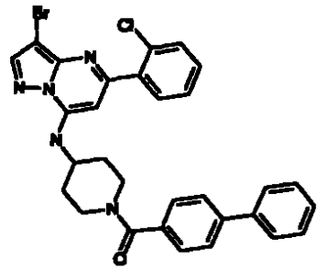
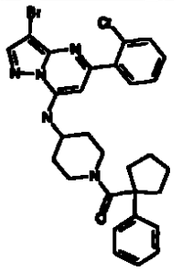
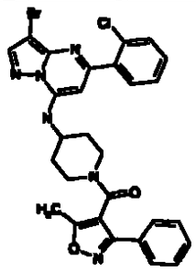
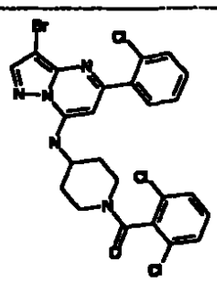
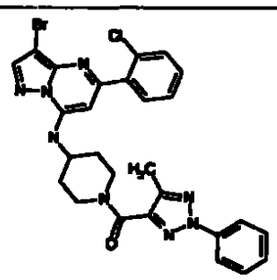
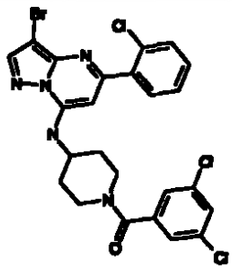
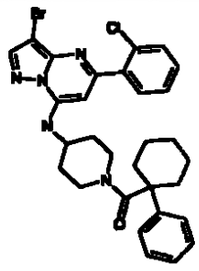
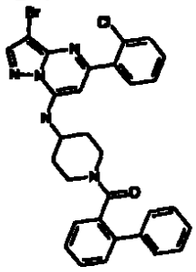
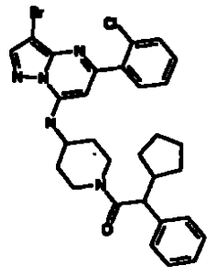
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5021 2. 532.29		1. 5026 2. 538.3
	1. 5022 2. 532.29		1. 5027 2. 540.3
	1. 5023 2. 532.29		1. 5028 2. 540.3
	1. 5024 2. 537.3		1. 5029 2. 542.3
	1. 5025 2. 537.3		1. 5030 2. 542.3

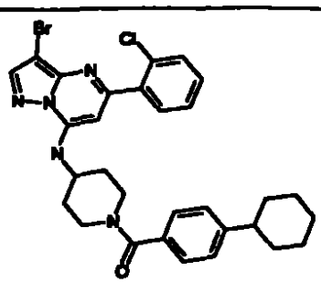
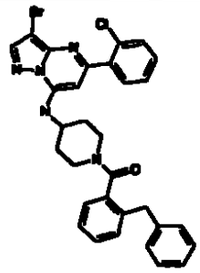
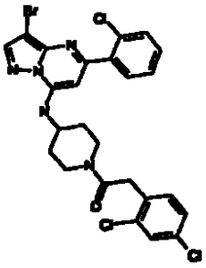
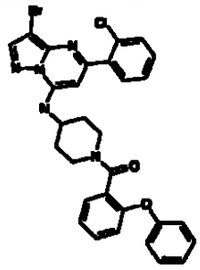
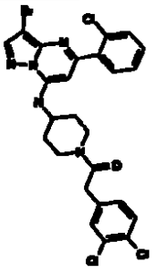
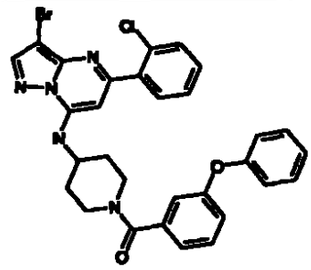
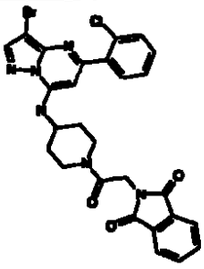
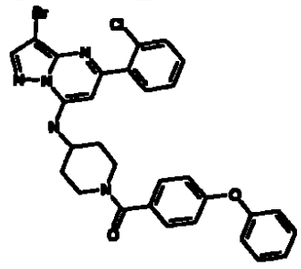
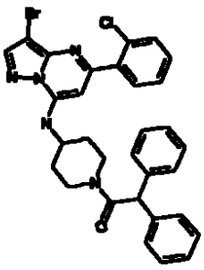
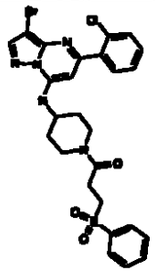
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5031 2. 542.3		1. 5036 2. 546.3
	1. 5032 2. 542.3		1. 5037 2 .546.3
	1. 5033 2. 544.3		1. 5038 2. 551.3
	1. 5034 2. 544.3		1. 5039 2. 551.3
	1. 5035 2 .546.3		1. 5040

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5041 2. 552.3		1. 5046 2. 556.31
	1. 5042 2. 552.3		1. 5047 2. 556.31
	1. 5043 2. 552.3		1. 5048 2. 556.31
	1. 5044 2. 552.3		1. 5049 2. 558.31
	1. 5045 2. 554.3		1. 5050 2. 558.31

Product	1. Ex. 2. m/z		Product	1. Ex. 2. m/z
	1. 5051 2. 558.31			1. 5056 2. 566.31
	1. 5052 2. 560.31			1. 5057 2. 566.31
	1. 5053 2. 562.31			1. 5058 2. 568.31
	1. 5054 2. 562.31			1. 5059 2. 569.31
	1. 5055 2. 565.31			1. 5060 2. 569.31

Product	1. Ex. 2. m/z		Product	1. Ex. 2. m/z
	1. 5061			1. 5066 2. 576.32
	1. 5062 2. 570.31			1. 5067 2. 576.32
	1. 5063 2. 570.31			1. 5068 2. 577.32
	1. 5064 2. 570.31			1. 5069 2. 580.32
	1. 5065 572.31			1. 5070 2. 580.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5071 2. 580.32		1 5076 2. 588.32
	1. 5072 2. 580.32		1. 5077 2. 593.33
	1 5073 2. 580.32		1 5078 2. 593.33
	1 5074 2. 580.32		1. 5079 2. 594.33
	1 5075 2. 588.32		1. 5080 2. 594.33

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5081 2. 594.33		1. 5086 2. 602.33
	1. 5082 2. 594.33		1.5087 2. 604.33
	1. 5083 2. 594.33		1. 5088 2. 604.33
	1. 5084 2. 595.33		1. 5089 2. 604.33
	1.5085 2. 602.33		1. 5090 2. 604.33

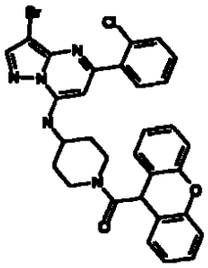
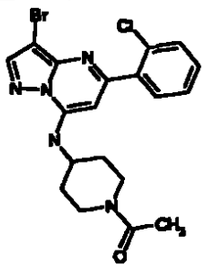
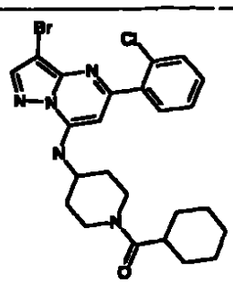
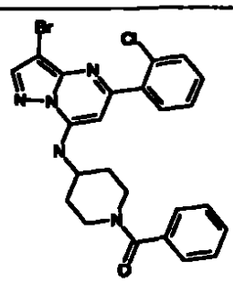
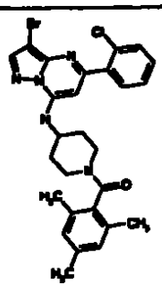
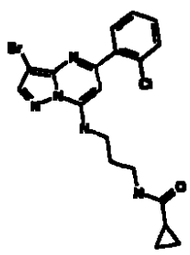
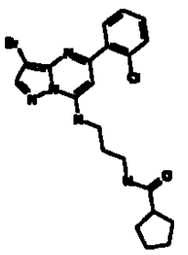
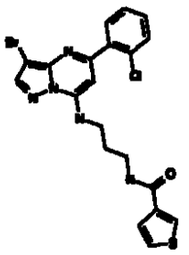
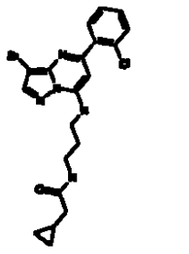
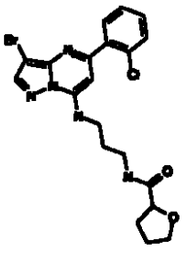
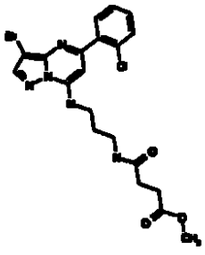
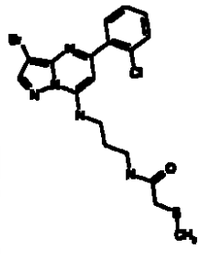
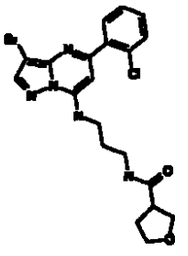
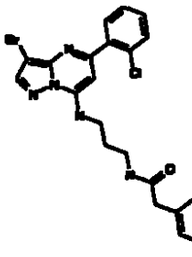
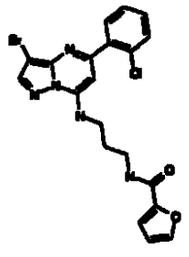
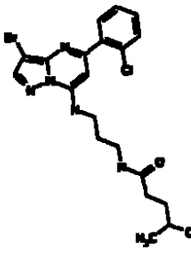
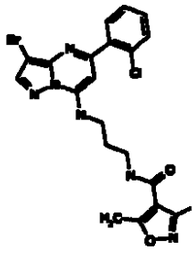
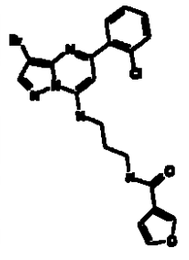
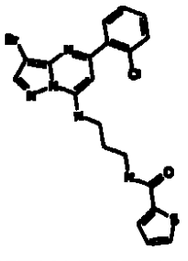
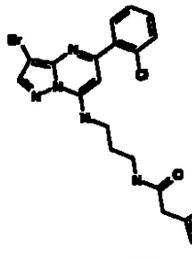
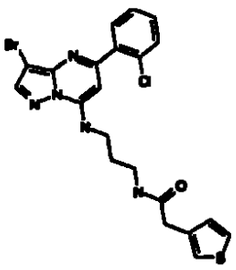
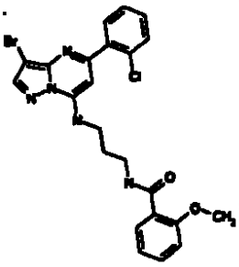
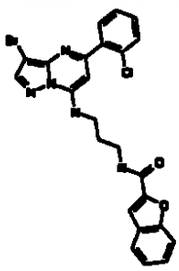
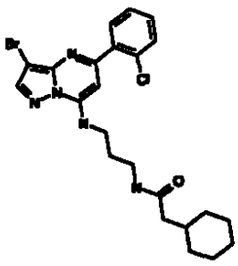
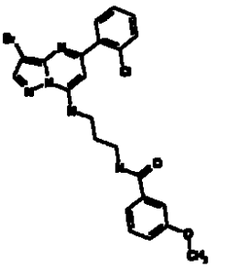
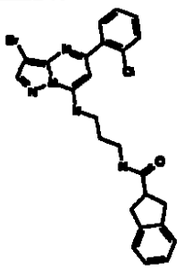
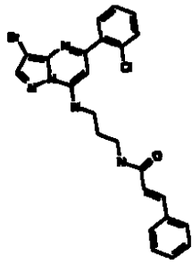
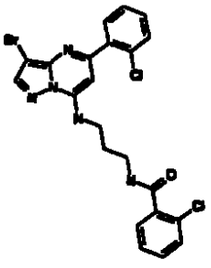
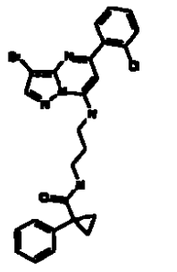
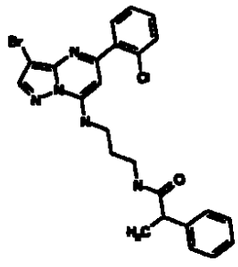
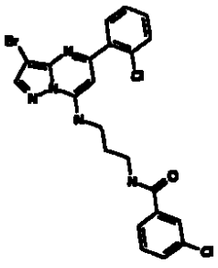
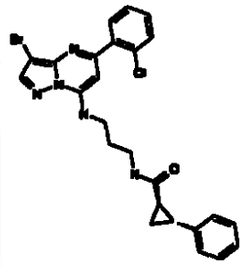
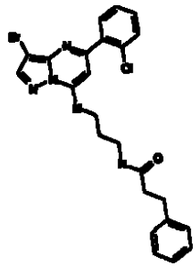
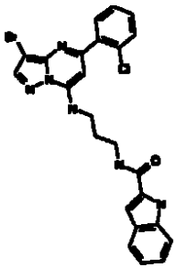
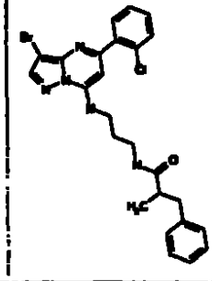
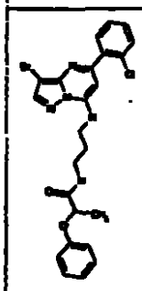
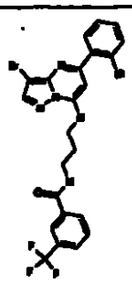
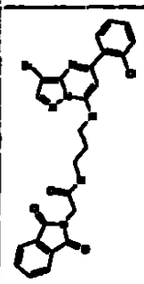
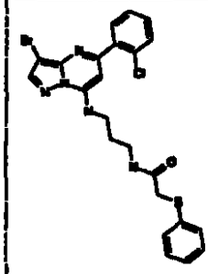
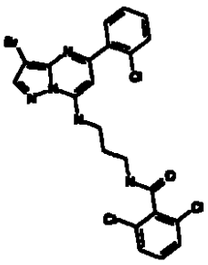
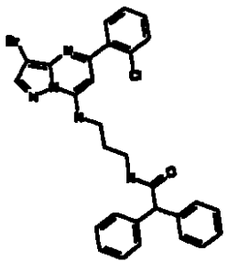
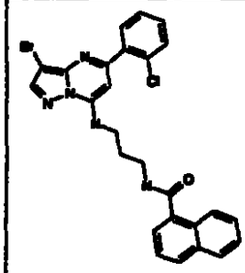
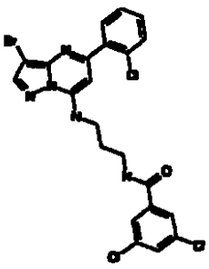
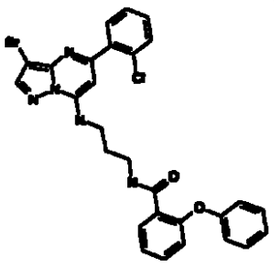
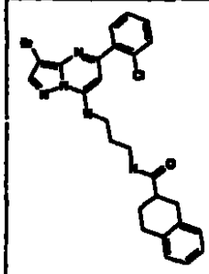
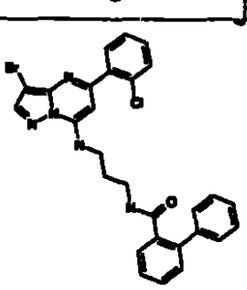
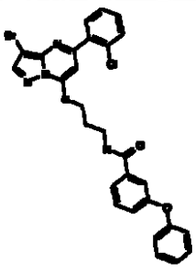
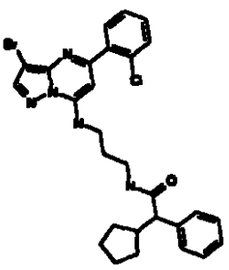
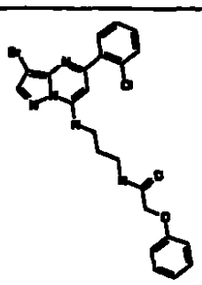
Product	1. Ex. 2. m/z
	1. 5091 2. 616.34
	1. 5092 2. 450.25
	1. 5093 2. 518.28
	1. 5094 2. 512.28
	1. 5095 2.554.3

TABLE 51

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5101 2. 448.8		1. 5106 2. 476.8		1. 5111 2. 490.8
	1. 5102 2. 462.8		1. 5107 2. 476.8		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
	1. 5105 2. 474.7		1. 5110 2. 490.8		1. 5115 2. 504.8

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5116 2. 504.8		1. 5121 2. 514.8		1. 5126 2. 524.8
	1. 5117 2. 504.9		1. 5122 2. 514.8		1. 5127 2. 524.9
	1. 5118 2. 510.8		1. 5123 2. 519.2		1. 5128 2 . 524.9
	1. 5119 2. 512.8		1. 5124 2. 519.2		1. 5129 2. 524.9
	1. 5120 2. 512.8		1. 5125 2. 523.8		1. 5130 2. 526.9

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5131 2. 528.8		1. 5136 2. 552.8		1. 5141 2. 567.8
	1. 5132 2. 530.9		1. 5137 2. 553.7		1. 5142 2. 574.9
	1. 5133 2. 534.8		1. 5138 2. 553.7		1. 5143 2. 576.9
	1. 5134 2. 538.9		1. 5139 2. 560.9		1. 5144 2. 576.9
	1. 5135 2. 552.8		1. 5140 2. 566.9		1. 5145 2. 514.8

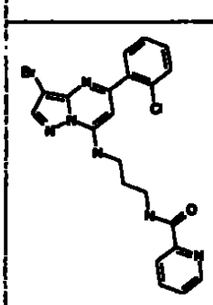
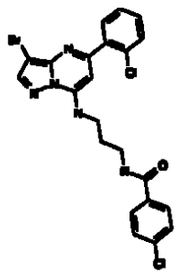
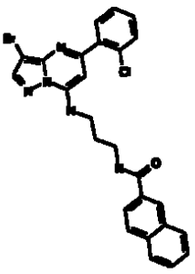
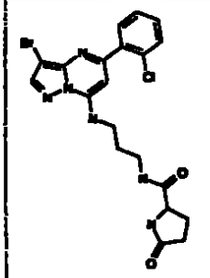
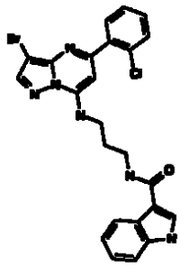
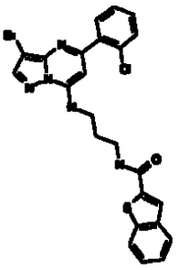
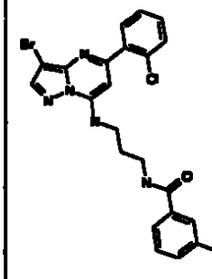
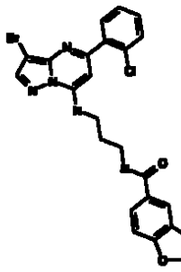
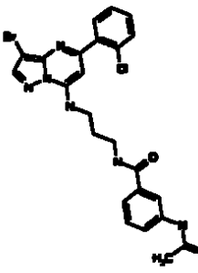
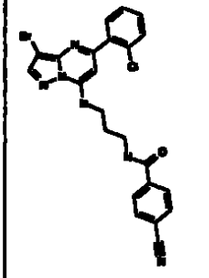
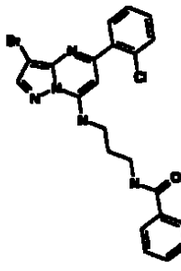
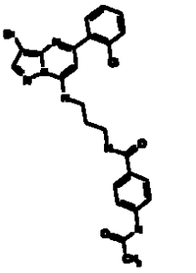
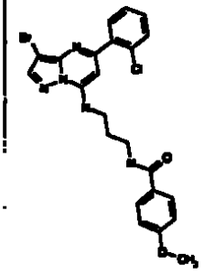
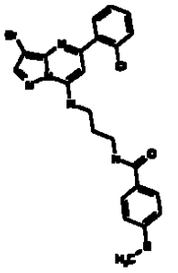
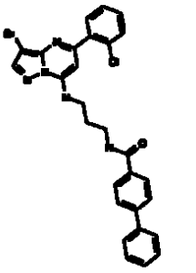
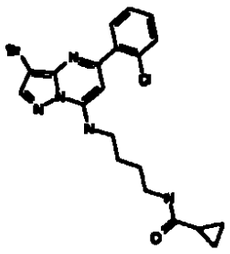
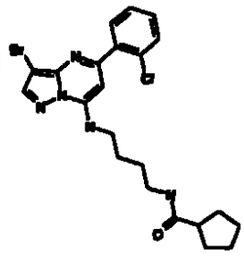
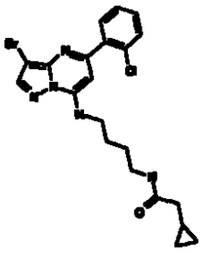
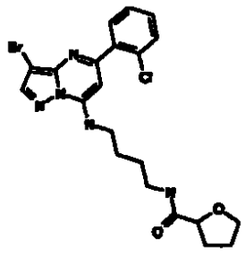
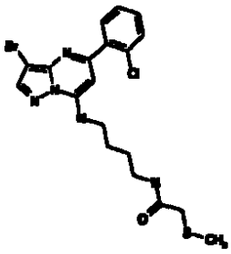
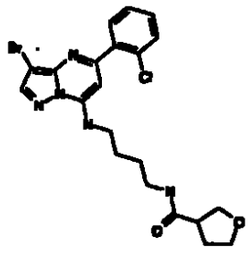
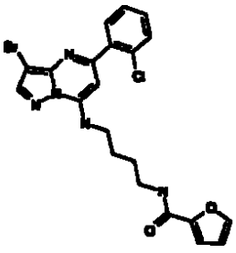
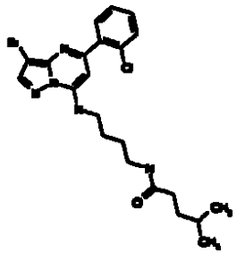
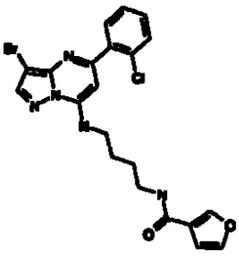
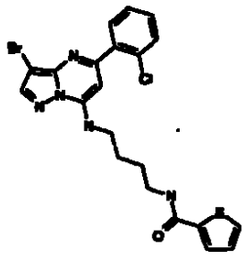
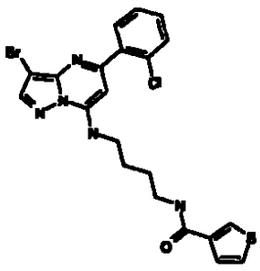
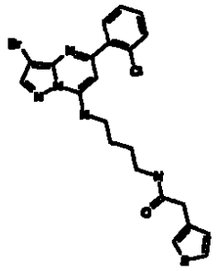
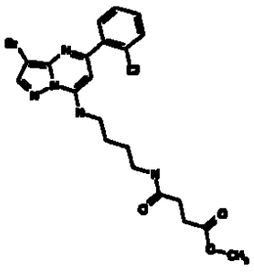
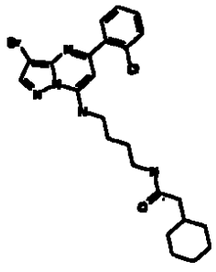
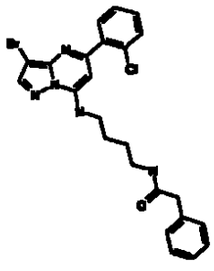
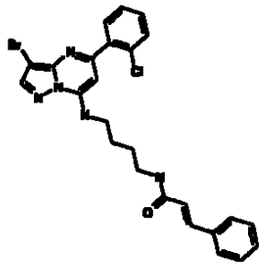
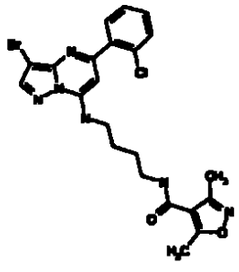
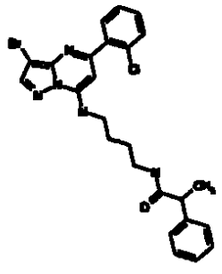
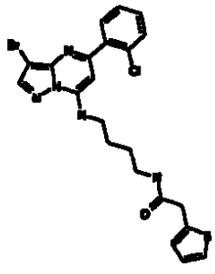
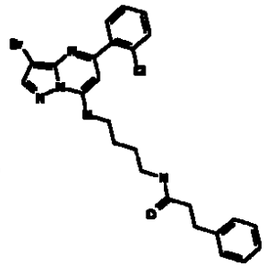
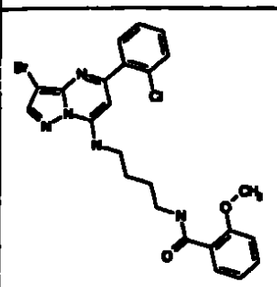
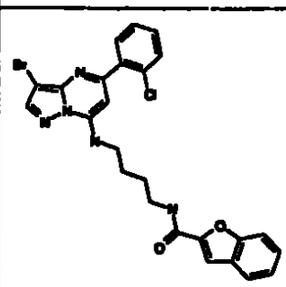
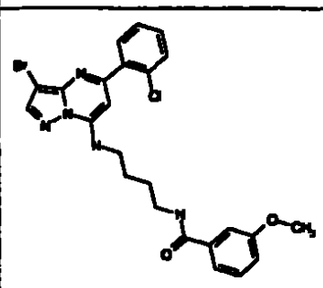
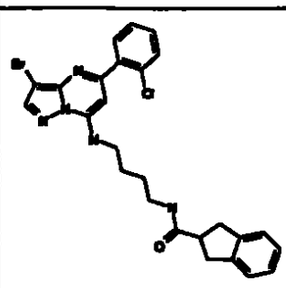
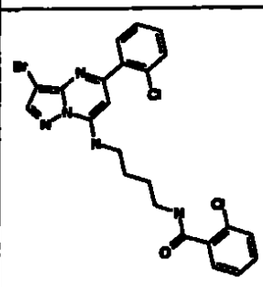
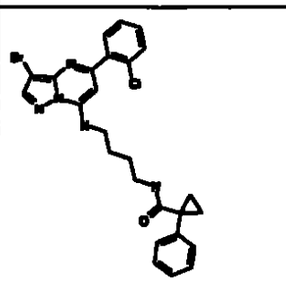
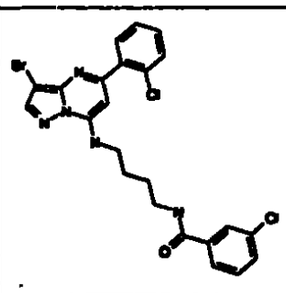
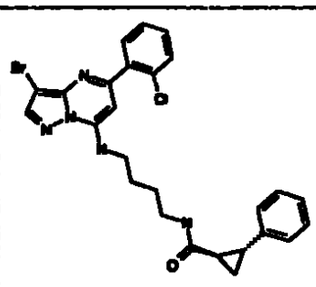
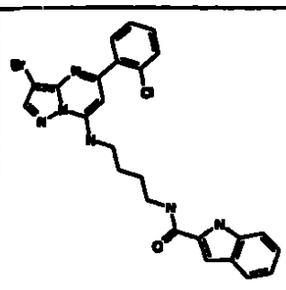
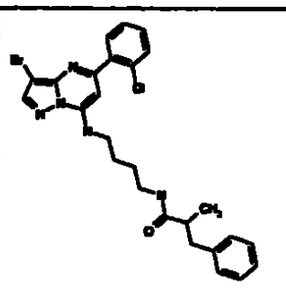
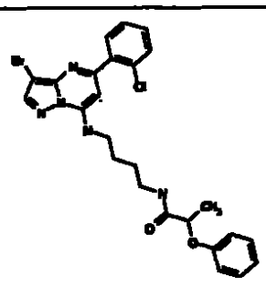
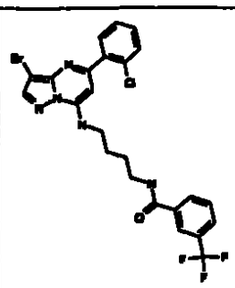
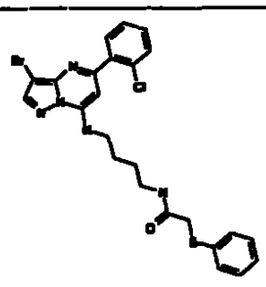
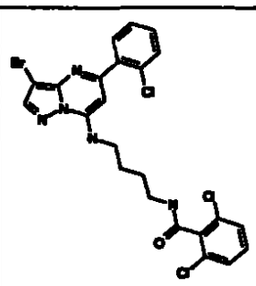
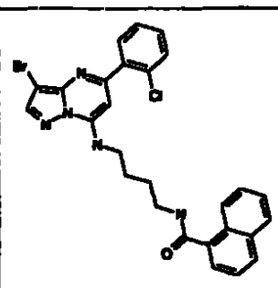
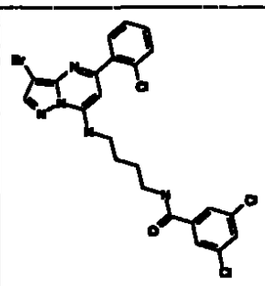
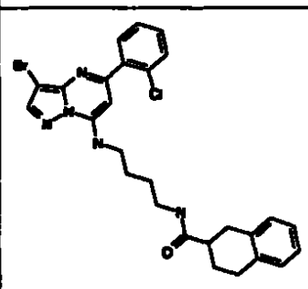
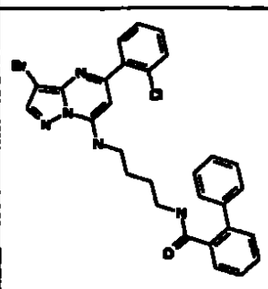
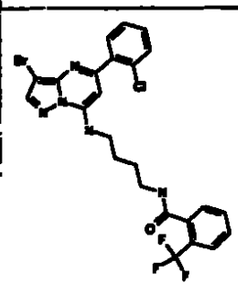
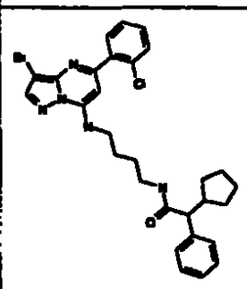
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5146 2. 485.8		1. 5151 2. 519.2		1. 5156 2. 534.8
	1. 5147 2. 491.8		1. 5152 2. 523.8		1. 5157 2. 540.9
	1. 5148 2. 509.8		1. 5153 2. 528.8		1. 5158 2. 541.8
	1. 5149 2. 509.8		1. 5154 2. 530.9		1. 5159 2. 541.8
	1. 5150 2. 514.8	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

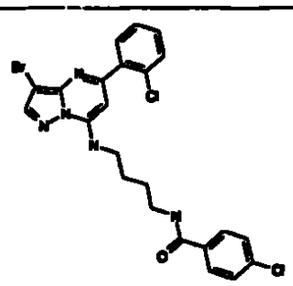
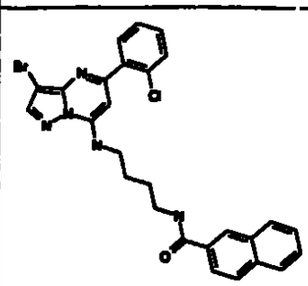
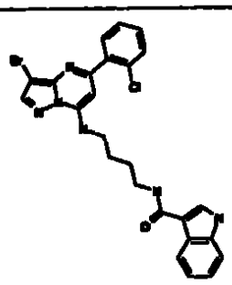
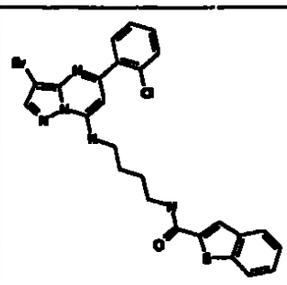
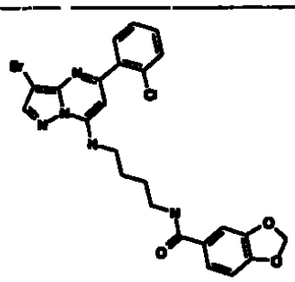
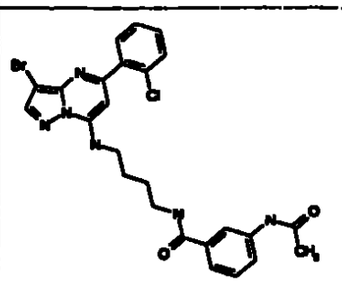
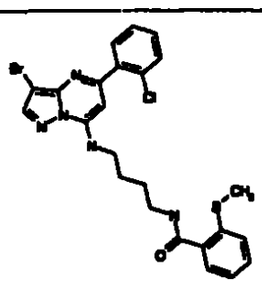
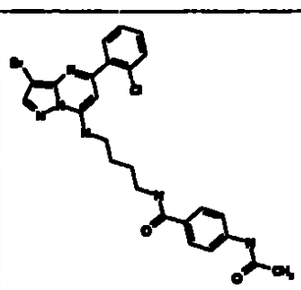
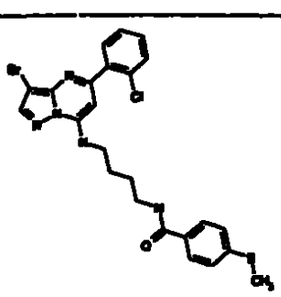
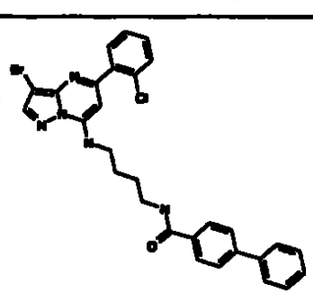
TABLE 52

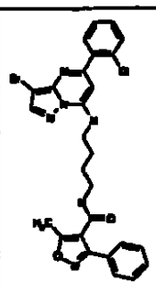
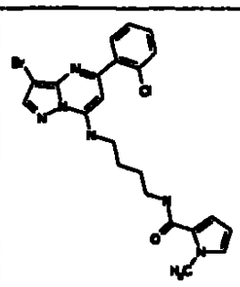
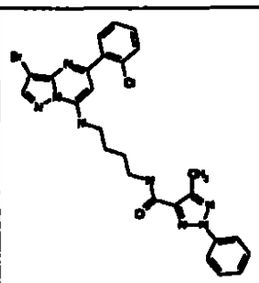
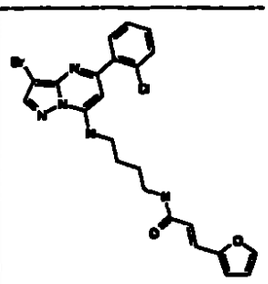
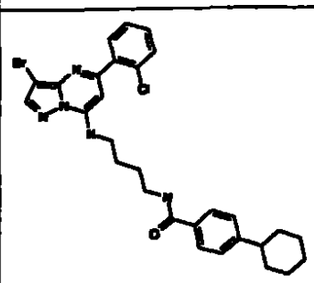
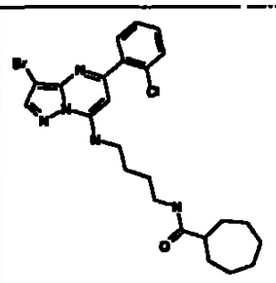
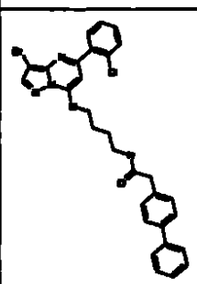
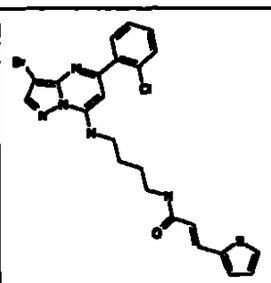
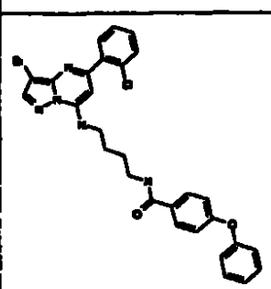
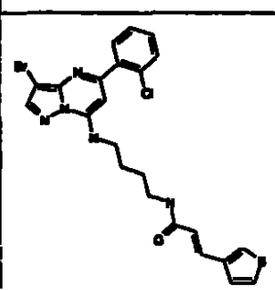
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5201 2. 462.8		1. 5206 2. 490.8
	1. 5202 2. 476.8		1. 5207 2. 492.8
	1. 5203 2. 482.8		1. 5208 2. 492.8
	1. 5204 2. 488.8		1. 52009 2. 492.9
	1. 5205 2. 488.8		1. 5210 2. 504.8

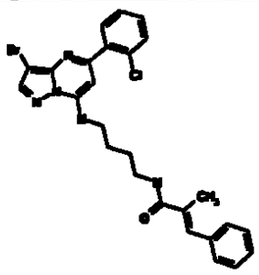
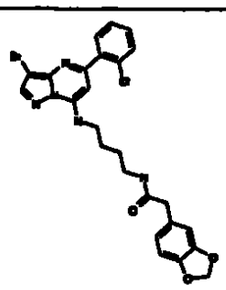
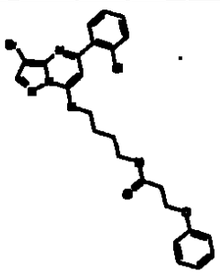
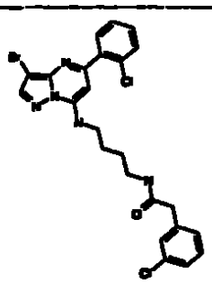
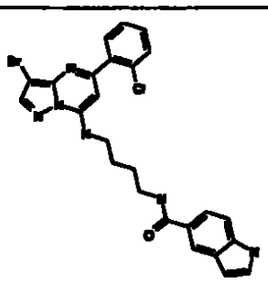
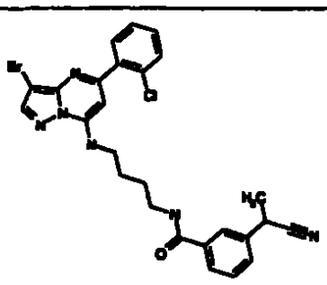
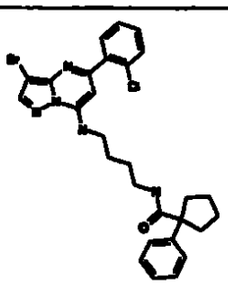
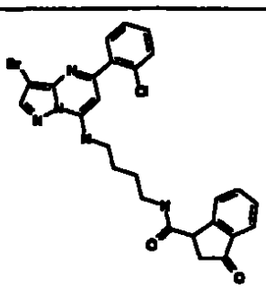
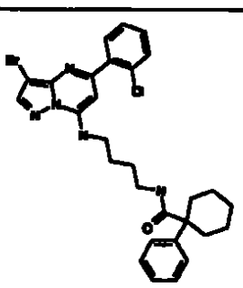
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5211 2. 504.8		1. 5216 2. 518.9
	2. 5212 2. 508.8		1. 5217 2. 518.9
	1. 5213 2. 512.8		1. 5218 2. 524.9
	1. 5214 2. 517.8		1. 5219 2. 526.9
	1. 5215 2. 518.9		1. 5220 2. 526.9

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5221 2. 528.8		1. 5226 2. 538.8
	1. 5222 2. 528.8		1. 5227 2. 538.9
	1. 5223 2. 533.3		1. 5228 2. 538.9
	1. 5224 2. 533.3		1. 5229 2. 538.9
	1. 5225 2. 537.9		1. 5230 2. 540.9

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
	1. 5265 2. 552.9		1. 5270 2. 581

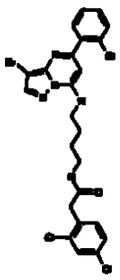
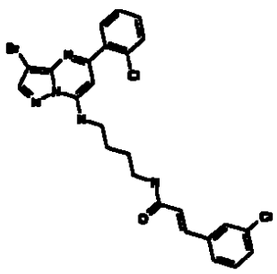
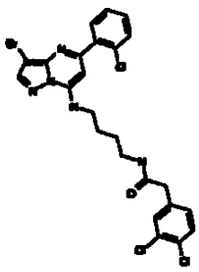
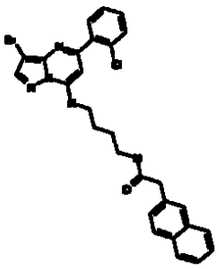
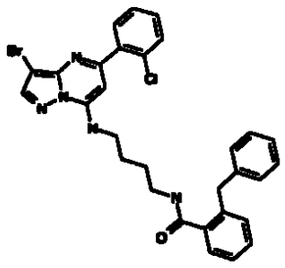
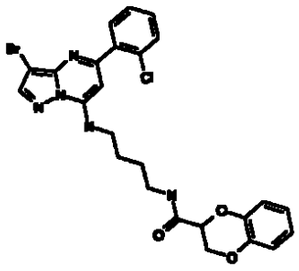
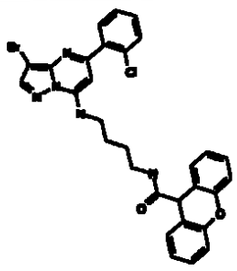
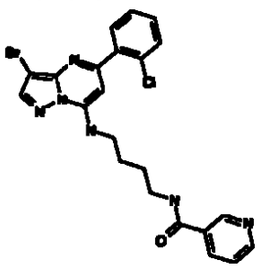
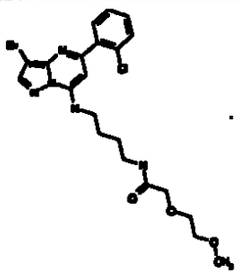
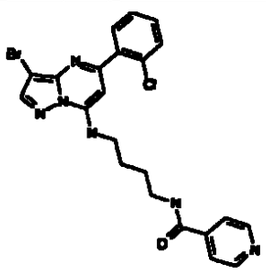
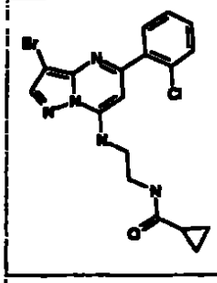
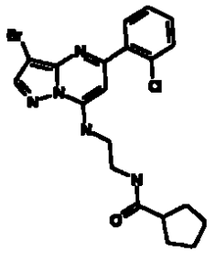
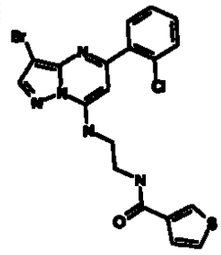
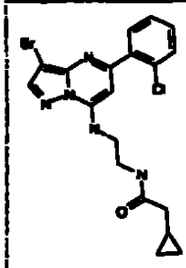
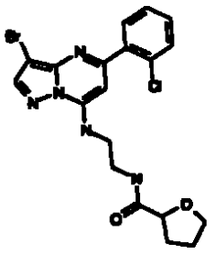
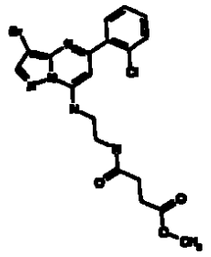
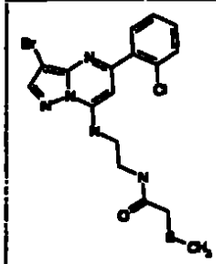
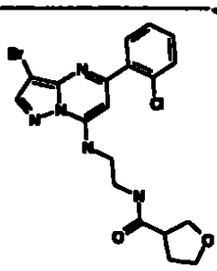
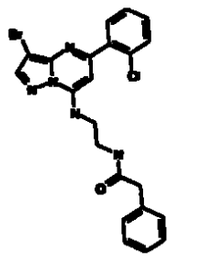
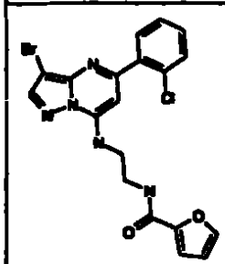
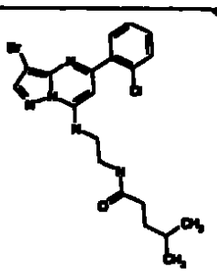
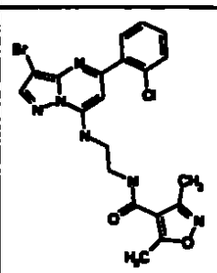
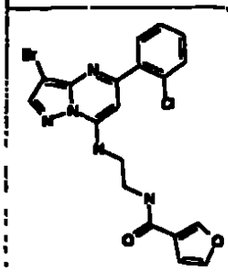
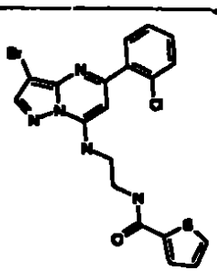
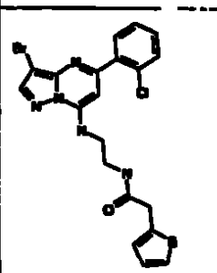
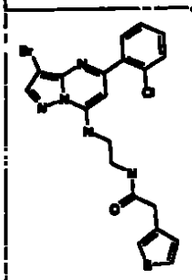
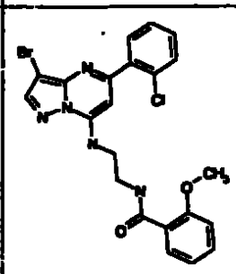
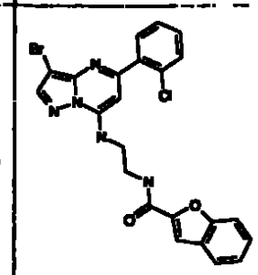
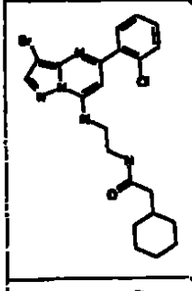
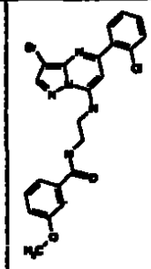
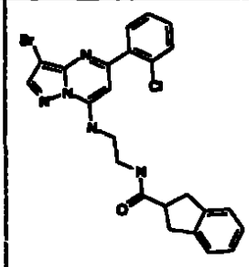
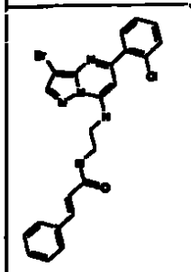
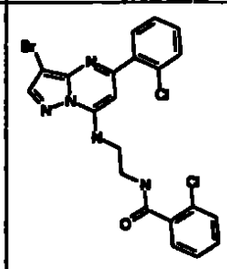
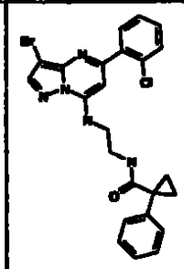
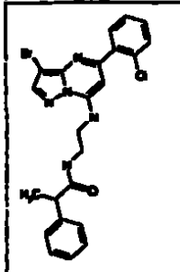
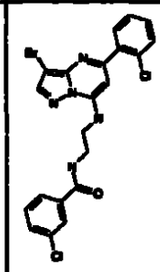
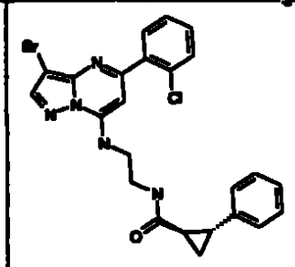
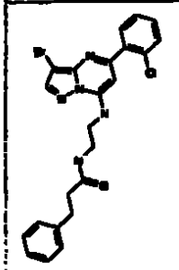
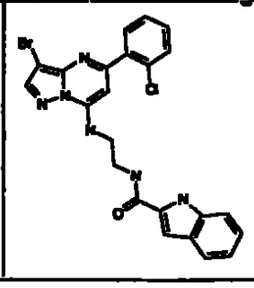
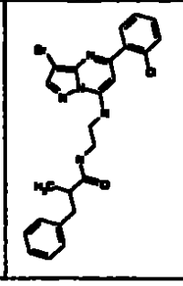
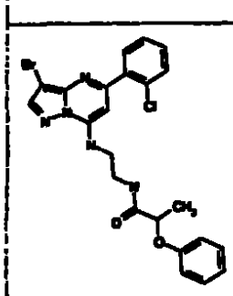
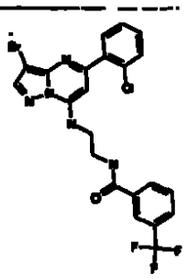
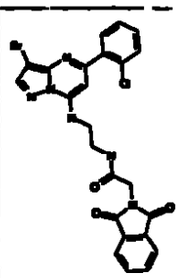
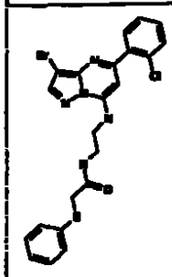
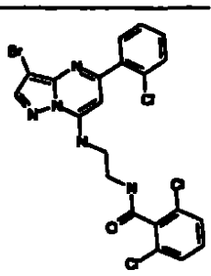
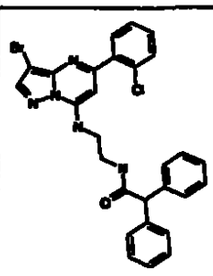
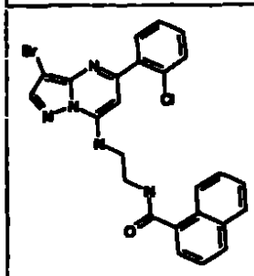
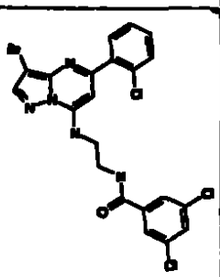
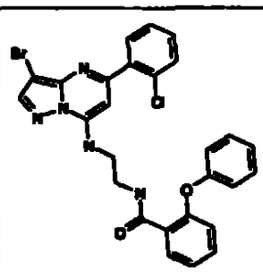
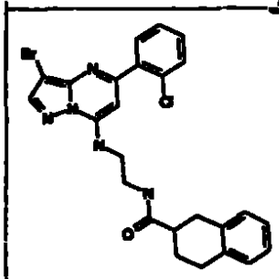
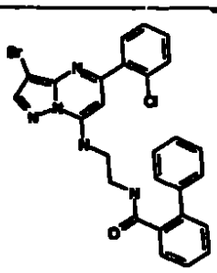
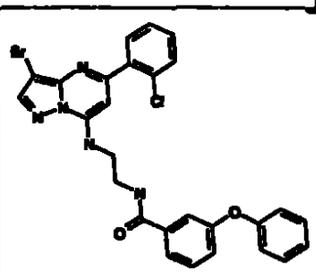
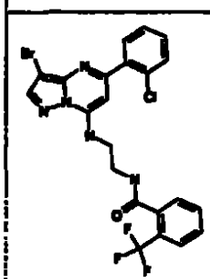
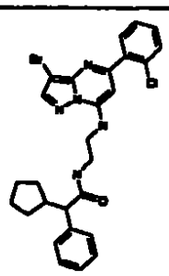
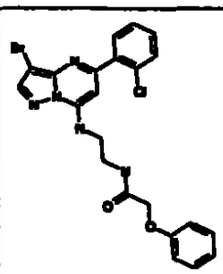
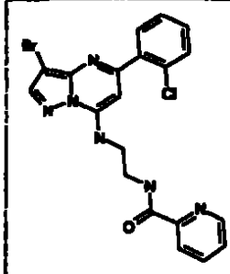
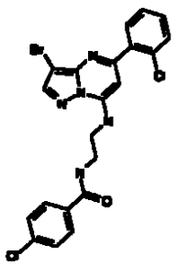
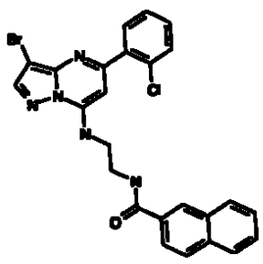
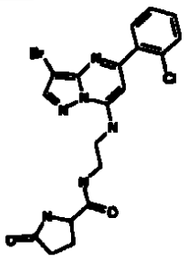
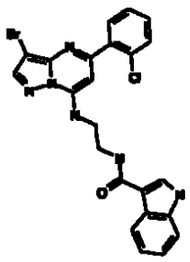
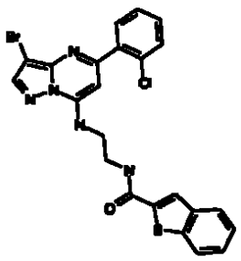
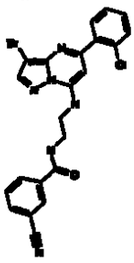
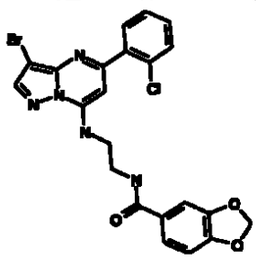
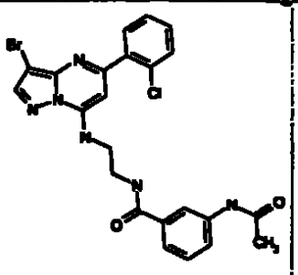
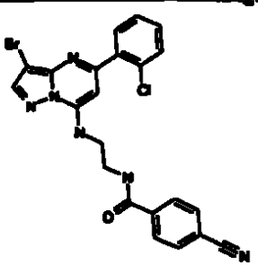
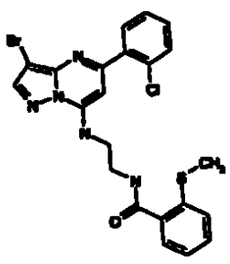
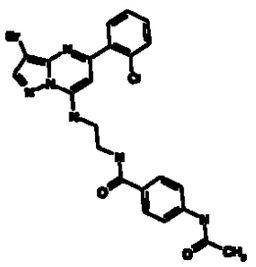
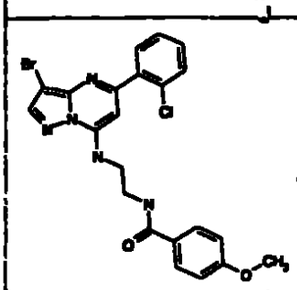
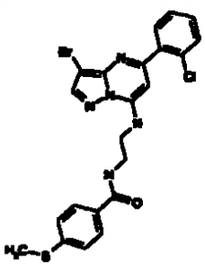
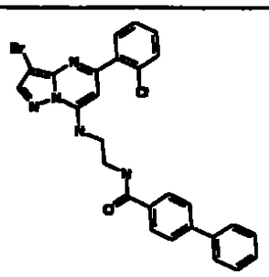
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5271 2. 581.7		1. 5276 2. 559.3
	1. 5272 2. 581.7		1. 5277 2. 562.9
	1. 5273 2. 588.9		1. 5278 2. 556.9
	1. 5274 2. 602.9		1. 5279 2. 499.8
	1. 5275 2. 510.8		1. 5280 2. 499.8

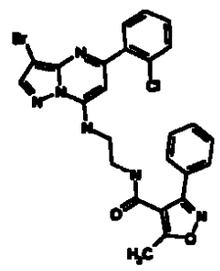
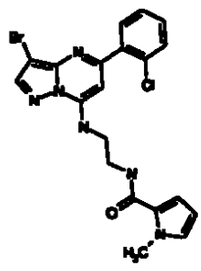
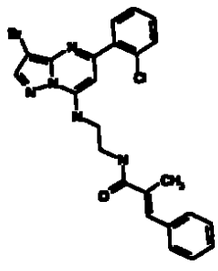
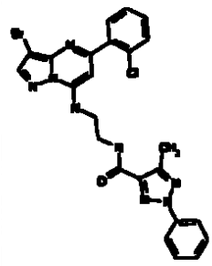
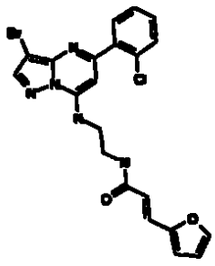
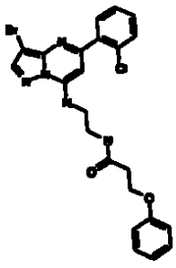
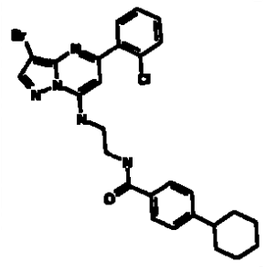
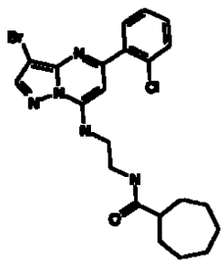
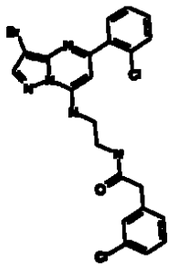
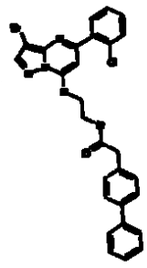
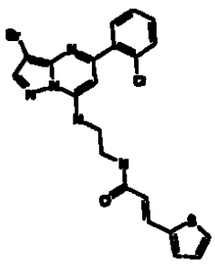
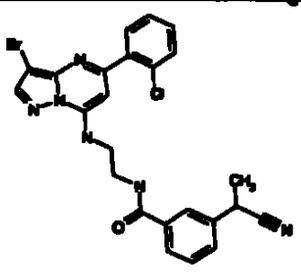
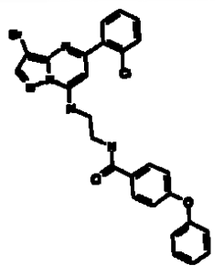
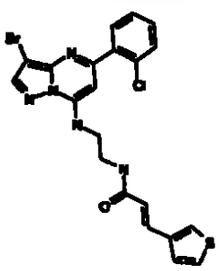
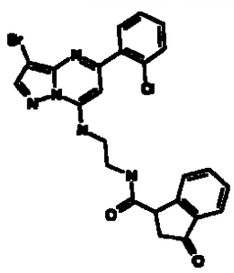
TABLE 53

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5301 2. 434.7		1. 5306 2. 462.8		1. 5311 2. 476.8
	1. 5302 2. 448.8		1. 5307 2. 464.8		1. 5312 2. 480.8
	1. 5303 2. 454.8		1. 5308 2. 464.8		1. 5313 2. 484.8
	1. 5304 2. 460.7		1. 5309 2. 464.8		1. 5314 2. 489.8
	1. 5305 2. 460.7		1. 5310 2. 476.8		1. 5315 2. 490.8

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5316 2. 490.8		1. 5321 2. 500.8		1. 5326 2. 510.8
	1. 5317 2. 490.8		1. 5322 2. 500.8		1. 5327 2. 510.8
	1. 5318 2. 496.8		1. 5323 2. 505.2		1. 5328 2. 510.8
	1. 5319 2. 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. 538.8		1. 5341 2. 553.8
	1. 5332 2. 516.9		1. 5337 2. 539.6		1. 534 2. 560.9
	1. 5333 2. 520.8		1. 5338 2. 539.6		1. 5343 2. 562.9
	1. 5334 2. 524.9		1. 5339 2. 546.9		1. 5344 2. 562.9
	1. 5335 2. 538.8		1.5340 2. 552.9		1. 5345 2. 500.8

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5346 2. 471.7		1. 5351 2. 505.2		1. 5356 2. 520.8
	1. 5347 2. 477.8		1. 5352 2. 509.8		1. 5357 2. 526.8
	1. 5348 2. 495.8		1. 5353 2. 514.8		1. 5358 2. 527.8
	1. 5349 2. 495.8		1. 5355 2. 516.9		1. 5359 2. 527.8
	. 5350 . 500.8		1. 5356 2. 516.9		1. 5360 2. 546.9

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5361 2. 551.8		1. 5366 2. 473.8		1. 5371 2.510.8
	1. 5362 2. 551.8		1. 5367 2. 486.8		1. 5372 2. 514.8
	1. 5363 2. 552.9		1. 5368 2. 490.8		1. 5373 2. 519.2
	1. 5364 2. 560.9		1. 5369 2. 502.8		1. 5374 2. 523.8
	1. 5365 2. 562.9		1. 5370 2. 502.8		1. 5375 2. 524.8

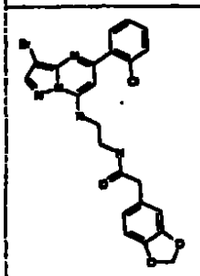
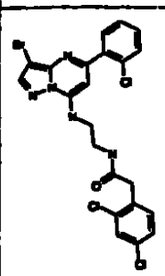
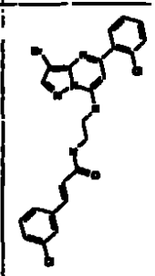
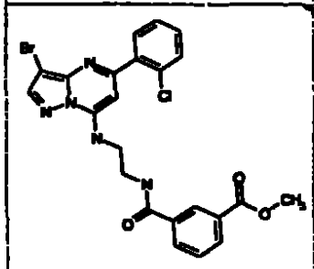
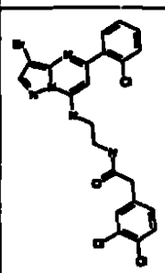
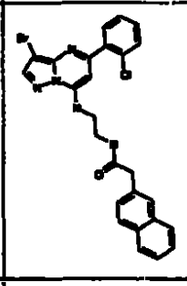
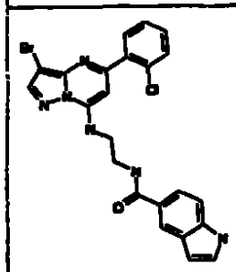
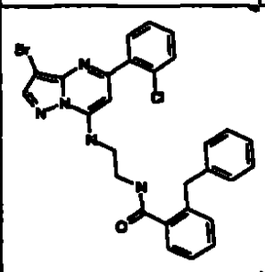
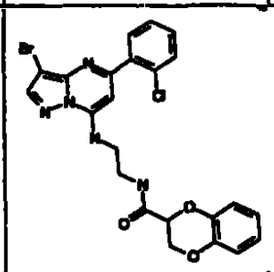
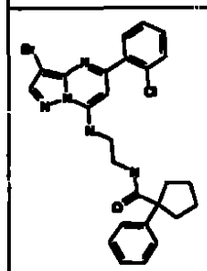
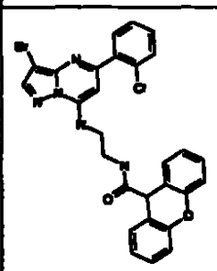
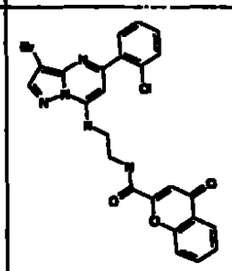
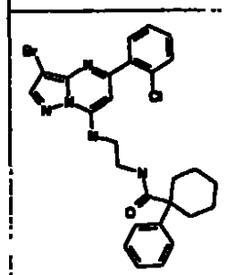
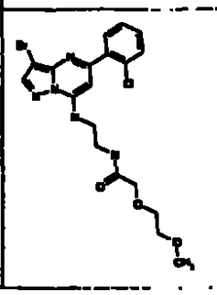
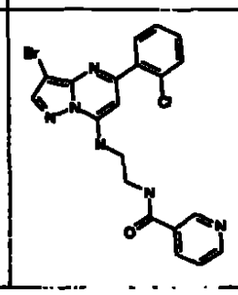
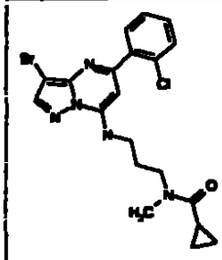
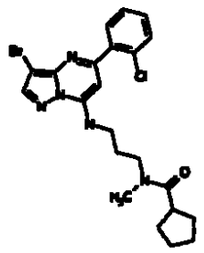
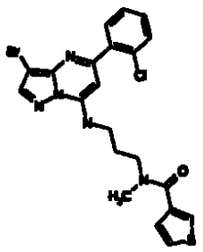
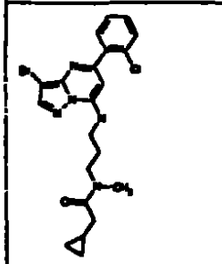
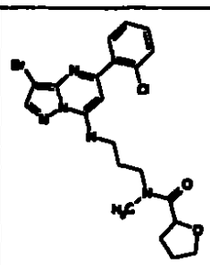
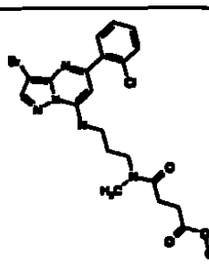
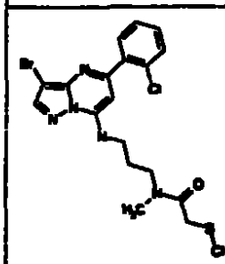
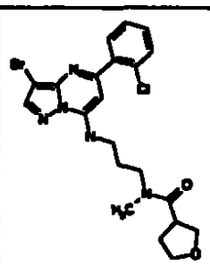
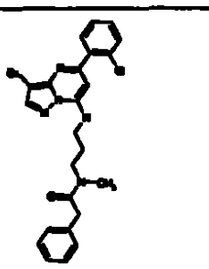
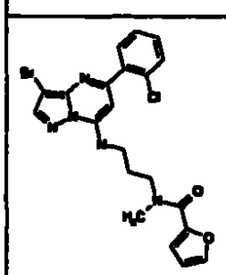
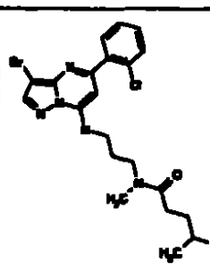
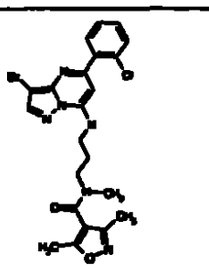
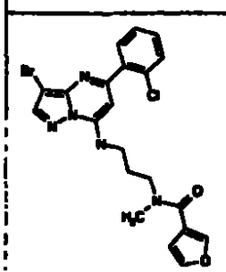
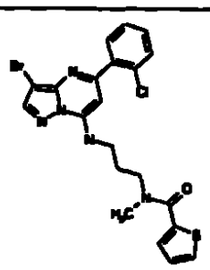
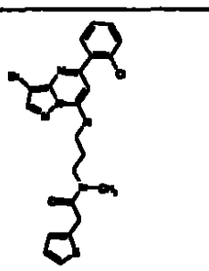
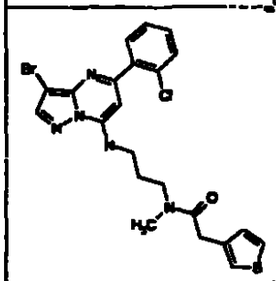
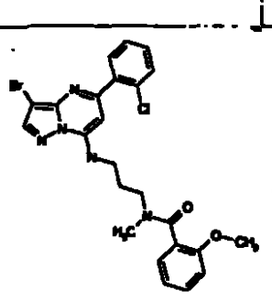
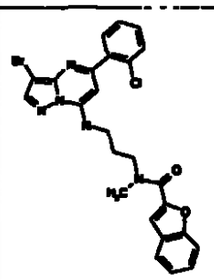
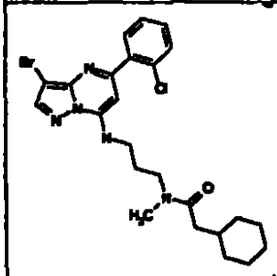
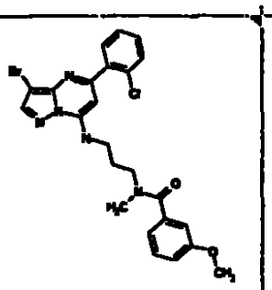
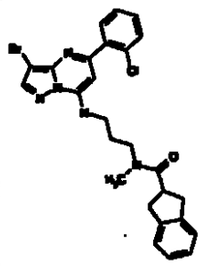
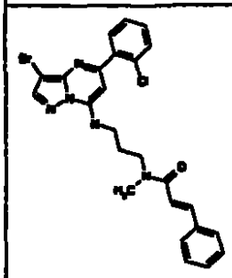
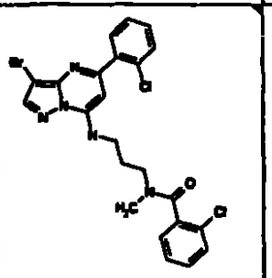
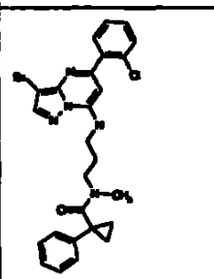
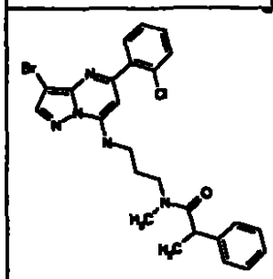
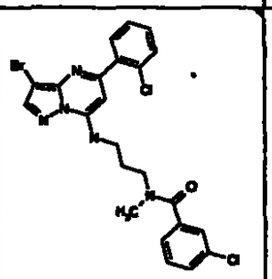
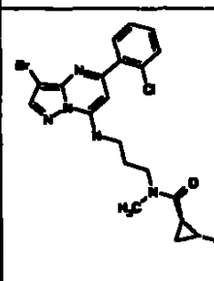
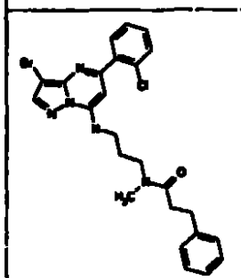
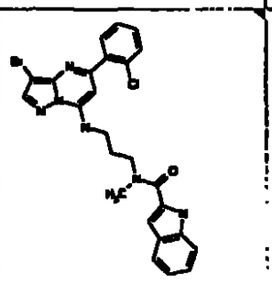
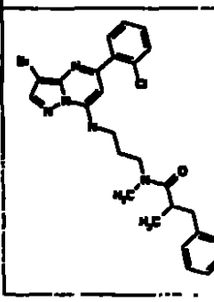
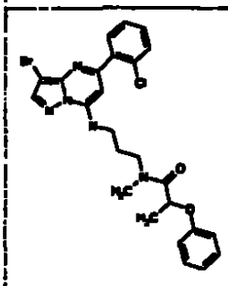
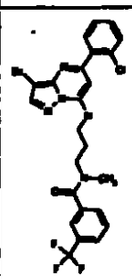
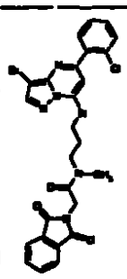
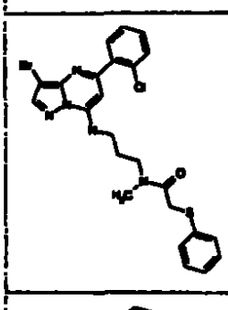
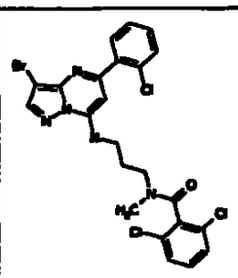
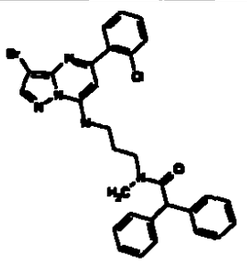
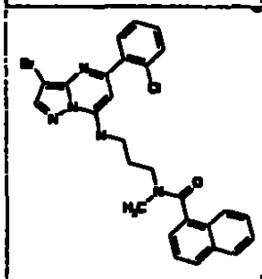
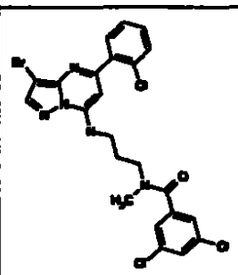
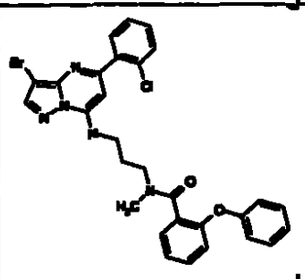
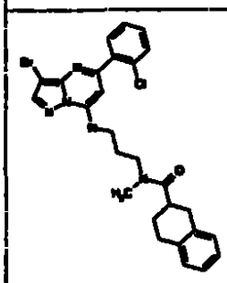
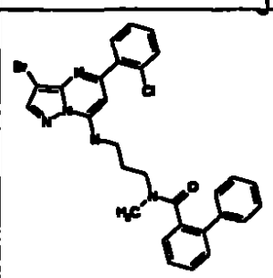
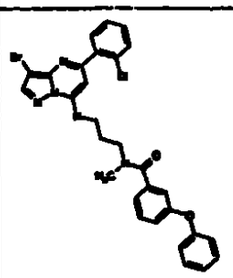
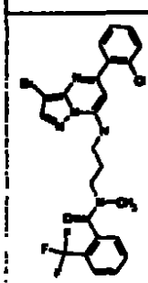
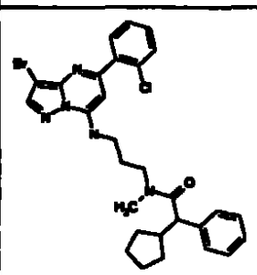
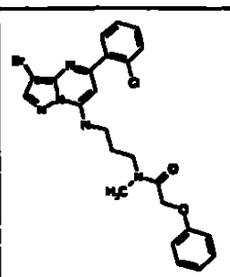
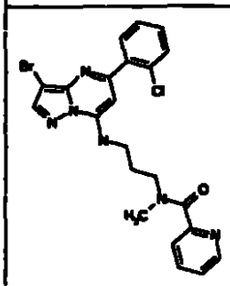
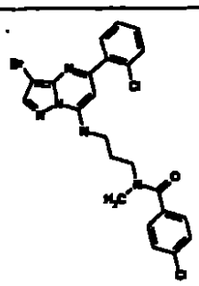
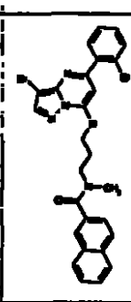
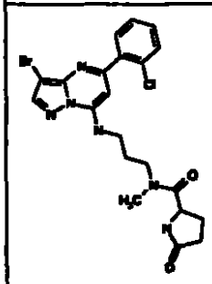
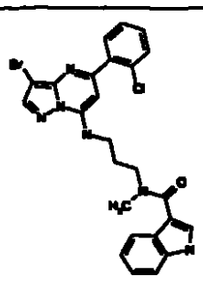
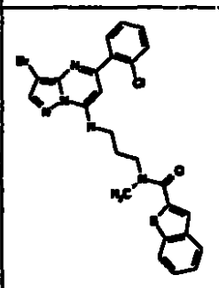
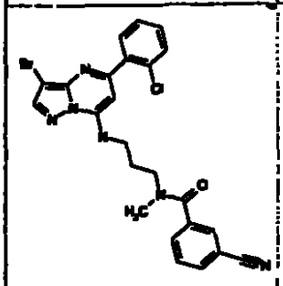
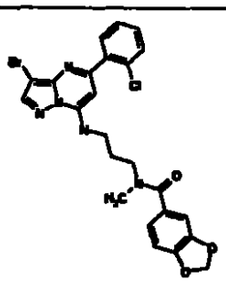
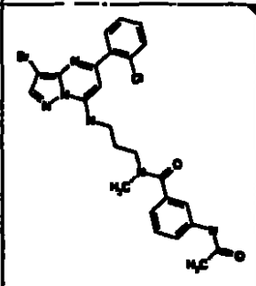
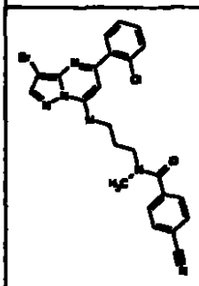
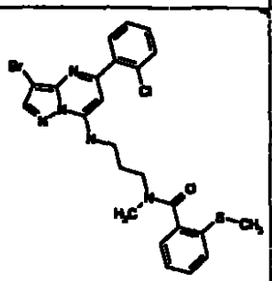
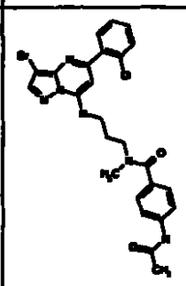
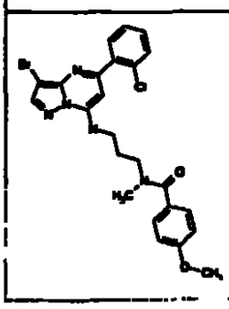
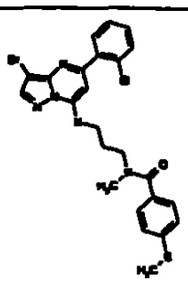
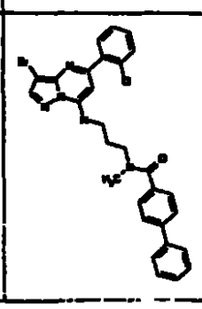
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5376 2. 528.8		1. 5381 2. 553.7		1. 5386 2. 531.2
	1. 5377 2. 528.8		1. 5382 2. 553.7		1. 5387 2. 534.8
	1. 5378 2. 509.8		1. 5383 2. 560.9		1. 5388 2. 526.8
	1. 5379 2. 538.9		1. 5384 2. 574.9		1. 5389 2. 538.8
	1. 5380 2. 552.9		1. 5385 2. 482.8		1. 5390 2. 471.7

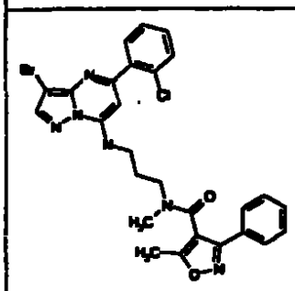
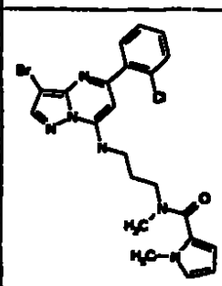
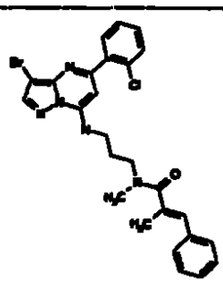
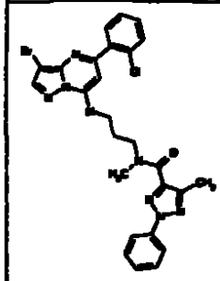
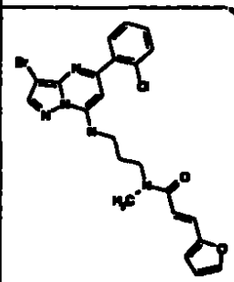
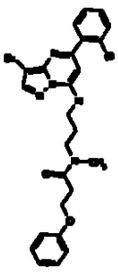
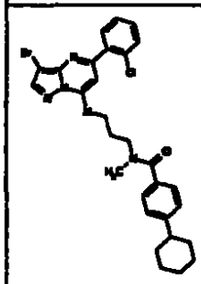
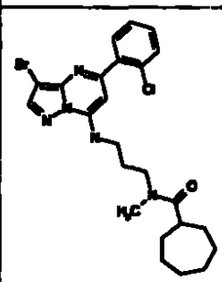
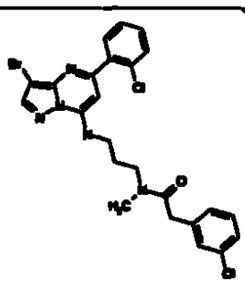
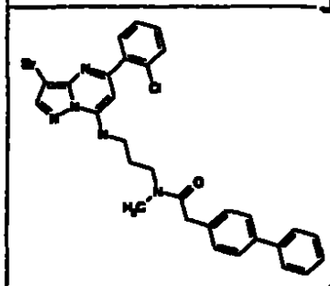
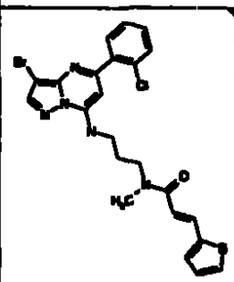
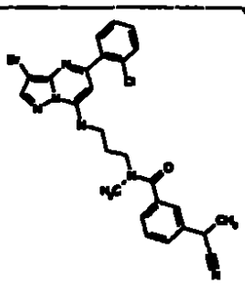
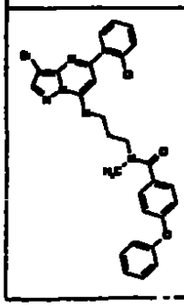
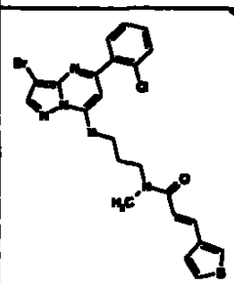
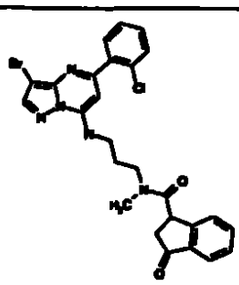
TABLE 54

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5401 2. 463.3		1. 5406 2. 491.3		1. 5411 2. 505.3
	1. 5402 2. 477.3		1. 5407 2. 493.3		1. 5412 2. 509.3
	1. 5403 2. 483.3		1. 5408 2. 493.3		1. 5413 2. 513.3
	1. 5404 2. 489.3		1. 5409 2. 493.3		1. 5414 2. 518.3
	1. 5405 2. 489.3		1. 5410 2. 505.3		1. 5415 2. 519.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5416 2. 519.3		1. 5121 2. 529.3		1. 5426 2. 539.3
	1. 5417 2. 519.3		1. 5422 2. 529.3		1. 5427 2. 539.3
	1. 5418 2. 525.3		1. 5423 2. 533.3		1. 5428 2. 539.3
	1. 5419 2. 527.3		1. 5424 2. 533.3		1. 5429 2. 539.3
	1. 5420 2. 527.3		1. 5425 2. 538.3		1. 5430 2. 541.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5431 2. 543.3		1. 5436 2. 567.3		1. 5441 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. 547 2. 543.3
	1. 5463 2. 581.3		1. 5468 2. 519.3		1. 5473 2. 547.3
	1. 5464 2. 589.3		1. 5469 2. 531.3		1. 5474 2. 552.3
	1. 5465 2. 591.3		1. 5470 2. 531.3		1. 5475 2. 553.3

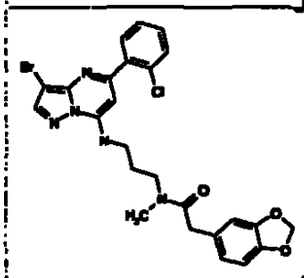
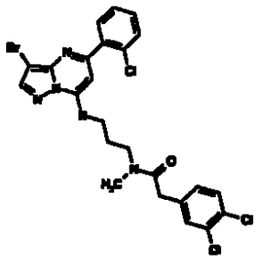
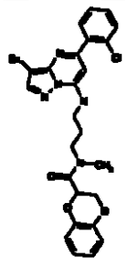
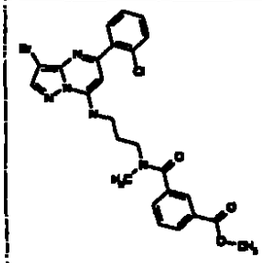
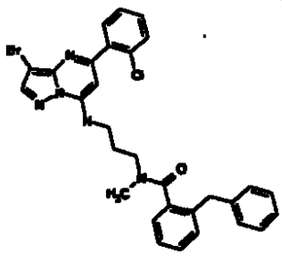
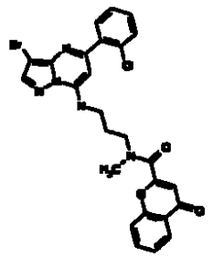
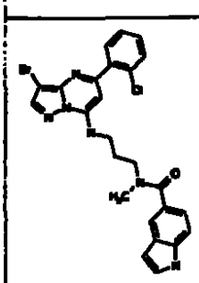
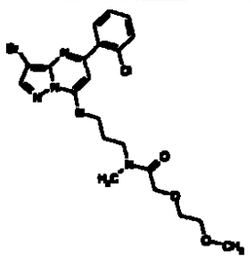
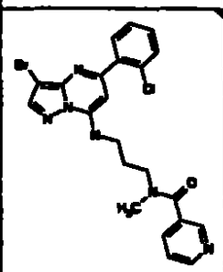
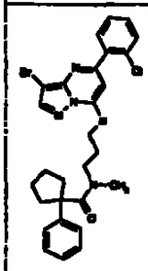
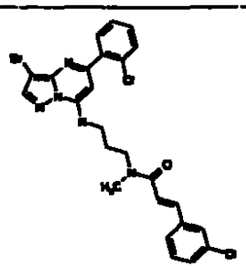
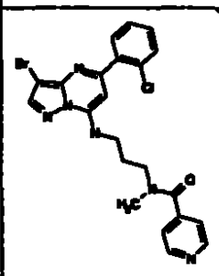
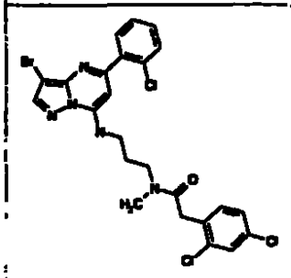
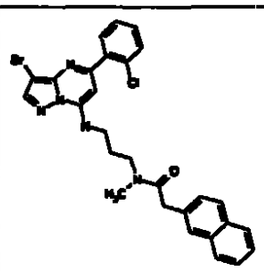
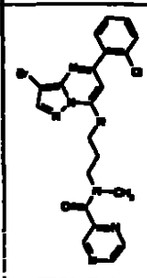
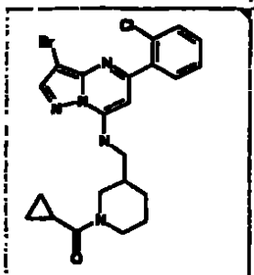
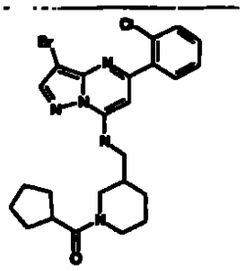
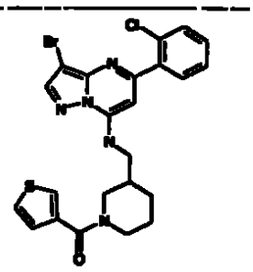
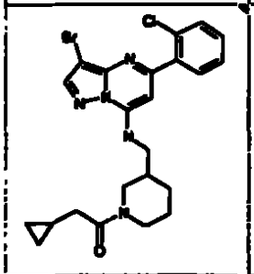
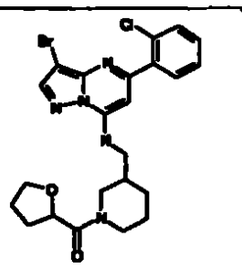
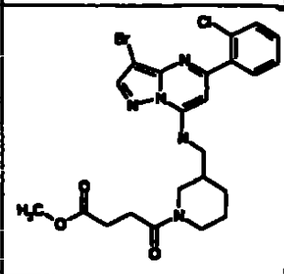
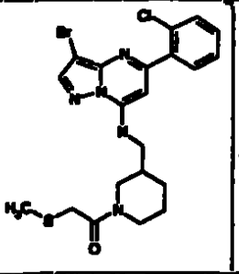
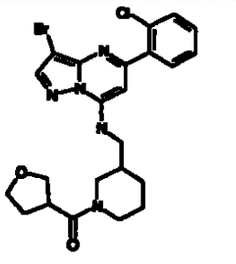
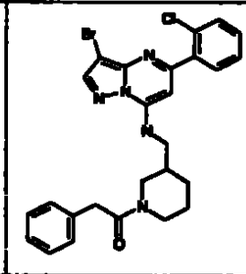
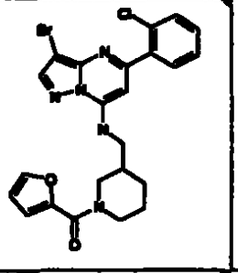
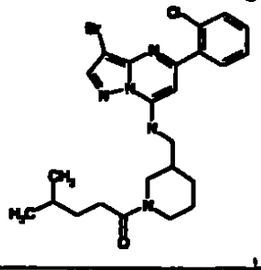
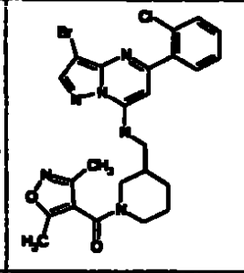
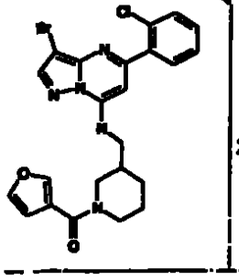
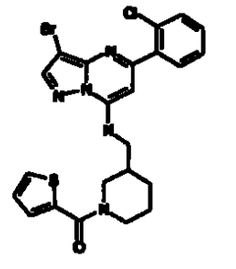
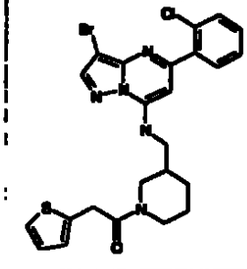
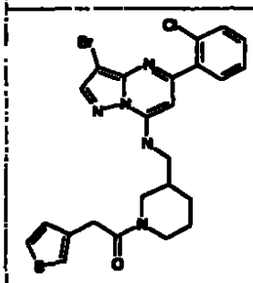
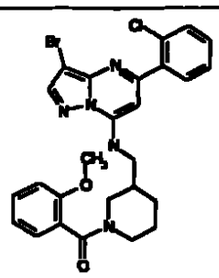
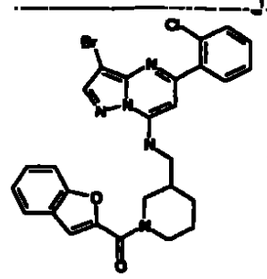
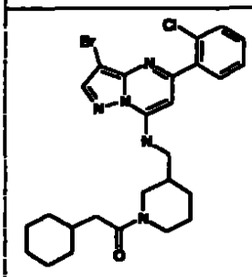
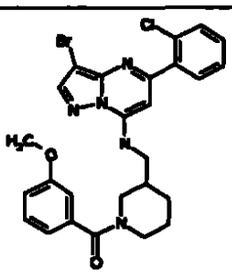
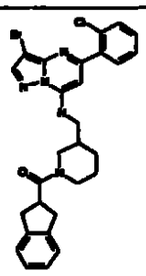
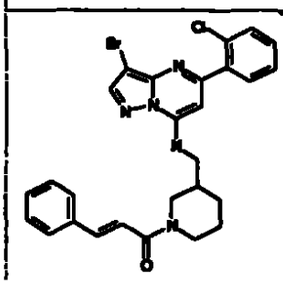
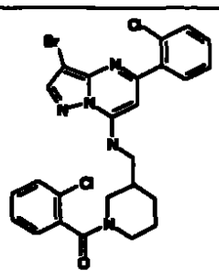
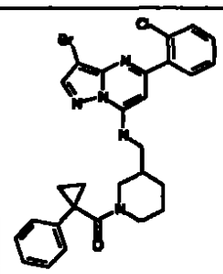
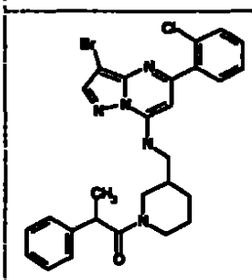
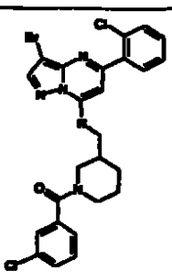
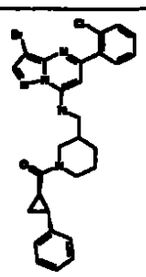
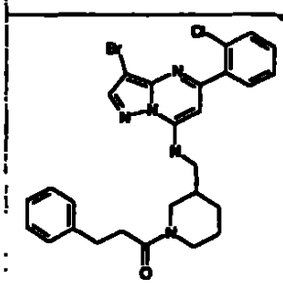
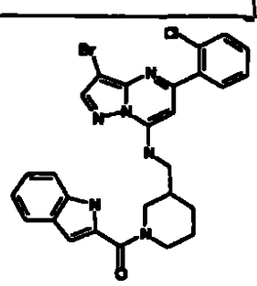
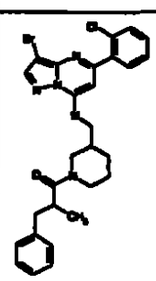
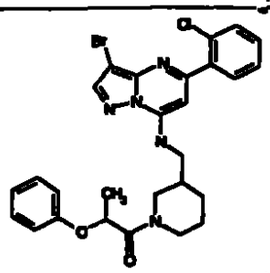
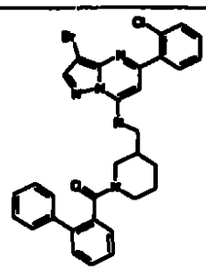
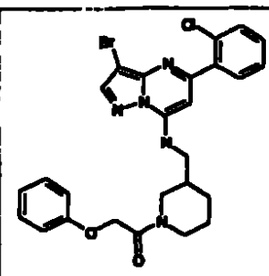
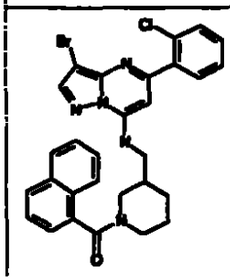
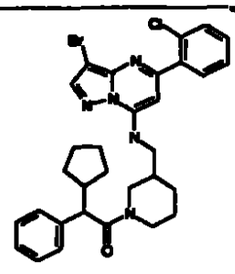
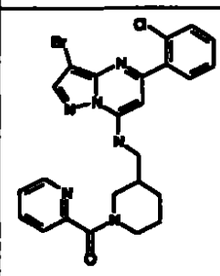
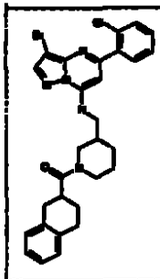
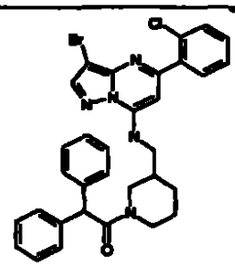
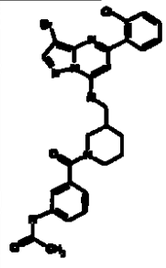
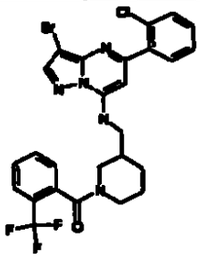
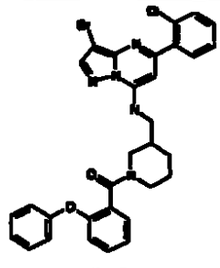
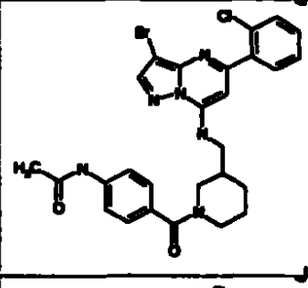
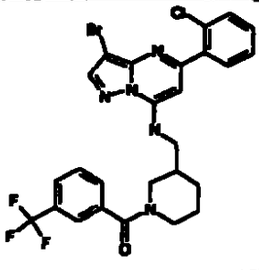
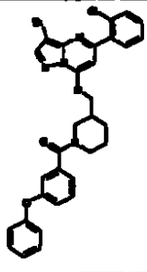
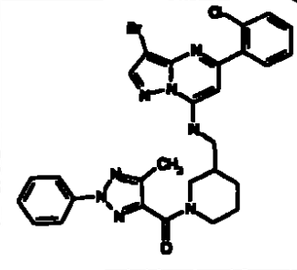
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5476 2. 557.3		1. 5481 2. 581.3		. 5486 2.
	1. 5477 2. 557.3		1. 5482 2. 589.3		1. 5487 2. 891.5
	1. 5478 2. 536.3		1. 5483 2. 511.3		1. 5488 2. 500.3
	1. 5479 2. 567.3		1. 5484 2. 559.3		1. 5489 2. 500.3
	1. 5480 2. 581.3		1. 5485 2. 563.3		1. 5490 2. 501.3

TABLE55

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5501 2. 488.81		1. 5506 2. 516.87		1. 5511 2. 530.87
	1. 5502 2. 502.84		1. 5507 2. 518.84		1. 5512 2. 534.84
	1. 5503 2. 508.87		1. 5508 2. 518.84		1. 5513 2. 538.87
	1. 5504 2. 514.81		1. 5509 2. 518.88		1. 5514 2. 543.85
	1. 5505 2. 514.81		1. 5510 2. 530.87		1. 5515 2. 544.9

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5516 2. 544.9		1. 5521 2. 554.87		1. 5526 2. 584.87
	1. 5517 2. 544.92		1. 5522 2. 554.87		1. 5527 2. 584.91
	1. 5518 2. 550.89		1. 5523 2. 559.29		1. 5528 2. 584.91
	1. 5519 2. 552.9		1. 5524 2. 559.29		1. 5529 2. 584.91
	1. 5520 2. 552.9		1. 5525 2. 563.88		1. 5530 2. 566.93

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5531 2. 568.9		1. 5536 2. 600.95		1. 5541
	1. 5532 2. 574.91		1. 5537 2. 606.99		1. 5542 2. 525.85
	1. 5533 2. 578.94		1. 5538 2. 614.97		1. 5543 2. 581.9
	1. 5534 2. 592.85		1. 5539 2. 616.95		1. 5544 2. 581.9
	1. 5535 2. 592.85		1. 5540 2. 616.95		1. 5545 2. 605.92

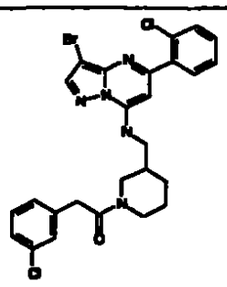
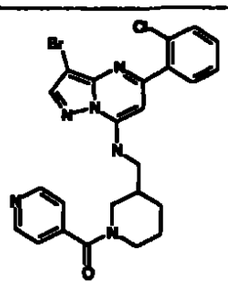
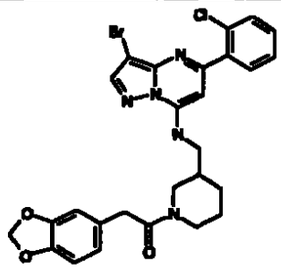
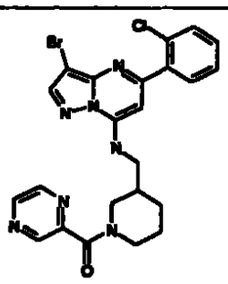
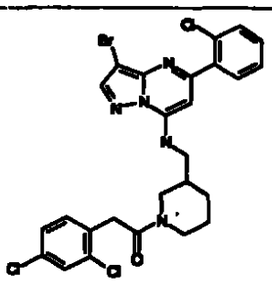
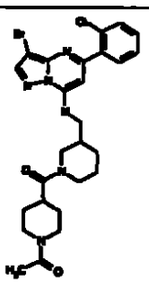
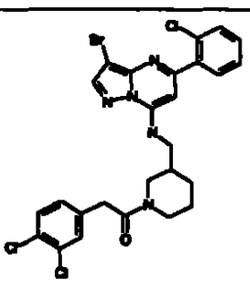
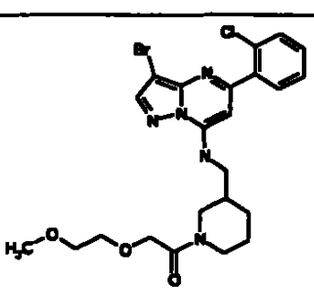
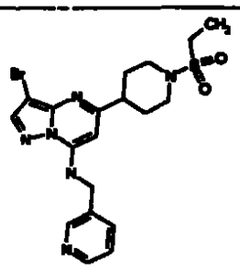
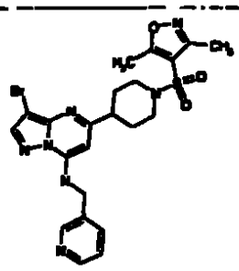
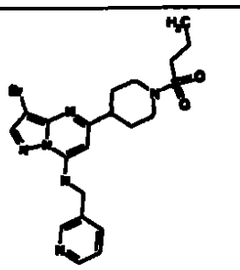
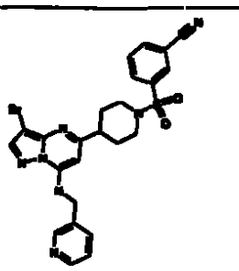
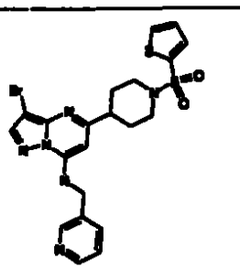
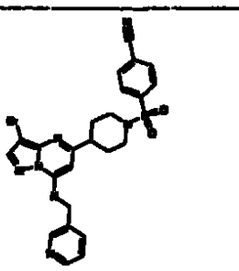
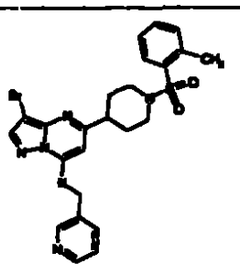
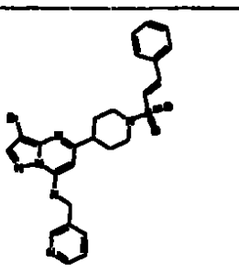
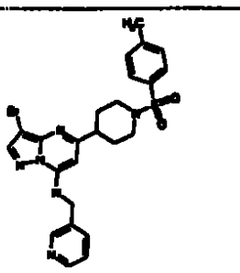
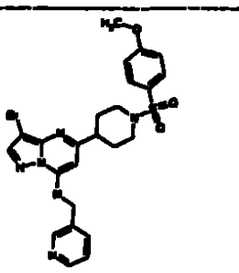
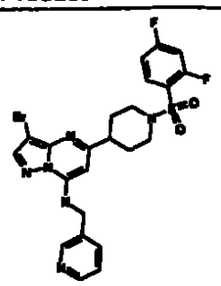
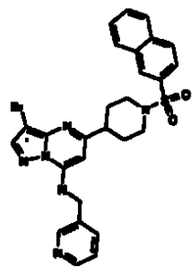
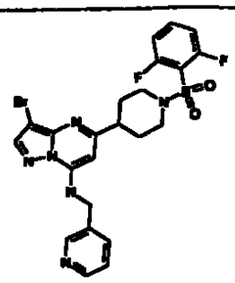
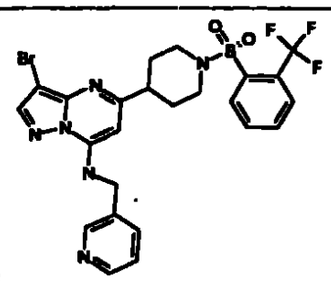
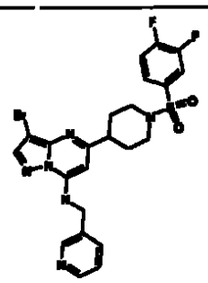
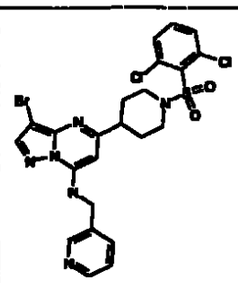
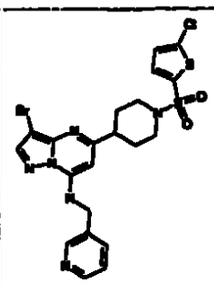
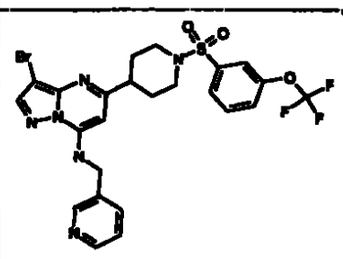
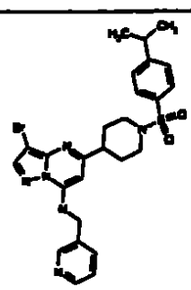
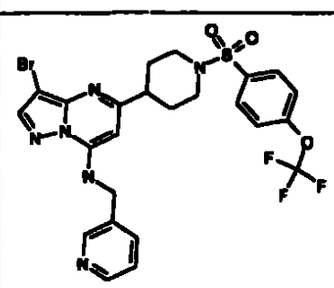
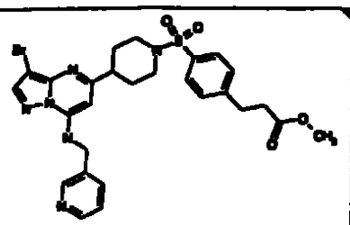
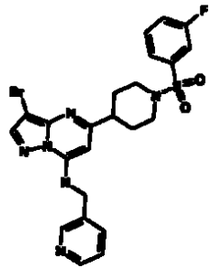
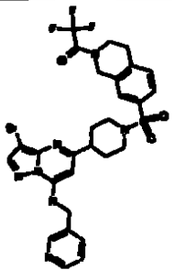
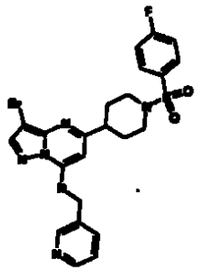
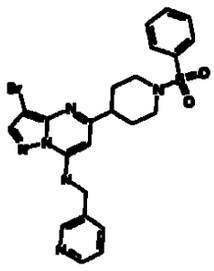
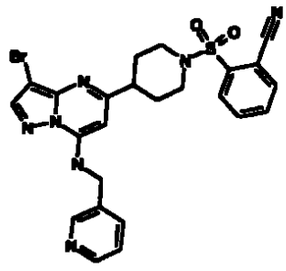
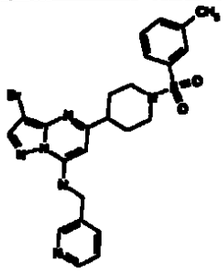
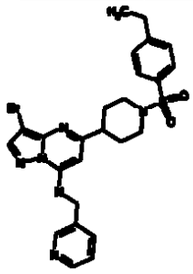
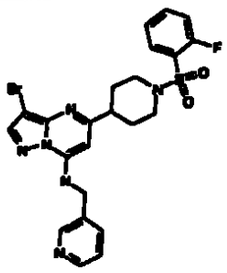
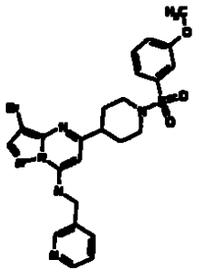
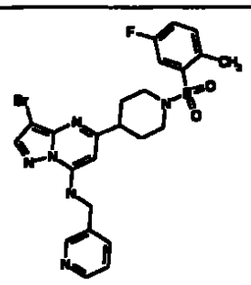
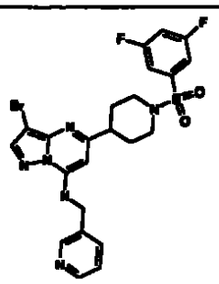
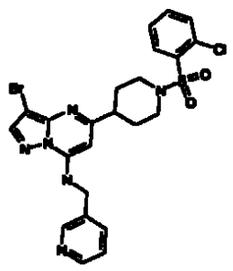
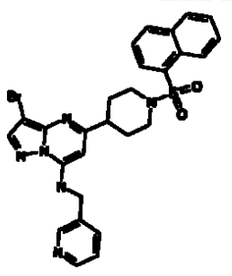
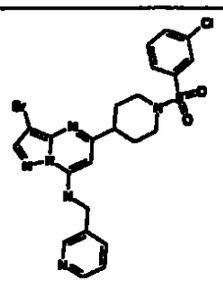
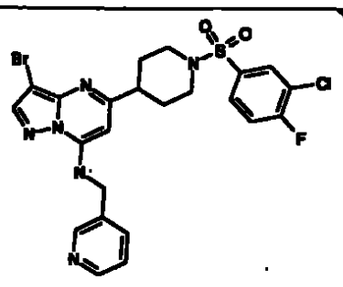
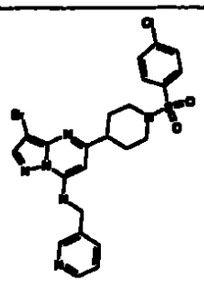
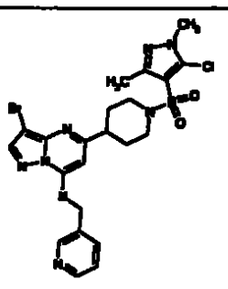
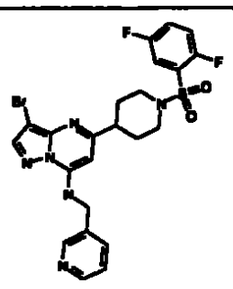
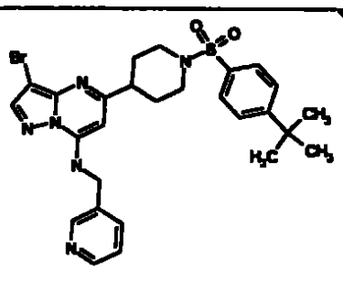
Product	1. Ex. 2. m/z		Product	1. Ex. 2. m/z
	1. 5546 2. 573.32			1. 5551 2. 525.83
	1. 5547 2. 582.88			1. 5552 2. 526.82
	1. 5548 2. 607.76			1. 5553 2. 573.92
	1. 5549 2. 607.76			
	1. 5550 2. 536.86			

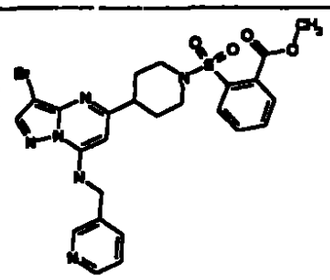
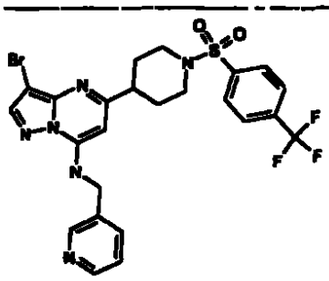
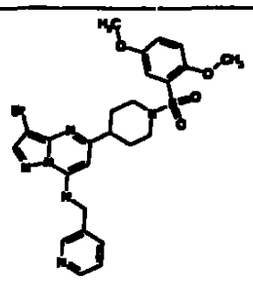
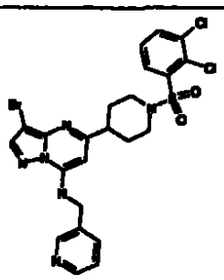
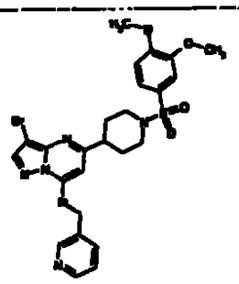
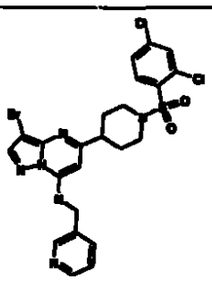
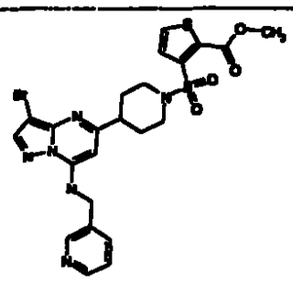
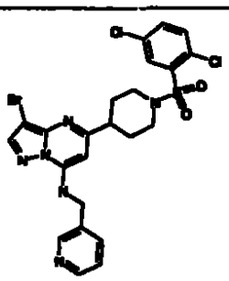
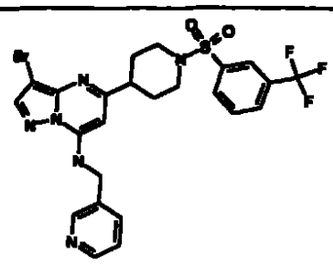
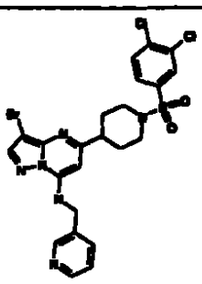
TABLE 56

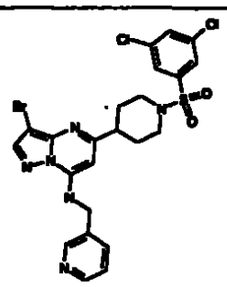
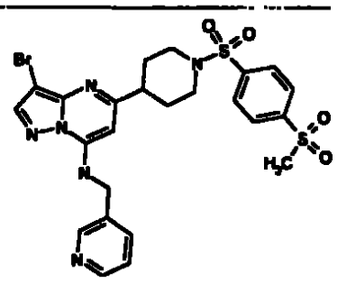
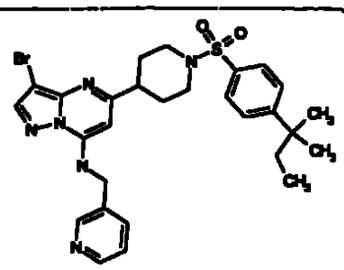
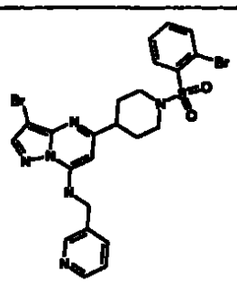
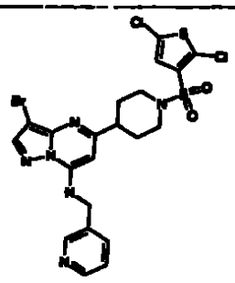
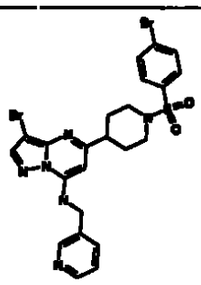
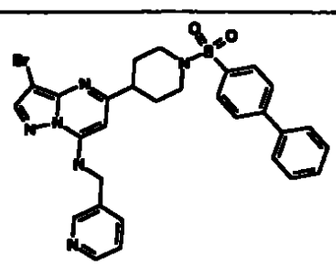
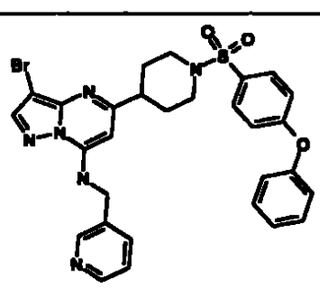
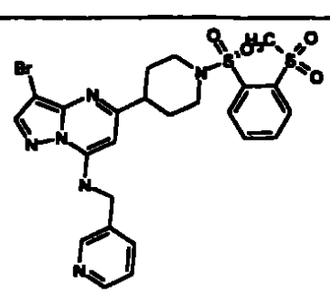
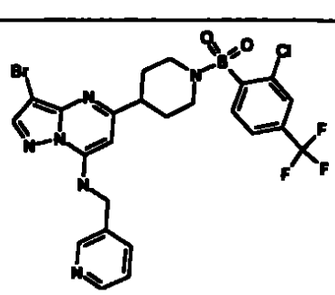
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5601 2. 481.26		1. 5606 2. 548.3
	1. 5602 2. 495.27		1. 5607 2. 554.3
	1. 5603 2. 535.29		1. 5608 2. 554.3
	1. 5604 2. 543.3		1. 5609 2. 555.31
	1. 5605 2. 543.3		1. 5610 2. 559.31

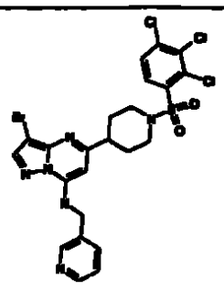
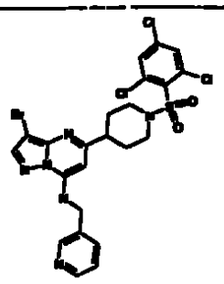
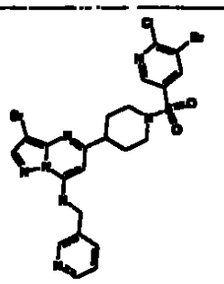
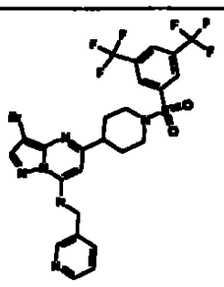
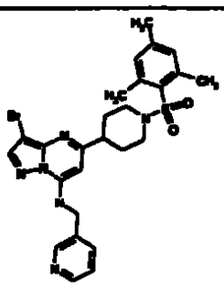
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5611 2. 565.31		1 .5616 2. 579.32
	1. 5612 2. 585.31		1. 5617
	1. 5613 2. 565.31		1. 5618
	1. 5614 2. 569.31		1. 5619
	1. 5615 2. 571.31		1. 5620

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. 555.31
	1. 5625 2. 547.3			1. 5630 2. 559.31

Product	1. Ex. 2. m/z .	Product	1. Ex. 2. m/z
	1. 5631 2. 561.31		1. 5636 2. 565.31
	1. 5632 2. 563.31		1. 5637 2. 579.32
	1. 5633 2. 563.31		1. 5638 2. 581.32
	1. 5634 2. 563.31		1. 5639 2. 581.32
	1. 5635 2. 563.31		1. 5640 2. 585.32

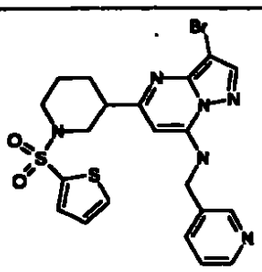
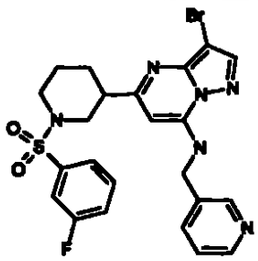
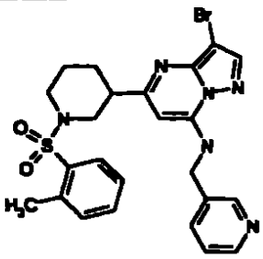
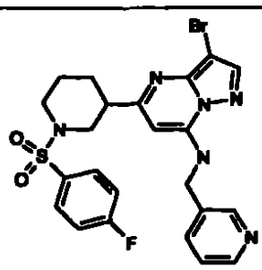
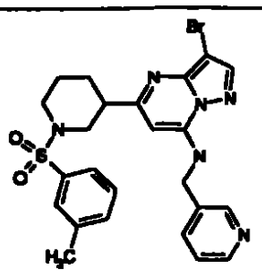
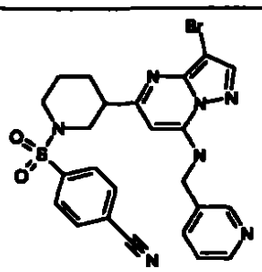
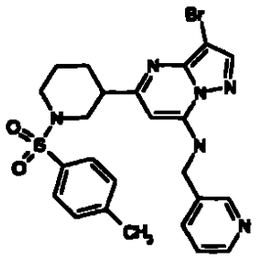
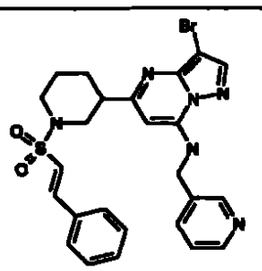
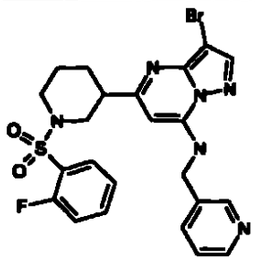
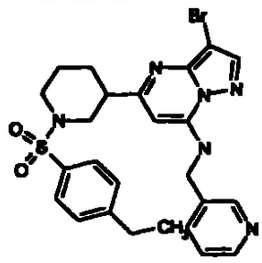
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5641 2. 587.32		1. 5646
	1. 5642 2. 589.32		1. 5647 2. 597.33
	1. 5643 2. 589.32		1. 5648 2. 597.33
	1. 5644 2. 593.33		1. 5649 2. 597.33
	1. 5645 2. 597.33		1. 5650 2. 597.33

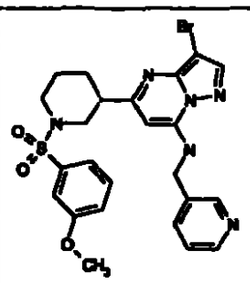
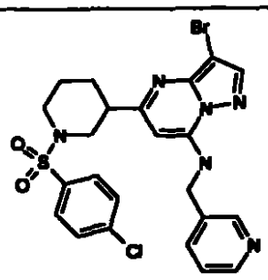
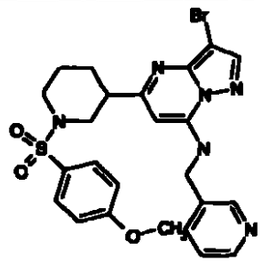
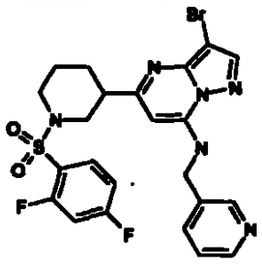
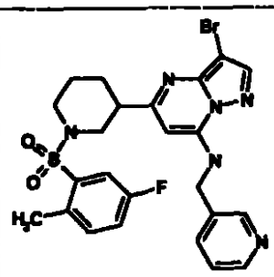
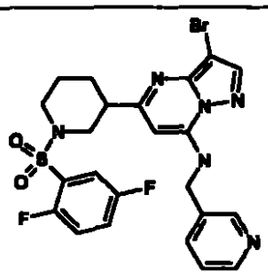
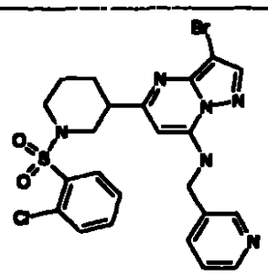
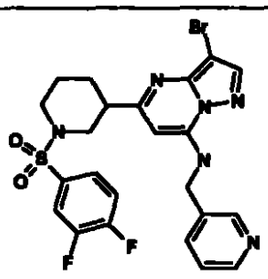
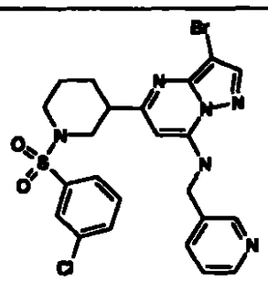
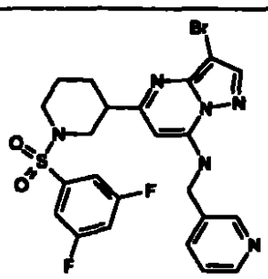
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5651 2. 597.33		1. 5656 2. 607.33
	1. 5652 2. 599.33		1. 5657 2. 607.33
	1. 5653 2. 603.33		1. 5658 2. 607.33
	1. 5654 2. 605.33		1. 5659 2. 621.34
	1. 5655 2. 607.33		1. 5660 2. 631.35

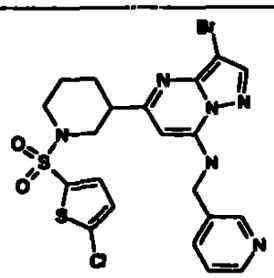
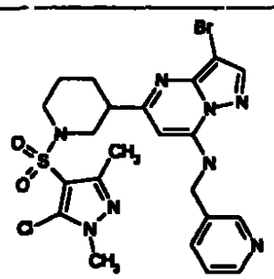
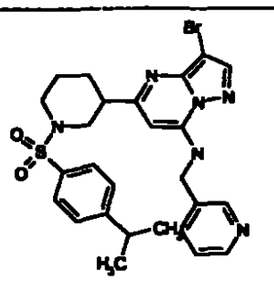
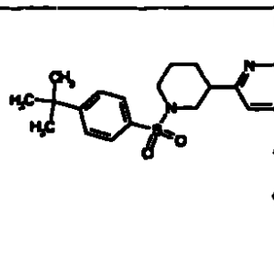
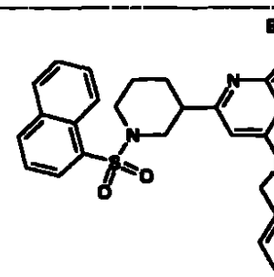
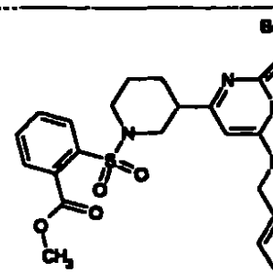
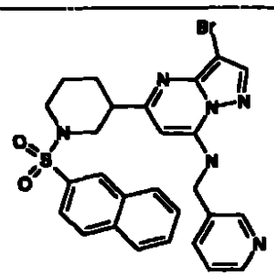
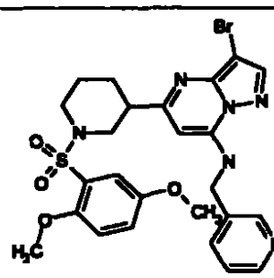
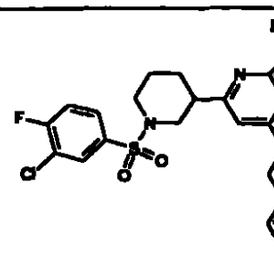
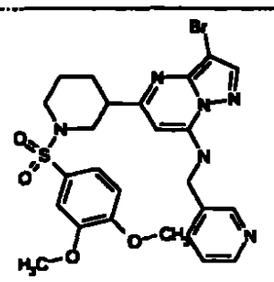
Product	1. Ex. 2. m/z
	1. 5661 2. 631.35
	1. 5662 2. 631.35
	1. 5663 2. 642.35
	1. 5664 2. 665.37
	1. 5665 2. 571.31

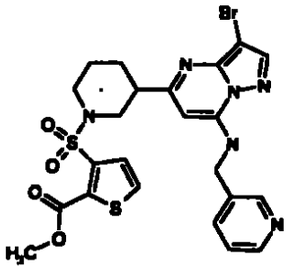
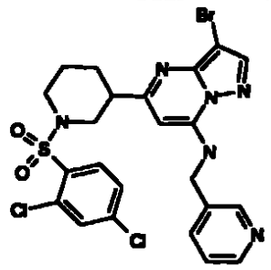
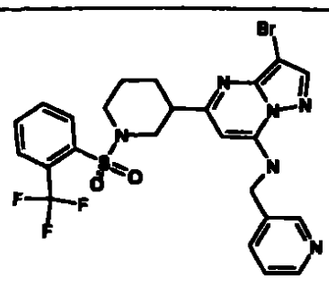
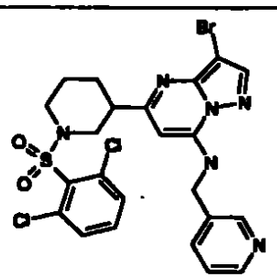
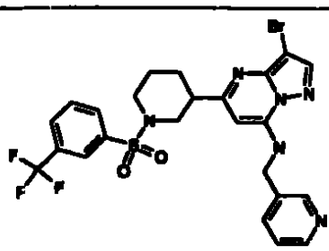
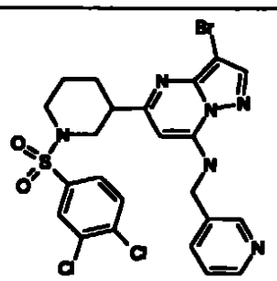
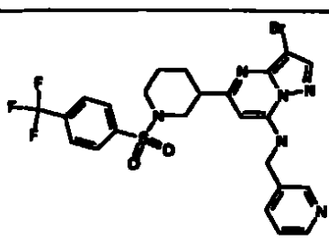
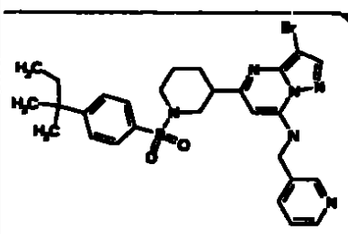
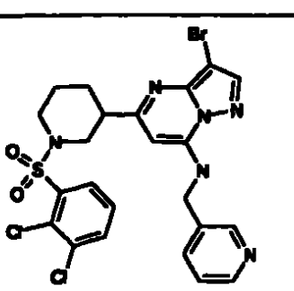
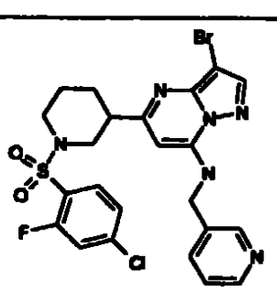
5

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

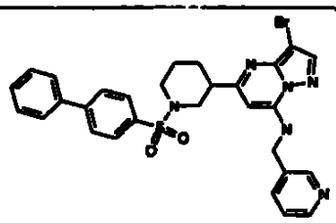
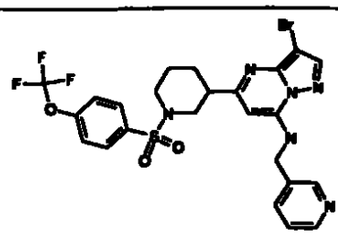
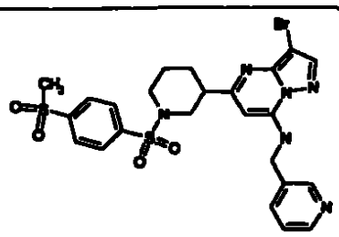
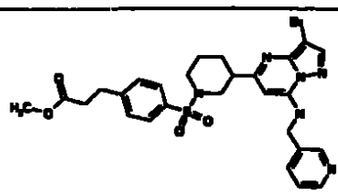
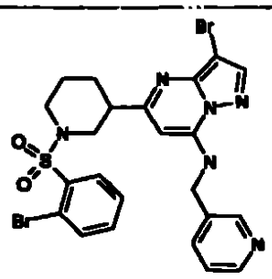
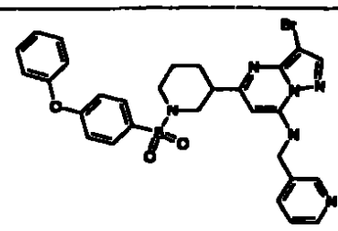
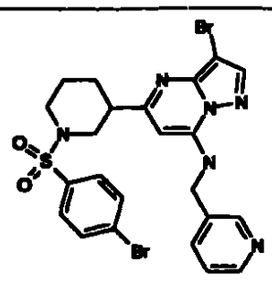
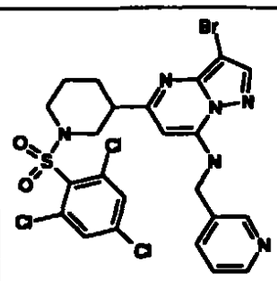
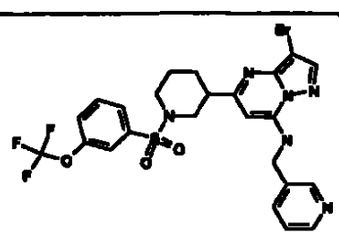
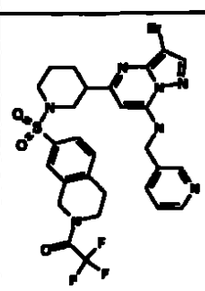
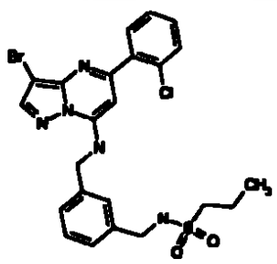
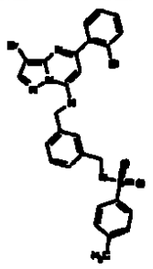
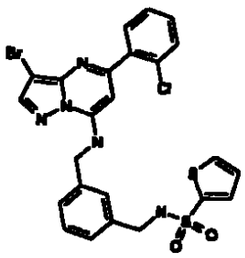
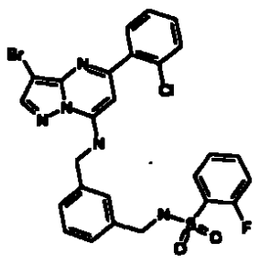
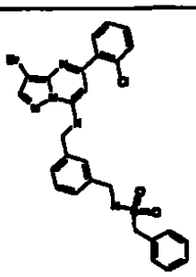
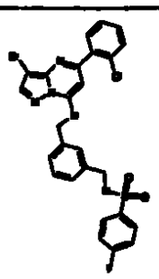
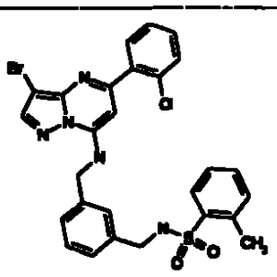
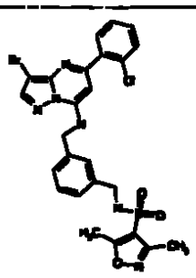
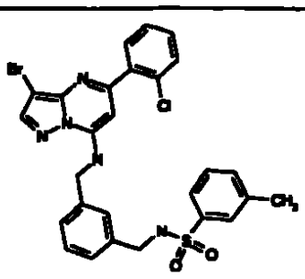
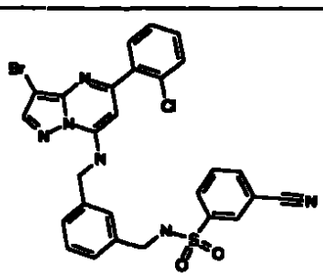
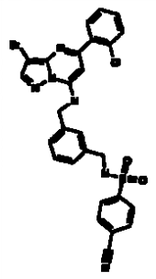
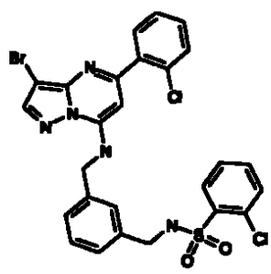
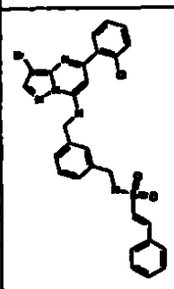
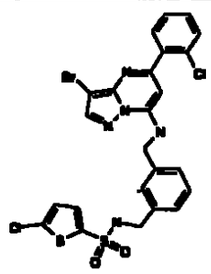
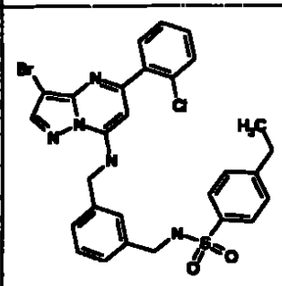
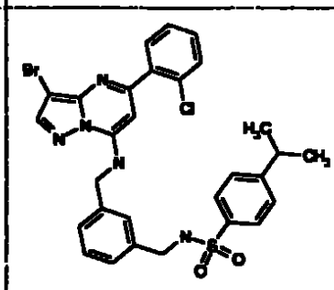
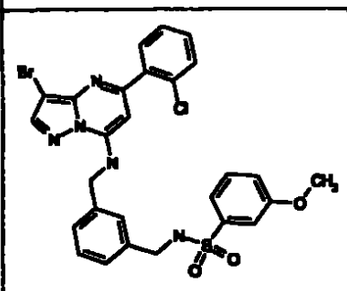
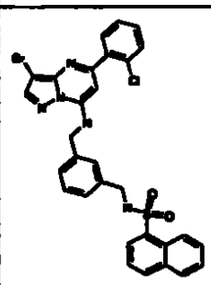
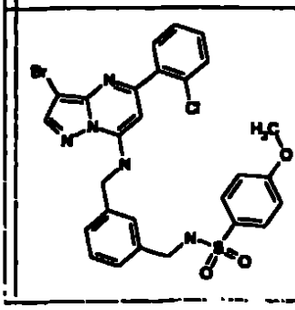
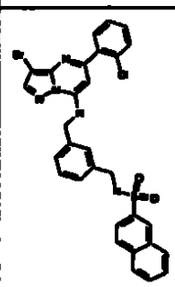
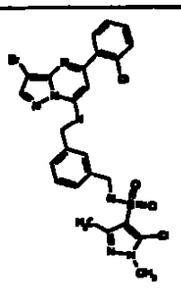
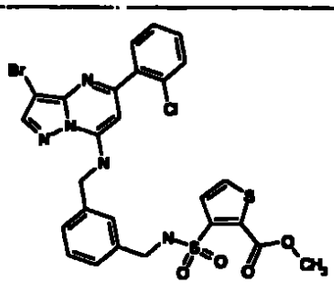
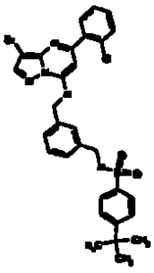
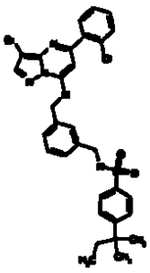
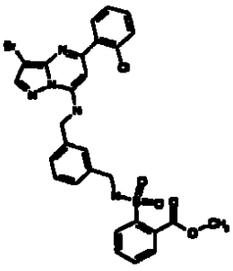
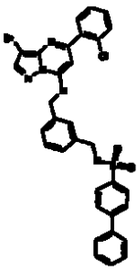
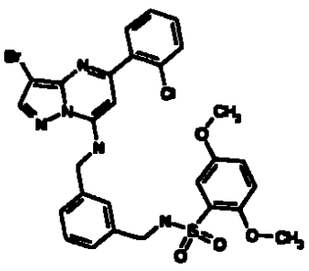
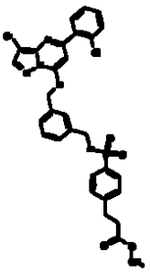
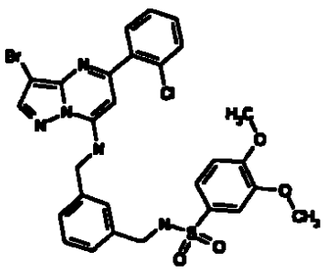
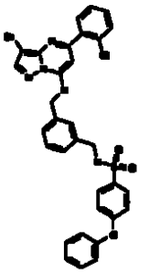
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5741 2. 605.33		1. 5746 2. 613.34
	1. 5742 2. 607.33		1. 5747 2. 615.34
	1. 5743 2. 607.33		1. 5748 2. 621.34
	1. 5744 2. 607.33		1. 5749 2. 631.35
	1. 57454 2. 613.34		1. 5750 2. 680.37

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

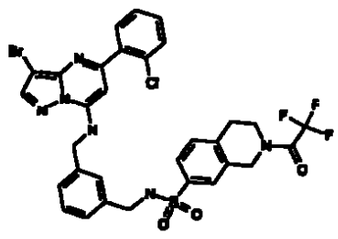
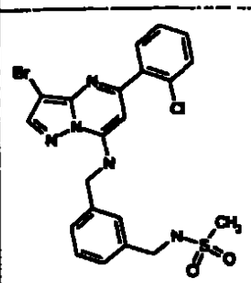
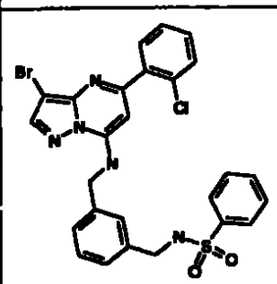
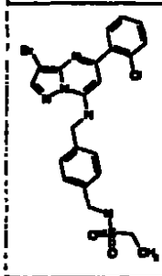
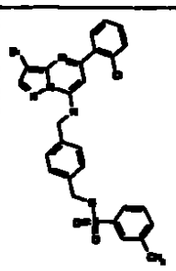
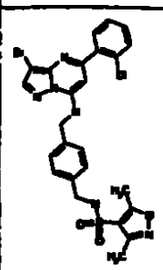
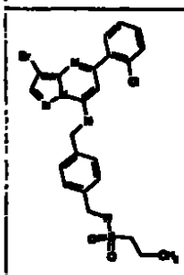
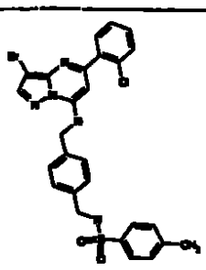
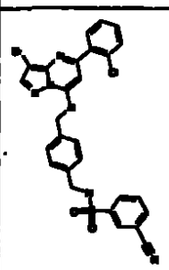
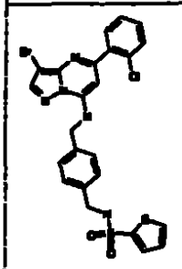
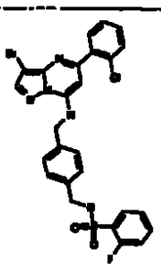
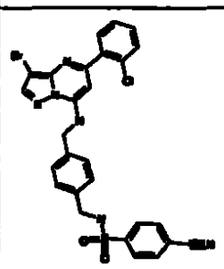
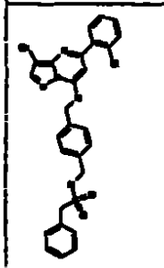
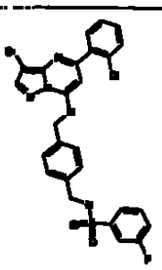
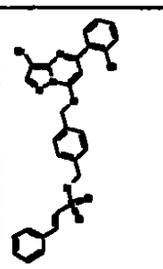
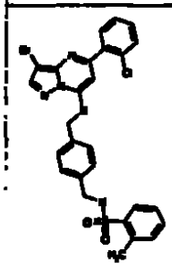
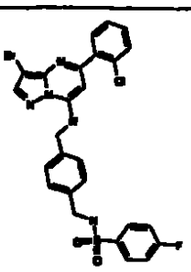
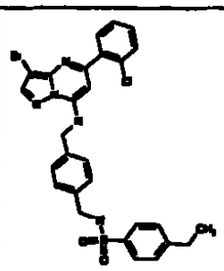
Product	1. Ex. 2. m/z
	1. 5831 2. 735.4
	1. 5832 2. 522.29
	1. 5833 2. 584.32

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

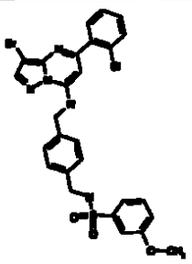
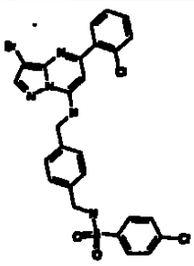
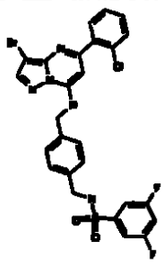
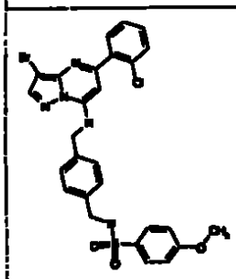
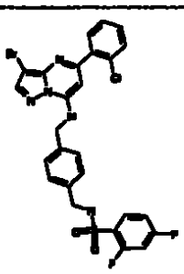
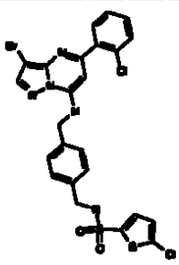
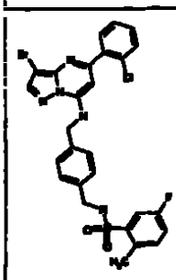
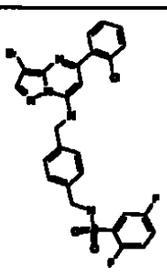
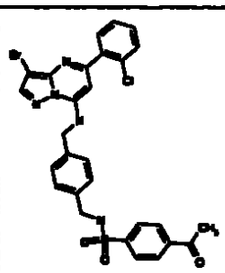
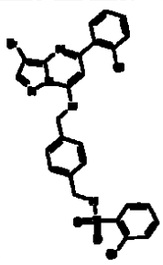
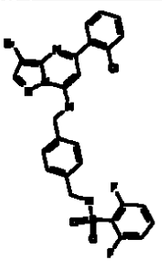
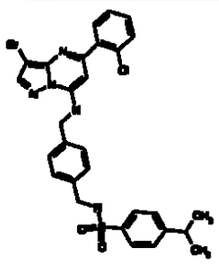
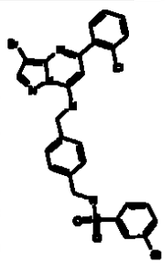
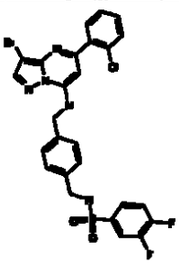
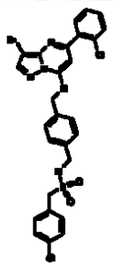
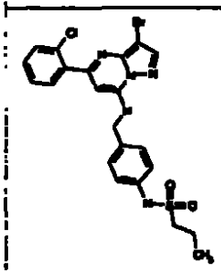
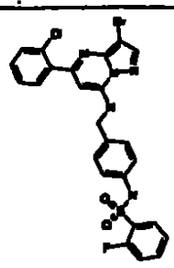
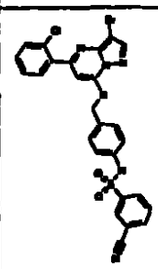
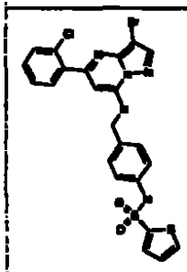
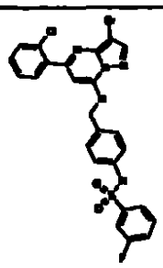
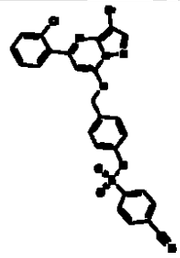
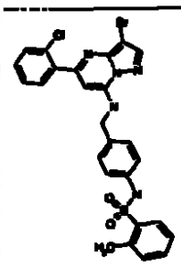
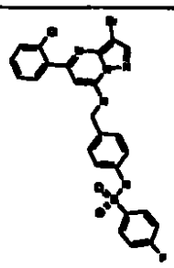
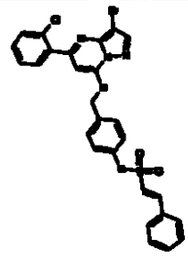
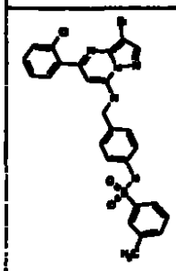
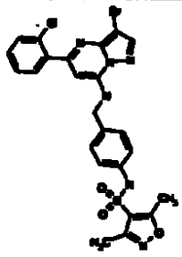
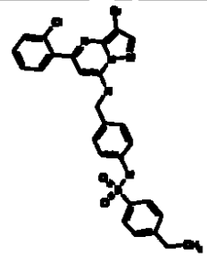
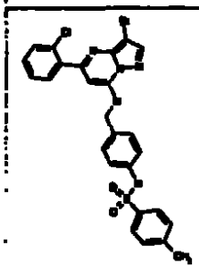
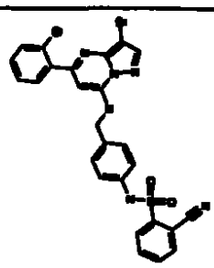
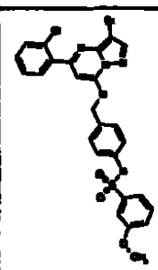
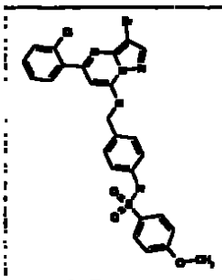
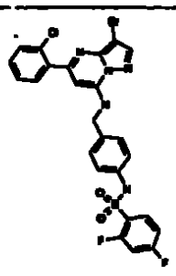
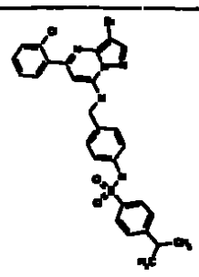
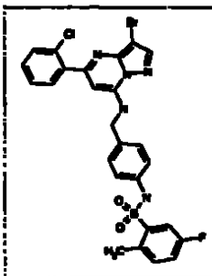
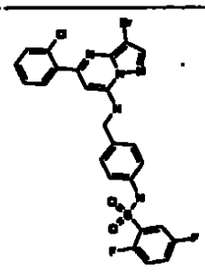
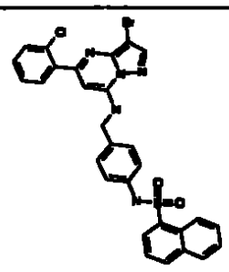
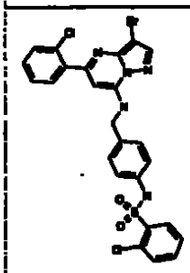
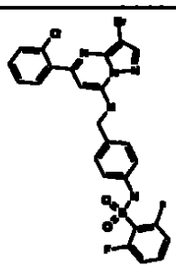
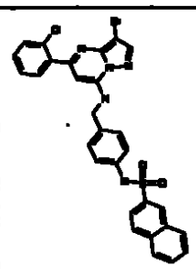
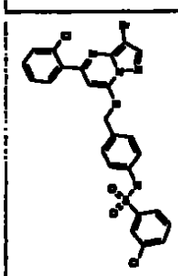
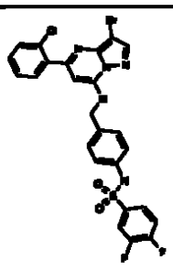
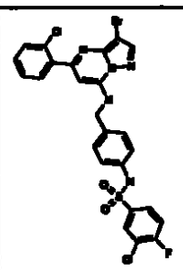
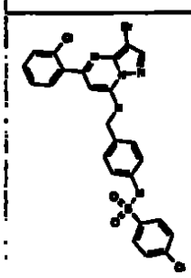
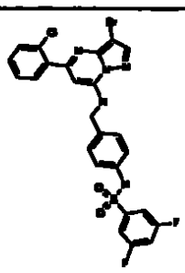
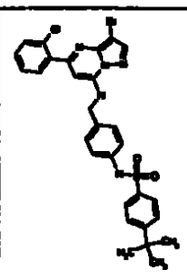
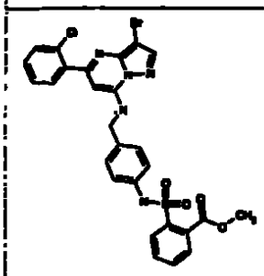
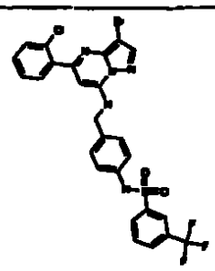
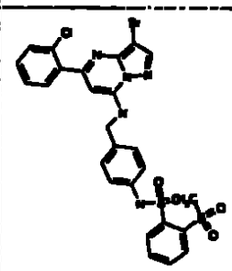
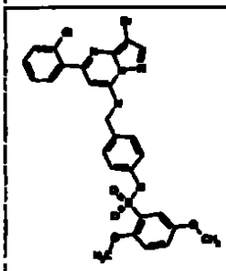
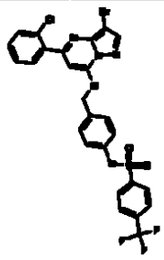
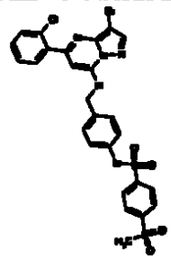
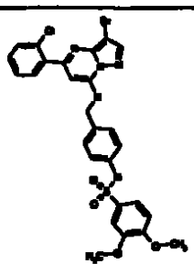
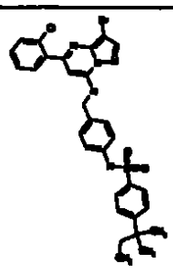
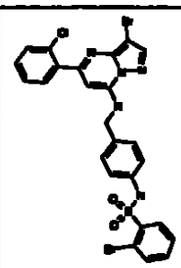
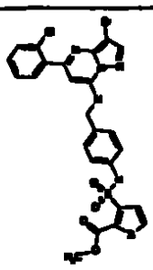
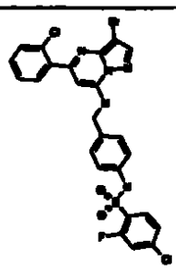
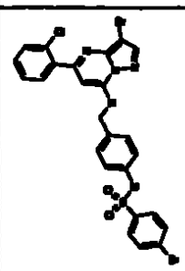
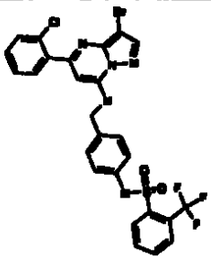
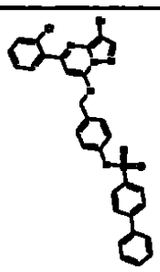
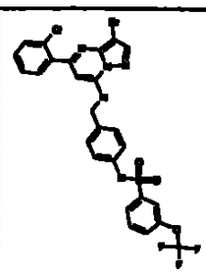
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 5916 2. 614.34		1. 5921 2. 618.34		1. 5926 2. 620.34
	1. 5917 2. 614.34		1. 5922 2. 620.34		1. 5927 2. 624.34
	1. 5918 2. 616.34		1. 5923 2. 620.34		1. 5928 2. 626.34
	1. 5919 2. 618.34		1. 5924 2. 620.34		1. 5929 2. 626.34
	1. 5920 2. 618.34		1. 5925 2. 620.34		1. 5930 2. 632.35

TABLE60

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6001 2. 536.29		1. 6006 2. 588.32		1. 6011 2. 595.33
	1. 6002 2. 576.32		1. 6007 2. 588.32		1. 6012 2. 595.33
	1. 6003 2. 584.32		1. 6008 2. 588.32		1. 6013 2. 596.33
	1. 6004 2. 584.32		1. 6009 2. 589.32		1. 6014 2. 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. 636.35		1. 60425 2. 648.36
	1. 6033 2. 630.35		1. 6038 2. 638.35		1. 6043 2. 648.36
	1. 6034 2. 634.35		1. 6039 2. 622.34		1. 6044 2. 648.36
	1. 6035 2. 638.35		1. 6040 2. 646.36		1. 6045 2. 654.36

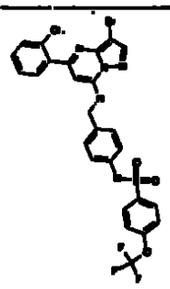
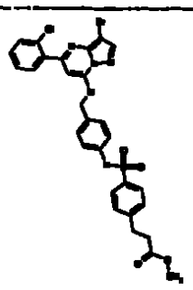
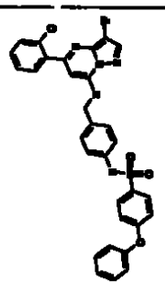
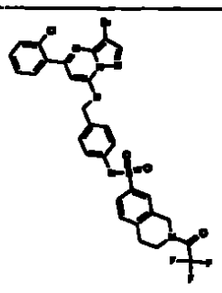
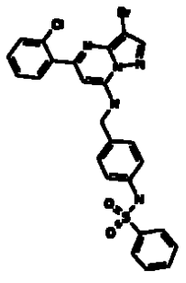
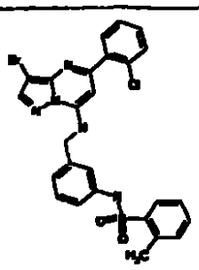
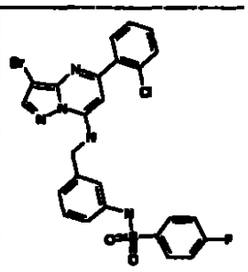
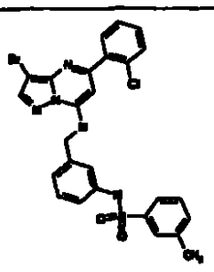
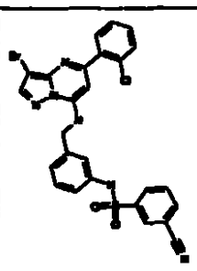
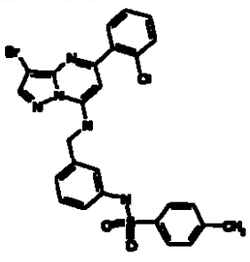
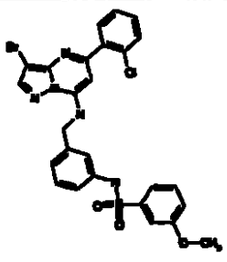
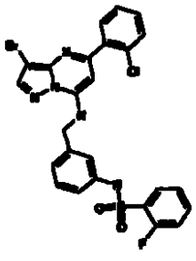
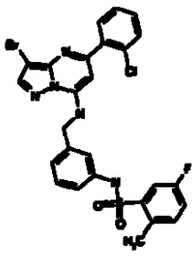
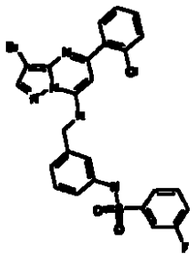
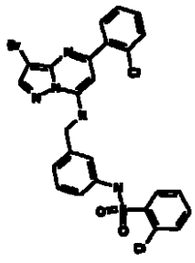
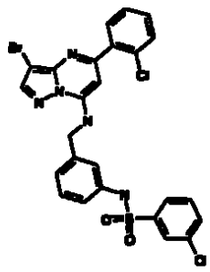
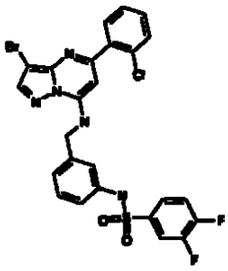
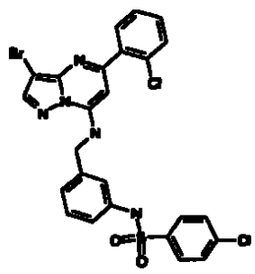
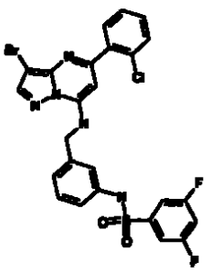
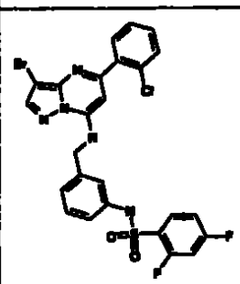
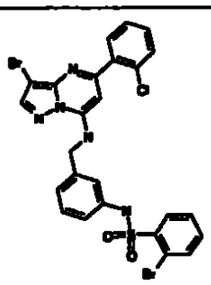
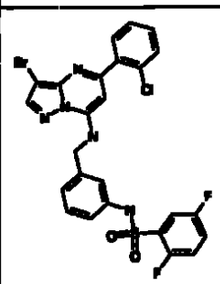
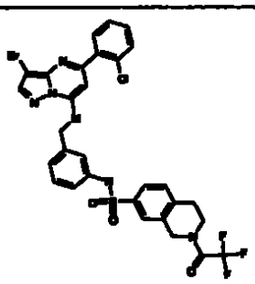
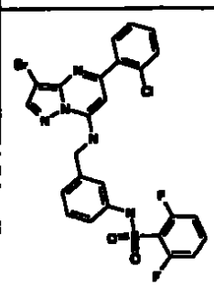
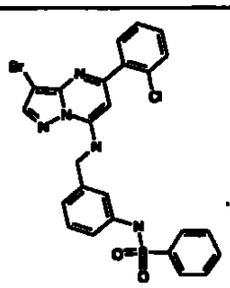
Product	1. Ex. 2. m/z
	1. 6046 2. 654.36
	1. 6047 2. 656.36
	1. 6048 2. 662.36
	1. 6049 2. 721.4
	1. 6050 2. 570.31

TABLE 61

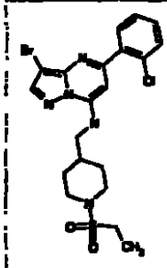
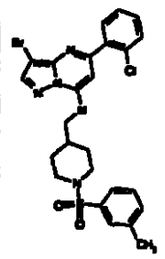
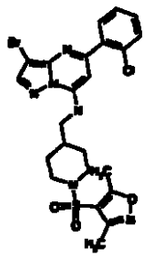
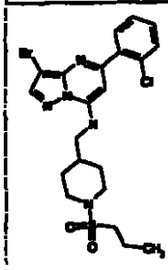
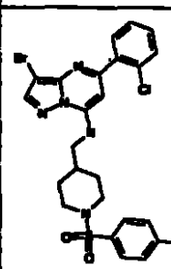
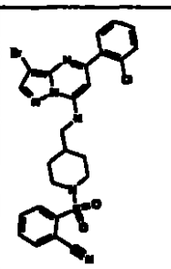
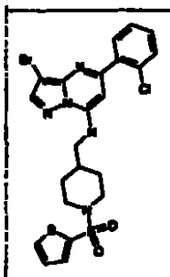
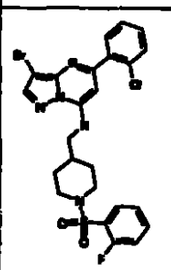
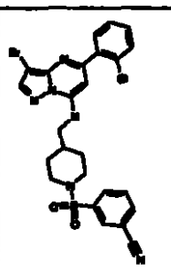
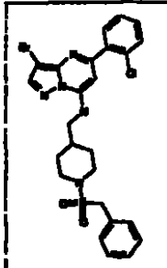
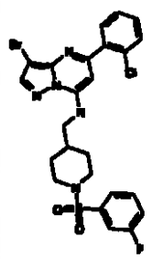
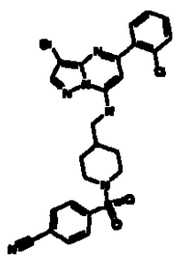
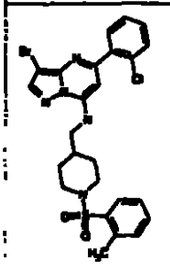
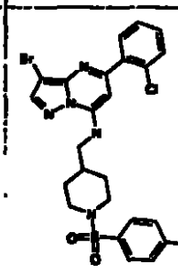
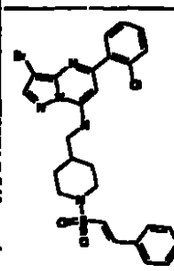
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6101 2. 584.32		1. 6106 2. 588.32
	1. 6102 2. 584.32		1. 6107 2. 595.33
	1. 6103 2. 584.32		1. 6108 2. 600.33
	1. 6104 2. 588.32		1. 6109 2. 602.33
	1. 6105 2. 588.32		1. 6110 2. 604.33

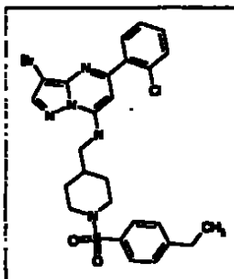
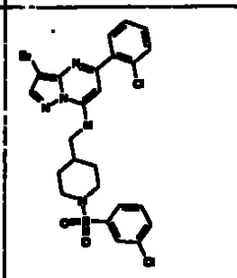
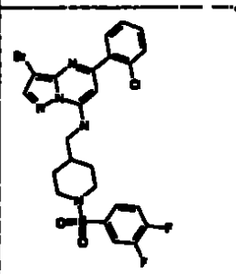
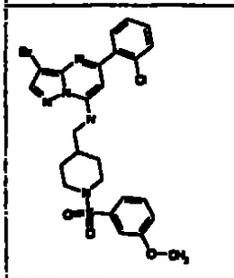
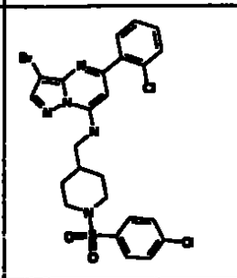
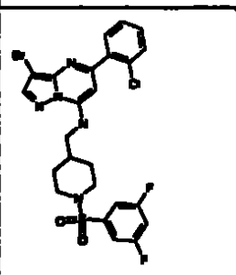
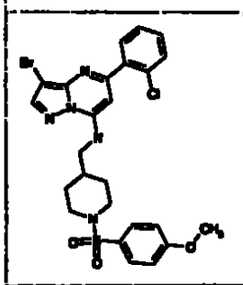
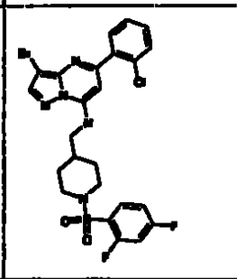
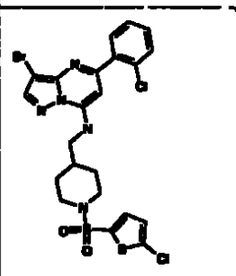
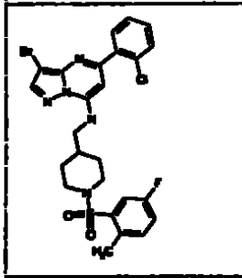
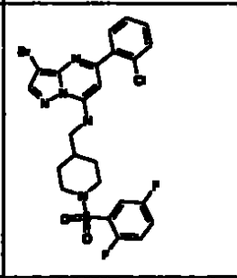
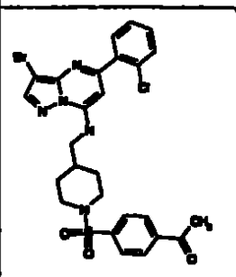
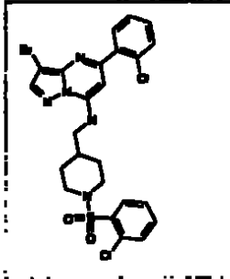
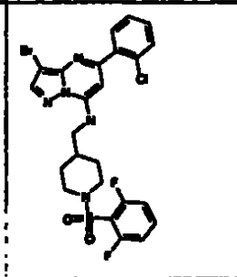
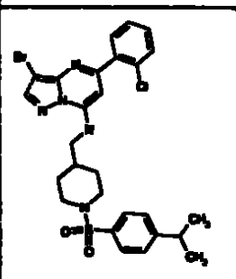
5

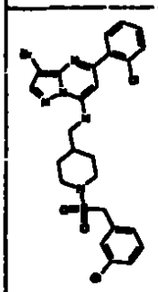
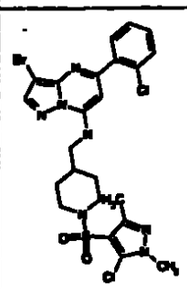
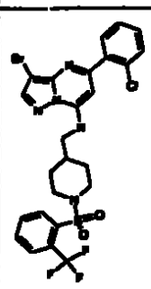
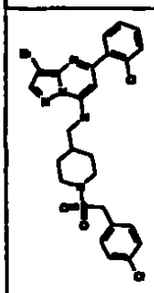
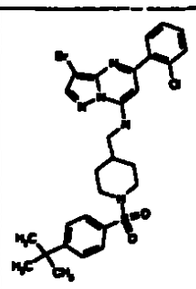
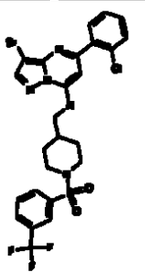
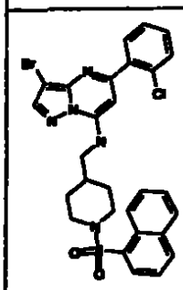
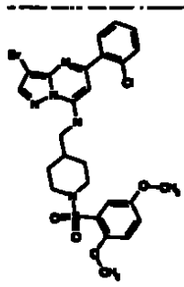
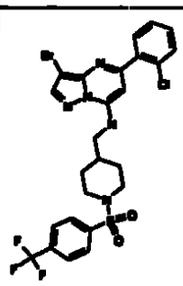
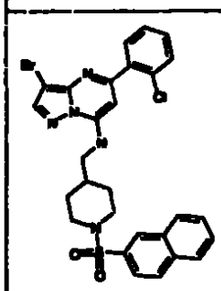
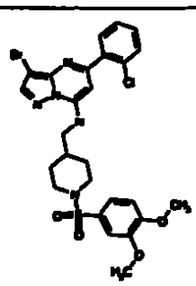
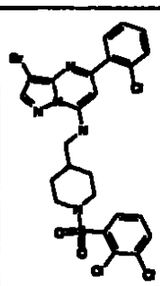
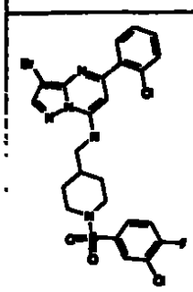
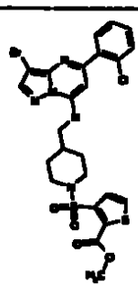
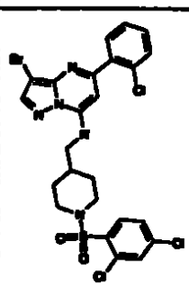
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6111 2. 604.33		1. 6116 2. 606.33
	1. 6112 2. 604.33		1. 6117 2. 606.33
	1. 6113 2. 606.33		1. 6118 2. 648.36
	1. 6114 2. 606.33		1. 6119 2. 721.4
	1. 6115 2. 606.33		1. 6120 2. 570.31

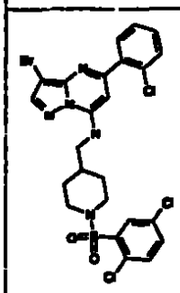
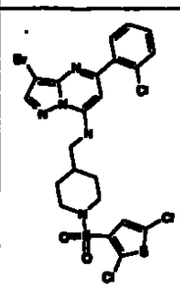
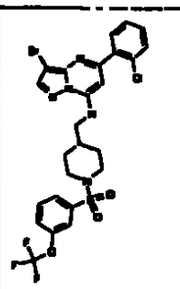
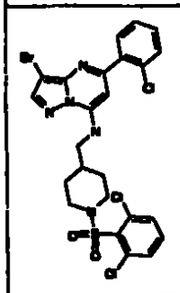
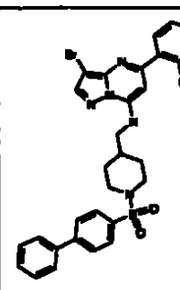
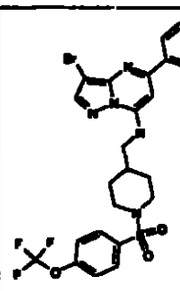
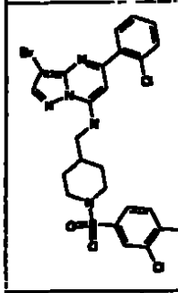
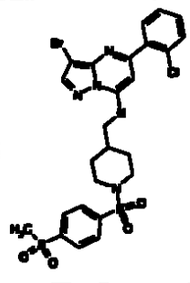
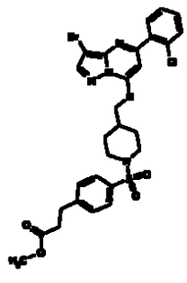
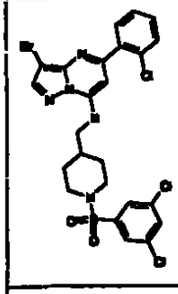
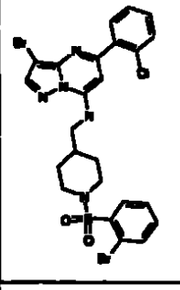
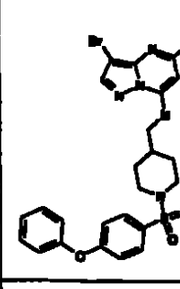
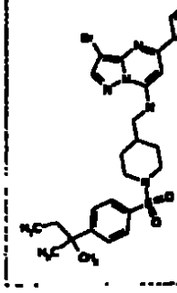
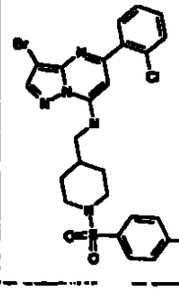
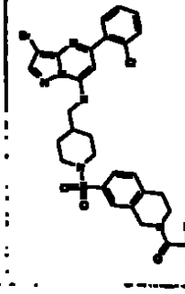
5

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. 598.33
	1. 6217 2. 592.33		1. 6222 2. 596.33		1. 6227 2. 596.33
	1. 6218 2. 592.33		1. 6223 2. 598.33		1. 6228 2. 602.33
	1. 6219 2. 592.33		1. 6224 2. 596.33		1. 6229 2. 604.33
	1. 6220 2. 594.33		1. 6225 2. 598.33		1. 6230 2. 604.33

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6231 2. 610.34		1. 6236 2. 614.34		1. 6241 2. 630.35
	1. 6232 2. 610.34		1. 6237 2. 618.34		1. 6242 2.
	1. 6233 2. 612.34		1. 6238 2. 622.34		1. 6243 2. 630.35
	1. 6234 2. 612.34		1. 6239 2. 622.34		1. 6244 2. 630.35
	1. 6235 2. 614.34		1. 6240 2. 626.34		1. 6245 2. 630.35

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1 .6246 2. 630.35		1 .6251 2. 636.35		1. 6256 2. 646.36
	1. 6247 2. 630.35		1.0 6252 2. 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

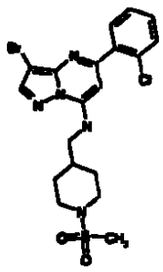
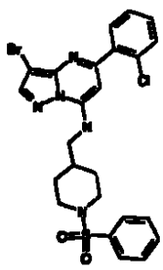
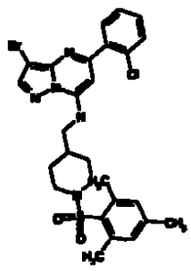
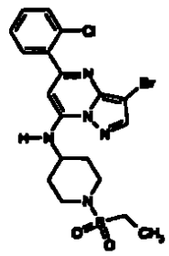
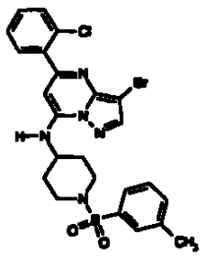
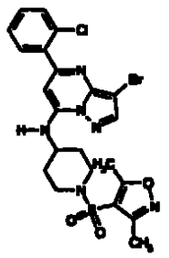
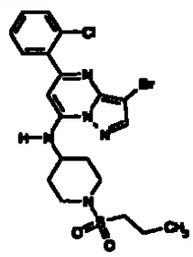
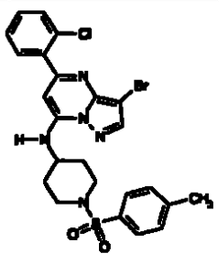
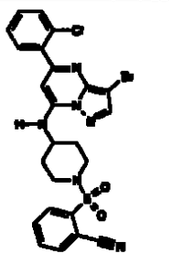
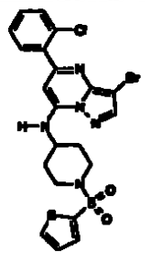
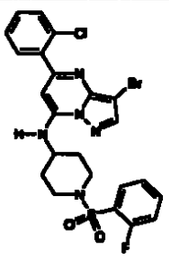
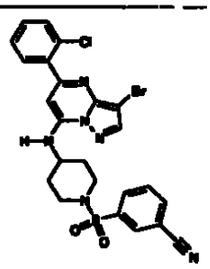
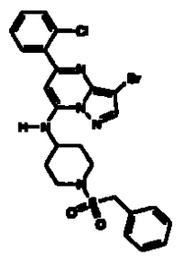
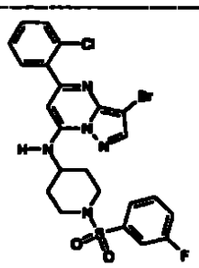
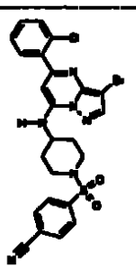
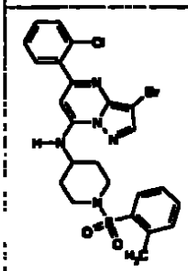
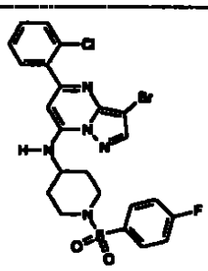
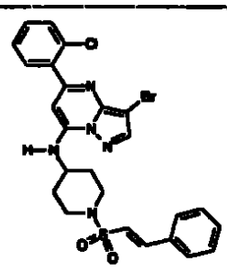
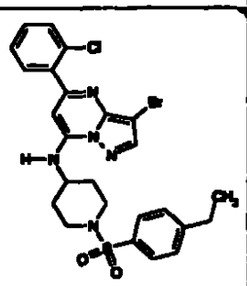
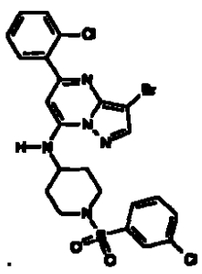
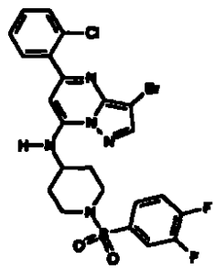
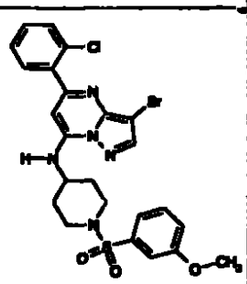
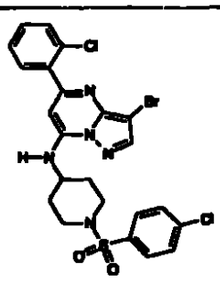
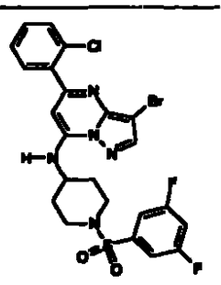
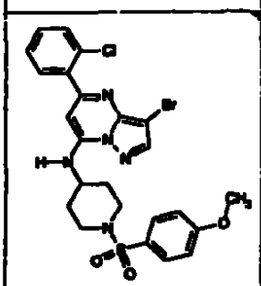
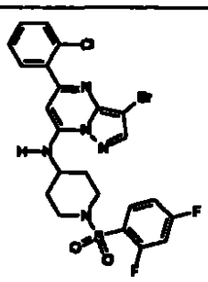
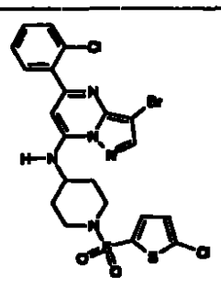
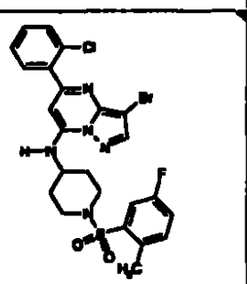
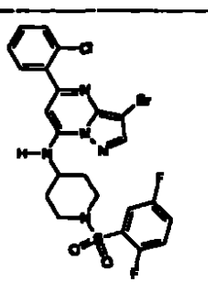
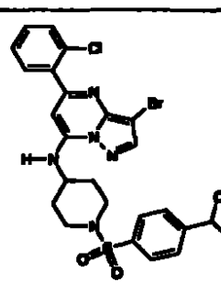
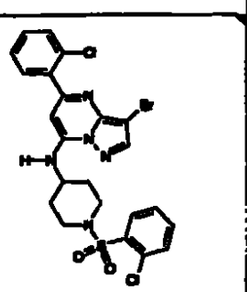
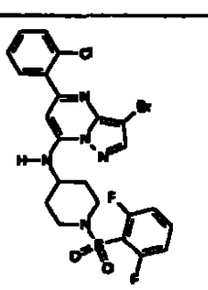
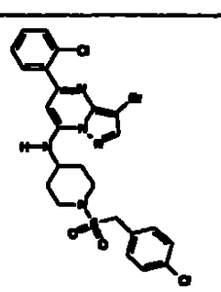
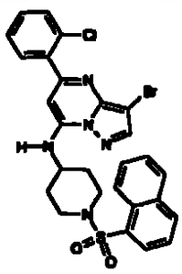
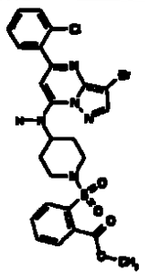
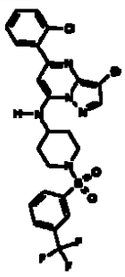
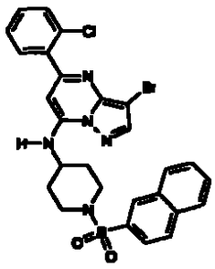
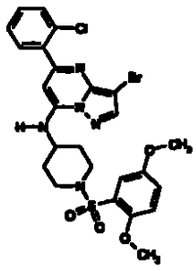
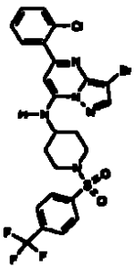
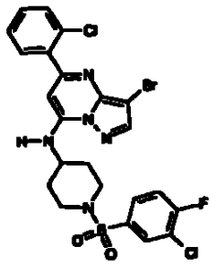
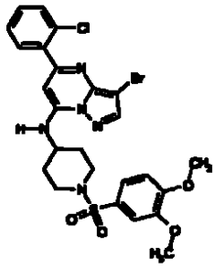
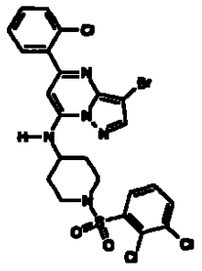
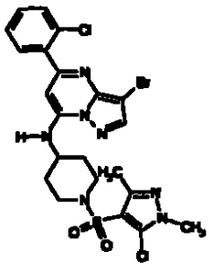
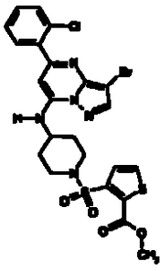
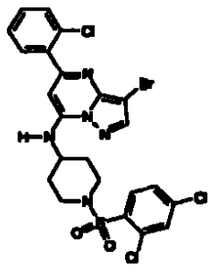
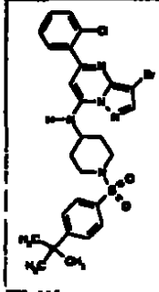
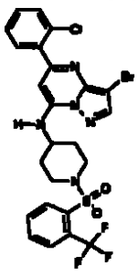
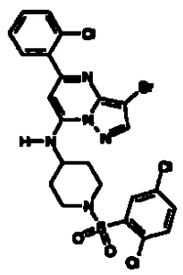
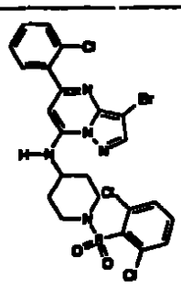
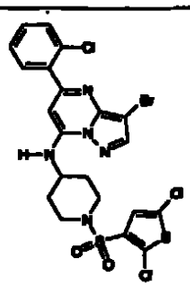
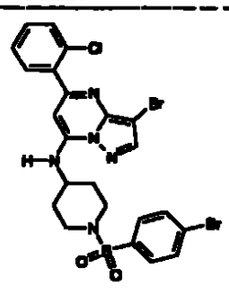
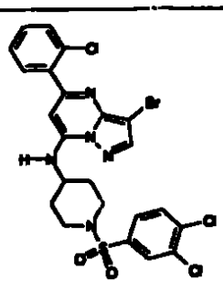
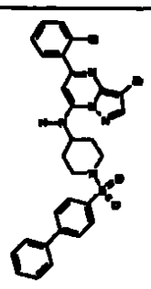
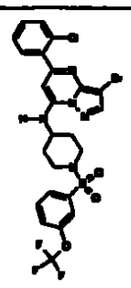
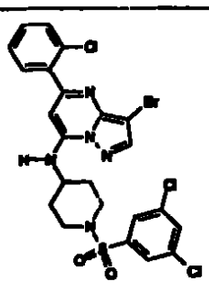
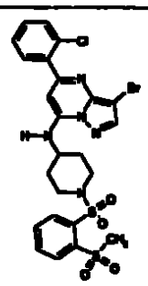
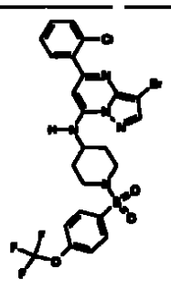
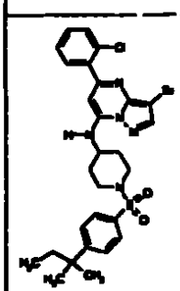
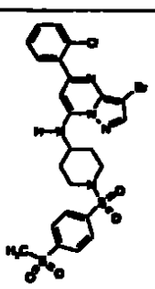
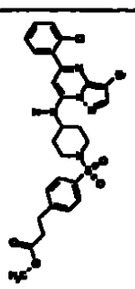
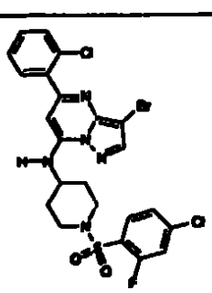
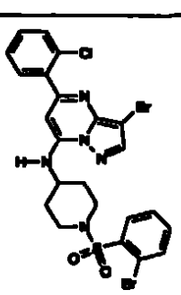
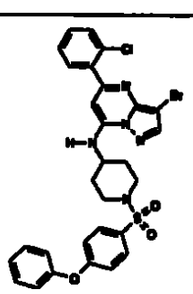
Product	1. Ex. 2. m/z
	1. 6261 2. 500.27
	1. 6262 2. 562.31
	1. 6263 2. 604.33

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. 576.32		1. 6322 2. 582.32		1. 6327 2. 584.32
	1. 6318 2. 576.32		1. 6323 2. 584.32		1. 6328 2. 588.32
	1. 6319 2. 580.32		1. 6324 2. 582.32		1. 6329 2. 590.32
	1. 6320 2. 582.32		1. 6325 2. 584.32		1. 6330 2. 598.33

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6331 2. 598.33		1. 6336 2. 606.33		1. 6341 2. 616.34
	1. 6332 2. 598.33		1. 6337 2. 608.33		1. 6342 2. 616.34
	1. 6333 2. 600.33		1. 6338 2. 608.33		1. 6343 2. 616.34
	1. 6334 2. 600.33		1. 6339 2. 612.34		1.6344 2. 616.34
	1. 6335 2. 604.33		1. 6340 2. 616.34		1. 6345 2. 616.34

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6346 2. 616.34		1. 6351 2. 622.34		1. 6356 2. 626.34
	1. 6347 2. 616.34		1. 6352 2. 624.34		1. 6357 2. 632.35
	1. 6348 2. 616.34		1. 6353 2. 626.34		1. 6358 2. 632.35
	1. 6349 2. 618.34		1. 6354 2. 626.34		1. 6359 2. 634.35
	1. 6350 2. 600.33		1. 6355 2. 626.34		1. 6360 2. 640.35

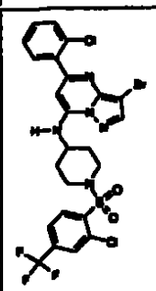
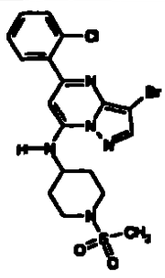
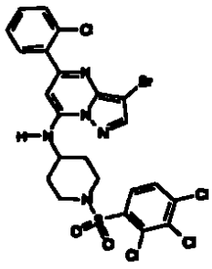
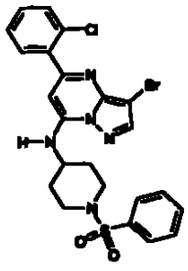
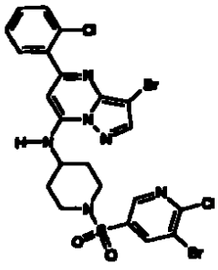
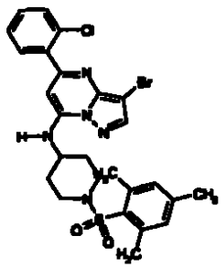
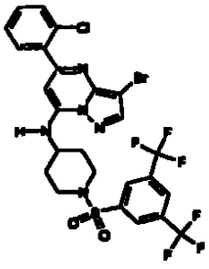
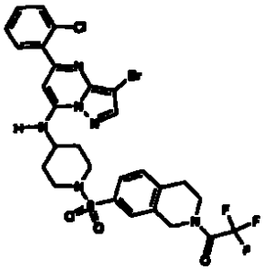
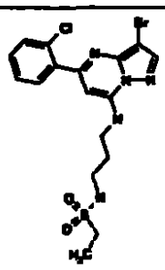
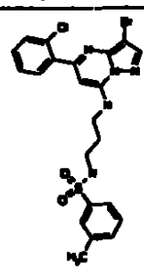
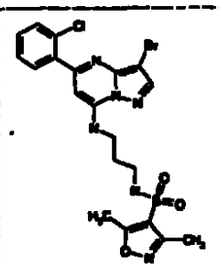
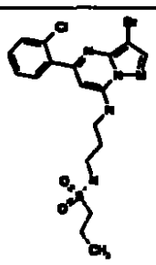
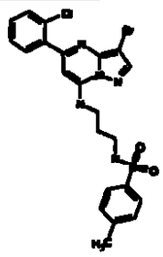
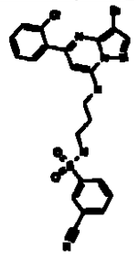
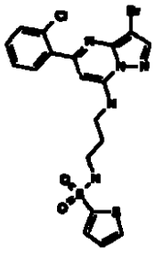
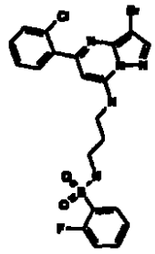
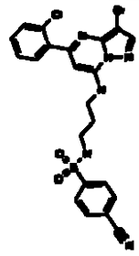
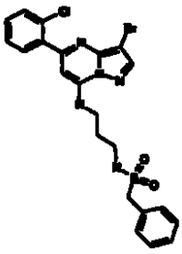
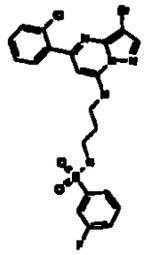
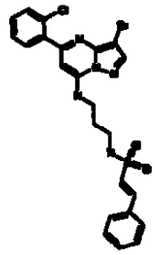
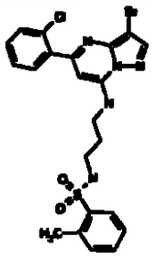
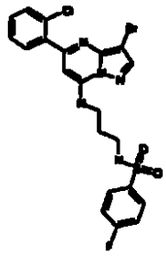
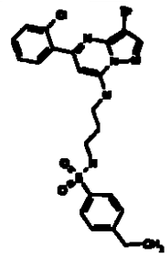
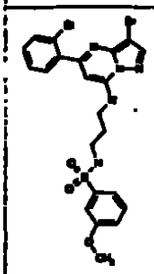
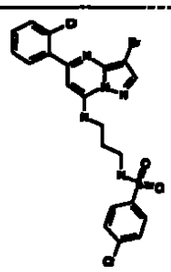
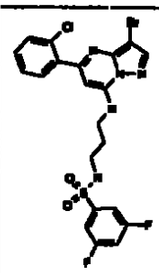
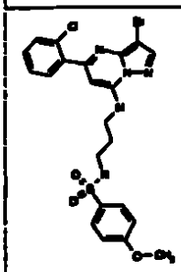
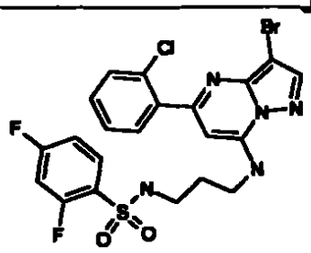
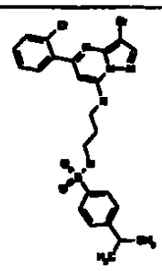
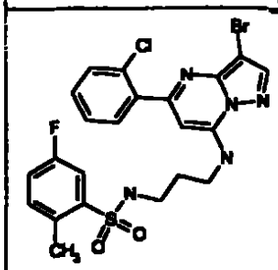
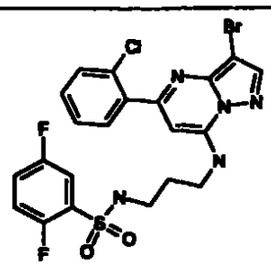
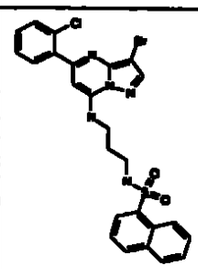
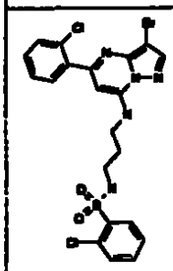
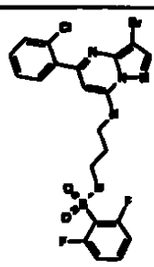
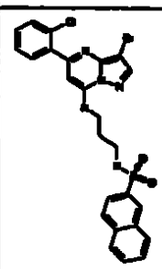
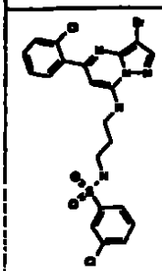
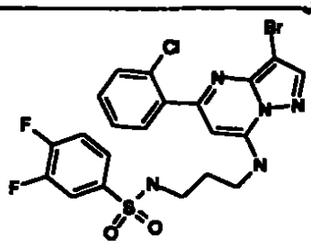
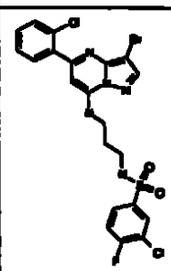
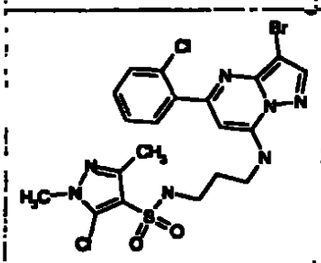
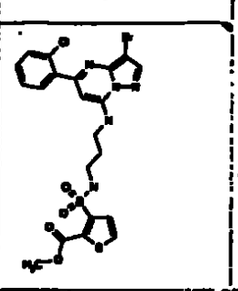
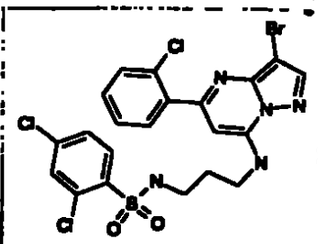
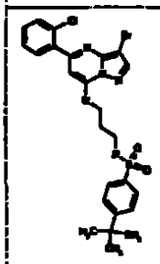
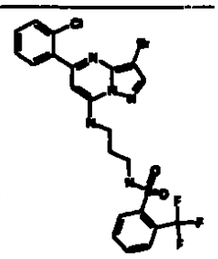
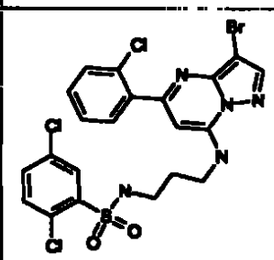
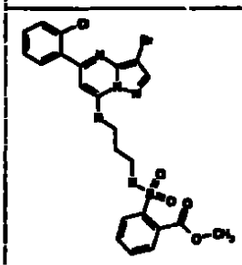
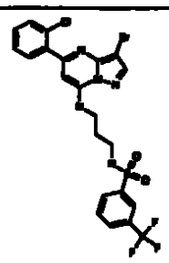
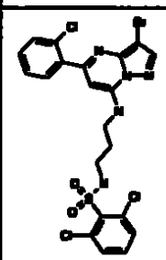
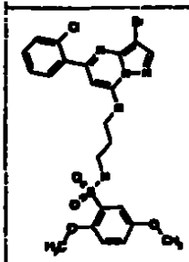
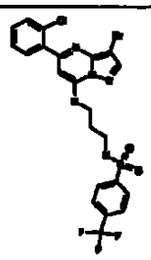
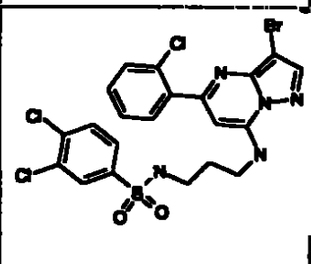
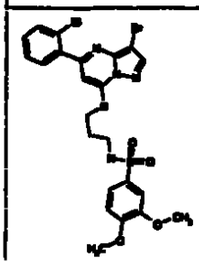
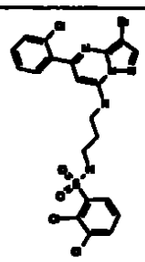
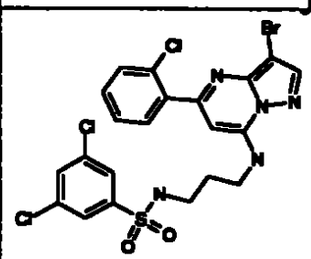
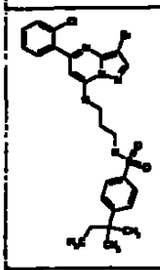
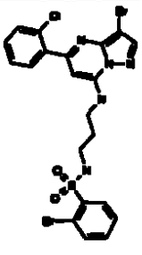
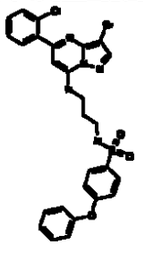
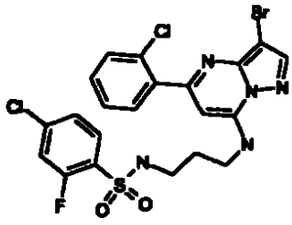
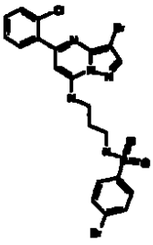
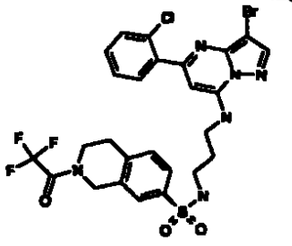
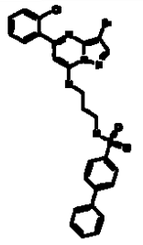
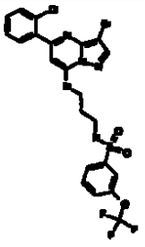
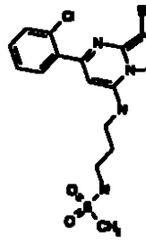
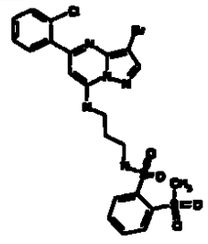
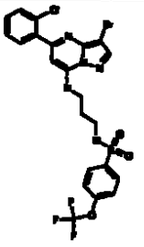
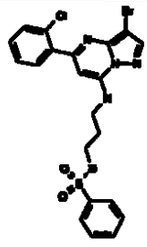
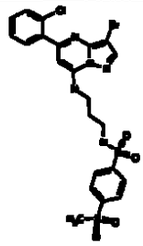
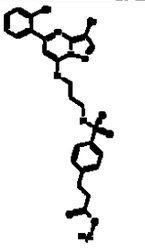
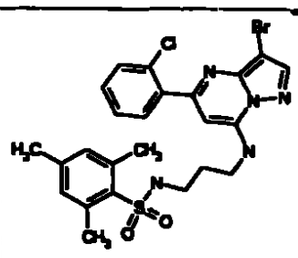
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6361 2. 650.36		1. 6366 2. 486.27
	1. 6362 2. 650.36		1. 6367 2. 548.3
	1. 6363 2. 661.36		1. 6368 2. 590.32
	1. 6364 2. 684.38		
	1. 6365 2. 699.38		

TABLE 64

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6401 2. 474.26		1. 6406 2. 536.29		1. 6411 2. 541.3
	1. 6402 2. 488.27		1. 6407 2. 536.29		1. 6412 2. 547.3
	1. 6403 2. 526.29		1. 6408 2. 540.3		1. 6413 2. 547.3
	1. 6404 2. 536.29		1. 6409 2. 540.3		1. 6414 2. 548.3
	1. 6405 2. 536.29		1. 6410 2. 540.3		1. 6415 2. 550.3

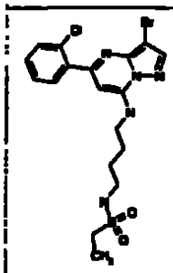
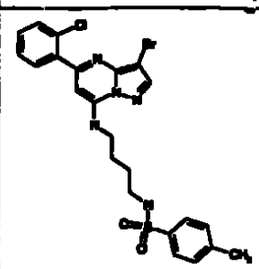
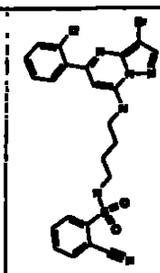
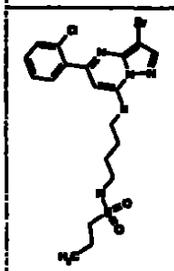
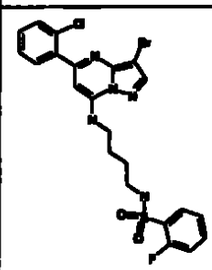
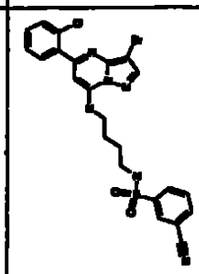
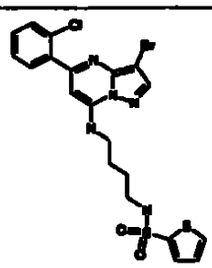
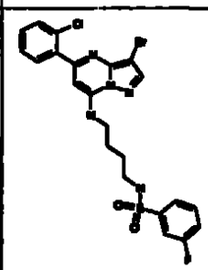
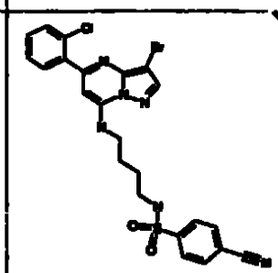
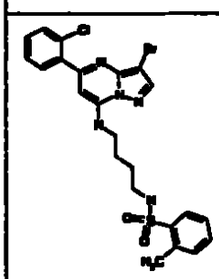
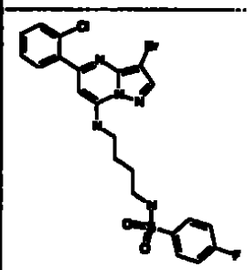
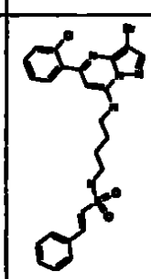
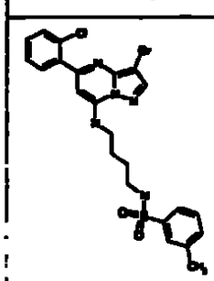
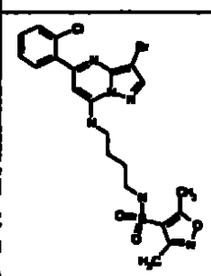
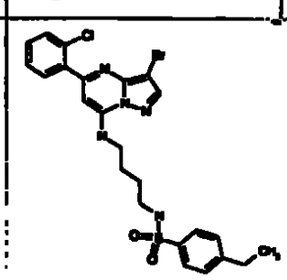
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6416 2. 552.3		1. 6421 2. 556.31		1. 6426 2. 558.31
	1. 6417 2. 552.3		1. 6122 2. 558.31		1. 6427 2. 564.31
	1. 6418 2. 554.3		1. 6423 2. 558.31		1. 6428 2. 572.31
	1. 6419 2. 558.31		1. 6424 2. 558.31		1. 6429 2. 572.31
	1. 6420 2. 558.31		1. 6425 2. 558.31		1. 6430 2. 574.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6431 2. 574.32		1. 6436 2. 586.32		1. 6441 2. 590.32
	1. 6432 2. 578.32		1. 6437 2. 590.32		1. 6442 2. 590.32
	1. 6433 2. 580.32		1. 6438 2. 590.32		1. 6443 2. 590.32
	1. 6434 2. 582.32		1. 6439 2. 590.32		1. 6444 2. 590.32
	1. 6435 2. 582.32		1. 6440 2. 589.32		1. 6445 2. 590.32

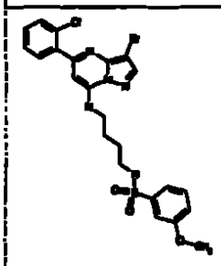
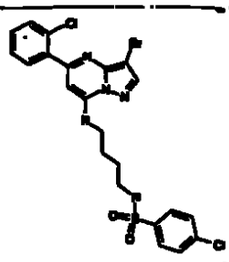
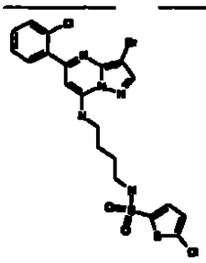
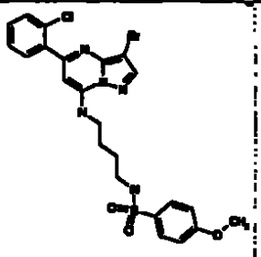
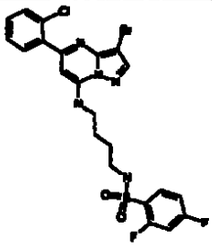
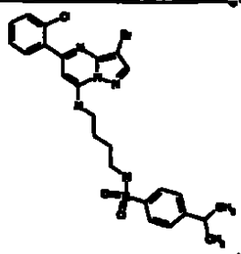
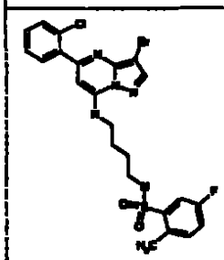
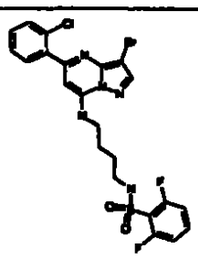
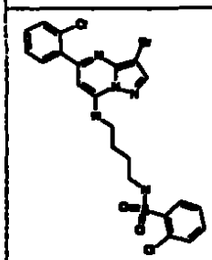
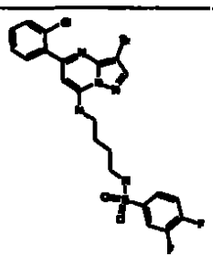
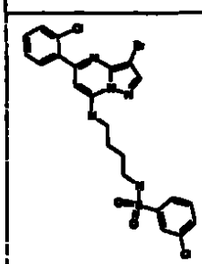
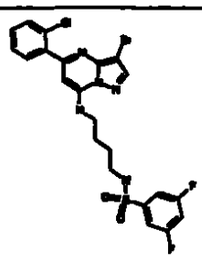
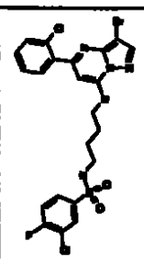
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6446 2. 592.33		1. 6451 2. 600.33		1. 6456 2. 614.34
	1. 6447 2. 574.32		1. 6452 2. 600.33		1. 6447 2. 673.37
	1. 6448 2. 598.33		1. 6453 2. 606.33		1. 6458 2. 460.25
	1. 6449 2. 600.33		1. 6454 2. 606.33		6459 2.
	1. 6450 2. 600.33		1. 6455 2. 606.33		1. 6460 2. 564.31

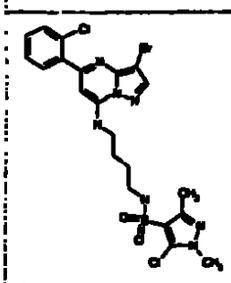
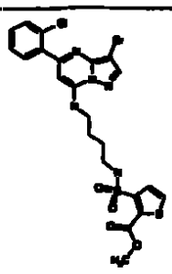
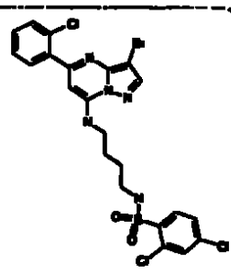
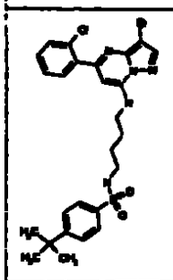
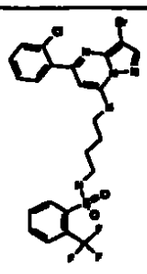
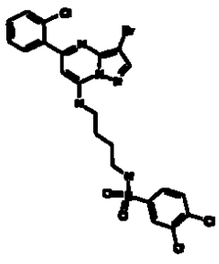
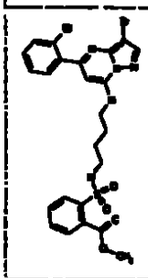
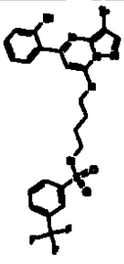
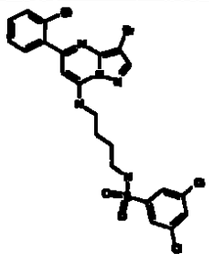
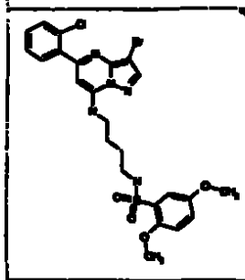
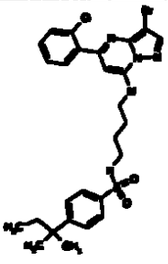
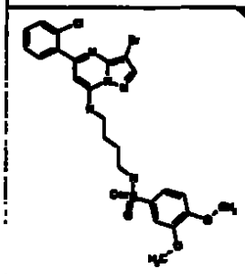
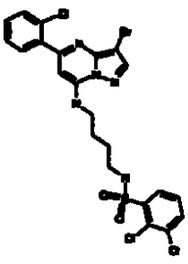
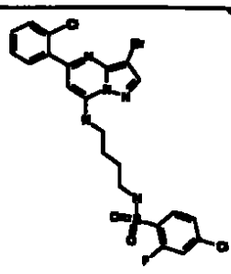
5

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

5

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6516 2. 566.31		1. 6521 2. 570.31		1. 6526 2. 576.32
	1. 6517 2. 566.31		1. 6522 2. 572.31		1. 6527 2. 578.32
	1. 6518 2. 568.31		1. 6523 2. 572.31		1. 6528 2. 586.32
	1. 6519 2. 570.31		1. 6524 2. 572.31		1. 6529 2. 586.32
	1. 6520 2. 570.31		1. 6525 2. 572.31		1. 6530 2. 588.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6531 2. 588.32		1. 6536 2. 600.33		1. 6541 2. 604.33
	1. 6532 2. 592.33		1. 6537 2. 604.33		1. 6542 2. 604.33
	1. 6533 2. 594.33		1. 6538 2. 604.33		1. 6543 2. 604.33
	1. 6534 2. 596.33		1. 6539 2. 604.33		1. 6544 2. 606.33
	1. 6535 2. 596.33		1. 6540 2. 604.33		1. 6545 2. 588.32

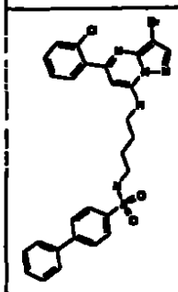
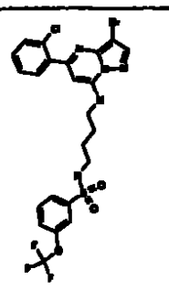
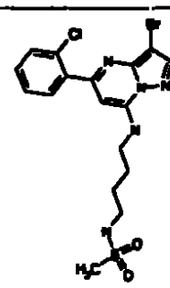
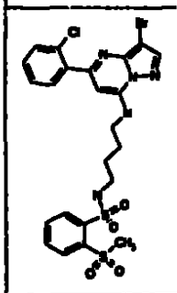
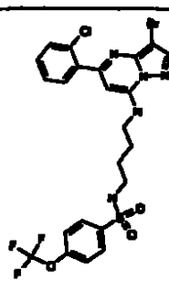
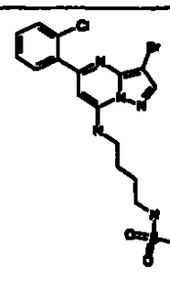
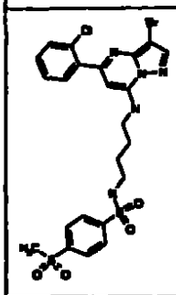
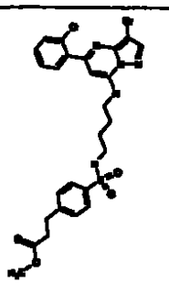
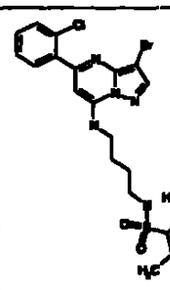
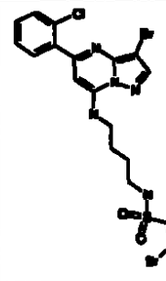
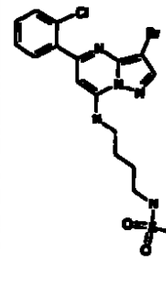
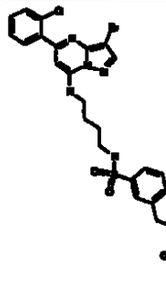
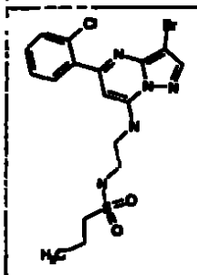
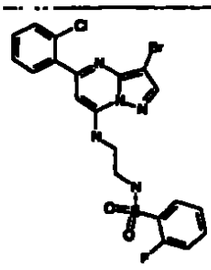
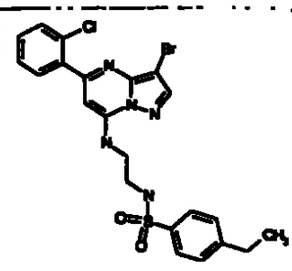
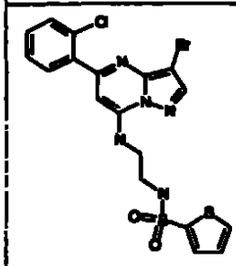
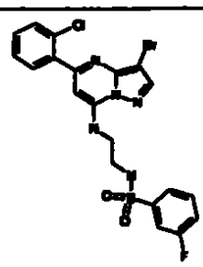
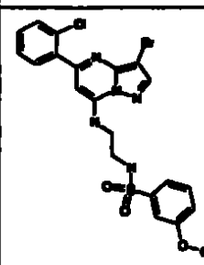
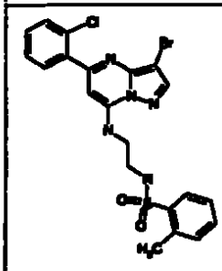
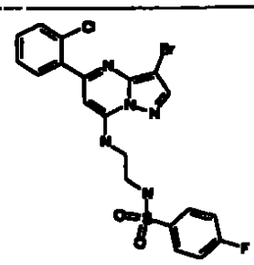
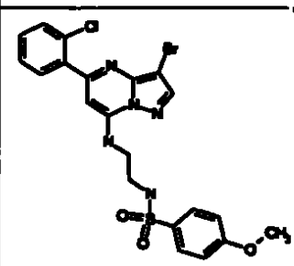
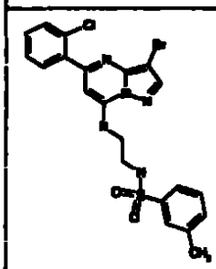
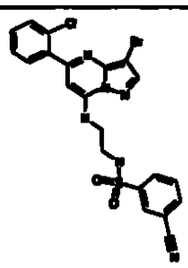
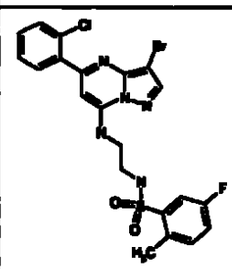
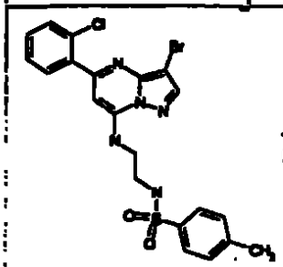
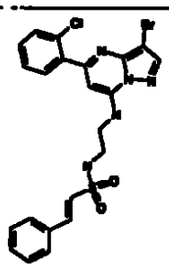
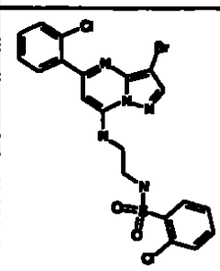
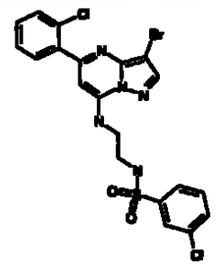
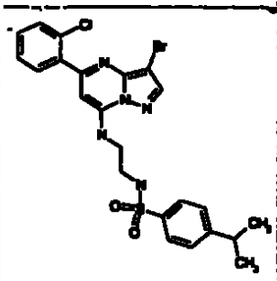
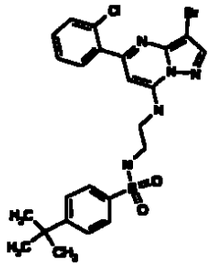
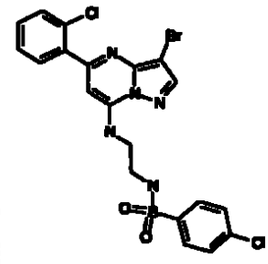
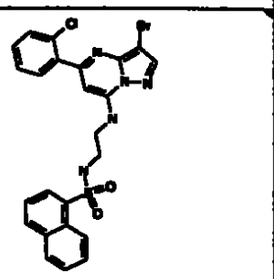
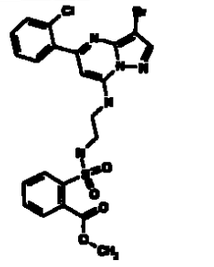
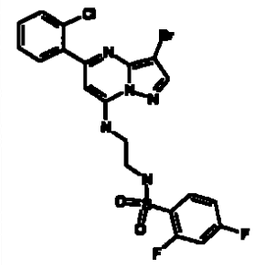
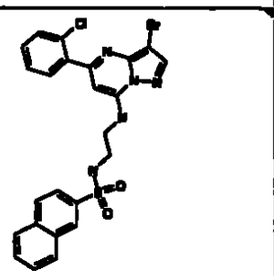
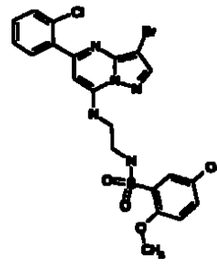
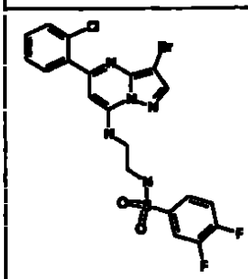
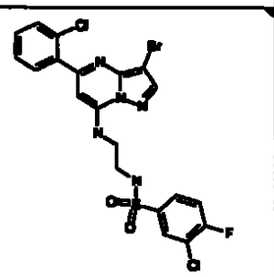
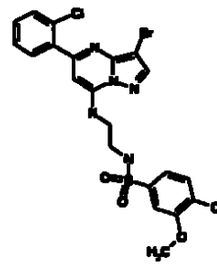
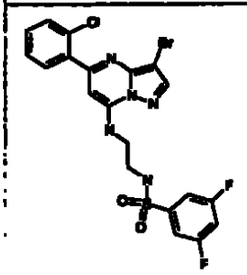
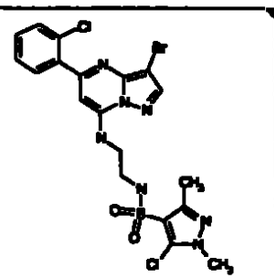
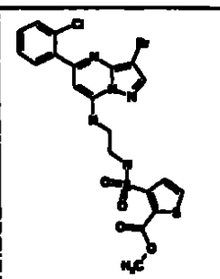
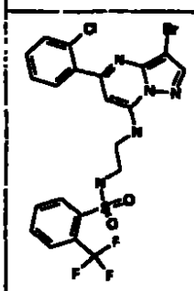
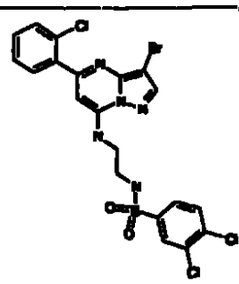
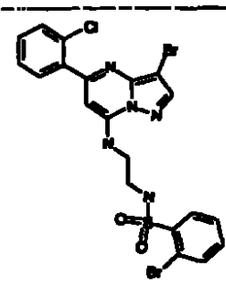
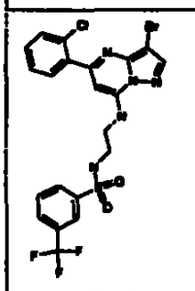
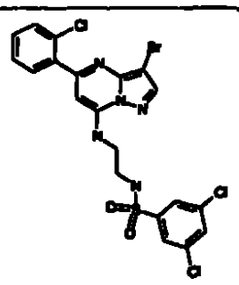
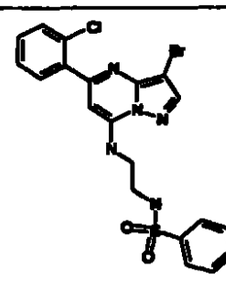
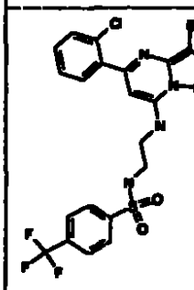
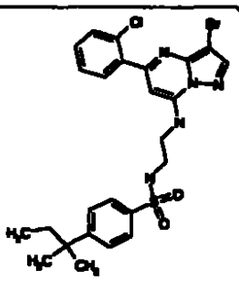
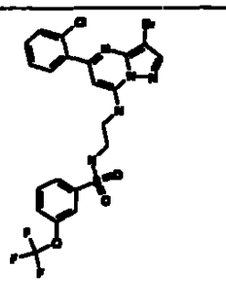
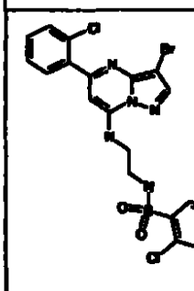
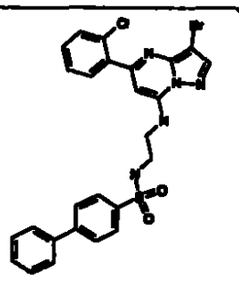
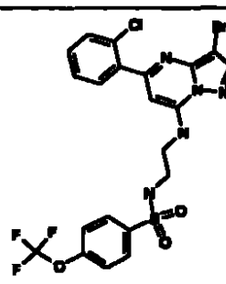
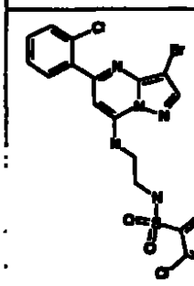
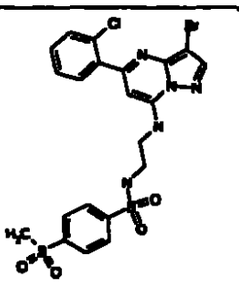
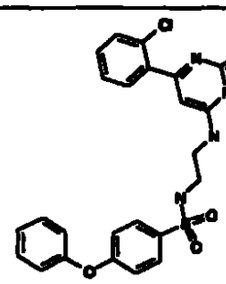
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6546 2. 612.34		1. 6551 2. 620.34		1. 6556 2. 474.26
	1. 6547 2. 614.34		1. 6552 2. 620.34		1. 6557 2. 536.29
	1. 6548 2. 614.34		1. 6553 2. 622.34		1. 6558 2. 578.32
	1. 6549 2. 614.34		1. 6554 2. 628.35		
	1. 6550 2. 614.34		1. 6555 2. 687.38		

TABLE 67

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6701 2. 474.26		1. 6706 2. 526.29		1. 6711 2. 536.29
	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
	1. 6704 2. 522.29		1. 6709 2. 533.29		1. 6714 2.
	. 6705 522.29		1. 6710 2. 534.29		1. 6715 2. 542.3

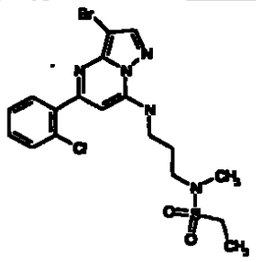
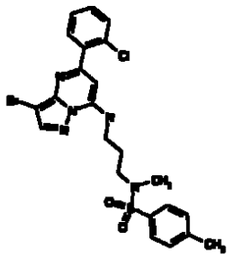
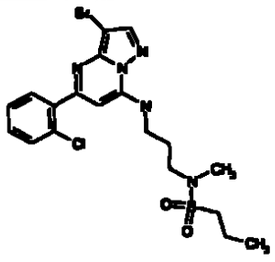
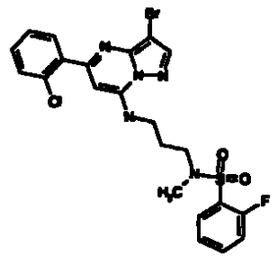
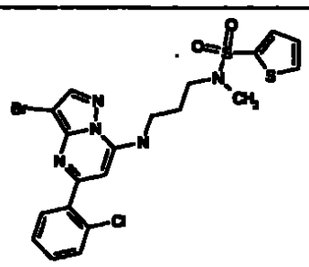
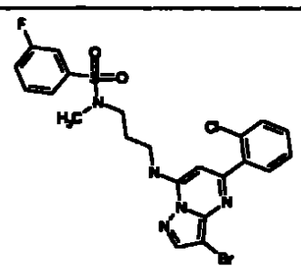
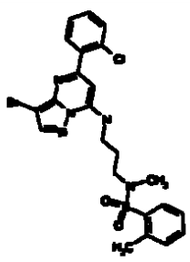
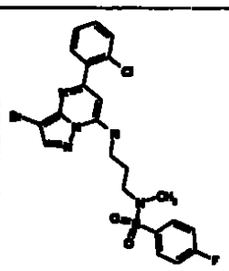
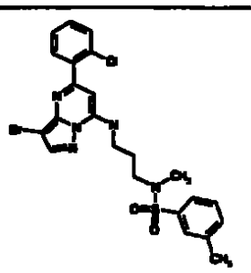
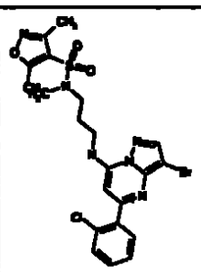
5

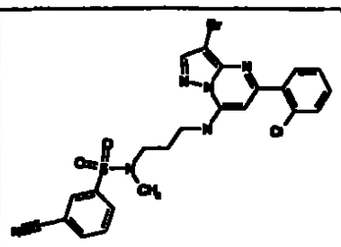
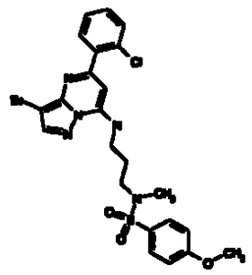
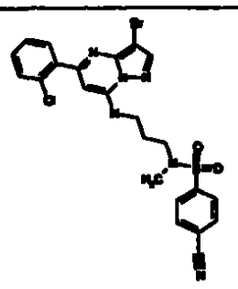
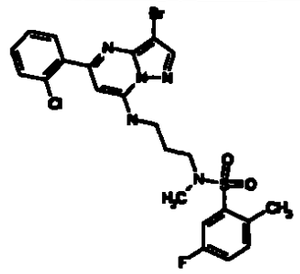
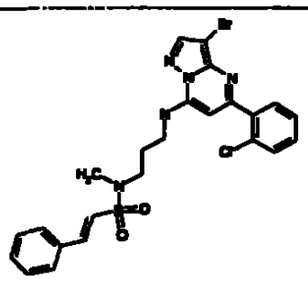
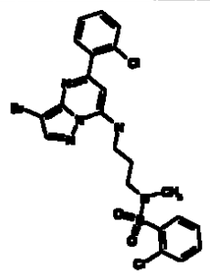
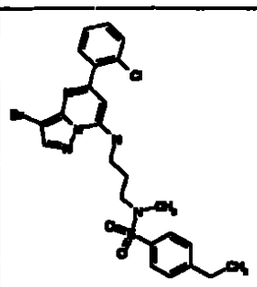
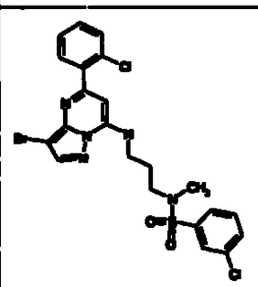
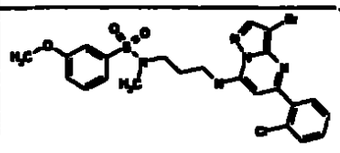
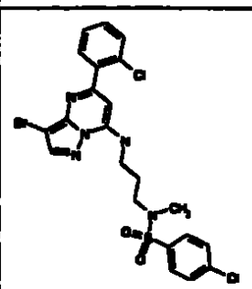
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6716 2. 542.3		1. 6721 2. 550.3		1. 6726 2. 564.31
	1. 6717 2. 542.3		1. 6722 2. 558.31		1. 6727 2. 566.31
	1. 6718 2. 544.3		1. 6723 2. 558.31		1. 6728 2. 568.31
	1. 6719 2. 544.3		1. 6724 2. 560.31		1. 6729 2. 568.31
	1. 6720 2. 544.3		1. 6725 2. 560.31		1. 6730 2. 572.31

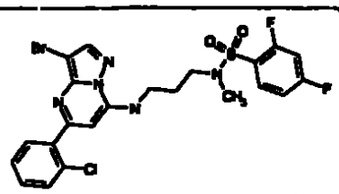
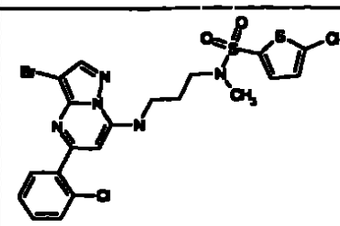
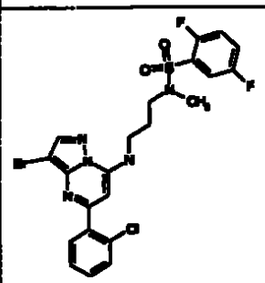
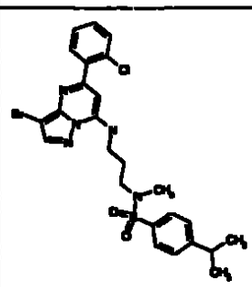
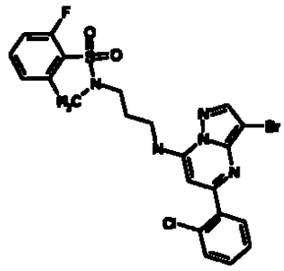
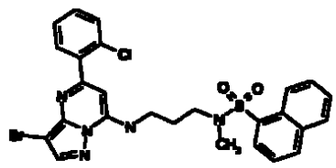
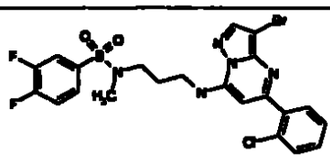
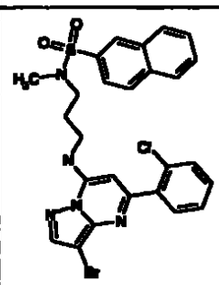
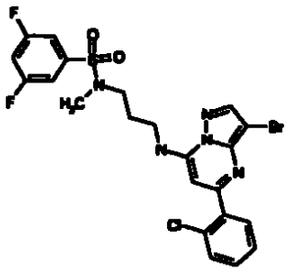
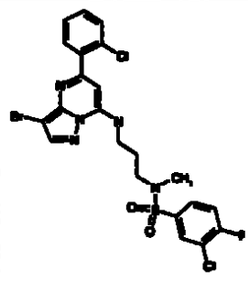
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6731 2. 576.32		1. 6736 2. 576.32		1. 6741 2. 586.32
	1. 6732 2. 576.32		1. 6737 2. 576.32		1. 674 2. 586.32
	1. 6733 2. 576.32		1. 6738 2. 576.32		1. 6743 2. 592.33
	1. 6734 2. 576.32		1. 6739 2. 584.32		1. 6744 2. 592.33
	1. 6735 2. 576.32		1. 6740 2. 586.32		1. 6745 2. 600.33

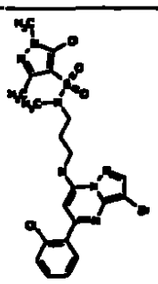
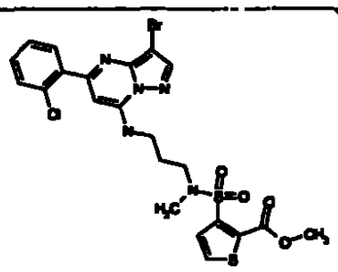
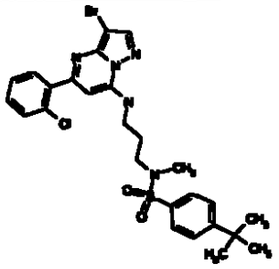
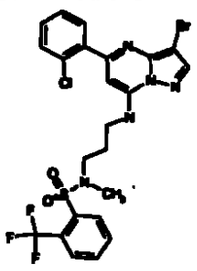
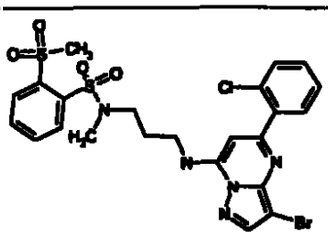
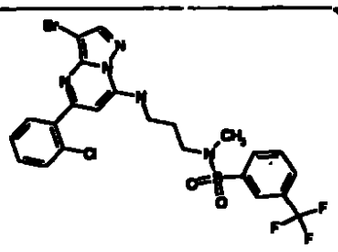
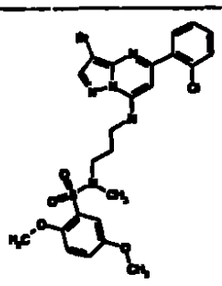
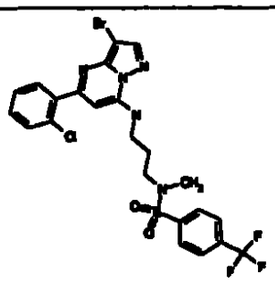
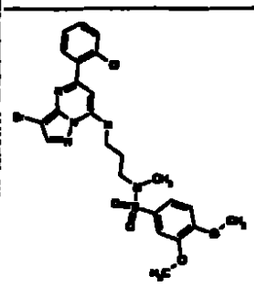
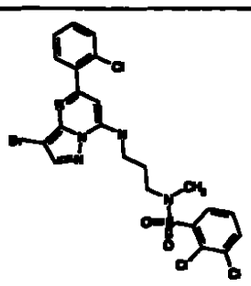
5

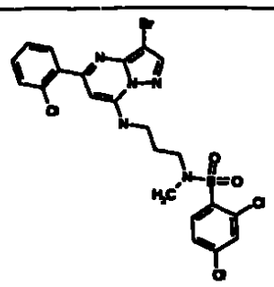
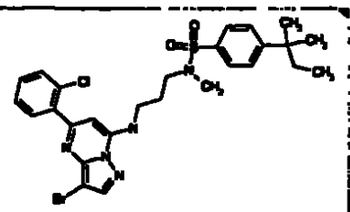
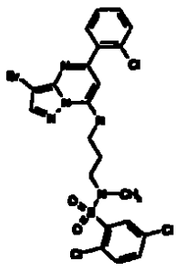
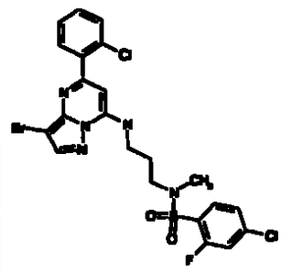
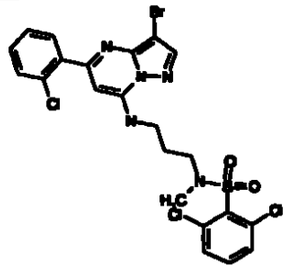
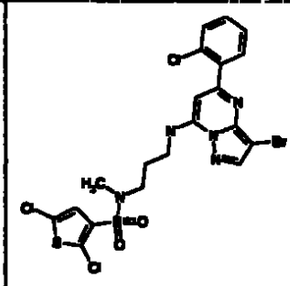
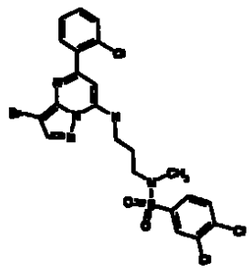
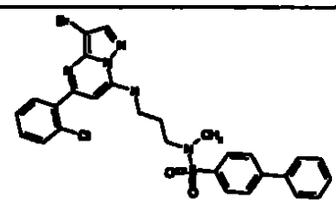
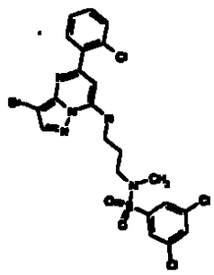
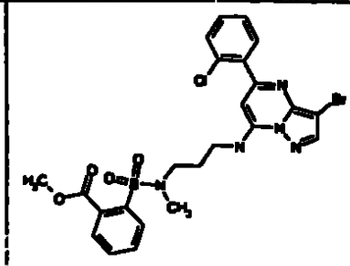
TABLE 68

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

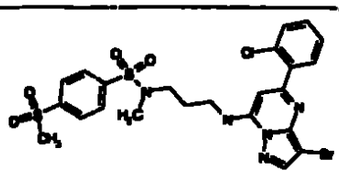
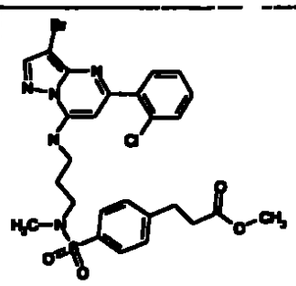
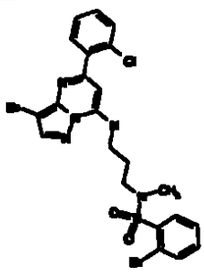
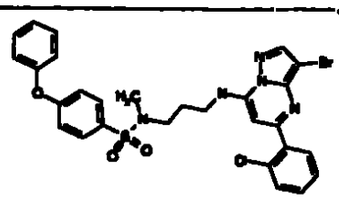
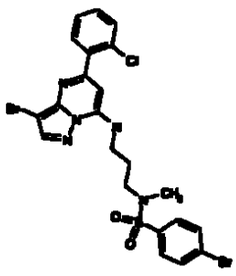
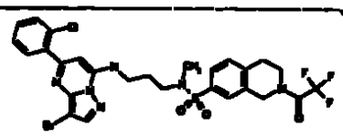
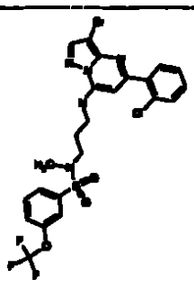
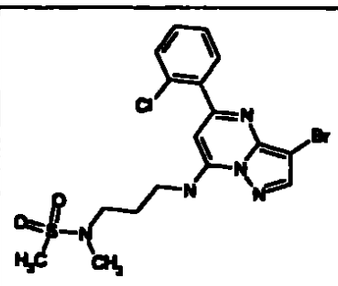
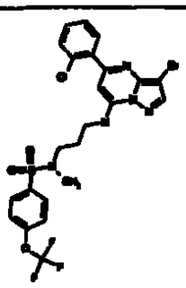
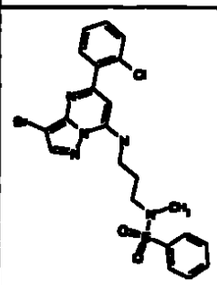
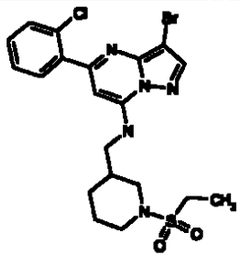
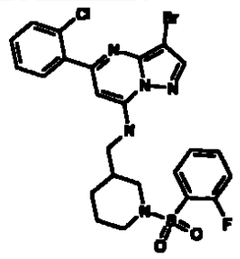
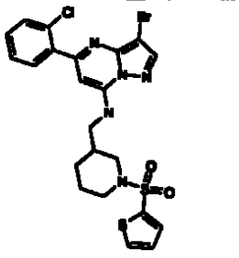
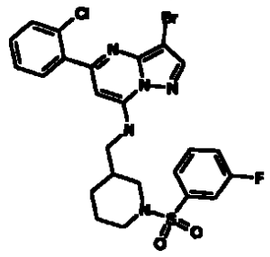
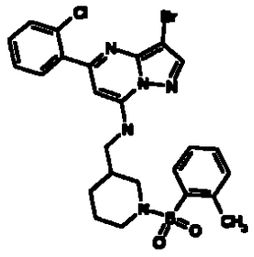
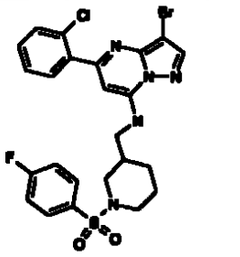
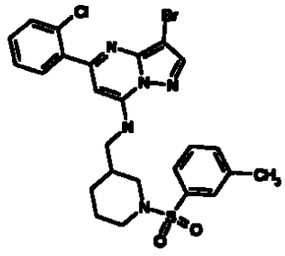
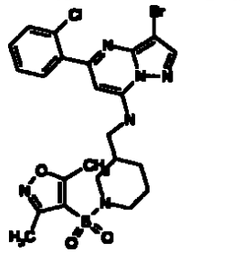
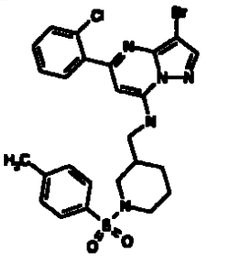
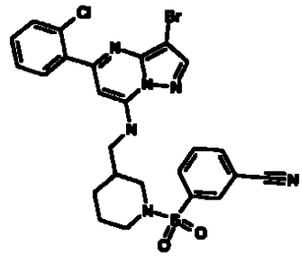
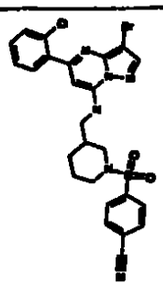
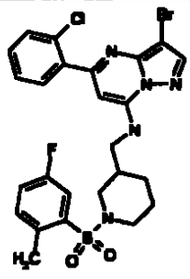
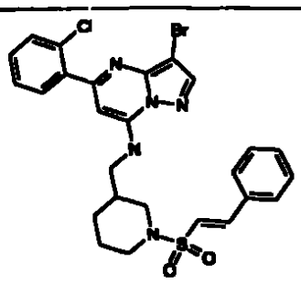
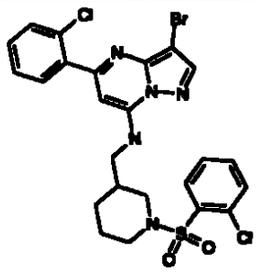
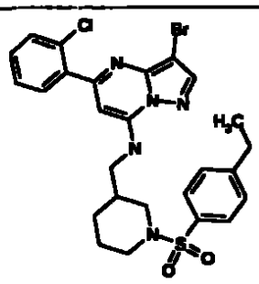
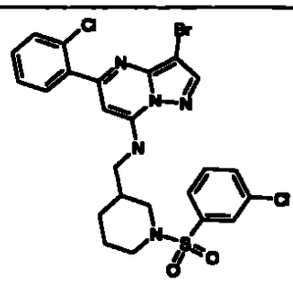
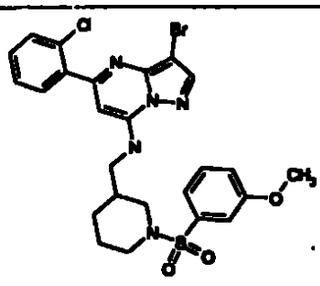
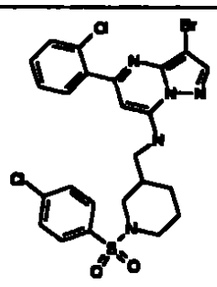
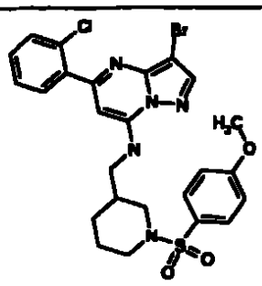
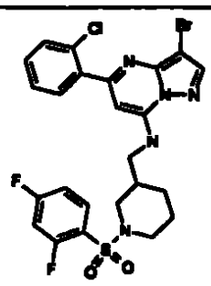
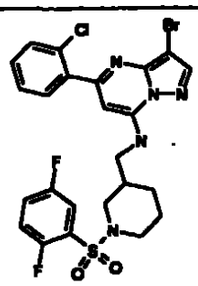
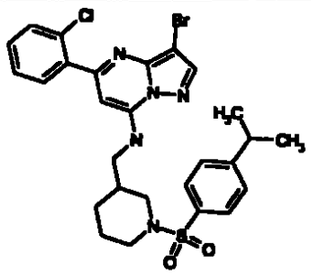
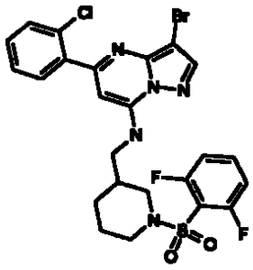
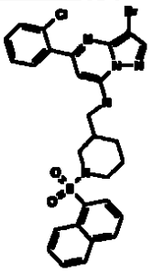
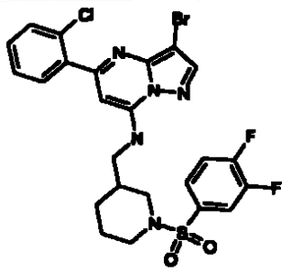
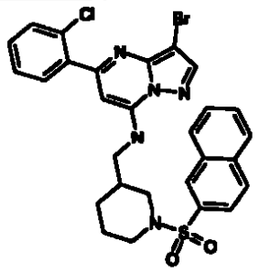
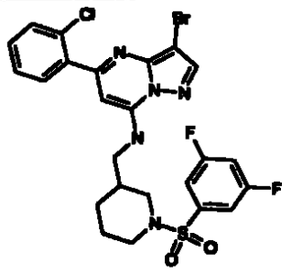
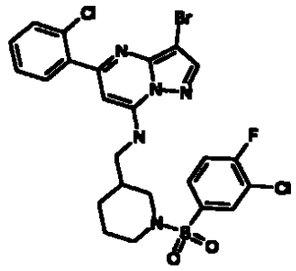
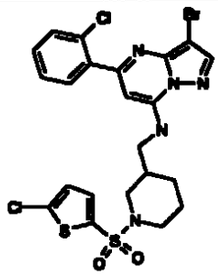
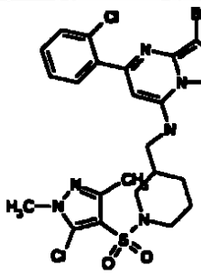
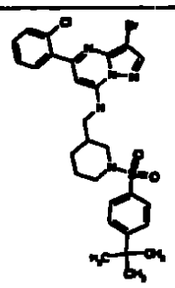
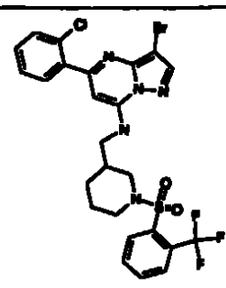
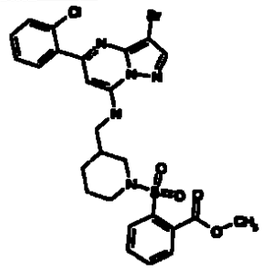
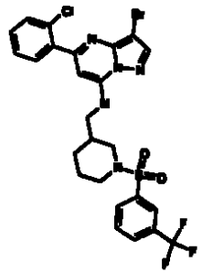
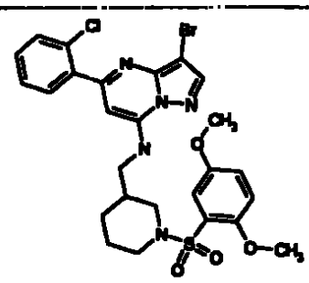
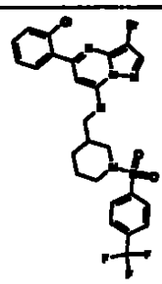
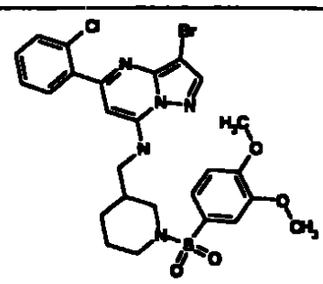
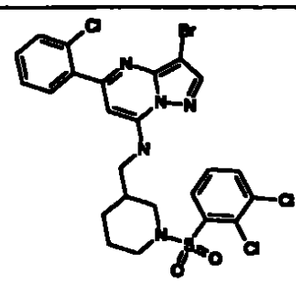
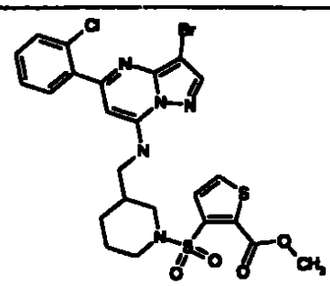
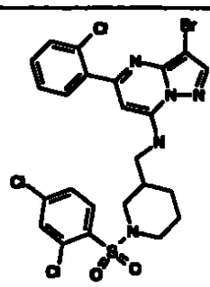
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6851 2. 614.34		1. 6856 2. 620.34
	1. 6852 2. 614.34		1. 6856 2. 628.35
	1. 6853 2. 614.34		1. 6857 2. 687.38
	1. 6854 2. 620.34		1. 6859 2. 474.26
	1. 6855 2. 620.34		1. 6860 2. 536.29

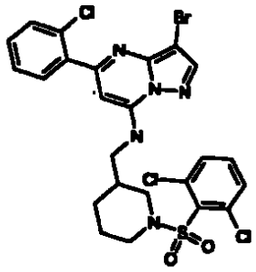
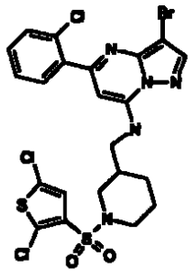
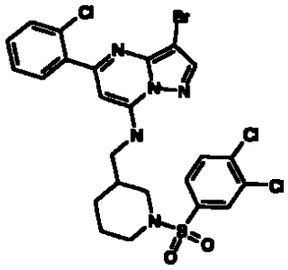
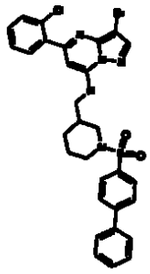
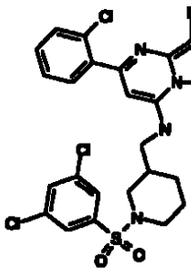
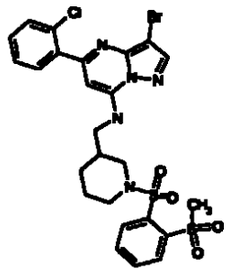
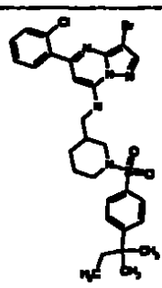
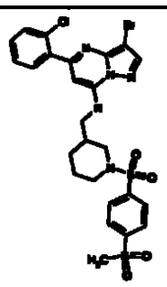
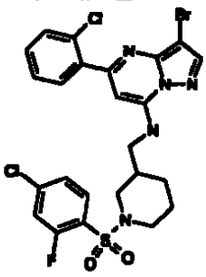
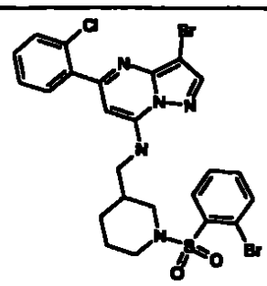
TABLE 69

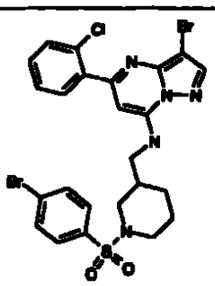
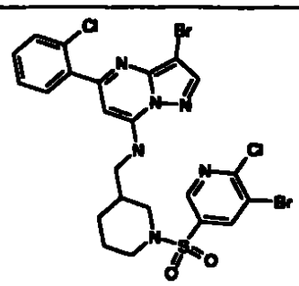
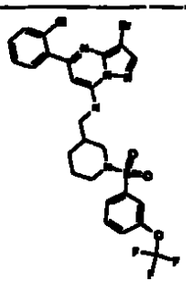
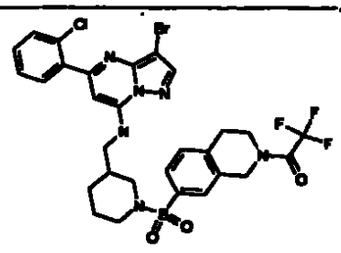
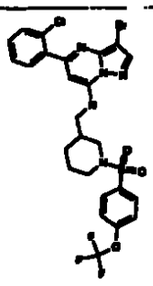
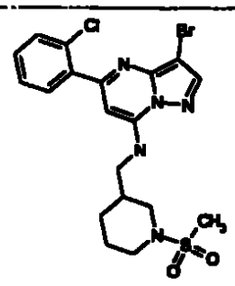
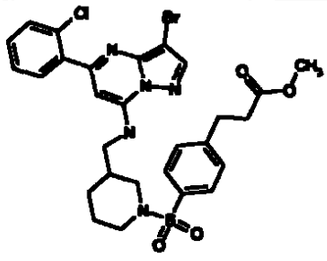
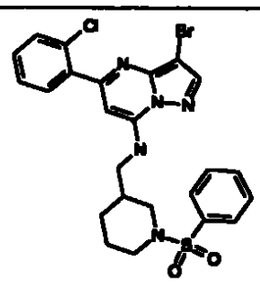
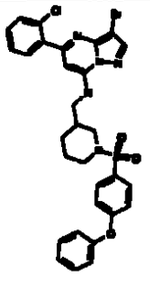
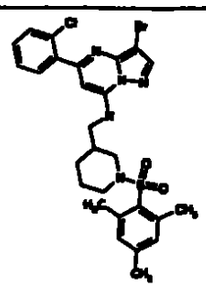
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1 .6901 2. 514.28		1. 6906 2. 580.32
	1. 6902 2. 568.31		1. 6907 2. 580.32
	1. 6903 2. 576.32		1. 6908 2. 580.32
	1. 6904 2. 576.32		1. 6909 2. 581.32
	1. 6905 2. 576.32		1. 6910 2. 587.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6911 2. 587.32		1. 6916 2. 594.33
	1. 6912 2. 588.32		1. 6917 2. 596.33
	1. 6913 2. 590.32		1. 6918 2. 596.33
	1. 6914 2. 592.33		1. 6919 2. 596.33
	1. 6915 2. 592.33		1. 6920 2. 596.33

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6921 2. 598.33		1. 6926 2. 604.33
	1. 6922 2. 598.33		1. 6927 2. 612.34
	1. 6923 2. 598.33		1. 6928 2. 612.34
	1. 6924 2. 598.33		1. 6929 2. 614.34
	1. 6925 2. 602.33		1. 6930 2. 614.34

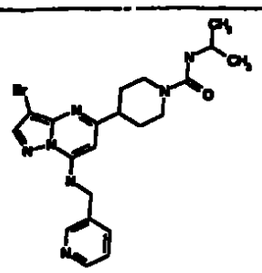
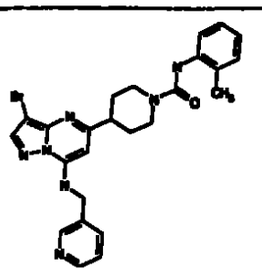
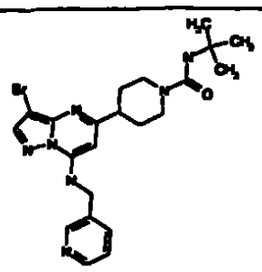
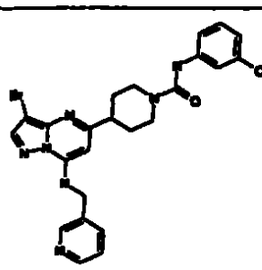
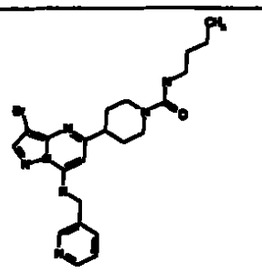
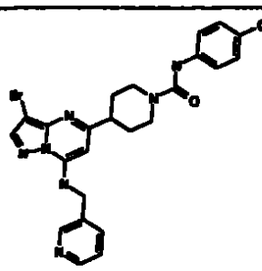
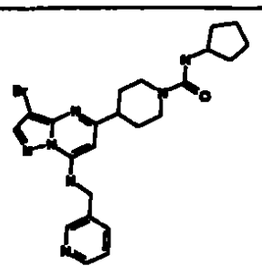
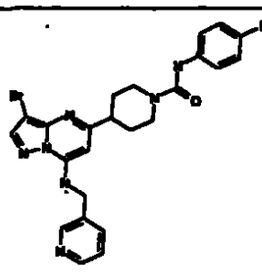
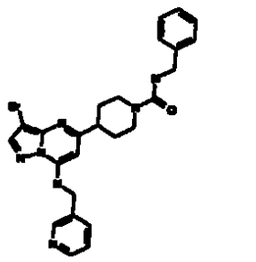
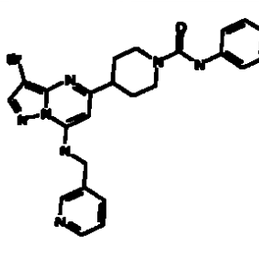
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6931 2. 618.34		1. 6936 2. 630.35
	1. 6932 2. 620.34		1. 6937 2. 630.35
	1. 6933 2. 622.34		1. 6938 2. 630.35
	1. 6934 2. 622.34		1. 6939 2. 630.35
	1. 6935 2. 626.34		1. 6940 2. 630.35

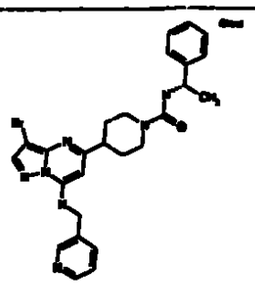
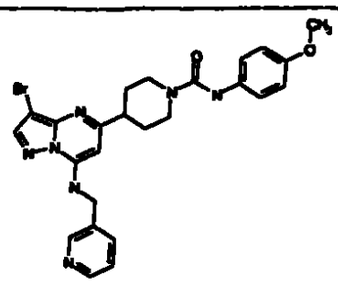
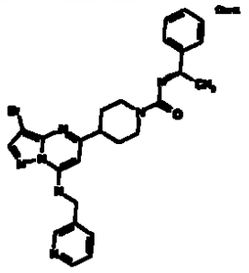
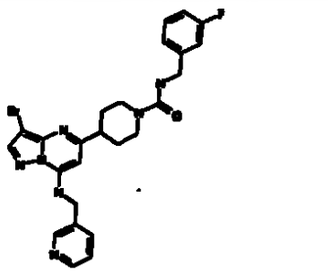
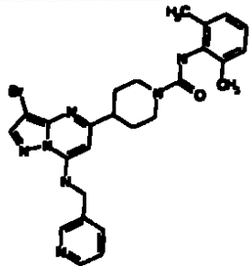
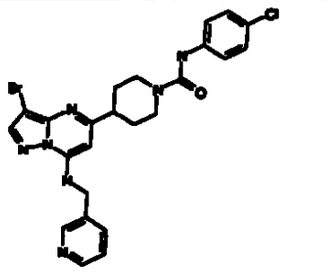
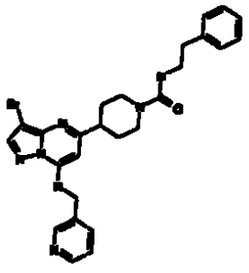
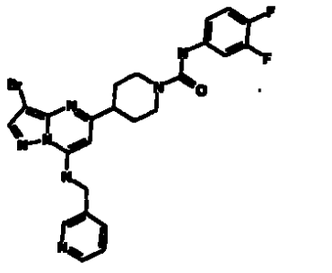
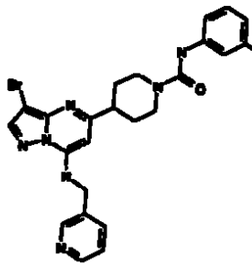
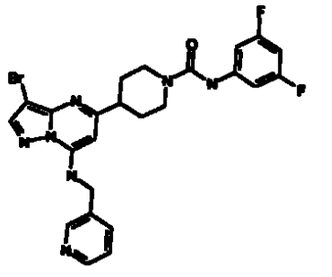
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6941 2. 630.35		1. 6946 2. 636.35
	1. 6942 2. 630.35		1. 6947 2. 638.35
	1. 6943 2. 630.35		1. 6948 2. 640.35
	1. 6944 2. 632.35		1. 6949 2. 640.35
	1. 6945 2. 614.34		1. 6950 2. 640.35

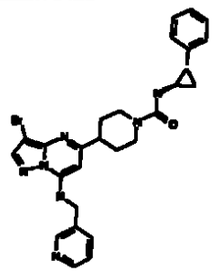
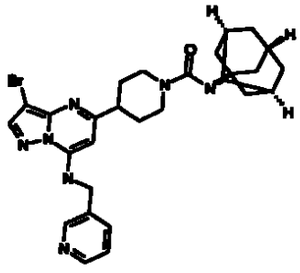
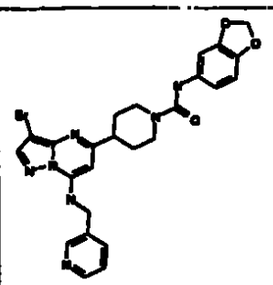
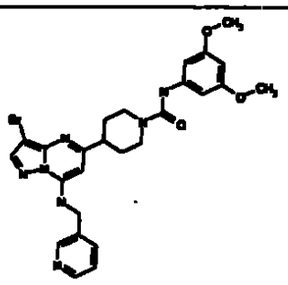
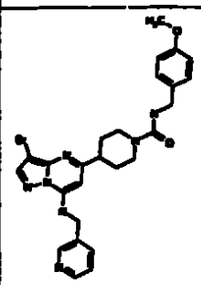
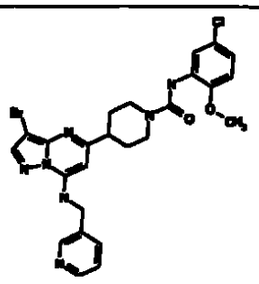
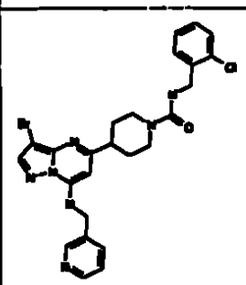
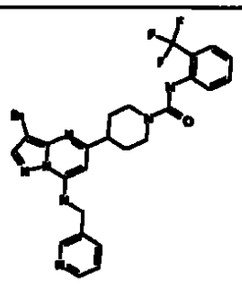
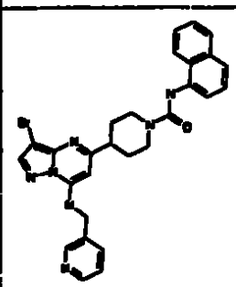
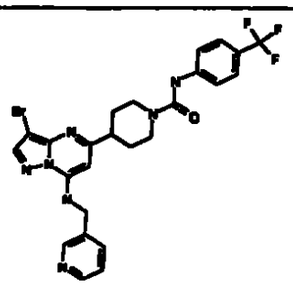
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 6951 2. 640.35		1. 6956 2. 675.23
	1. 6952 2. 648.36		1. 6957 2. 713.39
	1. 6953 2. 646.36		1. 6958 2. 500.27
	1. 6954 2. 648.36		1. 6959 2. 562.31
	1. 6955 2. 654.36		1. 6960 2. 604.33

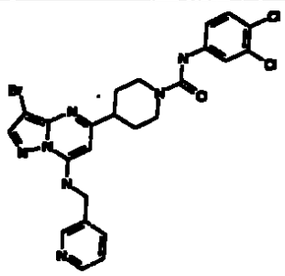
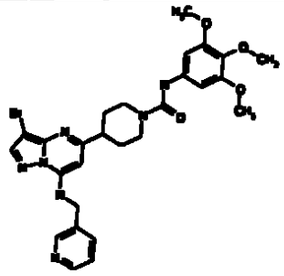
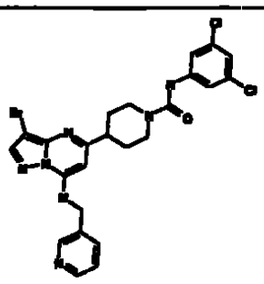
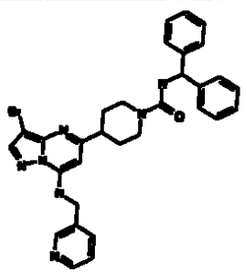
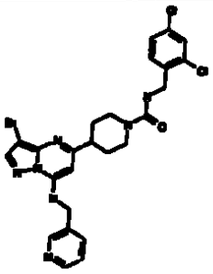
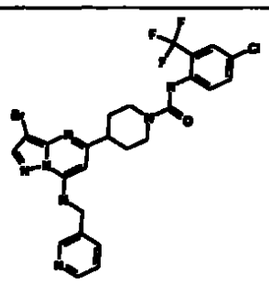
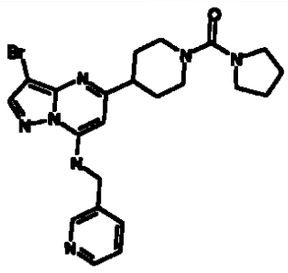
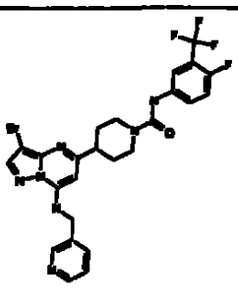
5

TABLE 70

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7001 2. 472.26		1. 7006 2. 522.29
	1. 7002 2. 488.27		1. 7007 2. 520.29
	1. 7003 2. 488.27		1. 7008 2. 520.29
	1. 7004 2. 500.27		1. 7009 2. 526.29
	1. 7005 2. 520.29		1. 7010 2. 533.29

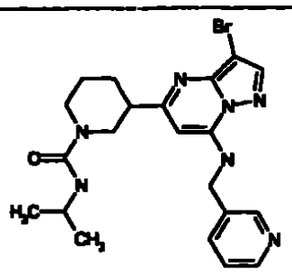
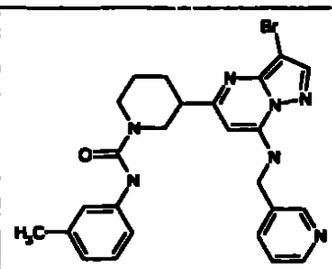
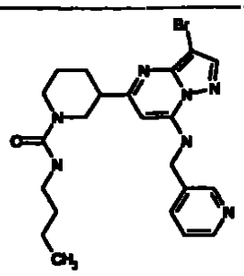
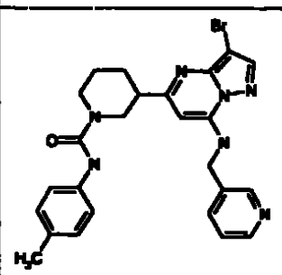
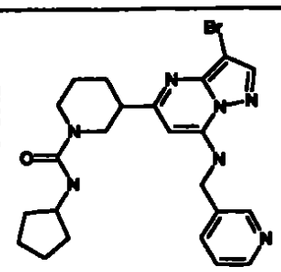
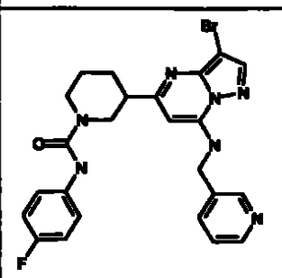
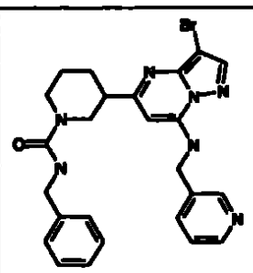
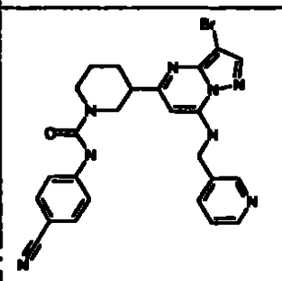
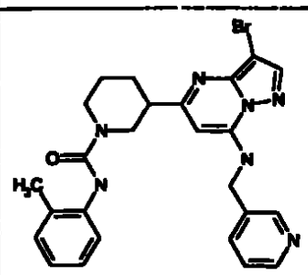
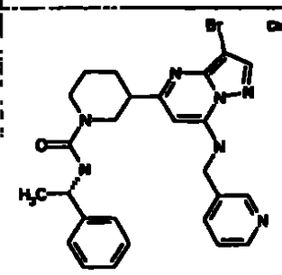
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7011 2. 536.29		1. 7016 2. 538.3
	1. 7012 2. 536.29		1. 7017 2. 540.3
	1. 7013 2. 536.29		1. 7018 2. 542.3
	1. 7014 2. 536.29		1. 7019 2. 544.3
	1. 7015 2. 536.29		1. 7020 2. 544.3

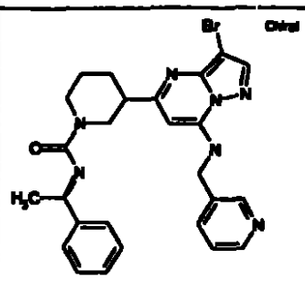
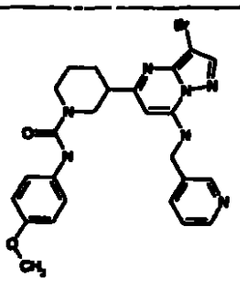
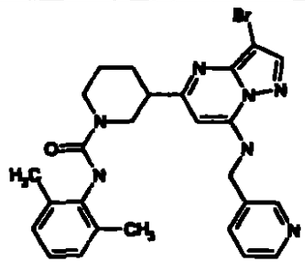
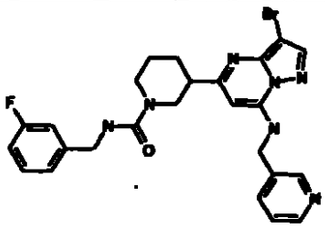
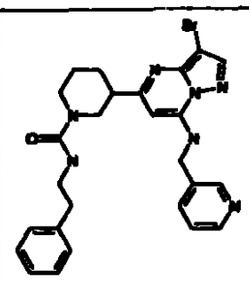
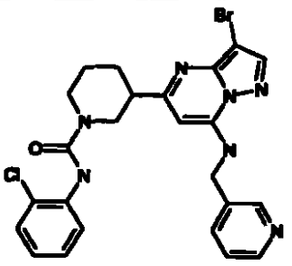
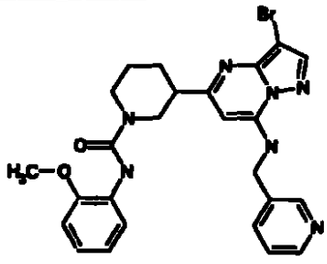
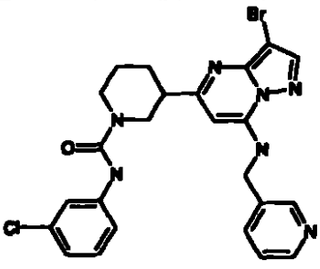
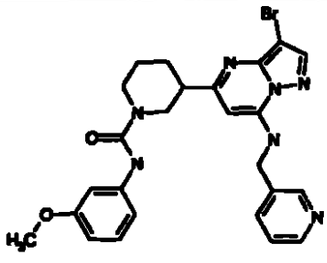
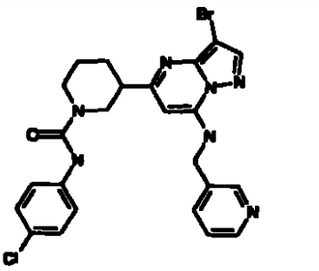
Product	1. Ex. 2. m/z.	Product	1. Ex. 2. m/z
	1. 7021 2. 548.3		1. 7026 2. 566.31
	1. 7022 2. 552.3		1. 7027 2. 568.31
	1. 7023 2. 552.3		1. 7028 2. 572.31
	1. 7024 2. 556.31		1. 7029 2. 576.32
	1. 7025 2. 556.31		1. 7030 2. 576.32

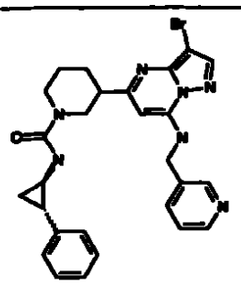
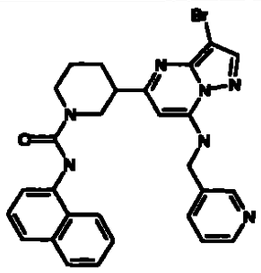
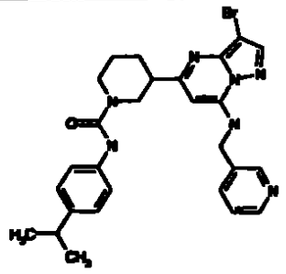
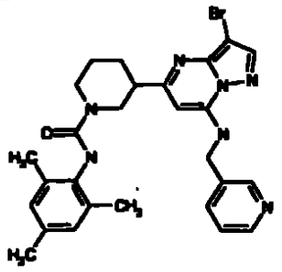
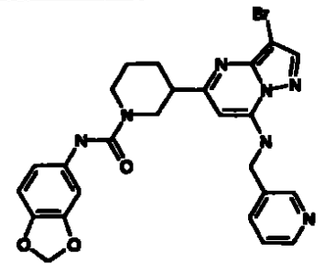
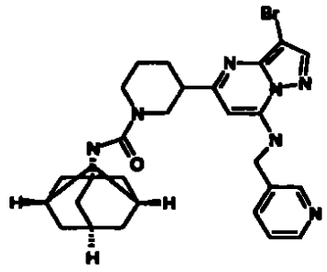
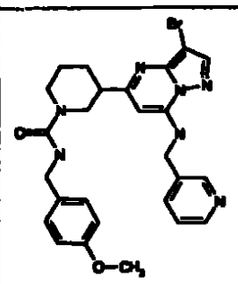
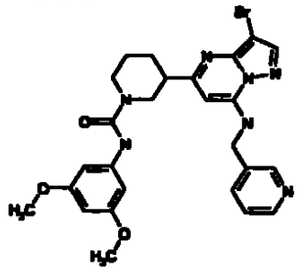
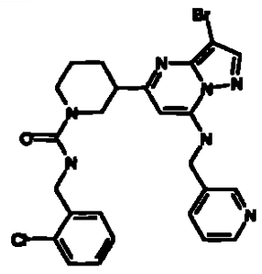
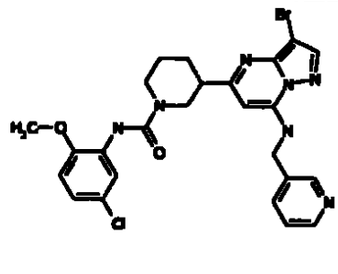
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7031 2. 576.32		1. 7036 2. 598.33
	1. 7032 2. 576.32		1. 7037 2. 598.33
	1. 7033 2. 590.32		1. 7038 2. 610.34
	1. 7034 2. 486.27		
	1. 7035 2. 594.33		

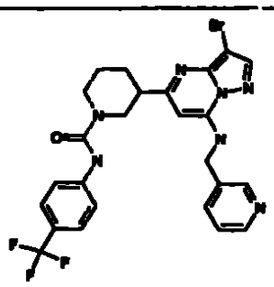
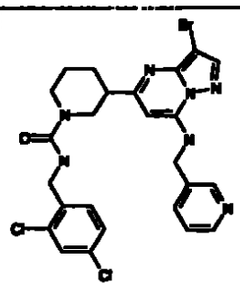
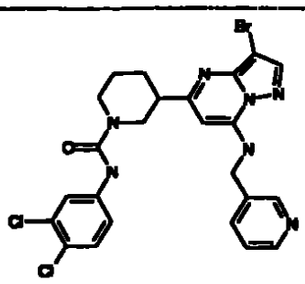
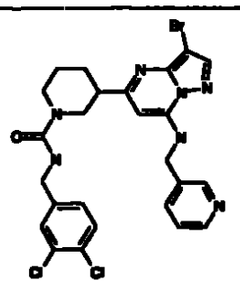
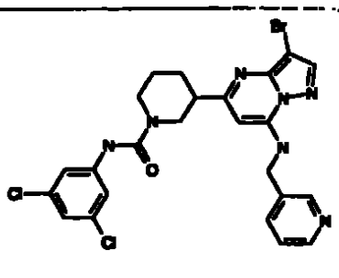
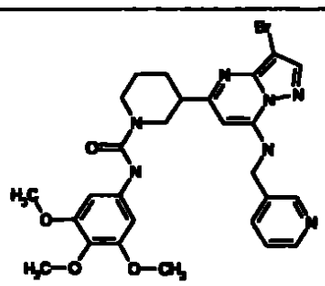
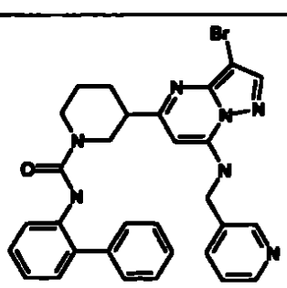
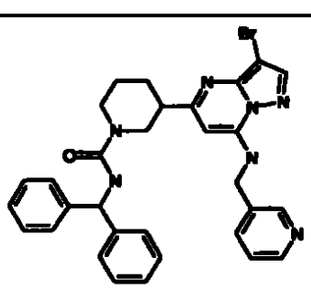
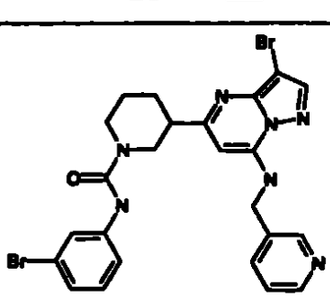
5

TABLE 71

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1 . 7101 2. 474.26		1. 7106 2. 522.29
	1. 7102 2. 488.27		1. 7107 2. 522.29
	1. 7103 2. 500.27		1. 7108 2. 526.3
	1. 7104 2. 522.29		1. 7109 2. 533.29
	1. 7105 2. 522.29		1. 7110 2. 536.29

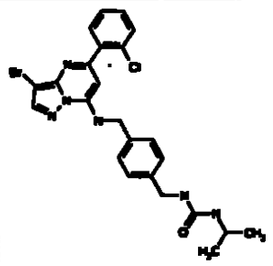
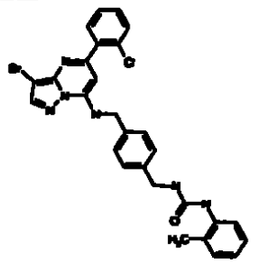
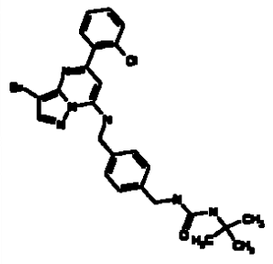
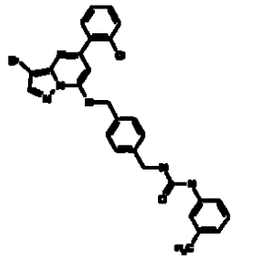
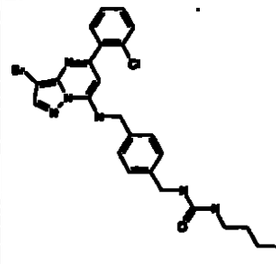
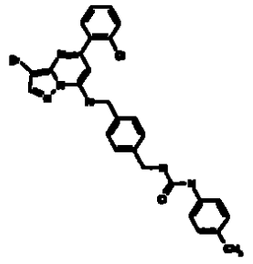
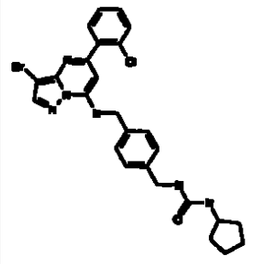
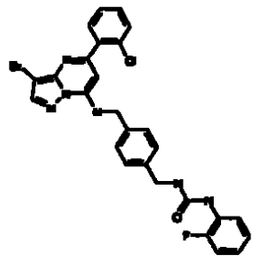
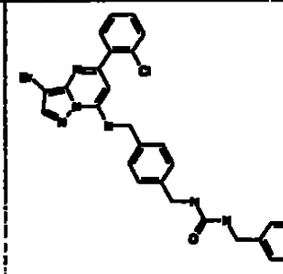
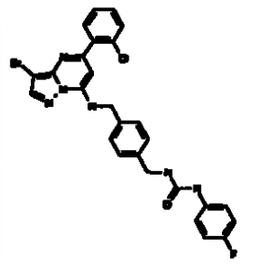
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7111 2. 536.29		1. 7116 2. 538.3
	1. 7112 2. 536.29		1. 7117 2. 540.3
	1. 7113 2. 536.29		1. 7118 2. 542.3
	1. 7114 2. 536.29		1. 7119 2. 542.3
	1. 7115 2. 536.3		1. 7120 2. 542.3

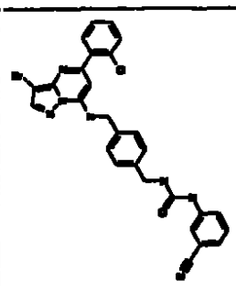
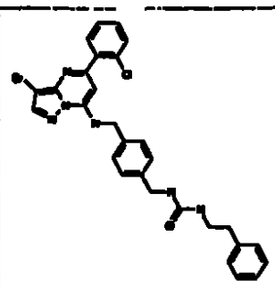
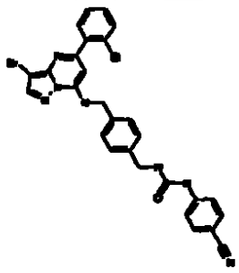
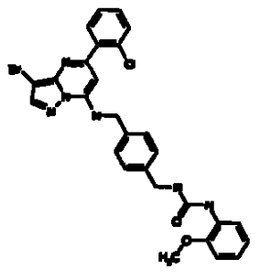
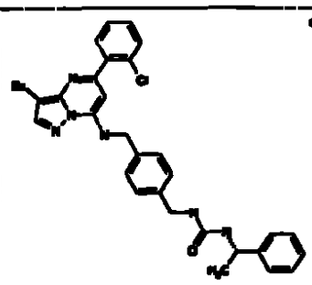
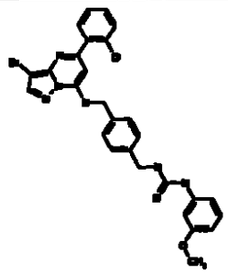
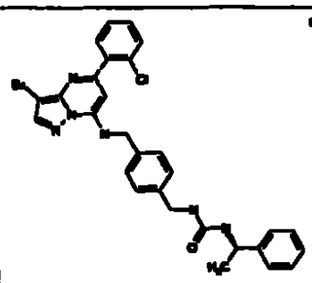
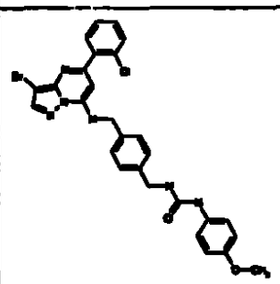
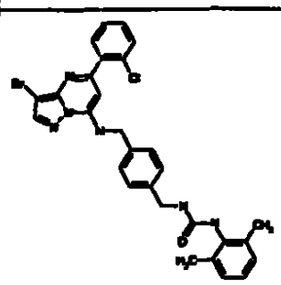
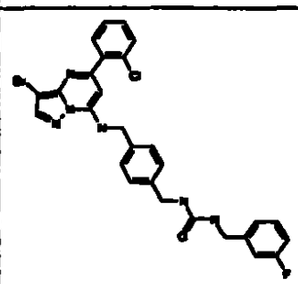
Product	1. Ex. 2. m/z		Product	1. Ex. 2. m/z
	1. 7121 2. 546.3			1. 7126 2. 558.31
	1. 7122 2. 550.3			1. 7127 2. 550.3
	1. 7123 2. 552.3			1. 7128 2. 566.31
	1. 7124 2. 552.3			1. 7129 2. 585.31
	1. 7125 2. 556.31			1. 7130 2. 572.31

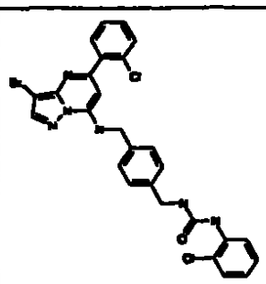
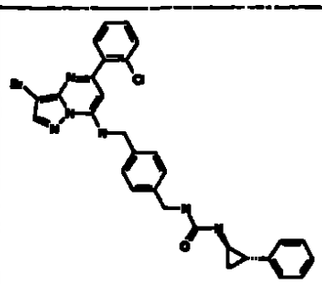
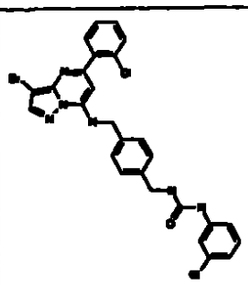
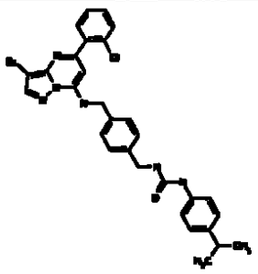
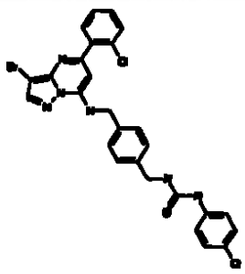
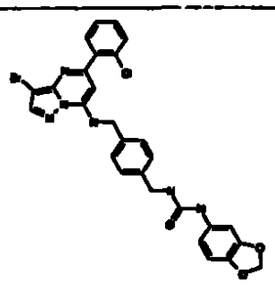
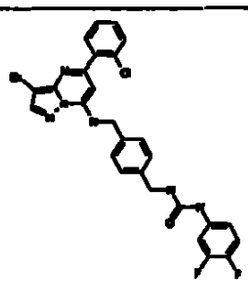
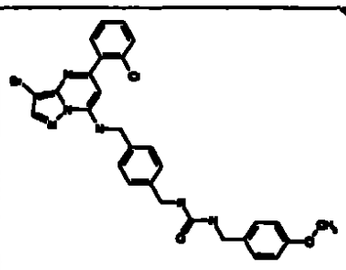
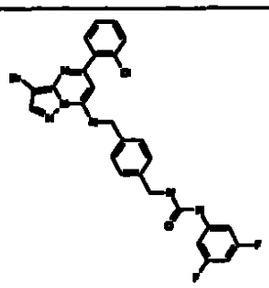
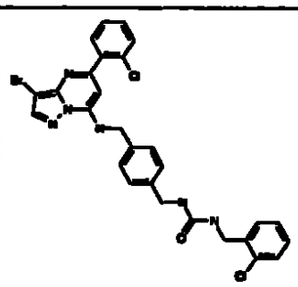
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7131 2. 576.32		1. 7136 2. 590.32
	1. 7132 2. 576.32		1. 7137 2. 590.32
	1. 7133 2. 576.32		1. 7138 2. 588.33
	1. 7134 2. 584.32		1. 7139 2. 598.33
	1. 7135 2. 585.3		

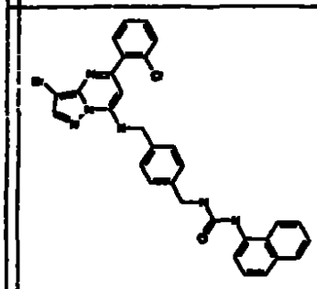
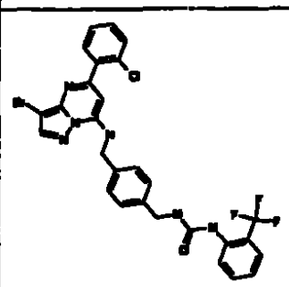
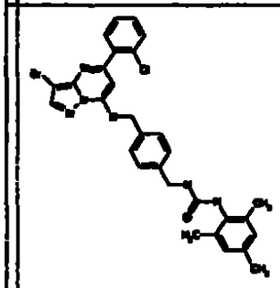
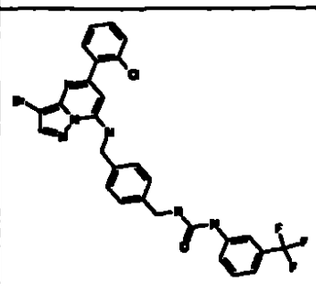
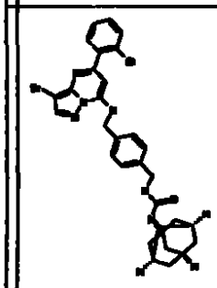
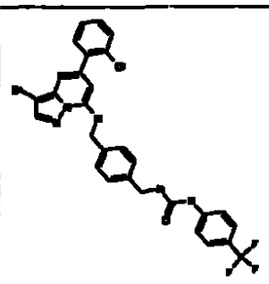
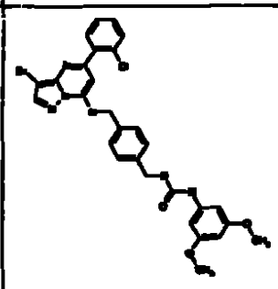
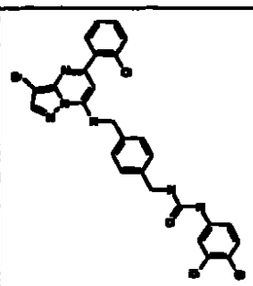
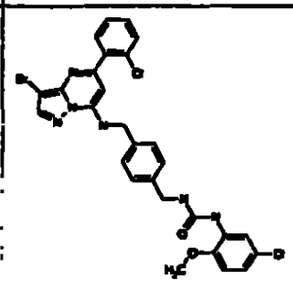
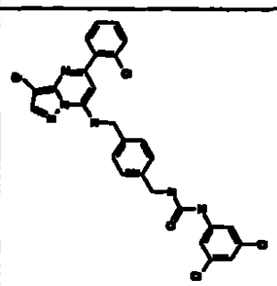
5

TABLE 72

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7201 2. 529.29		1. 7206 2. 577.32
	1. 7202 2. 543.3		1. 7207 2. 577.32
	1. 7203 2. 543.3		1. 7208 2. 577.32
	1. 7204 2. 555.31		1. 7209 2. 581.32
	1. 7205 2. 577.32		1. 7210 2. 581.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7211 2. 588.32		1. 7216 2. 591.33
	1. 7212 2. 588.32		1. 7217 2. 593.33
	1. 7213 2. 591.33		1. 7218 2. 593.33
	1. 7214 2. 591.33		1. 7219 2. 593.33
	1. 7215 2. 591.33		1. 7220 2. 595.33

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7221 2. 597.33		1. 7226 2. 603.33
	1. 7222 2. 597.33		1. 7227 2. 603.33
	1. 7223 2. 597.33		1. 7228 2. 607.33
	1. 7224 2. 599.33		1. 7229 2. 607.14
	1. 7225 2. 599.33		1. 7230 2. 611.34

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7231 2. 613.34		1. 7236 2. 631.35
	1. 7232 2. 605.33		1. 7237 2. 631.35
	1. 7233 2. 621.34		1. 7238 2. 631.35
	1. 7234 2. 623.34		1. 7239 2. 631.35
	1. 7235 2. 627.34		1. 7240 2. 631.35

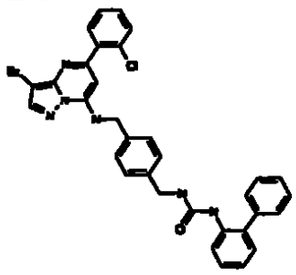
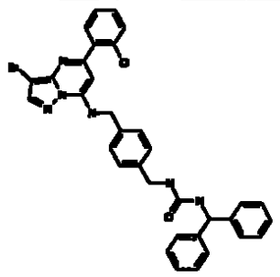
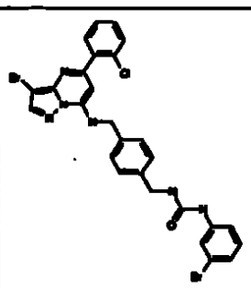
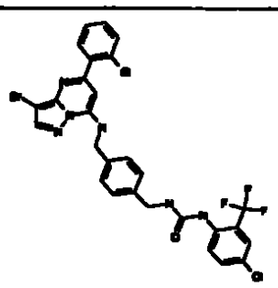
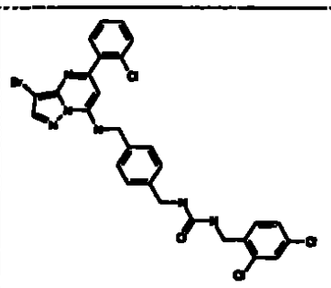
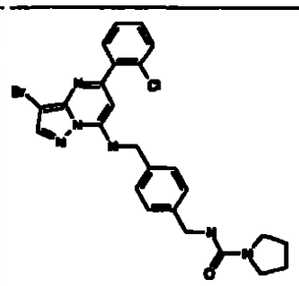
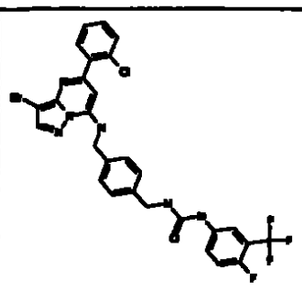
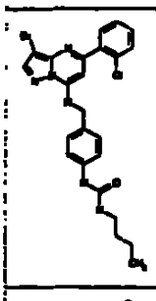
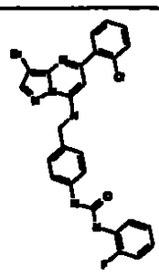
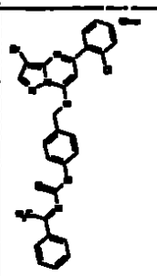
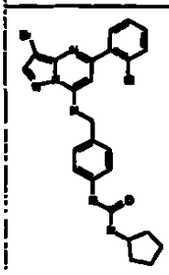
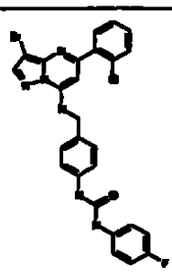
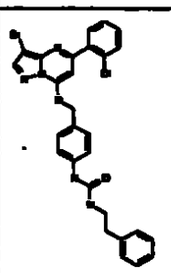
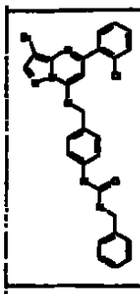
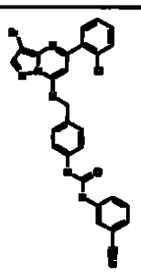
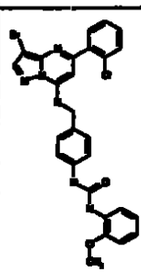
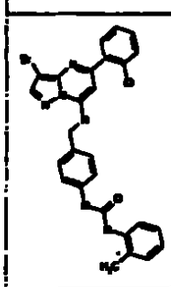
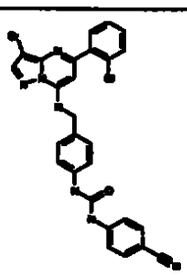
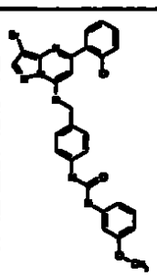
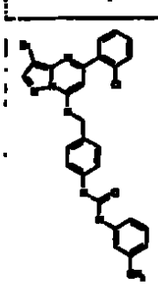
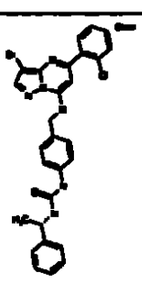
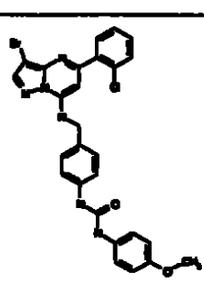
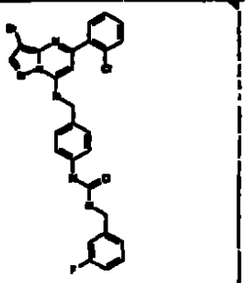
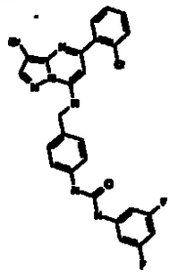
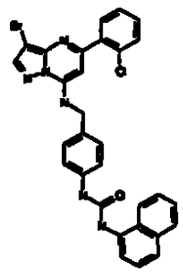
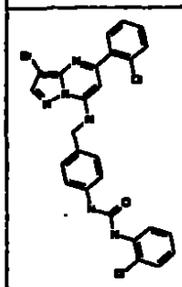
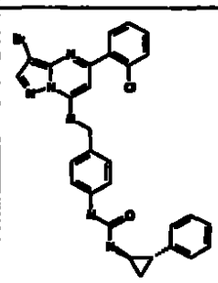
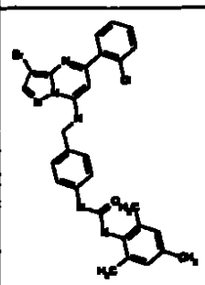
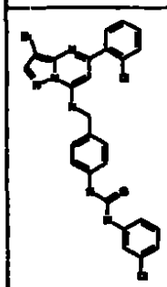
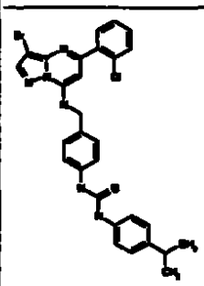
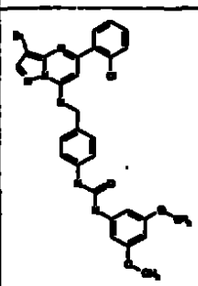
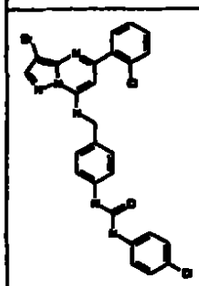
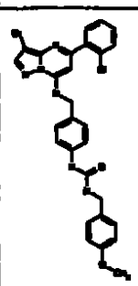
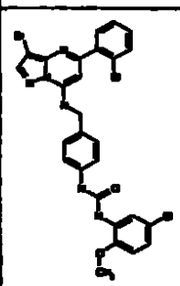
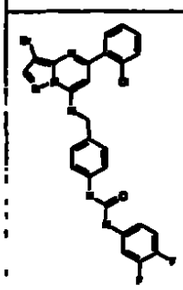
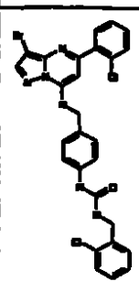
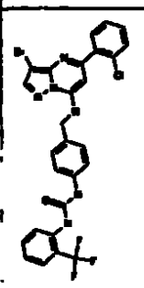
Product	1. Ex. 2. m/z		Product	1. Ex. 2: m/z
	1. 7241 2. 639.35			1. 7246 2. 653.36
	1. 7242 2. 641.35			1. 7247 2. 665.37
	1. 7243 2. 645.35			
	1. 7244 2. 541.3			
	1. 7245 2. 649.36			

TABLE 73

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7301 2. 529.29		1. 7306 2. 567.31		1. 7311 2. 577.32
	1. 7302 2. 541.3		1. 7307 2. 567.31		1. 7312 2. 577.32
	1. 7303 2. 563.13		1. 7308 2. 574.32		1. 7313 2. 579.32
	1. 7304 2. 563.31		1. 7309 2. 574.32		1. 7314 2. 579.32
	1. 7305 2. 563.31		1. 7310 2. 577.32		1. 7315 2. 579.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7316 2. 581.32		1. 7321 2. 585.32		1. 7326 2. 599.33
	1. 7317 2. 583.32		1. 7322 2. 589.32		1. 7327 2. 591.33
	1. 7318 2. 583.32		1. 7323 2. 591.33		1. 7328
	1. 7319 2. 583.32		1. 7324 2. 593.33		1.7329 2. 613.34
	1. 7320 2. 585.32		1. 7325 2. 597.33		1. 7330 2. 617.34

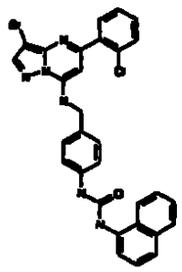
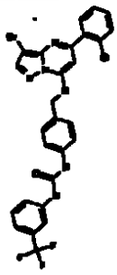
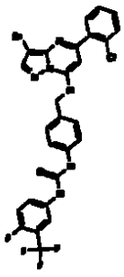
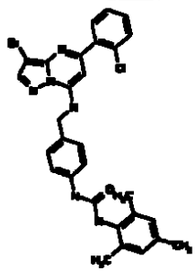
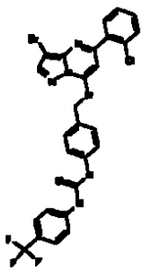
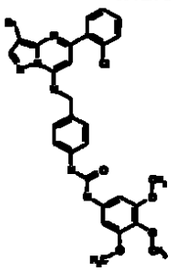
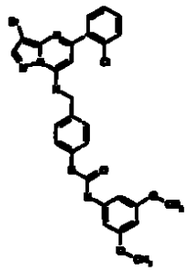
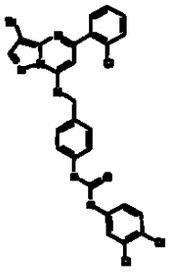
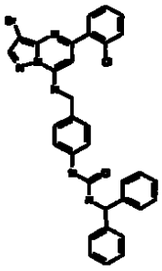
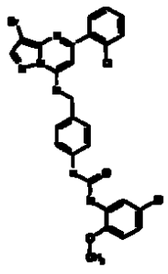
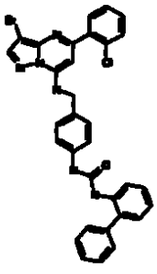
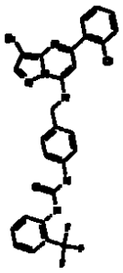
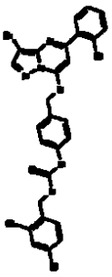
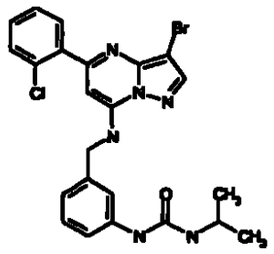
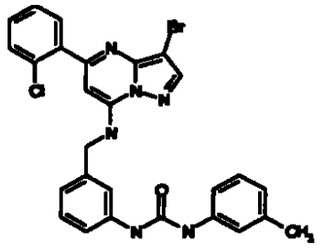
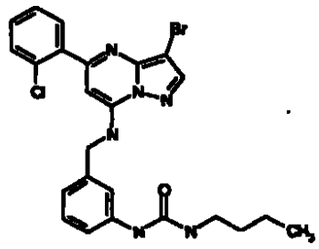
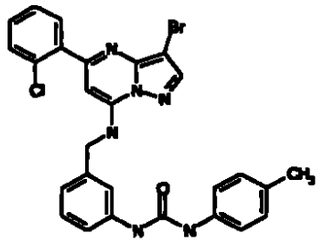
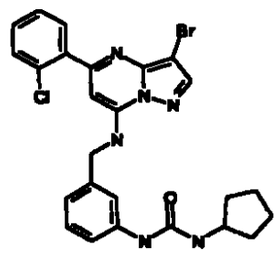
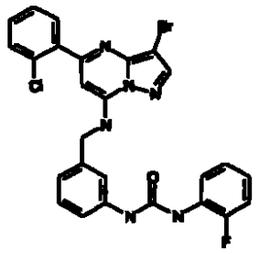
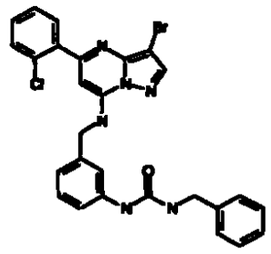
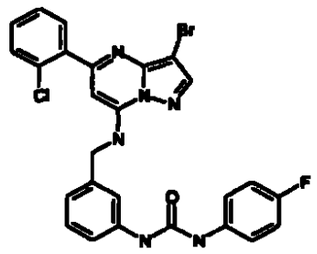
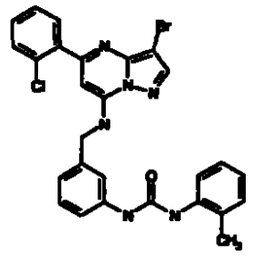
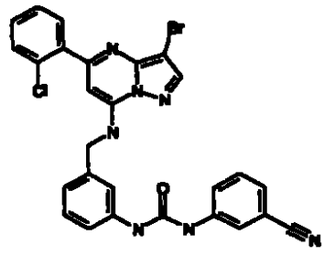
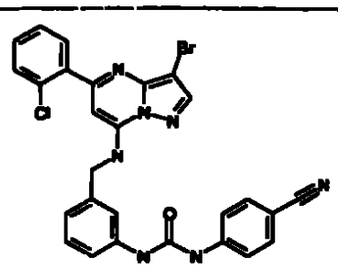
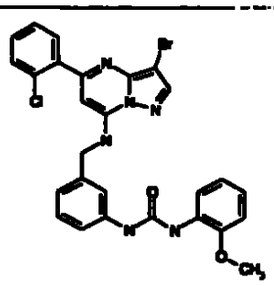
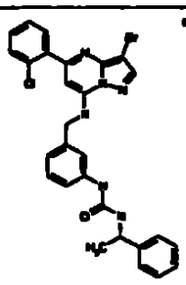
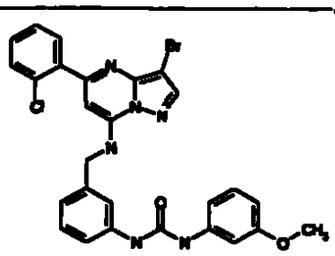
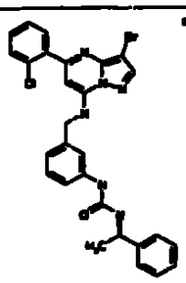
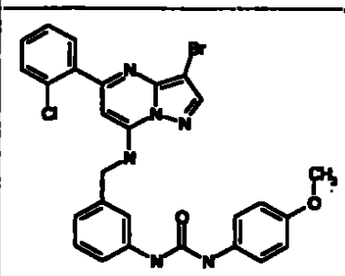
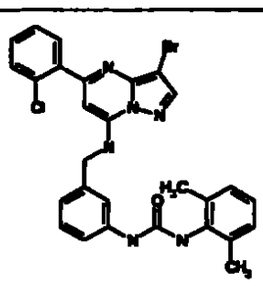
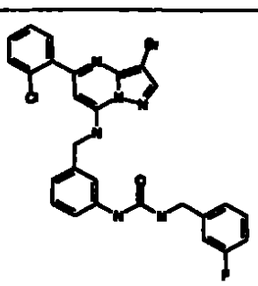
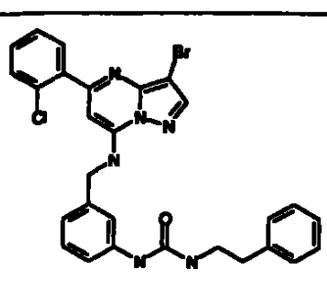
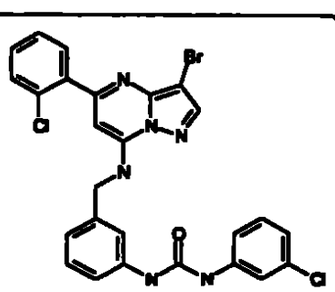
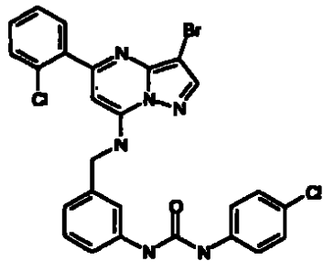
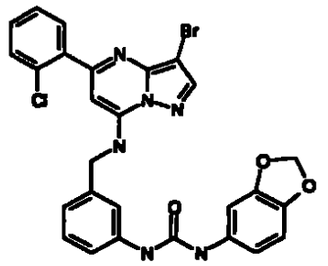
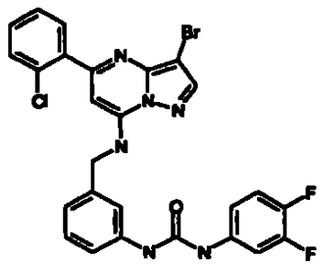
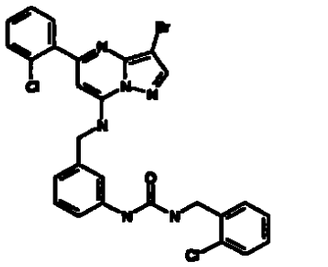
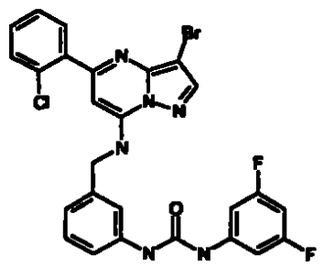
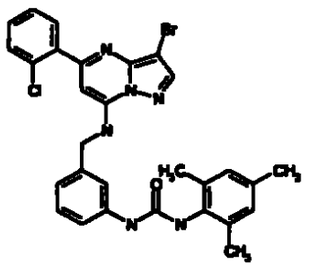
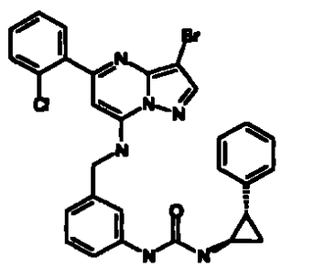
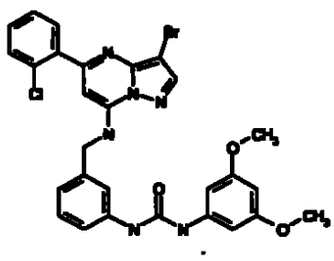
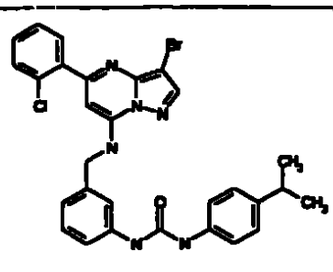
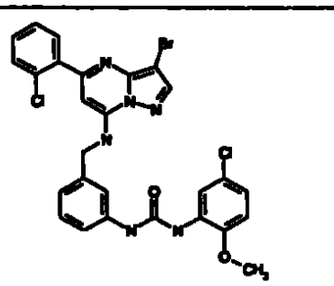
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7331 2. 599.33		1. 7336 2. 617.34		1. 73412. 635.35
	1. 7332 2. 591.33		1. 7337 2. 617.34		1. 7342 2. 639.35
	1. 7333 2. 609.33		1. 7338 2. 617.34		1. 7343 2. 639.35
	1. 7334 2. 613.34		1. 7339 2. 625.34		
	1. 7335 2. 617.34		1. 7340 2. 631.35		

TABLE 74

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7401 2. 515.28		1. 7406 2. 563.31
	1. 7402 2. 529.29		1. 7407 2. 563.31
	1. 7403 2. 541.3		1. 7408 2. 567.31
	1. 7404 2. 563.13		1. 7409 2. 567.31
	1. 7405 2. 563.31		1. 7410 2. 574.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7411 2. 574.32		1. 7416 2. 579.32
	1. 7412 2. 577.14		1. 741 7 2. 579.32
	1. 7413 2. 577.32		1. 7418 2. 579.32
	1. 7414 2. 577.32		1. 7419 2. 581.32
	1. 7415 2. 577.32		1. 7420 2. 583.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7421 2. 583.32		1. 7426 2. 593.33
	1. 7422 2. 585.32		1. 7427 2. 597.33
	1. 7423 2. 585.32		1. 7428 2. 591.33
	1. 7424 2. 589.32		1. 7429 2. 609.33
	1. 7425 2. 591.33		1. 7430 2. 613.34

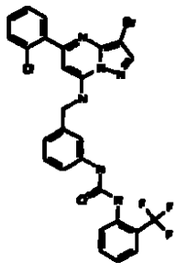
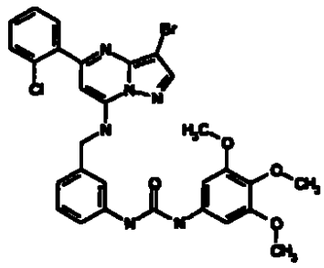
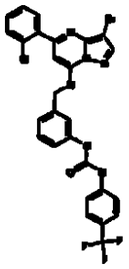
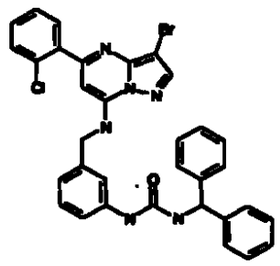
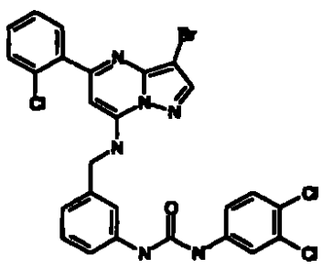
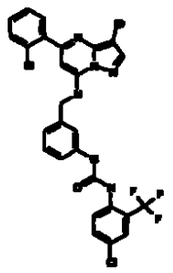
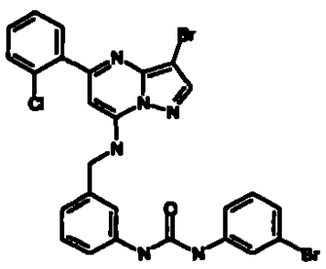
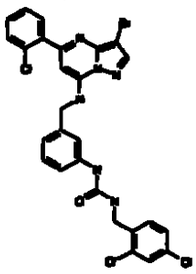
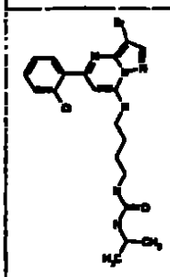
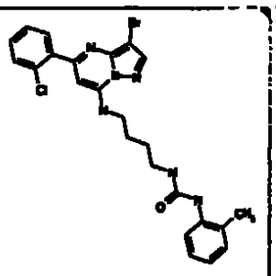
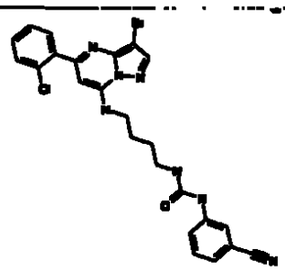
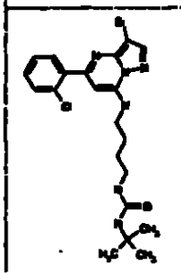
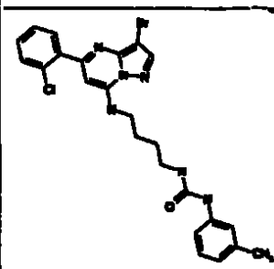
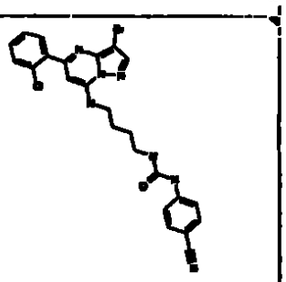
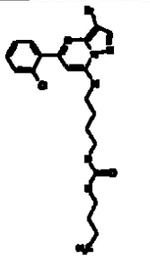
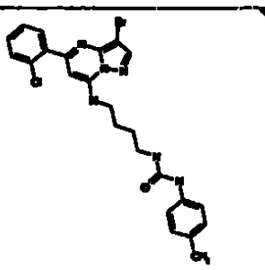
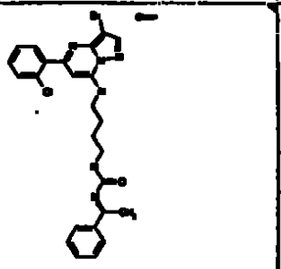
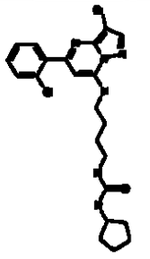
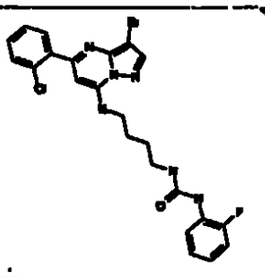
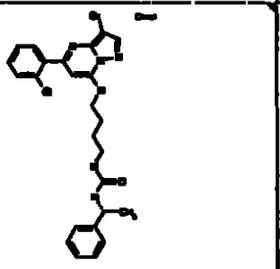
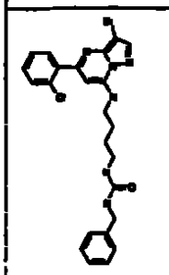
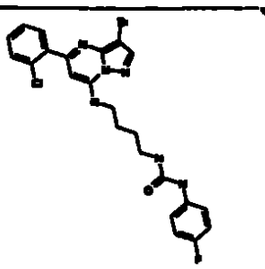
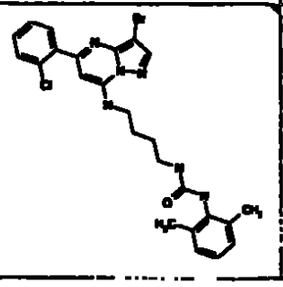
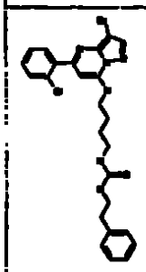
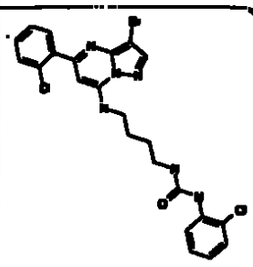
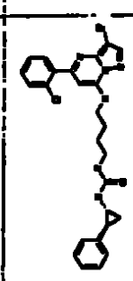
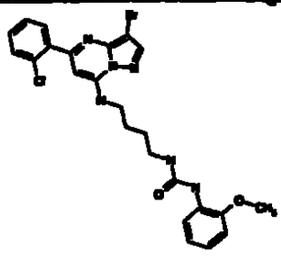
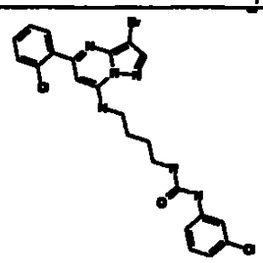
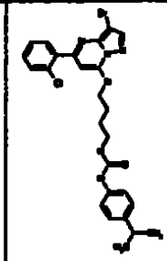
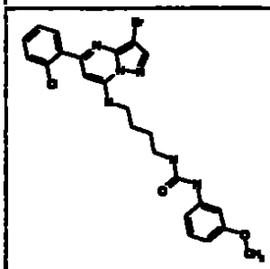
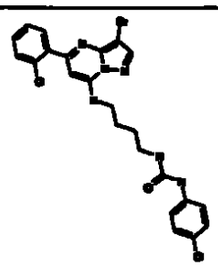
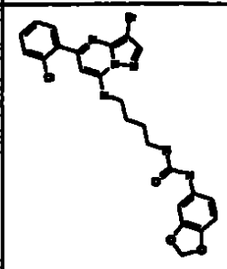
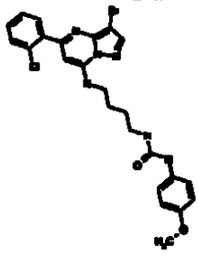
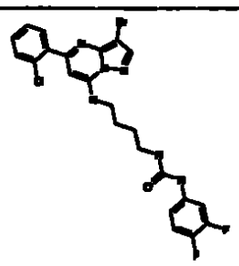
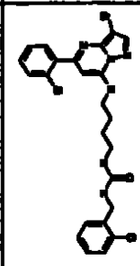
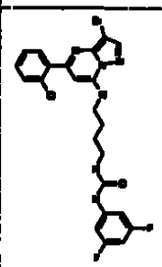
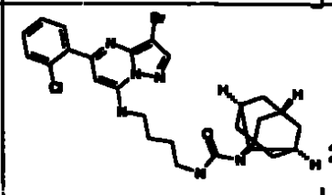
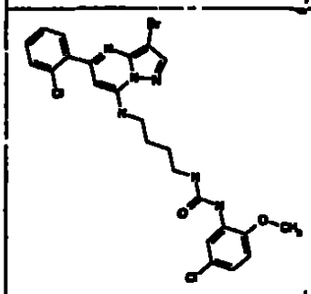
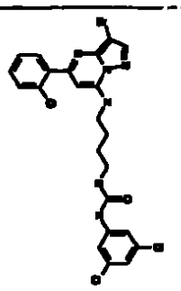
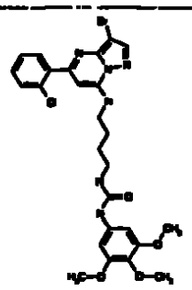
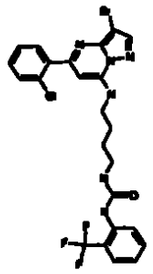
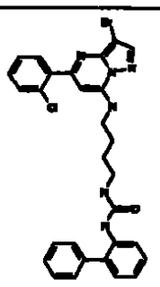
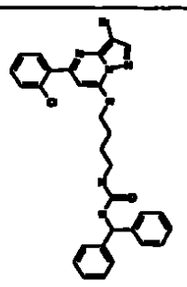
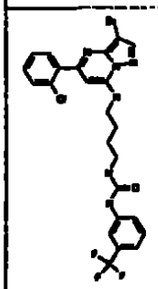
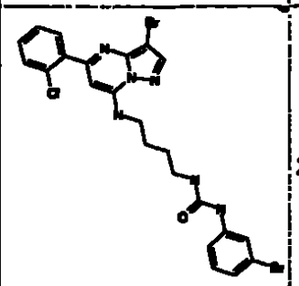
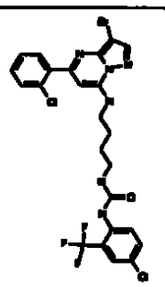
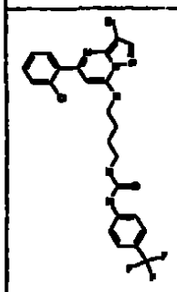
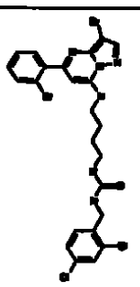
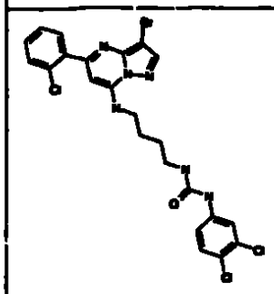
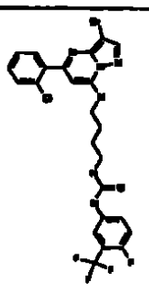
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7431 2. 617.34		1. 7436 2. 639.35
	1. 7432 2. 617.34		1. 7437 2. 639.35
	1. 7433 2. 617.34		1. 7438 2. 651.36
	1. 7434 2. 627.34		
	1. 7435 2. 631.35		

TABLE75

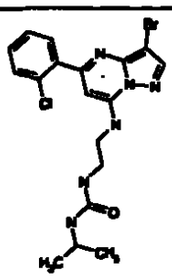
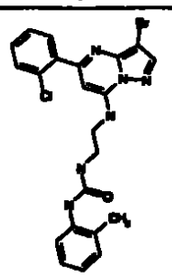
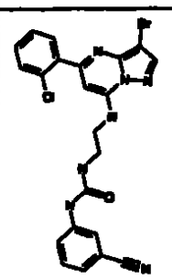
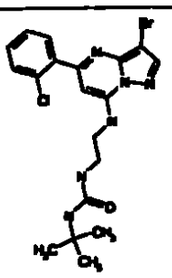
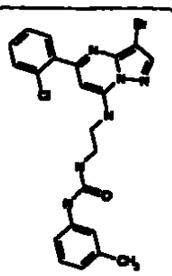
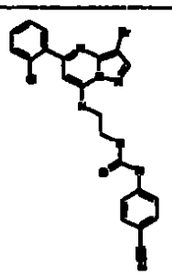
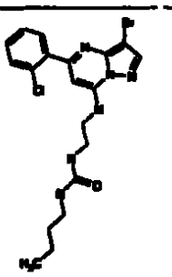
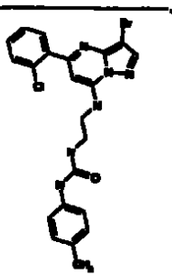
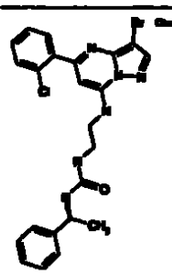
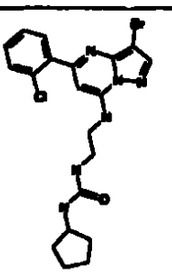
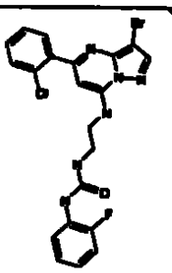
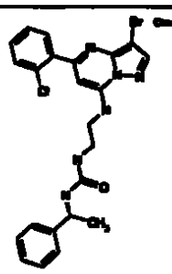
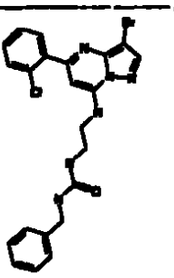
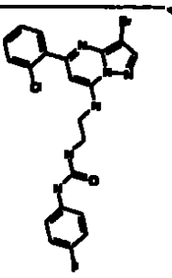
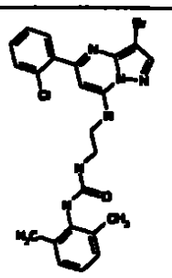
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7501 2. 481.26		1. 7506 2. 529.29		1. 7511 2. 540.3
	1. 7502 2. 495.27		1. 7507 2. 529.29		1. 7512 2. 540.3
	1. 7503 2. 495.27		1. 7508 2. 529.29		1. 7513 2. 543.3
	1. 7504 2. 507.28		1. 7509 2. 533.29		1. 7514 2. 543.3
	1. 7505 2. 529.29		1. 7510 2. 533.29		1. 7515 2. 543.3

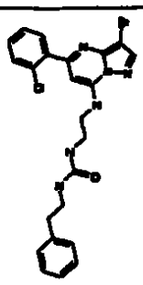
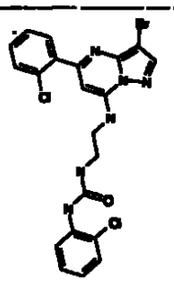
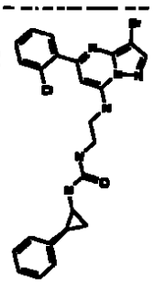
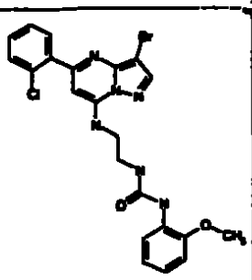
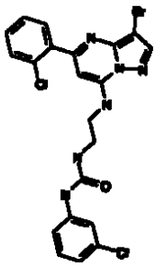
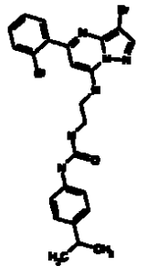
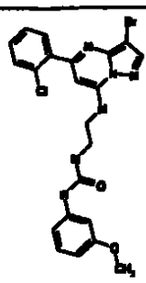
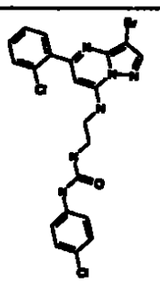
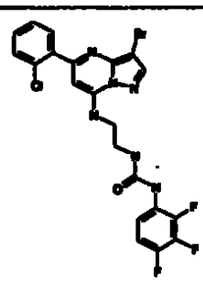
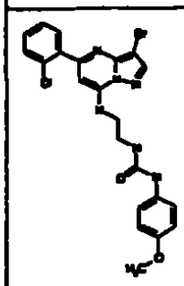
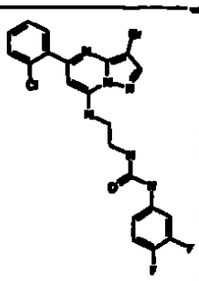
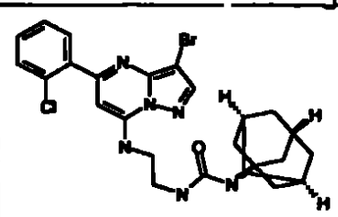
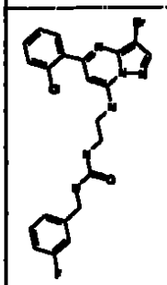
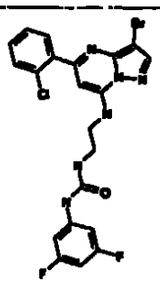
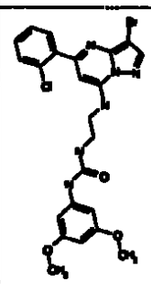
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7516 2. 543.3		1. 7521 2. 549.3		1. 7526 2. 555.31
	1. 7517 2. 545.3		1. 7522 2. 549.3		1. 7527 2. 557.31
	1. 7518 2. 545.3		1. 7523 2. 549.3		1. 7528 2. 559.31
	1. 7519 2. 545.3		1. 7524 2. 551.3		1. 7529 2. 560.31
	1. 7520 2. 547.3		1. 7525 2. 551.3		1. 7530 2. 573.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7531 2. 579.32		1. 7536 2. 583.32		1. 7541 2. 605.33
	1. 7532 2. 583.32		1. 7537 2. 591.33		1. 7542 2. 605.33
	1. 7533 2. 583.32		1. 7538 2. 593.33		1. 7543 2. 614.34
	1. 7534 2. 583.32		1. 7539 2. 597.33		
	1. 7535 2. 583.32		1. 7540 2. 601.33		

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
	1. 7620 2. 519.29		1. 7625 2. 523.29		1. 7630 2. 547.3

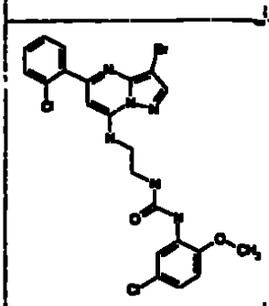
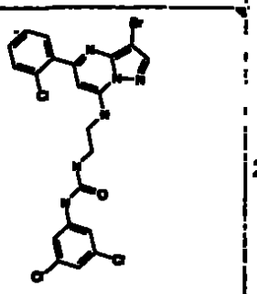
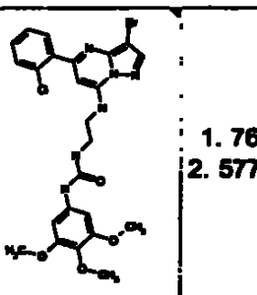
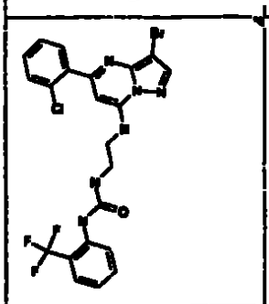
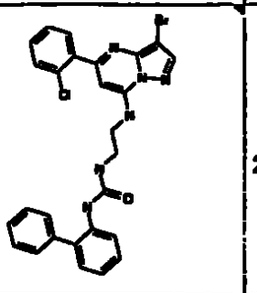
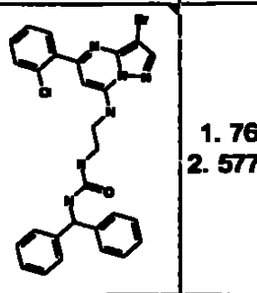
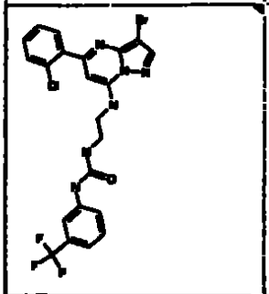
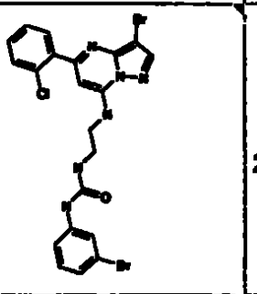
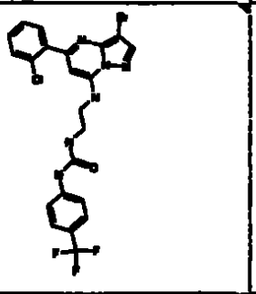
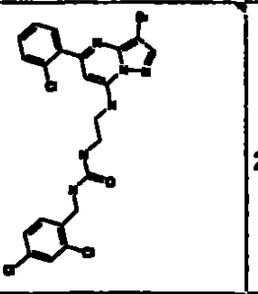
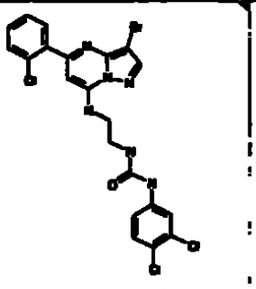
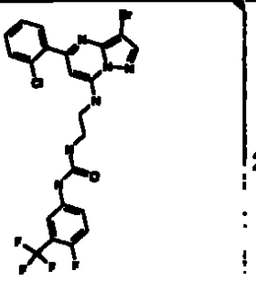
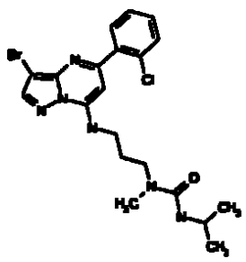
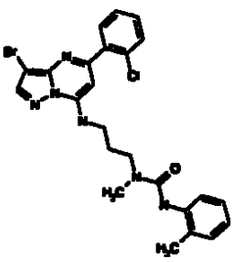
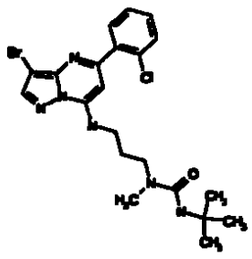
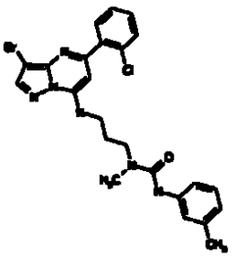
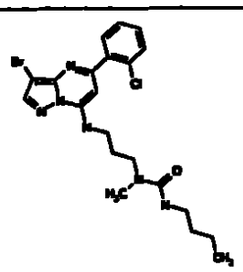
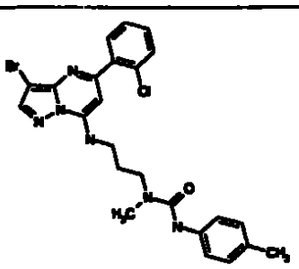
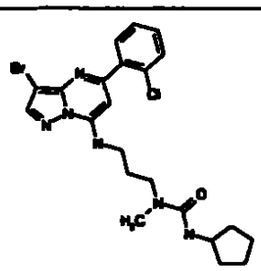
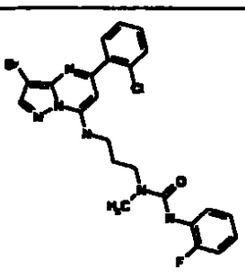
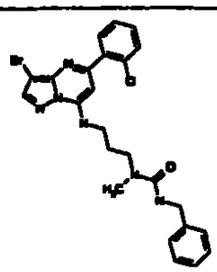
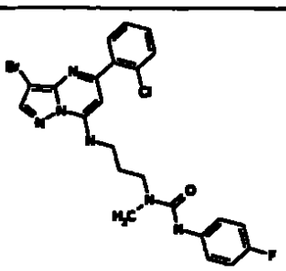
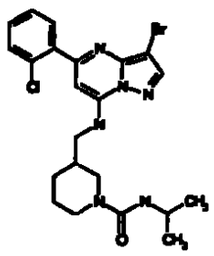
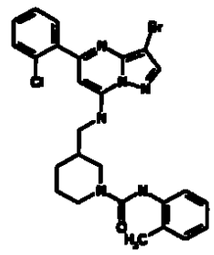
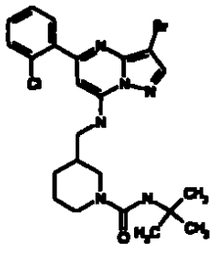
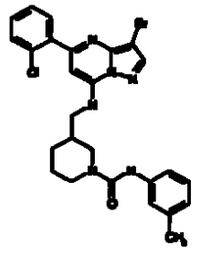
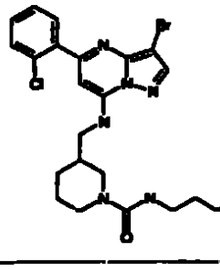
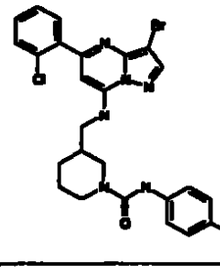
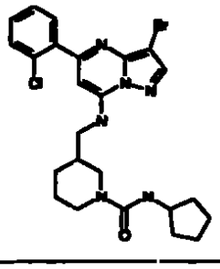
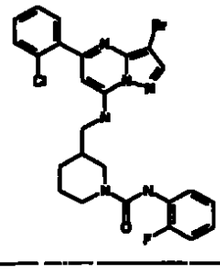
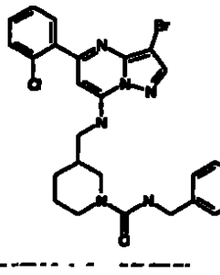
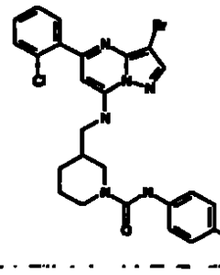
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7631 2. 551.3		1. 7636 2. 555.31		1. 7641 2. 577.32
	1. 7632 2. 555.31		1. 7637 2. 563.31		1. 7642 2. 577.32
	1. 7633 2. 555.31		1. 7638 2. 565.31		
	1. 7634 2. 555.31		1. 7639 2. 589.31		
	1. 7635 2. 555.31		1. 7640 2. 573.32		

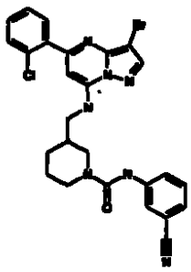
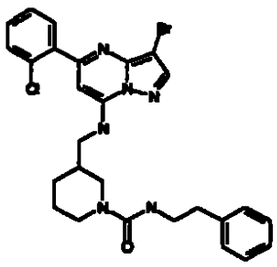
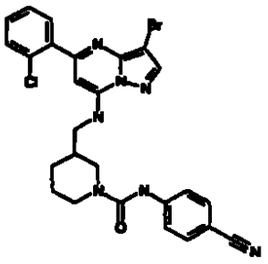
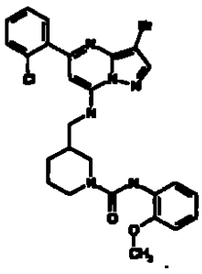
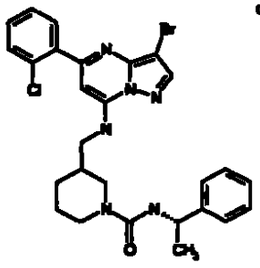
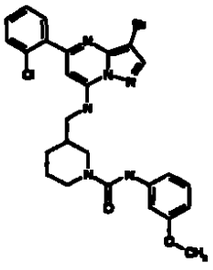
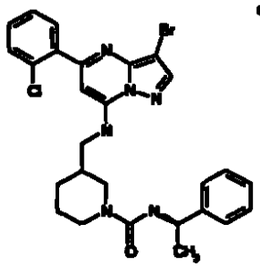
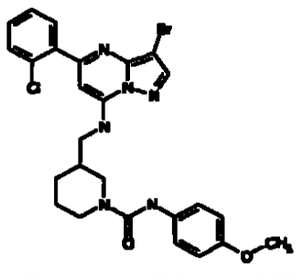
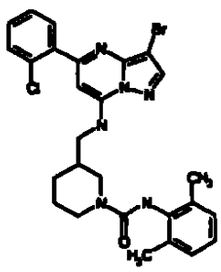
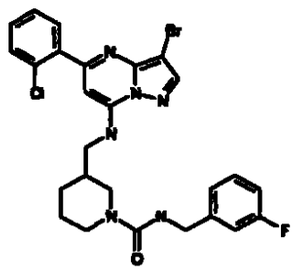
TABLE 77

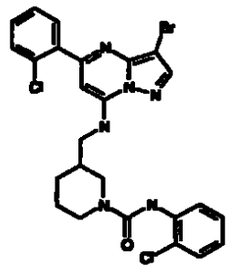
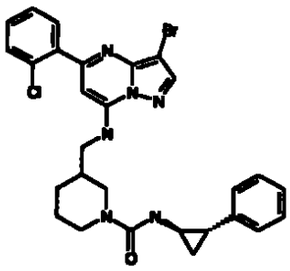
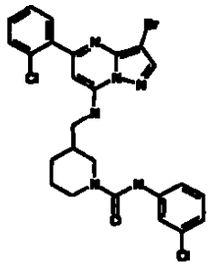
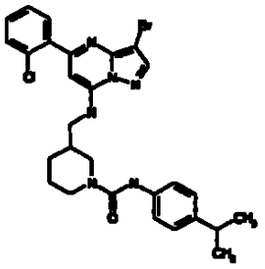
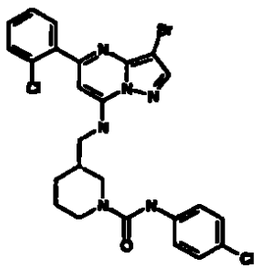
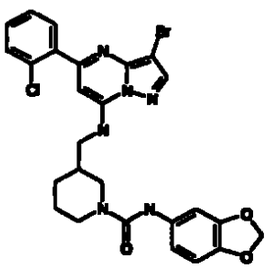
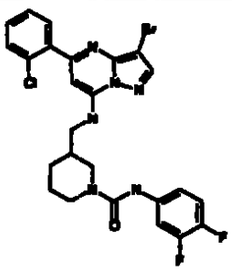
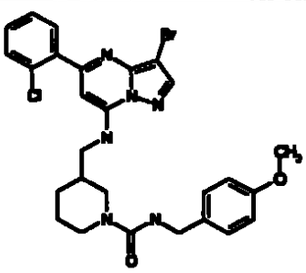
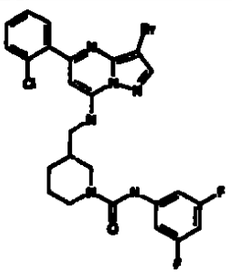
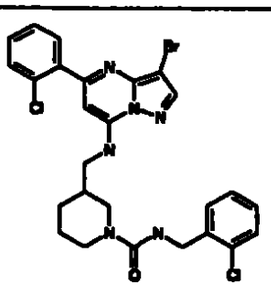
Product	1. Ex. 2. m/z		Product	1. Ex. 2. m/z
	1. 7701 2. 481.26			1. 7706 2. 529.29
	1. 7702 2. 495.27			1. 7707 2. 529.29
	1. 7703 2. 495.27			1. 7708 2. 529.29
	1. 7704 2. 507.26			1. 7709 2. 533.29
	1. 7705 2. 529.29			1. 7710 2. 533.29

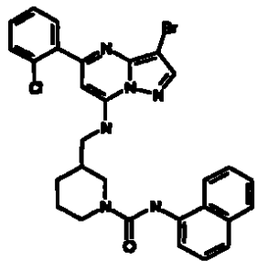
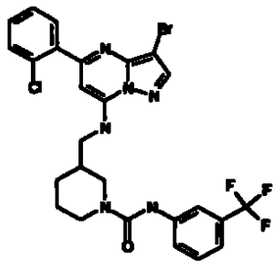
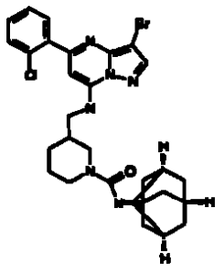
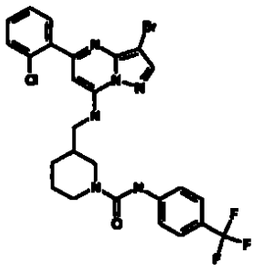
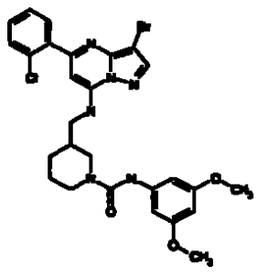
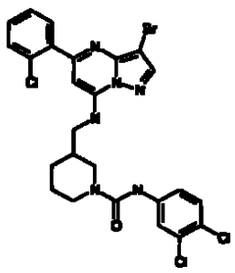
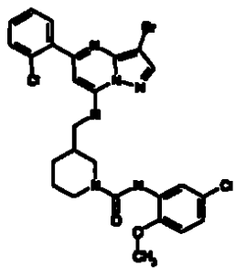
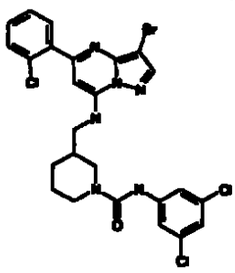
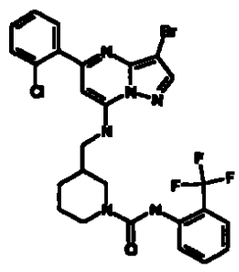
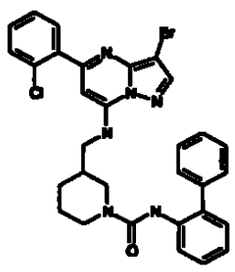
5

TABLE 78

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7801 2. 507.28		1. 7806 2. 555.31
	1. 7802 2. 521.29		1. 7807 2. 555.31
	1. 7803 2. 521.29		1. 7808 2. 555.31
	1. 7804 2. 533.29		1. 7809 2. 559.31
	1. 7805 2. 555.31		1. 7810 2. 559.31

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7811 2. 566.31		1. 7816 2. 569.31
	1. 7812 2. 566.31		1. 7817 2. 571.31
	1. 7813 2. 569.31		1. 7818 2. 571.31
	1. 7814 2. 569.31		1. 7819 2. 571.31
	1. 7815 2. 569.31		1. 7820 2. 573.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7821 2. 575.32		1. 7826 2. 581.32
	1. 7822 2. 575.32		1. 7827 2. 583.32
	1. 7823 2. 575.32		1. 7828 2. 585.32
	1. 7824 2. 577.32		1. 7829 2. 585.32
	1. 7825 2. 577.32		1. 7830 2. 589.32

Product	1. Ex. 2. m/z.		Product	1. Ex. 2. m/z
	1. 7831 2. 591.33			1. 7836 2. 609.33
	1. 7832 2. 599.33			1. 7837 2. 609.33
	1. 7833 2. 601.33			1. 7838 2. 609.33
	1. 7834 2. 605.33			1. 7839 2. 609.33
	1. 7835 2. 609.33			1. 7840 2. 617.34

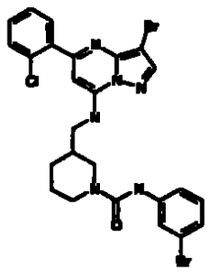
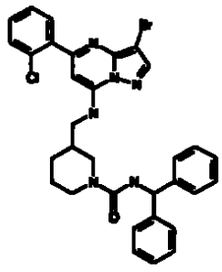
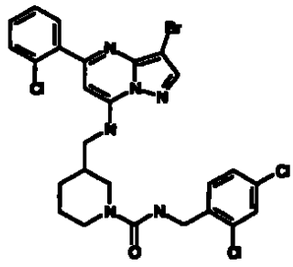
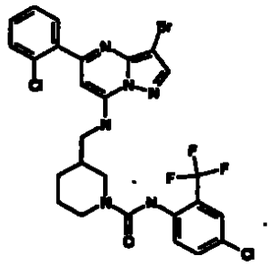
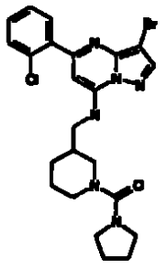
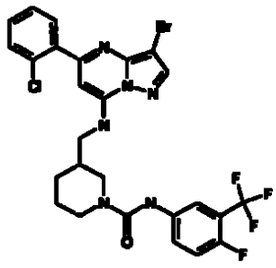
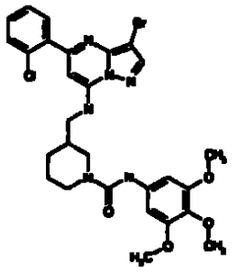
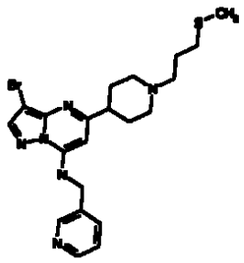
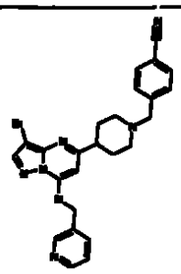
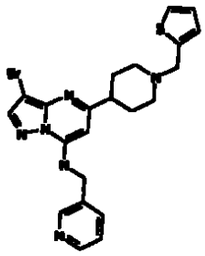
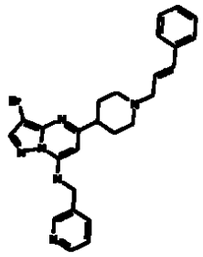
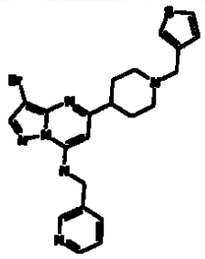
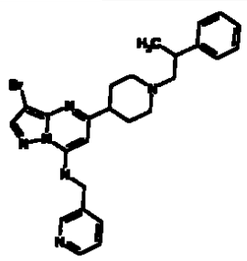
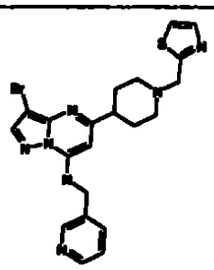
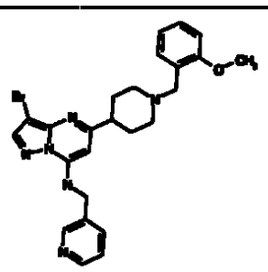
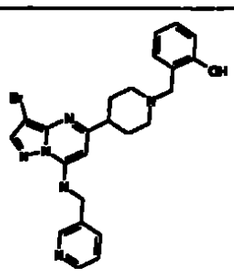
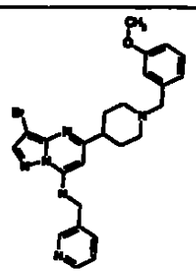
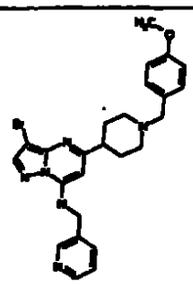
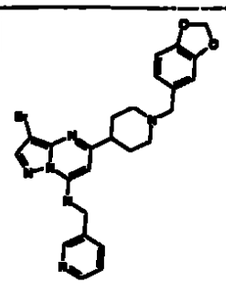
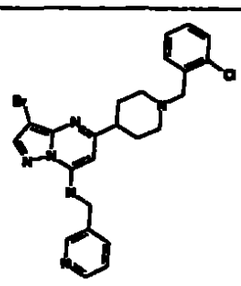
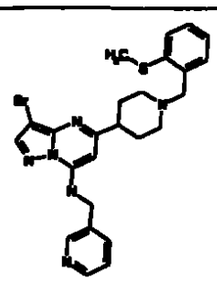
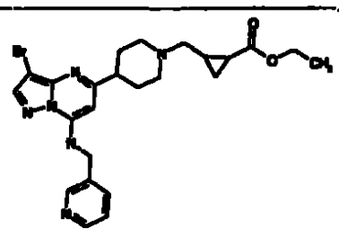
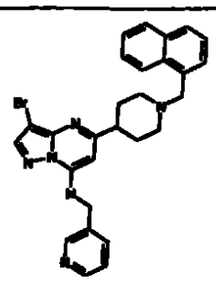
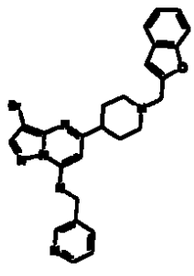
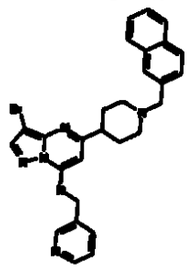
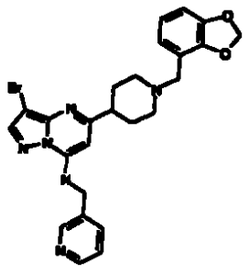
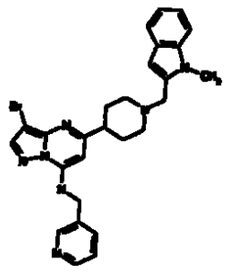
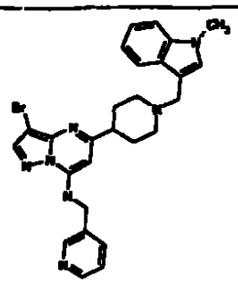
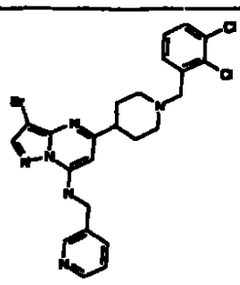
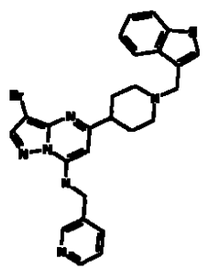
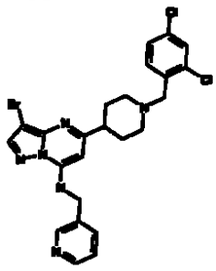
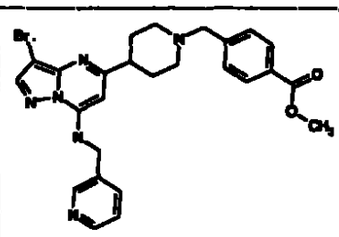
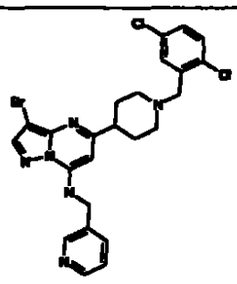
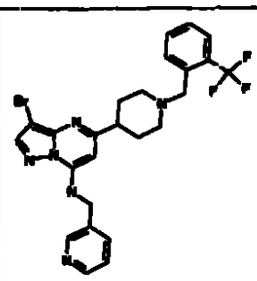
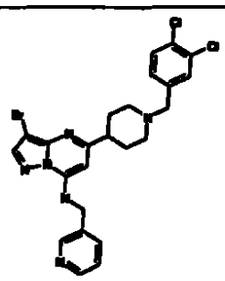
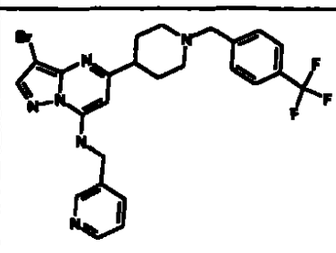
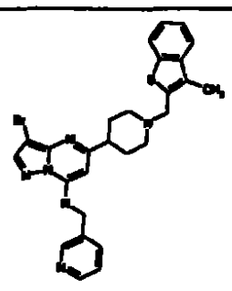
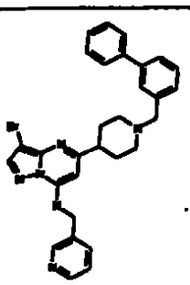
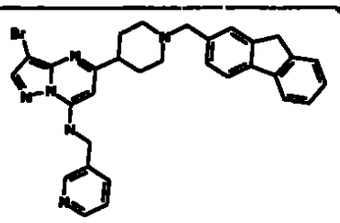
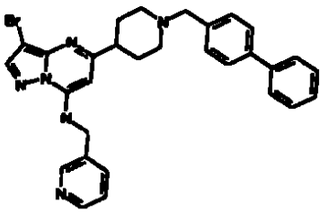
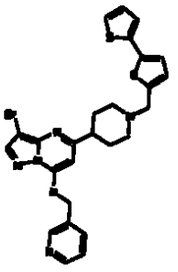
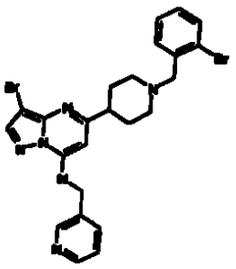
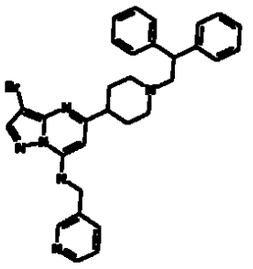
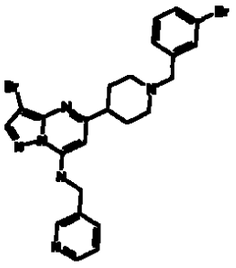
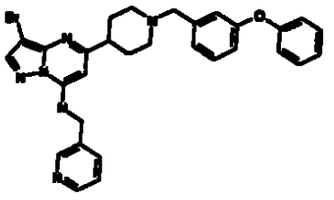
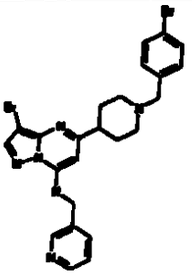
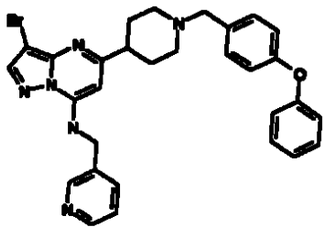
Product	1. Ex. 2. m/z		Product	1. Ex. 2. m/z
	1. 7841 2. 619.34			1. 7846 2. 631.35
	1. 7842 2. 623.34			1. 7847 2. 643.35
	1. 7843 2. 519.29			
	1. 7844 2. 627.34			
	1. 7845 2. 631.35			

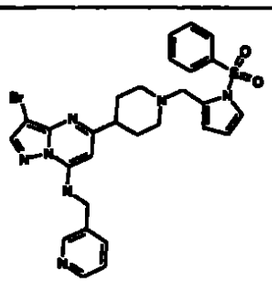
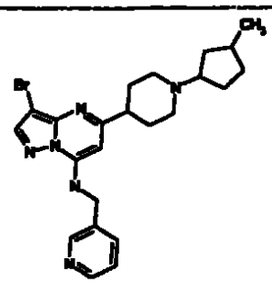
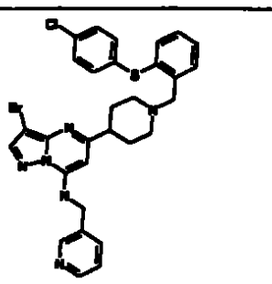
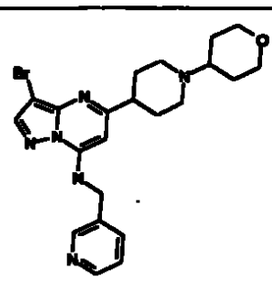
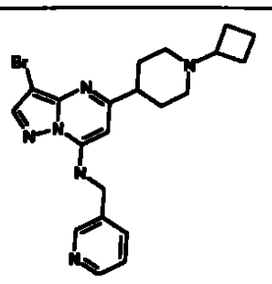
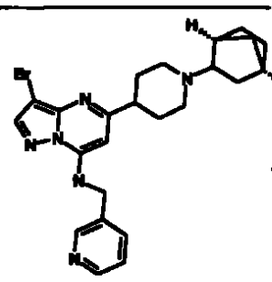
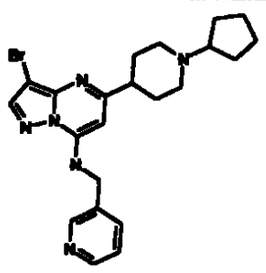
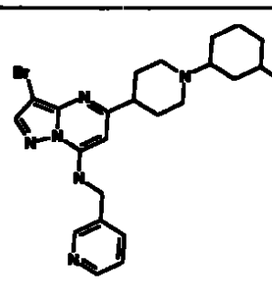
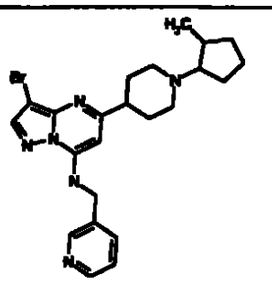
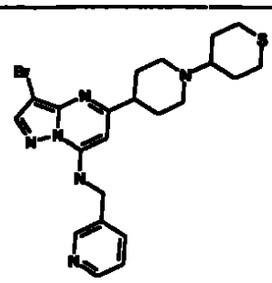
TABLE 79

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7901 2. 477.26		1. 7906 2. 504.28
	1. 7902 2. 485.27		1. 7907 2. 505.28
	1. 7903 2. 485.27		1. 7908 2. 507.28
	1. 7904 2. 486.27		1. 7909 2. 509.28
	1. 7905 2. 495.27		1. 7910 2. 509.28

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7911 2. 509.28		1. 7916 2. 523.29
	1. 7912 2. 513.28		1. 7917 2. 525.29
	1. 7913 2. 515.28		1. 7918 2. 529.29
	1. 7914 2. 519.29		1. 7919 2. 529.29
	1. 7915 2. 523.29		1. 7920 2. 530.29

Product	1. Ex. 2. m/z		Product	1. Ex. 2. m/z
	1. 7921 2. 530.29			1. 7926 2. 547.3
	1. 7922 2. 535.29			1. 7927 2. 547.3
	1. 7923 2. 537.3			1. 7928 2. 547.3
	1. 7924 2. 547.3			1. 7929 2. 547.3
	1. 7925 2. 547.3			1. 7930 2. 549.3

Product	1. Ex. 2. m/z		Product	1. Ex. 2. m/z
	1. 7931 2. 555.31			1. 7936 2. 567.31
	1. 7932 2. 555.31			1. 7937 2. 567.31
	1. 7933 2. 557.31			1. 7938 2. 569.31
	1. 7934 2. 557.31			1. 7939 2. 571.31
	1. 7935 2. 557.31			1. 7940 2. 571.31

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7941 2. 608.33		1. 7946 2. 471.26
	1. 7942 2. 621.34		1. 7947 2. 473.26
	1. 7943 2. 443.24		1. 7948 2. 483.27
	1. 7944 2. 457.25		1. 7949 2. 485.27
	1. 7945 2. 471.26		1. 7950 2. 489.27

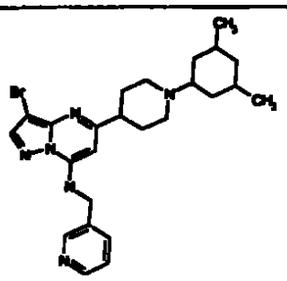
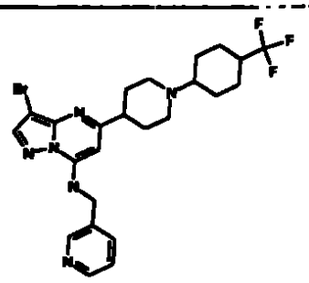
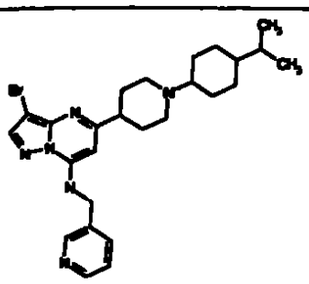
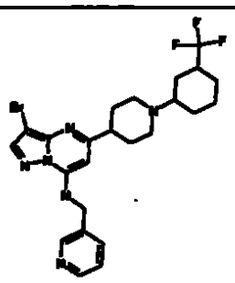
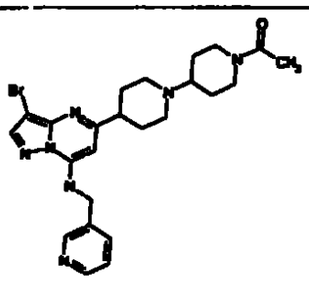
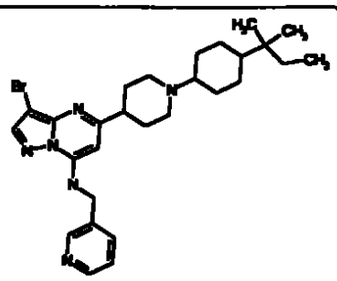
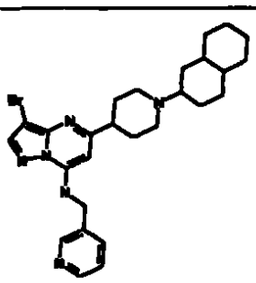
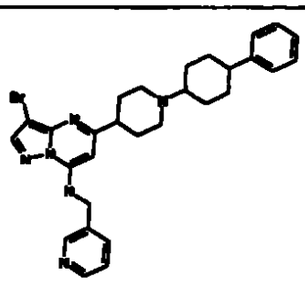
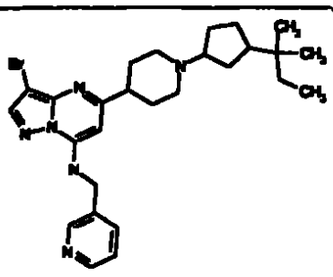
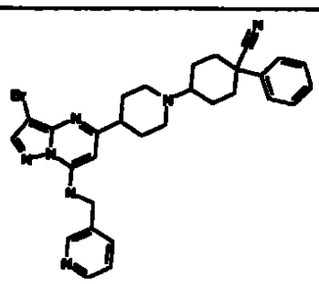
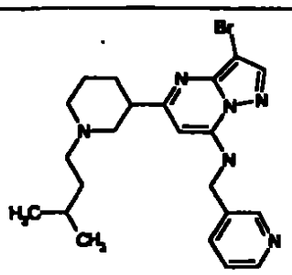
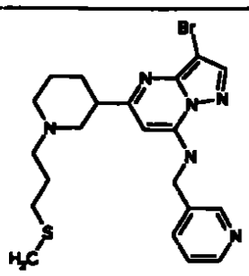
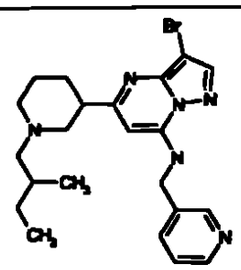
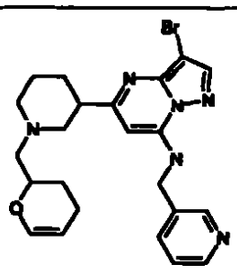
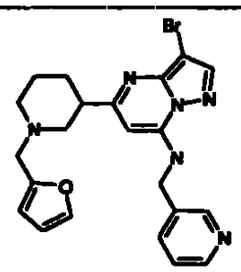
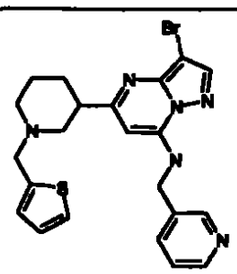
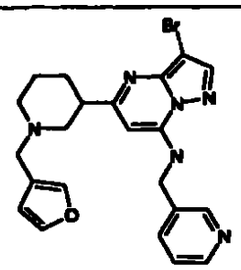
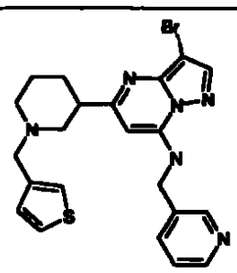
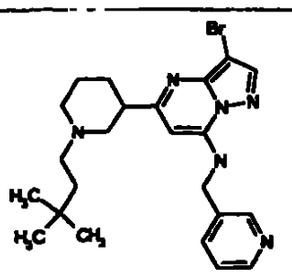
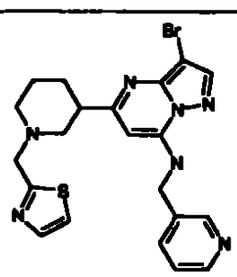
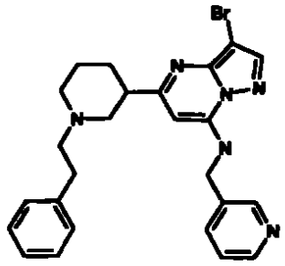
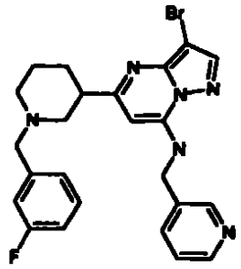
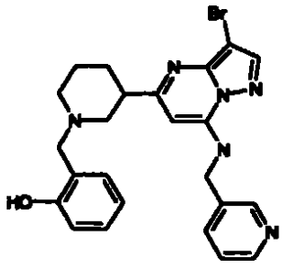
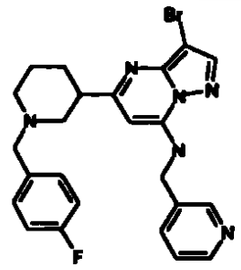
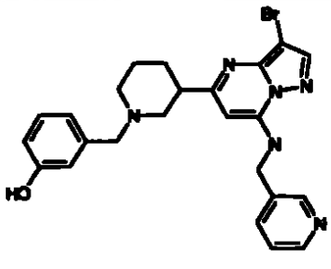
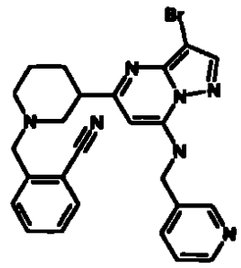
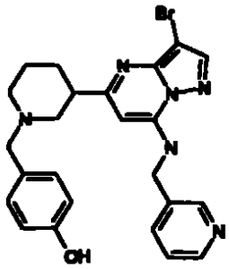
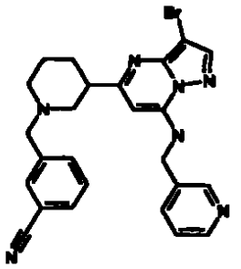
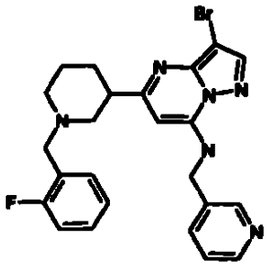
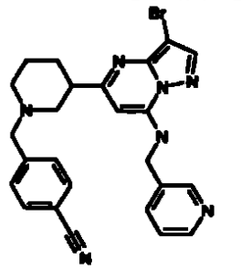
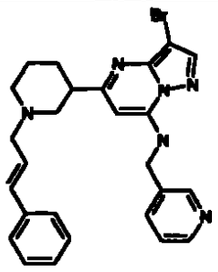
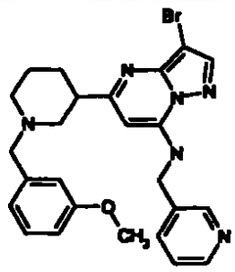
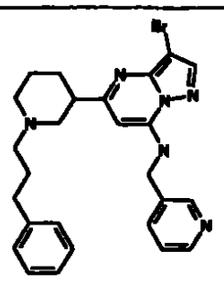
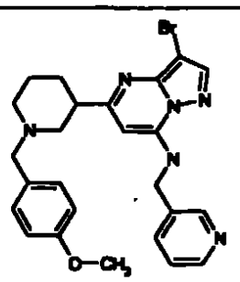
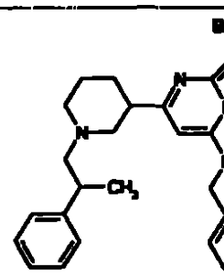
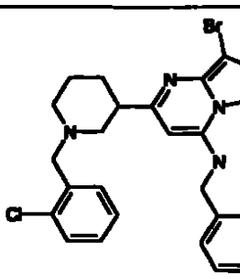
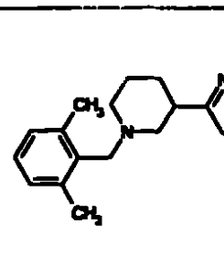
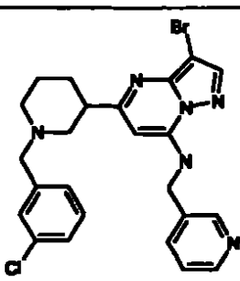
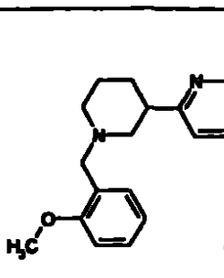
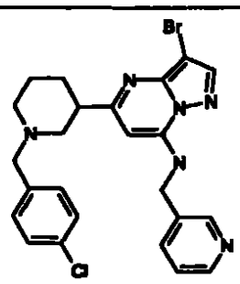
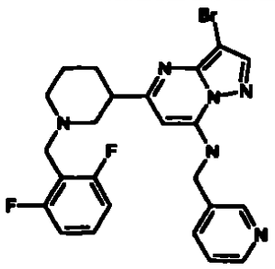
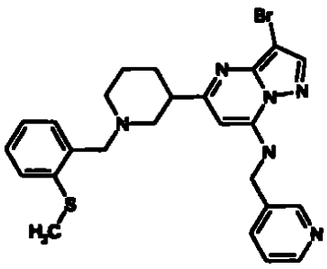
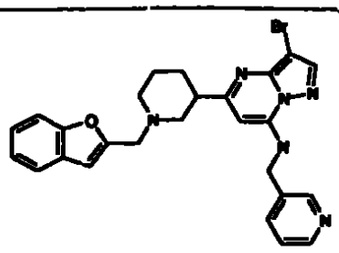
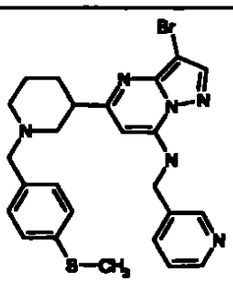
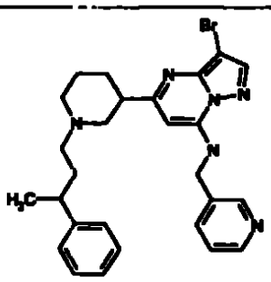
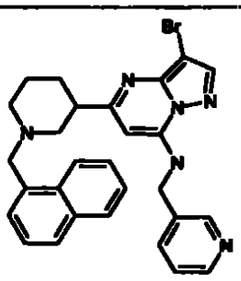
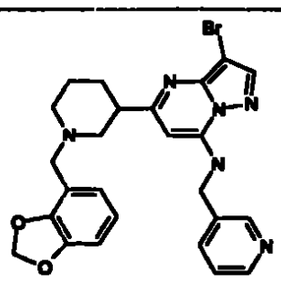
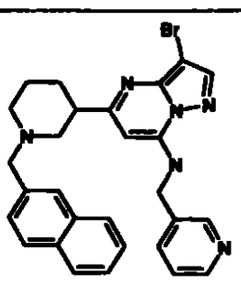
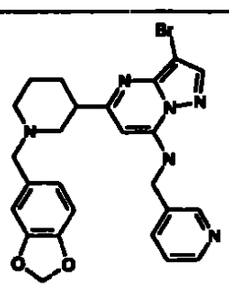
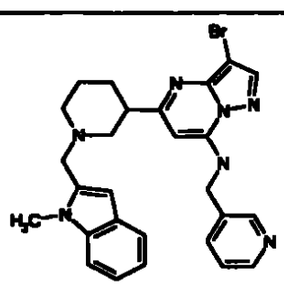
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 7951 2. 499.27		1. 7956 2. 536.29
	1. 7952 2. 513.28		1. 7957 2. 539.3
	1. 7953 2. 514.28		1. 7958 2. 541.3
	1. 7954 2. 525.29		1. 7959 2. 547.3
	1. 7955 2. 525.29		1. 7960 2. 572.31

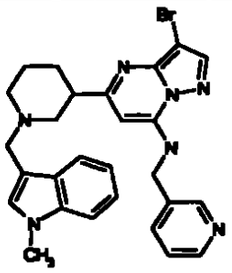
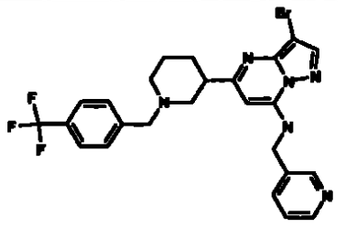
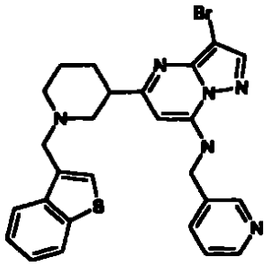
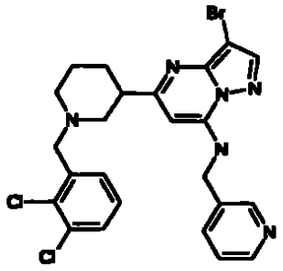
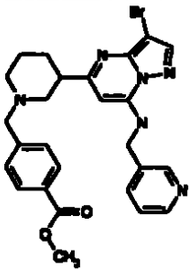
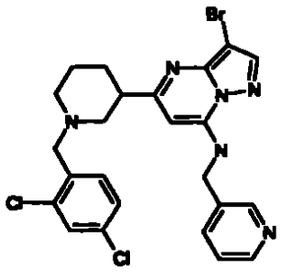
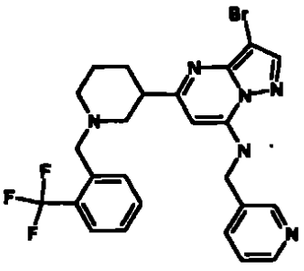
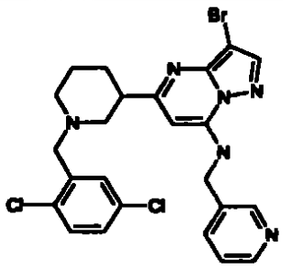
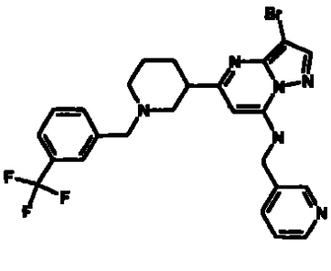
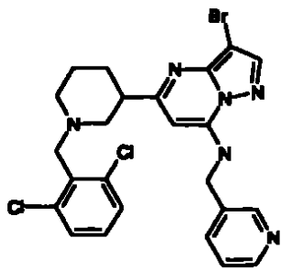
TABLE 80

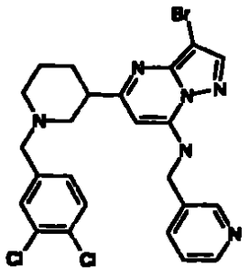
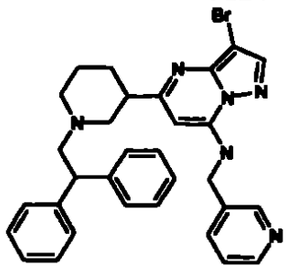
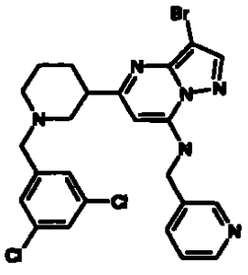
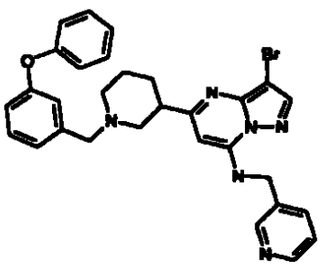
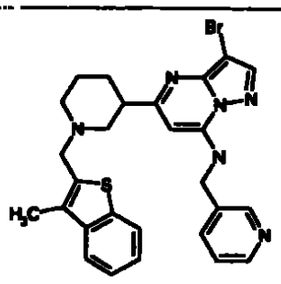
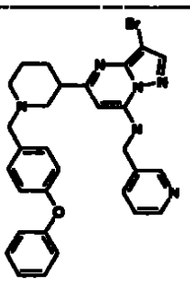
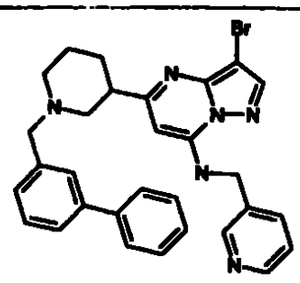
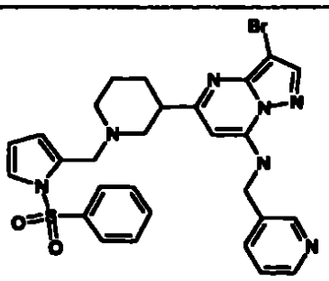
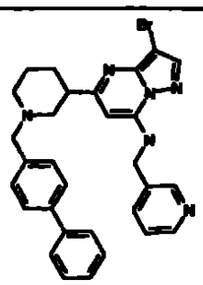
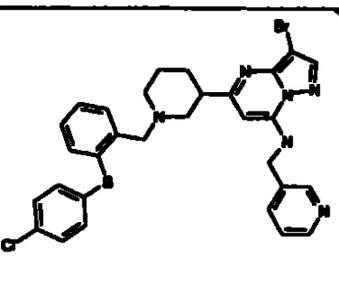
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8001 2. 459.25		1. 8006 2. 477.26
	1.8002 2. 459.25		1. 8007 2 485.27
	1. 8003 2. 469.26		1. 8008 2. 485.27
	1. 8004 2. 469.26		1. 8009 2. 485.27
	1. 8005 2. 473.26		1. 8010 2. 486.27

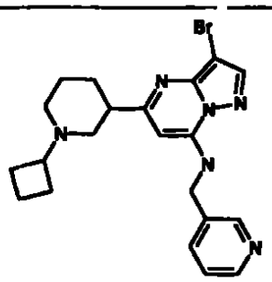
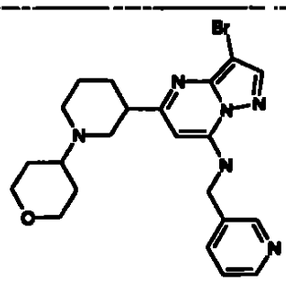
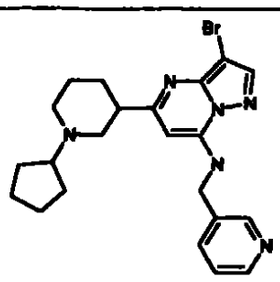
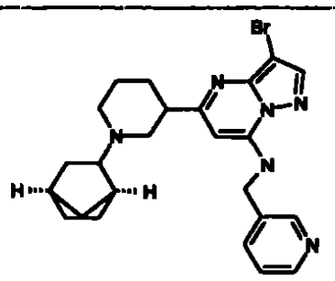
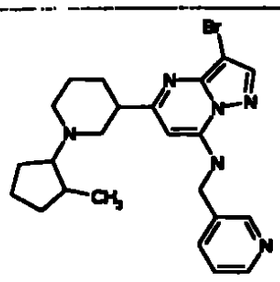
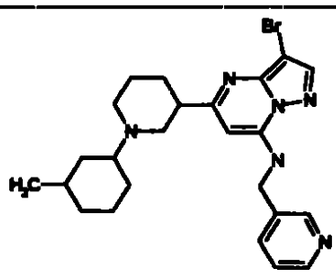
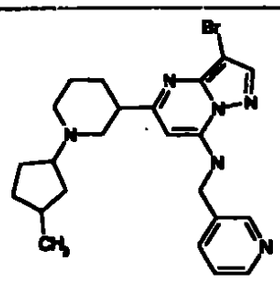
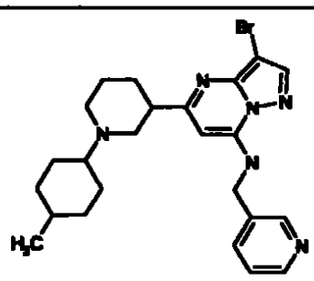
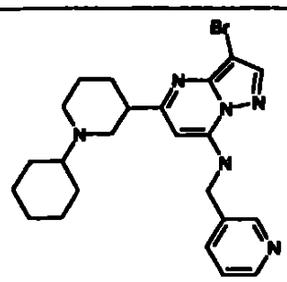
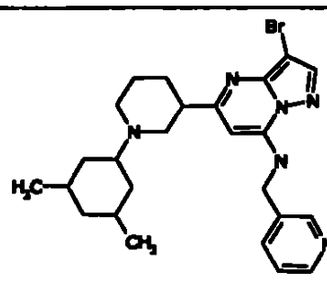
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8011 2. 493.27		1. 8016 2. 495.27
	1. 8012 2. 495.27		1. 8017 2. 495.27
	1. 8013 2. 495.27		1. 8018 2. 502.28
	1. 8014 2. 495.27		1. 8019 2. 502.28
	1. 8015 2. 495.27		1. 8020 2. 502.28

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8021 2. 505.28		1. 8026 2. 509.28
	1. 8022 2. 505.28		1. 8027 2. 509.28
	1. 8023 2. 507.28		1. 8028 2. 513.28
	1. 8024 2. 507.28		1. 8029 2. 513.28
	1. 8025 2. 507.28		1. 8030 2. 513.28

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8031 2. 515.28		1. 8036 2. 523.29
	1. 8032 2. 519.29		1. 8037 2. 525.29
	1. 8033 2. 521.29		1. 8038 2. 529.29
	1. 8034 2. 523.29		1. 8039 2. 529.29
	1. 8035 2. 523.29		1. 8040 2. 530.29

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8041 2. 530.29		1. 8046 2. 547.3
	1. 8042 2. 535.29		1. 8047 2. 544.3
	1. 8043 2. 537.3		1. 8048 2. 547.3
	1. 8044 2. 547.3		1. 8049 2. 547.3
	1. 8045 2. 547.3		1. 8050 2. 547.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8051 2. 548.3		1. 8056 2. 569.31
	1. 8052 2. 548.3		1. 8057 2. 569.31
	1. 8053 2. 547.3		1. 8058 2. 571.31
	1. 8054 2. 555.31		1. 8059 2. 608.33
	1. 8055 2. 553.3		1. 8060 2. 621.34

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8061 2. 443.24		1. 8066 2. 473.26
	1. 8062 2. 457.25		1. 8067 2. 483.27
	1. 8063 2. 471.26		1. 8068 2. 485.27
	1. 8064 2. 471.26		1. 8069 2. 483.27
	1. 8065 2. 469.26		1. 8070 2. 499.27

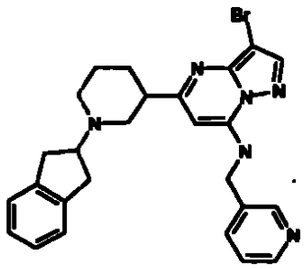
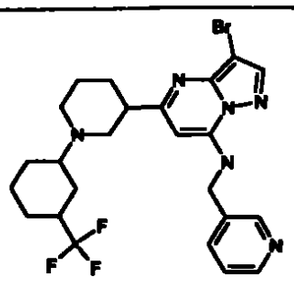
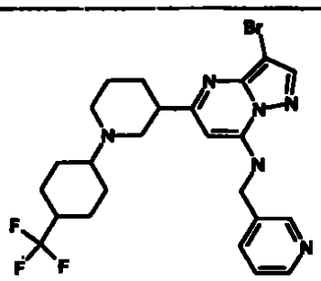
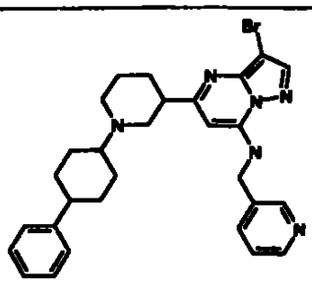
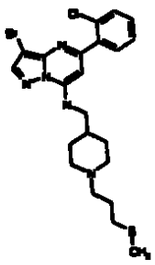
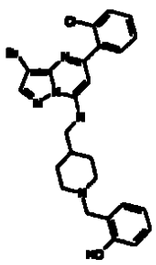
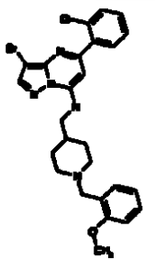
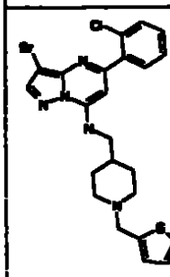
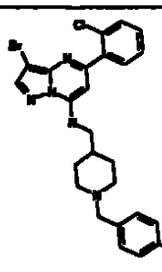
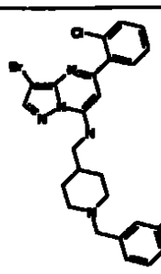
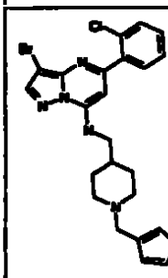
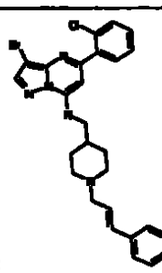
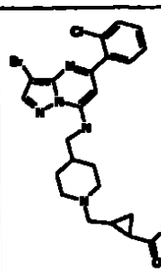
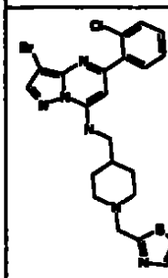
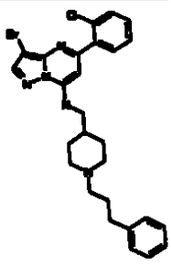
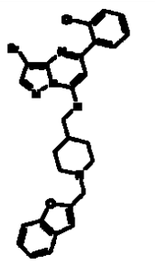
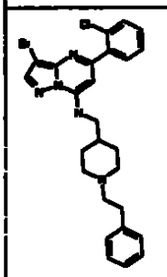
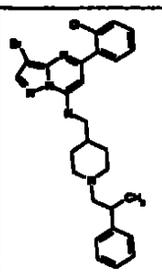
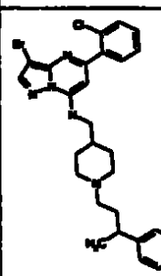
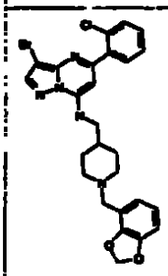
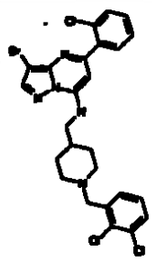
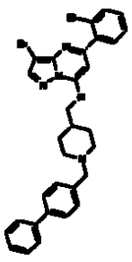
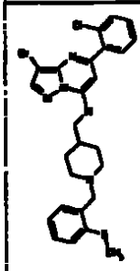
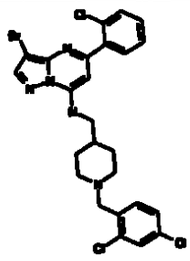
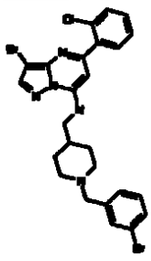
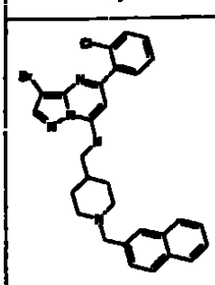
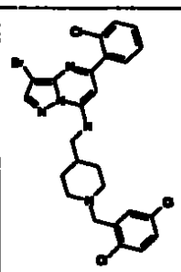
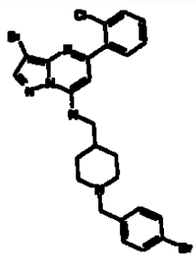
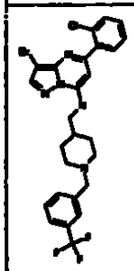
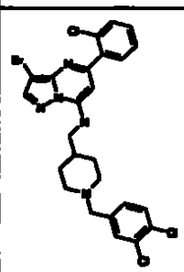
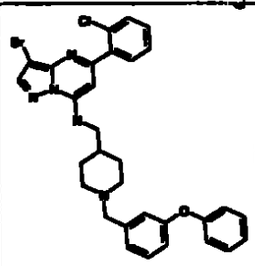
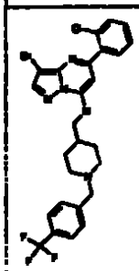
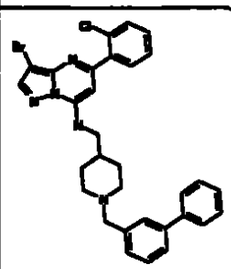
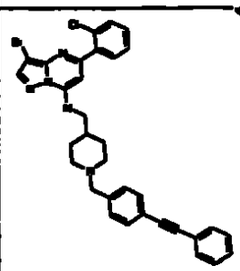
Product	1. Ex. 2. m/z
	1. 8071 2. 505.28
	1. 8072 2. 537.3
	1. 8073 2. 537.3
	1. 8074 2. 547.3

TABLE81

Product	1. Ex. 2. m/zz	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8101 2. 510.28		1. 8106 2. 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. 588.32
	1. 8117 2. 558.31		1. 8122 2. 580.32		1. 8127 2. 590.32
	1. 8118 2. 562.31		1. 8123 2. 580.32		1. 8128 2. 590.32
	1. 8119 2. 580.32		1. 8125 2. 580.32		1. 8129 2. 604.33
	1. 8120 2. 580.32		1. 8126 2. 588.32		1. 8130 2. 612.34

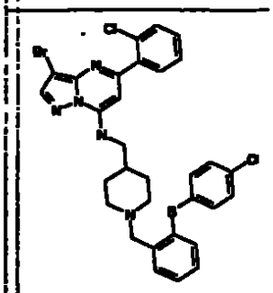
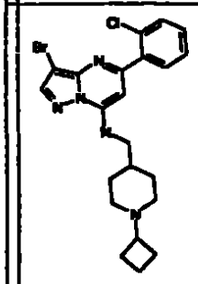
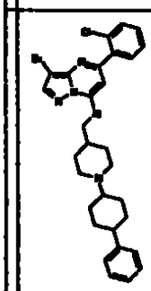
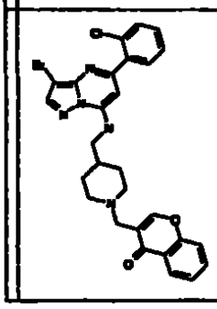
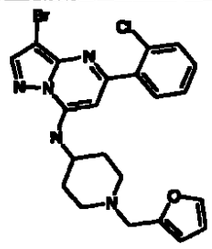
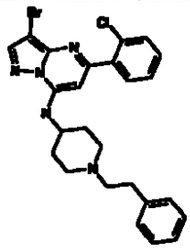
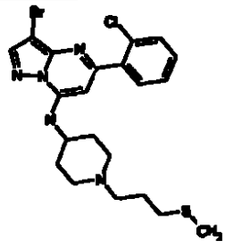
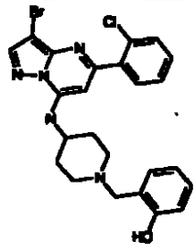
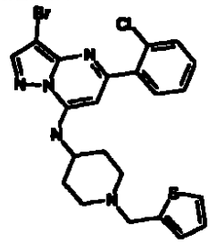
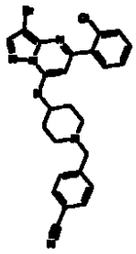
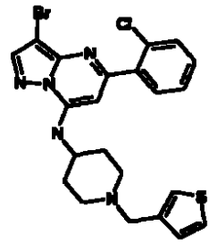
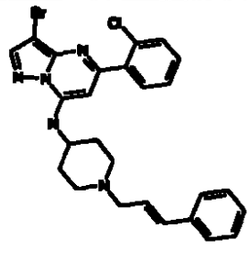
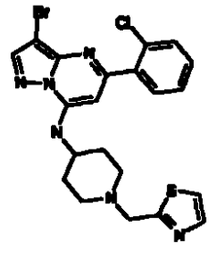
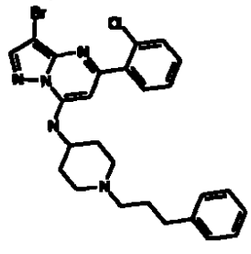
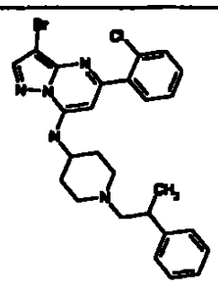
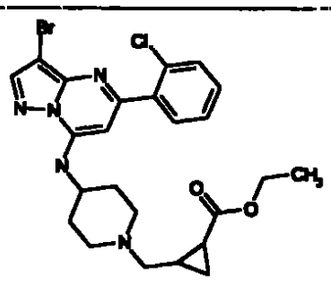
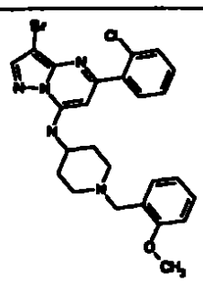
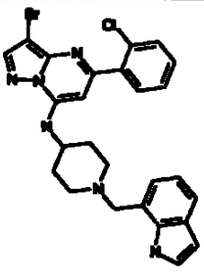
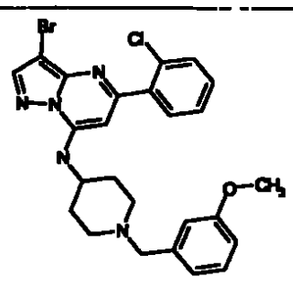
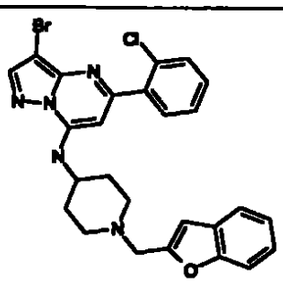
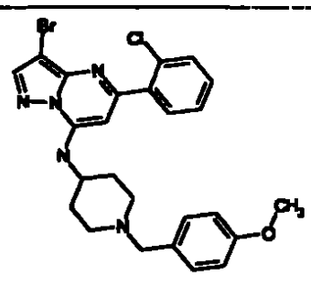
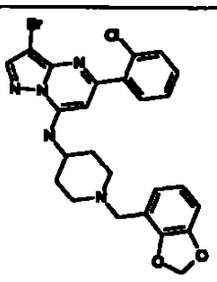
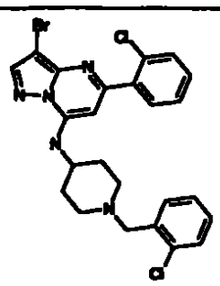
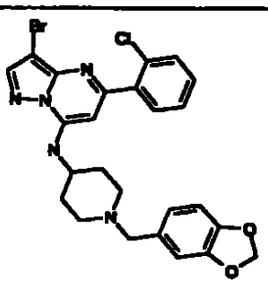
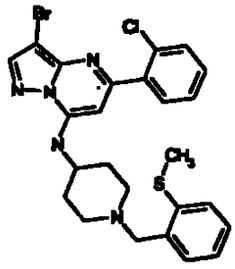
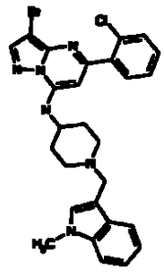
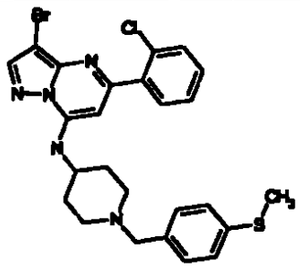
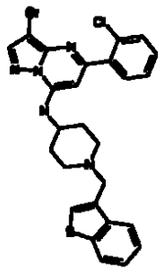
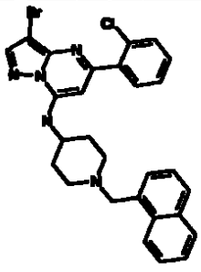
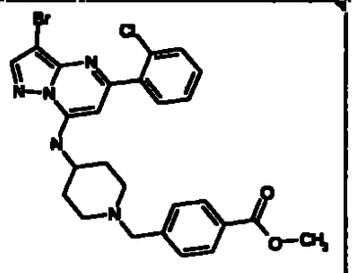
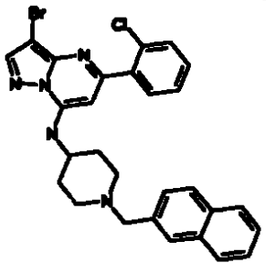
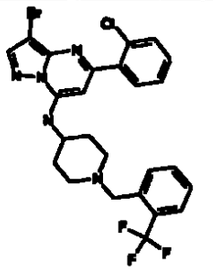
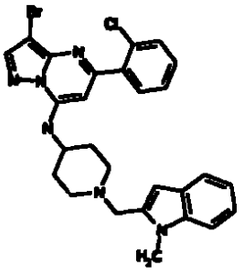
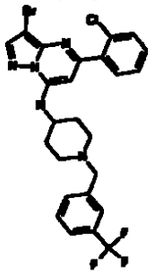
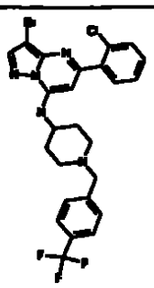
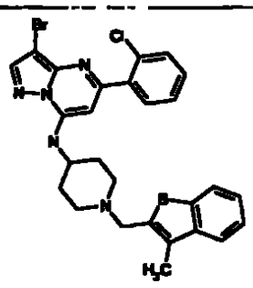
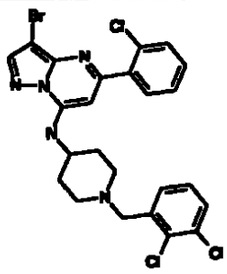
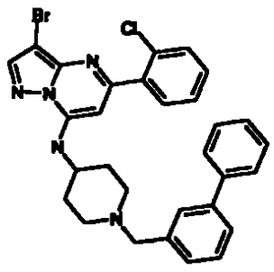
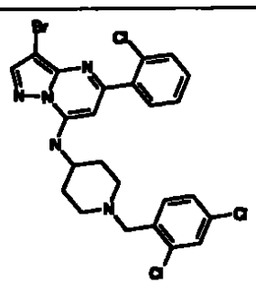
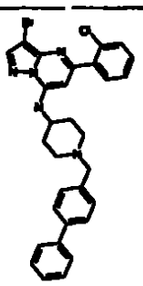
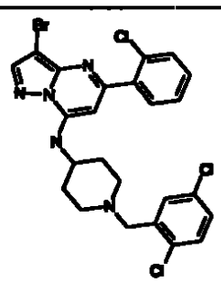
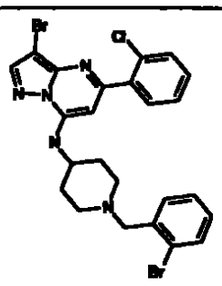
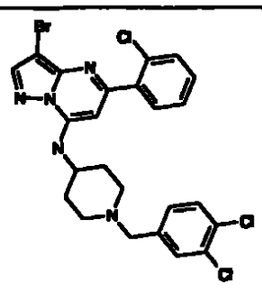
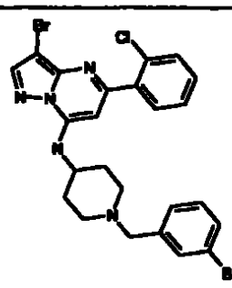
Product	1. Ex. 2. m/z
	1. 8131 2. 654.36
	1. 8132 2. 476.26
	1. 8133 2. 580.32
	1. 8134 2. 580.32

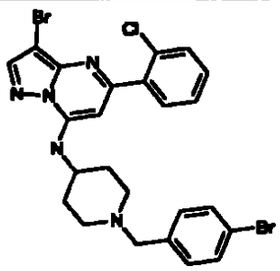
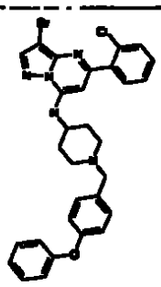
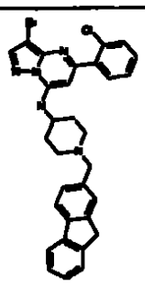
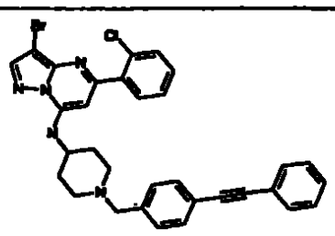
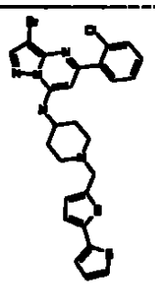
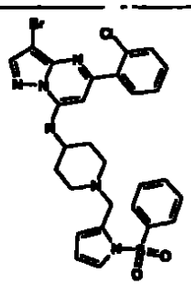
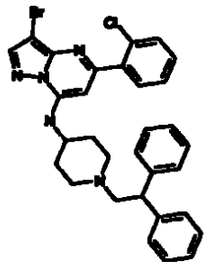
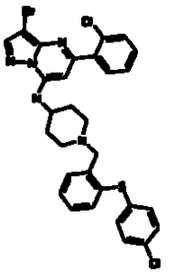
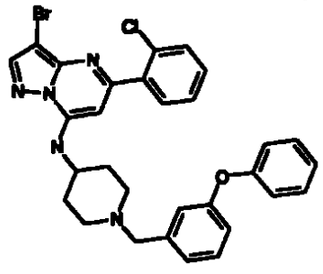
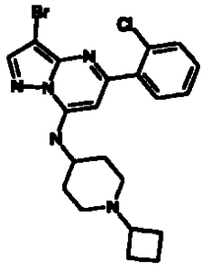
TABLE 82

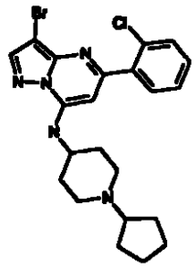
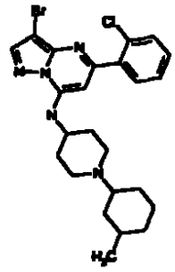
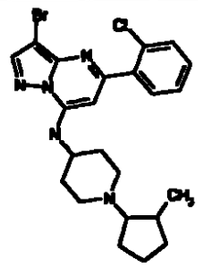
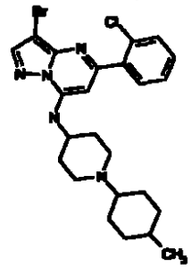
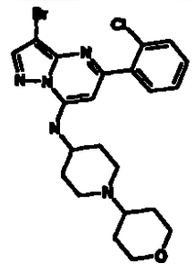
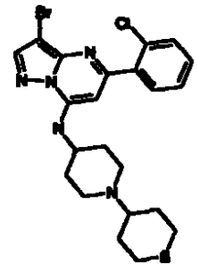
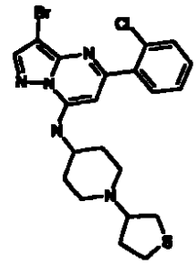
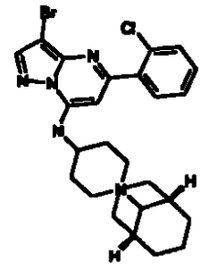
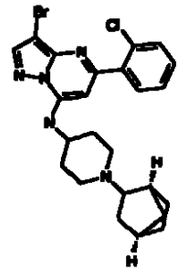
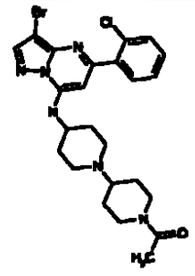
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8201 2. 488.27		1. 8206 2. 512.28
	1. 8202 2. 496.27		1. 8207 2. 514.28
	1. 8203 2. 504.28		1. 8208 2. 523.29
	1. 8204 2. 504.28		1. 8209 2. 524.29
	1. 8205 2. 505.28		1. 8210 2. 526.29

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8211 2. 526.29		1. 8216 2. 534.29
	1. 8212 2. 528.29		1. 8217 2. 537.3
	1. 8213 2. 528.29		1. 8218 2. 538.3
	1. 8214 2. 528.29		1. 8219 2. 542.3
	1. 8215 2. 532.29		1. 8220 2. 542.3

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8221 2. 544.3		1. 8226 2. 551.3
	1. 8222 2. 544.3		1. 8227 2. 554.3
	1. 8223 2. 548.3		1. 8228 2. 556.31
	1. 8224 2. 548.3		1. 8229 2. 566.31
	1. 8225 2. 551.3		1. 8230 2. 566.31

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8231 2. 566.31		1. 8236 2. 568.31
	1. 8232 2. 566.31		1. 8237 2. 574.32
	1. 8233 2. 566.31		1. 8238 2. 574.32
	1. 8243 2. 566.31		1. 8239 2. 576.32
	1. 8235 2. 566.31		1. 8240 2. 576.32

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8241 2. 576.32		1. 8246 2. 590.32
	1. 8242 2. 586.32		1. 8247 2. 598.33
	1. 8243 2. 586.32		1. 8248 2. 627.34
	1. 8244 2. 588.32		1. 8249 2. 640.35
	1. 8245 2. 590.32		1. 8250 2. 462.25

Product	1. Ex. 2. m/z		Product	1. Ex. 2. m/z
	1. 8251 2. 476.26			1. 8256 2. 504.28
	1. 8252 2. 490.27			1. 8257 2. 504.28
	1. 8253 2. 492.27			1. 8258 2. 508.28
	1. 8254 2. 492.27			1. 8259 2. 530.29
	1. 8255 2. 502.28			1. 8260 2. 533.29

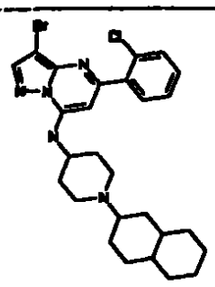
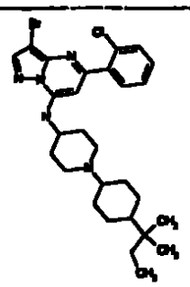
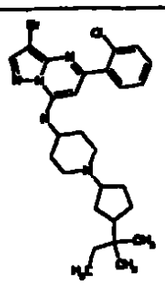
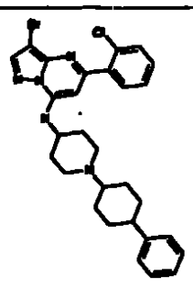
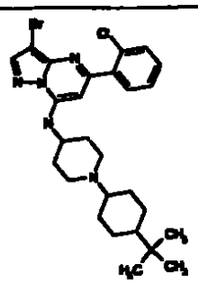
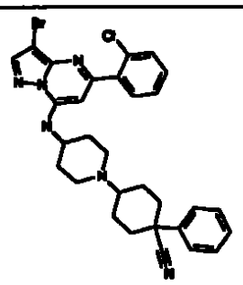
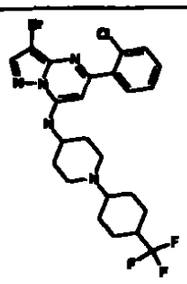
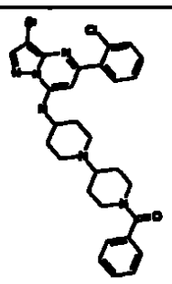
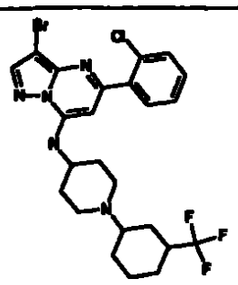
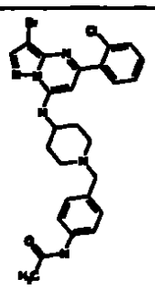
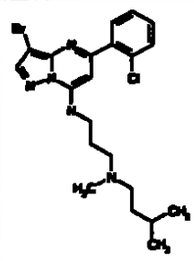
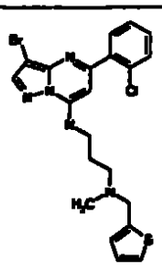
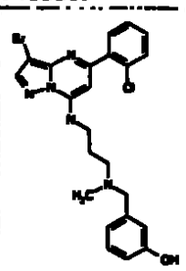
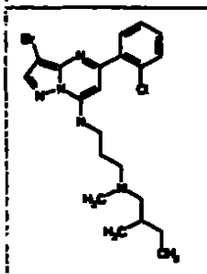
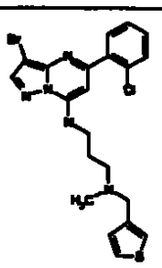
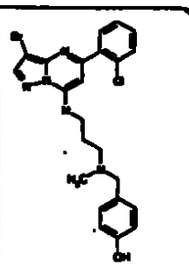
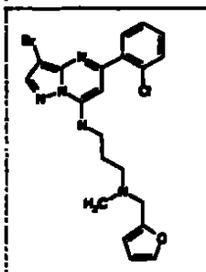
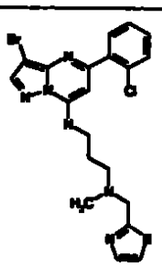
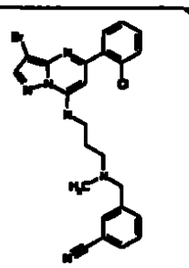
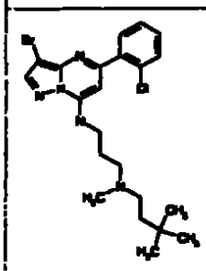
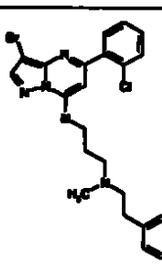
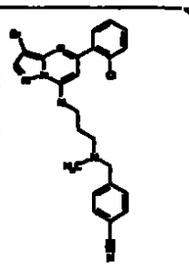
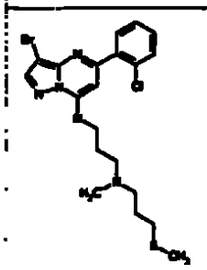
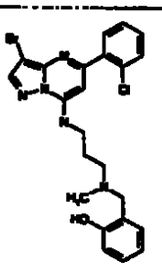
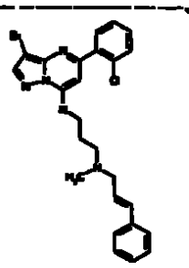
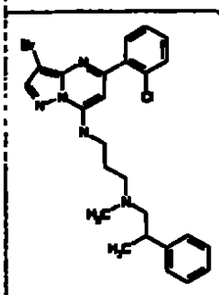
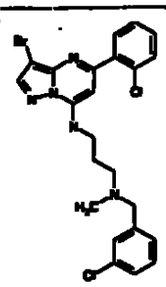
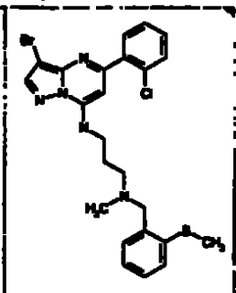
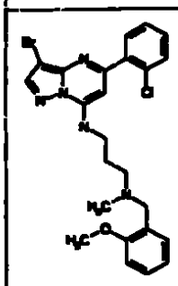
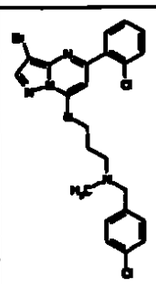
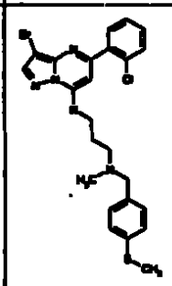
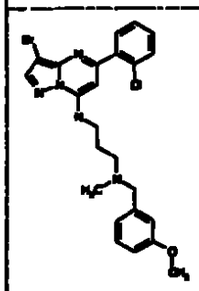
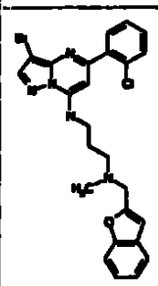
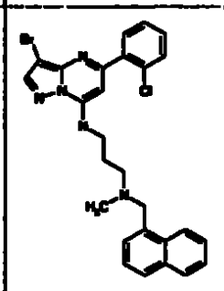
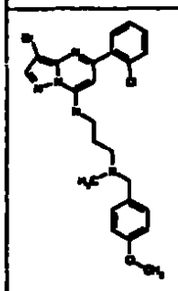
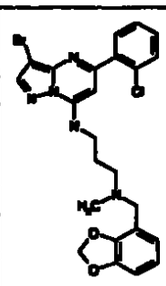
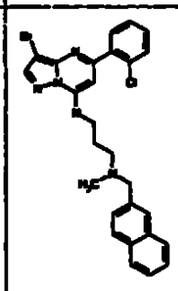
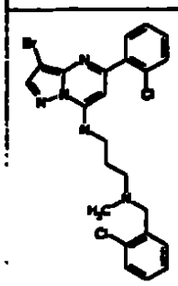
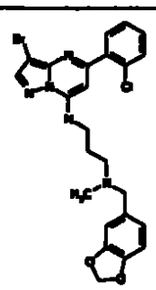
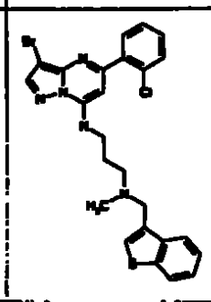
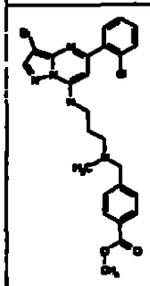
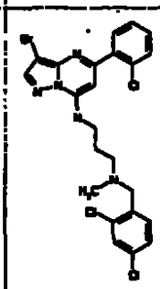
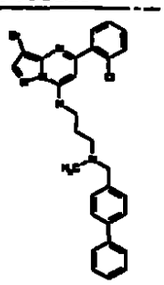
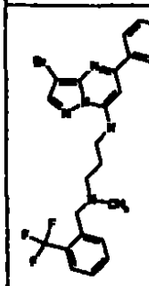
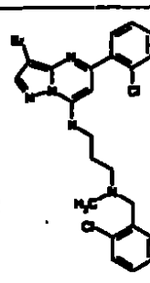
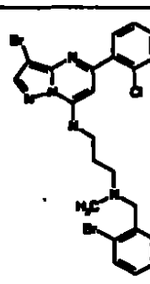
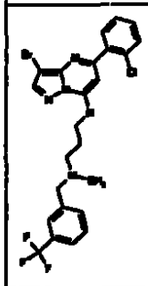
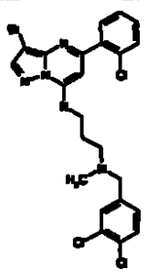
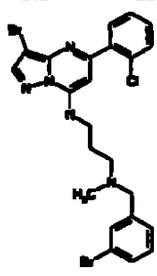
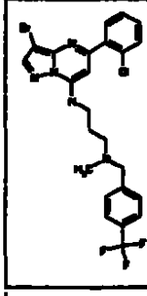
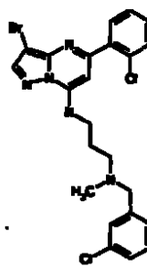
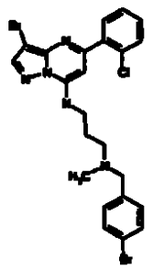
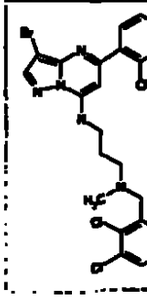
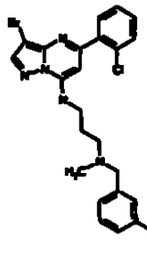
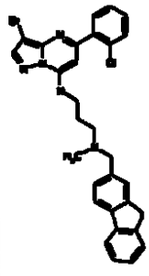
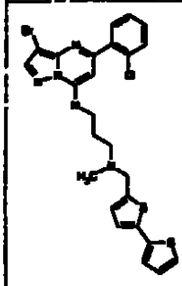
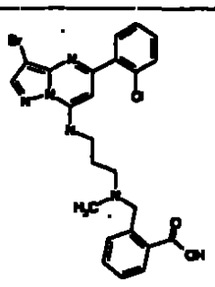
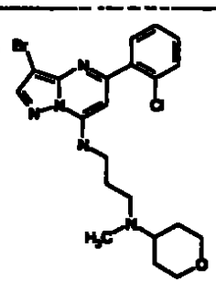
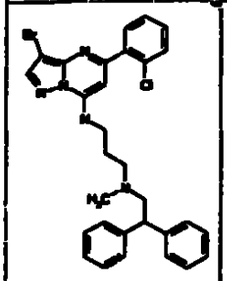
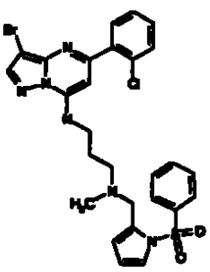
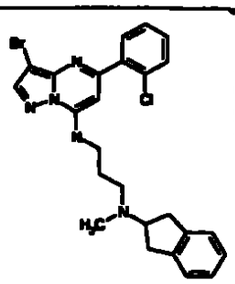
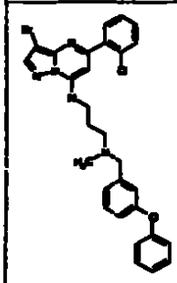
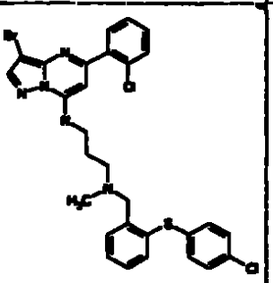
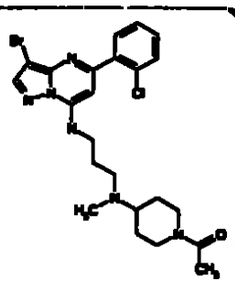
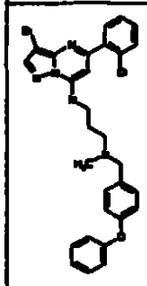
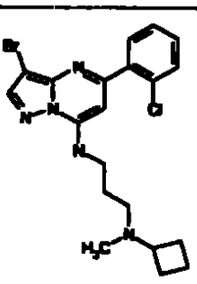
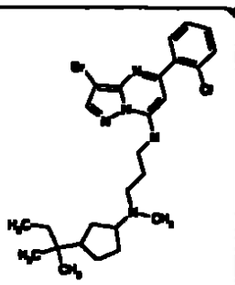
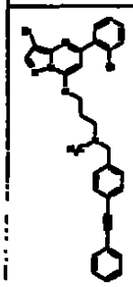
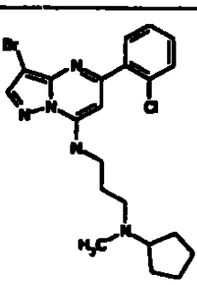
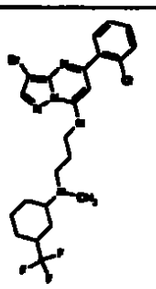
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8261 2. 544.3		1. 8266 2. 560.31
	1. 8262 2. 546.3		1. 8267 2. 566.31
	1. 8263 2. 546.3		1. 8268 2. 591.33
	1. 8264 2. 558.31		1. 8269 2. 595.33
	1. 8265 2. 558.31		1. 8270 2. 555.31

TABLE 83

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8301 2. 465.882		1. 8306 2. 491.79		1. 8311 2. 501.825
	1. 8302 2. 465.885		1. 8307 2. 491.792		1. 8312 2. 501.833
	1. 8303 2. 475.827		1. 8308 2. 492.787		1. 8313 2. 510.822
	1. 8304 2. 479.89		1. 8309 2. 499.846		1. 8314 2. 510.821
	1. 8305 2. 483.829		1. 8310 2. 501.826		1. 8315 2. 511.841

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8316 2. 513.855		1. 8321 2. 519.783		1. 8326 2. 531.804
	1. 8317 2. 515.832		1. 8322 2. 519.781		1. 8327 2. 531.812
	1. 8318 2. 515.832		1. 8323 2. 525.813		1. 8328 2. 535.83
	1. 8319 2. 515.837		1. 8324 2. 529.806		1. 8329 2. 535.831
	1. 8320 2. 519.782		1. 8325 2. 529.81		1. 8330 2. 541.788

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8331 2. 543.821		1. 8336 2. 554.727		1. 8341 2. 561.838
	1. 8332 2. 553.797		1. 8337 2. 554.738		1. 8342 2. 564.714
	1. 8333 2. 553.798		1. 8338 2. 554.738		1. 8343 2. 564.704
	1. 8334 2. 553.795		1. 8339 2. 554.727		1. 8344 2. 564.72
	1. 8335 2. 554.73		1. 8340 2. 561.836		1. 8345 2. 573.823

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8346 2. 573.735		1. 8351 2. 529.808		1. 8356 2. 479.856
	1. 8347 2. 575.839		1. 8352 2. 614.763		1. 8357 2. 511.842
	1. 8348 2. 577.818		1. 8353 2. 628.727		1. 8358 2. 520.859
	1. 8349 2. 577.814		1. 8354 2. 449.857		1. 8359 2. 533.903
	1. 9350 2. 585.818		1. 8355 2. 463.867		1. 8360 2. 545.823

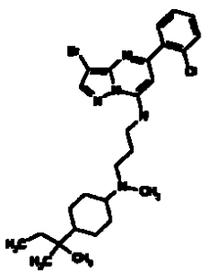
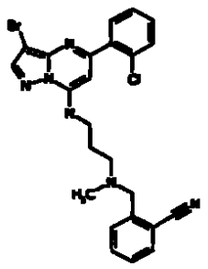
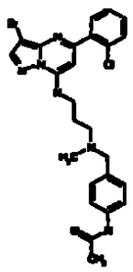
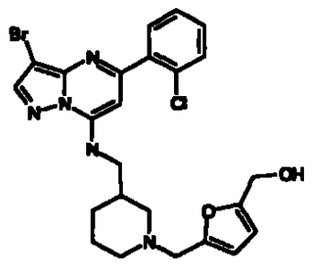
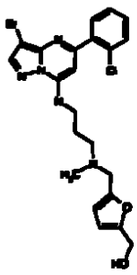
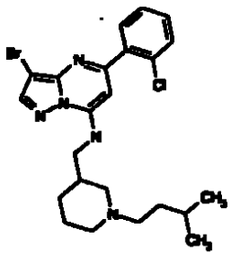
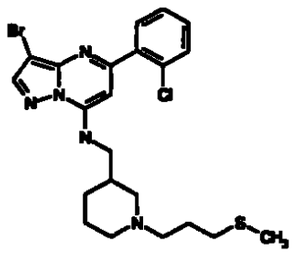
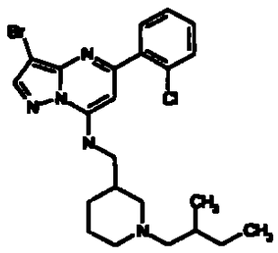
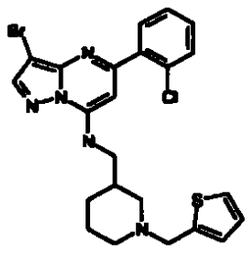
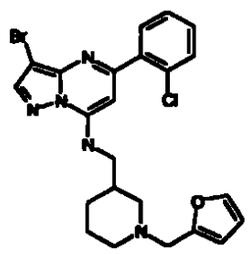
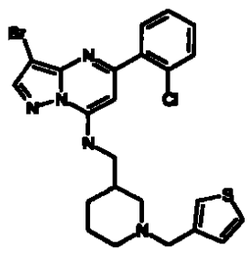
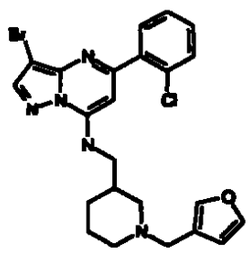
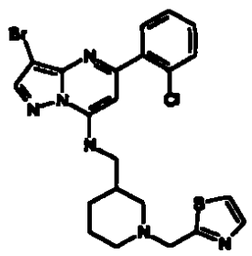
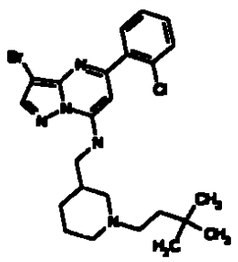
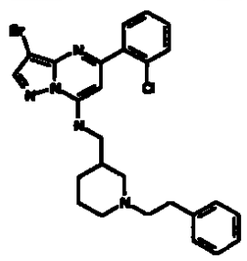
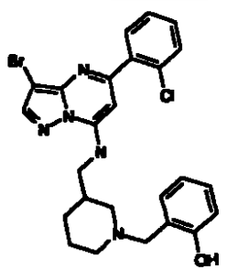
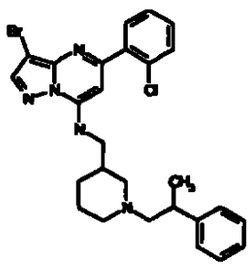
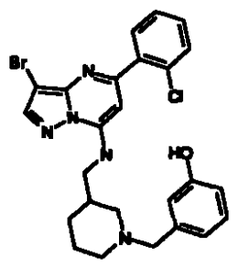
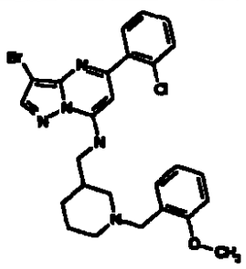
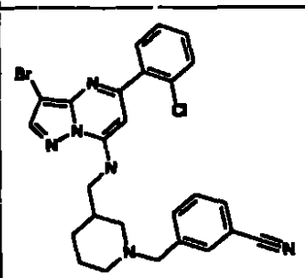
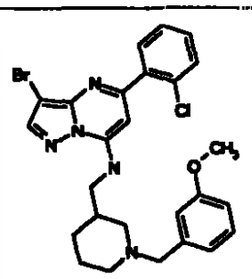
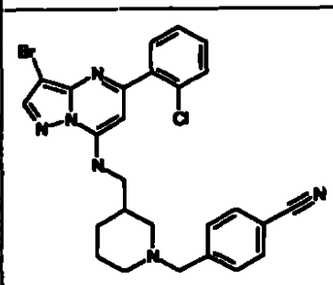
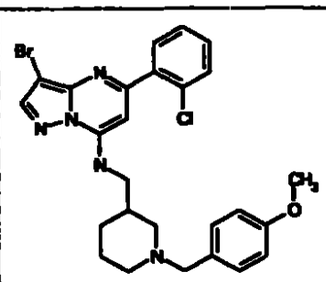
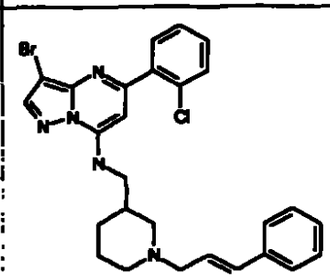
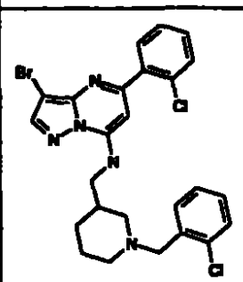
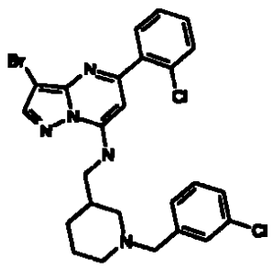
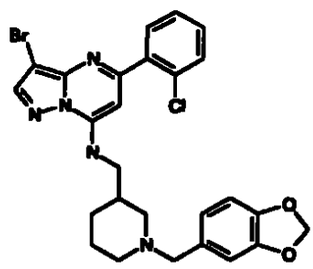
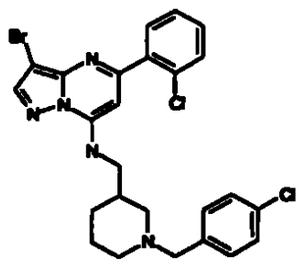
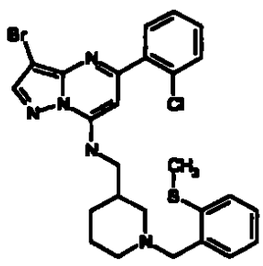
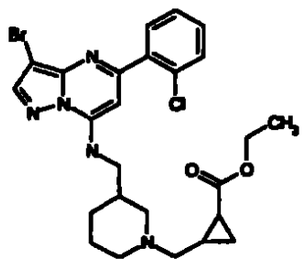
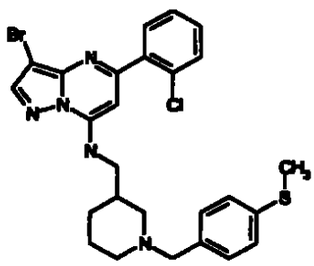
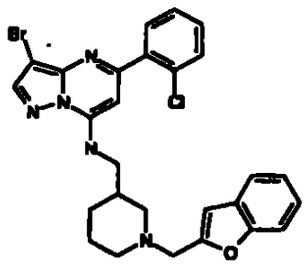
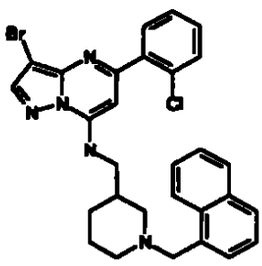
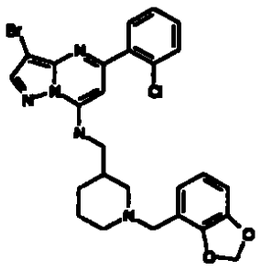
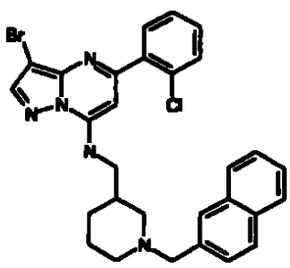
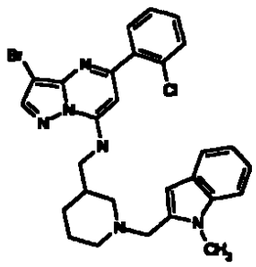
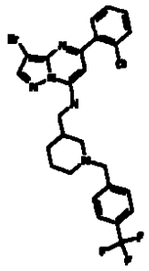
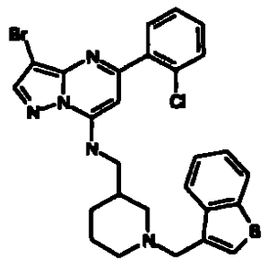
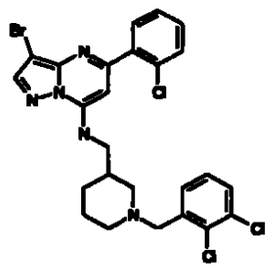
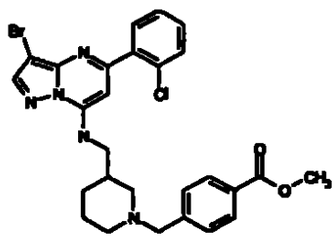
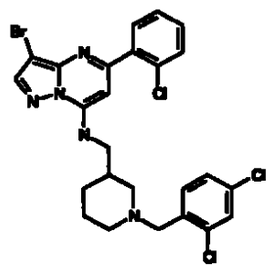
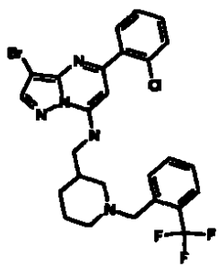
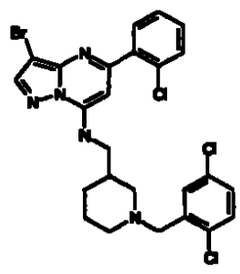
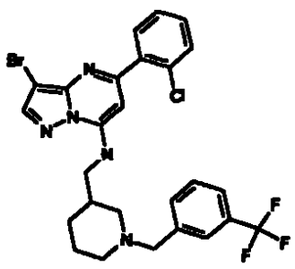
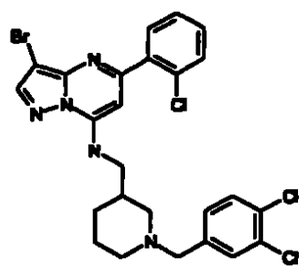
Product	1. Ex. 2. m/z
	1. 8361 2. 547.909
	1. 8362 2. 510.817
	1. 8363 2. 542.833
	1. 8364 2. 573.815
	1. 8365 2. 547.798

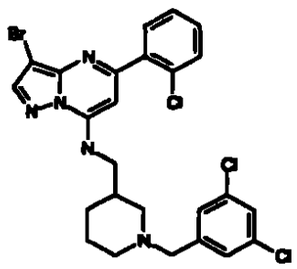
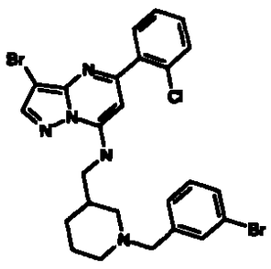
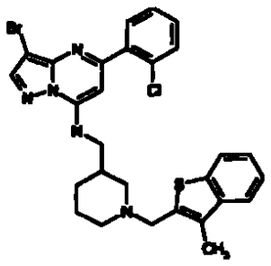
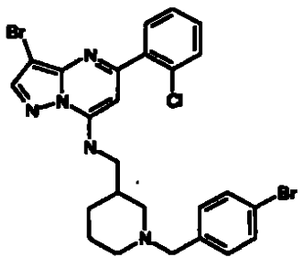
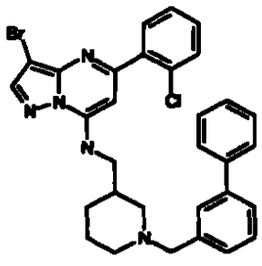
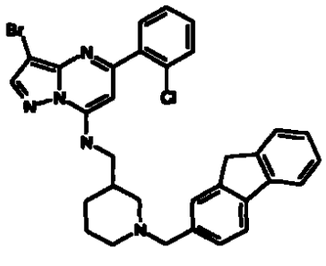
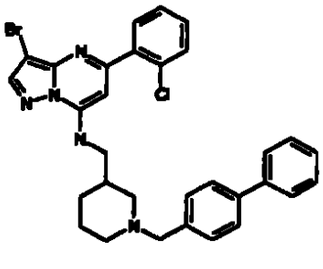
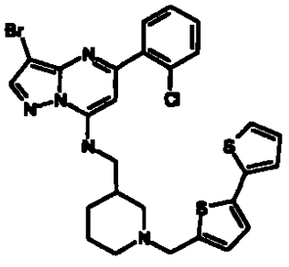
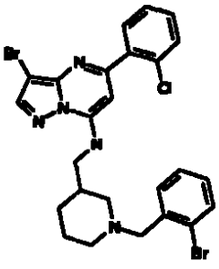
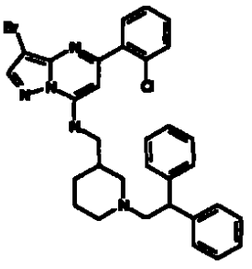
TABLE 84

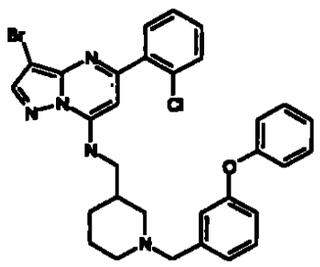
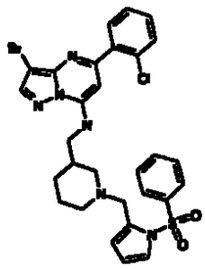
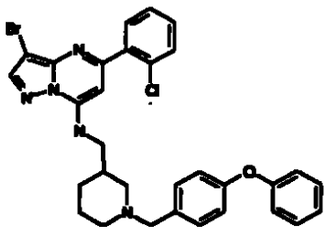
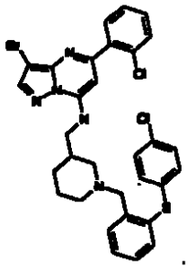
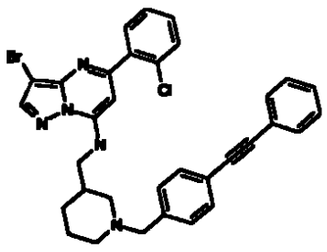
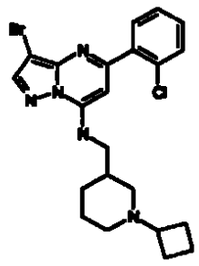
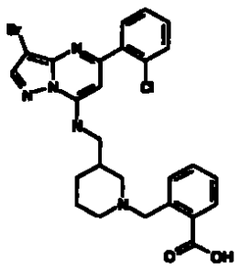
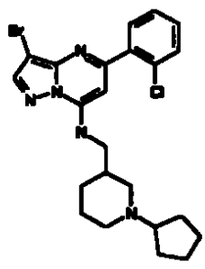
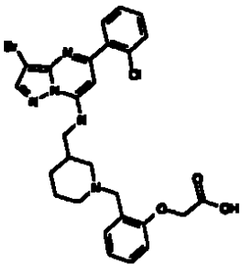
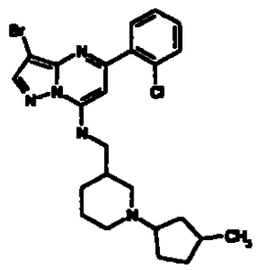
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8401 2. 491.883		1. 8406 2. 509.829
	1. 8402 2. 491.883		1. 8407 2. 517.795
	1. 8403 2. 501.823		1. 8408 2. 517.799
	1. 8404 2. 501.827		1. 8409 2. 518.796
	1. 8405 2. 505.89		1. 8410 2. 525.851

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8411 2. 527.831		1. 8416 2. 539.859
	1. 8412 2. 527.833		1. 8417 2. 541.84
	1. 8413 2. 536.833		1. 8418 2. 541.843
	1. 8414 2. 536.829		1. 8419 2. 541.843
	1. 8415 2. 537.845		1. 8420 2. 546.786

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8421 2. 546.792		1. 8426 2. 555.817
	1. 8422 2. 546.79		1. 8427 2. 557.81
	1. 8423 2. 547.854		1. 8428 2. 557.813
	1. 8424 2. 551.826		1. 8429 2. 561.839
	1. 8425 2. 555.819		1. 8430 2. 561.833

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8431 2. 564.841		1. 8436 2. 579.794
	1. 8432 2. 567.795		1. 8437 2. 580.738
	1. 8433 2. 569.823		1. 8438 2. 580.732
	1. 8434 2. 579.797		1. 8439 2. 580.733
	1. 8435 2. 579.796		1. 8440 2. 580.734

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8441 2. 580.726		1. 8446 2. 590.726
	1. 8442 2. 581.805		1. 8447 2. 590.724
	1. 8443 2. 587.844		1. 8448 2. 599.834
	1. 8444 2. 587.835		1. 8449 2. 599.749
	1. 8445 2. 590.723		1. 8450 2. 601.854

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8451 2. 603.831		1. 8456 2. 640.779
	1. 8452 2. 603.83		1. 8457 2. 654.746
	1. 8453 2. 611.83		1. 8458 2. 475.871
	1. 8454 2. 555.824		1. 8459 2. 489.879
	1. 8455 2. 585.817		1. 8460 2. 503.885

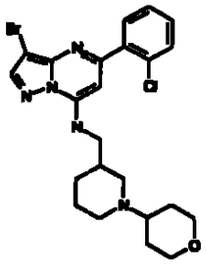
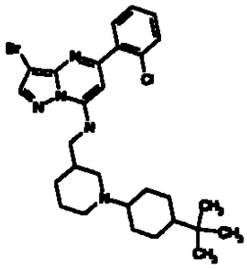
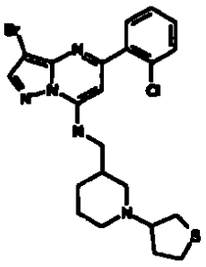
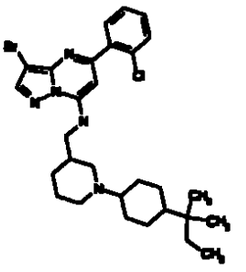
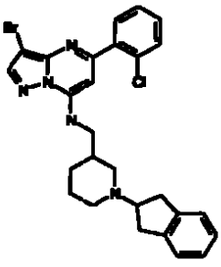
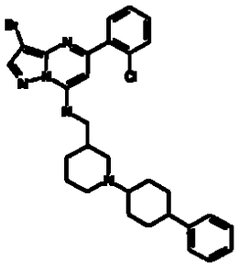
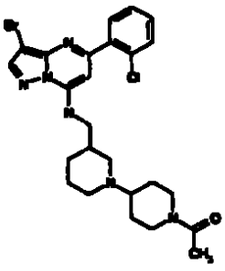
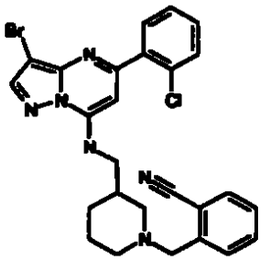
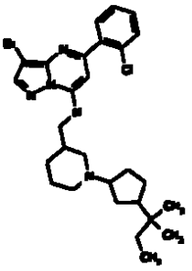
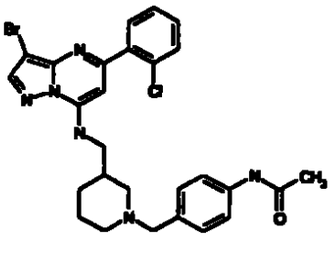
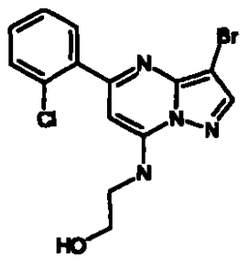
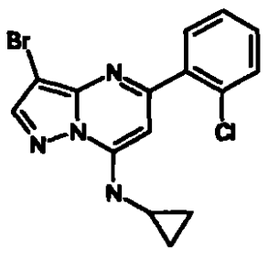
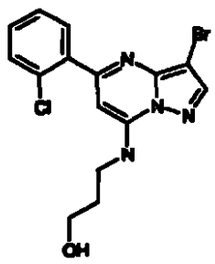
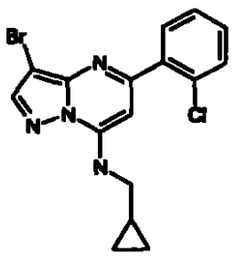
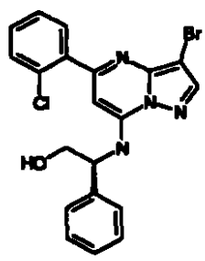
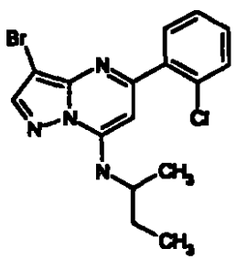
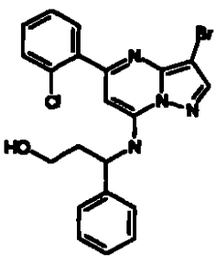
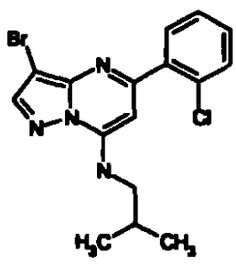
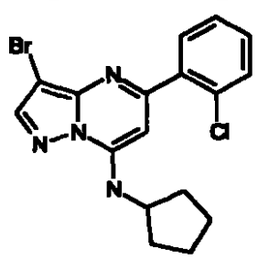
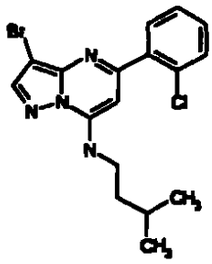
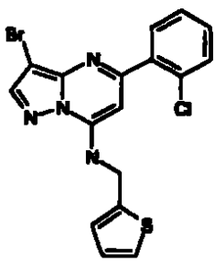
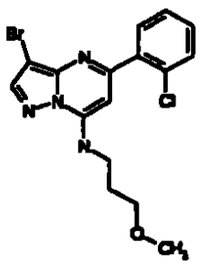
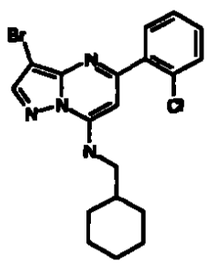
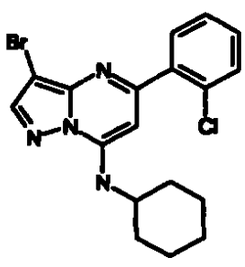
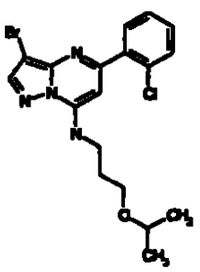
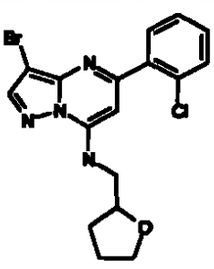
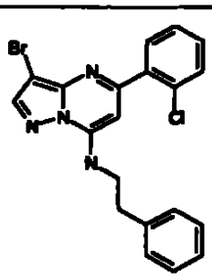
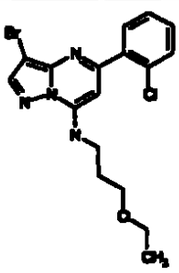
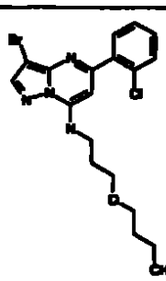
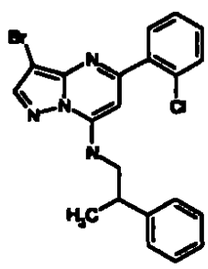
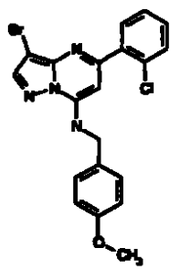
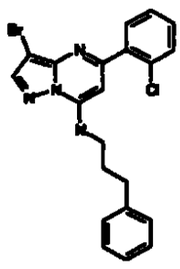
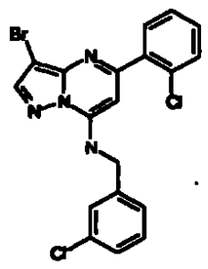
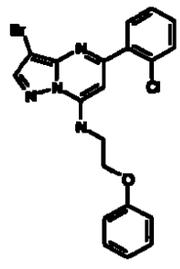
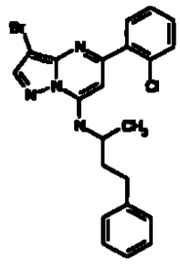
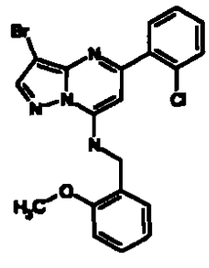
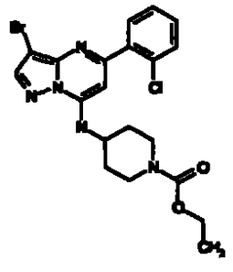
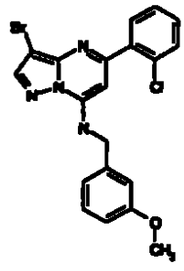
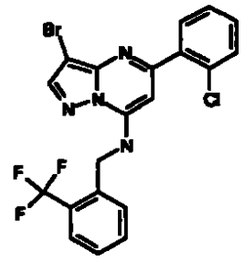
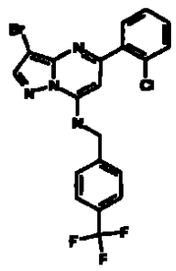
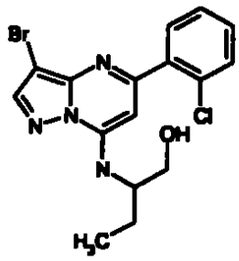
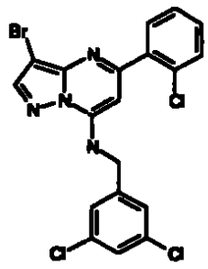
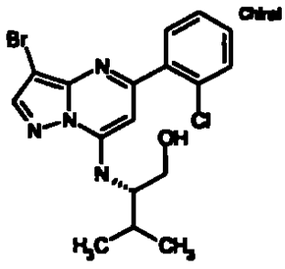
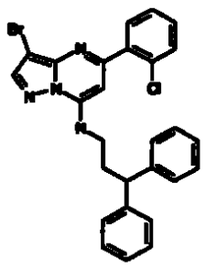
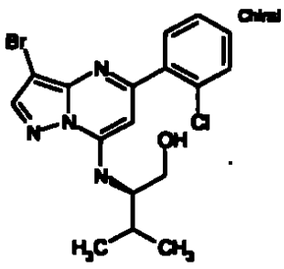
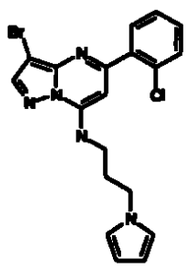
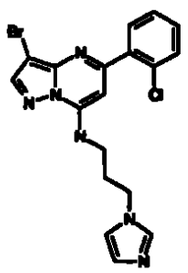
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8461 2. 505.866		1. 8466 2. 559.919
	1. 8462 2. 507.828		1. 8467 2. 573.925
	1. 8463 2. 537.859		1. 8468 2. 579.876
	1. 8464 2. 546.877		1. 8469 2. 536.831
	1. 8465 2. 559.921		1. 8470 2. 568.843

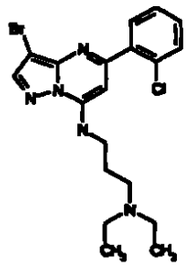
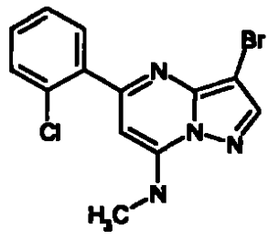
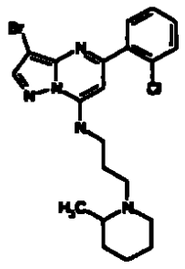
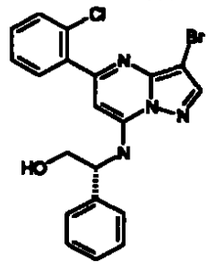
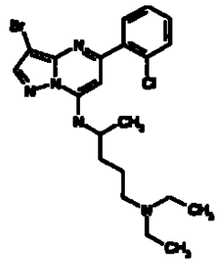
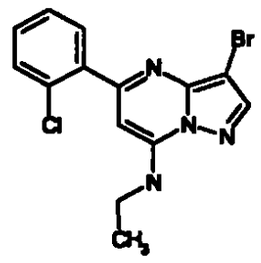
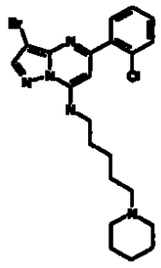
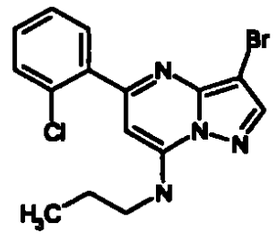
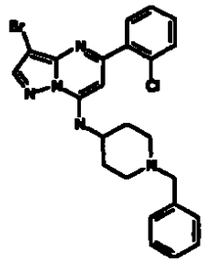
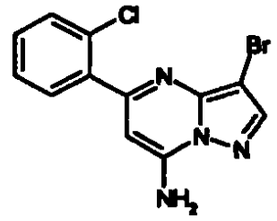
TABLE 85

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1.8501 2. 367.2		1. 8506 2. 443.1
	1. 8502 2. 381.2		1. 8507 2. 323.1
	1. 8503 2. 443.2		1. 8508 2. 365.2
	1. 8504 2. 457.3		1. 8509 2. 379.21
			1. 8510 2. 381.21

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8511 2. 381.21		1. 8516 2. 409.22
	1. 8512 2. 393.22		1. 8517 2. 411.23
	1. 8513 2. 395.22		1. 8518 2. 421.23
	1. 8514 2. 397.22		1. 8519 2. 421.23
	1. 8515 2. 407.22		1. 8520 2. 425.23

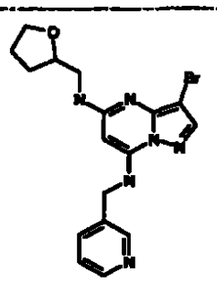
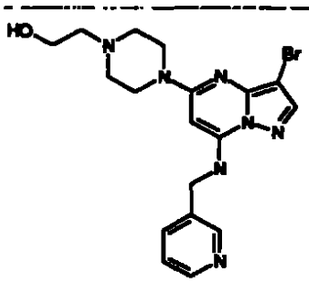
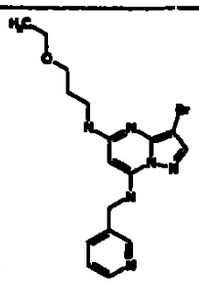
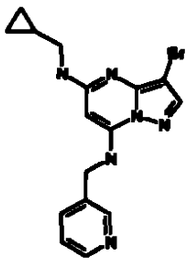
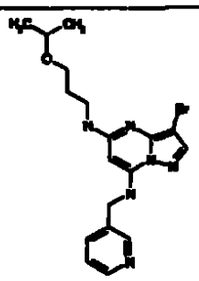
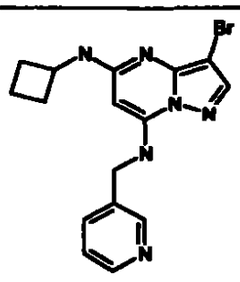
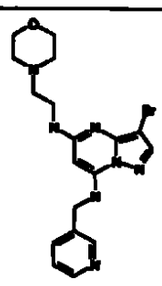
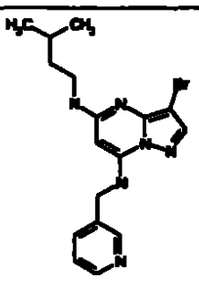
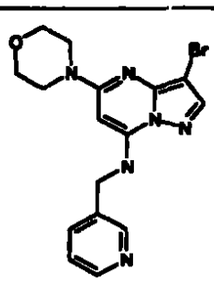
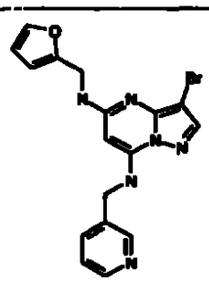
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8521 2. 429.24		1. 8526 2. 445.24
	1. 8522 2. 439.24		1. 8527 2 .444.24
	1. 8523 2. 443.24		1. 8528 2. 444.24
	1. 8524 2. 443.24		1. 8529 2. 446.25
	1. 8525 2. 445.24		1. 8530 2. 457.25

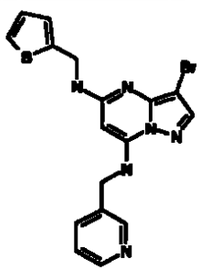
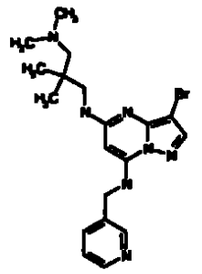
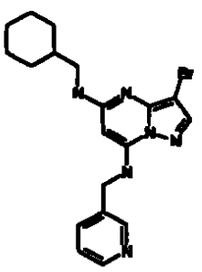
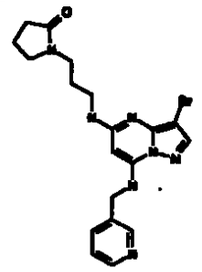
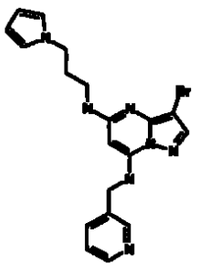
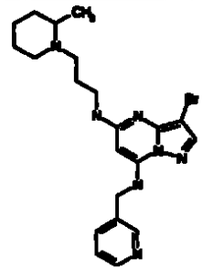
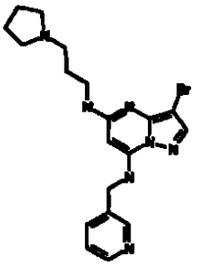
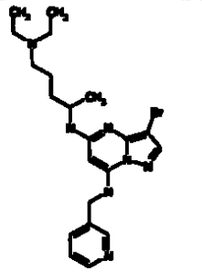
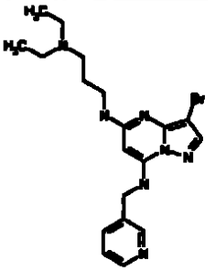
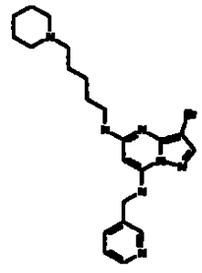
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8531 2. 480.26		1. 8536 2. 431.24
	1. 8532 2. 483.27		1. 8537 2. 429.24
	1. 8533 2. 483.27		1. 8538 2. 397.22
			1. 8539 2. 411.23
			1. 8540 2. 411.23

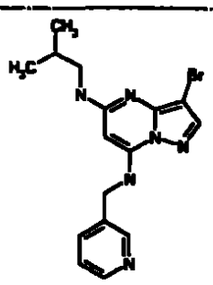
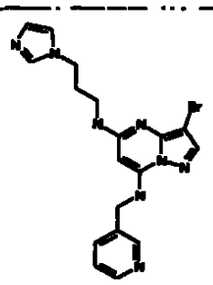
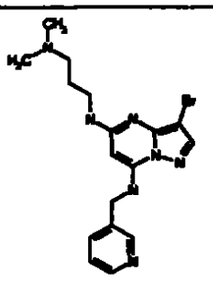
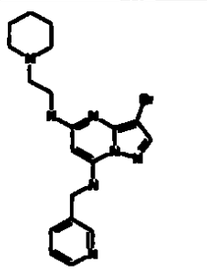
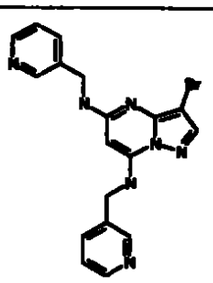
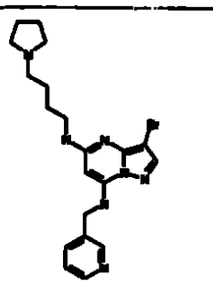
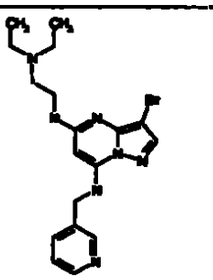
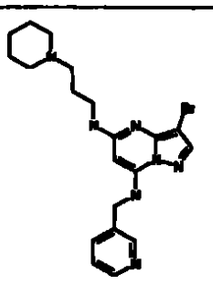
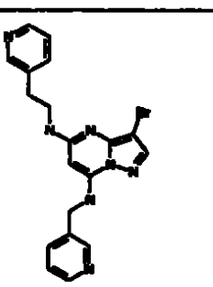
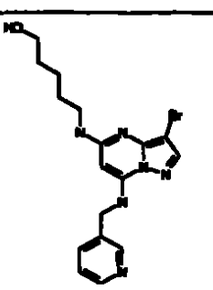
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8541 2. 432.24		1. 8547 2. 478.26
	1. 8542 2. 433.24		1. 8548 2. 498.27
	1. 8543 2. 438.24		1. 8549 2. 365.1
	1. 8545 2. 464.26		1. 8549 2. 337.1
	1. 8546 2. 466.26		1. 8550 2. 351.1

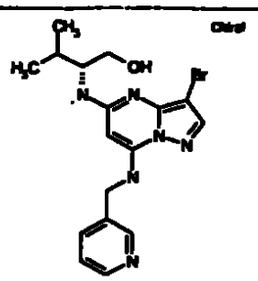
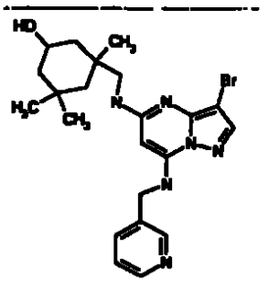
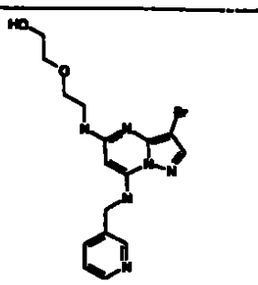
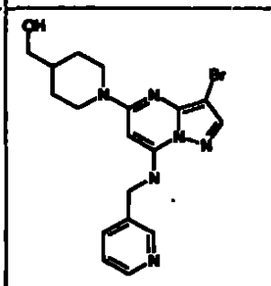
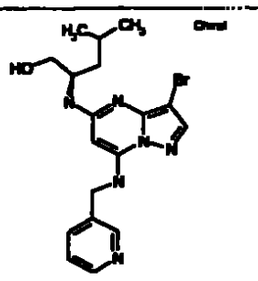
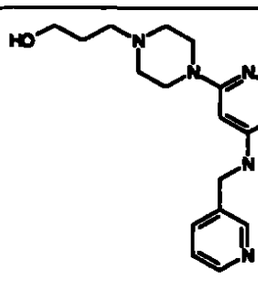
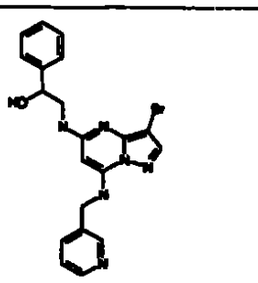
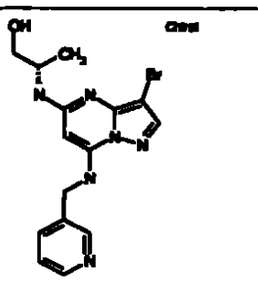
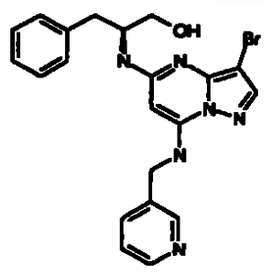
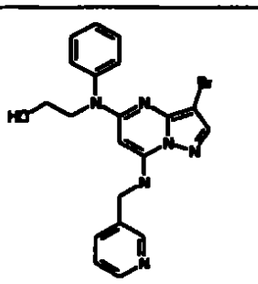
5

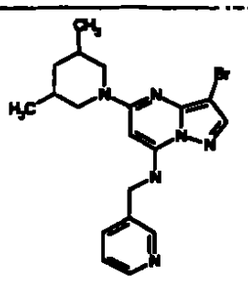
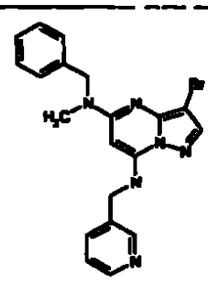
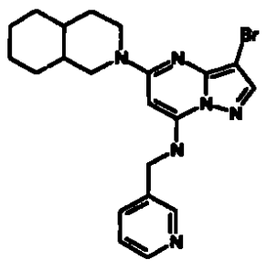
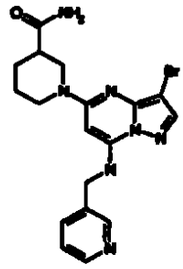
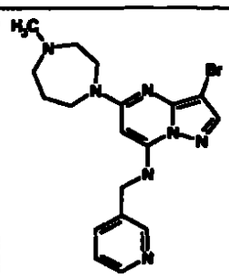
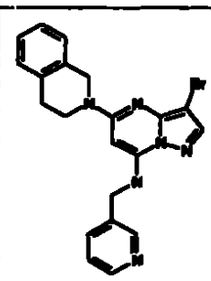
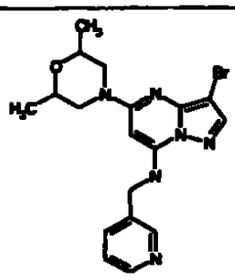
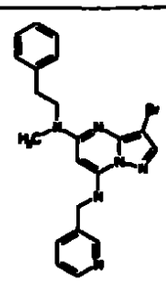
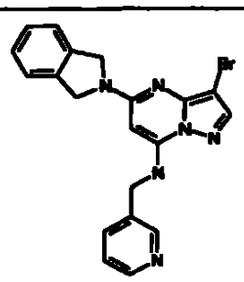
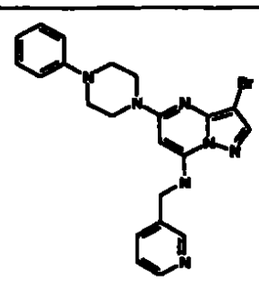
TABLE 86

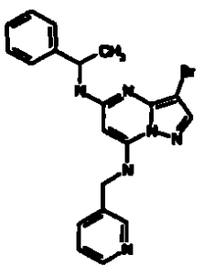
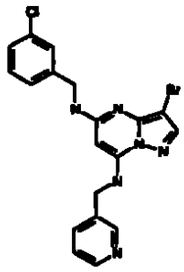
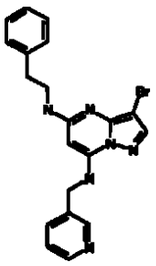
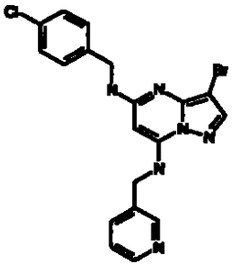
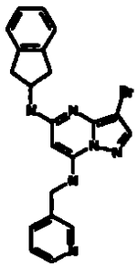
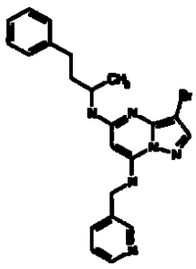
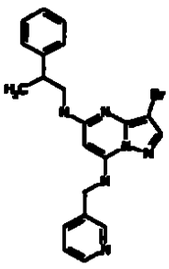
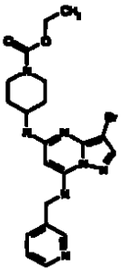
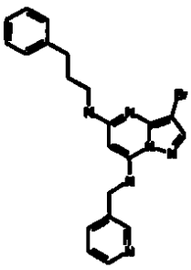
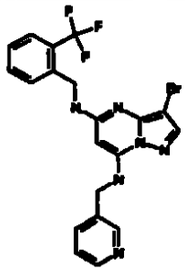
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8601 2. 403.22		1. 8606 2. 434.24
	1. 8602 2. 407.22		1. 8607 2. 375.21
	1. 8603 2. 421.23		1. 8608 2. 375.21
	1. 8604 2. 434.24		1. 8609 2. 391.22
	1. 8605 2. 391.22		1. 8610 2. 399.22

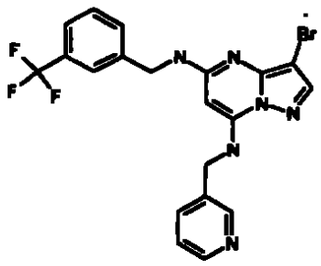
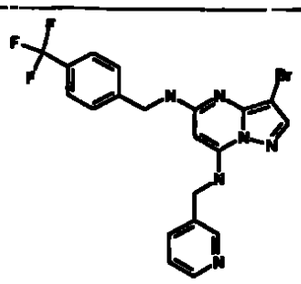
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8611 2. 417.23		1. 8616 2. 434.24
	1. 8612 2. 415.23		1. 8617 2. 446.25
	1. 8613 2. 428.24		1. 8618 2. 460.25
	1. 8614 2. 430.24		1. 8619 2. 459.25
	1. 8615 2. 434.24		1. 8620 2. 474.26

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8621 2. 377.21		1. 8626 2. 427.23
	1. 8622 2. 406.22		1. 8627 2. 431.24
	1. 8623 2. 412.23		1. 8628 2. 446.25
	1. 8624 2. 420.23		1. 8629 2. 446.25
	1. 8625 2. 426.23		1. 8630 2. 407.2

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8631 2. 407.2		1. 8636 2. 475.3
	1. 8632 2. 409.2		1. 8637 2. 419.2
	1. 8633 2. 421.2		1. 8638 2. 448.2
	1. 8634 2. 439.2		1. 8639 2. 379.2
	1. 8635 2. 455.3		1. 8640 2. 437.2

Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8641 2. 415.23		1. 8646 2. 423.23
	1. 8642 2. 443.24		1. 8647 2. 430.24
	1. 8643 2. 416.23		1. 8648 2. 437.24
	1. 8644 2. 417.23		1. 8649 2. 439.24
	1. 8645 2. 423.23		1. 8650 2. 466.26

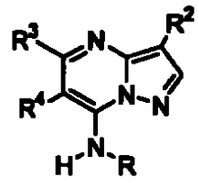
Product	1. Ex. 2. m/z	Product	1. Ex. 2. m/z
	1. 8651 2. 423.23		1. 8656 2. 445.24
	1. 8652 2. 425.23		1. 8657 2. 445.24
	1. 8653 2. 437.24		1. 8658 2. 451.25
	1. 8654 2. 437.24		1. 8659 2. 476.26
	1. 8655 2. 437.24		1. 8660 2. 479.26

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

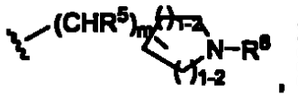
CLAIMS

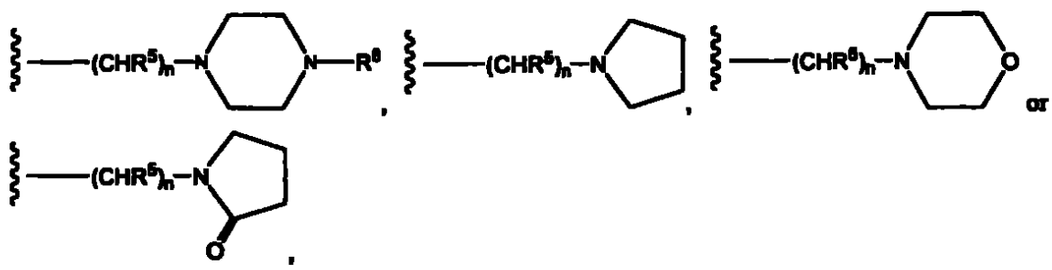
What is claimed is:

1. A compound represented by the structural formula:



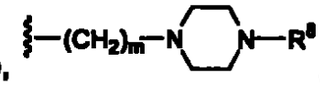
or a pharmaceutically acceptable salt or solvate of said compound, wherein:

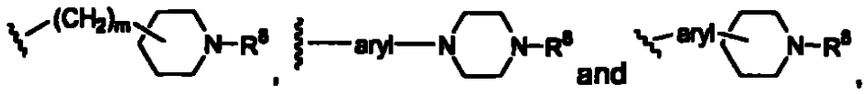
R is H, alkyl, alkenyl, alkynyl, arylalkyl, arylalkenyl, cycloalkyl, cycloalkylalkyl, alkenylalkyl, alkynylalkyl, heterocyclyl, heterocyclylalkyl, heteroarylalkyl (including N-oxide of said heteroaryl), -$(CHR^5)_n$-aryl, -$(CHR^5)_n$-heteroaryl, 



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

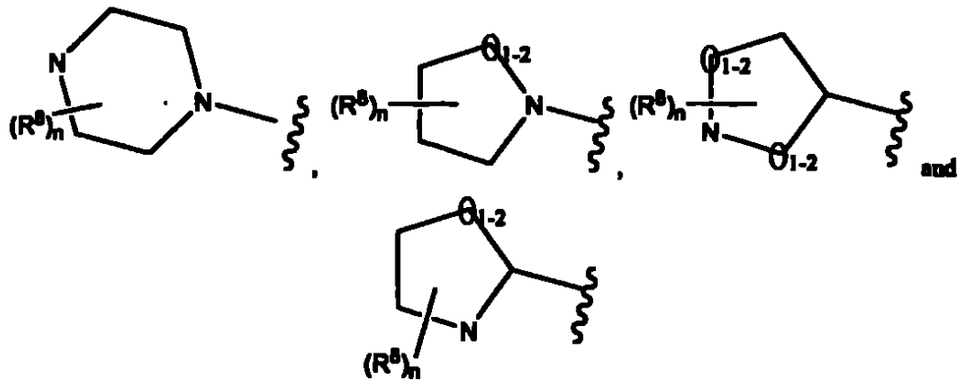
R^2 is selected from the group consisting of R^9, alkyl, alkenyl, alkynyl, CF_3, heterocyclyl, heterocyclylalkyl, halogen, haloalkyl, aryl, arylalkyl, heteroarylalkyl, alkynylalkyl, cycloalkyl, heteroaryl, alkyl substituted with 1-6 R^9 groups which can be the same or different and are independently 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, $-OCF_3$,

$-(CR^4R^5)_pOR^5$, $-OR^5$, $-NR^5R^6$, $-(CR^4R^5)_pNR^5R^6$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^6$, $-SR^6$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ 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, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)NR^4R^5$, $-C(O)R^5$, $-SO_3H$, $-SR^5$, $-S(O_2)R^7$, $-S(O_2)NR^4R^5$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ and $-N(R^5)C(O)NR^4R^5$;

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

R^7 is selected from the group consisting of alkyl, cycloalkyl, aryl, arylalkenyl, heteroaryl, arylalkyl, heteroarylalkyl, heteroarylalkenyl, and

heterocyclyl, wherein each of said alkyl, cycloalkyl, heteroarylalkyl, aryl, heteroaryl and arylalkyl can be unsubstituted or optionally independently substituted with one or more moieties which can be the same or different, each moiety being independently selected from the group consisting of halogen, alkyl, aryl, cycloalkyl, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^{10}$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^{10}$, $-C(O)R^5$, $-SR^{10}$, $-S(O_2)R^{10}$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^{10}$, $-N(R^5)C(O)R^{10}$ and $-N(R^5)C(O)NR^5R^{10}$;

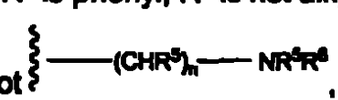
R^6 is selected from the group consisting of R^8, $-OR^8$, $-C(O)NR^5R^{10}$, $-S(O_2)NR^5R^{10}$, $-C(O)R^7$, $-C(=N-CN)-NH_2$, $-C(=NH)-NHR^5$, heterocyclyl, and $-S(O_2)R^7$;

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

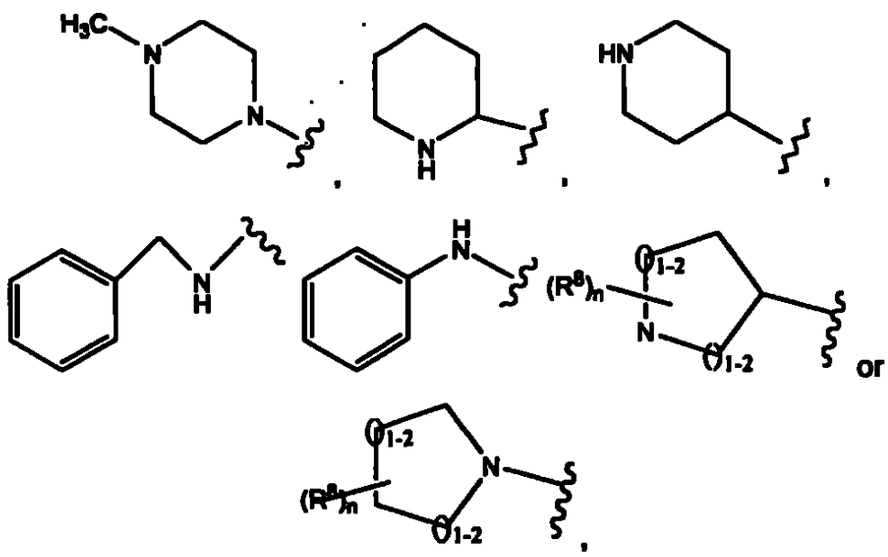
p is 1 to 4,

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;

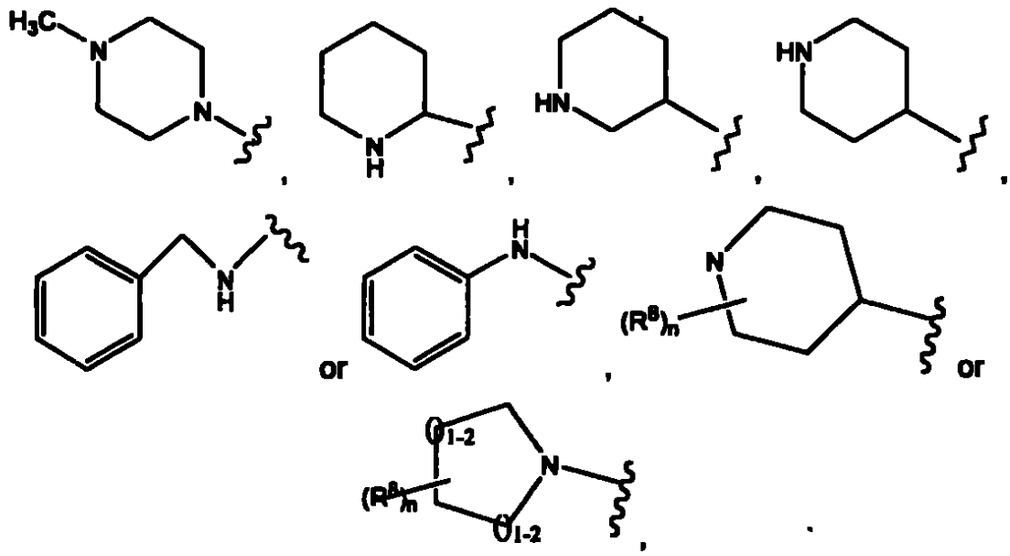
n is 1 to 2; and

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.

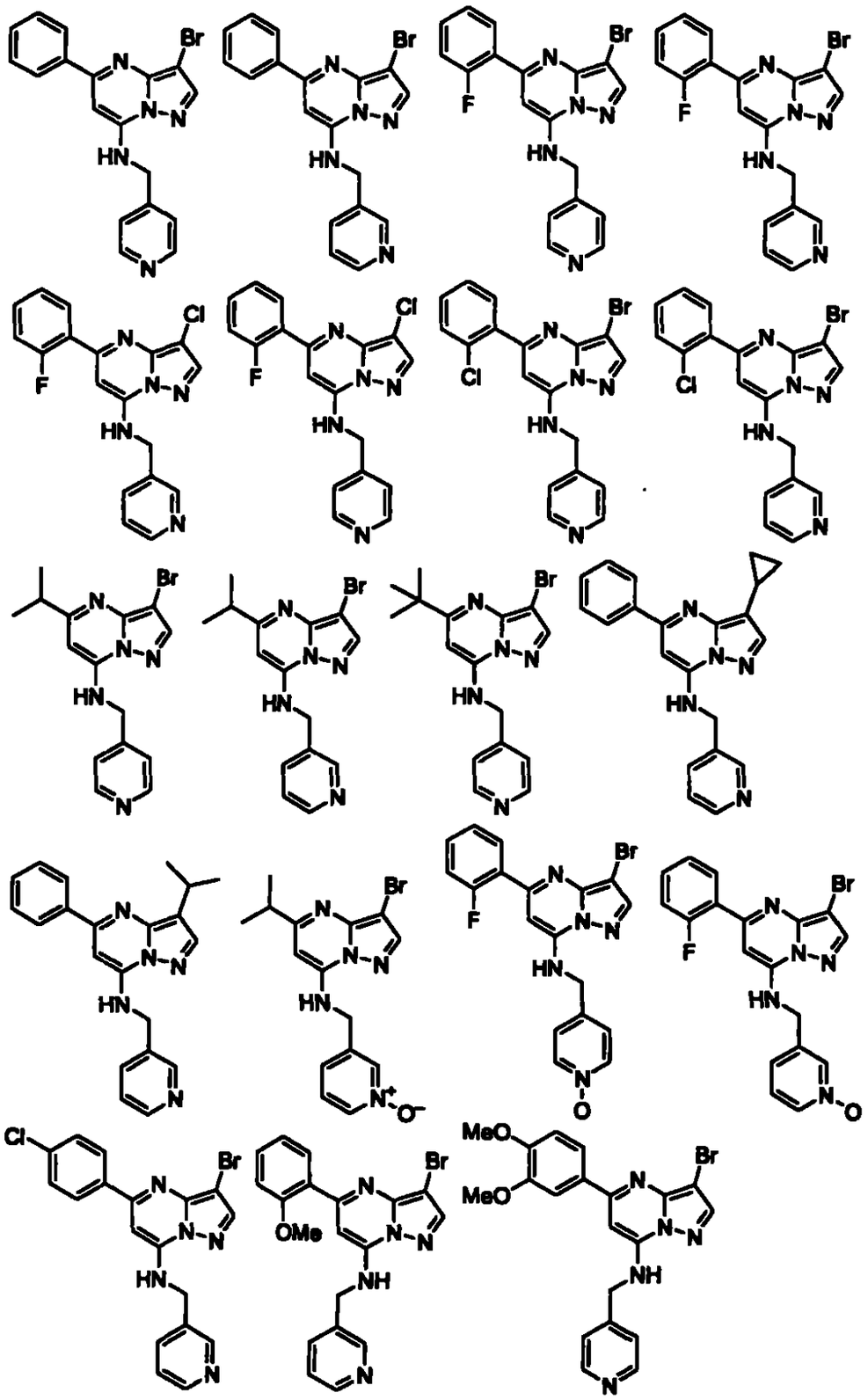
23. The compound of claim 19, wherein R^3 is a phenyl substituted with one or moieties which can be the same or different, each moiety being independently selected from the group consisting of F, Br, Cl and CF_3.

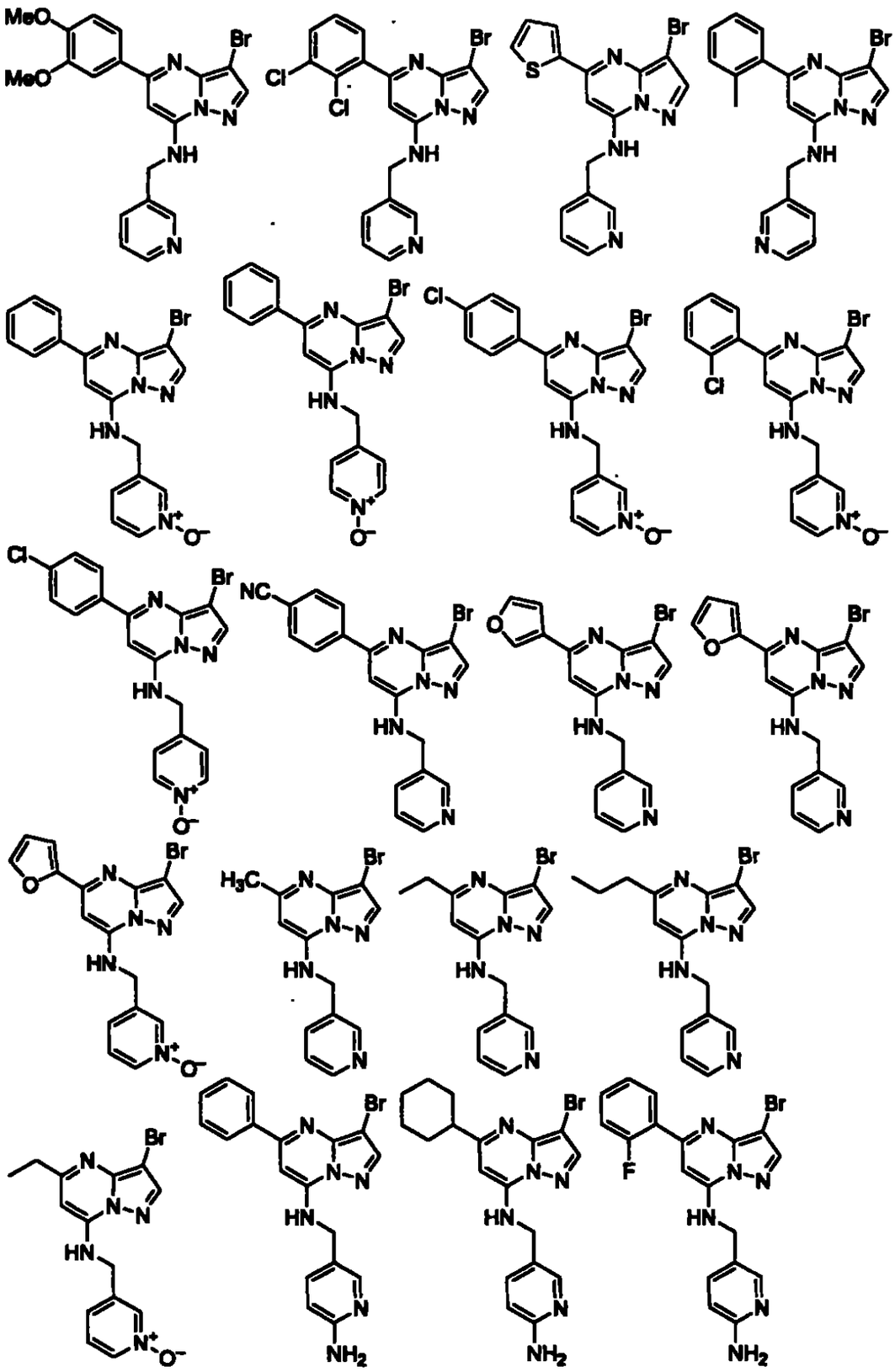
24. The compound of claim 19, wherein R^5 of said $-N(R^5R^6)$ is H or hydroxyalkyl, and R^6 of said $-N(R^5R^6)$ is selected from the group consisting of alkyl, hydroxyalkyl, cycloalkyl and methylenedioxy, wherein each of said alkyl and cycloalkyl can be unsubstituted or substituted with one or more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

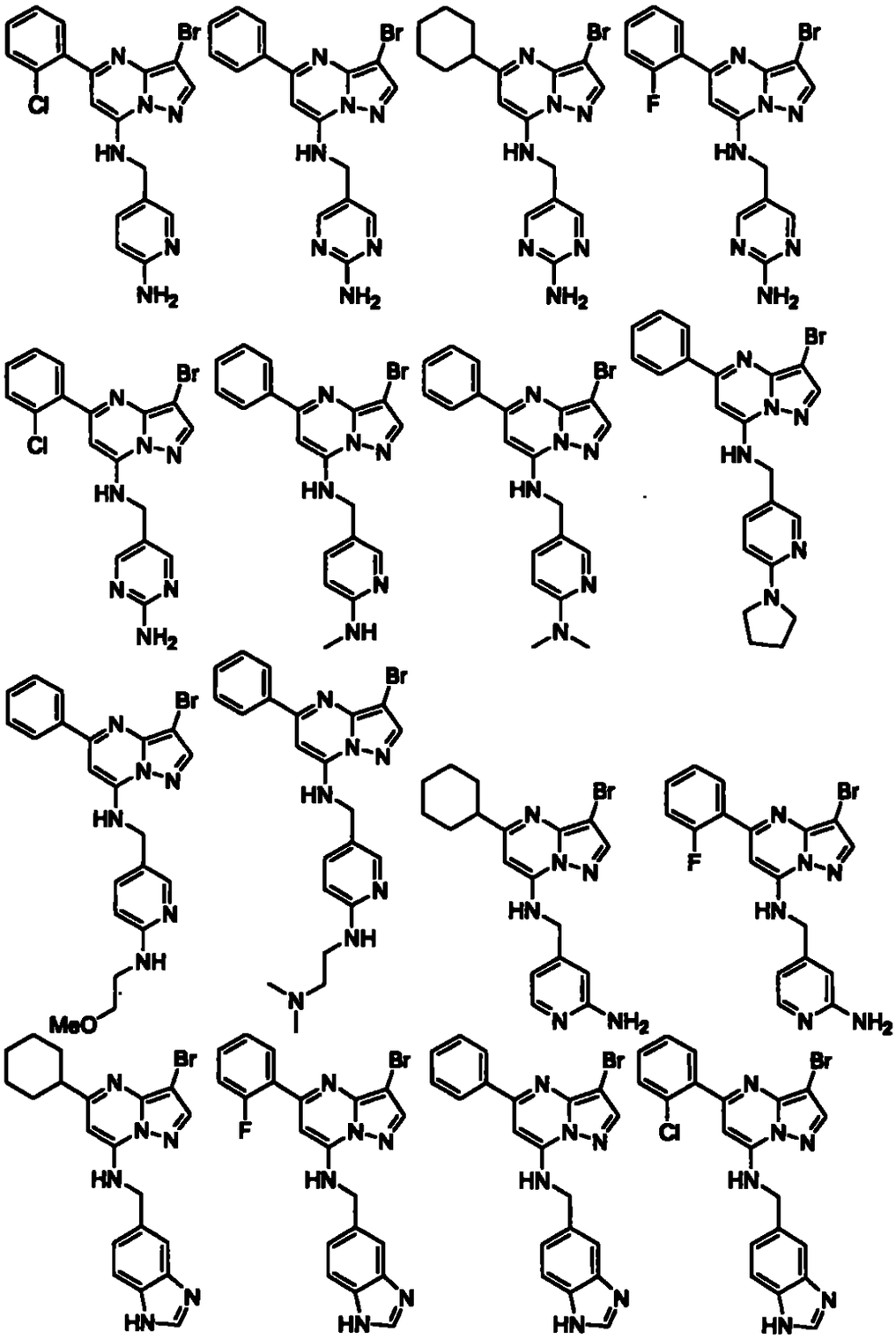
25. The compound of claim 19, wherein R^5 and R^6 of said $-N(R^5R^6)$ are joined together to form a heterocyclyl moiety, wherein said heterocyclyl moiety can be unsubstituted or optionally independently substituted with one or more groups which can be the same or different, each group being selected 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 $-C(=N\text{-}CN)N(R^5R^6)$.

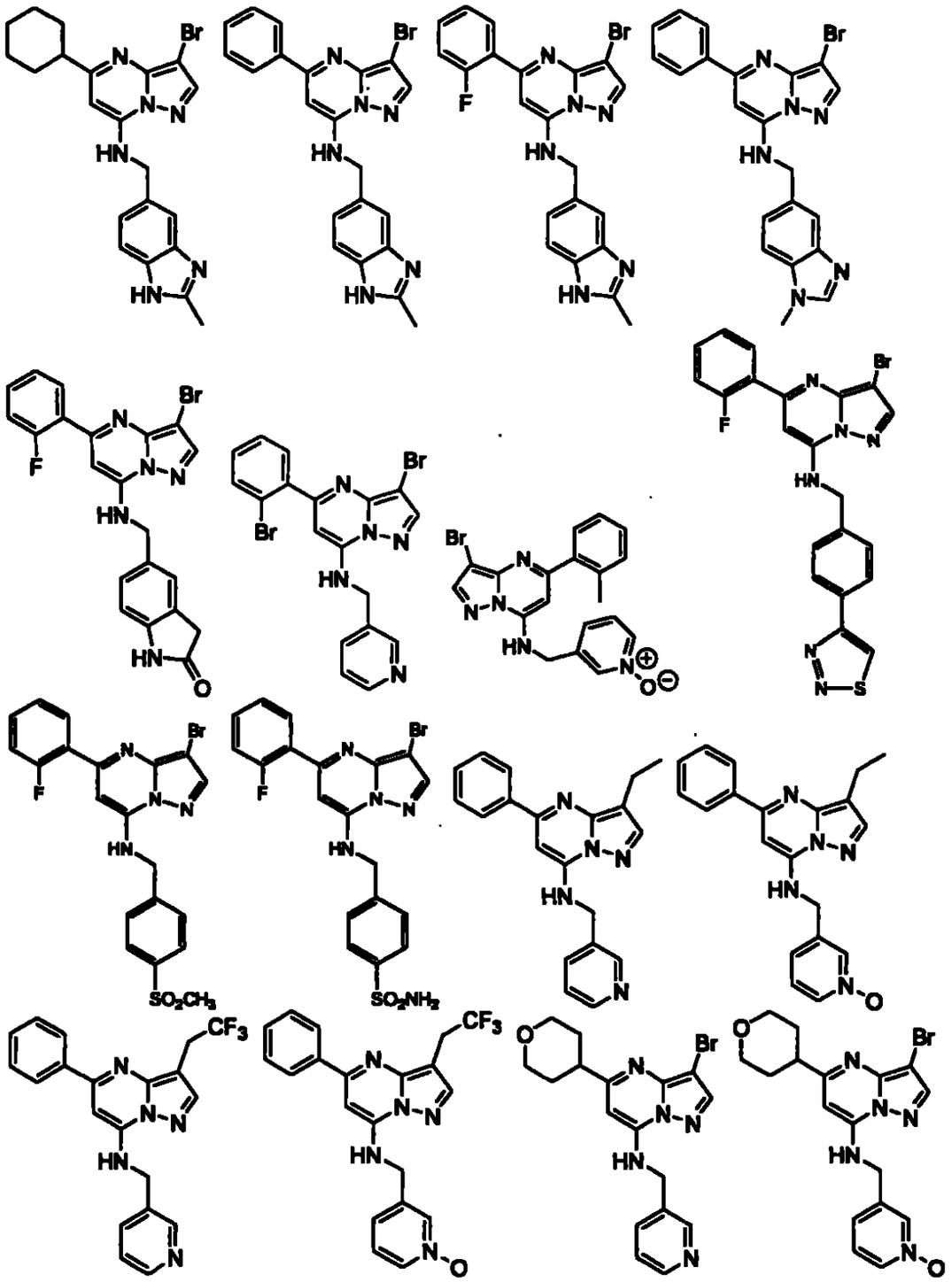
26. The compound of claim 25, wherein said heterocyclyl moiety formed by R^5 and R^6 is a pyrrolidine or piperidine ring.

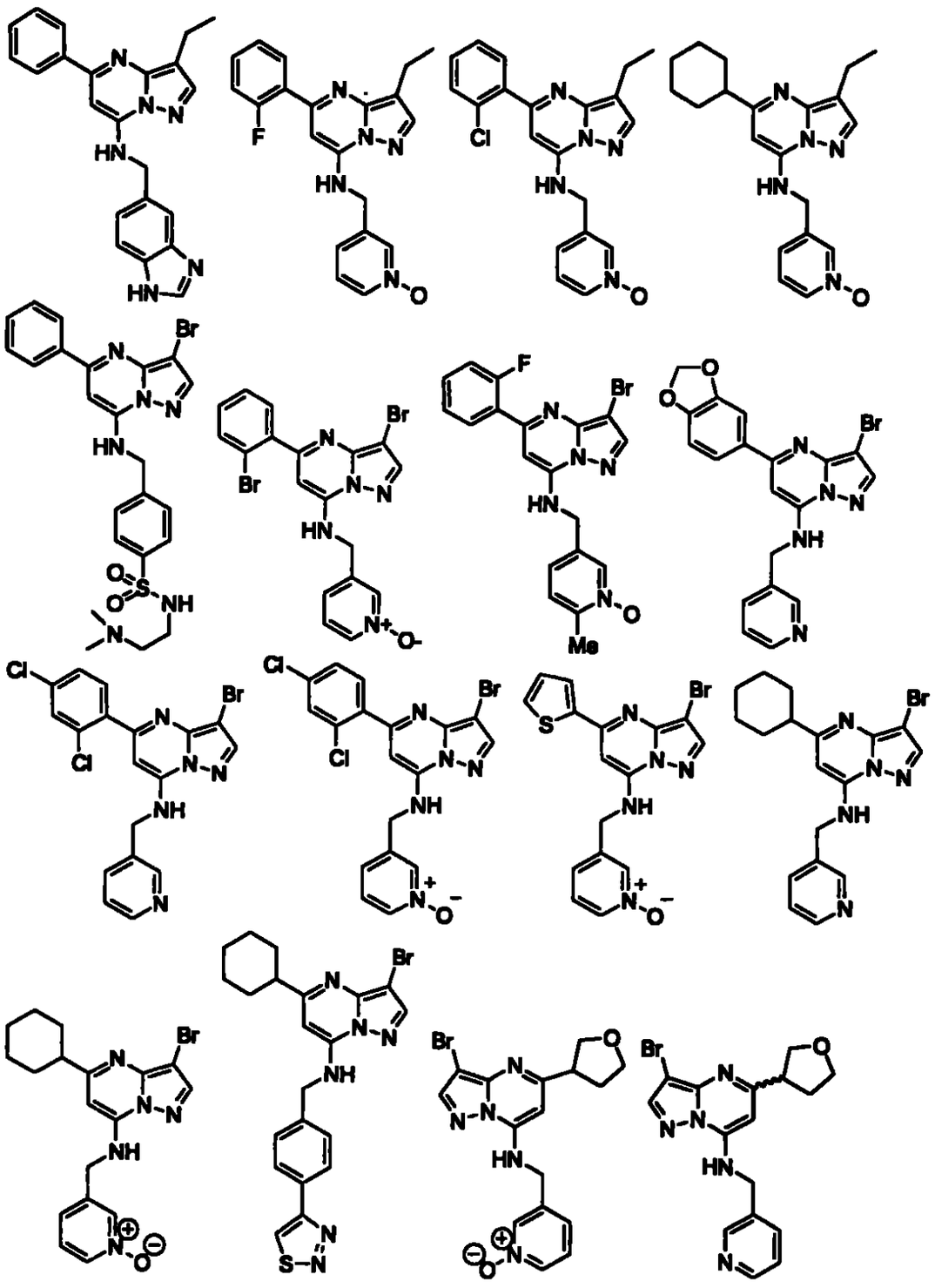
27. A compound of the formula:

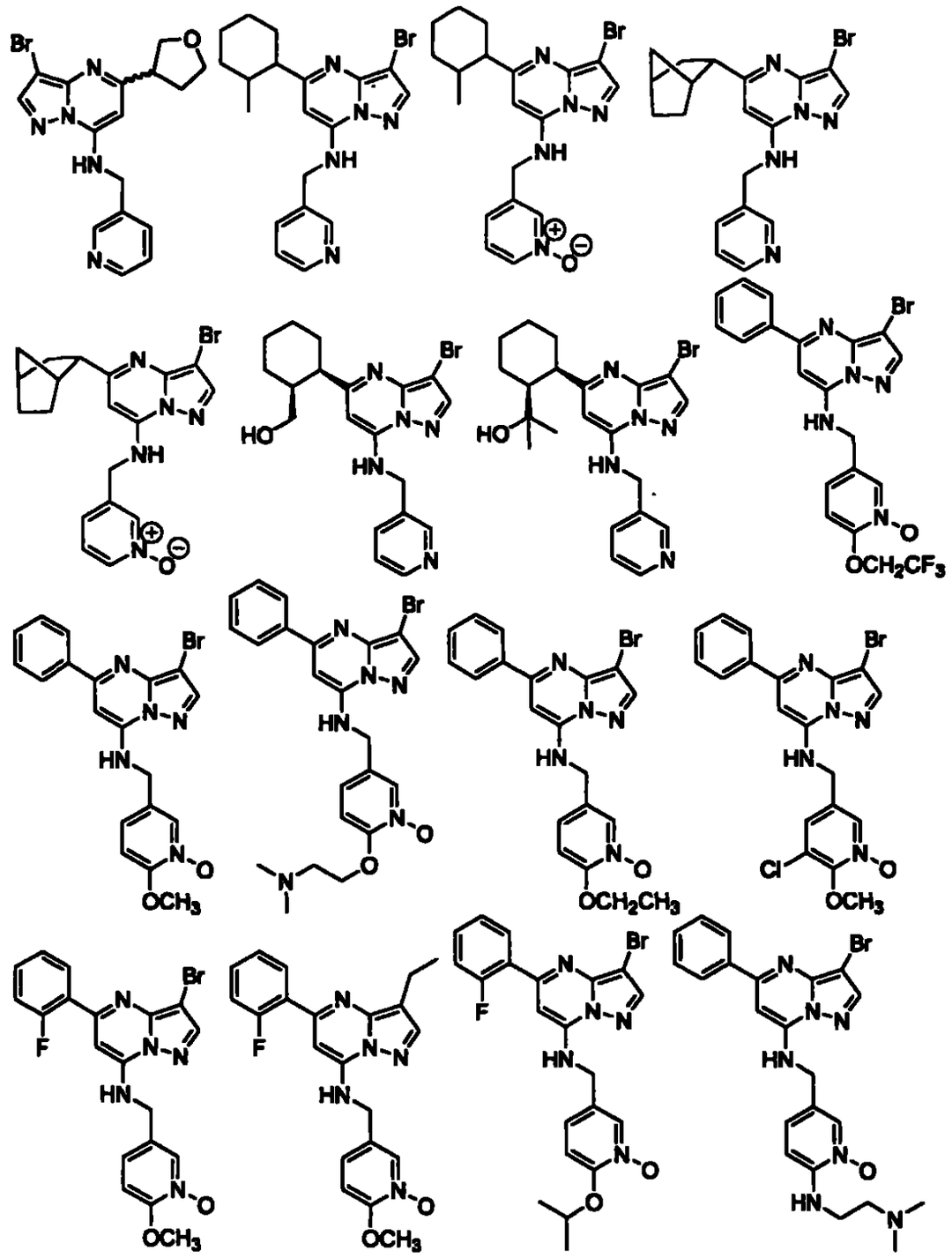


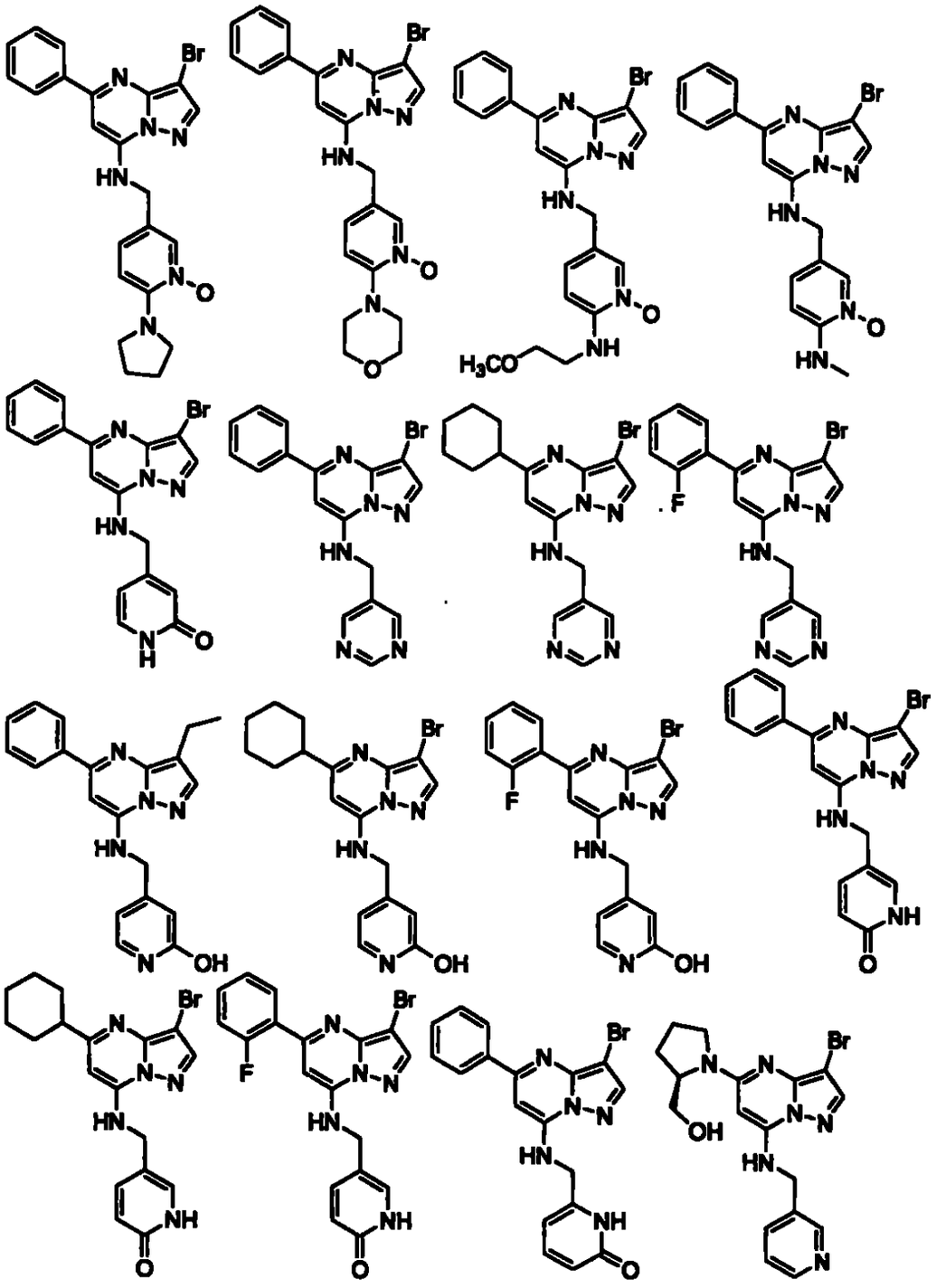


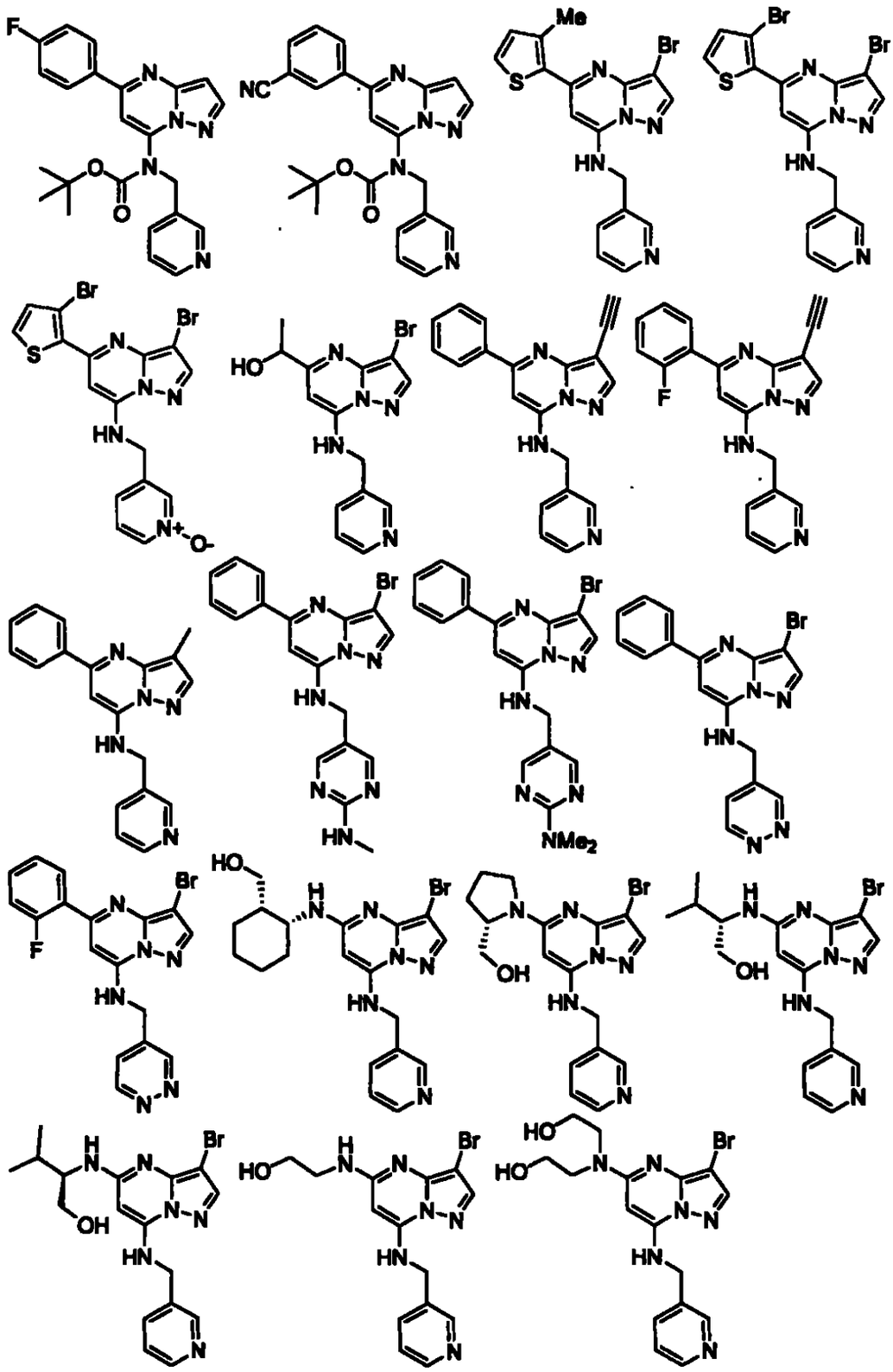




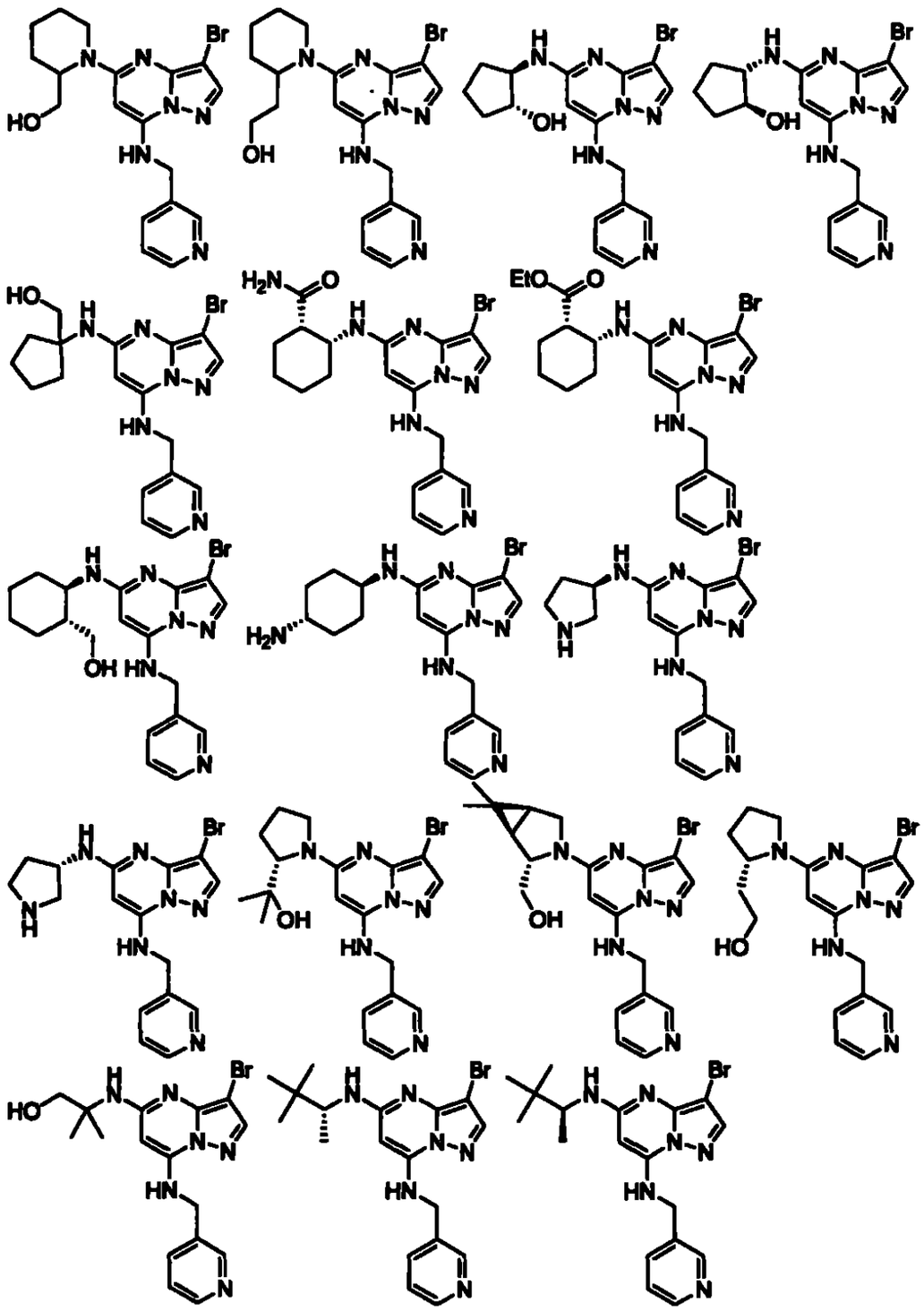


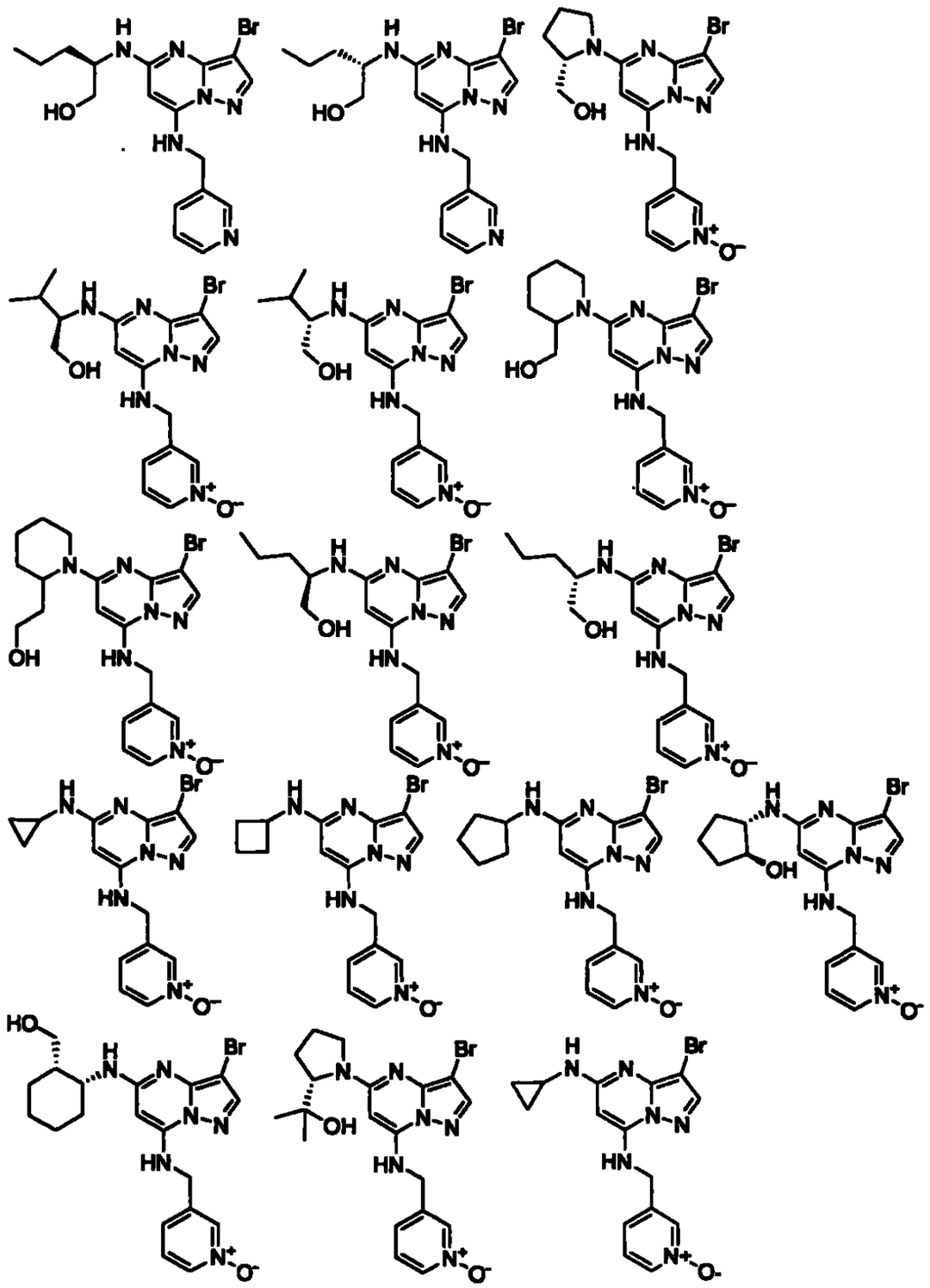


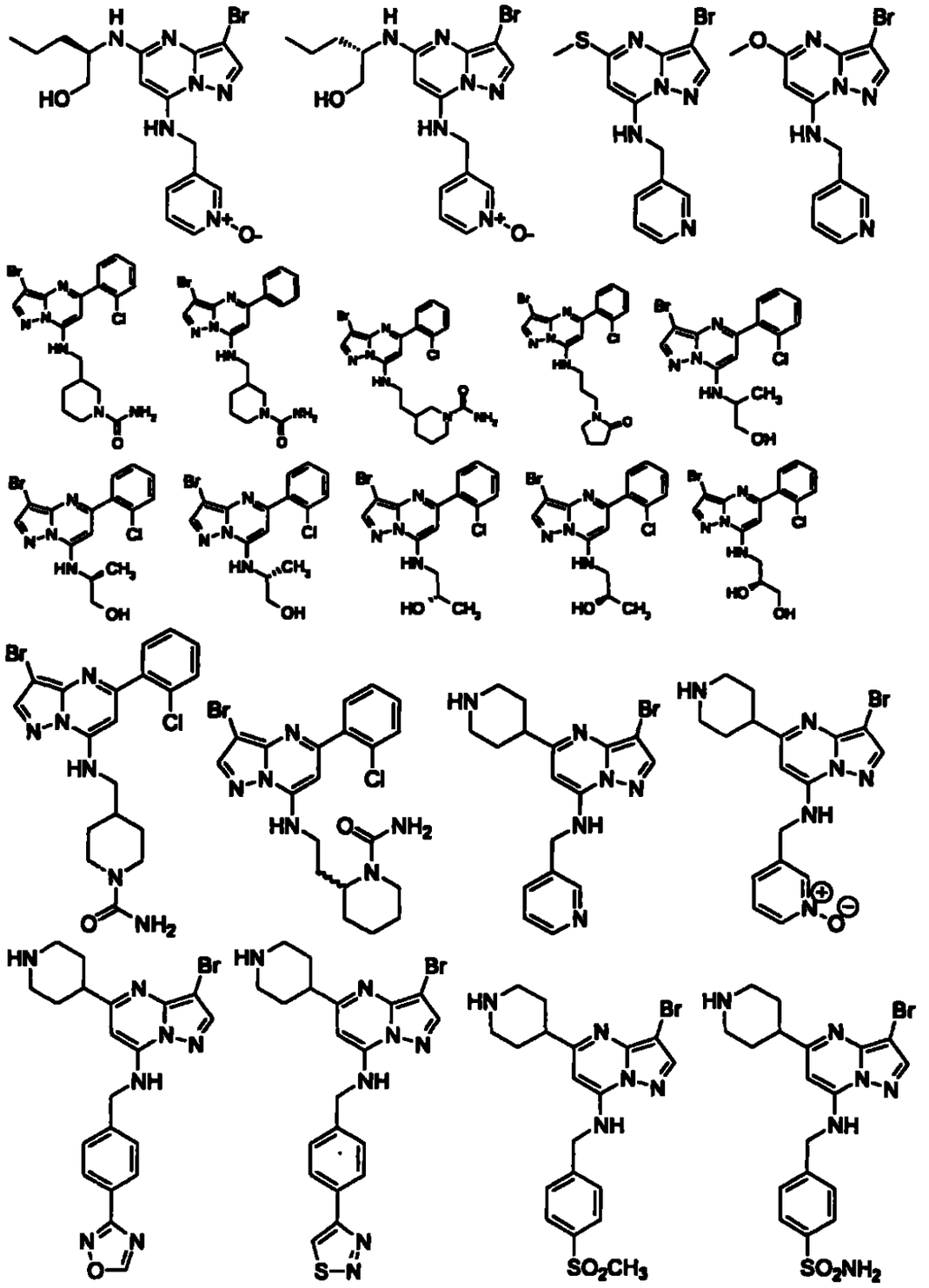


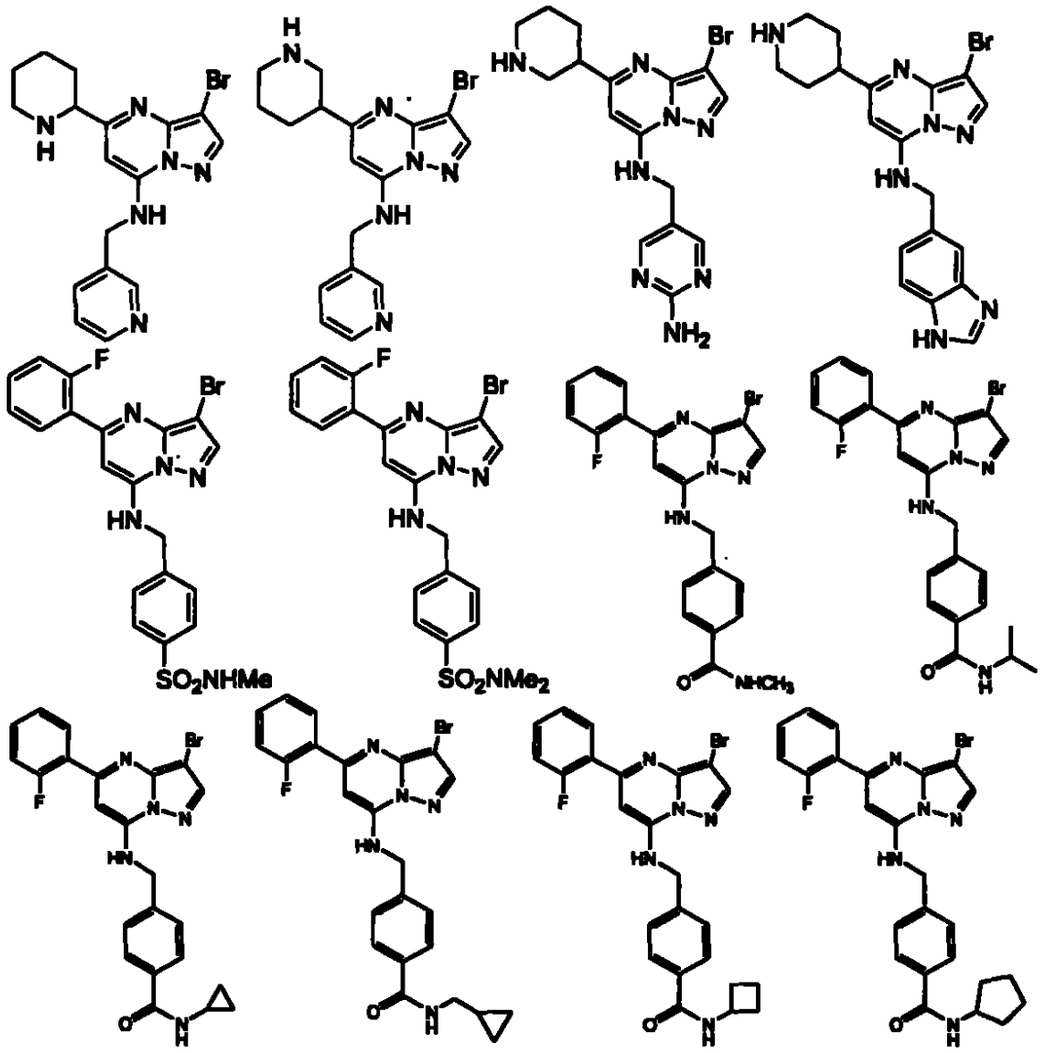


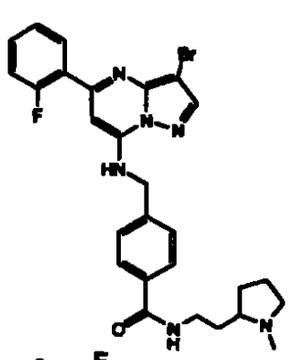
5

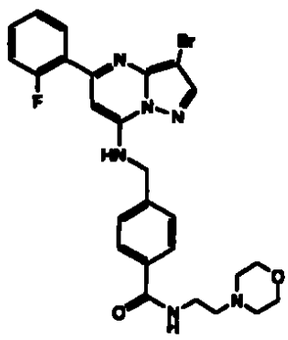


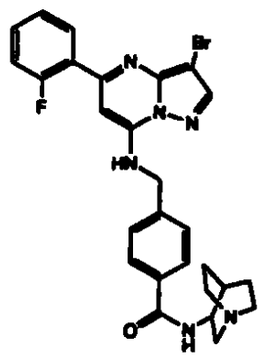


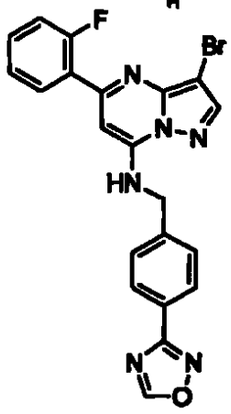


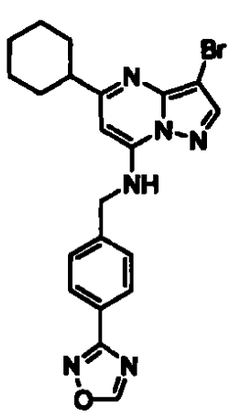

Br
NH
N
HN
NH2
F
SO2NHMe
SO2NMe2
NHCH3
O

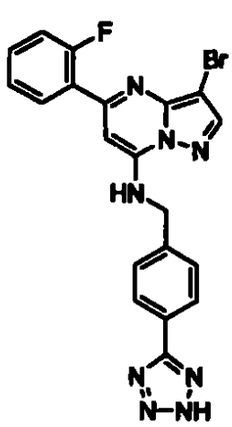


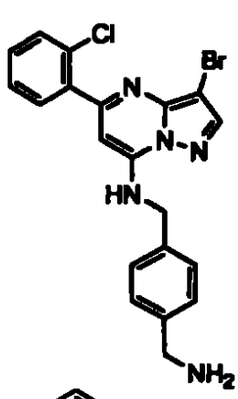


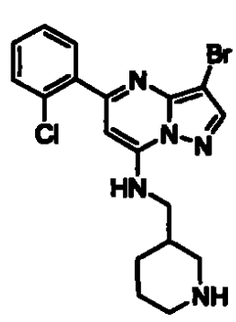


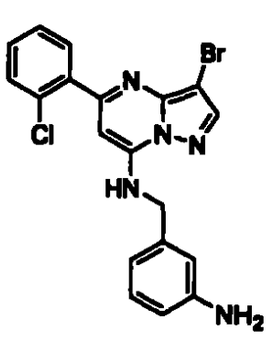


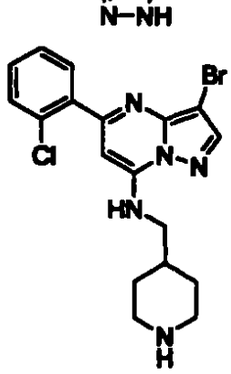


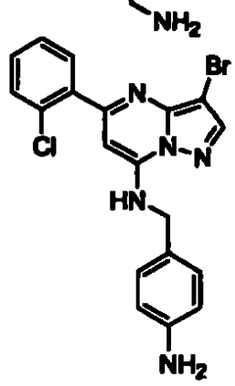


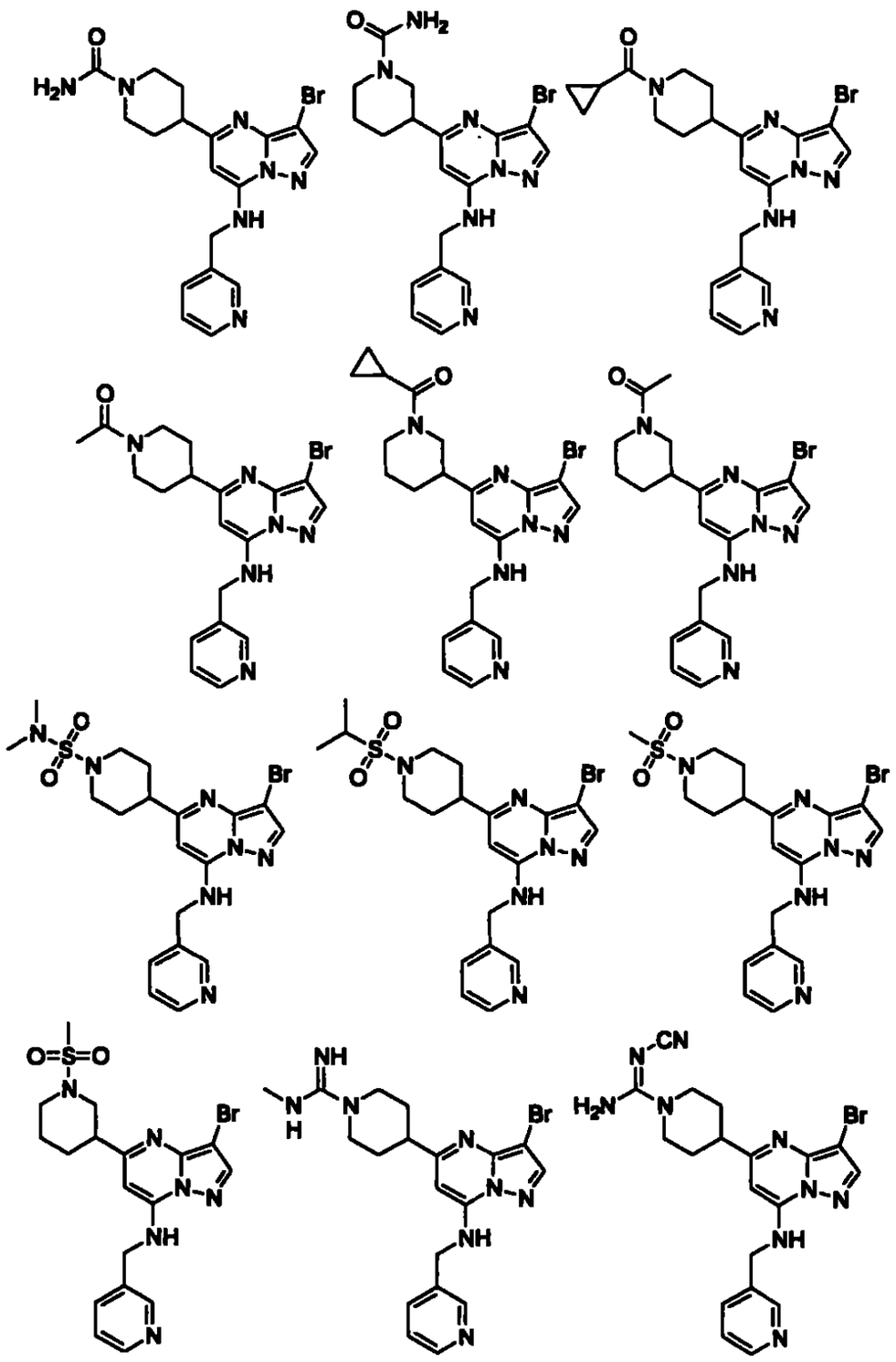


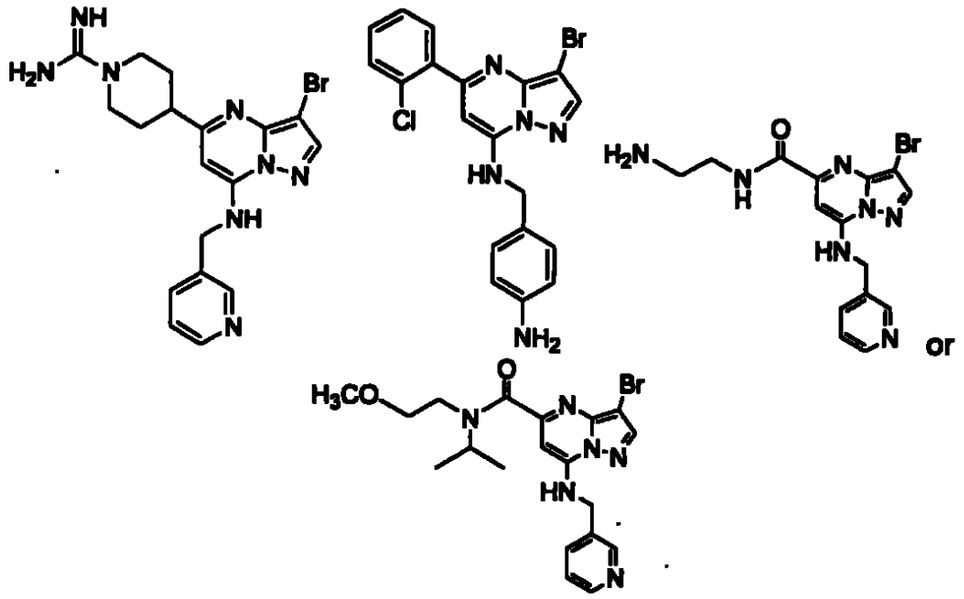






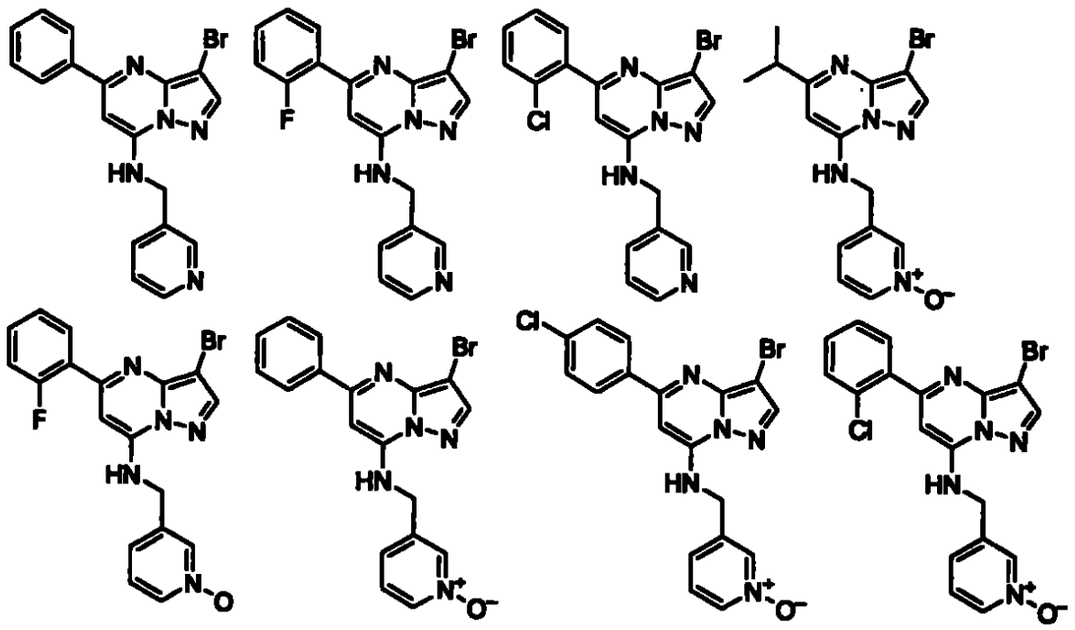


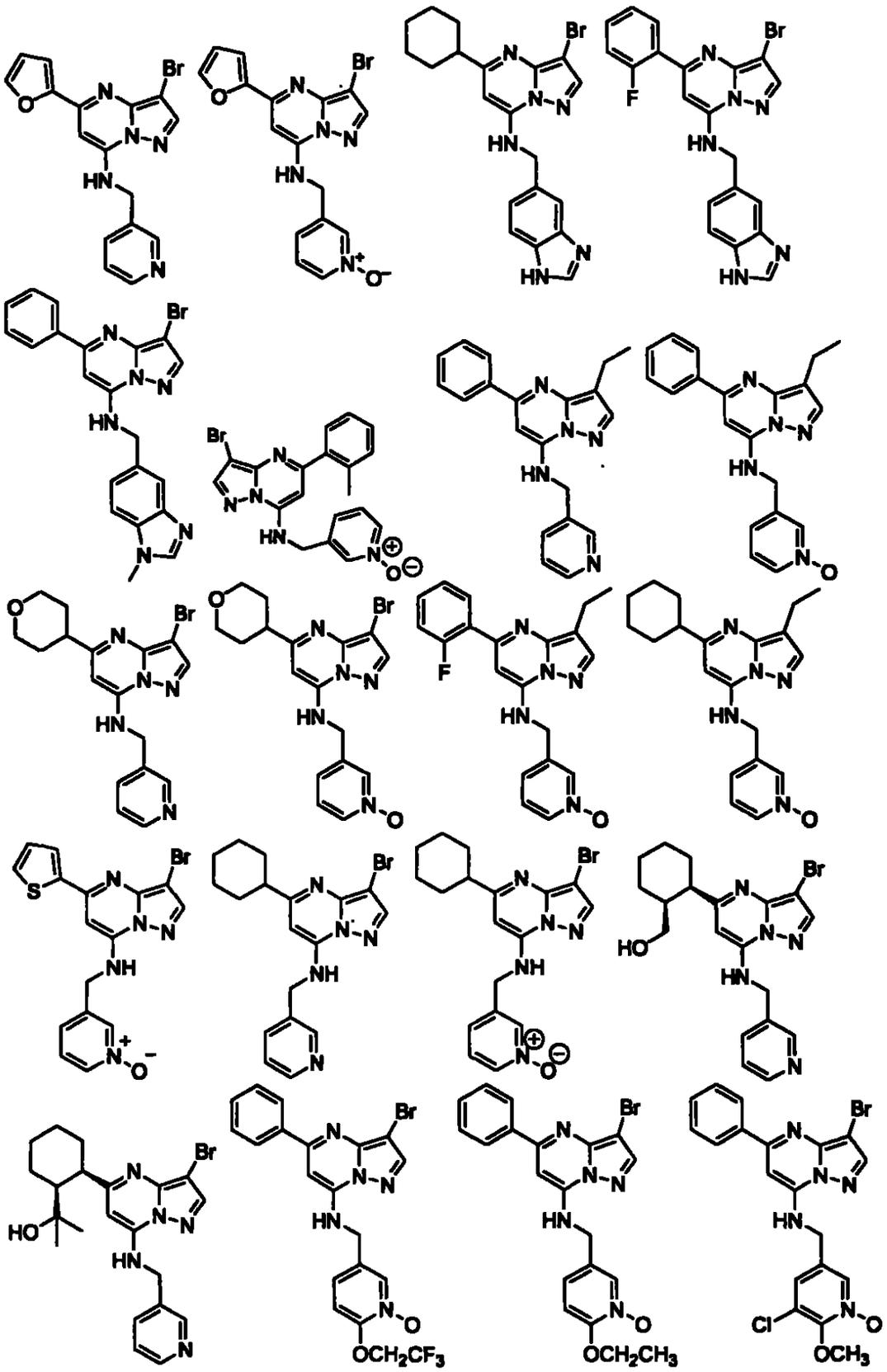




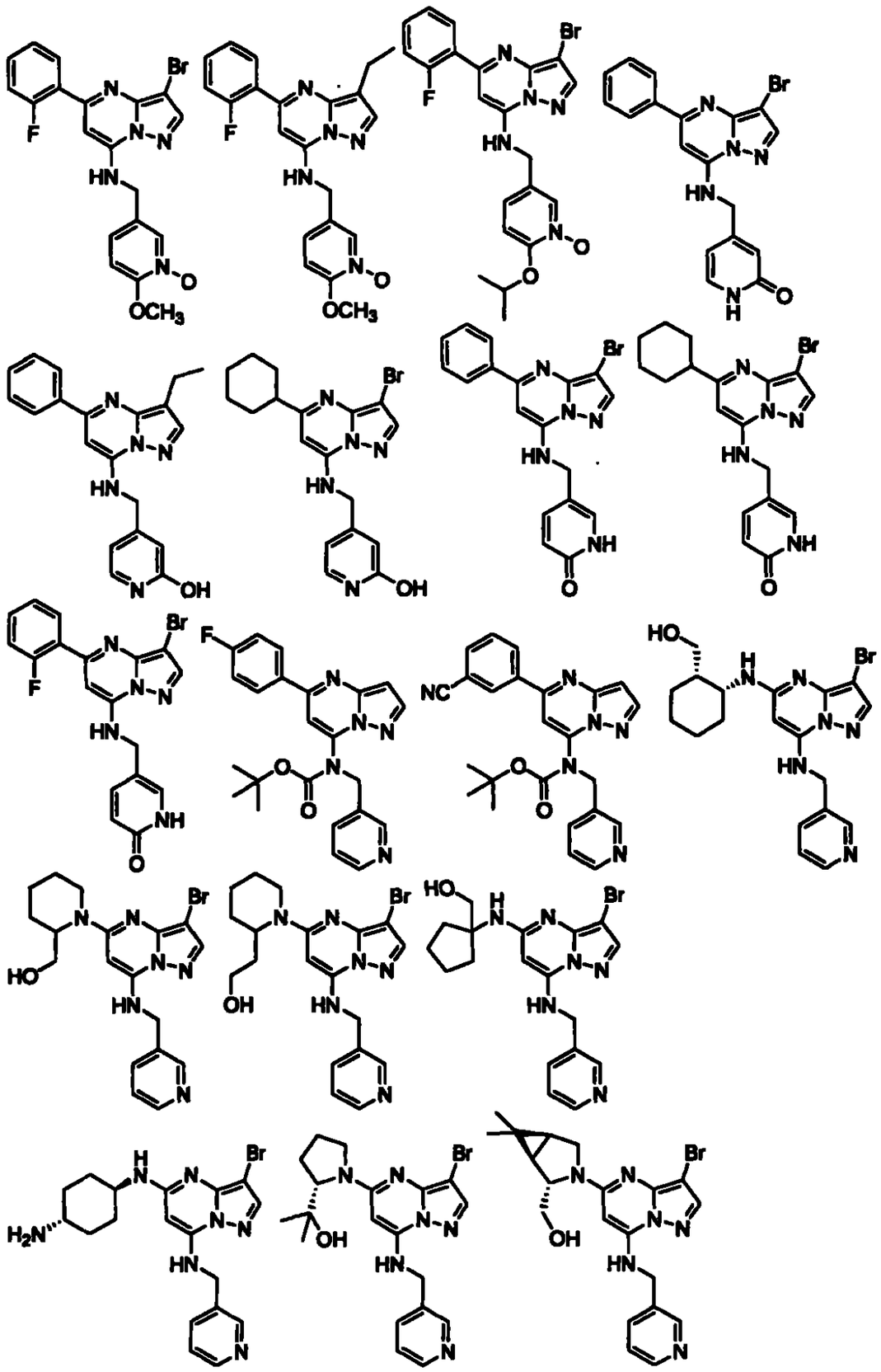
or a pharmaceutically acceptable salt or solvate thereof.

28. A compound of the formula:

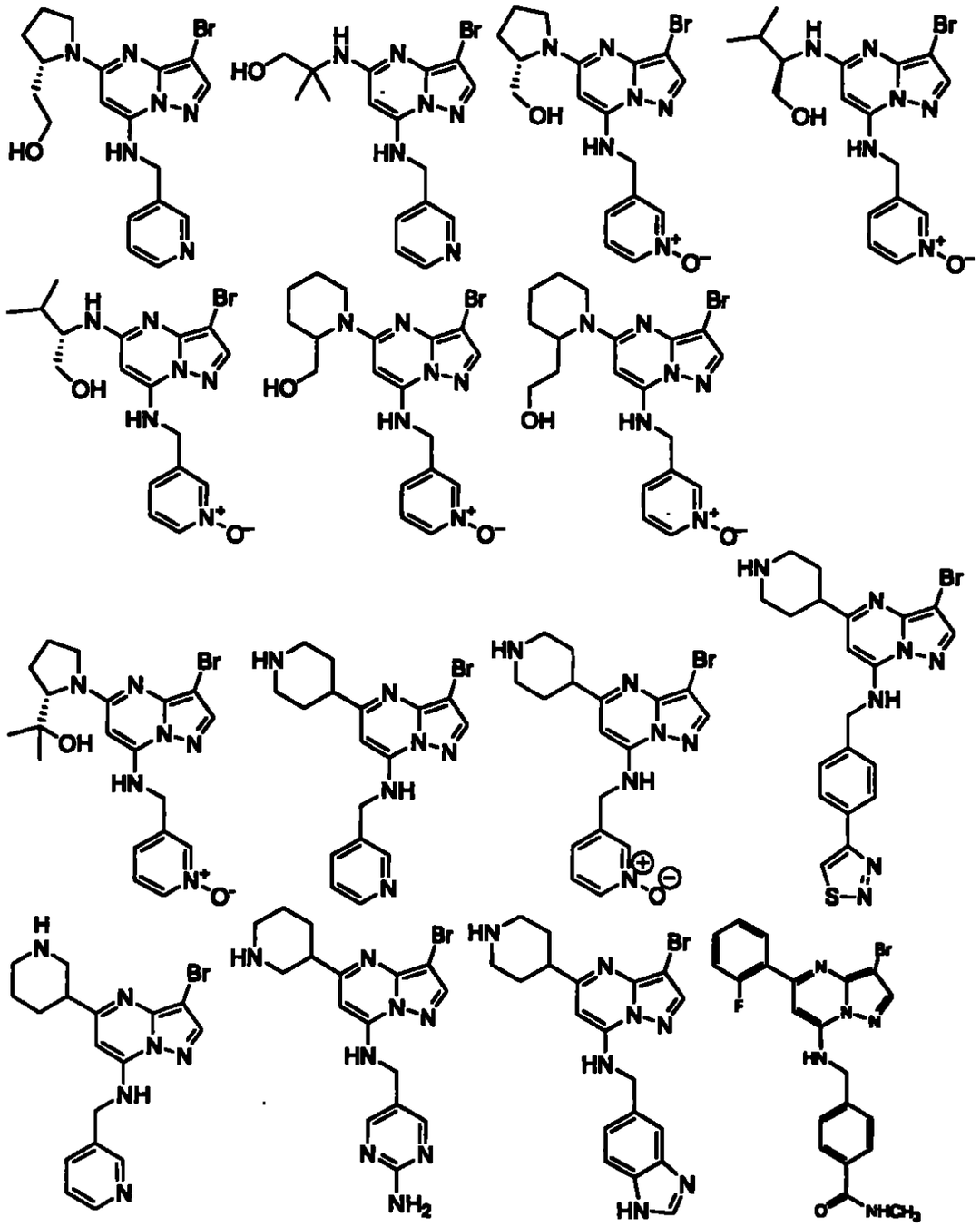


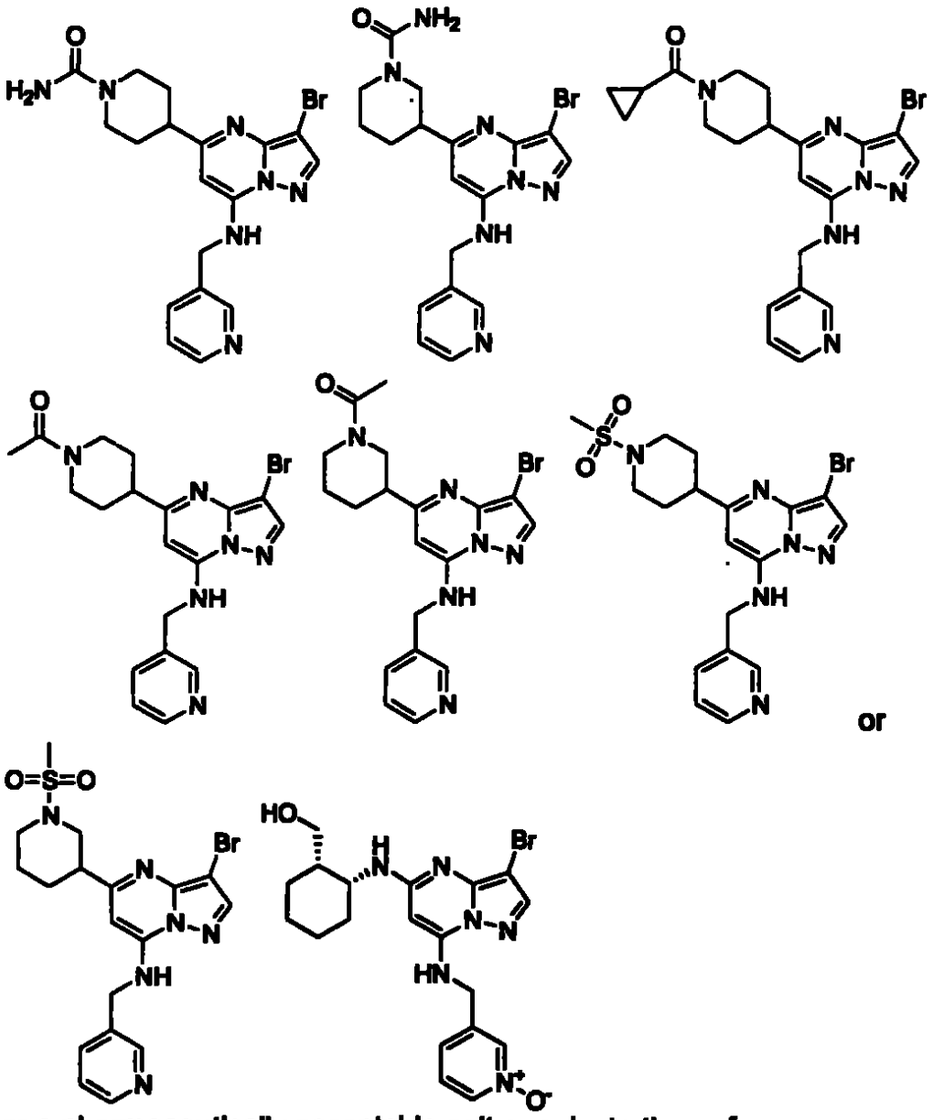


5



5

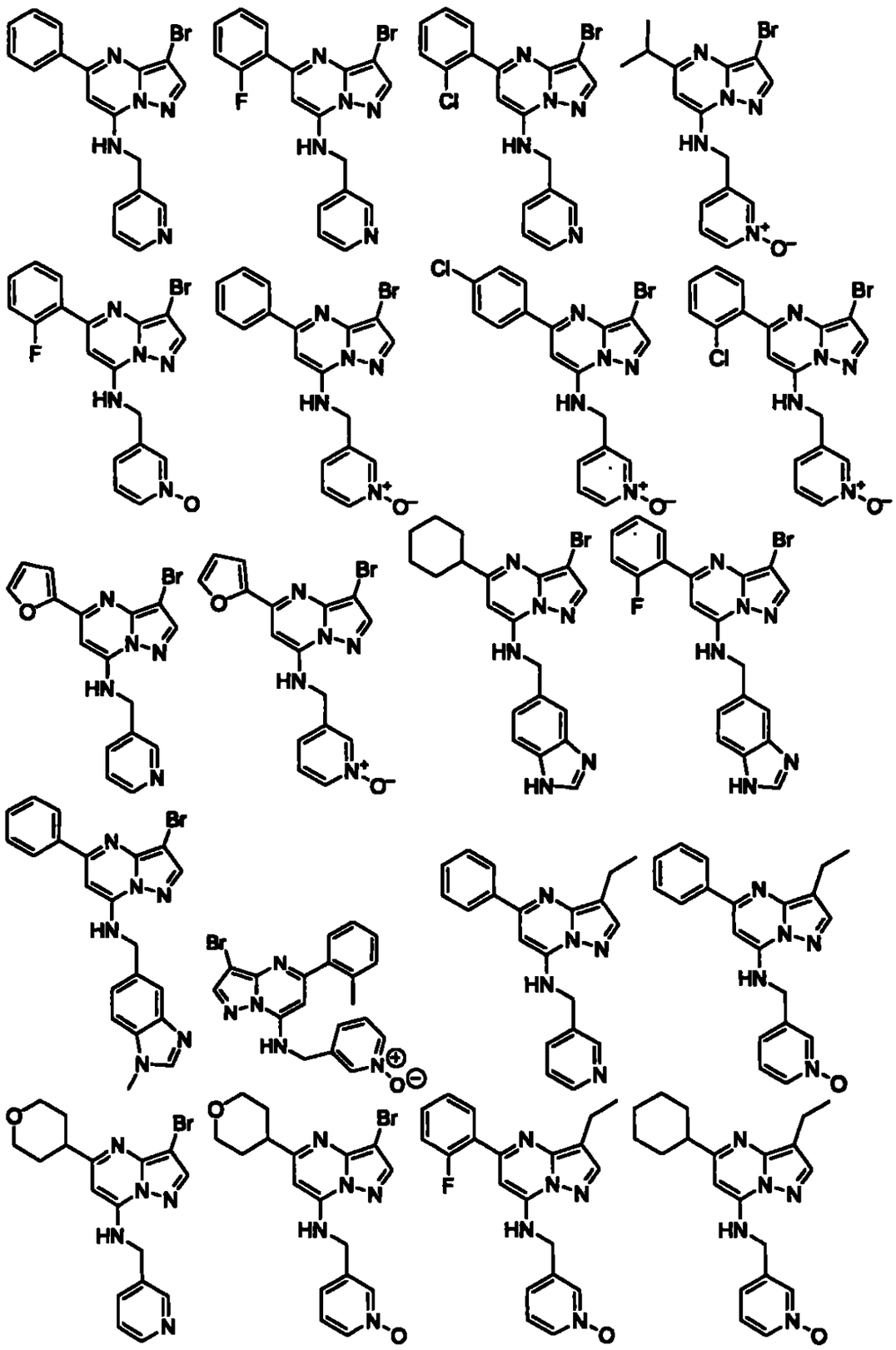


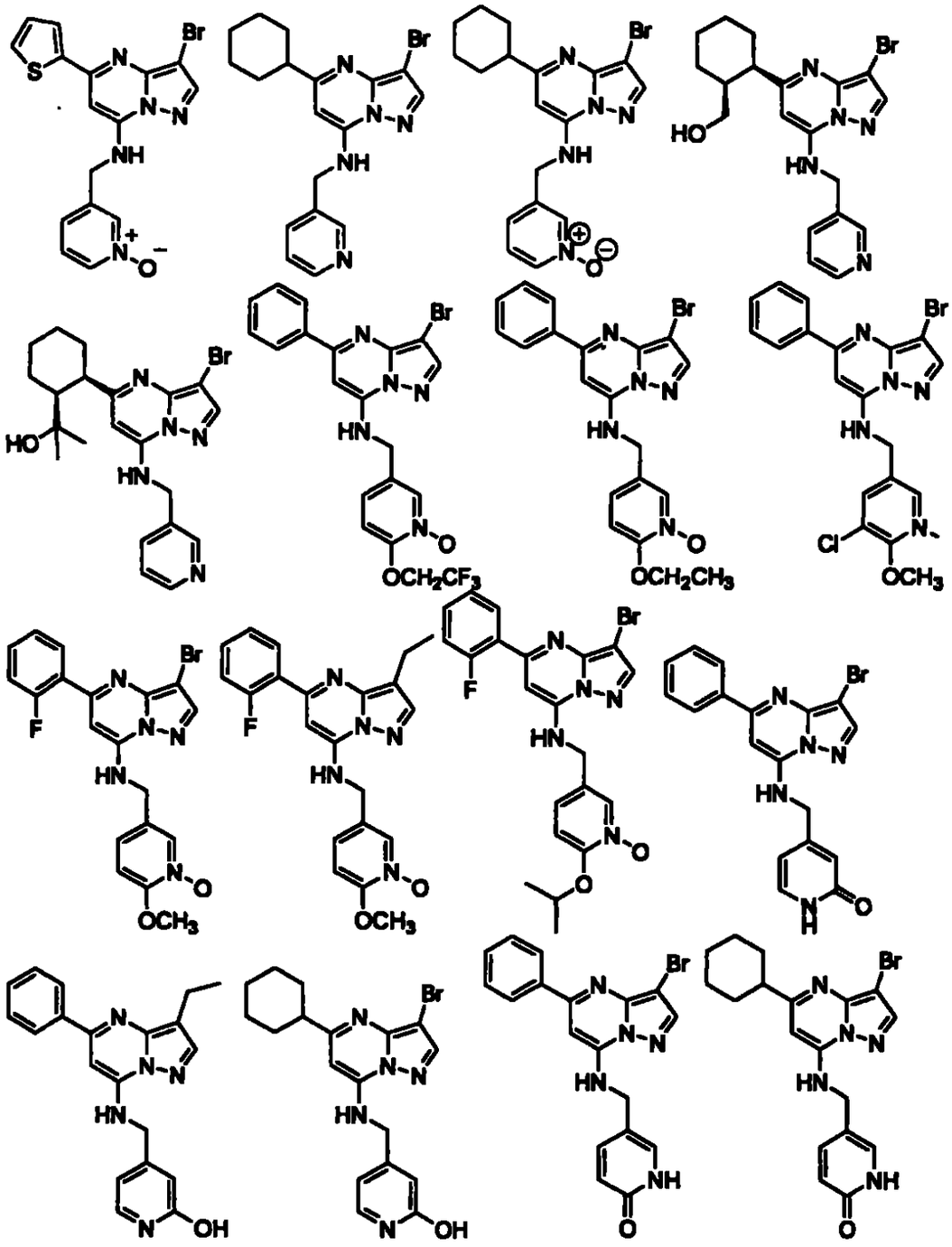


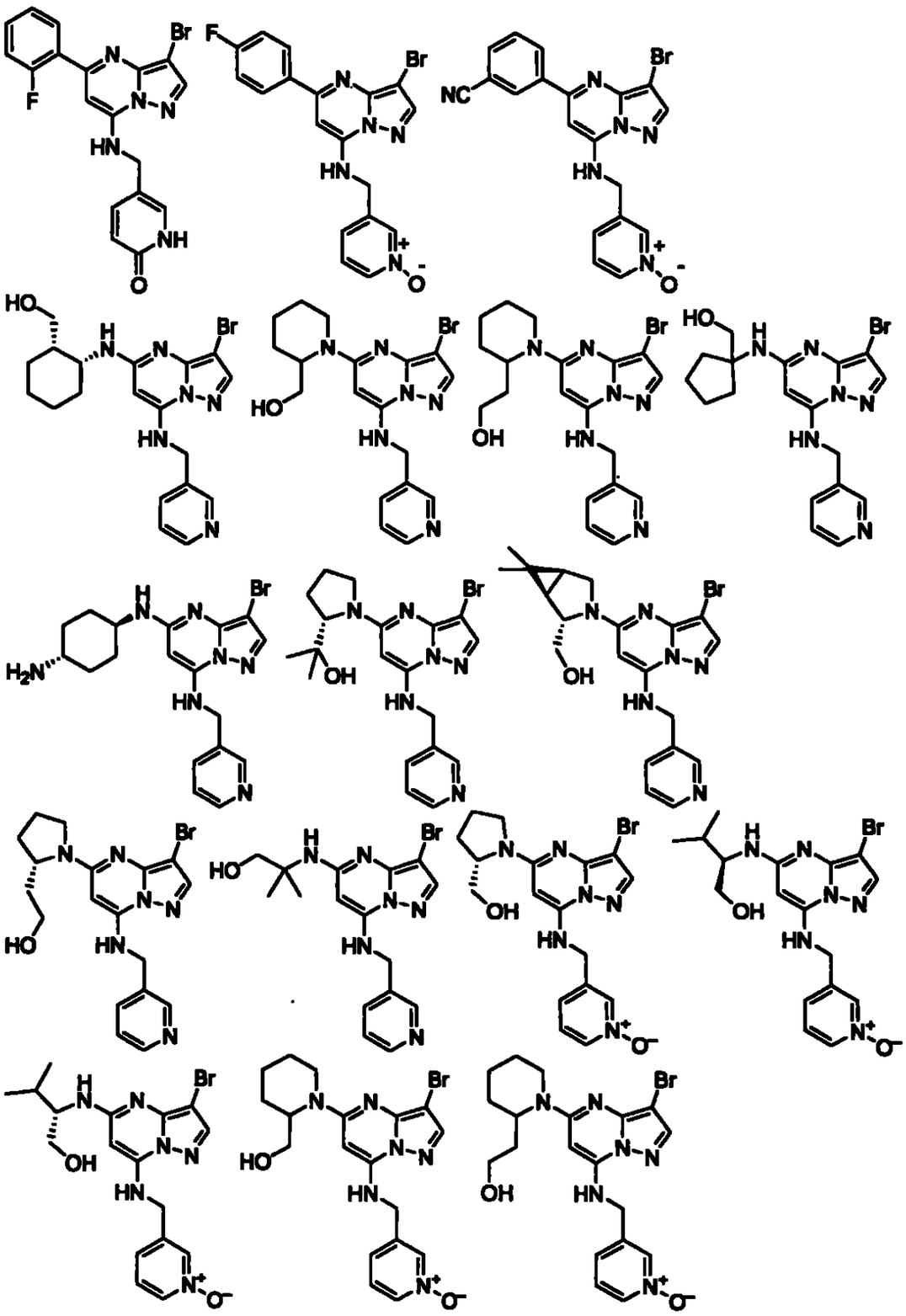
or

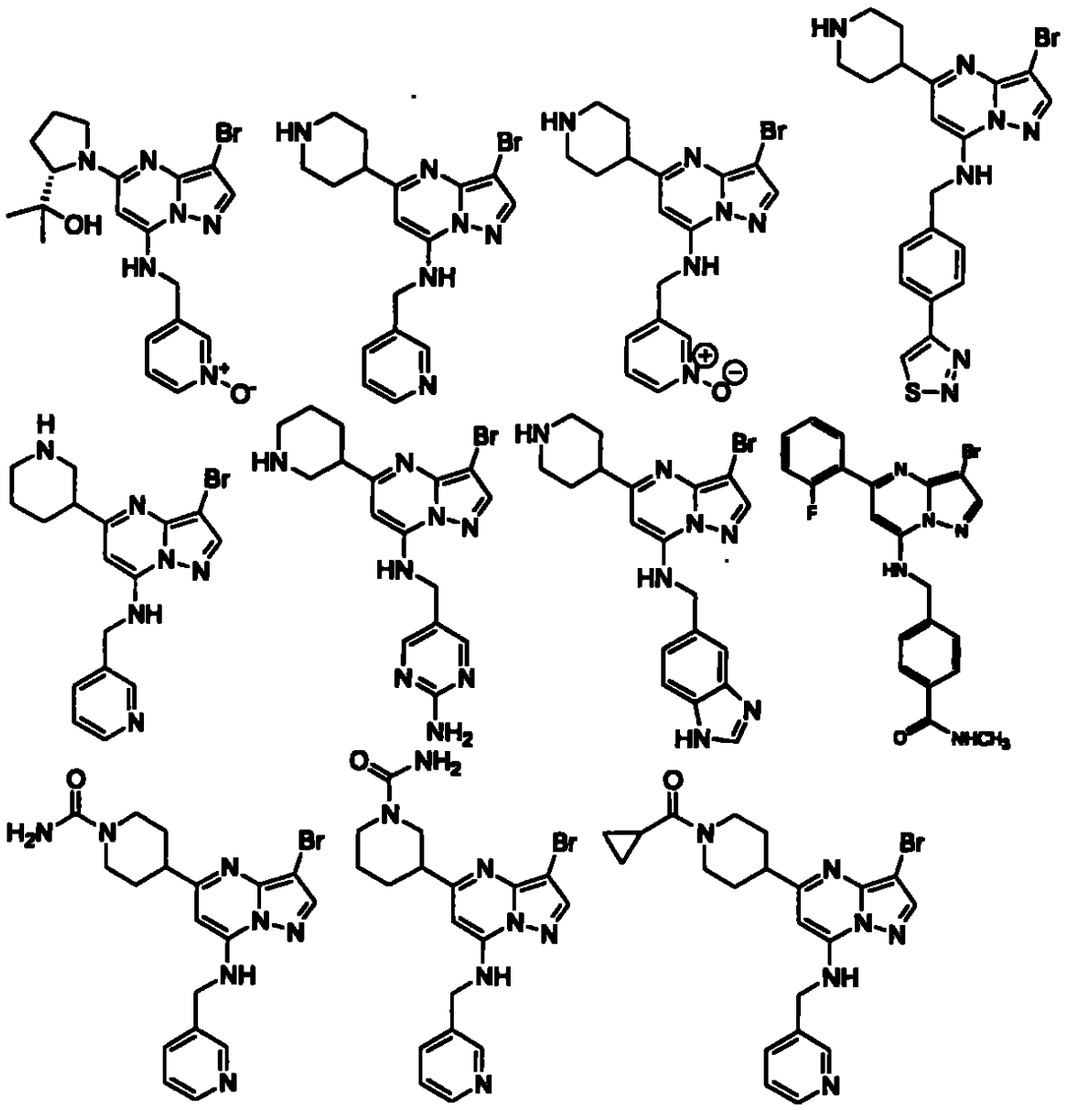
or a pharmaceutically acceptable salt or solvate thereof.

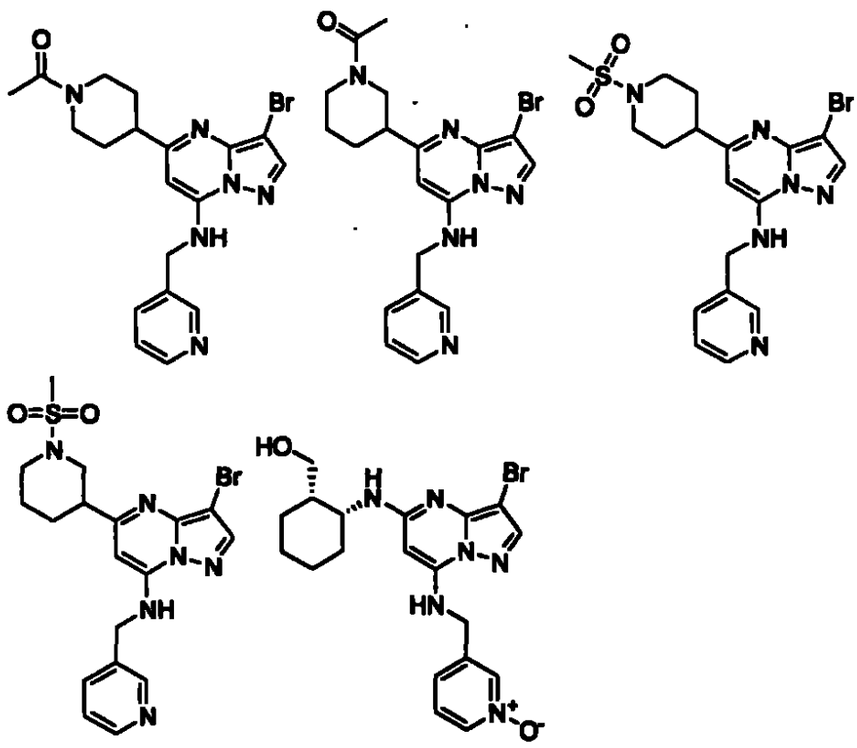
29. A compound of the formula:





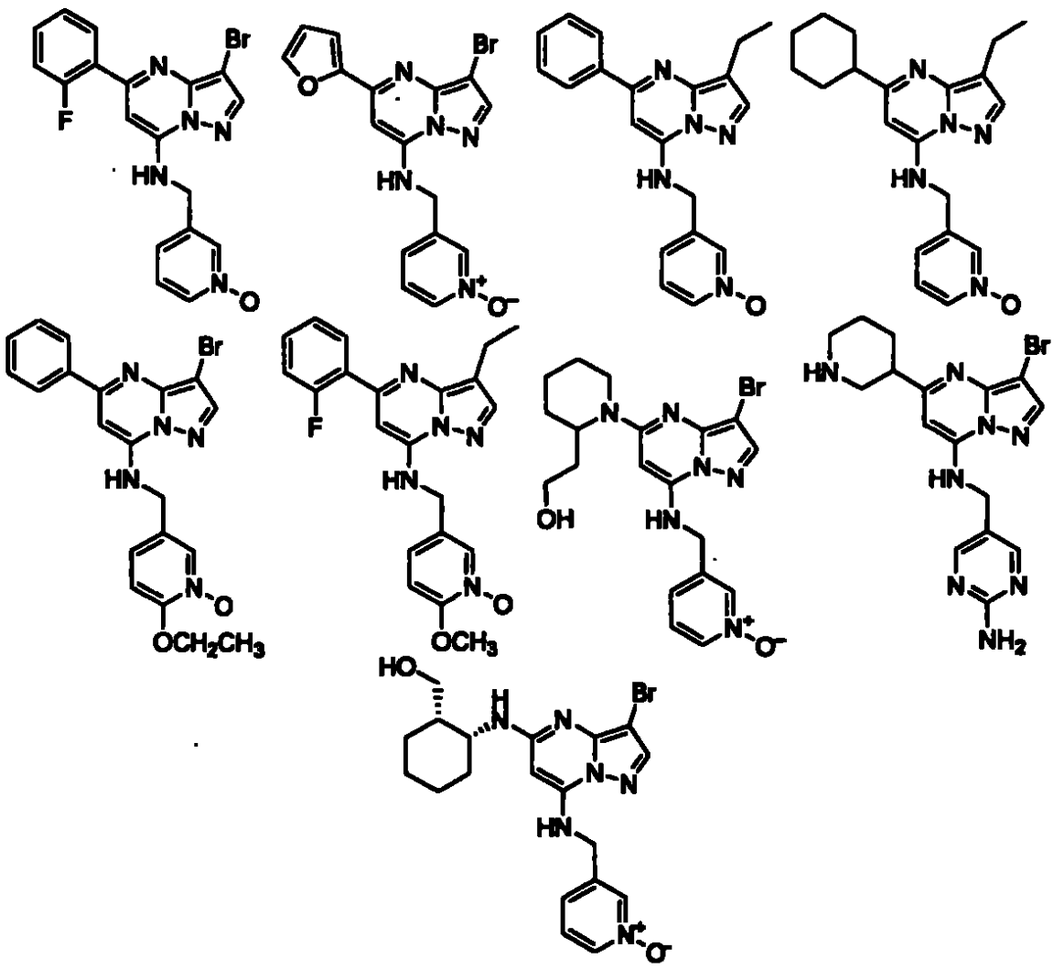






or a pharmaceutically acceptable salt or solvate thereof.

30. A compound of the formula:



or a pharmaceutically acceptable salt or solvate thereof.

31. 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.

32. 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.

33. The method of claim 32, wherein said cyclin dependent kinase is CDK2.

34. The method of claim 32, wherein said cyclin dependent kinase is mitogen activated protein kinase (MAPK/ERK).

35. The method of claim 32, wherein said cyclin dependent kinase is glycogen synthase kinase 3 (GSK3beta).

36. The method of claim 32, 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, neuroblastoma, glioma and schwannomas;

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

37. 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.

38. The method of claim 37, further comprising radiation therapy.

39. The method of claim 37, 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..

40. 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.

41. The pharmaceutical composition of claim 38, 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.

42. A compound of claim 1 in purified form.

OC01617K-AR-nf

Memoria Descriptiva

de la

Patente de Invención

Sobre

"NUEVOS PIRAZOLOPIRIMIDINAS COMO INHIBIDORES DE QUINASA DEPENDIENTES DE CICLINAS"

Solicitada por:

SCHERING CORPORATION * PHARMACOPEIA, INC., residente en 2000 Galloping Hill Road, Kenilworth, Nueva Jersey 07033-0530 * 3000 Eastpark Boulevard, Cranberry, Nueva Jersey 08512, E. U. DE NORTEAMERICA.

210092
CRF

NUEVOS PIRAZOLOPIRIMIDINAS COMO INHIBIDORES DE QUINASA DEPENDIENTES DE CICLINAS

La presente invención se refiere a compuestos de pirazolo[1,5-a]pirimidina útiles como inhibidores de la proteína quinasa (tales como por ejemplo, los inhibidores de las quinasas dependientes de ciclina, proteína quinasa activada por mitógeno (MAPK/ERK), sintasa quinasa 3 de glicógeno (GSK3beta) y similares), composiciones farmacéuticas que contienen los compuestos, y a los métodos de tratamiento que usan los compuestos y composiciones para tratar enfermedades tales como por ejemplo, cáncer, inflamación, artritis, enfermedades virales, enfermedades neurodegenerativas tal como la enfermedad de Alzheimer, enfermedades cardiovasculares, y enfermedades fungales. Esta solicitud reivindica el beneficio de la prioridad de las solicitudes de patente provisionales Norteamericanas Acta No. 60/408,027 presentada el 4 de Setiembre del 2002, y el Acta No. 60/421,959 presentada el 29 de Octubre del 2002.

Antecedentes de la Invención

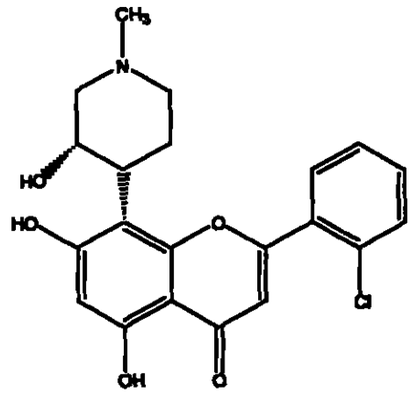
Los inhibidores de la proteína quinasa incluyen quinasas tales como, por ejemplo, los inhibidores de las quinasas dependientes de ciclina (CDKs), la proteína quinasa activada por mitógeno (MAPK/ERK), la sintasa quinasa 3 de glicógeno (GSK3beta),y similares. Los inhibidores de la proteína quinasa han sido descriptos por ejemplo por M. Hale et al en WO02/22610 A1 y por Y. Mettey et al en J. Med. Chem., (2003) 46 222-236. Las quinasas dependientes de ciclina son proteína quinasas de serina/treonina, que son la fuerza impulsora detrás del ciclo celular y de la proliferación de células. Las CDK individuales, tales como CDK1, CDK2, CDK3, CDK4, CDK5, CDK6 y CDK7, CDK8 y similares, cumplen distintas funciones en el progreso del ciclo celular y pueden clasificarse como enzimas de

320

fase G1, S, o G2M. Una proliferación descontrolada es una señal que denota células cancerosas, y la des-regulación de la función CDK ocurre con alta frecuencia en muchos tumores sólidos importantes. Las CDK2 y CDK4 son particularmente interesantes debido a que sus actividades están frecuentemente mal reguladas en una amplia variedad de cánceres humanos. La actividad de la CDK2 es necesaria para avanzar a través de G1 hasta la fase S del ciclo celular, y la CDK2 es uno de los componentes del punto de control G1. Los puntos de control sirven para mantener la secuencia apropiada de los eventos del ciclo celular y para permitir que la célula responda a las agresiones y las señales proliferativas, mientras que la pérdida de un control apropiado del punto de control en las células cancerosas contribuye a la oncogenia. La vía de CDK2 influencia la oncogenia al nivel de la función supresora de tumores (por ejemplo p52, RB, y p27) y la activación oncogénica (ciclina E). Muchos informes han demostrado que tanto el coactivador, la ciclina E y el inhibidor, p27,de CDK2 están sobre – o subexpresados, respectivamente, en cáncer de mama, de colon, carcinomas pulmonares amicrocíticos, gástricos, de próstata, de vejiga, linfoma no Hodgkiniano, cáncer de ovario y otros cánceres. Su expresión alterada ha demostrado que está correlacionada con un aumento de los niveles de actividad de la CDK2 y una baja supervivencia general. Esta observación convierte a los CDK2 y a sus vías reguladoras en objetivos apremiantes para los años venideros, puesto que una variedad de moléculas orgánicas pequeñas competitivas de 5'-trifosfato de adenosina (ATP) así como también péptidos han sido mencionados en la literatura como inhibidores de CDK para el tratamiento potencial de cánceres. La patente Norteamericana 6:413.974,- columna. 1, línea 23- columna. 15, línea 10 ofrece una buena descripción de las varias CDK y de su relación con varios tipos de cáncer.

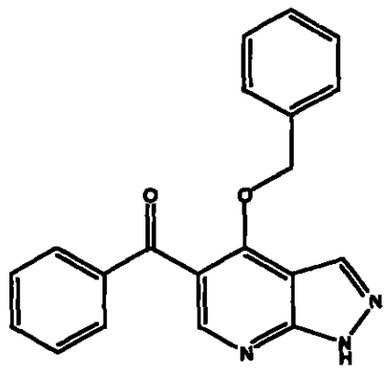
Los inhibidores de CDK son conocidos. Por ejemplo, el flavopiridol (Fórmula

l) es un inhibidor de CDK no selectivo que es corrientemente sometido a pruebas clínicas humanas, A. M. Sanderowicz et al, J. Clin. Oncol. (1998) 16, 2986-2999.



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 Norteamericana Nº 6,107,305 describe algunos compuestos de pirazolo[3,4-b] piridina como inhibidores de CDK. Un compuesto ilustrativo de la patente 6.107.305 tiene la Fórmula II:



Fórmula II

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

Las pirazolopirimidinas son conocidas. Por ejemplo, WO92/18504, WO02/50079, WO95/35298, WO02/40485, EP94304104.6, EP0628559

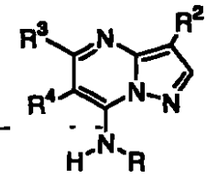
(equivalente a las Patentes US 5,602,136, 5,602,137 y 5,571,813), patente Norteamericana. 6,383,790, Chem. Pharm. Bull., (1999) 47 928, J. Med. Chem., (1977) 20, 296, J. Med. Chem., (1976) 19 517 y Chem. Pharm. Bull., (1962) 10 620 describen varias pirazolopirimidinas.

Existe la necesidad de nuevos compuestos, formulaciones, tratamientos y terapias para tratar enfermedades y desórdenes asociados con las CDK. Por lo tanto, es un objeto de esta invención proveer compuestos útiles en el tratamiento o prevención o mejoría de dichas enfermedades y desórdenes.

Compendio de la Invención

En sus muchas realizaciones, la presente invención provee una nueva clase de compuestos de pirazolo[1,5-a]pirimidina como inhibidores de quinasas dependientes de ciclina, los métodos para la preparación de dichos compuestos, las composiciones farmacéuticas que comprenden uno o más de dichos compuestos, los métodos de preparación de las formulaciones farmacéuticas que comprenden uno o más de dichos compuestos, y los métodos de tratamiento, prevención, inhibición o mejoría de una o más enfermedades asociadas con las CDK usando dichos compuestos o composiciones farmacéuticas.

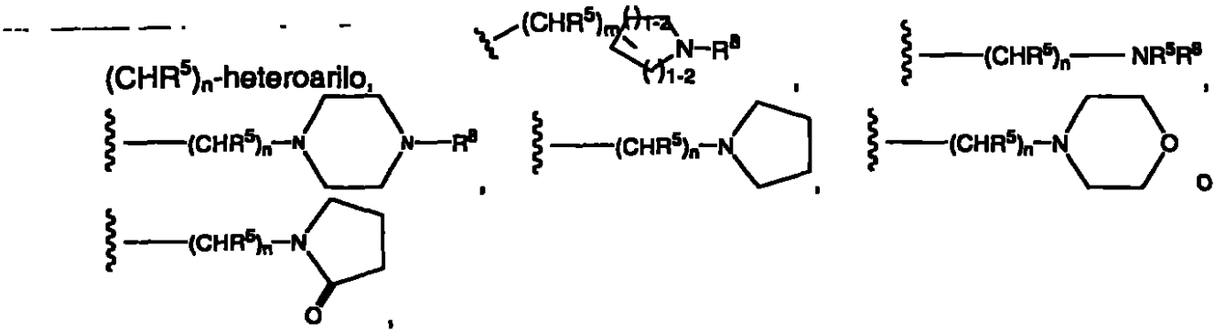
En un aspecto, la presente invención describe un compuesto o sales o solvatos farmacéuticamente aceptables de dicho compuesto, donde dicho compuesto tiene la estructura general que se muestra en la Fórmula III:



Fórmula III

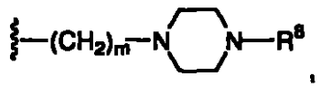
en la cual

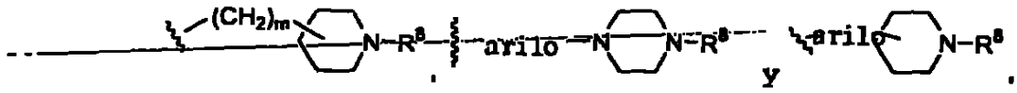
R is H, alquilo, alquenilo, alquinilo, arilalquilo, arilalquenilo, cicloalquilo, cicloalquilalquilo, alquenilalquilo, alquinilalquilo, heterociclilo, heterociclilalquilo, heteroarilalquilo (incluyendo el N-óxido de dicho heteroarilo), -$(CHR^5)_n$-arilo, -



donde cada uno de dichos alquilo, alquenilo, alquinilo, arilo, cicloalquilo, heterociclilo, y heteroarilo pueden estar no sustituidos o pueden estar opcionalmente insustituidos con una o más porciones que pueden ser iguales o diferentes, donde cada porción está independientemente seleccionada del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, heterociclilalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^{10}$, $-C(R^4R^5)_p-R^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^{10}$, $-SO_3H$, $-SR^{10}$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^{10}$;

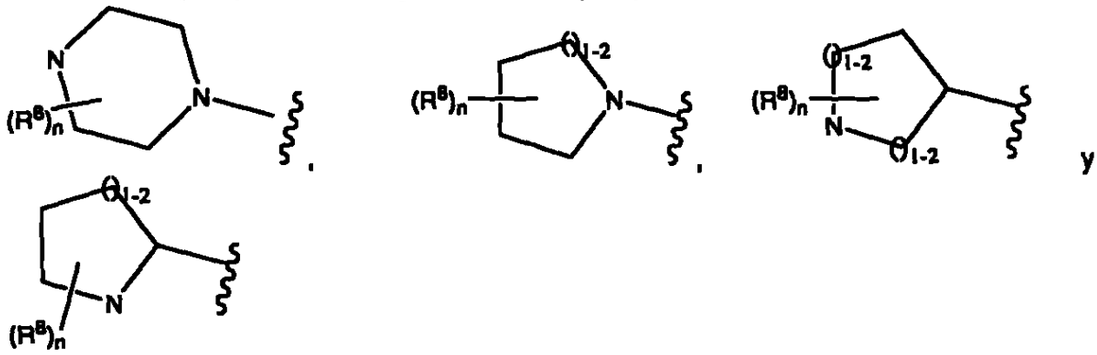
R^2 está seleccionado del grupo que consiste en R^9, alquilo, alquenilo, alquinilo, CF_3, heterociclilo, heterociclilalquilo, halógeno, haloalquilo, arilo, arilalquilo, heteroarilalquilo, alquinilalquilo, cicloalquilo, heteroarilo alquilo sustituido con 1-6 grupos R^9 que pueden ser iguales o diferentes y que están independientemente seleccionados de la lista de R^9 que se muestra en lo que sigue, arilo sustituido con 1-3 grupos arilo o heteroarilo que pueden ser iguales o diferentes y que están independientemente seleccionados entre los grupos fenilo, piridilo, tiofenilo, furanilo y tiazolo, arilo fusionado con un grupo arilo o heteroarilo, heteroarilo sustituido con 1-3 grupos arilo o heteroarilo que pueden ser iguales o diferentes y que están independientemente seleccionados de los grupos que consisten en 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 previamente indicadas para R^2 puede estar no sustituido o puede estar opcionalmente sustituido con una o más porciones que pueden ser iguales o diferentes, estando cada porción independientemente seleccionada del grupo que consiste en halógeno, -CN, -OR^5, -SR^5, -$S(O_2)R^6$, -$S(O_2)NR^5R^6$, -NR^5R^6, -$C(O)NR^5R^6$, CF_3, alquilo, arilo y OCF_3;

R^3 está seleccionado del grupo que consiste en H, halógeno, -NR^5R^6, -OR^6, -SR^6, -$C(O)N(R^5R^6)$, alquilo, alquinilo, cicloalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heteroarilo y heteroarilalquilo,



donde cada uno de dichos alquilo, cicloalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heteroarilo y heteroarilalquilo para R^3 y las porciones heterociclilo cuyas estructuras se muestran inmediatamente en lo que antecede para R^3 pueden estar no sustituidas o pueden estar opcionalmente sustituidas independientemente con una o más porciones que pueden ser iguales o diferentes, donde cada porción está independientemente seleccionada del gurpo 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 condición de que ningún carbono adyacente a un átomo de nitrógeno en un anillo heterociclilo es portador de una porción –OR^5;

R^4 es H, halo o alquilo;

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

R^6 está seleccionado 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 pueden estar no sustituidos o pueden estar opcionalmente sustituidos con una o más porciones las cuales pueden ser iguales o diferentes, estando cada porción independientemente seleccionada del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, heterociclilalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^{10}$, $-C(R^4R^5)_p-R^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^6$, $-C(O)R^5$, $-C(O)NR^5R^{10}$, $-SO_3H$, $-SR^{10}$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^{10}$;

R^{10} está seleccionado del grupo que consiste en H, alquilo, arilo, arilalquilo, cicloalquilo, heterociclilo, heterociclilalquilo, heteroarilo, y heteroarilalquilo, donde cada uno de dichos alquilo, arilo, arilalquilo, cicloalquilo, heterociclilo, heterociclilalquilo, heteroarilo y heteroarilalquilo pueden estar no sustituidos o pueden estar opcionalmente sustituidos con una o más porciones que pueden ser iguales o diferentes, estando cada porción independientemente seleccionada del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, heterociclilalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^4R^5$, $-C(R^4R^5)_p-R^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)NR^4R^5$, $-C(O)R^5$, $-SO_3H$, $-SR^5$, $-S(O_2)R^7$, $-S(O_2)NR^4R^5$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^4R^5$;

u opcionalmente (i) R^5 y R^{10} en la porción $-NR^5R^{10}$, o (ii) R^5 y R^6 en la porción $-NR^5R^6$, pueden estar unidos conjuntamente para formar una porción cicloalquilo o heterociclilo, donde cada porción cicloalquilo o heterociclilo está no

sustituida o está opcionalmente independientemente sustituida con uno o más grupos R^9;

R^7 está seleccionado del grupo que consiste en alquilo, cicloalquilo, arilo, arilalquenilo, heteroarilo, arilalquilo, heteroarilalquilo, heteroarilalquenilo y heterociclilo, donde cada uno de dichos alquilo, cicloalquilo, heteroarilalquilo, arilo, heteroarilo, y arilalquilo pueden estar no sustituidos o pueden estar opcionalmente independientemente sustituidos con una o más porciones que pueden ser iguales o diferentes, estando cada porción independientemente seleccionada del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^{10}$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^{10}$, $-C(O)R^5$, $-SR^{10}$, $-S(O_2)R^{10}$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^{10}$, $-N(R^5)C(O)R^{10}$ y $-N(R^5)C(O)NR^5R^{10}$;

R^8 está seleccionado del grupo que consiste en halógeno, R^6, $-OR^6$, $-C(O)NR^5R^{10}$,$-S(O_2)NR^5R^{10}$, $-C(O)R^7$, $-C(=N-CN)-NH_2$, $-C(=NH)-NHR^5$, heterociclilo, y $-S(O_2)R^7$;

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

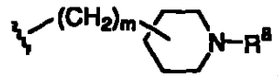
con la condición de que cuando R^2 es fenilo, R^3 no sea alquilo, alquinilo o halógeno, y que cuando R^2 es arilo, R no sea , y con la condición adicional de que cuando R es arilalquilo, entonces cualquier sustituyente heteroarilo en el arilo de dicho arilalquilo contenga por lo menos tres heteroátomos

Los compuestos de la Fórmula III pueden ser útiles como inhibidores de proteína quinasa y pueden ser útiles en el tratamiento y prevención de enfermedades proliferativas, por ejemplo, cáncer, inflamación y artritis. También

pueden ser útiles en el tratamiento de enfermedades neurodegenerativas tales como la enfermedad de Alzheimer, enfermedades cardiovasculares, enfermedades virales y enfermedades fungales.

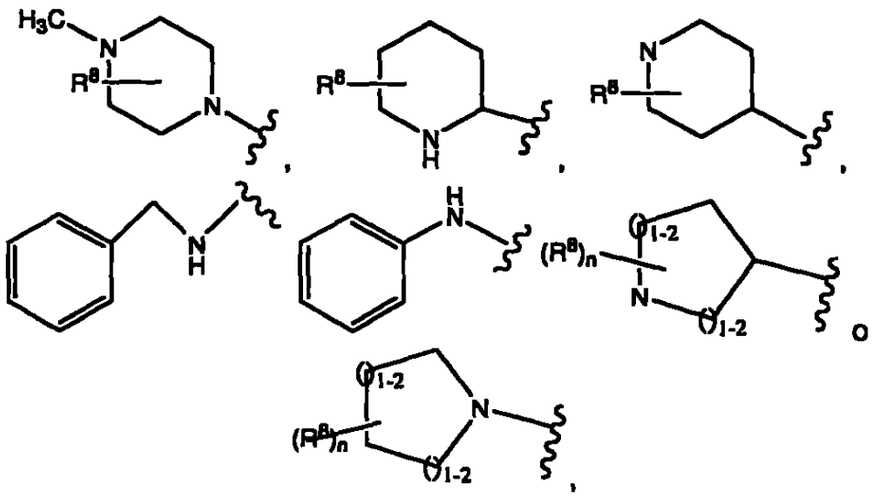
Descripción Detallada

En una realización, la presente invención describe compuestos de pirazolo[1,5-a]pirimidina que están representados por la Fórmula estructural III, o con una sal o solvato de la misma farmacéuticamente aceptable, donde las varias porciones son tal como se han descripto anteriormente.

En otra realización, R es -$(CHR^5)_n$-arilo, -$(CHR^5)_n$-heteroarilo, -$(CHR^5)_n$-heteroarilo (donde dicho heteroarilo está sustituido con un heteroarilo adicional igual o diferente), $(CHR^5)_n$-heterociclilo (donde dicho heterociclilo está 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, arilo, heteroarilo, cicloalquilo y las estructuras heterociclilo que se muestran inmediatamente en lo que antecede para R^3 están opcionalmente sustituidas con una o más porciones que pueden ser iguales o diferentes, donde cada porción está independientemente seleccionada del grupo que consiste en halógeno, CF3, OCF_3, alquilo inferior, CN, $-C(O)R^5$, $-S(O_2)R^5$, $-C(=NH)-NH_2$, $-C(=CN)-NH_2$, hidroxialquilo, alcoxicarbonilo, $-SR^5$, y OR^5, con la condición de que ningún átomo de carbono adyacente a un átomo de nitrógeno en un anillo heterociclilo es portador de una porción $-OR^5$.

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

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

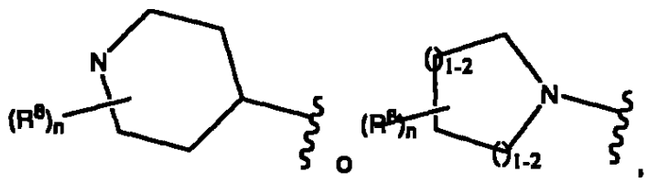
En otra realización, n es 1 a 2.

En una realización adicional, R es $-(CHR^5)_n$-arilo, $-(CHR^5)_n$-heteroarilo.

En una realización adicional, R^2 es halógeno, CF_3, CN, alquilo inferior, alquinilo o alquilo sustituido con $-OR^6$.

En una realización adicional, R^2 es alquilo inferior, alquinilo o Br.

En una realización adicional, R^3 es H, alquilo inferior, arilo,



donde dichas porciones alquilo, arilo y heterociclilo que se muestran inmediatamente en lo que antecede para R^3 están opcionalmente sustituidas con una o más porciones que pueden ser iguales o diferentes, estando cada porción independientemente seleccionada del grupo que consiste en halógeno, CF_3, alquilo inferior, hidroxialquilo, alcoxi, $-S(O_2)R^5$, y CN.

En una realización adicional, R^4 es H.

En una realización adicional, R^5 es H, etilo, ciclopropilo, ciclobutilo,

ciclopentilo o ciclohexilo.

En una realización adicional, R^8 es alquilo o hidroxialquilo.

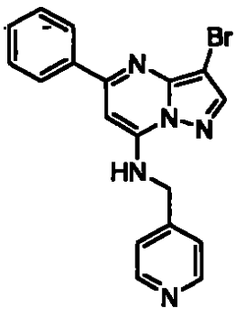
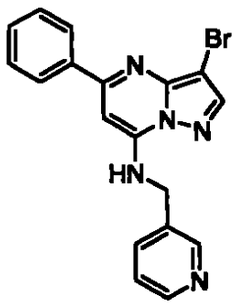
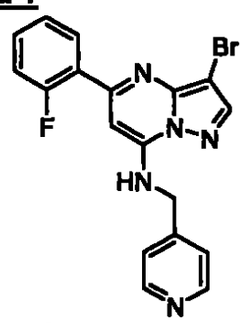
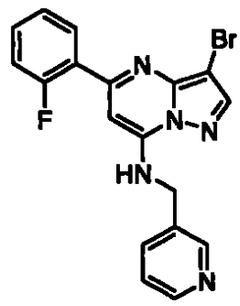
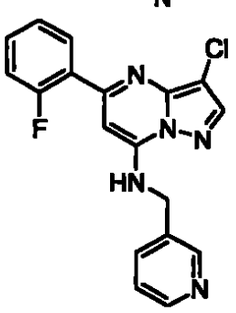
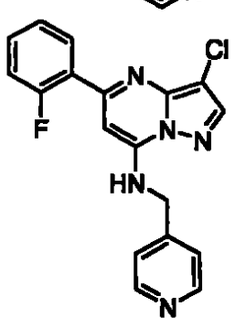
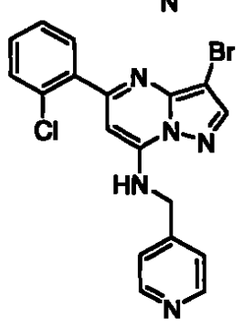
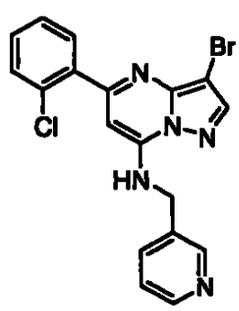
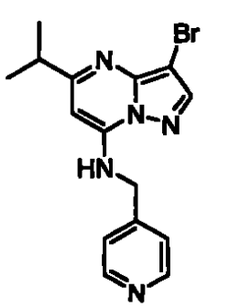
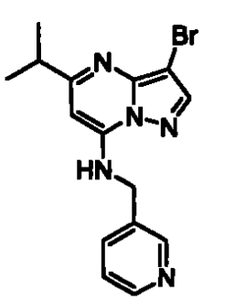
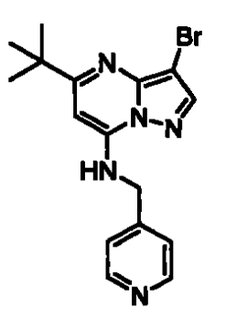
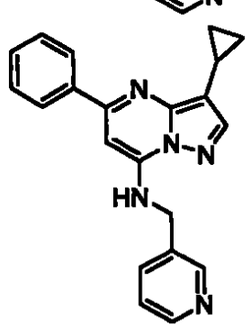
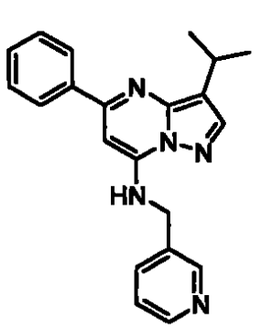
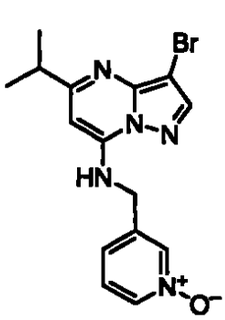
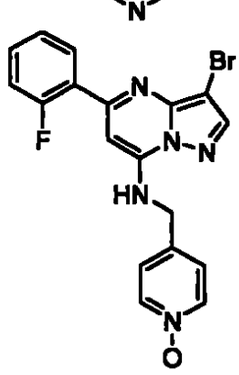
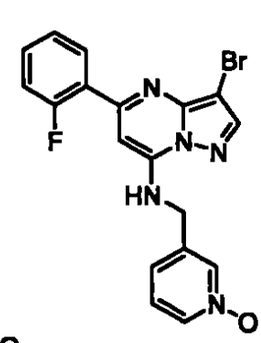
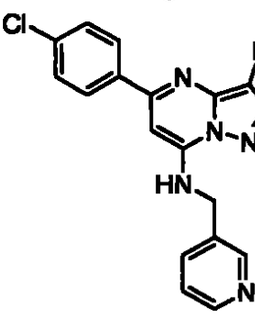
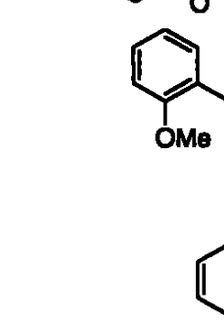
En una realización adicional, n es 1.

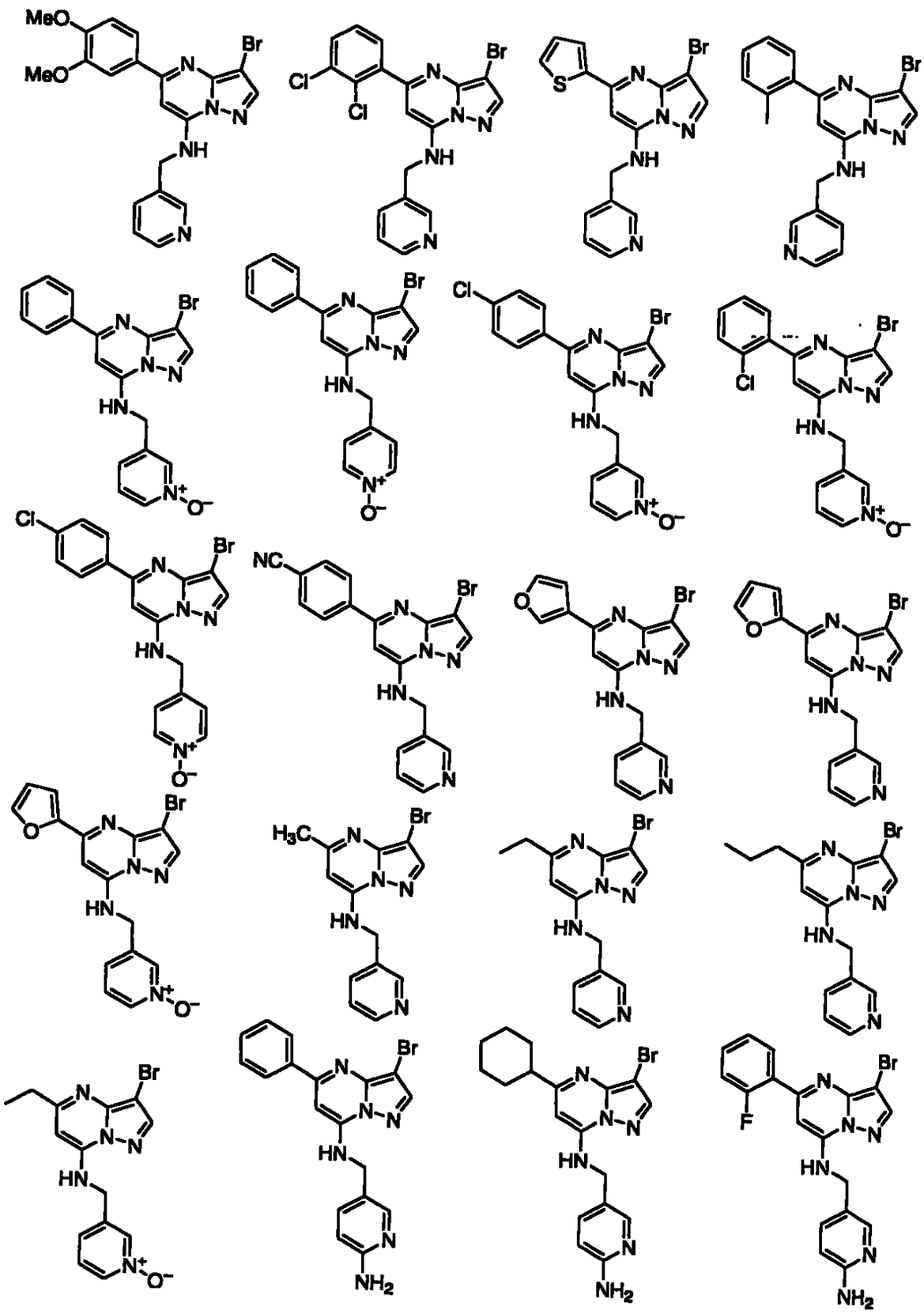
En una realización adicional, p es 1 ó 2.

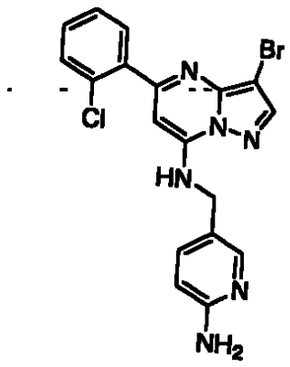
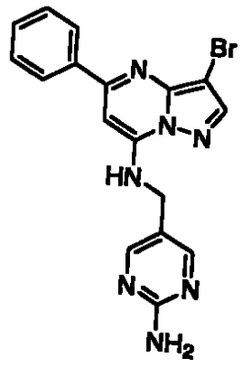
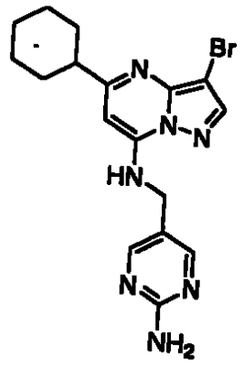
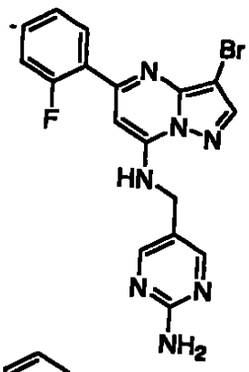
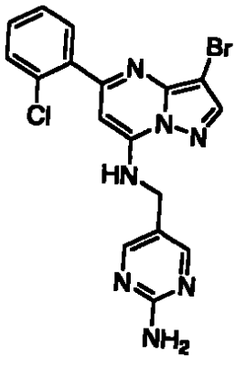
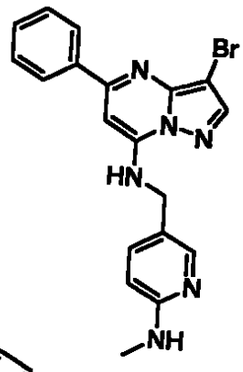
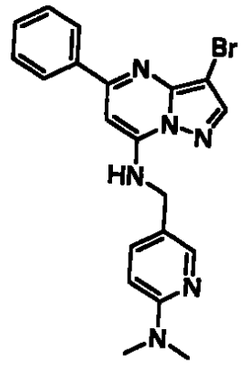
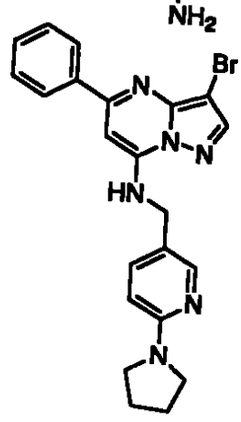
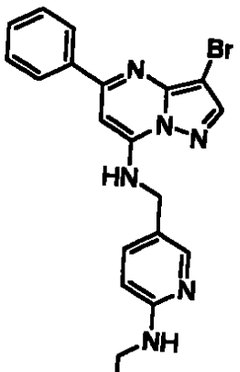
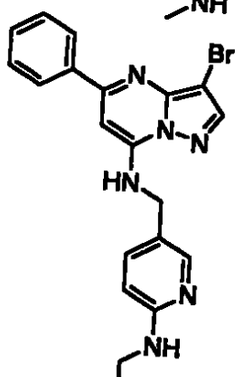
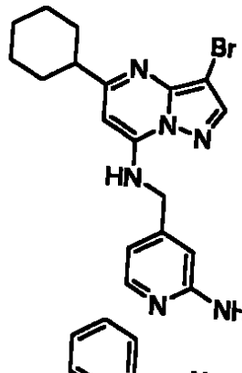
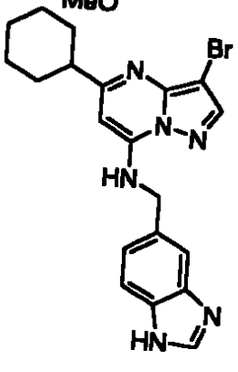
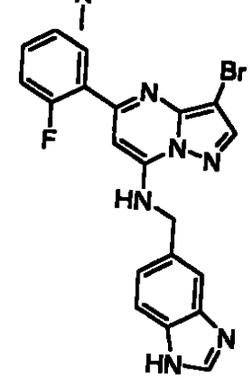
Otra realización describe los compuestos de la invención que se muestran en la Tabla 1,que exhibieron una actividad inhibidora de aproximadamente 0.0001μM hasta > aproximadamente 5 μM. Los métodos de ensayo se describen posteriormente (desde la página 368 hacia adelante).

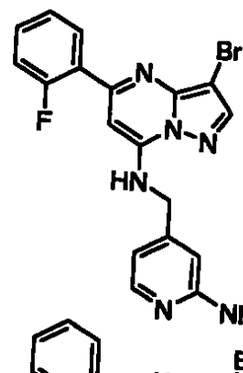
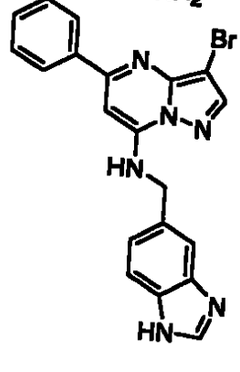
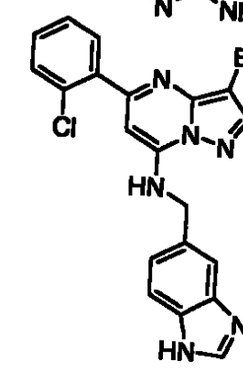
330

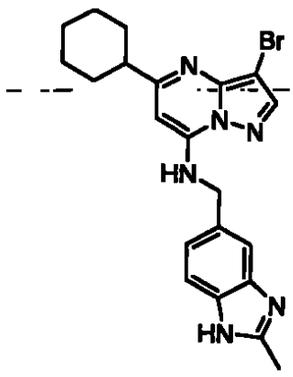
Tabla 1

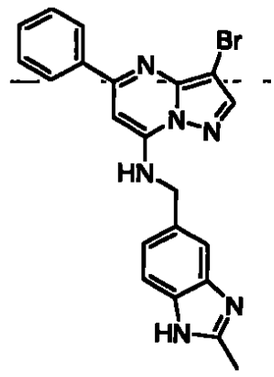



















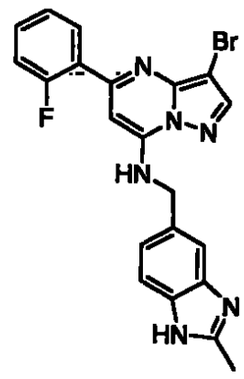


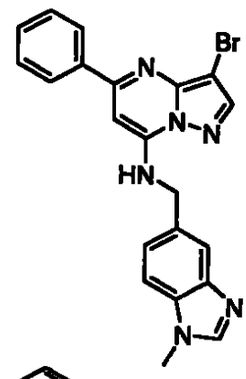














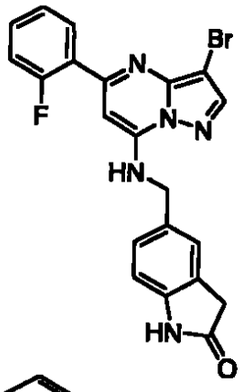




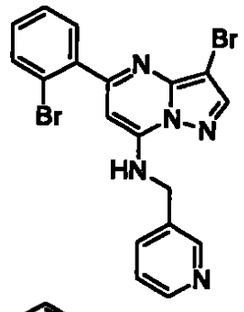


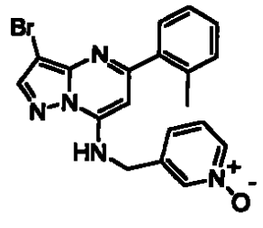


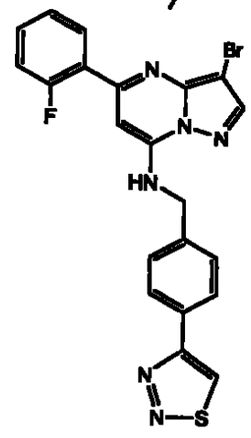


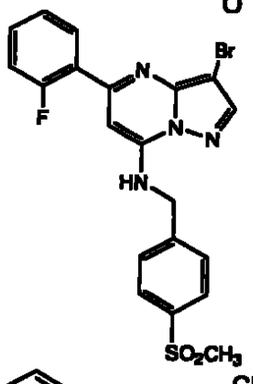


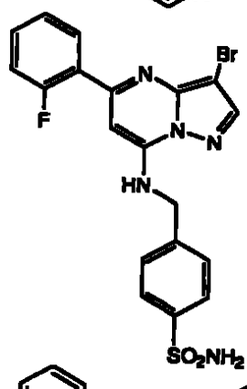


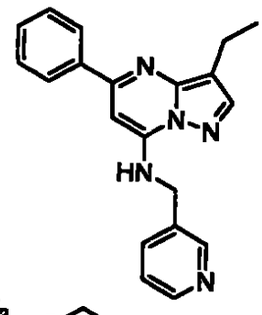


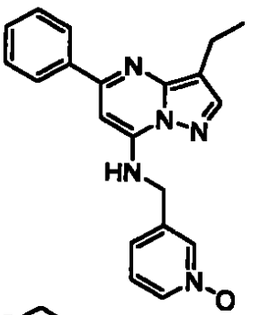


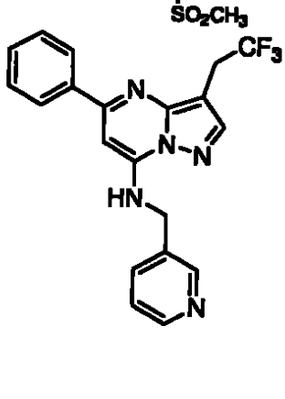


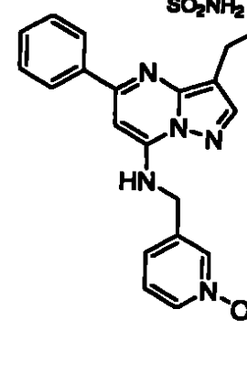


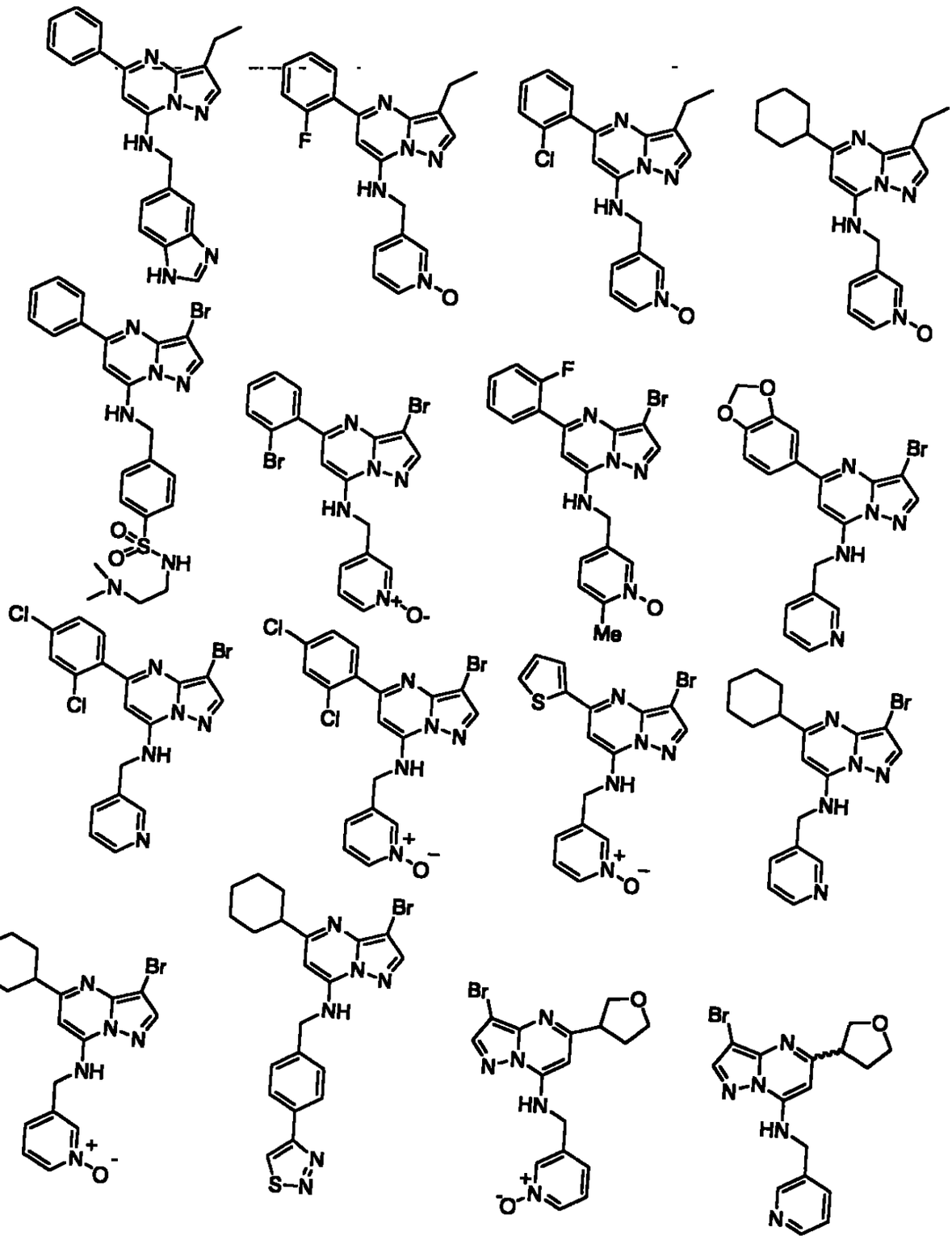




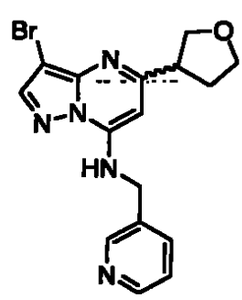


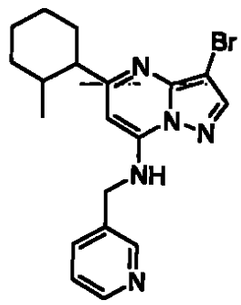


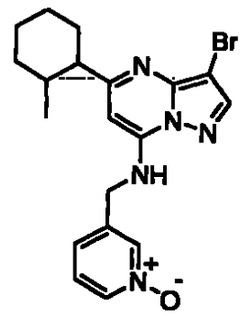


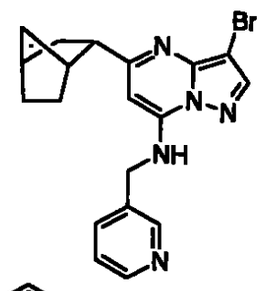


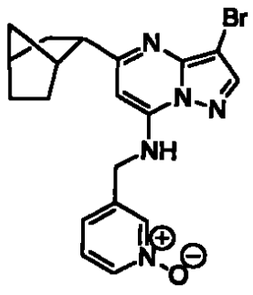
335

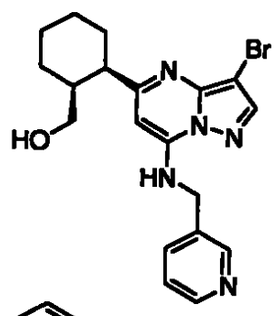


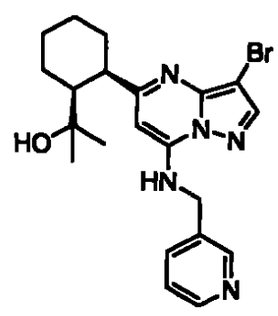


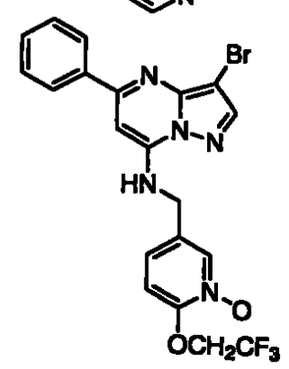


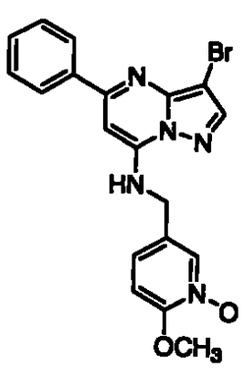


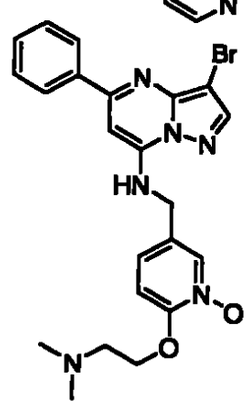


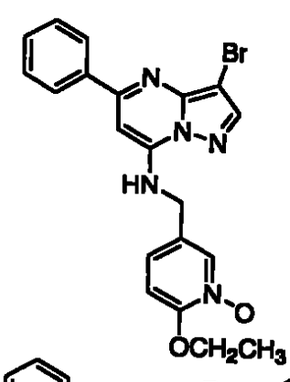


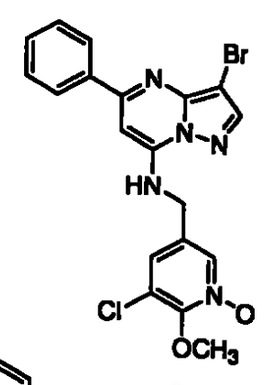


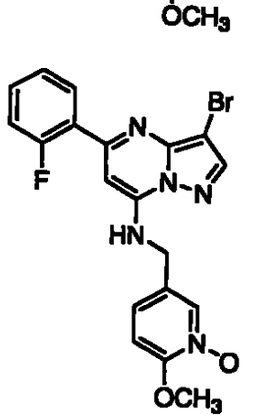


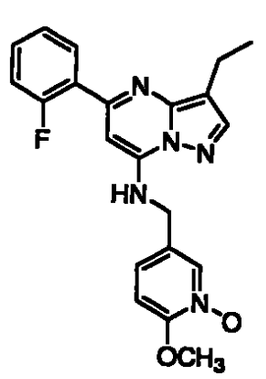


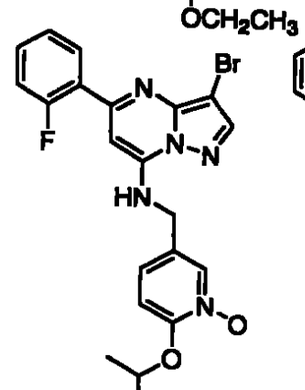


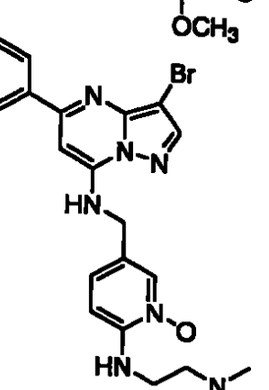


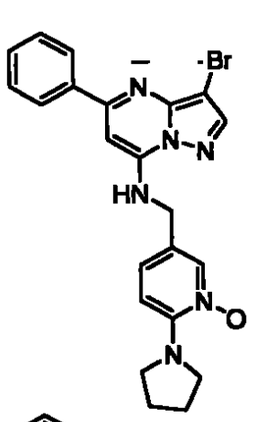


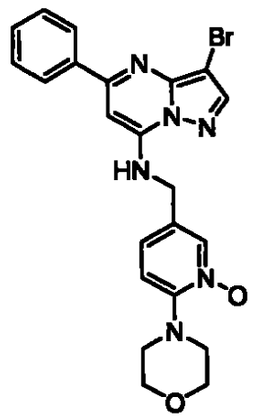


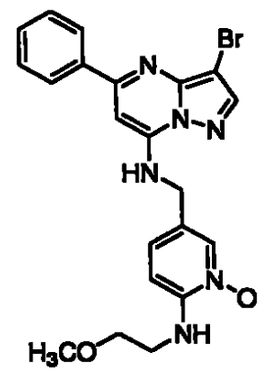


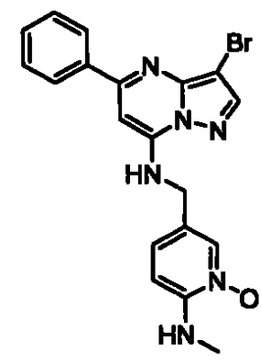


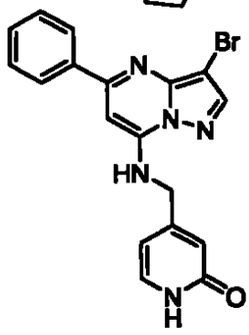


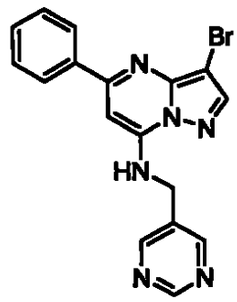


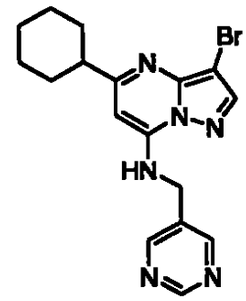


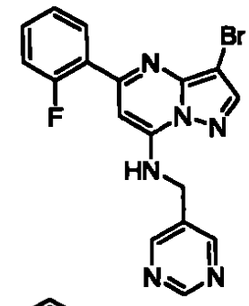


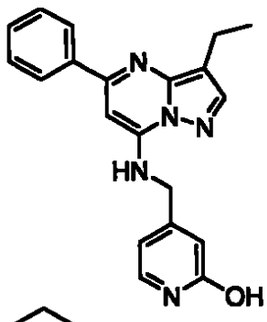


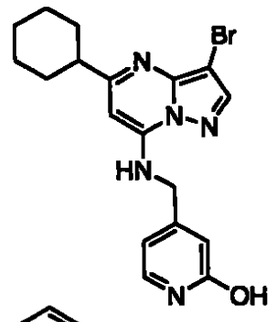


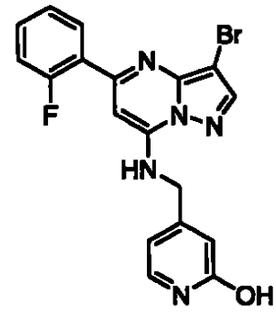


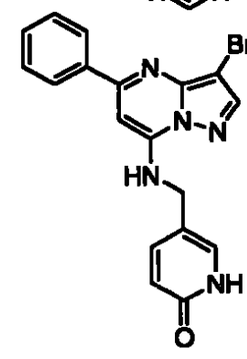


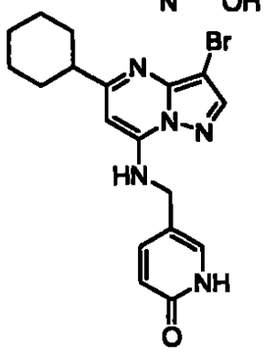


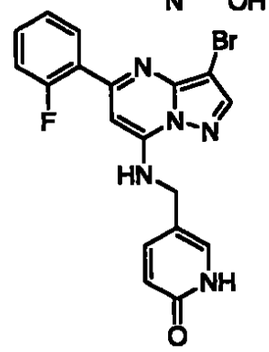


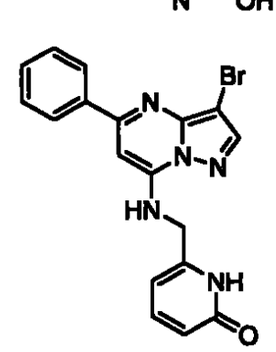


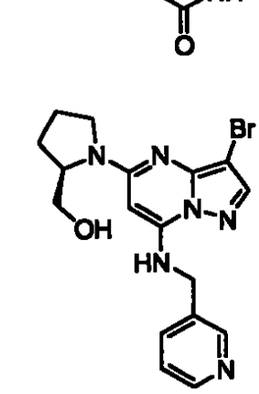


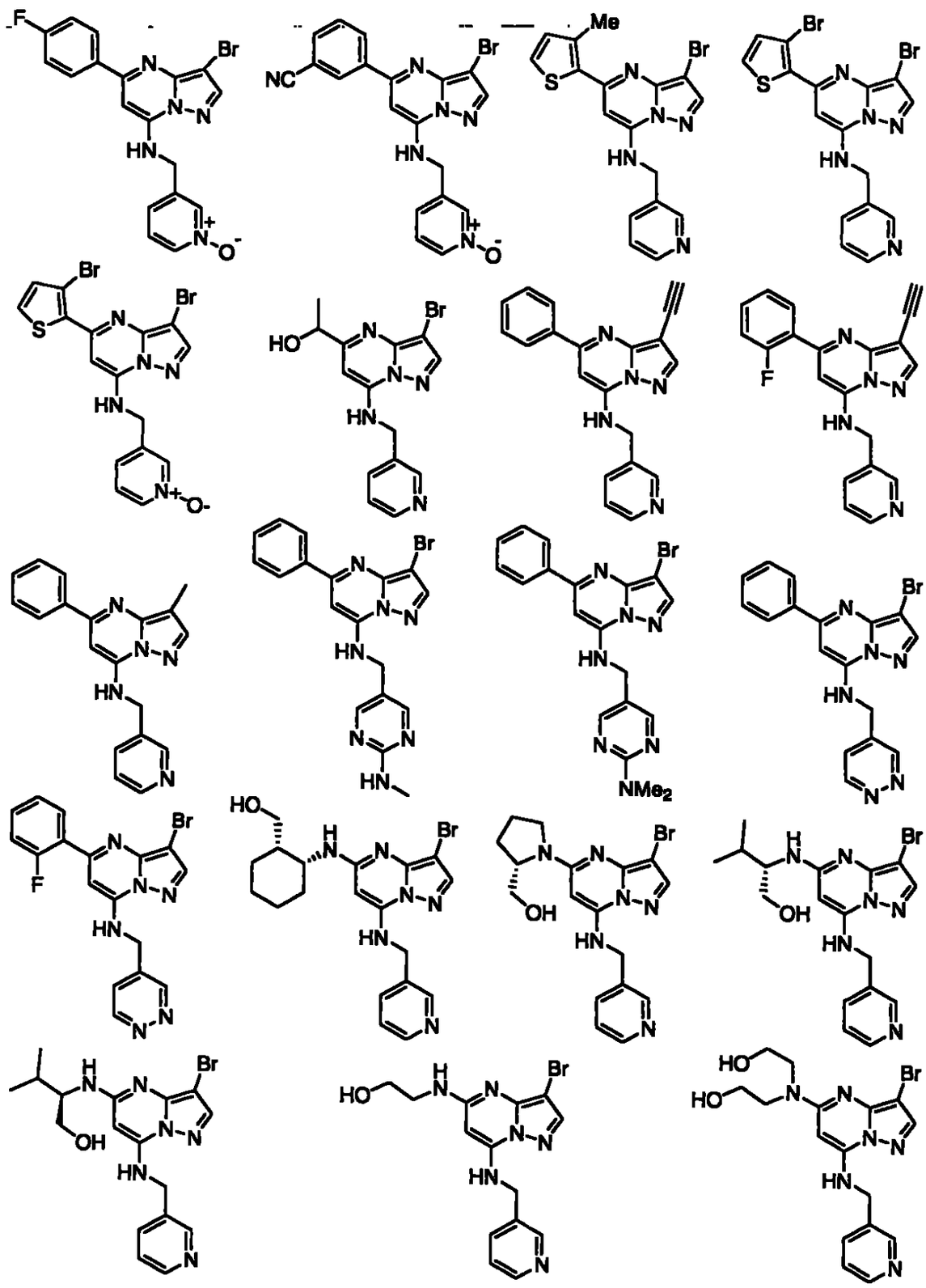


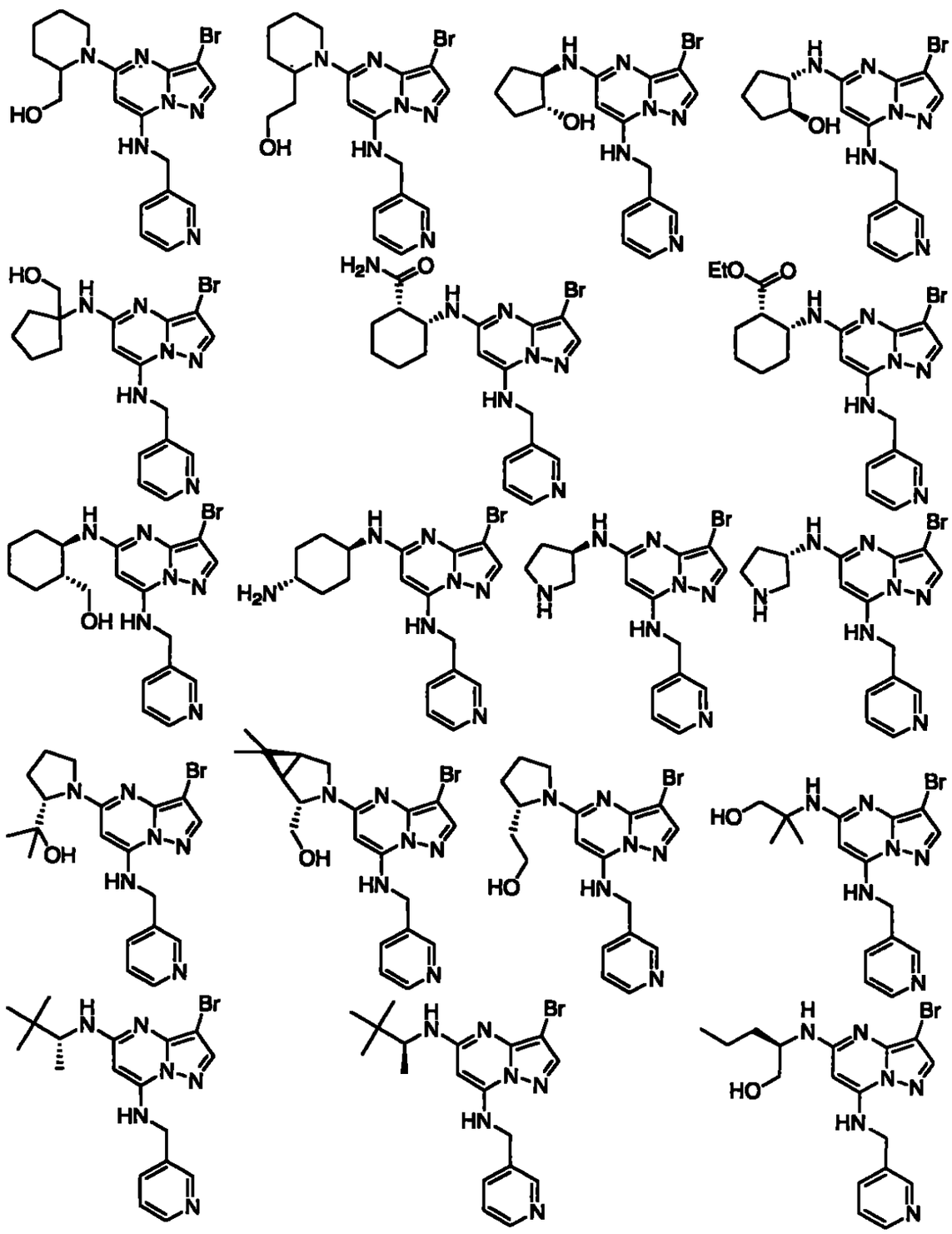


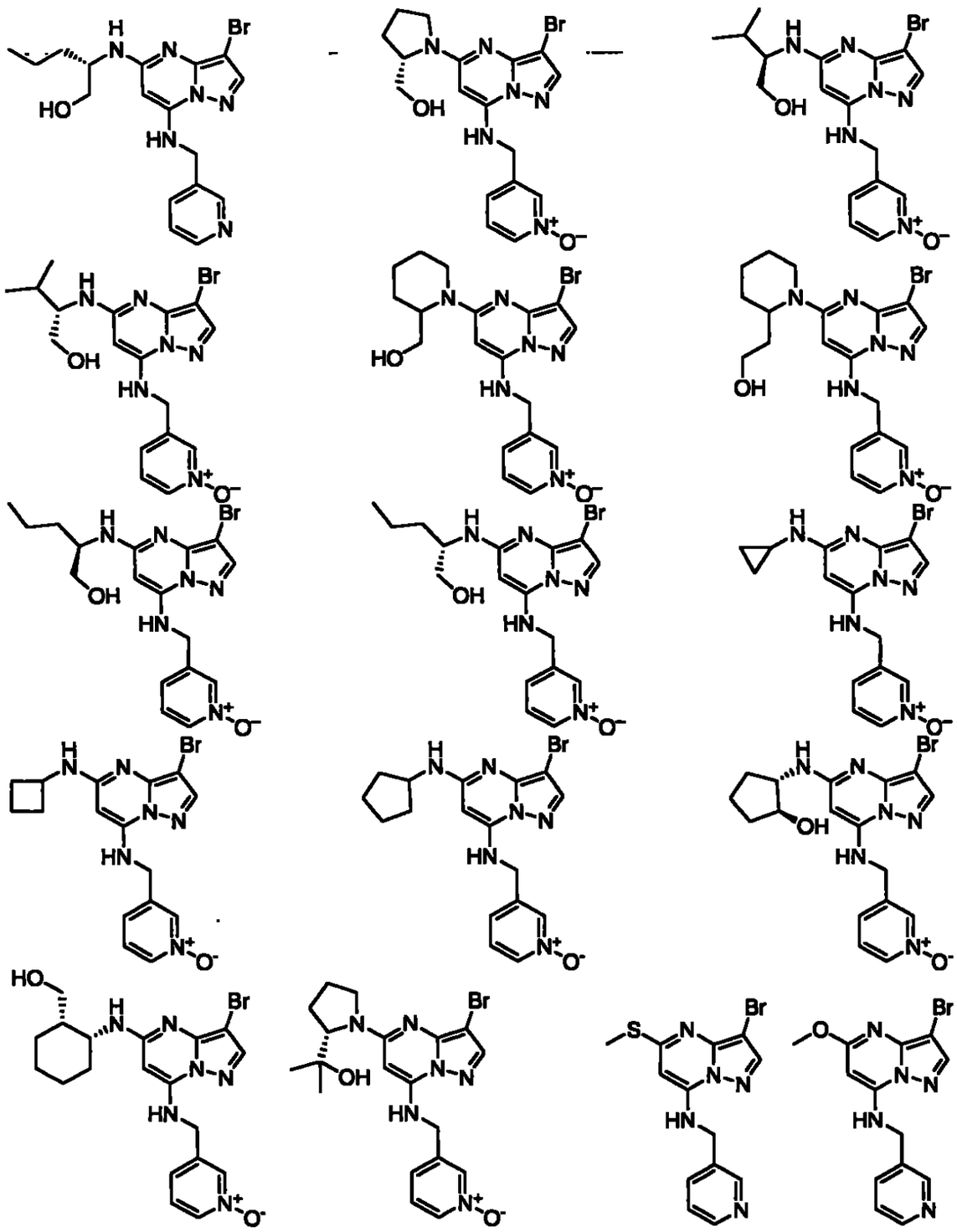




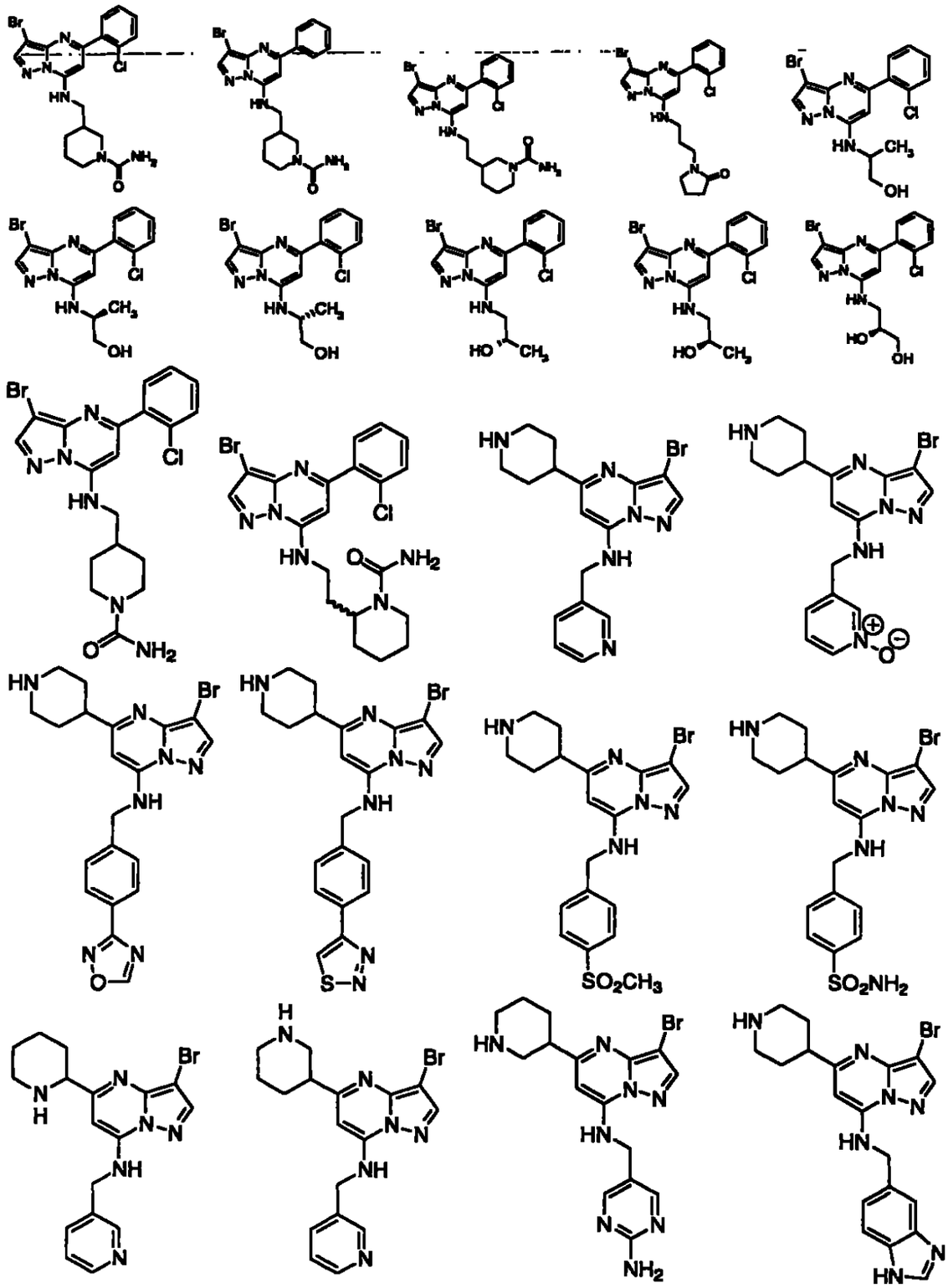


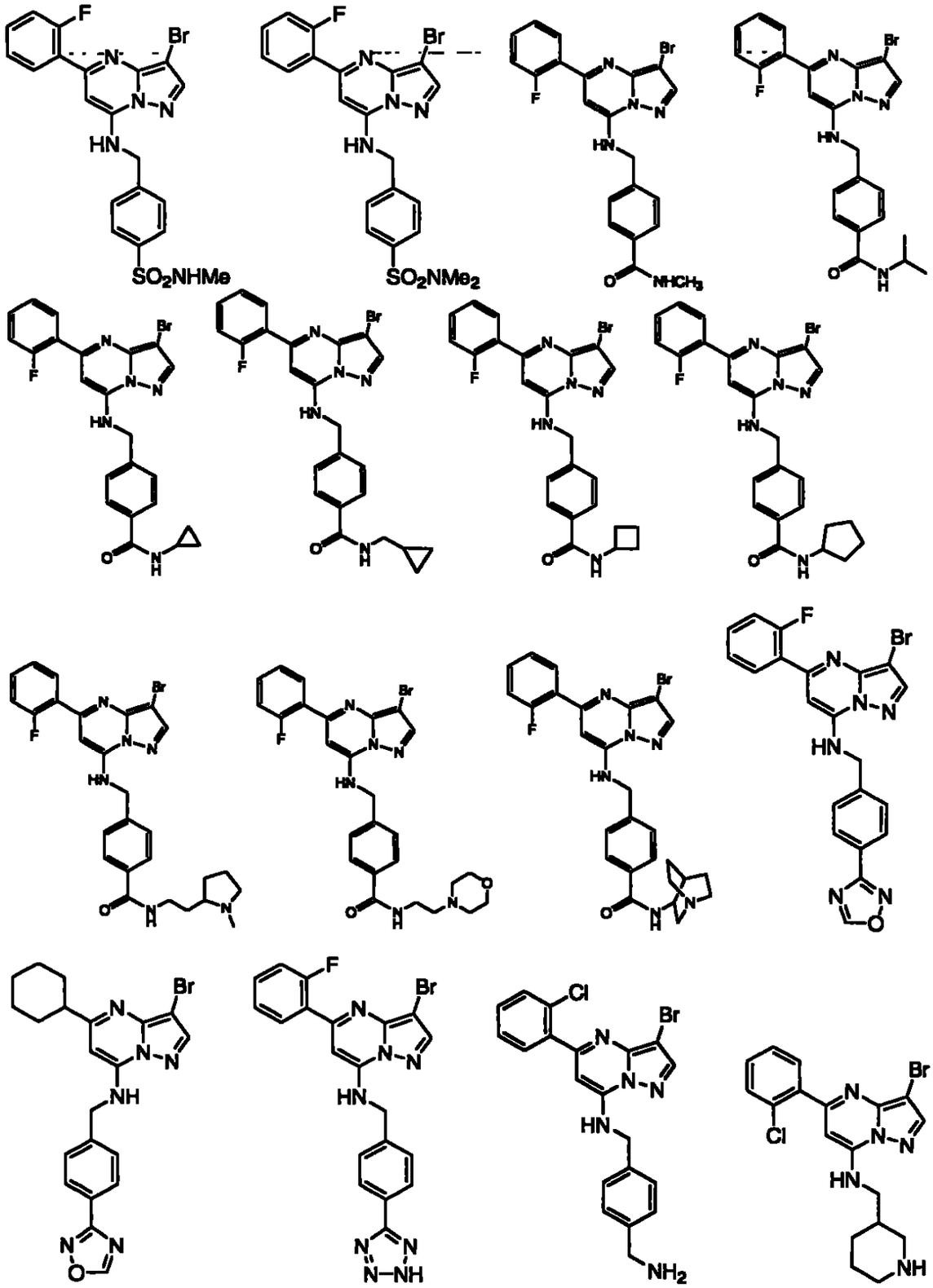




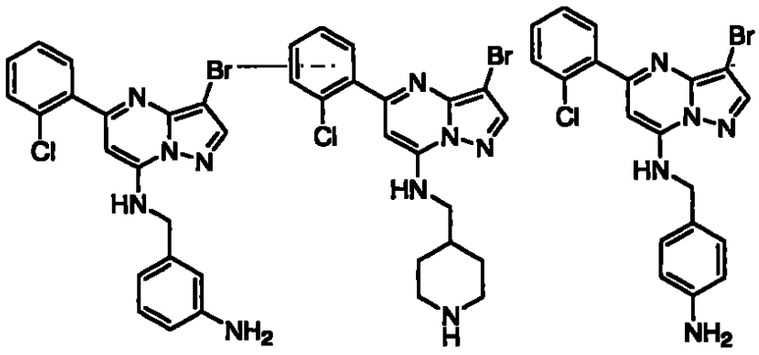


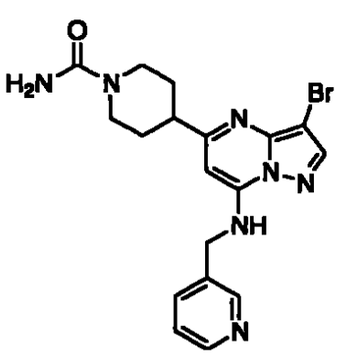
340

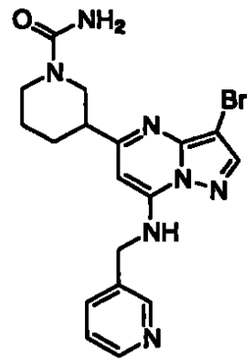


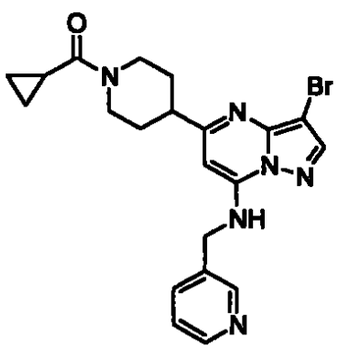

F
Br
N
HN
SO2NHMe
SO2NMe2
NHCH3
O
NH

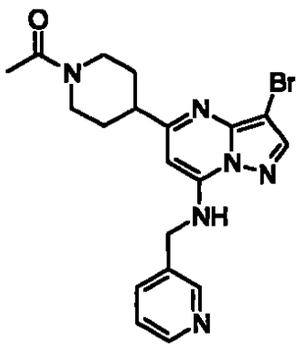
342

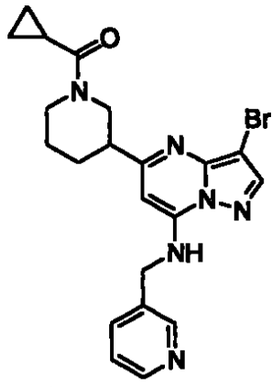


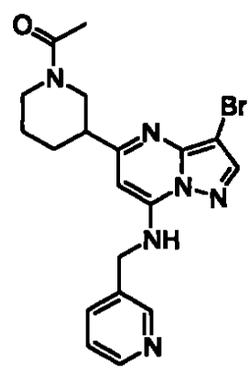


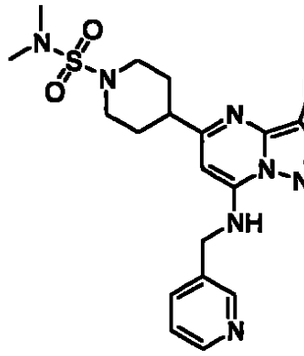


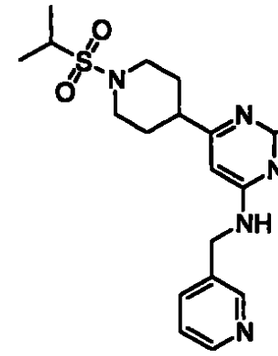


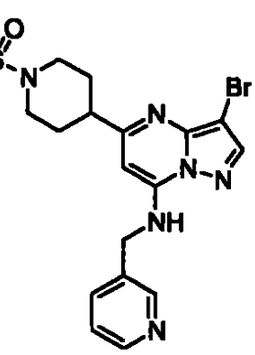




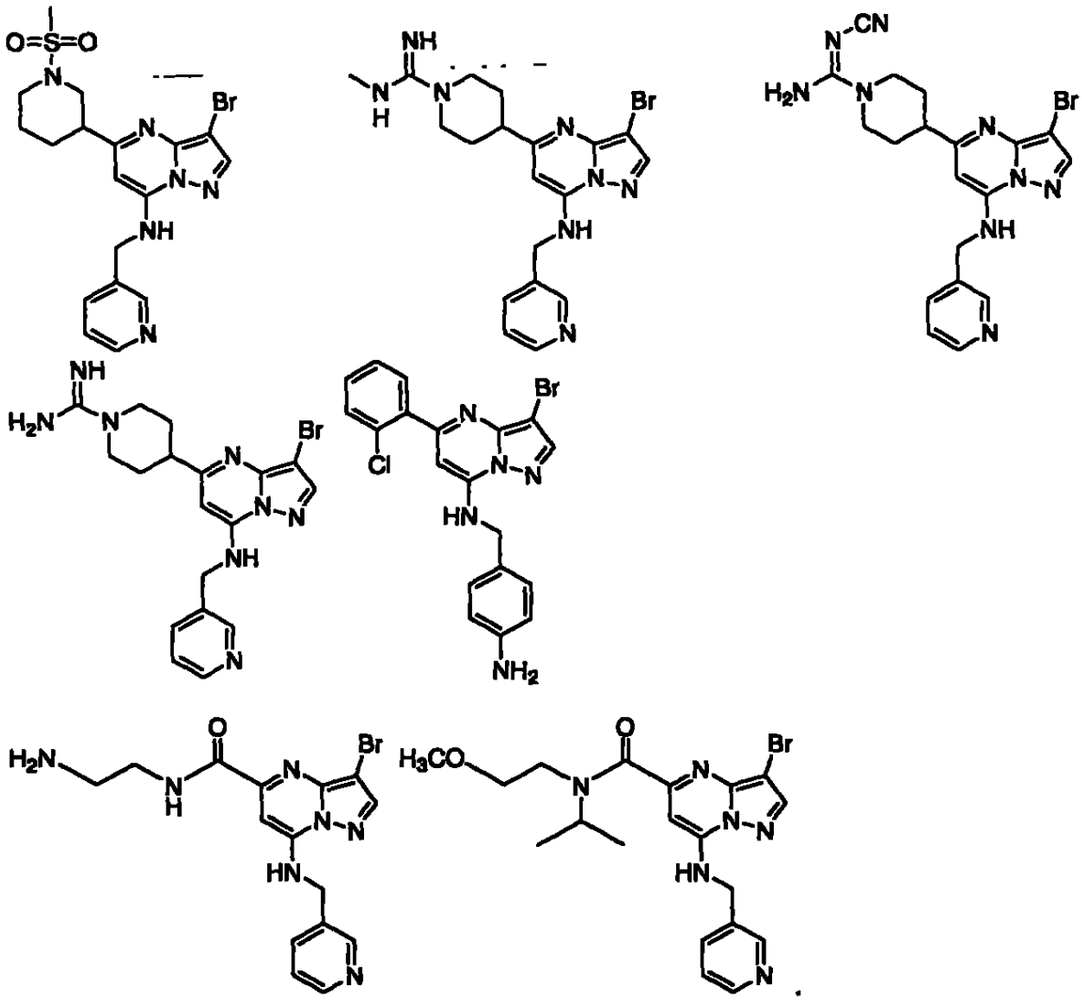




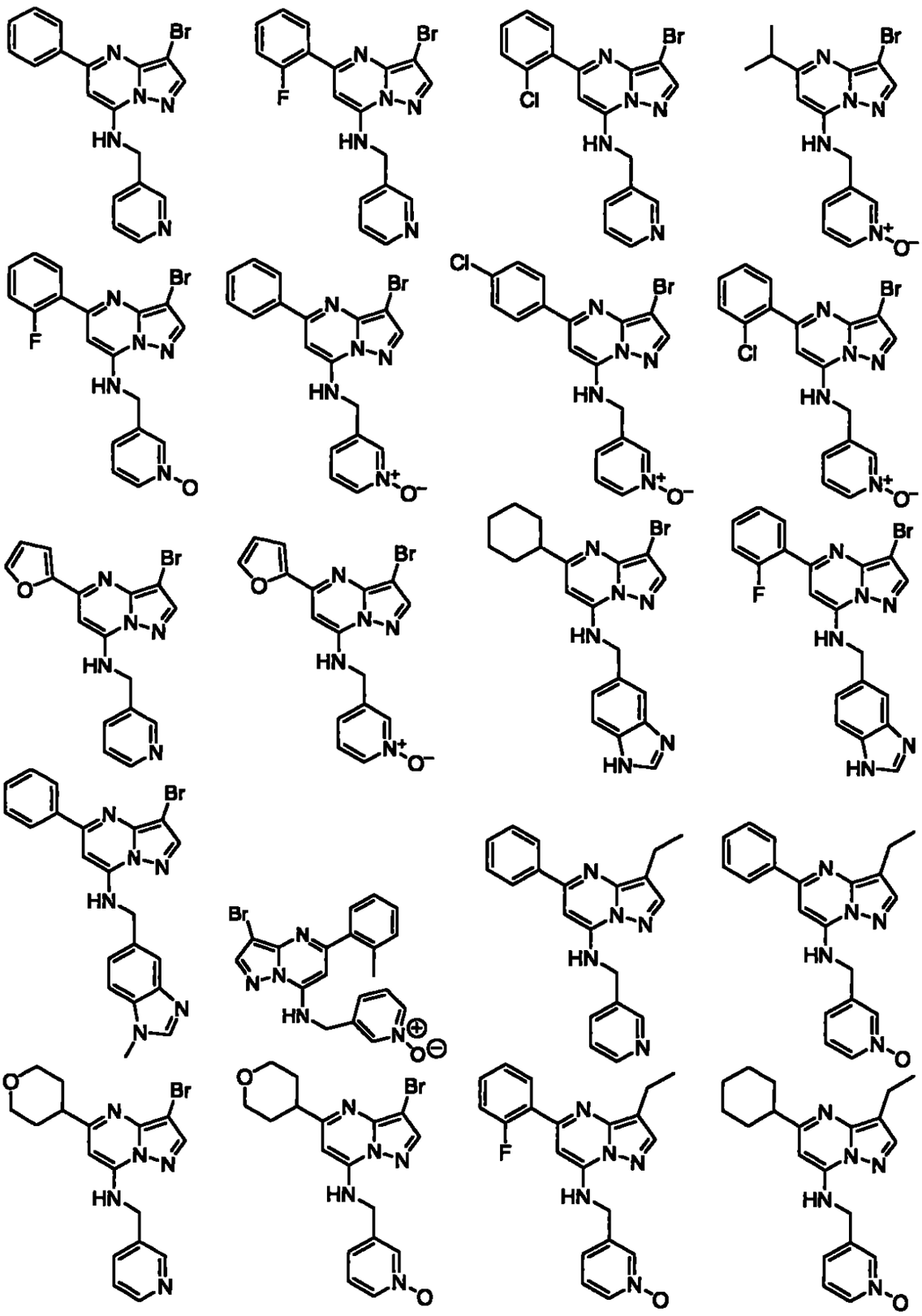




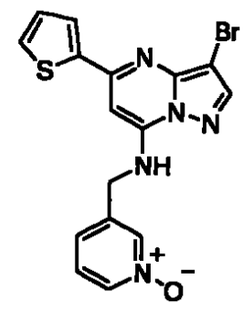
343

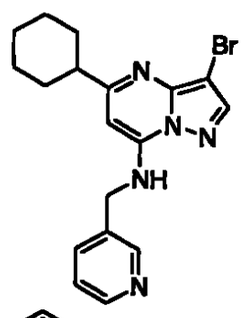


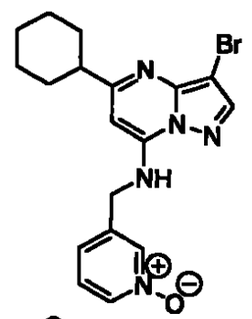
Otra realización de la invención describe los compuestos siguientes, que exhibieron actividad inhibidora CDK2 de aproximadamente 0.0001μM hasta aproximadamente 0.5μM:

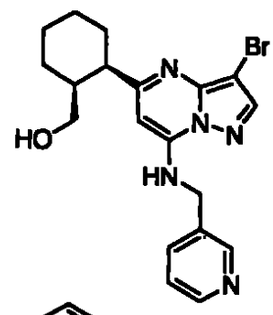


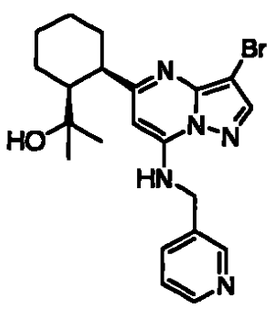
345

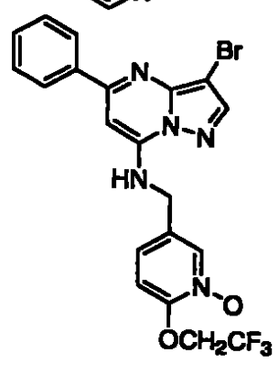


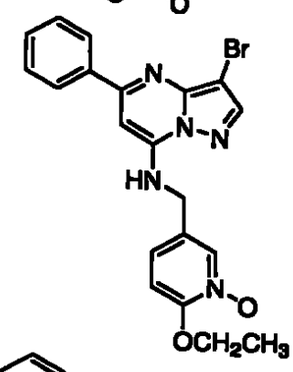


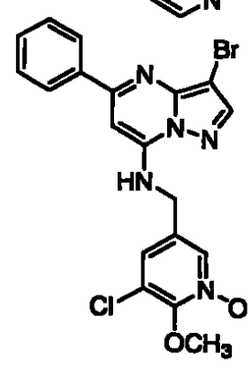


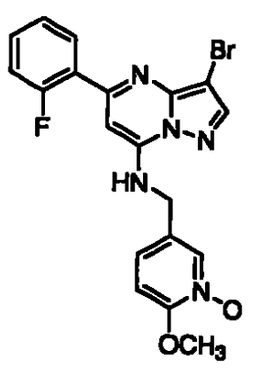


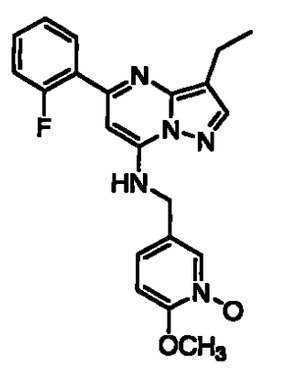


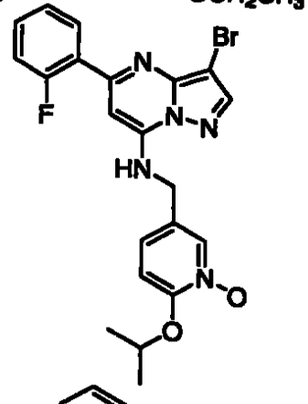


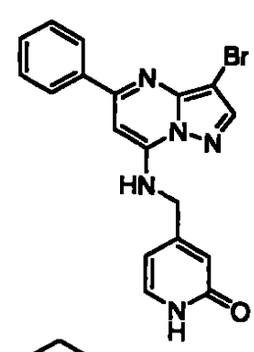


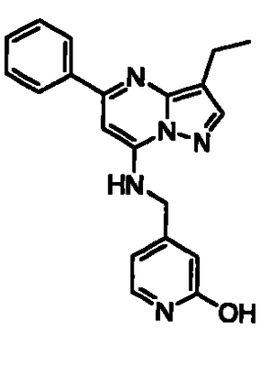


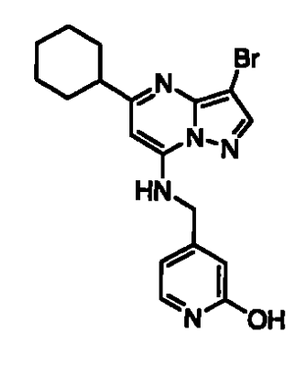


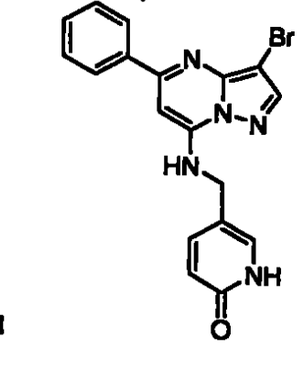


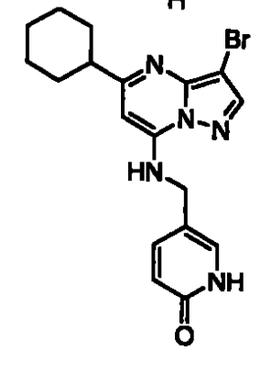




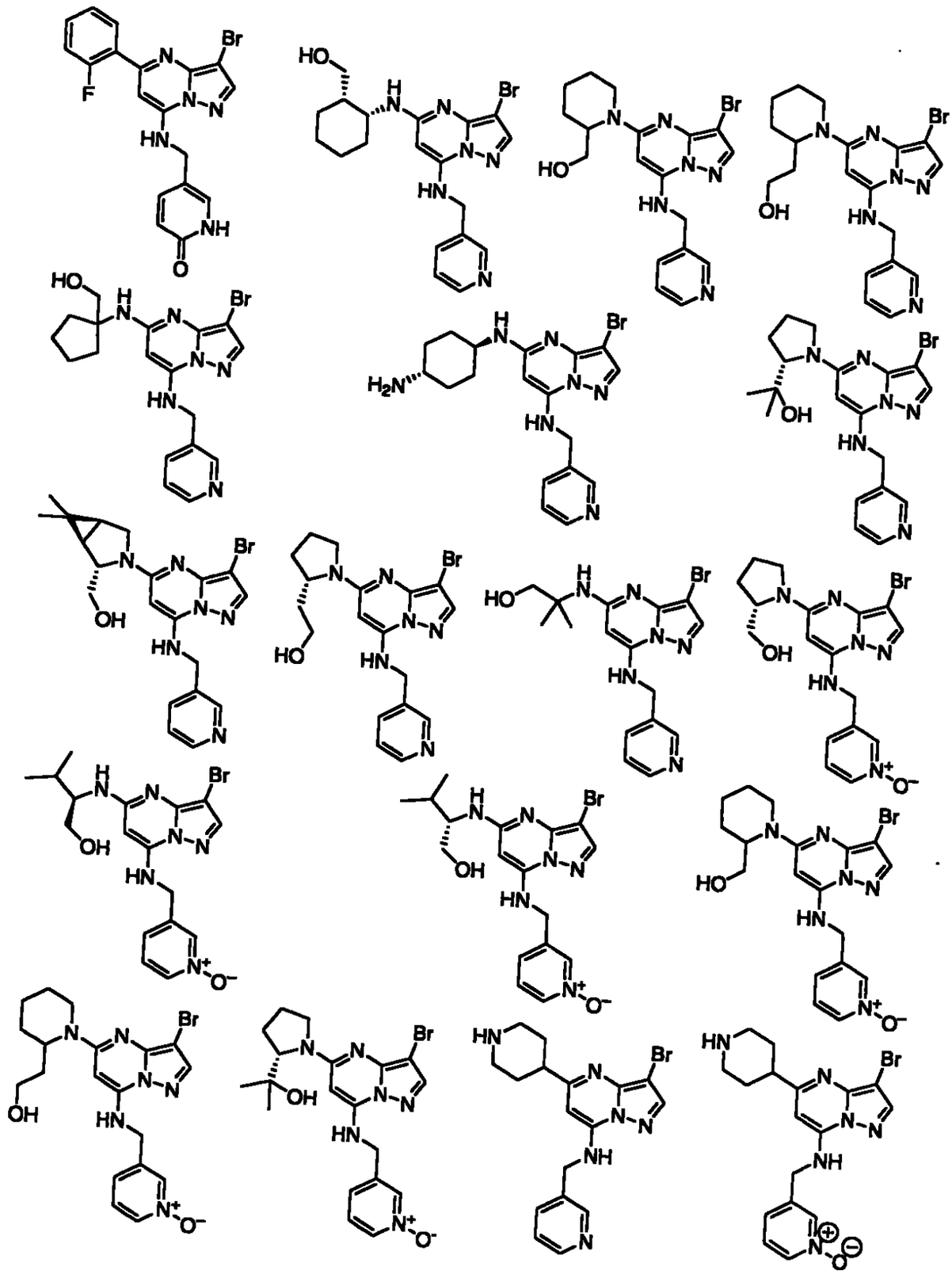




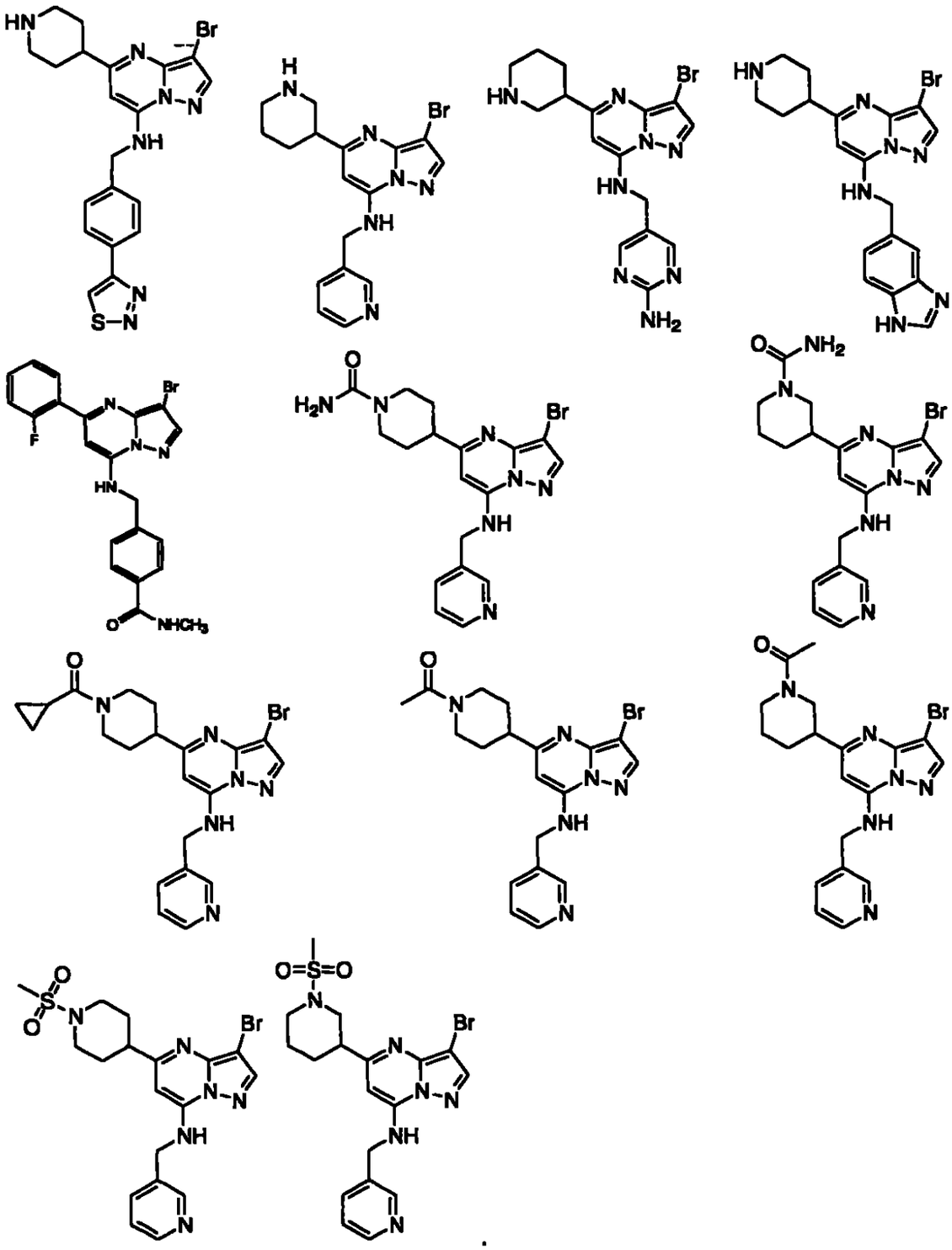




346

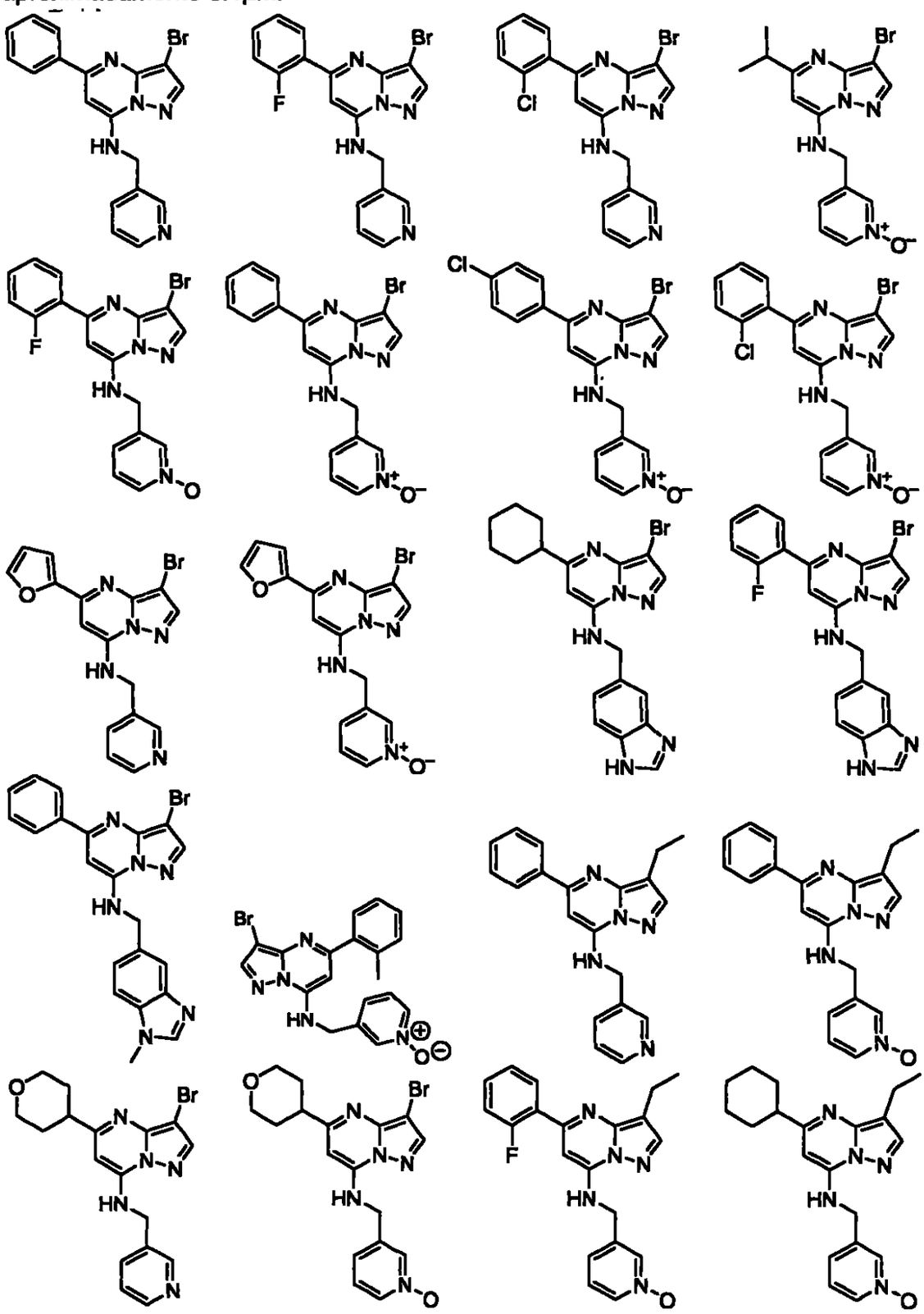


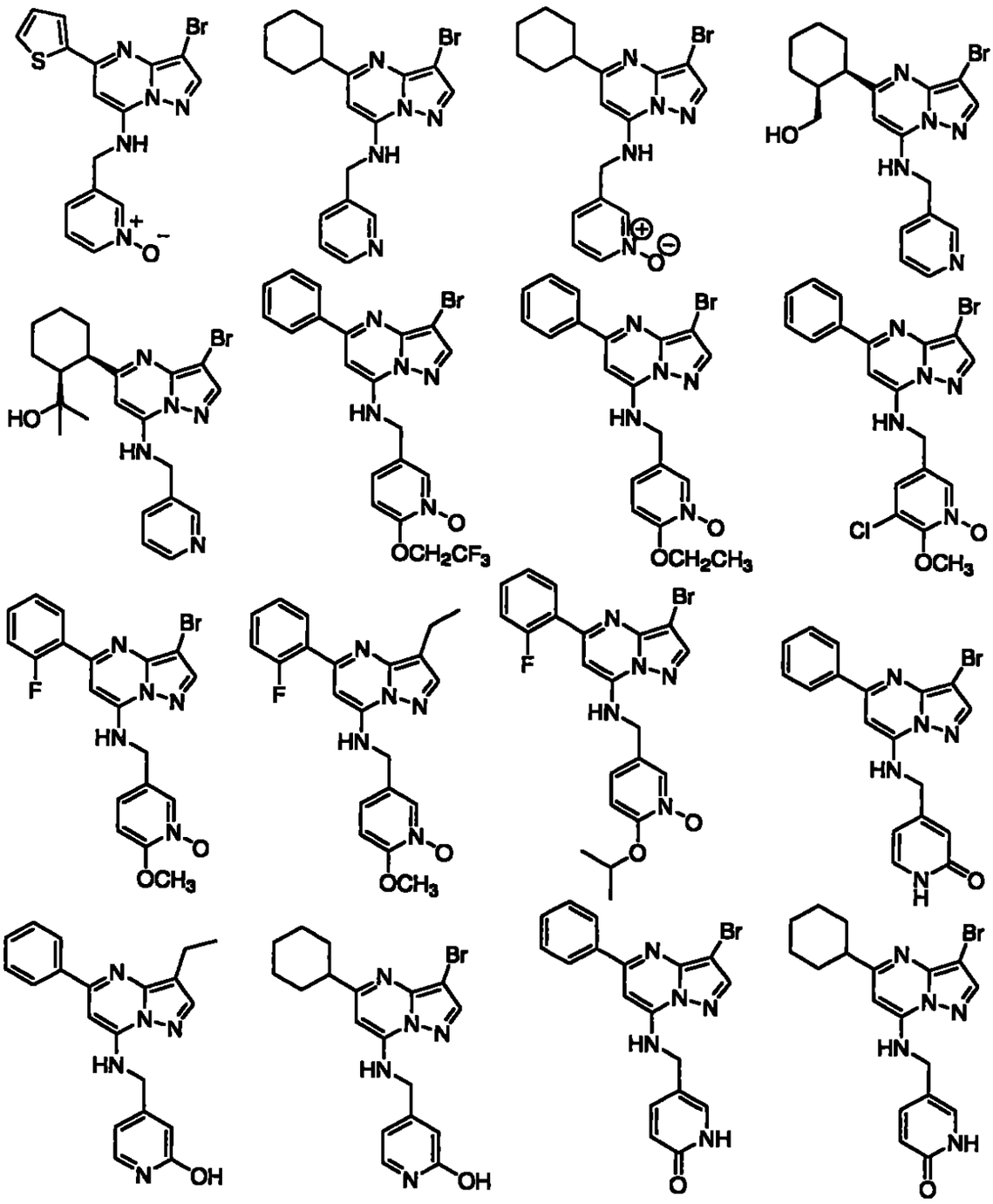
347

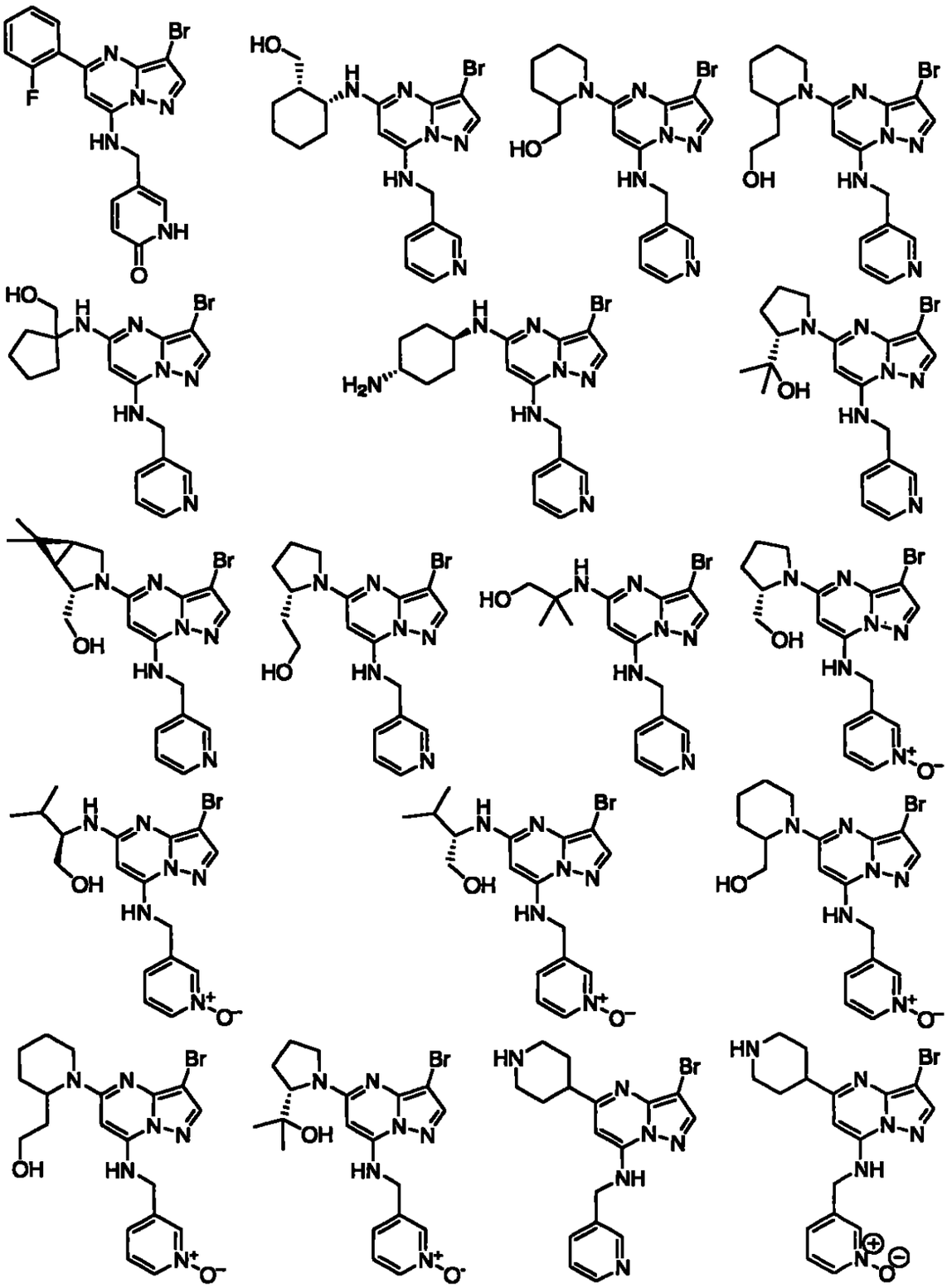


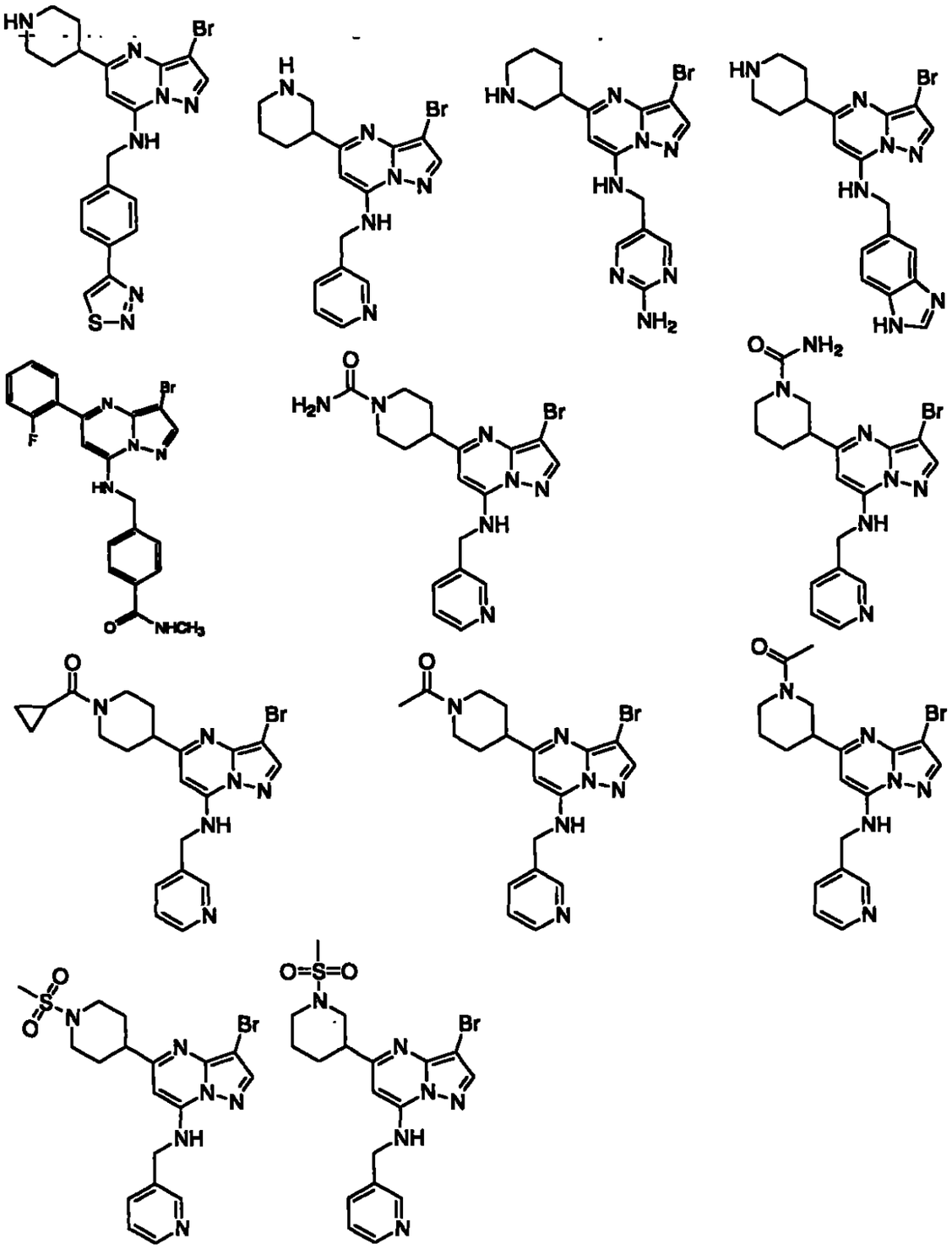
Otra realización de la invención describe los compuestos siguientes, que exhibieron actividad inhibidora CDK2 de aproximadamente 0.0001μM hasta

aproximadamente 0.1μM:









Tal como se usaron en lo que antecede, y a través de toda esta descripción, los siguientes términos, a menos que se indique lo contrario, se interpretarán con los siguientes significados:

"Paciente" incluye tanto a los seres humanos como a los animales.

"Mamífero" significa seres humanos y otros animales mamíferos.

"Alquilo" significa un grupo hidrocarbonado alifático que puede ser recto o ramificado y que comprende aproximadamente 1 hasta aproximadamente 20 átomos de carbono en la cadena. Los grupos alquilo preferidos contienen aproximadamente 1 hasta aproximadamente 12 átomos de carbono en la cadena. Los grupos alquilo más preferidos contienen aproximadamente 1 hasta aproximadamente 6 átomos de carbono en la cadena. Ramificado significa que uno o más grupos de alquilo inferior tales como metilo, etilo o propilo están unidos a una cadena alquilo lineal. "Alquilo inferior" significa un grupo que tiene aproximadamente 1 hasta aproximadamente 6 átomos de carbono en la cadena que puede ser recto o ramificado. El término "alquilo sustituido" significa que el grupo alquilo puede estar sustituido con uno o más sustituyentes que pueden ser iguales o diferentes , donde cada sustituyente está independientemente seleccionado del grupo que consiste en halo, alquilo, arilo, cicloalquilo, ciano, hidroxi, alcoxi, alquiltio, amino, -NH(alquilo), -NH(cicloalquilo), -N(alquilo)$_2$, carboxi y –C(O)O-alquilo. Entre los grupos no limitativos de los grupos alquilo apropiados se incluye metilo, etilo, n-propilo, isopropilo y t-butilo.

"Alquinilo" significa un grupo hidrocarbonado alifático que contiene por lo menos un triple enlace de carbono a carbono y que puede ser de cadena recta o ramificada y que comprende aproximadamente 2 hasta aproximadamente 15 átomos de carbono en la cadena. Los grupos alquinilo preferidos tienen aproximadamente 2 hasta aproximadamente 12 átomos de carbono en la cadena; y más preferiblemente aproximadamente 2 hasta aproximadamente 4 átomos de carbono en la cadena. Ramificado significa que uno o más grupos alquilo inferior tales como metilo, etilo o propilo, están unidos a una cadena alquilo lineal. "Alquinilo inferior" significa que aproximadamente 2 hasta aproximadamente 6 átomos de carbono en la cadena los cuales pueden ser rectos o ramificados. Ejemplos no limitativos de grupos alquinilo apropiados incluyen etinilo, propinilo,

352
353

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, y cada sustituyente está independientemente seleccionado del grupo que consiste en alquilo, arilo y cicloalquilo.

"Arilo" significa un sistema de anillo monocíclico o multicíclico aromático que comprende aproximadamente 6 hasta aproximadamente 14 átomos de carbono, prefereiblemente aproximadamente 6 hasta aproximadamente 10 átomos de carbono. El grupo arilo puede estar opcionalmente sustituido con uno o más "sustituyentes de sistema de anillo" que pueden ser iguales o diferentes, y que son tal como se definen aquí. Ejemplos no limitativos de grupos arilo apropiados incluyen fenilo y naftilo.

"Heteroarilo" siginifica un sistema de anillo monocíclico o multicíclico aromático que comprende 5 hasta aproximadamente 14 átomos de anillo, preferiblemente aproximadamente 5 hasta aproximadamente 10 átomos de anillo, donde uno o más de los átomos del anillo consisten en un elemento distinto de carbono, por ejemplo nitrógeno, oxígeno o azufre, solos o en combinación. Los heteroarilos preferidos contienen aproximadamente 5 hasta 6 átomos de anillo. El "heteroarilo" pueden estar opcionalmente sustituido con uno o más "sustituyentes de sistema de anillo" que pueden ser iguales o diferentes, y que son tal como se definen aquí. El prefijo aza, oxa o tia antes del nombre de raíz heteroarilo significa que por lo menos un átomo de nitrógeno, oxígeno o azufre respectivamente están presentes como uno de los átomos del anillo. Un átomo de nitrógeno de un heteroarilo puede estar opcionalmente oxidado al correspondiente N-óxido. Ejemplos no limitativos de heteroarilo apropiados incluyen piridilo, pirazinilo, furanilo, tienilo, pririmidinilo, piridona (incluyendo piridona N-sustituida), isoxazolilo, isotiazolilo, oxazolilo, tiazolilo, pirazolilo, furazonilo, pirrolilo, pirazolilo, triazolilo, 1,2,4-tiadiazolilo, pirazinilo, piridazinilo, quinoxalinilo, ftalazinilo, oxindolilo, imidazo[1,2-a]piridinilo, imidazo[2,1-b]tiazolilo, benzofurazanilo, indolilo,

353
354

azaindolilo, benzimidazolilo, benzotienilo, quinolinilo, imidazolilo, tienopiridilo, quinazolinilo, tienopirimidilo, pirrolopiridilo, imidazolipiridilo, isoquinolinilo, benzoazaindolilo, 1,2,4-triazinilo, benzotiazolilo y similares. El término "heteroarilo" se refiere también a porciones heteroarilo parcialmente saturadas tales como por ejemplo, tetrahidroisoquinolilo, tetrahidroquinolilo y similares.

"Aralquilo" o "arilalquilo" se refiere a un grupo arilo-alquilo en el cual el arilo y el alquilo son tal como se han descripto previamente. Los aralquilos preferidos comprenden un grupo alquilo inferior. Ejemplos no limitativos de grupos aralquilos apropiados incluyen bencilo, 2-fenetilo y naftalenilmetilo. El enlace con la porción principal se efectúa a través de alquilo.

"Alquilarilo" significa un grupo alquilo-arilo- en el cual el alquilo y el arilo son tal como se han descripto previamente. Los alquilarilos preferidos comprenden un grupo alquilo inferior. Un ejemplo no limitativo de un grupo alquilarilo apropiado es tolilo. El enlace con la porción principal es a través del arilo.

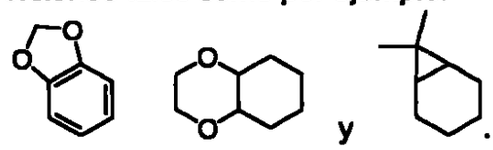
"Cicloalquilo" significa un sistema de anillo mono-o multicíclico no aromático que comprende aproximadamente 3 hasta aproximadamente 10 átomso de carbono, preferentemente aproximadamente 5 hasta aproximadamente 10 átomos de carbono. Los anillo cicloalquilos preferidos contienen aproximadamente 5 hasta aproximadamente 7 átomos en el anillo. El cicloalquilo puede estar opcionalmente sustituido con uno o más "sustituyentes de sistema de anillo" que puede ser igual o diferente, y que son tal como se han definido anteriormente. Ejemplos no limitativos de cicloalquilos monocíclicos apropiados incluyen ciclopropilo, ciclopentilo, ciclohexilo, cicloheptilo y similares. Ejemplos no limitativos de cicloalquilos multicíclicos apropiados incluyen 1-decalinilo, norbornilo, adamantilo y similares, así como también especies parcialmente saturadas tales como por ejemplo, indanilo, tetrahidronaftilo y similares.

"Halógeno" se refiere a flúor, cloro, bromo o yodo. Se prefieren flúor, cloro y

354
355

bromo.

"Sustituyente de sistema de anillo" significa un sustituyente unido a un sistema de anillo aromático o no aromático que, por ejemplo, reemplaza un hidrógeno disponible en el sistema de anillo. Los sustituyentes del sistema de anillos pueden ser iguales o diferentes, y cada uno está independientemente seleccionado del grupo que consiste en alquilo, alquenilo, alquinilo, arilo, heteroarilo, aralquilo, alquilarilo, heteroarilo, heteroarilalquenilo, heteroarilalquinilo, alquilheteroarilo, hidroxi, hidroxialquilo, alcoxi, ariloxi, aralkoxi, acilo, aroilo, halo, nitro, ciano, carboxi, alcoxicarbonilo, ariloxicarbonilo, aralcoxicarbonilo, alquilsulfonilo, arilsufonilo, heteroarilsulfonilo, alquiltio, ariltio, heteroariltio, arlaquiltio, heteroarilquiltio, cicloalquilo, heterociilo, $-C(=N-CN)-NH_2$, $-C(=NH)-NH_2$, $-C(=NH)-NH(alkyl)$, Y_1Y_2N-, $Y_1Y_2N-alkyl-$, $Y_1Y_2NC(O)-$, $Y_1Y_2NSO_2-$ y $-SO_2NY_1Y_2$, donde Y_1 y Y_2 pueden ser iguales o diferentes y están independientemente seleccionados del grupo que consiste en hidrógeno, alquilo, arilo, cicloalquilo, y aralquilo. "Sustituyente del sistema de anillo" puede significar también una sola porción que simultáneamente reemplaza los hidrógenos disponibles en dos átomos de carbono adyacentes (uno de H en cada carbono) en un sistema de anillo. Ejemplos de dicha porción son metileno dioxi, etilenedioxi, $-C(CH_3)_2-$ y similares que forman porciones tales como por ejemplo:

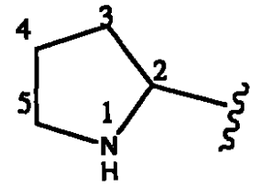


"Heterociclilo" significa un sistema de anillo monocíclico o multicíclico saturado no aromático que comprende aproximadamente 3 hasta aproximadamente 10 átomos de anillo, preferiblemente aproximadamente 5 hasta aproximadamente 10 átomos de anillo, donde uno o más de los átomos en el sistema de anillo es un elemento distinto de carbono, por ejemplo nitrógeno,

355
356

oxígeno o azufre, solo o en combinación. No hay átomos de oxígeno y/o azufre adycentes presentes en el sistema de anillo. Los heterociclilos preferidos contienen aproximadamente 5 hasta aproximadamente 6 átomos en el anillo. El prefijo aza, oxa o tia antes del nombre de raíz heterociclilo significa que por lo menos un átomo de nitrógeno, oxígeno o azufre respectivamente está presente como átomo del anillo. Cualquier –NH en un anillo heterociclilo puede existir protegido tal como por ejemplo un grupo -N(Boc), -N(CBz), -N(Tos) y similares; dichas protecciones se consideran también parte de esta invención. El heterociclilo puede estar opcionalmente sustituido con uno o más "sustituyentes de sistema de anillos" que pueden ser iguales o diferentes y que son tal como se definen aquí. El átomo de nitrógeno o azufre del heterociclilo puede estar opcionalmente oxidado al correspondiente N-óxido, S-óxido o S, S-dióxido. Ejemplos no limitativos de anillos heterociclilo monocíclicos apropiados incluyen piperidilo,pirrolidinilo, piperazinilo, morfolinilo, tiomorfolinilo, tiazolidinilo, 1,4-dioxanilo, tetrahidrofuranilo, tetrahidrotiofenilo, lactano, lactona, y similares.

Debe observarse que en los sistemas de anillo de esta invención que contienen heteroátomos, no hay grupos de oxilo en los átomos de carbono, adyacentes a un N, O o S, así como tampoco hay grupos N o S en el carbono adyacente a otro heteroátomo. Por lo tanto, por ejemplo, en el anillo:



no existe ningún –OH unido directamente a los carbonos marcados 2 y 5.

Debe observarse que las formas tautoméricas tales como por ejemplo las porciones:

se consideran equivalentes en algunas realizaciones de esta invención.

356
357

"Alquinilalquilo" significa un grupo alquinil-alquilo en el cual el alquinilo y el alquilo son tal como se han descripto previamente. Los alquinilaquilos preferidos contienen un grupo alquinilo inferior y un grupo alquilo inferior. El enlace con la porción principal es a través del alquilo. Ejemplos no limitativos de grupos alquinilauqilos apropiados incluyen propargilmetilo.

"Heteroaralquilo" significa un grupo heteroaril-alquilo- en el cual el heteroarilo y el alquilo son tal como se han descrito previamente. Los heteroarilquilos preferidos contienen un grupo alquilo inferior. Ejemplos no limitativos de grupos aralquilos apropiados incluyen piridilmetilo, y quinolin-3-ilmetilo. El enlace con la porción principal es a través del alquilo.

"Hidroxialquilo" significa un grupo HO-alquilo- en el cual el alquilo es tal como se ha definido previamente. Los hidroxialquilos preferidos contienen alquilo inferior. Ejemplos no limitativos de grupos hidroxialquilo a propiados incluyen hidroximetilo y 2-hidroxietilo.

"Acilo" significa un grupo H-C(O)-, alquilo –C(O)- o cicloalquilo-C(O)-, en el cual los varios grupos son tal como se han descrito previamente. El enlace con la porción principal es a través del carbonilo. Los acilos preferidos contienen un alquilo inferior. Ejemplos no limitativos de grupos de acilo apropiados incluyen formilo, acetilo y propanoilo.

"Aroilo" significa un grupo aril-C(O)- en el cual el grupo arilo es tal como se ha descrito previamente. El enlace con la porción principal es a través del carbonilo. Ejemplos no limitativos de grupos apropiados incluyen benzoilo y 1-naftoilo.

"Alcoxi" significa un grupo alquilo alquilo-O- en el cual el grupo alquilo es tal como se ha descrito previamente. Ejemplos no limitativos de grupos alcoxi apropiados incluyen metoxi, etoxi, n-propoxi, isopropoxi y n-butoxi. El enlace con la porción principal es a través del éter oxígeno.

357
358

"Ariloxi" significa un grupo aril-O- en el cual el grupo arilo es tal como se ha descrito previamente. Ejemplos no limitativos de grupos ariloxi apropiados incluyen fenoxi y naftoxi. El enlace con la porción principal es a través del éter oxígeno.

"Aralquiloxi" significa un grupo aralquilo-O- en el cual el grupo aralquilo es tal como se ha descrito previamente. Ejemplos no limitativos de grupos aralquiloxi apropiados incluyen benciloxi y 1- o 2-nafalenmetoxi. El enlace con la porción principal es a través del éter oxígeno.

"Alquiltio" significa un grupo alquilo-S- en el cual el grupo alquilo es tal como se ha descrito previamente. Ejemplos no limitativos de grupos alquiltio apropiados incluyen metiltio y etiltio. El enlace con la porción principal es a través del azufre.

"Ariltio" significa un grupo arilo-S- en el cual el grupo arilo es tal como se ha descrito previamente. Ejemplos no limitativos de grupos ariltio apropiados incluyen feniltio y naftiltio. El enlace con la porción principal es a través del azufre.

"Aralquiltio" significa un grupo aralquilo –S- en el cual el grupo aralquilo es tal como se ha descrito previamente. Ejemplo no limitativo de un grupo aralquiltio apropiado es benciltio. El enlace con la porción principal es a través del azufre.

"Alcoxicarbonilo" significa un grupo alquilo-O-CO-. Ejemplos no limitativos de grupos alcoxicarbonil apropiados incluyen metoxicarbonilo y etoxicarbonilo. El enlace con la porción principal es a través del carbonilo.

"Ariloxicarbonilo" significa un grupo arilo-O-C(O)-. Ejemplos no limitativos de grupos ariloxicarbonil apropiados incluyen fenoxicarbonilo y naftoxicarbonilo. El enlace con la porción principal es a través del carbonilo.

"Aralcoxicarbonilo" significa un grupo aralquilo-O-C(O)-. Un ejemplo no limitativo de un grupo aralcoxicarbonilo apropiado es el benciloxicarbonilo. El enlace con la porción principal es a través del carbonilo.

~~350~~
391

-"Alquilsulfonilo"-significa un grupo alquilo-$S(O_2)$-. Los grupos preferidos son aquellos en los cuales el grupo alquilo es alquilo inferior. El enlace con la porción principal es a través del sulfonilo.

"Arilsulfonilo" significa un grupo aril-$S(O_2)$-. El enlace con la porción principal es a través del sulfonilo.

El término "sustituido" significa que uno o más hidrógenos en el átomo designado se reemplazan con una selección del grupo indicado, con la condición de que la valencia normal del átomo designado bajo las circunstancias existentes no esté excedida, y que la sustitución de como resultado un compuesto estable. Las combinaciones de sustituyentes y/o variables son permisibles únicamente si dichas combinaciones dan como resultado compuestos estables. Mediante "compuesto estable" o "estructura estable" se indica un compuesto que es suficientemente robusto para sobrevivir al aislamiento hasta un grado de pureza útil a partir de una mezcla de reacción, y para ser formulado como un agente terapéutico eficaz.

El término "opcionalmetne sustituido" significa una sustitución opcional con los grupos radicales o porciones especificados.

El término "aislado" o "en forma aislada" para un compuesto se refiere al estado físico de dicho compuesto después de haber sido aislado de un procedimiento de síntesis o de una fuente natural o una combinación de ambos. El "purificado" o "en forma purificada" para un compuesto se refiere al estado físico de dicho compuesto después de haber sido obtenido a partir de un procedimiento o procedimientos aquí descritos o que son bien conocidos por los expertos en la materia, con una pureza caracterizable mediante las técnicas analíticas convencionales aquí descritas o bien conocido por los expertos en la materia.

Debería observarse también que cualquier heteroátomo con valencias no

359
360

satisfechas en el texto, esquemas, ejemplos y tablas presentes se considera que tiene el átomo o átomos de hidrógeno para satisfacer las valencias.

Cuando un grupo funcional en un compuesto se denomina "protegido", esto significa que el grupo está en forma modificada para evitar cualquier reacción secundaria indeseable en el sitio protegido cuando el compuesto se somete a una reacción. Los grupos protectores apropiados serán reconocidos por los expertos en la materia así como también con referencia a los libros de texto convencionales tales como por ejemplo T. W. Greene *et al*, *Protective Groups in organic Synthesis* (1991), Wiley, New York.

Cuando ocurre cualquier variable (e.g., arilo, heterociclo, R^2, etc.) más de una vez en cualquier constituyente o en la Fórmula III, su definición cada vez que ocurre es independiente de su definición cada vez que vuelve a ocurrir.

Tal como se usa aquí, el término "composición" se da para abarcar un producto que comprende los ingredientes especificados las cantidades así como también producto resultante, en forma directa o indirecta, de la combinación de los ingredientes especificados en las cantidades especificadas.

Las prodrogas solvatos de los compuestos de la invención están también contemplados aquí. El término "prodroga" tal como se emplea aquí denota un compuesto que es un precursor de una droga el cual, al ser administrado a un sujeto sufre una conversión química causada por procesos metabólicos o químicos que provee un compuesto de Fórmula III o una salida y/o solvato del mismo. Una consideración de las prodrogas ha sido provista en T. Higuchi y V. Stella, *Pro-drugs as Novel Delivery Systems* (1987) 14 de la A.C.S. Symposium Series, y en *Bioreversible Carriers in Drug Design,* (1987) Edward B. Roche, ed., American Pharmaceutical Association and Pergamon Press, que se incorporan aquí como referencia.

"Solvato" significa una asociación física de un compuesto de esta invención

360
361

con una o más moléculas disolventes. Esta asociación física involucra grados variados de unión iónica ecovalente, que incluyen unión de hidrógeno. En algunos casos el solvato será capaz de aislación, por ejemplo cuando se incorporan una o más moléculas disolventes en el retículo cristalino del sólido cristalino. "Solvato" abarca tantò la fase en solución como los solvatos aislables. Ejemplos no limitativos de solvatos apropiados incluyen etanolatos, metanolatos, y similares. "Hidrato" es un solvato en el cual la molécula disolvente es H_2O.

"Cantidad eficaz" o "cantidad terapéuticamente eficaz" se provee para describir una cantidad de compuesto o una composición de la presente invención eficaz para inhibir la CDK(s) y por lo tanto para producir el efecto terapéutico, mejorador, inhibidor o preventivo deseado.

Los compuestos de Fórmula III pueden formar sales que están también dentro del alcance de esta invención. La referencia a un compuesto de Fórmula III tal como se interpreta aquí incluye referencias a sus sales a menos que se indique lo contrario. El témino "sal(es)", tal como se emplea aquí, denota las sales ácidas formadas con ácidos inorgánicos y/o orgánicos así como también las sales básicas formadas con bases inorgánicas y/o orgánicas. Además, cuando un compuesto de Fórmula III contiene una porción básica, tal como, pero sin limitarla a una piridina o un imidazol, además de una porción ácida, tal como pero sin limitarla a un ácido carboxílico, pueden formarse zwitteriones ("sales internas") y están incluídos dentro del término "sal(es)" tal como se usa aquí. Se prefieren las sales farmacéuticamente aceptables (es decir no tóxicas, fisiológicamente aceptables) aunque también son útiles otras sales. Las sales de los compuestos de la Fórmula III pueden formarse por ejemplo mediante reacción de un compuesto de Fórmula III con una cantidad de ácido o base, tal como un cantidad de equivalente, en un medio tal como aquel en el cual precipita la sal o en un medio acuso seguido de liofilización.

Ejemplos de sales de adición de ácido incluyen acetatos, ascorbatos,

benzoatos, benzenesulfonatos, bisulfatos, boratos, butiratos, citratos, alcanforatos, alcansulfonatos, fumaratos, clorhidratos, bromhidratos, yohitratos, lactatos, maleatos, metansulfonatos, naftalensulfonatos, nitratos, oxalatos, fosfatos, propionatos, salicilatos, succinatos, sulfatos, tartratos, tiocianatos, toluensulfonatos (conocidos también como tosilatos), y similares. Adicionalmente, los ácidos que generalmente se consideran apropiados para la formación de sales farmacéuticamente útiles a partir de compuestos farmacéuticos básicos han sido discutidos 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; and in *The Orange Book* (Food & Drug Administration, Washington, D.C. o su sitio de Internet). Estas descripciones se incorporan aquí como referencia.

Ejemplos de sales básicas incluyen sales de amonio, sales de metales alcalinos tales como sales de sodio, litio y potasio, sales de metales alcalino férreos 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 similares. Los grupos básicos que contienen nitrógeno pueden cuaternizarse con agentes tales como aluros de alquilo inferior (por ejemplo cloruros, bromuros y yoduros de metilo, etilo y butilo), sulfatos de dialquilo (por ejemplo sulfatos de dimetilo, dietilo y dibutilo), aluros de cadena larga (por ejemplo cloruros, bromuros y yoduros de decilo, laurilo y estearilo), aluros de aralquilo (por ejemplo bromuros de bencilo y fenetilo), y otros.

Todas dichas sales ácidas y sales básicas son sales farmacéuticamente aceptables dentro del alcance de la invención y todas las sales ácidas y básicas se consideran equivalentes a las formas libres de los correspondientes compuestos para los propósitos de la inveción.

Los compuestos de la Fórmula III, y las sales, solvatos y prodrogas de los mismos, pueden existir en su forma tautomérica (por ejemplo en forma de una amida o imino éter). Todas dichas formas tautoméricas están contempladas aquí

362
363

como parte de la presente invención.

Todos los estereoisómeros (por ejemplo los isómeros geométricos, los isómeros ópticos y similares) de los presentes compuestos (incluyendo los de las sales, solvatos y prodrogas de los compuestos así como también las sales y solvatos de las prodrogas), tales como los que pueden existir debido a carbonos asimétricos en varios sustituyentes, incluyendo las formas enantioméricas (las cuales pueden existir incluso en ausencia de carbonos asimétricos), las formas rotaméricas, los atropisómeros, y las formas diasteroméricas, están contempladas dentro del alcance de esta invención, así como también lo están los isómeros posicionales (tales como, por ejemplo, 4-piridilo y 3-piridilo). Los estereoisómeros individuales de los compuestos de la invención pueden estar, por ejemplo como sustancialmente libres de otros isómeros, o pueden estar mezclados por ejemplo como racematos o todos los otros o con otros estereoisómeros seleccionados. Los centros quirales de la presente invención pueden tener la configuración S o R tal como se define en las Recomendaciones *IUPAC* 1974. El uso de los términos "sal", "solvato""prodroga" y similares, se aplica igualmente a la sal, el solvato y la prodroga de los enantiómeros, estereoisómeros, rotámeros, tautómeros, isómeros posicionales, racematos o prodrogas de los compuestos de la invención.

Los compuestos de acuerdo con la invención tienen propiedades farmacológicas; en particular, los compuestos de la Fórmula III pueden ser inhibidores de las proteínas quinasas tales como, por ejemplo los inhibidores de las quinasas dependientes de ciclina, la quinasa de proteína activada por mitógeno (MAPK/ERK), la sintasa quinasa de glicógeno 3(GSK3beta) y similares. Las quinasas dependientes de ciclina (CDKs) incluyen, por ejemplo, CDC2 (CDK1), CDK2, CDK4, CDK5, CDK6, CDK7 y CDK8. Se espera que los nuevos compuestos de la Fórmula III serán útiles en la terapia de las enfermedades proliferativas tales como cáncer, enfermedades autoinmunes, enfermedades virales, enfermedades fungales, desórdenes neurológicos/neurodegenerativos, artritis, inflamación, enfermedad anti-proliferativa (por ejemplo retinopatía ocular),

363
364

neuronales, alopecia y cardiovasculares. Muchas de estas enfermedades y desórdenes se ennumeran en la patente norteamericana 6.413.974, citada anteriormente, cuya descripción se incorpora aquí.

Más específicamente, los compuestos de la Fórmula III pueden ser útiles en el tratamiento de una variedad de cánceres que incluyen, (pero que no están limitados a) lo siguiente: carcinoma, incluyendo el carcinoma de vejiga, mama, colon, de riñón, de hígado, de pulmón, incluyendo carcinoma pulmonar amicrocítico, de esófagos, de vesícula, de ovario, de pancreas, de estómago, de cuello uterino, de tiroide, de próstata y de piel, incluyendo carcinoma escamoso; tumores hematopoyéticos de linaje linfoide, incluyendo leucemia, leucemia linfocítica aguda, leucemia linfoblástica aguda, linfoma de célula B, linfoma de célula T, linfoma de Hodgkins hodgkiniano, linfoma no hodgkiniano, linfoma de tricoleucocitos y linfoma de Burkett's;

tumores hematopoyéticos de linaje mieloide, incluyendo leucemias mielógenas agudas y crónicas, síndrome mielodisplástico y leucemia promielocítica;

tumores de origen mesenquimatoso, incluyendo fibrosarcoma y rabdomiosarcoma;

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

otras tumores, que incluyen melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosum, queratoctantoma, cáncer folicular de tiroides y sarcoma de Kaposi.

Debido a la importante función de las CDK en la regulación de la proliferación celular en general, los inhibidores podrían actuar como agentes citostático reversible que pueden ser útiles en el tratamiento de cualquier proceso de enfermedad que se caracteriza por la proliferación celular anormal, por ejemplo próstata de benigna, hiperplasia, poliposis adenomatosa familiar, neuro-

9661
365

fibrematosis, ateroesclerosis, fibrosis pulmonar, artritis, psoriasis, glomerulonefritis, restenosis después de cirugía vascular y angioplastia, formación hipertrófica de cicatrices, enfermedad inflamatoria del intestino, rechazo a los transplantes, shock endotóxico e infecciones fungales.

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

Los compuestos de la Fórmula III pueden inducir o inhibir la apoptosis. La respuesta apoptótica es aberrante en una variedad de enfermedades humanas. Los compuestos de la Fórmula III, como moduladores de la apoptosis, serán útiles en el tratamiento del cáncer (incluyendo pero sin limitarlo a aquellos tipos de cáncer mencionado anteriormente) como infecciones virales (incluyendo pero sin limitarlo a herpevirus, poxvirus, virus de Epstein- Barr, virus de Sindbis y adenovirus), prevensión del desarrollo del SIDA en individuos infectados con HIV, enfermedades autoinmunes (incluyendo pero sin limitarlo a lupus sistémico, eritematoso, glomerulonefritis intermediada por autoinmunidad, artritis reumatoide, psoriasis, enfermedad inflamatoria del intestino y diabetes mellitus autoinmune), desórdenes degenerativos (que incluyen pero que no están limitados a la enfermedad de Alzheimer, demencia relacionada con SIDA, enfermedad de Parkinson, esclerosis lateral amiotrófica, retinitis pigmentosa, atrofia muscular espinal y degeneración del cerebelo), síndromes mielodisplásticos, anemia aplástica, lesiones isquémicas asociadas con infartos de miocardio, apoplegía y lesiones de reperfusión, arritmias, ateroesclerosis, enfermedades hepáticas relacionadas con alcohol o inducidas por toxinas, enfermedades hematológicas (que incluyen pero que no están limitadas a anemia crónica y anemia aplástica), enfermedades degenerativas del sistema músculoesqueletal (que incluyen pero

que no están limitados a osteosporosis y artritis), rinosinusitis sensible a la aspirina, fibrosis quítica, esclerosis múltiple, enfermedades renales y dolor causado por cáncer.

Los compuestos de la Fórmula III, como inhibidores de las CDK, pueden modular el nivel de la síntesis celular de ARN y ADN. Estos agente serían por lo tanto útiles en el tratamiento de infecciones virales (incluyendo pero sin limitarlo a HIV, virus de papiloma humano, virus herpes, poxvirus, virus de Epstein-Bar, virus de Sindbis y adenovirus).

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

Los compuestos de la Fórmula III pueden ser también útiles para inhibir la angiogénesis y metástasis tumoral.

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

Otro aspecto de esta invención es un método para el tratamiento de un mamífero (por ejemplo un ser humano) que tiene una enfermedad o trastorno asociado con las CDK mediante la administración de una cantidad terapéuticamente eficaz de por lo menos un compuesto de la Fórmula III, o una sal o solvato farmacéuticamente aceptable de dicho compuesto al mamífero.

Una dosis preferida es de aproximadamente 0,001 a 500 mg/kg de peso corporal/día del compuesto de Fórmula III. Una dosis especialmente preferida es

366
367

de aproximadamente 0,01 a 25 mg/kg de peso coproral/día de un compuesto de la Fórmula III, o de una sal o solvato farmacéuticamente aceptable de dicho compuesto.

Los compuestos de esta invención pueden también útiles en combinación (administrados conjuntamente o en secuencia) con uno o más tratamientos anti-cáncer tales como terapia de radiación y/o uno o más agentes anti-cancerígenos seleccionados del grupo que consiste en agentes citostáticos, agentes citotóxicos (tales como por ejemplo pero sin limitarlo a agentes interactivos ADN (tales como cisplatino o doxorubicina); taxanos (por ejemplo taxotere, taxol); inhibidores de topoisomerasa II (tales como etoposide); inhibidores de topoisomerasa I (tales como irinotecan (o CPT-11), camptostar o topotecan); agentes que interactúan con tubulina (tales como paclitaxel, docetaxel o los epotilones); agentes hormonales (tales como tamoxifen); inhibidores de timidilato sintasa (tales como 5-fluoruracilo); anti-metabolitos (tales como metotrexato); agentes alquilantes (tales como temozolomida (TEMODAR™ de Schering-Plough Corporation, Kenilworth, New Jersey), ciclofosfamida); inhibidores de la proteína transferasa 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-yl-]-1-piperidinil]-2-oxoetil]-1-piperidinacarboxamida, o SCH 66336 de Schering-Plough Corporation, Kenilworth, New Jersey), tipifarnib (Zarnestra® o R115777 de Janssen Pharmaceuticals), L778,123 (un inhbidor de la proteína transferasa farnesilo de Merck & Company, Whitehouse Station, New Jersey), BMS 214662 (un inhibidor de la proteína transferasa farnesilo de from Bristol-Myers Squibb Pharmaceuticals, Princeton, New Jersey); inhibidores de la transducción de señales (tales como, Iressa (de Astra Zeneca Pharmaceuticals, England), Tarceva (inhibidores de la quinasa EGFR), anticuerpos para EGFR (por ejemplo, C225), GLEEVEC™ (inhibidor de la quinasa C-abl de Novartis Pharmaceuticals, East Hanover, New Jersey); interferones tales como por ejemplo, intron (de Schering-Plough Corporation), Peg-Intron (from Schering-Plough Corporation); combinaciones para

terapia hormonal; combinaciones de aromatasa; ara-C, adriamicina, citoxan, y gemcitabina.

Otros agentes anti-cáncer (también conocidos como anti-neoplásticos) incluyen pero no están limitados a Uracilo mostaza, Clormetina, Ifosfamida, Melfalan, Clorambucil, Pipobroman, Trietilenmelamina, Trietilentiofosforamina, Busulfan, Carmustina, Lomustina, Estreptozocina, Dacarbazina, Floxuridina, Citarabina, 6-Mercaptopurina, 6-Tioguanina, fosfato de Fludarabina, oxaliplatino, leucovirina, oxaliplatino (ELOXATIN™ de Sanofi-Synthelabo Pharmaceuticals, France), Pentostatina, Vinblastina, Vincristina, Vindesina, Bleomicina, Dactinomicina, Daunorubicina, Doxorubicina, Epirubicina, Idarubicina, Mitramicina, Deoxicoformicina, Mitomicina-C, L-Asparaginasa, Teniposida 17□-Etinilestradiol, Dietilestilbestrol, Testosterona, Prednisona, Fluoximesterona, propionato de Dromostanolona, Testolactona, Megestrolacetato, Metilprednisolona, Metiltestosterona, Prednisolona, Triamcinolona, Clorotrianisena, Hidroxiprogesterona, Aminoglutetimida, Estramustina, acetato de Medroxiprogesterona, Leuprolida, Flutamida, Toremifeno, goserelina, Cisplatina, Carboplatina, Hidroxiurea, Amsacrina, Procarbazina, Mitotano, Mitoxantrona, Levamisol, Navelbeno, Anastrazol, Letrazol, Capecitabina, Reloxafina, Droloxafina, o Hexametilmelamina.

Si se formulan como dosis fija, dichos productos de combinación emplean los compuestos de esta invención dentro de un rango de dosificación descripto aquí y el otro agente farmecéuticamente activo o el tratamiento dentro de su rango de dosificación. Por ejemplo se ha hallado que el inhibidor de CDC2 olomucina actúa sinérgicamente con agentes citotóxicos conocidos para inducir apoptosis (*J. Cell Sci.*, (1995) 108, 2897. Los compuestos de la Fórmula III pueden administrarse también secuencialmente con agentes citotóxicos o anti-cáncer cuando la formulación de combinaciones es inapropiada. La invención no está limitada a la secuencia de administración; los compuestos de la Fórmula III pueden administrarse antes o después de la administración del agente anti-

368
369

cancerosos o citotóxico conocido. Por ejemplo, la actividad citotóxica del inhibidor de quinasa dependiente de ciclino flavopiridol es afectada por la secuencia de administración con agentes anti-cáncer. *Cancer Research*, (1997) 57, 3375. Estas técnicas están dentro de la experiencia de los expertos en la materia así como también de los médicos.

Por consiguiente, en un aspecto, esta invención incluye combinaciones que comprenden una cantidad de por lo menos un compuesto de la Fórmula III, o de una sal o solvato del mismo farmacéuticamente aceptable, y una cantidad de uno o más tratamientos anti-cáncer y agentes anti-cáncer enumerados más arriba donde las cantidades de los compuestos/tratamientos dan como resultado el efecto terapéutico deseado.

Las propiedades farmacológicas de los compuestos de esta invención pueden confirmarse mediante una variedad de ensayos farmacológicos. En los ensayos farmacológicos ejemplificados que se describen a continuación se llevaron a cabo con los compuestos de acuerdo con la invención y sus sales.

Esta invención está también dirigida a las composiciones farmacéuticas que comprenden por lo menos un compuesto de la Fórmula III, o una sal o solvato farmacéuticamente aceptable de dicho compuesto y por lo menos un portador famacéuticamente aceptable.

Para preparar las composiciones farmacéuticas de los compuestos descritos en esta invención, los portadores inertes, farmacéuticamente aceptables pueden ser sólidos o líquidos. Las preparaciones de forma sólida incluyen polvo, tabletas, gránulos dispersables, cápsulas, sellos y supositorios. Los polvos y tabletas pueden estar constituidos por desde aproximadamente 5 a 95 por ciento de ingrediente activo. Los portadores sólidos apropiados son conocidos en el arte, por ejemplo carbonato de magnesio, estearato de magnesio, talco, azúcar o lactosa. Pueden usarse tabletas, polvos, sellos y cápsulas como formas de dosificación sólida para administración oral. Pueden encontrarse ejemplos de portadores farmacéuticamente aceptables y métodos de manufactura para varias

composiciones en A. Gennaro (ed.), *Remington's Pharmaceutical Sciences*, 18ª Edición, (1990), Mack Publishing Co., Easton, Pennsylvania.

Las preparaciones de formas líquidas incluyen soluciones como suspensiones y emulsiones. Como ejemplo pueden mencionarse agua o soluciones de agua-propilenglicol para inyección parenteral o adición de edulcorantes y opacantes para soluciones como suspensiones y emulsiones orales.

Las preparaciones en forma líquida pueden incluir también soluciones para administración intra nasal.

Las preparaciones en aerosol apropiadas para inhalación pueden incluir soluciones y sólidos en forma pulverulenta, que pueden estar en combinación con un portador farmacéuticamente aceptable tal como gas comprimido inerte por ejemplo nitrógeno.

Asímismo se incluyen las preparaciones de forma sólida que están destinadas a convertirse poco tiempo antes de su uso a preparaciones de forma líquida para administración oral o parenteral. Dichas formas líquidas incluyen soluciones, suspensiones y emulsiones.

Los compuestos de la invención pueden liberarse también por vía transdérmica. Las composiciones transdérmicas pueden tener la forma de cremas, lociones, aerosoles y/o emulsiones y pueden estar incluídos en un parche transdérmico del tipo de matriz o de tipo reservorio que son convencionales en la técnica para este propósito.

Los compuestos de esta invención pueden liberarse también por vía subcutánea.

Preferiblemente el compuesto se administra por vía oral.

Preferiblemente, la preparación farmacéutica está en una forma de dosificación unitaria. En dicha forma, la preparación se subdivide en dosis unitarias del tamaño apropiado que contienen cantidades apropiadas del componente activo, como por ejemplo una cantidad eficaz para lograr el propósito

~~370~~ 371

deseado.

La cantidad de compuesto activo en una dosis unitaria de preparación puede variarse o puede ajustarse desde aproximadamente 1 mg hasta aproximadamente 100 mg, preferiblemente desde aproximadamente 1 mg hasta aproximadamente 50 mg, más preferiblemente desde aproximadamente 1 mg hasta aproximadamente 25 mg, de acuerdo con la aplicación particular.

La dosis real empleada puede variar dependiendo de los requisitos del paciente y de la gravedad de la enfermedad tratada. La determinación del régimen de dosificación adecuado para una situación particular está dentro de la experiencia en la materia. Por razones de conveniencia, la dosis diaria total puede dividirse y administrarse en porciones durante el día de acuerdo a lo que se requiera.

La cantidad y frecuencia de administración de los compuestos de la invención y/o de sus sales farmacéuticamente aceptables se regulará de acuerdo con la opinión del médico autorizado considerando factores tales como la edad, las condiciones, y el peso del paciente así como también la gravedad de los síntomas que se tratan. Un régimen de dosificación diaria típico recomendado para administración oral puede estar comprendido dentro de aproximadamente 1 mg/día hasta aproximadamente 500 mg/día, preferiblemente un 1 mg/día a 200 mg/día, divididos en dos a cuatro dosis.

Otro aspecto de esta invención es un equipo que comprende una cantidad terapéuticamente eficaz de por lo menos un compuesto de Fórmula III o una sal o solvato farmacéuticamente aceptable del mismo y un portador, vehículo o diluyente farmacéuticamente aceptable.

Otro aspecto de esta invención es un equipo que comprende la cantidad de por lo menos un compuesto de Fórmula III, o una sal o solvato farmacéuticamente aceptable de dicho compuesto y una cantidad de por lo menos un agente anti-cáncer y/o para terapia anti-cáncer enumerados en lo que antecede, donde las cantidades de los dos o más ingredientes dan como resultado el efecto

terapéutico deseado.

La invención aquí descrita se ejemplifica mediante las siguientes preparaciones y ejemplos que no deben considerarse limitativos del alcance de la descripción. Las vías mecánicas alternativas y las estructuras análogas serán aparentes para los expertos en la materia.

Cuando se presentan los datos de la RMN, los espectros ^1H se obtuvieron con Varian VXR-200 (200 MHz, ^1H), con Varian Gemini-300 (300 MHz) o con XL-400 (400 MHz) y se informan como ppm en sentido descendente desde Me_4Si con un número de protones, las multiplicidades y las constantes de acoplamiento en Hertz indicados entre paréntesis. Cuando se presentan datos de LC/EM, los análisis se llevan a cabo usando un espectrómetro de masa Applied Biosystems API-100 y columna Shimadzu SCL-10A LC: Altech platino C18, 3 micrones, 33mm x 7mm DI; gradiente de flujo: 0 min – 10% CH_3CN, 5 min – 95% CH_3CN, 7 min – 95% CH_3CN, 7.5 min – 10% CH_3CN, 9 min – stop. Se dan el tiempo de retención y el ion principal observado.

Se hace referencia a los solventes y reactivos mediante sus abreviaturas entre paréntesis:

Cromatografía de capa delgada: TLC

diclorometano: CH_2Cl_2

acetato de etilo: AcOEt o EtOAc

metanol: MeOH

trifluoracetato: TFA

trietilamino: Et_3N o TEA

butoxicarbonilo: n-Boc o Boc

espectroscopio de resonancia magnética nuclear: RMN

espectrómetro de masa por cromatografía líquida: LCMS

378
373

espectrometría de masa de alta resolución: HRMS

mililitros: mL

milimoles: mmol

microlitros: µl

gramos: g

milligramos: mg

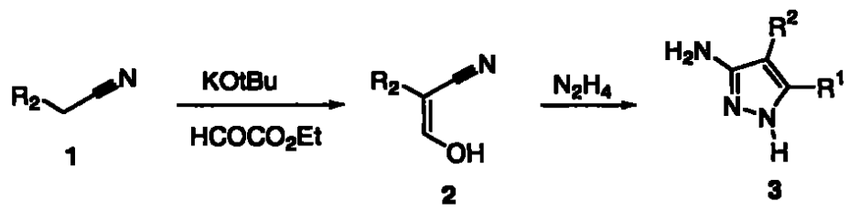
temperatura ambiente o rt (ámbiente): aproximadamente 25ºC.

dimetoxietano: DME

EJEMPLOS

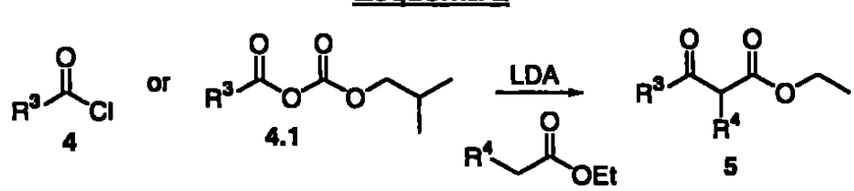
En general, los compuestos descritos en esta invención pueden prepararse a través de las vías generales descritas más abajo en el Esquema 1.

Esquema 1



El tratamiento del nitrilo de partida con t-butóxido de potasio y formiato de etilo da lugar al intermediario enol 2 el cual por tratamiento con hidrazina proporciona el 3-aminopirazol sustituido deseado. La condensación de los compuestos de tipo 3 con el ceto éster apropiadamente funcionalizado de tipo 5 da lugar a las piridonas 6 tal como se muestran en Esquema 3. Los ceto ésteres usando en esta vía general son comercialmente obtenibles o bien pueden prepararse tal como se ilustra en el Esquema 2. 2.

Esquema 2



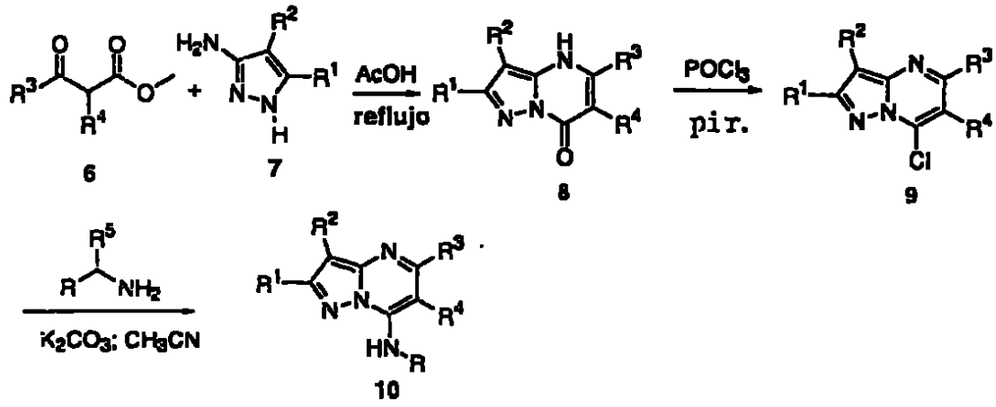
Los cloruros de tipo 9 pueden prepararse por tratamiento de las piridonas 8 con $POCl_3$. Cuando R^2 es igual a H, la sustitución en esta posición es posible en

373
374

los compuestos de tipo 9 por halogenación electrofílica, acilación, y mediante varias otras sustituciones electrofílicas aromáticas.

La introducción de la funcionalidad N7-amino puede llevarse a cabo a través del desplazamiento del cloruro de los compuestos de tipo 9 por reacción con la amina apropiada tal como se muestra en el Esquema 3.

Esquema 3

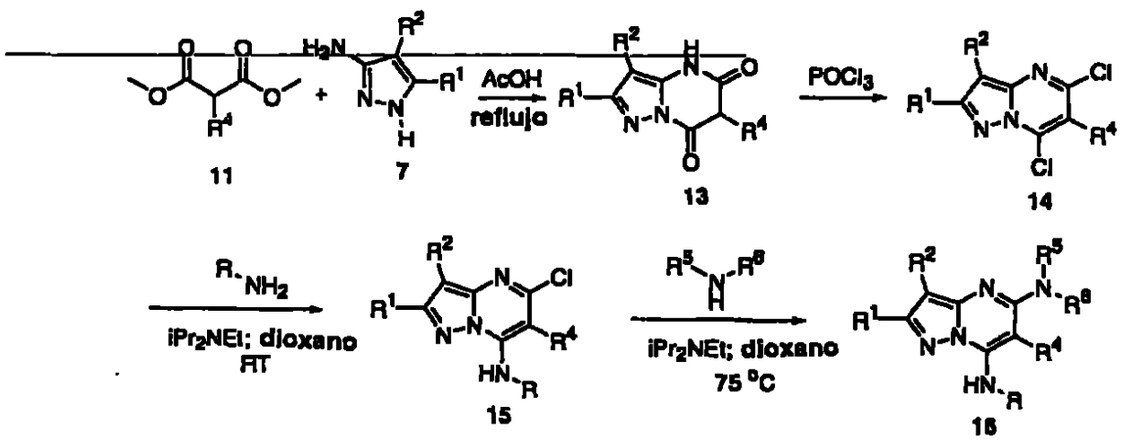


La condensación de los compuestos de tipo 7 con el éster de malonato apropiadamente funcionalizado de tipo 11 da lugar a las piridonas 13 tal como se muestran en le Esquema 4.

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

La incorporación de la funcionalidad N7-amino puede llevarse a cabo a través del desplazamiento regioselectivo del cloruro de los compuestos de tipo 14. Incorporación de la funcionalidad N5-amino por adición de una amina apropiada a temperatura superior.

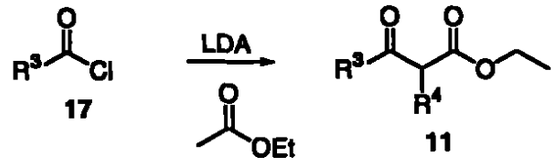
Esquema 4



11 7 13 14 15 16

Alternativamente, las condensaciones del os aminopirazoles de tipo 7 con un ceto éster apropiadamente funcionalizado tal como el preparado en el Esquema 5, conduce a la obtención de los compuestos de tipo 13 tal como los que se muestran en el Esquema 4.

Esquema 5



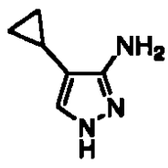
17 11

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

La incorporación de la funcionalidad N7-amino puede llevarse a cabo a través del desplazamiento del cloruro de los compuestos de tipo 15.

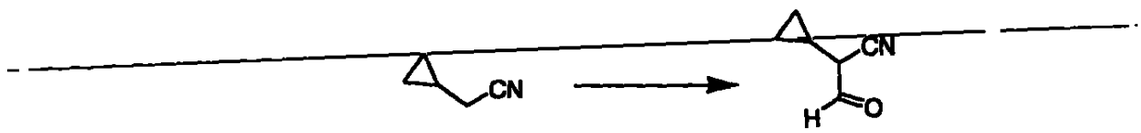
Ejemplos Preparativos:

EJEMPLO PREPARATIVO 1:



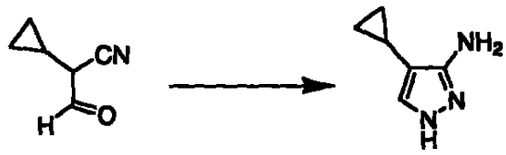
Etapa A:

375
376



Se siguió un procedimiento de la Patente Alemana DE 19834047 A1, p 19. A una solución de KOtBu (6,17 g, 0,055 mol) in THF anhidro (40 mL) se le agregó, por goteo, una solución de ciclopropilacetonitrilo (2,0 g, 0,025 mol) y formiato de etilo (4,07 g, 0,055 mol) en THF anhidro (4 mL). Inmediatamente se formó un precipitado. Esta mezcla se agitó durante 12 horas. Se concentró al vacío y el residuo se agitó con Et_2O (50 mL). El residuo resultante se decantó y se lavó con Et_2O (2 x 50 mL) y se removió el Et_2O del residuo bajo vacío. El residuo se disolvió en H_2O fría (20 mL) y se ajustó el pH a 4 – 5 con HCl 12N. La mezcla se extrajo con CH_2Cl_2 (2 x 50 mL). Las capas orgánicas se combinaron, se secaron sobre $MgSO_4$ y se concentraron al vacío para proporcionar el aldehído en forma de un líquido de color tostado.

Etapa B:



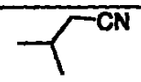
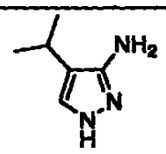
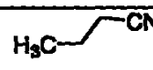
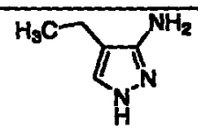
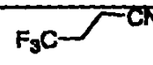
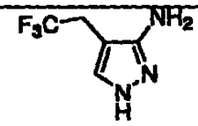
El producto del Ejemplo Preparativo 1, Etapa A (2,12 g, 0,0195 mol), $NH_2NH_2 \cdot H_2O$ (1,95 g, 0,039 mol) y 1,8 g (0,029 mol) de CH_3CO_2H glacial (1,8 g, 0,029 mol) se disolvieron en EtOH (10 mL). Se reflujó durante 6 horas y se concentró al vacío. El residuo se suspendió en CH_2Cl_2 (150 mL) y se ajustó el pH a 9 con NaOH 1N. Se lavó la capa orgánica con salmuera, se secó sobre $MgSO_4$ y se concentró al vacío para proporcionar el producto en forma de un sólido ceroso de color naranja.

EJEMPLOS PREPARATIVOS 2-4:

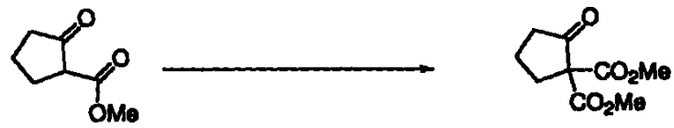
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo Preparativo 1, sustituyendo únicamente el nitrilo que se muestra en la Columna en la Tabla 2, se prepararon los compuestos de la Columna 3 de la Tabla 2:

376
377

TABLA 2

Ej. Prep.	Columna 2	Columna 3
2		
3		
3.10		

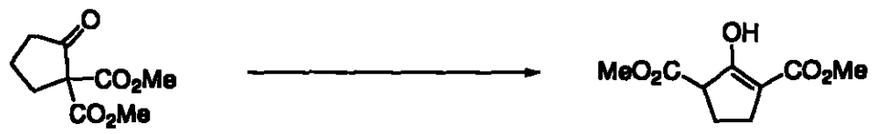
EJEMPLO PREPARATIVO 4



Se agregó por goteo 2-carbometoxiciclopentanona (6,6 ml, 0,05 mol) en THF (15 ml) a una suspensión vigorosamente agitada de NaH (60% en aceite mineral, 4 g, 0,1 mol) en THF (100 ml) a 0 –10°C. Cuando cesó el burbujeo, se trató la mezcla de reacción 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 detectar la desaparición del material de partida. La mezcla de reacción se apagó cuidadosamente con agua y se dividió entre acetato de etilo y una solución saturada de cloruro de amonio en un matraz. Se agitó y se separó, se lavó la capa orgánica con salmuera y se secó sobre sulfato de sodio anhidro. Se extrajeron los solventes, y el residuo se purificó por cromatografía evaporativa, se eluyó con 5% y luego con 10% de acetato de tilo en hexano. Se obtuvieron 9,4 g de un aceite incoloro con un rendimiento del 94%. ^{1}H RMN ($CDCl_3$) δ 3,90(s, 3H), 3,73(s, 3H), 2,65(m, 4H), 1,98(m, 2H).

~~377~~
~~377~~
378

EJEMPLO PREPARATIVO 5



A una solución de diisopropilamida de litio en THF (2,0 N, 0,04 mol) a –65°C, se agregó por goteo 2,2-dicarbometoxiciclopentanona (4 g, 0,02 mol) in THF (60 ml). La mezcla de reacción resultante se agitó a la misma temperatura antes de agregar cloroformiato de metilo (1,54 ml, 0,02 mol). La mezcla de reacción se agito durante 1 hora y se vertió en una solución saturada de cloruro de amonio con hielo. Esta solución se extrajo tres veces con éter, y las capas de éter combinadas se secaron sobre sulfato de sodio. Se extrajeron los solventes al vacío y el residuo se purificó por cormatografía evaporativa, y se eluyó con un incremento del 30% hasta 50% de acetato de etilo en hexano. Se obtuvieron 2,3 g de un aceite amarillento con un rendimiento del 58%. ^{1}H RMN ($CDCl_3$) δ 3,77(s, 6H), 3,32(t, 1H), 3,60-3.10(m, 4H).

EJEMPLO PREPARATIVO 6:

Las reacciones se llevaron a cabo de acuerdo a lo señalado en (K. O. Olsen, *J. Org. Chem.*, (1987) 52, 4531 – 4536). Por lo tanto, a una solución agitada de diisopropilamida de litio en THF a -65 a –70ºC se le agregó por goteo acetato de etilo recientemente destilado. Se agitó la solución resultante durante 30 minutos y se agregó el cloruro ácido en forma de una solución en THF. La mezcla de reacción se agitó a –65 a –70°C durante 30 minutos y luego se terminó con adición de una solución de HCl 1N. La mezcla resultante de dos fases se dejó calentar a temperatura ambiente. La mezcla resultante se diluyó con EtOAc (100 mL), y se recogió la capa orgánica. La capa acuosa se extrajo con EtOAc (100 mL). Se combinaron las capas orgánicas, se lavaron con salmuera, se secaron

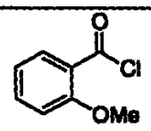
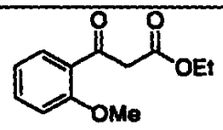
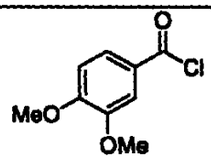
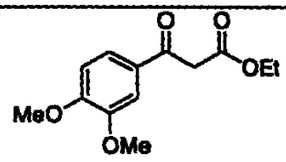
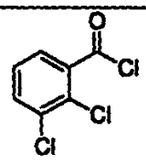
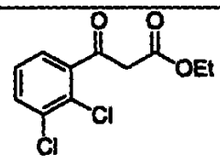
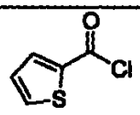
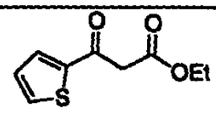
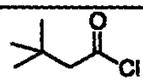
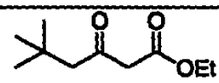
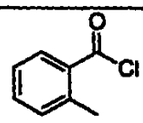
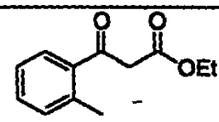
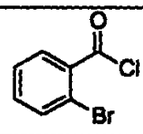
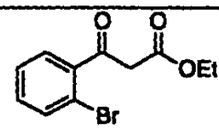
378
379

(Na_2SO_4), y se concentraron al vacío para proporcionar los β-ceto ésteres crudos, los cuales se usaron en las condensaciones subsiguientes.

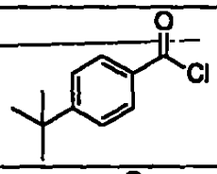
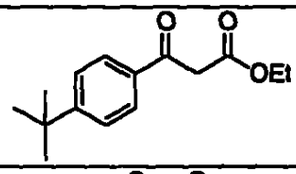
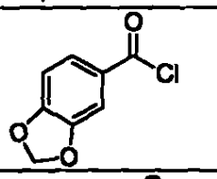
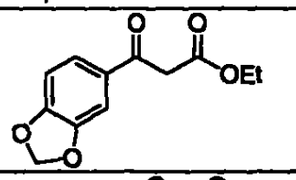
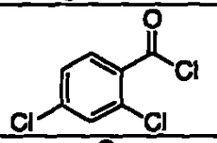
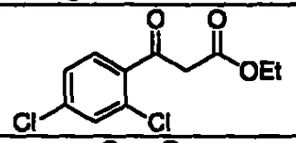
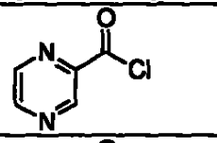
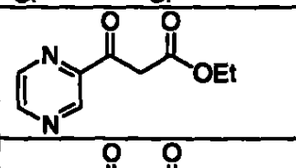
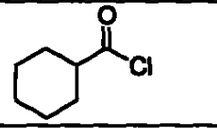
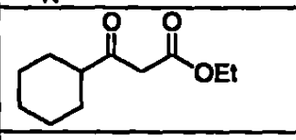
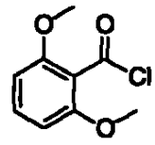
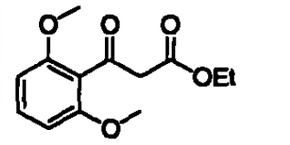
EJEMPLOS PREPARATIVOS 7-19:

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

TABLA 3

Ej. Prep.	Columna 2	Columna 3	DATOS
7			LCMS: $MH^+ = 223$
8			LCMS: $MH^+ = 253$
9			LCMS: $MH^+ = 261$
10			$MH^+ = 199$
11			
12			
13			LCMS: $MH^+ = 271$

379
380

14			Rend. = cuant. MH^+ =249
15			Rend. = cuant. MH^+ =237
16			Rend. = cuant. MH^+ = 262
17			Rend. = 48 MH^+ = 195
18			Rend. = 99 MH^+ =199
19			Rend.=77% ^{1}H 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:

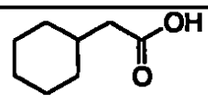
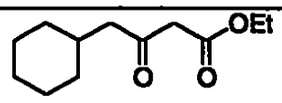
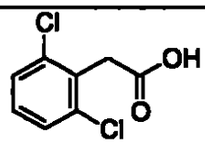
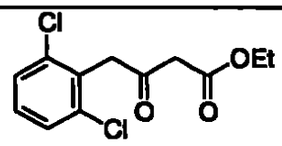
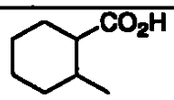
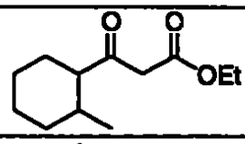
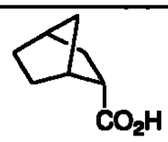
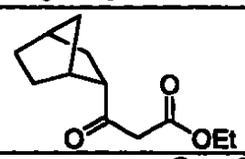
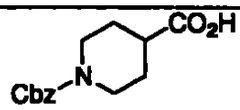
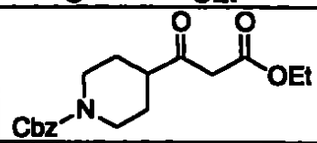
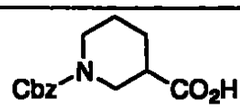
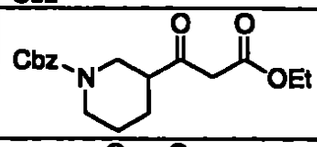
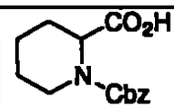
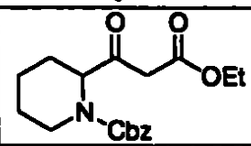
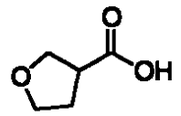
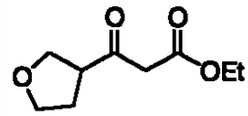
A una solución del ácido en THF se le agregó Et_3N, seguido de cloroformiato de isobutilo a –20 hasta –30°C. Después de agitar la mezcla durante 30 minutos a –20 hasta –30°C, se separó por filtración bajo argón clorhidrato de trietilamina, y se agregó el filtrado a la mezcla de reacción de LDA-EtOAc (preparado tal como se ha señalado en el Método A) a –65 a –70°C. Después de adición de HCl 1N, seguido de elaboración rutinaria de la mezcla de reacción y evaporación de los solventes, se aislaron los β-ceto ésteres crudos. El material crudo se usó en las condensaciones subsiguientes.

380
391

EJEMPLOS PREPARATIVOS 21 - 28:

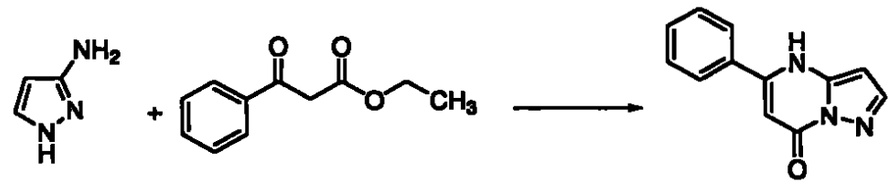
Siguiendo esencialmente las mismas condiciones que se indican en el Ejemplo Preparativo 20 sustituyendo únicamente el ácido carboxílico que se muestra en la Columna 2 de la Tabla 4, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 4:

TABLA 4

Ej. Prep.	Columna 2	Columna 3	COMP
21			Rend. = 98% MH^+ = 213
22			Rend. = 70% MH^+ = 275
23			Rend. = cuant MH^+ =213
24			Rend. = cuant MH^+ =211
25			Rend. = 99 MH^+ = 334
26			Rend. = 99 MH^+ = 334
27			Rend. = 99 MH^+ = 334
28			Rend.=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).

~~381~~
382

EJEMPLO PREPARATIVO 29:

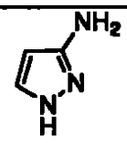
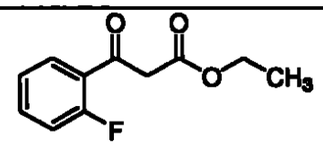
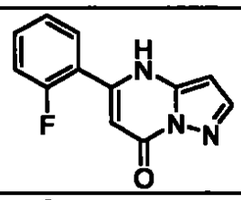
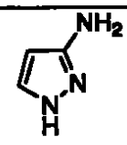
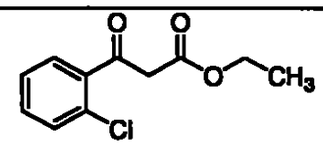
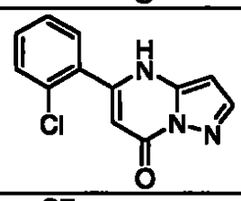
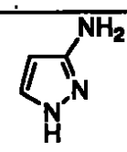
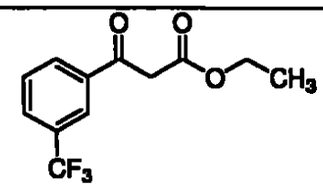
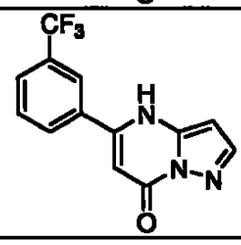


Una solución de 3-aminopirazol (2,0g, 24,07 mmol) y benzoilacetato de etilo (4,58 mL, 1,1 eq.) en AcOH (15 mL) se calentó a reflujo durante 3 horas. La mezcla de reacción se enfrió a temperatura ambiente y se concentró al vacío. El sólido resultante se diluyó con EtOAc y se filtró para proporcionar un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

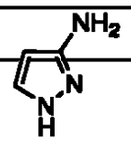
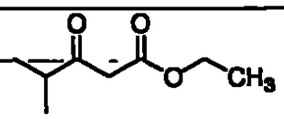
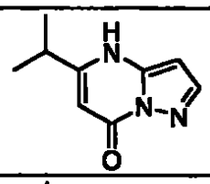
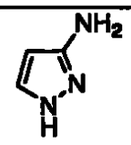
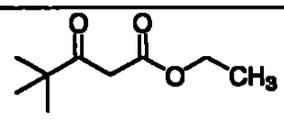
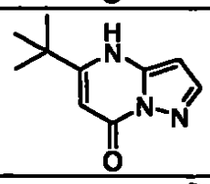
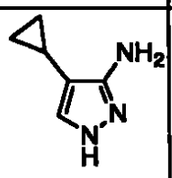
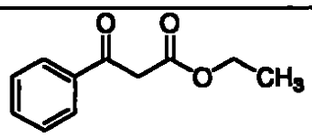
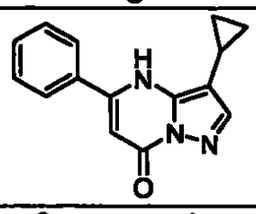
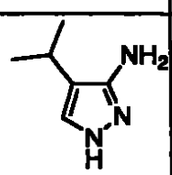
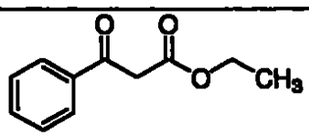
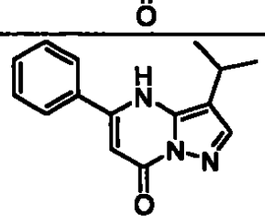
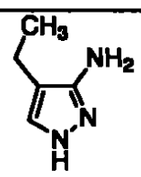
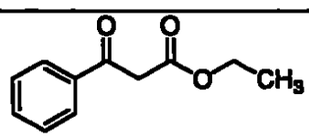
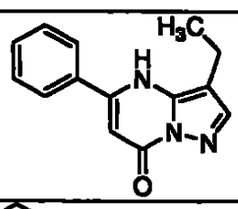
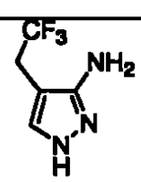
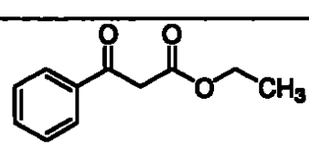
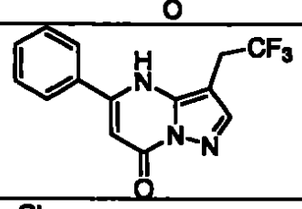
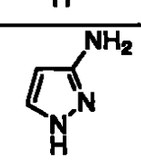
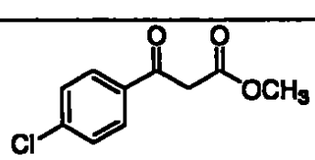
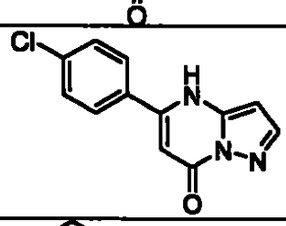
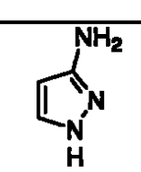
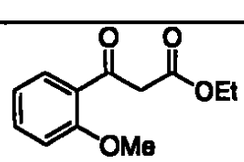
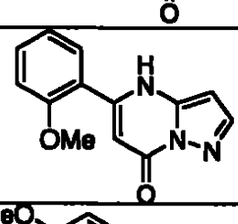
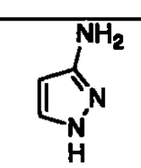
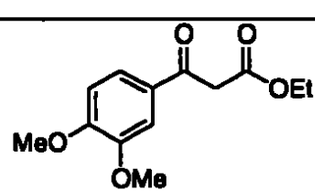
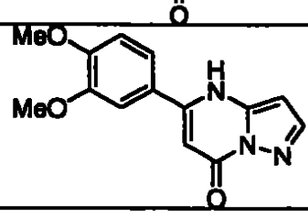
EJEMPLOS PREPARATIVOS 30-73:

Siguiendo esencialmente el mismo procedimiento del Ejemplo Preparativo 29 sustituyendo únicamente el aminopirazol que se muestra en la Columna 2 de la Tabla 5, y el éster que se muestra en la Columna 3 de la Tabla 5, se prepararon los compuestos que se muestran en la Columna 4 de la Tabla 5:

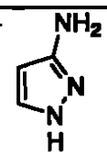
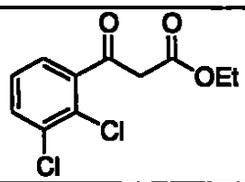
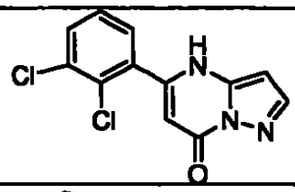
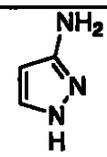
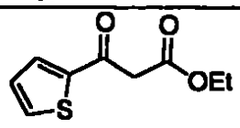
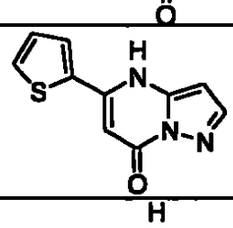
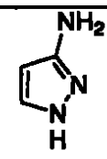
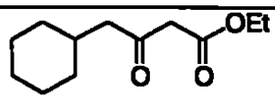
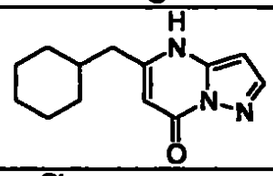
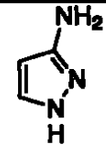
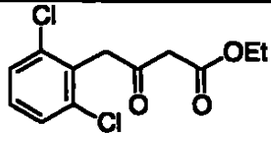
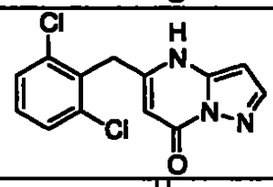
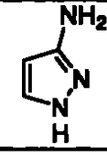
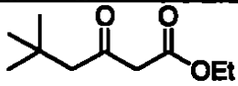
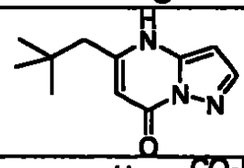
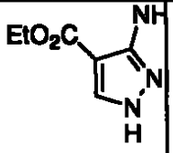
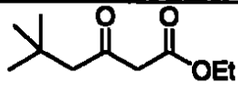
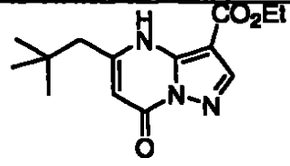
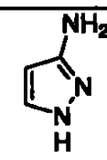
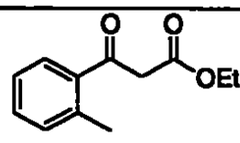
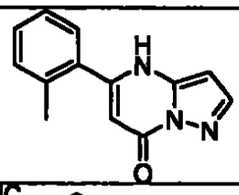
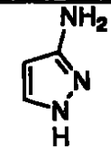
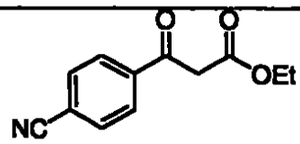
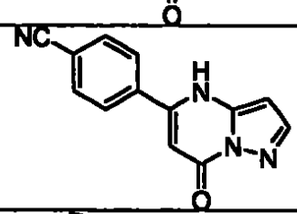
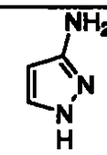
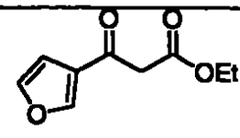
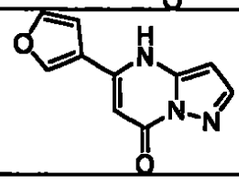
TABLA 5

Ej. Prep.	Columna 2	Columna 3	Columna 4	Columna 5
30				
31				
32				

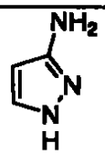
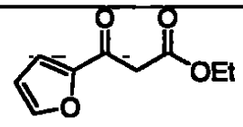
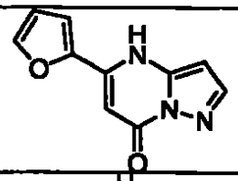
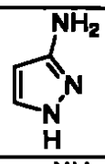
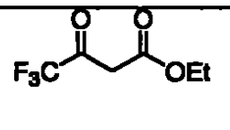
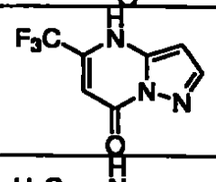
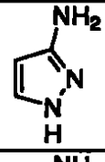
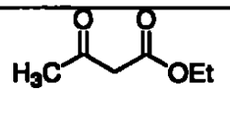
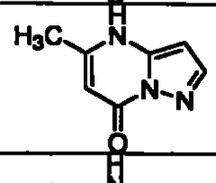
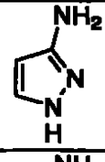
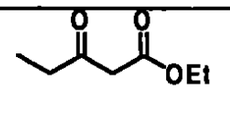
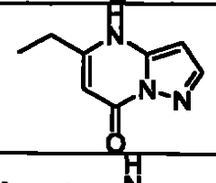
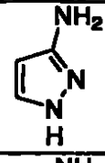
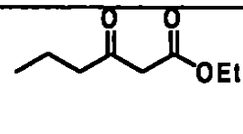
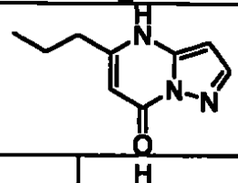
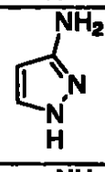
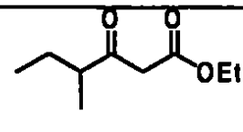
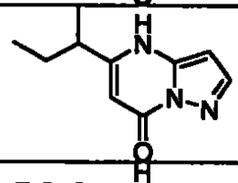
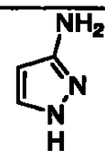
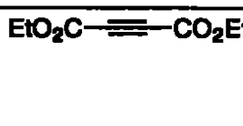
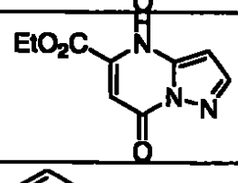
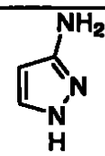
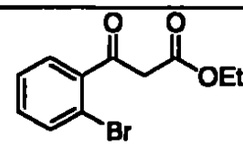
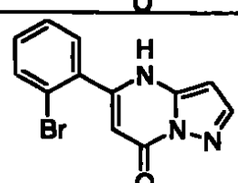
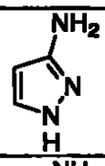
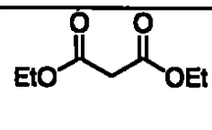
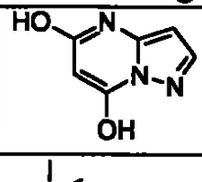
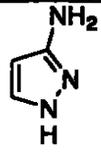
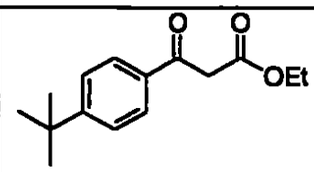
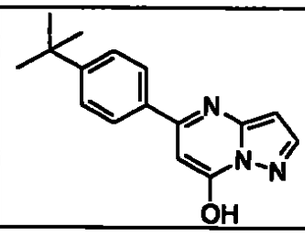
382
383

33				
34				
35				
36				
37				
37.10				
38				
39				
40				

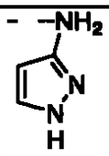
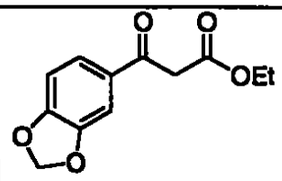
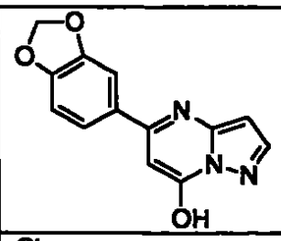
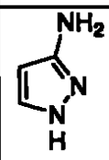
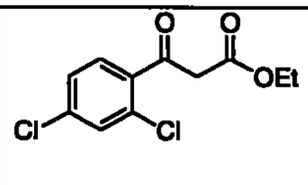
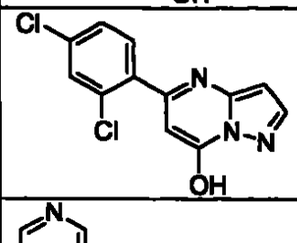
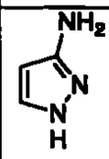
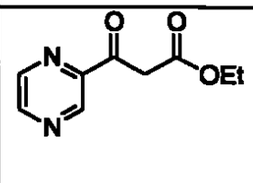
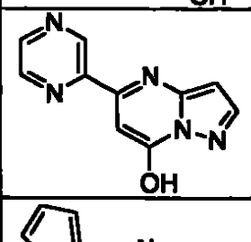
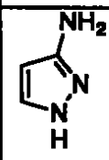
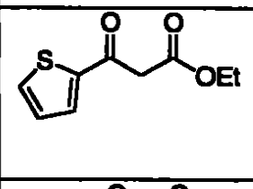
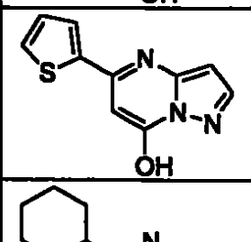
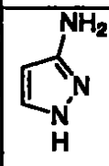
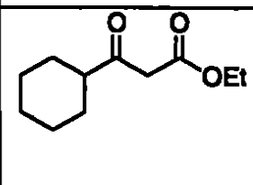
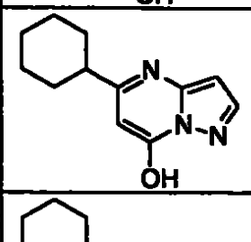
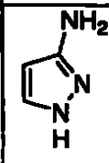
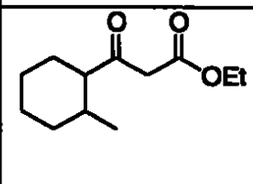
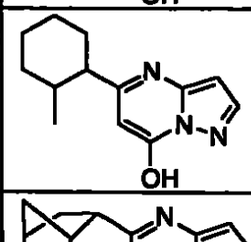
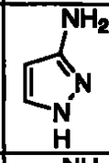
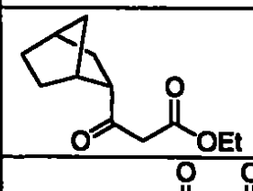
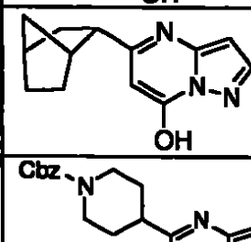
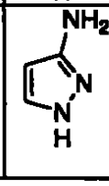
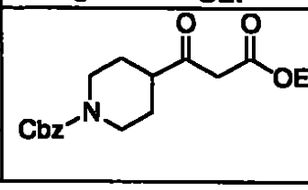
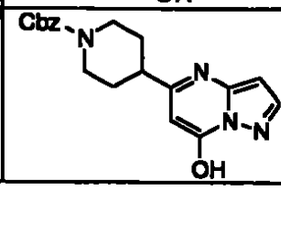
383
384

41				
42				
43				
44				
45				
46				
47				
48				
49				

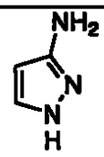
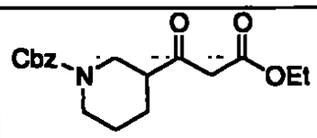
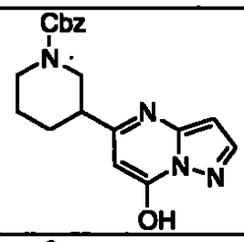
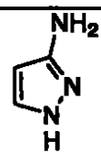
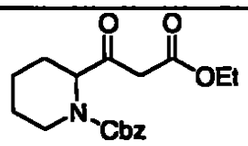
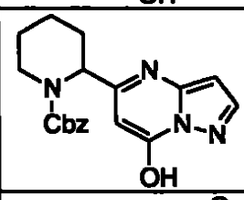
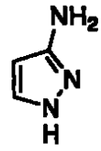
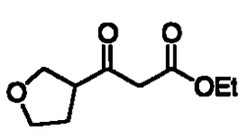
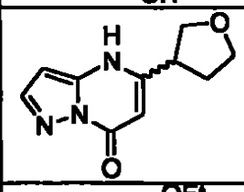
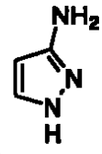
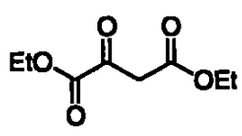
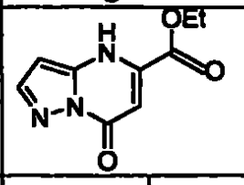
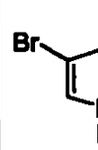
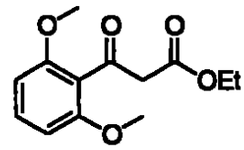
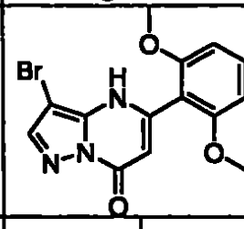
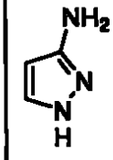
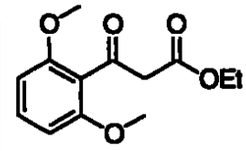
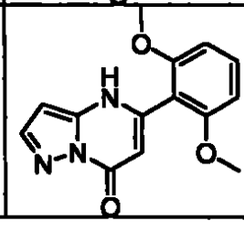
384
385

50				
51				
52				
53				
54				
55				
56				
57				
58				Rend. = 68 MH^+ = 152
59				Rend. = 46 MH^+ = 268

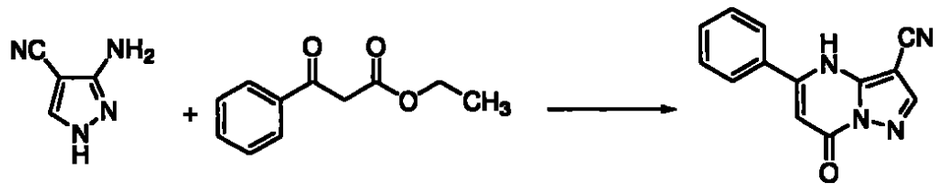
385
386

60				Rend. = 63 MH^+ = 255
61				Rend. = 80 MH^+ = 280
62				Rend. =72 MH^+ = 214
63				Rend. = 51 MH^+ = 218
64				Rend. = 82 MH^+ =218
65				Rend. = 39 MH^+ =232
66				Rend. = 30 MH^+ =230
67				Rend. = 80 MH^+ =353

386
387

68				Rend. = 49 MH^+ =353
69				Rend. = 42 MH^+ =353
70				
71				
72				
73				

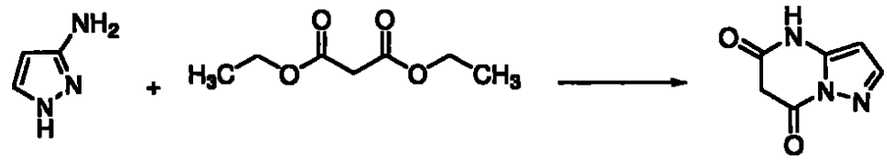
EJEMPLO PREPARATIVO 74:



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 durante 72 horas. La solución resultante se enfrió a temperatura ambiente, se concentró al vacío y se diluyó con EtOAc. El precipitado resultante se filtró, se lavó con

EtOAc, y se secó al vacío (0,47 g, 21% de rendimiento).

EJEMPLO PREPARATIVO 75

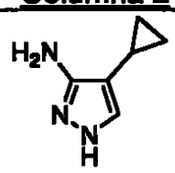
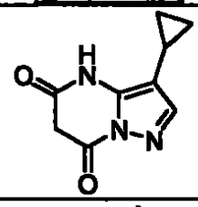
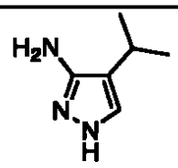
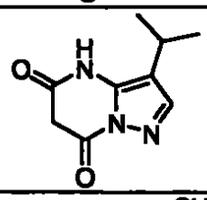
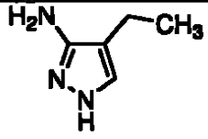
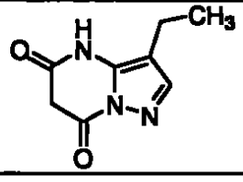


Se siguió el procedimiento de la Patnete Norteamericana Nº 3.907.799. Se agregó sodio (2,3 g, 2 eq.)a EtOH (150 mL) en porciones. Cuando el sodio estuvo completamente disuelto se agregaron 3-aminopirazol (4,2 g, 0,05 mol) y malonato de dietilo (8,7 g, 1,1 eq.) y la solución resultante se calentó a reflujo durante 3 horas. Se enfrió la suspensión resultante a temperatura ambiente y se filtró. La torta de filtro se lavó con EtOH (100 mL) y se disolvió en agua (250 mL). La solución resultante se enfrió en un baño de hielo y se ajustó el pH a 1-2 con HCl concentrado. La suspensión resultante se filtró, se lavó con agua (100 mL) y se secó al vacío para dar un sólido blanco (4.75 g, 63% de rendimiento).

EJEMPLOS PREPARATIVOS 76-78:

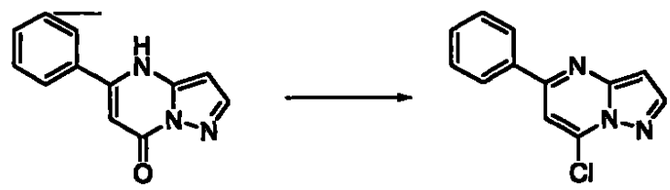
Siguiendo esencialmente el mismo procedimiento indicado en el Ejemplo Preparativo 75 sustituyendo únicamente el compuesto que se muestra en la Columna 2 de la Tabla 6, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 6:

TABLA 6

Ej. Prep.	Columna 2	Columna 3
76		
77		
78		

388
389

EJEMPLO PREPARATIVO 79:

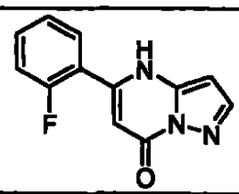
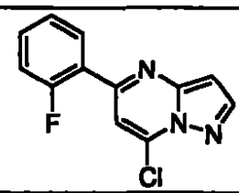
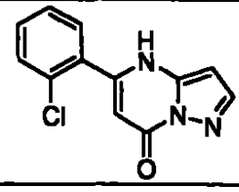
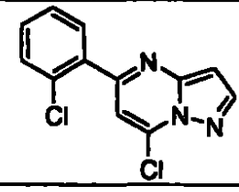


Una solución del compuesto preparado en el Ejemplo Preparativo 29 (1,0 g, 4,73 mmol) en $POCl_3$ (5 mL) y piridina (0.25 mL) se agitó a temperatura ambiente durante 3 días. La suspensión resultante se diluyó con Et_2O, se filtró, y el residuo sólido se lavó con Et_2O. Las lavazas de Et_2O combinadas se enfriaron a 0°C y se trataron con hielo. Cuando cesó la vigorosa reacción, se diluyó la mezcla resultante con H_2O, se separó, y se extrajo la capa acuosa con Et_2O. Los orgánicos combinados se lavaron con H_2O y con NaCl, se secaron sobre Na_2SO_4, se filtraron, y se concentraron para proporcionar un sólido de color amarillo pálido (0,86 g, 79% de rendimiento). LCMS: MH^+=230.

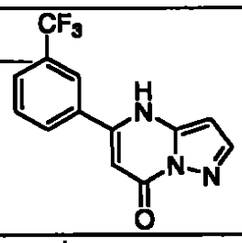
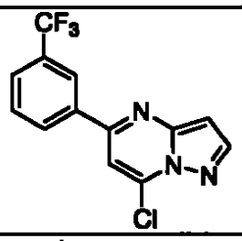
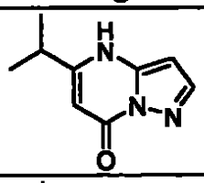
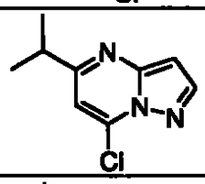
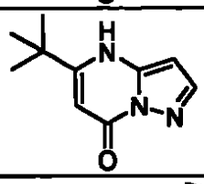
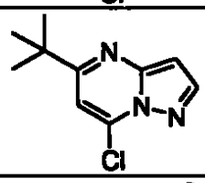
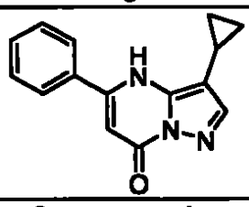
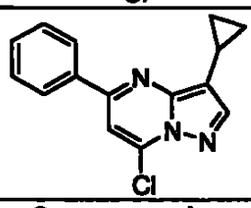
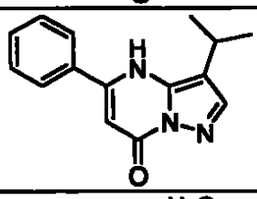
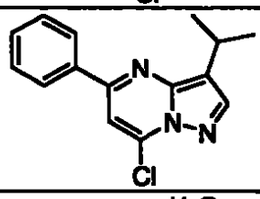
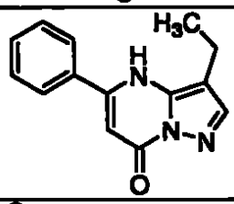
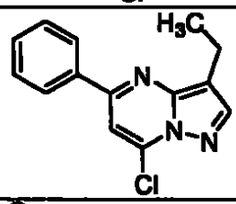
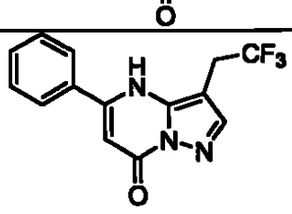
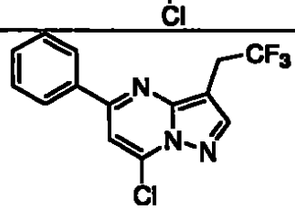
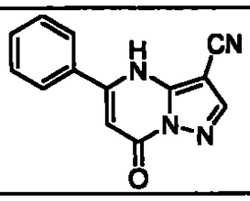
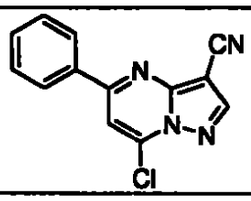
EJEMPLO PREPARATIVO 80-122:

Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo Preparativo 79, sustituyendo únicamente el compuesto que se muestra en la Columna 2 de la Tabla 7, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 7:

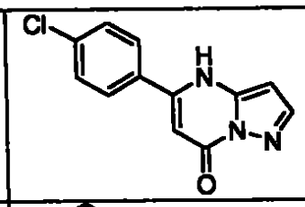
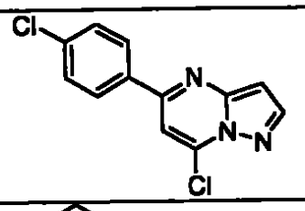
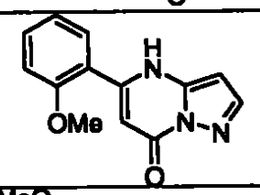
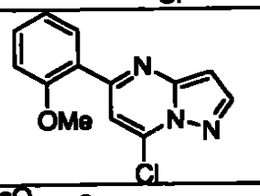
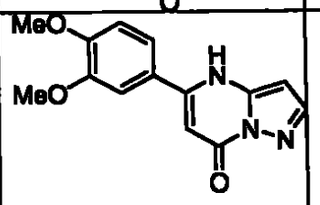
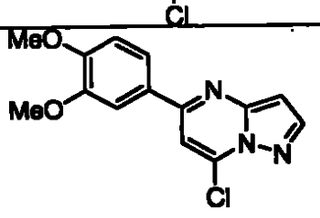
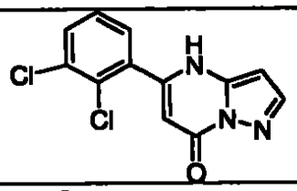
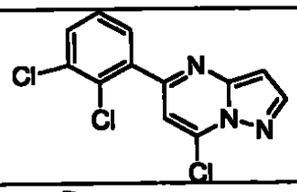
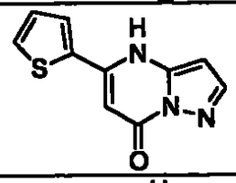
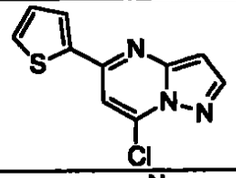
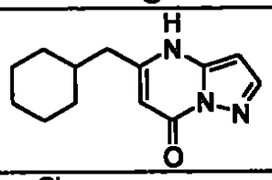
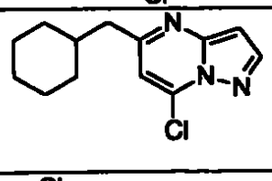
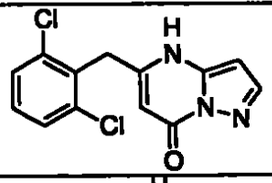
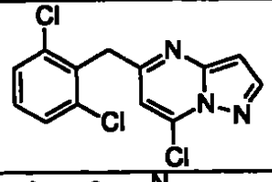
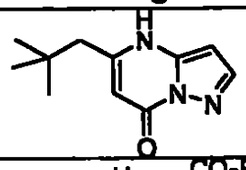
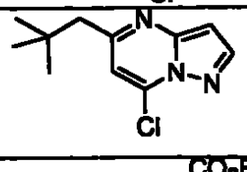
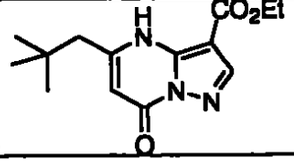
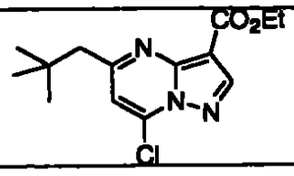
TABLA 7

Ej. Prep.	Columna 2	Columna 3	COMP
80			EM: MH^+=248
81			

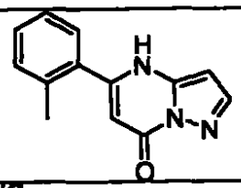
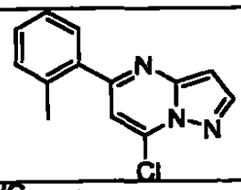
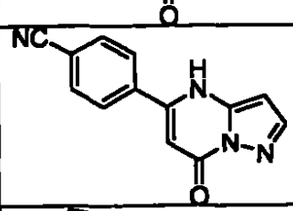
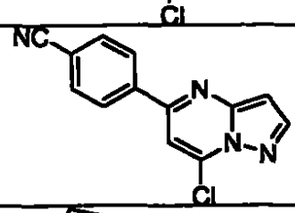
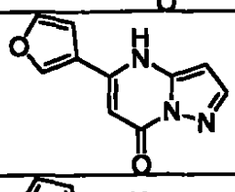
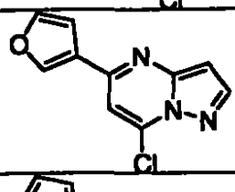
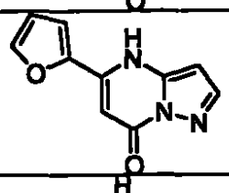
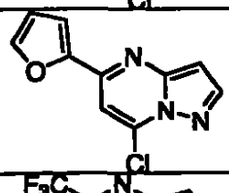
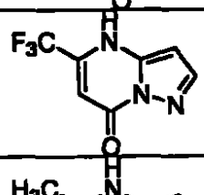
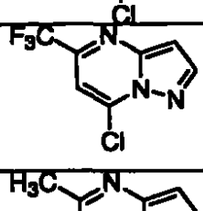
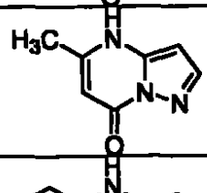
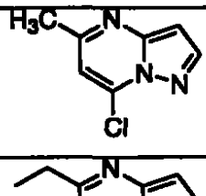
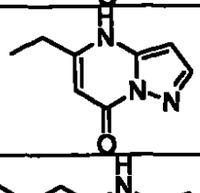
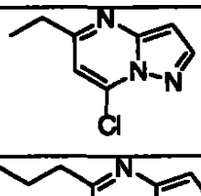
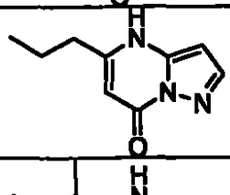
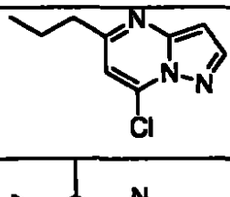
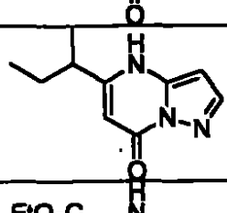
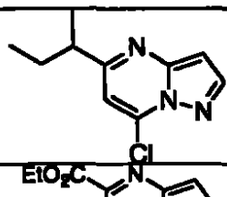
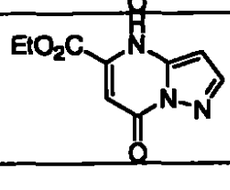
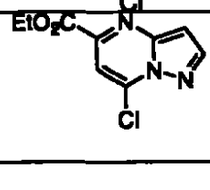
389
390

82			EM: MH^+=298
83			EM: MH^+=196
84			EM: MH^+=210
85			
86			EM: MH^+=272
87			
87.10			
88			EM: MH^+=255

390
391

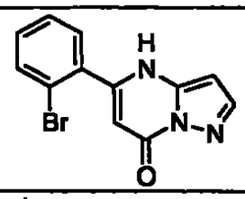
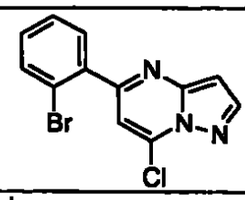
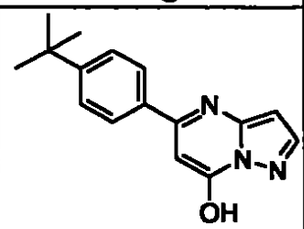
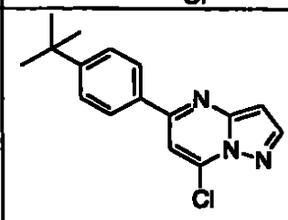
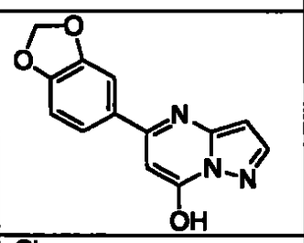
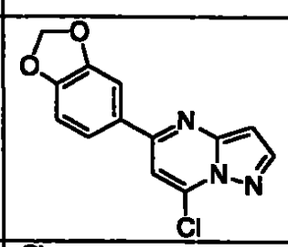
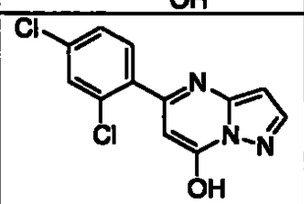
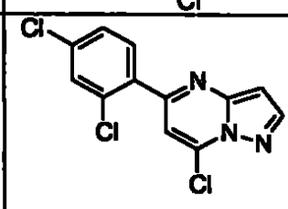
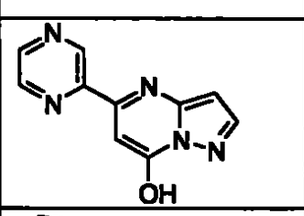
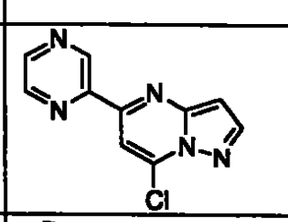
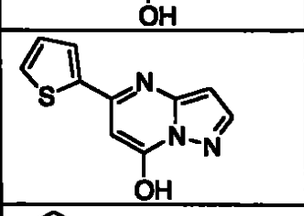
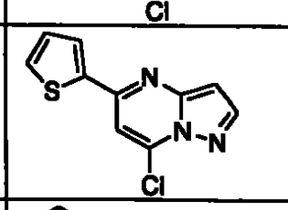
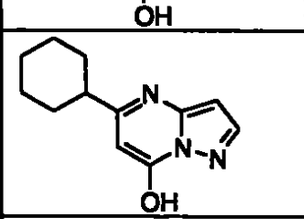
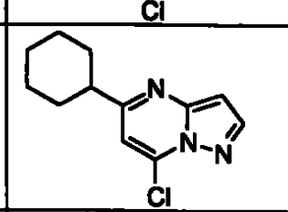
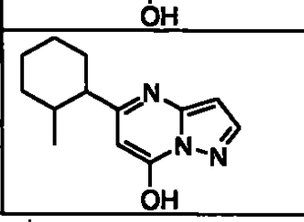
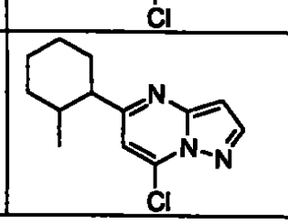
89			
90			Rend. = 65% EM: MH^+ = 260
91			Rend. = 35% EM: MH^+ = 290
92			Rend. = 32% EM: MH^+ = 298
93			Rend. = 45% EM: MH^+ = 236
94			Rend. = 100% LCMS: MH^+ = 250
95			Rend. = 88% EM: MH^+ = 314
96			Rend.=43% EM: MH^+=223
97			Rend.=30% EM: MH^+=295

391
392

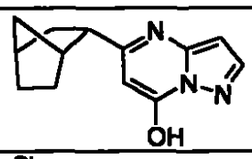
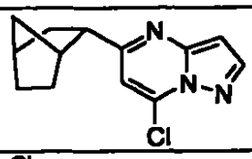
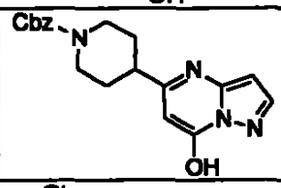
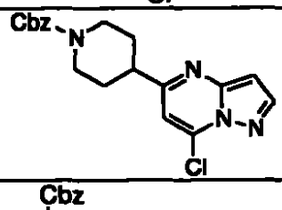
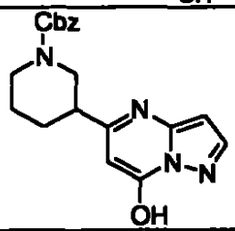
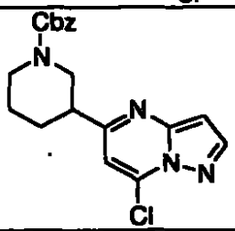
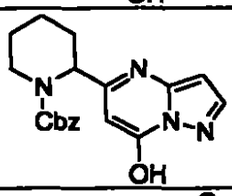
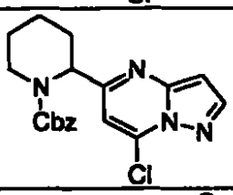
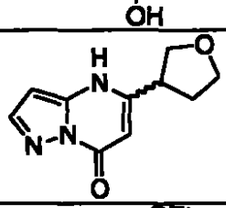
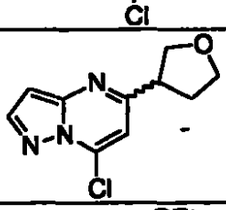
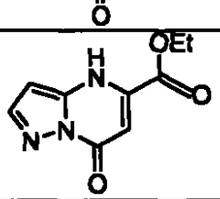
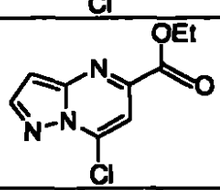
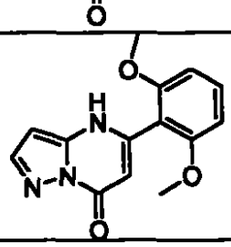
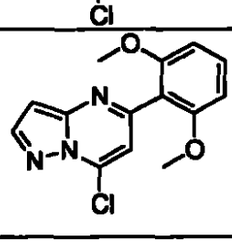
98			Rend.=98% EM: MH^+=244
99			
100			
101			
102			
103			
104			
105			
106			
107			45% Rend.; ME: MH^+=226

392-

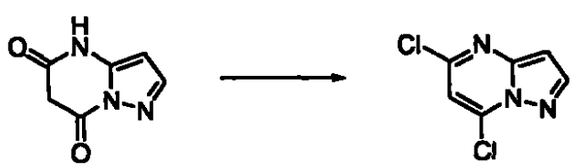
393

108			EM: $MH^+ = 308$
109			Rend. = Cuant. $MH^+ = 286$
110			Rend. = 50 $MH^+ = 272$
111			Rend. = 85 $MH^+ = 299$
112			Rend. = 97 $MH^+ = 231$
113			Rend. = 45 $MH^+ = 236$
114			Rend. = cuant. $MH^+ = 236$
115			Rend. = 57 $MH^+ = 250$

393
394

116			Rend. = 89 MH^+ =248
117			Rend.= 96 MH^+ =371
118			Rend. = 99 MH^+ =371
119			Rend.= 50 MH^+ =371
120			Rend. =57% LCMS: MH^+=224
121			Rend. =34% LCMS: MH^+=226
122			Rend. =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) a 5 °C bajo nitrógeno y dimetilanilina (11,4 g, 2,8

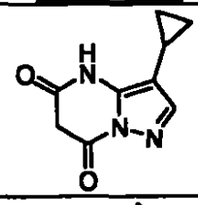
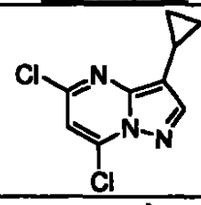
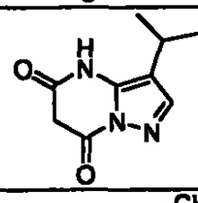
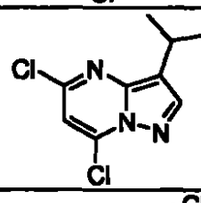
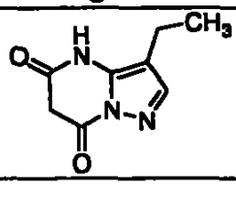
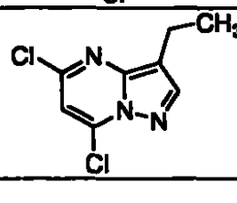
394
395

eq.) y el compuesto preparado en el Ejemplo Preparativo 75 (4,75 g, 0,032 mol). Se calentó la mezcla de reacción a 60°C y se agitó durante la noche. La mezcla de reacción se enfrió a 30°C y se separó por filtración el $POCl_3$ bajo presión reducida. El residuo se disolvió en CH_2Cl_2 (300 mL) y se vertió sobre hielo. Después de agitar durante 15 minutos se ajustó el pH de la mezcla a 7-8 con $NaHCO_3$ sólido. Se separaron las capas y la capa orgánica se lavó con H_2O (3 x 200 mL), se secó sobre $MgSO_4$, se filtró y se concentró. El producto crudo se purificó por cromatografía evaporativa, usando una solución de 50 : 50 CH_2Cl_2 : hexanos como eluyendo para eluir la dimetilanilina. El eluyente fue luego cambiado a 75 : 25 CH_2Cl_2 : hexanos para eluir el producto deseado (4,58 g, 77% de rendimiento). EM: MH^+=188.

EJEMPLOS PREPARATIVO 124-126

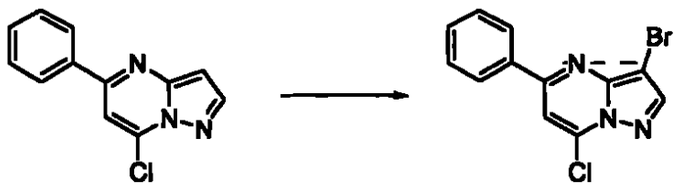
Siguiendo esencialmente el mismo procedimiento indicado en el Ejemplo Preparativo 123 sustituyendo únicamente el compuesto de la Columna 2 de la Tabla 8, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 8:

TABLA 8

Ej. Prep.	Columna 2	Columna 3
124		
125		
126		

EJEMPLO PREPARATIVO 127:

395
396

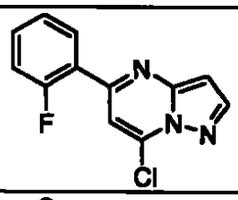
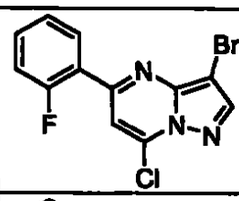
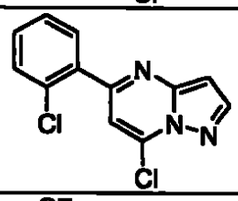
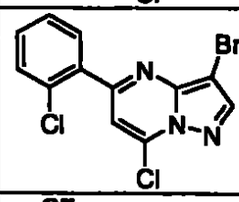
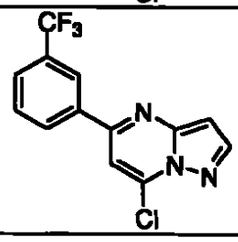
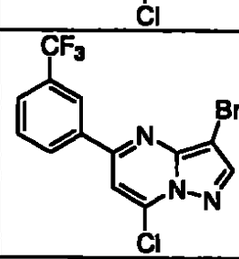


Una solución del compuesto preparado en el Ejemplo Preparativo 79 (0,10 g, 0,435 mmol) en CH_3CN (3 mL) se trató con NBS (0,085 g, 1,1 eq.). La mezcla de reacción se agitó a temperatura ambiente durante 1 hora y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía evaporativa usando una solución al 20% de EtOAc-en-hexanos como eluyente (0.,3 g, 100% de rendimiento). LCMS:MH^+=308.

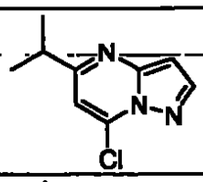
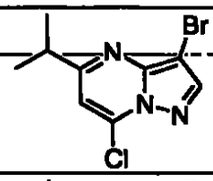
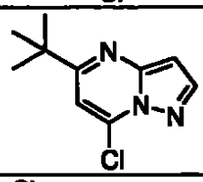
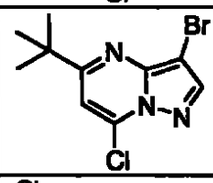
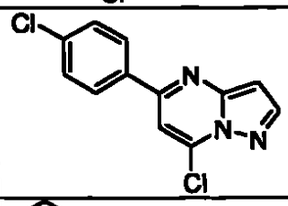
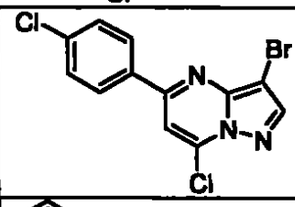
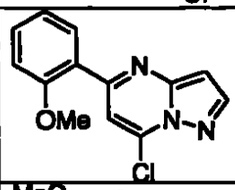
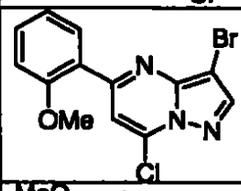
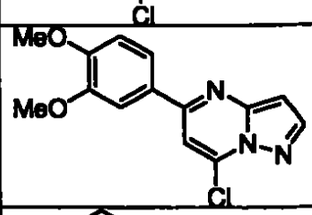
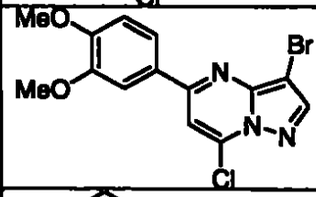
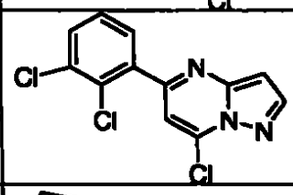
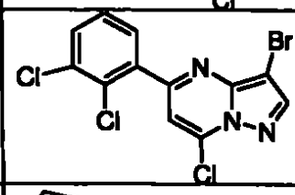
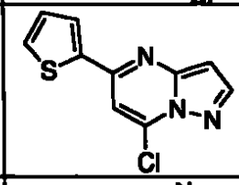
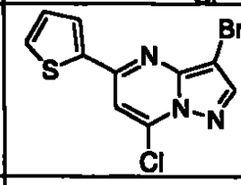
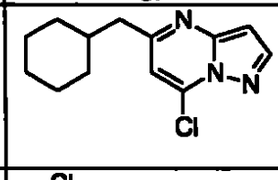
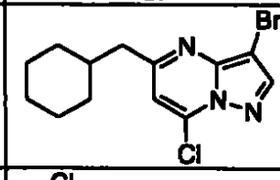
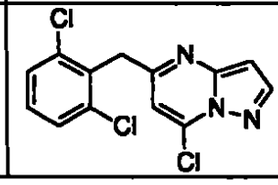
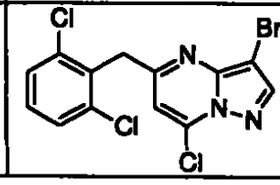
EJEMPLOS PREPARATIVOS 128-164:

Siguiendo esencialmente el mismo procedimiento indicado en el Ejemplo Preparativo 127 sustituyendo únicamente los compuestos que se muestran en la Columna 2 de la Tabla 9, se prepararon los compuestos que se muestran en al Columna 3 de la Tabla 9:

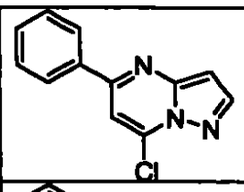
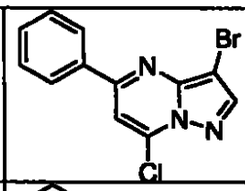
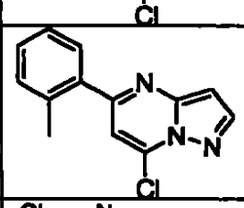
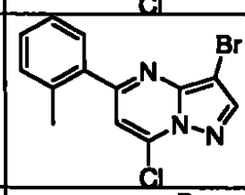
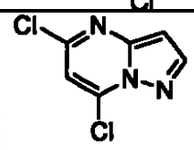
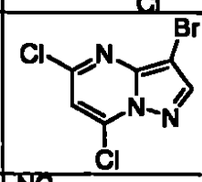
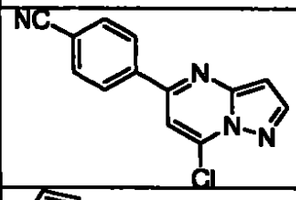
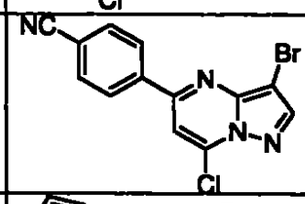
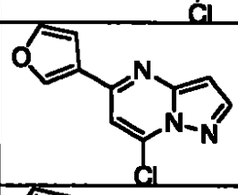
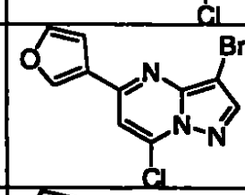
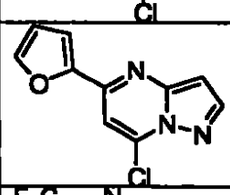
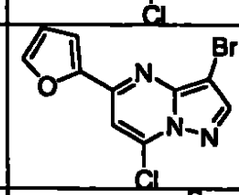
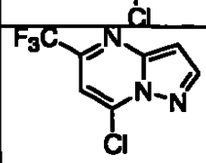
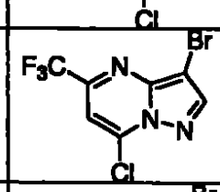
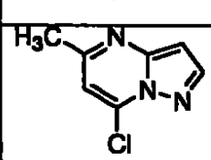
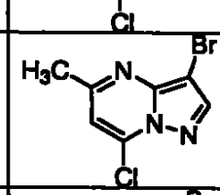
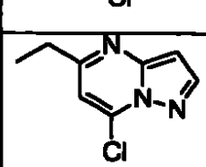
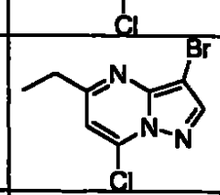
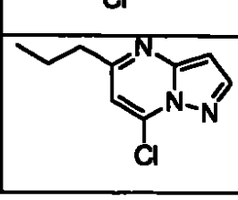
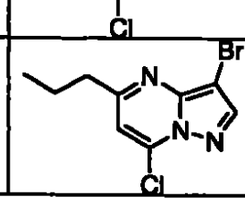
TABLA 9

Ej. Prep.	Columna 2	Columna 3	COMP
128			EM: MH^+= 326
129			ME: MH^+= 342
130			EM: MH^+= 376

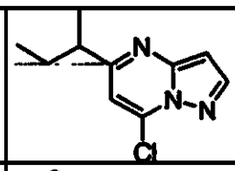
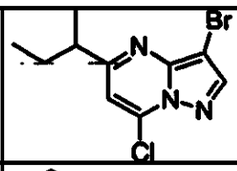
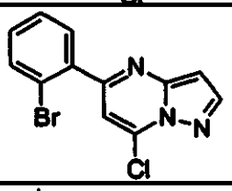
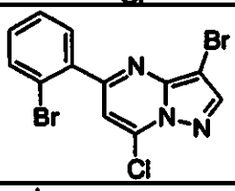
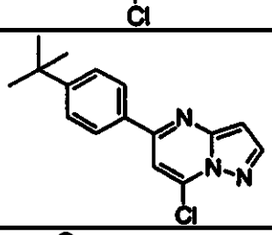
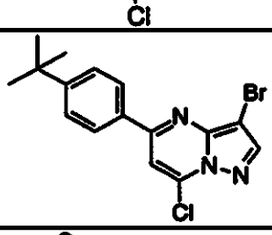
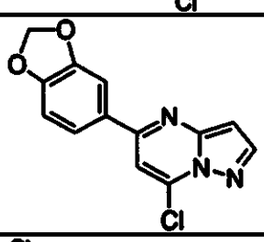
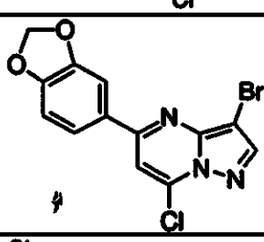
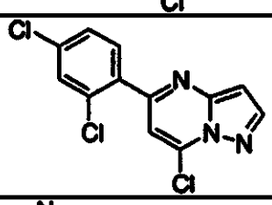
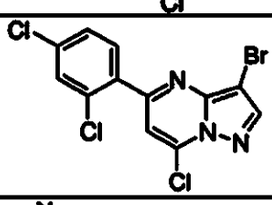
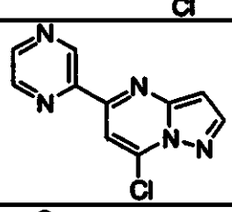
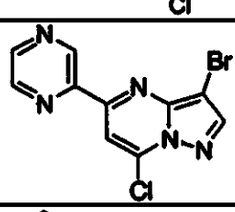
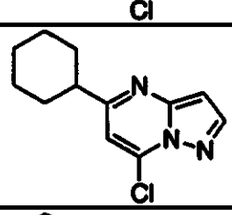
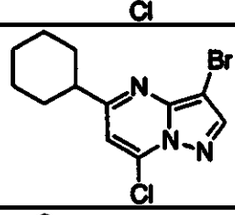
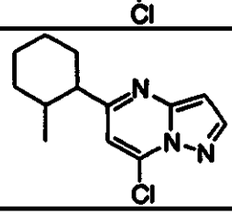
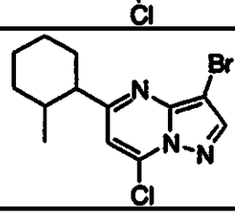
396
397

131			EM: MH^+=274
132			EM: MH^+=288
133			
134			Rend. = 75% EM: MH^+ = 338
135			Rend. = 52% EM: MH^+ = 368
136			Rend. = 87% EM: MH^+ = 376
137			Rend. = 100% EM: MH^+ = 316
138			Rend. = 92% EM: MH^+ = 330
139			Rend. = 82% EM: MH^+ = 395

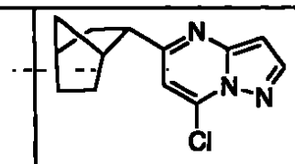
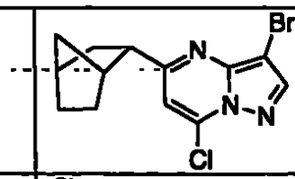
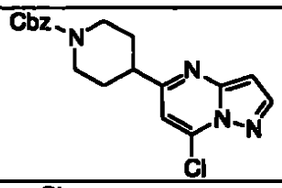
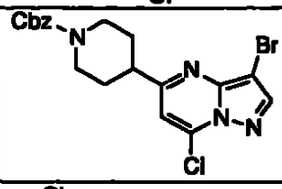
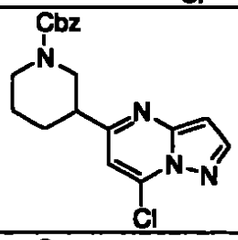
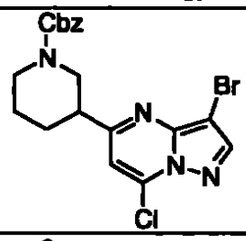
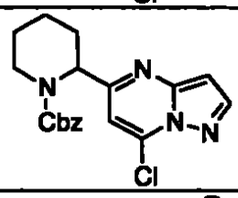
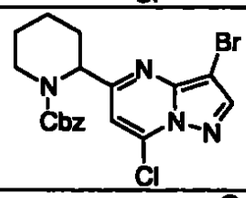
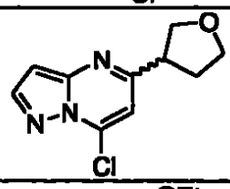
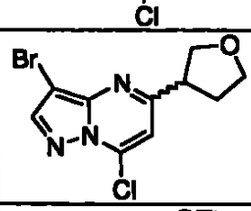
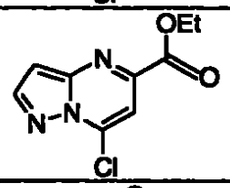
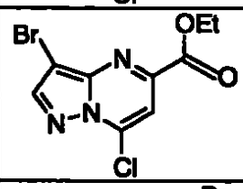
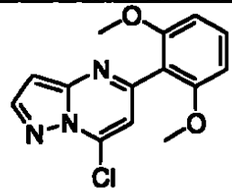
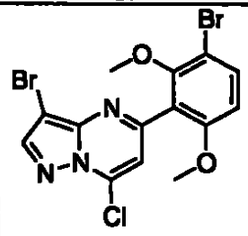
397-
38

140			Rend.=88% EM: MH^+=308
141			Rend.=100% EM: MH^+=322
142			MH^+=266
143			
144			
145			
146			
147			
148			
149			

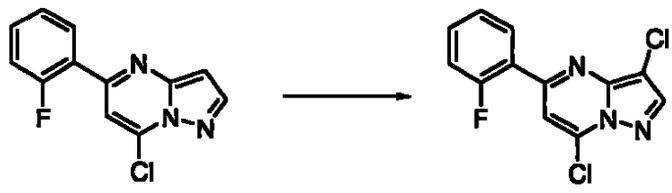
398
399

150			
151			LCMS: MH^+ = 386
152			Rend.= cuant MH^+ = 364
153			Rend.= cuant MH^+ = 353
154			Rend. = 95 MH^+ = 378
155			Rend. = 77 MH^+ = 311
156			Rend.=cuant. MH^+ =314
157			Rend. = 99 MH^+ =328

399
400

158			Rend. = 98 MH^+ =326
159			Rend. = 99 MH^+ =449
160			Rend. = 95 MH^+ =449
161			Rend. = 72 MH^+ =449
162			Rend. =98% LCMS: MH^+=302
163			Rend. =95% LCMS: MH^+=305
164			Rend. =50% ^1H 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:



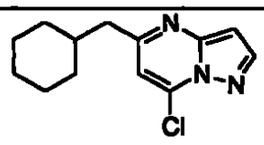
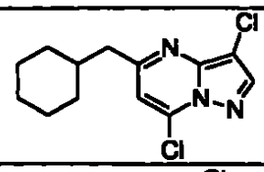
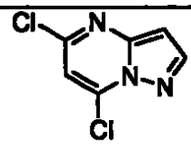
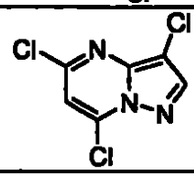
-400-
401

Una solución del compuesto preparado en el Ejemplo Preparativo 80 (0,3 g, 1,2 mmol) en CH_3CN (15 mL) se trató con NCS (0,18 g, 1,1 eq.) y la solución resultante se calentó a reflujo durante 4 horas. Se agregó en NCS adicional (0,032 g, 0,2 eq.) y la solución resultante se agitó a reflujo durante la noche. La mezcla de reacción se enfrió a temperatura ambiente, se concentró al vacío y el residuo se purificó por cromatografía evaporativa usando una solución al 20% de EtOAc en hexanos como eluyente (0,28 g, 83% de rendimiento). LCMS: MH^+= 282.

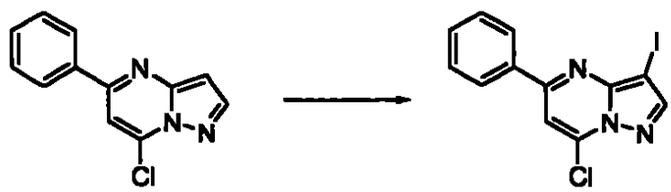
EJEMPLO PREPARATIVO 166-167:

Siguiendo esencialmente el mismo procedimiento indicado en el Ejemplo Preparativo 165 sustituyendo únicamente el compuesto que se muestra en la Columna 2 de la Tabla 10, se preparó el compuesto que se muestra en la Columna 3 de la Tabla 10:

TABLA 10

Ej. Prep.	Columna 2	Columna 3	COMP
166			Rend. = 82% LCMS: MH^+ = 286
167			

EJEMPLO PREPARATIVO 167.10:



401
402

Siguiendo esencialmente el mismo procedimiento del Ejemplo Preparativo 165 sustituyendo únicamente la N-iodosuccinimida, se preparó el compuesto precedente.

EJEMPLO PREPARATIVO 168:

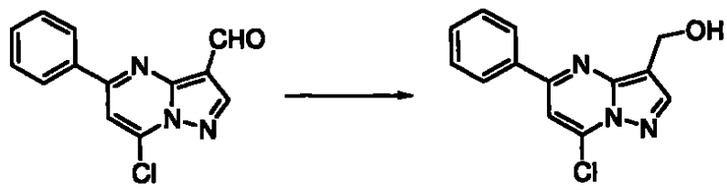
A una solución del compuesto del Ejemplo Preparativo 79 (1,0 g, 4,35 mmol) en DMF (6 mL) se le agregó $POCl_3$ (1,24 mL, 3,05 eq.) y la mezcla resultante se agitó a temperatura ambiente durante la noche. La mezcla de reacción se enfrió a 0ºC y se apagó el exceso de $POCl_3$ mediante adición de hielo. La solución resultante se neutralizó con NaOH 1N, se diluyó con H_2O, y se extrajo con CH_2Cl_2. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron y se concentraron al vacío. El producto crudo se purificó por cromatografía evaporativa usando una solución al 5% de MeOH en CH_2Cl_2 como eluyente (0,95 g, 85% de rendimiento). LCMS: MH^+=258.

EJEMPLO PREPARATIVO 169:

Siguiendo esencialmente el mismo procedimiento del Ejemplo Preparativo 168 sustituyendo únicamente el compuesto preparado en el Ejemplo Preparativo 80, se preparó el compuesto anterior (0,45 g, rendimiento 40%).

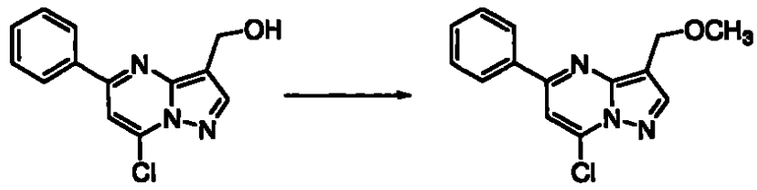
402
403

EJEMPLO PREPARATIVO 170:



A una solución del producto del Ejemplo Preparativo 169 (0,25 g, 0,97 mmol) en THF se le agregó $NaBH_4$ (0,041 g, 1,1 eq.) y la solución resultante se agitó a temperatura ambiente durante la noche. La mezcla de reacción se apagó con 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, y bajo presión reducida. El producto crudo se purificó por cromatografía evaporativa usando una mezcla de 60: 40 de hexanos : EtOAc como eluyente (0,17 g, 69% de rendimiento). ME: MH^+=260.

EJEMPLO PREPARATIVO 171:

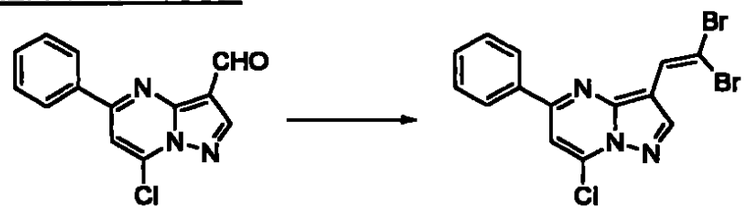


Una solución del compuesto preparado en el Ejemplo Preparativo 170 (0,12 g, 0,462 mmol), sulfate de dimetilo (0,088 mL, 2,0 eq), 50% NaOH (0.26 mL) y Bu_4NBr catalítico in CH_2Cl_2 (4 mL) se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con H_2O y se extrajo con CH_2Cl_2.

403
404

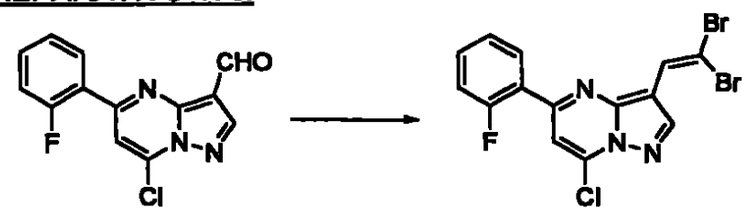
Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por cromatografía evaporativa usando una solución al 30% de EtOAc-en-hexanos como eluyente (0,062 g, 48% de rendimiento).

EJEMPLO PREPARATIVO 172



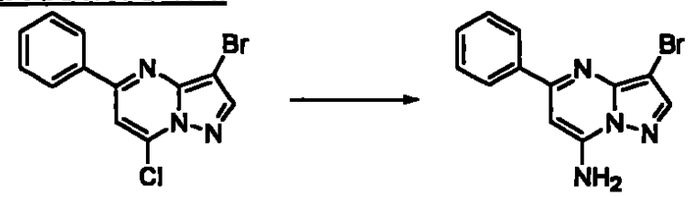
A una solución de PPh_3 (4,07 g, 4,0 eq.) y CBr_4 (2,57 g, 2,0 eq.) en CH_2Cl_2 (75 mL) a 0°C se le agregó el compuesto preparado en el Ejemplo Preparativo 168 (1,0 g, 3,88 mmol). La solución resultante se agitó a 0°C durante 1 hora y se concentró bajo presión reducida. El residuo se purificó por cromatografía evaporativa usando una solución al 20% de EtOAc en hexanos como eluyente (1,07 g, 67% de rendimiento).

EJEMPLO PREPARATIVO 173:



Esencialmente con el mismo procedimiento que se indica en el Ejemplo Preparativo 172 sustituyendo únicamente el compuesto preparado en el Ejemplo Preparativo 169 se preparó el compuesto anterior (0,5 g, 70% de rendimiento).

EJEMPLO PREPARATIVO 174:



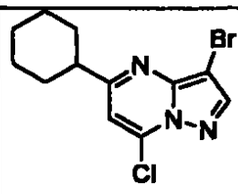
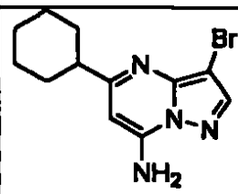
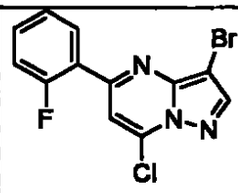
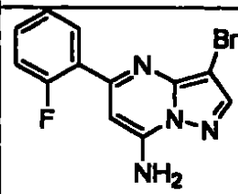
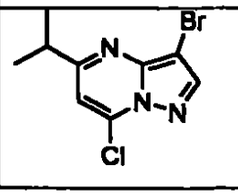
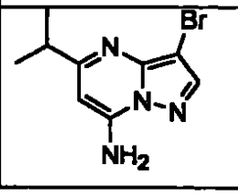
404
405

El compuesto preparado en el Ejemplo Preparativo 127 (3,08 g, 10,0 mmol), 2,0 M NH_3 en 2-propanol (50 mL, 100,0 mmol), y NH_3 acuoso al 37% (10,0 mL) se agitaron en un recipiente cerrado bajo presión a 50°C durante 1 día. El solvente se evaporó y el producto crudo se purificó por cromatografía evaporativa usando 3:1 de CH_2Cl_2:EtOAc como eluyente. Se obtuvo un sólido de color amarillo pálido (2,30 g, 80%). LCMS: M^+=289.

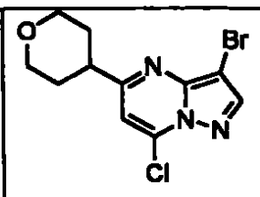
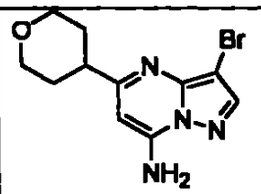
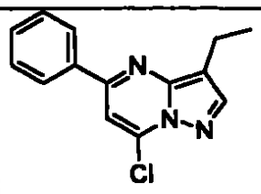
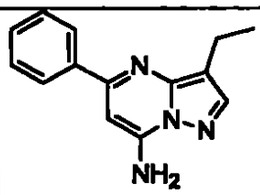
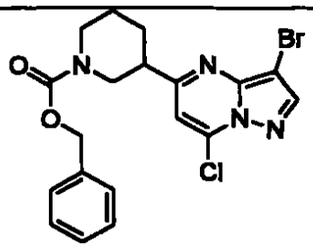
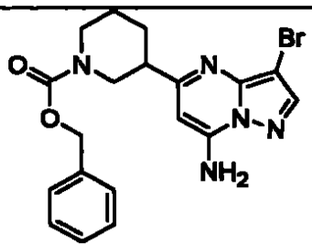
EJEMPLOS PREPARATIVOS 175-180:

Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo Preparativo 174 sustituyendo únicamente el compuesto que se muestra en la Columna 2 de la Tabla 11, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 11.

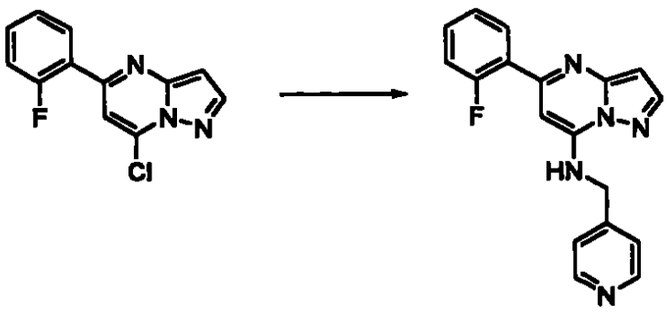
TABLA 11

Ej. Prep.	Columna 2	Columna 3
175		
176		
177		

405
406

178		
179		
180		

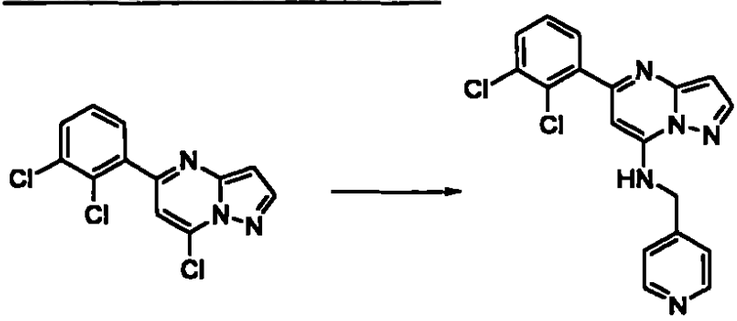
EJEMPLO PREPARATIVO 181:



Se calentaron 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.) a reflujo durante la noche. La mezcla de reacción se enfrió a temperatura ambiente y se concentró bajo presión reducida. El residuo se diluyó con H_2O y se extrajo con CH_2Cl_2. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron y, se concentraron. Se purificó el producto crudo por cromatografía evaporativa usando una solución al 5% (10% NH_4OH en MeOH) en CH_2Cl_2 como eluyente (0,051 g, 40% de rendimiento). LCMS: MH^+=320.

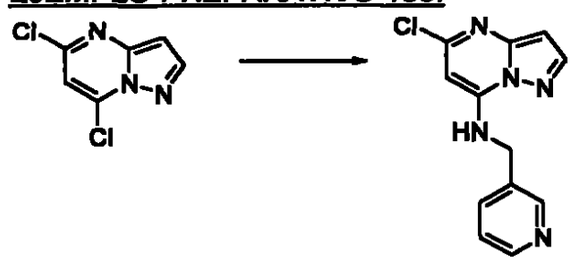
406
407

EJEMPLO PREPARATIVO 182:



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

EJEMPLO PREPARATIVO 183:



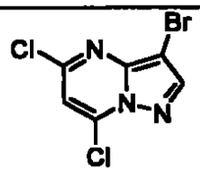
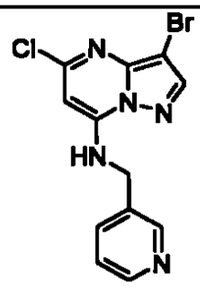
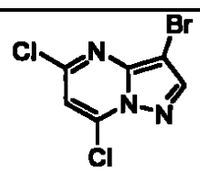
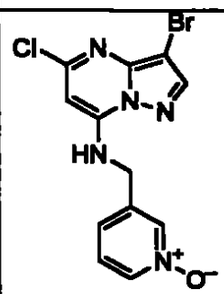
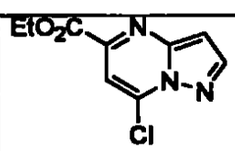
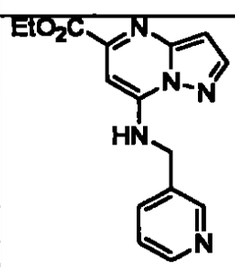
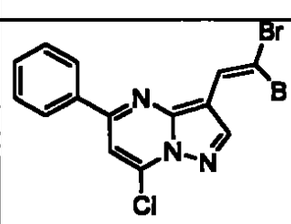
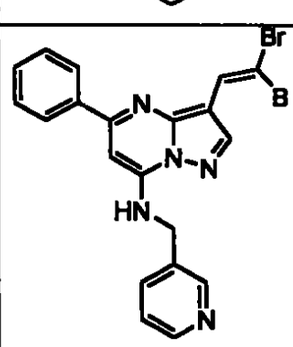
A una solución del compuesto preparado en el Ejemplo Preparativo 123 (0,25 g, 1,3 mmol) en dioxano (5 mL) se le agregó Pr_2NEt (0,47 mL, 2,0 eq.) y 3-aminometilpiridina (0,15 ml, 1,1 eq.). La solución resultante se agitó a temperatura ambiente durante 72 horas. La mezcla de reacción se diluyó con H_2O y se extrajo con EtOAc. Se lavaron los orgánicos combinados con H_2O y con NaCl saturado, se secaron sobre Na_2SO_4, se filtraron, y se concentraron al vacío. Se purificó el producto crudo por cromatografía evaporativa usando una solución como eluyente al 5% de MeOH en CH_2Cl_2 (0,29 g, 83% de rendimiento). EM: MH^+=260.

EJEMPLOS PREPARATIVOS 184-187:

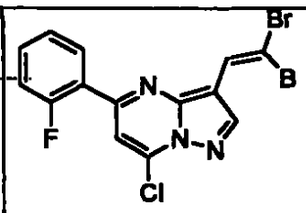
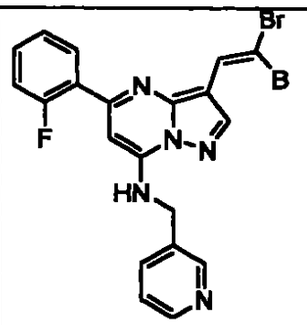
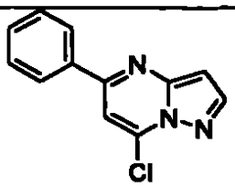
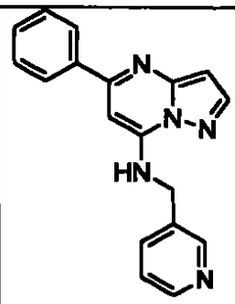
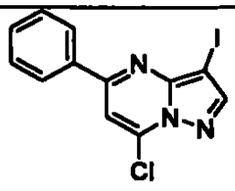
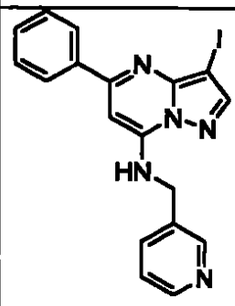
Esencialmente con el mismo procedimiento indicado en el Ejemplo Preparativo 183 sustituyendo únicamente el compuesto que se muestra en la Columna 2 de la Tabla 12, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 12.

407
408

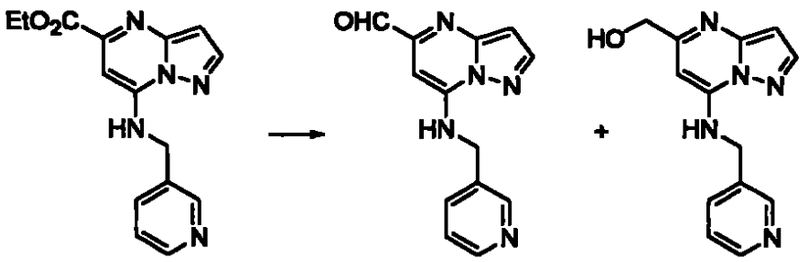
TABLA 12

Ej. Prep.	Columna 2	Columna 3
184		
184.1		
185		
186		

408
409

187		
187.1		
187.11		

EJEMPLO PREPARATIVO 188 Y EJEMPLO PREPARATIVO 189:



A una solución del compuesto preparado en el Ejemplo Preparativo 185 (1,18 g, 3,98 mmol) en THF (35 mL) a -78°C se le agregó LAH (4,78 mL, 1M en Et_2O, 1,0 eq.) por goteo. Se agitó la mezcla de reacción a -78°C durante 3 horas durante cuyo tiempo se agregó LAH adicional (2,0 mL, 1M en Et_2O, 0,42 eq.) por goteo. La mezcla de reacción se agitó durante 1,25 horas adicionales y se apagó por adición de Na_2SO_4 saturado (8,5 mL). La mezcla de reacción se diluyó con

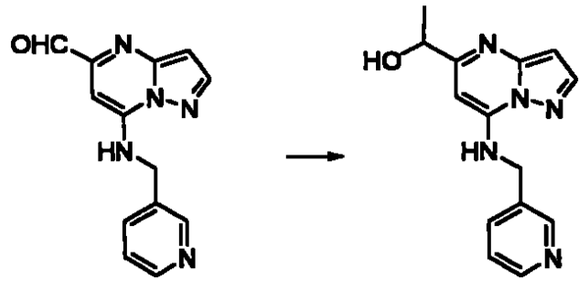
409
410

EtOAC (23 mL), H_2O (2 mL), y CH_3OH (50 mL). La suspensión resultante se filtró a través de un tapó de Celite. El Celite se lavó con CH_3OH y el filtrado se secó con Na_2SO_4, se filtró, y se concentró. El producto se purificó por cromatografía evaporativa usando una solución de CH_2Cl_2 : CH_3OH (93 : 7) como eluyente para proporcionar el aldehido como primer producto de elución y alcohol como segundo producto de elución.

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

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

EJEMPLO PREPARATIVO 190:



A una solución del compuesto preparado en el Ejemplo Preparativo 188 (0,075 g, 0,30 mmol) en THF (2,0 mL) a 0°C se le agregó una solución de CH_3MgBr (0,3 mL, 3,0M en Et_2O, 3,0 eq.) por goteo. La solución resultante se agitó a 0°C durante 1,5 horas adicionales, se calentó a temperatura ambiente, y se agitó durante la noche. Se agregó CH_3MgBr adicional (0,15 mL, 3,0M en Et_2O, 1. eq.) la solución resultante se agitó durante 1, 5 horas adicionales. La mezcla de reacción se enfrió a 0°C y se apagó por adición de NH_4Cl saturado. La solución resultante se diluyó con CH_2Cl_2 y H_2O y se extrajo con CH_2Cl_2. Los orgánicos combinados se lavaron con NaCl saturado y se secaron sobre Na_2SO_4, se filtraron, y se concentraron. El producto crudo se purificó por cromatografía evaporativa usando una solución de CH_2Cl_2 : CH_3OH (90 : 10) como eluyente (0,048 g, 60% de rendimiento). EM: MH^+ = 270.

EJEMPLO PREPARATIVO 191:

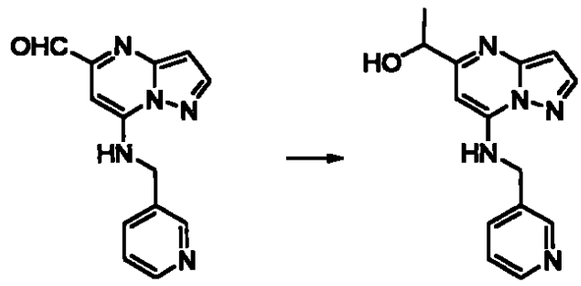
409
410

EtOAC (23 mL), H_2O (2 mL), y CH_3OH (50 mL). La suspensión resultante se filtró a través de un tapó de Celite. El Celite se lavó con CH_3OH y el filtrado se secó con Na_2SO_4, se filtró, y se concentró. El producto se purificó por cromatografía evaporativa usando una solución de CH_2Cl_2 : CH_3OH (93 : 7) como eluyente para proporcionar el aldehido como primer producto de elución y alcohol como segundo producto de elución.

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

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

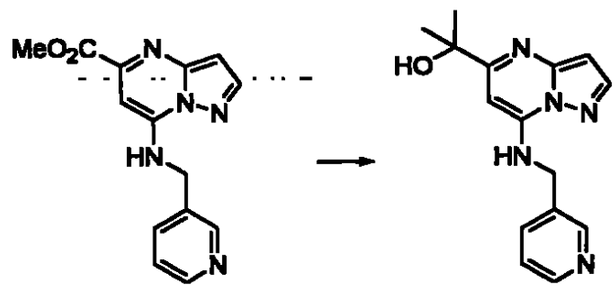
EJEMPLO PREPARATIVO 190:



A una solución del compuesto preparado en el Ejemplo Preparativo 188 (0,075 g, 0,30 mmol) en THF (2,0 mL) a 0°C se le agregó una solución de CH_3MgBr (0,3 mL, 3,0M en Et_2O, 3,0 eq.) por goteo. La solución resultante se agitó a 0°C durante 1,5 horas adicionales, se calentó a temperatura ambiente, y se agitó durante la noche. Se agregó CH_3MgBr adicional (0,15 mL, 3,0M en Et_2O, 1. eq.) la solución resultante se agitó durante 1, 5 horas adicionales. La mezcla de reacción se enfrió a 0°C y se apagó por adición de NH_4Cl saturado. La solución resultante se diluyó con CH_2Cl_2 y H_2O y se extrajo con CH_2Cl_2. Los orgánicos combinados se lavaron con NaCl saturado y se secaron sobre Na_2SO_4, se filtraron, y se concentraron. El producto crudo se purificó por cromatografía evaporativa usando una solución de CH_2Cl_2 : CH_3OH (90 : 10) como eluyente (0,048 g, 60% de rendimiento). EM: MH^+ = 270.

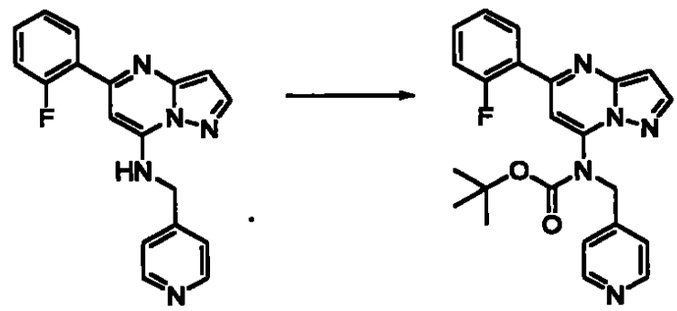
EJEMPLO PREPARATIVO 191:

410
411



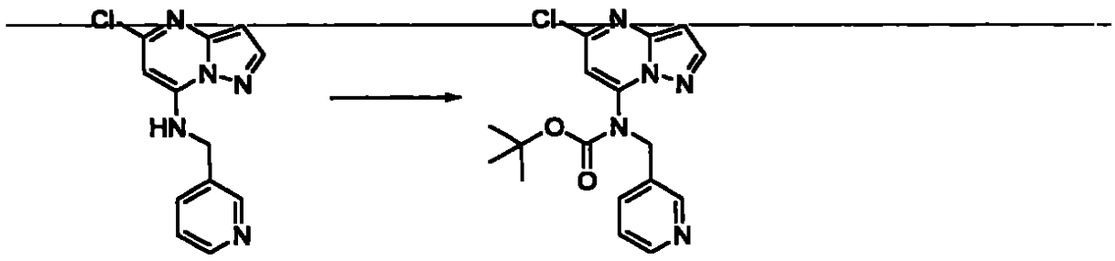
Con esencialmente el mismo procedimiento indicado en el Ejemplo Preparativo 190, sustituyendo únicamente el compuesto preparado en el Ejemplo Preparativo 185 y usando un exceso de MeMgBr (5 eq.), se preparó el compuesto anterior.

EJEMPLO PREPARATIVO 192:



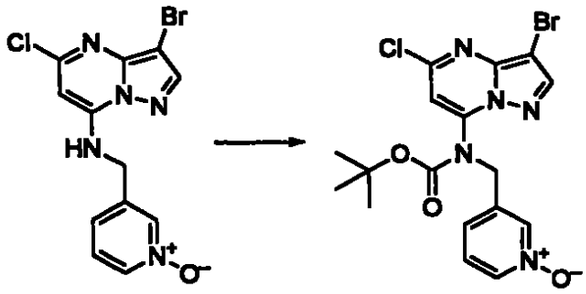
El compuesto preparado en el Ejemplo Preparativo 181 (0,29 g, 0,91 mmol), BOC_2O (0.22 g, 1,1 eq), y DMAP (0,13 g, 1,1 eq.) en dioxano (10 mL) se agitó a temperatura ambiente durante 3 días. Se agregó BOC_2O (0,10g, 0,5 eq.) adicional y la mezcla de reacción se agitó durante 4 horas. La mezcla de reacción se concentró *al vacío*, se diluyó con $NaHCO_3$ saturado (15 mL), y se extrajo con CH_2Cl_2 (2 x 100 mL). Se secaron los orgánicos combinados sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por cromatografía evaporativa usando una solución al 5% (10% NH_4OH en MeOH) en CH_2Cl_2 como eluyente (0,35 g, 91% de rendimiento). LCMS: MH^+= 420.

EJEMPLO PREPARATIVO 193:



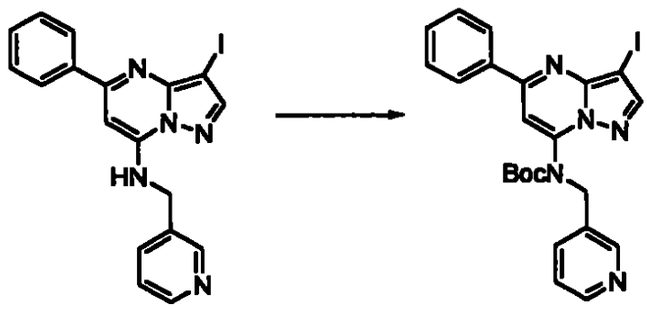
Esencialmente con el mismo procedimiento indicado en el Ejemplo Preparativo 192 sustituyendo únicamente el compuesto preparado en el Ejemplo Preparativo 183, se preparó el compuesto anterior. EM: MH^+ = 360.

EJEMPLO PREPARATIVO 193.10:



Esencialmente con el mismo procedimiento indicado en el Ejemplo Preparativo 192 sustituyendo únicamente el compuesto preparado en el Ejemplo Preparativo 184.1, se preparó el compuesto anterior. ES: MH^+ = 454.

EJEMPLO PREPARATIVO 194:

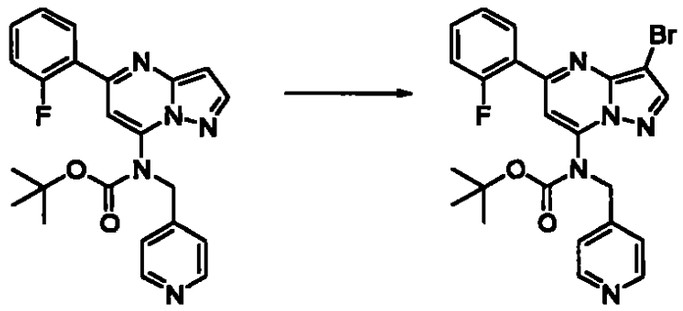


Esencialmente con el mismo procedimiento indicado en el Ejemplo Preparativo 192 sustituyendo únicamente el compuesto anterior preparado en el

412
413

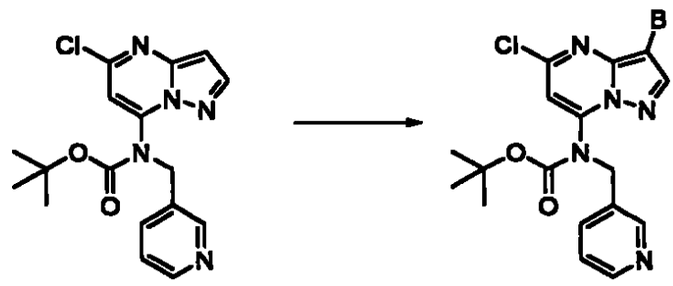
187.11, se preparó el compuesto anterior (0,223 g, 88% de rendimiento). ES: MH^+ = 528.

EJEMPLO PREPARATIVO 195:



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

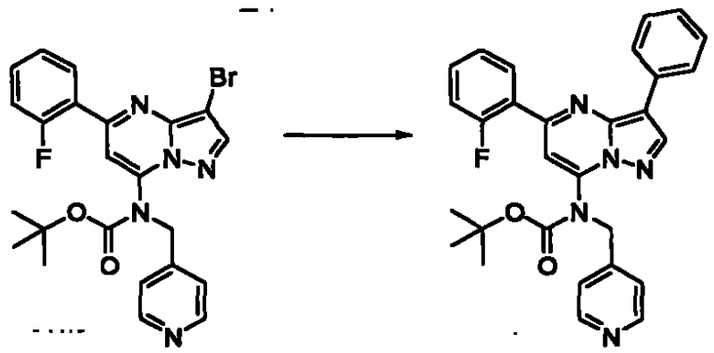
EJEMPLO PREPARATIVO 196:



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

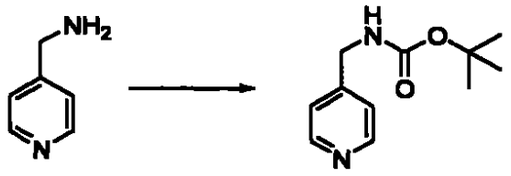
413
414

EJEMPLO PREPARATIVO 197:



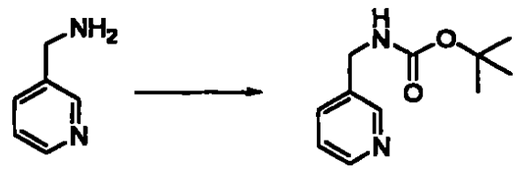
Una solución del compuesto preparado en el Ejemplo Preparativo 195 (0,15 g, 0,3 mmol), ácido fenilborónico (0,073 g, 2,0 eq.), K_3PO_4 (0,19 g, 3,0 eq.), y $Pd(PPh_3)_4$ (0,017 g, 5 mol %) se calentó a reflujo en DME (16 mL) y H_2O (4 mL) durante 7 horas. La solución resultante se enfrió a temperatura ambiente, se diluyó con H_2O (10 mL), y se extrajo con CH_2Cl_2 (3 x 50 mL). Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, y se concentraron. El producto crudo se purificó por cromatografía evaporativa usando 2,5% (10% NH_4OH en MeOH) en solución de CH_2Cl_2 como eluyente (0,16 g, 100% de rendimiento).

EJEMPLO PREPARATIVO 198:



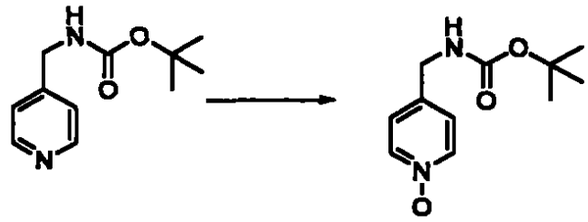
A una solución de 4-aminometilpiridina (1,41 mL, 13,87 mmol) en CH_2Cl_2 (50 mL) se le agregó BOC_2O (3,3 g, 1,1 eq.) y TEA y la solución resultante se agitó a temperatura ambiente durante 2 horas. La mezcla de reacción se diluyó con H_2O (50 mL) y se extrajo con CH_2Cl_2. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron y se concentraron bajo presión reducida. El producto crudo se purificó por cromatografía evaporativa usando una solución al 5% (10% NH_4OH en MeOH) en CH_2Cl_2 como eluyente para proporcionar un sólido de color amarillo (2,62 g, 91% de rendimiento). LCMS: MH^+= 209.

EJEMPLO PREPARATIVO 199:



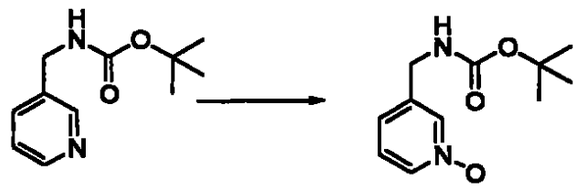
Esencialmente con el mismo procedimiento indicado en el Ejemplo Preparativo 198 sustituyendo únicamente 3-aminometilpiridina, se preparó el compuesto anterior en forma de un aceite de color amarillo (2,66 g, 92% de rendimiento). LCMS: MH^+= 209.

EJEMPLO PREPARATIVO 200:



A una solución del compuesto preparado en el Ejemplo Preparativo 198 (0,20 g, 0,96 mmol) en CH_2Cl_2 (5 mL) a 0°C se le agregó *m*-CPBA (0,17 g, 1,0 eq) y la solución resultante se agitó a 0°C durante 2 horas y se almacenó a 4°C durante la noche durante cuyo tiempo la mezcla de reacción se calentó a temperatura ambiente y se agitó durante 3 horas. La mezcla de reacción se diluyó con H_2O y se extrajo con CH_2Cl_2. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, y se concentraron. El producto crudo se purificó por cromatografía evaporativa usando una solución al 10% (10% NH_4OH en MeOH) como eluyente: LCMS: MH^+= 255.

EJEMPLO PREPARATIVO 201:

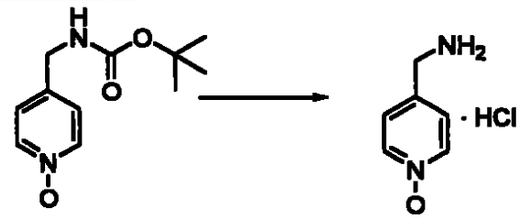


Una solución de oxona (58,6 g) en H_2O (250 mL) se agregó por goteo al compuesto preparado en el Ejemplo Preparativo 199 (27 g, 0,13 mol) y $NaHCO_3$

415
416

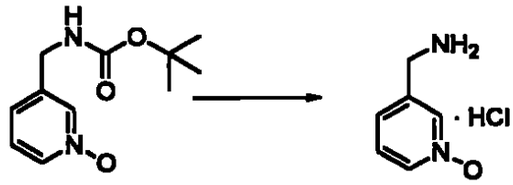
(21,8 g, 2,0 eq.) en MeOH (200 mL) y H_2O (250 mL). La solución resultante se agitó a temperatura ambiente durante la noche. La mezcla de reacción se diluyó con CH_2Cl_2 (500 mL) y se filtró. Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida para proporcionar un sólido blanco (21,0 g, 72% de rendimiento). ES: MH^+= 255.

EJEMPLO PREPARATIVO 202:



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

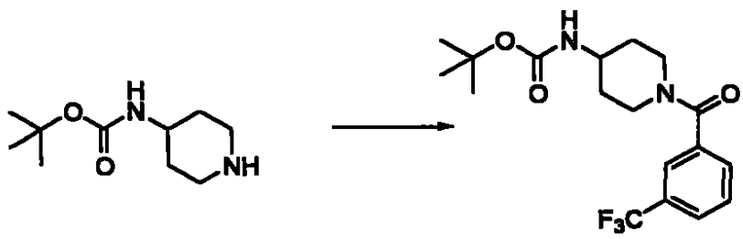
EJEMPLO PREPARATIVO 203:



Esencialmente con el mismo procedimiento indicado en el Ejemplo Preparativo 202 sustituyendo únicamente el compuesto preparado en el Ejemplo Preparativo 201, se preparó el compuesto que se muestra precedentemente. LCMS: MH^+= 125.

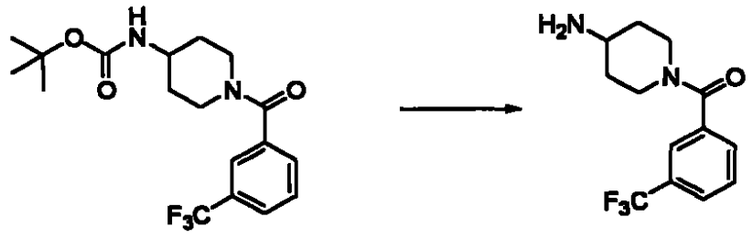
EJEMPLO PREPARATIVO 204:

416
417



A 4-N-t-Butoxicarbonilaminopiperidina (0,8 g, 4,0 mmol) en CH_2Cl_2 (10 mL) a 0°C se le agregó TEA (1,40 mL, 2,5 eq.) y cloruro de 3-trifluormetilbenzoilo (1,05 g, 1,25 eq.). La solución resultante se agitó durante 15 minutos y se calentó a temperatura ambiente y se agitó durante 3 horas. La mezcla de reacción se diluyó con CH_2Cl_2 y se lavó con 5% de Na_2CO_3 (2 x 100 mL). La capa orgánica se secó sobre Na_2SO_4, se filtró y se concentró para proporcionar un sólido de color amarillo pálido (rendimiento cuantitativo crudo).

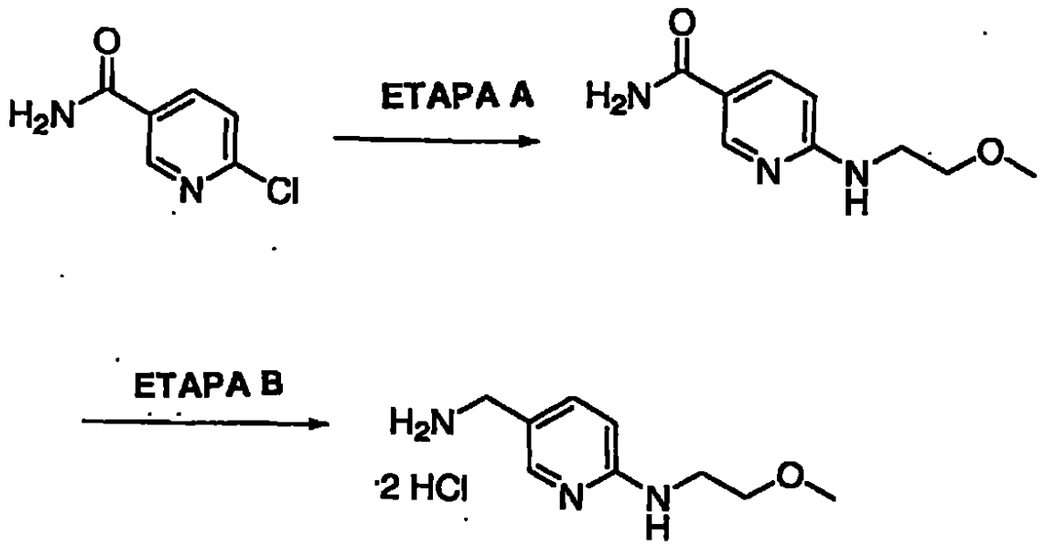
EJEMPLO PREPARATIVO 205:



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 se le agregó TFA (8 mL) y la solución resultante se agitó a 0°C durante 30 minutos y a temperatura ambiente durante 1 hora. La mezcla de reacción se vertió sobre Na_2CO_3 (40 g) y se agregó H_2O (400 mL) y la mezcla resultante se extrajo con CH_2Cl_2. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por cromatografía evaporativa usando una solución al 20% de (7N NH_3 en MeOH) en CH_2Cl_2 como eluyente (0,6 g, 82% de rendimiento).

EJEMPLO PREPARATIVOS 206:

417
418



ETAPA A:

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

ETAPA B:

A una solución de amida (1,2 g, 6,12 mmol) del Ejemplo Preparativo 206, Etapa A en THF (5 mL) a 0°C se le agregó una solución de BH_3-THF (43 mL; 43 mmol) por goteo durante 10 minutos. La solución resultante se calentó a temperatura ambiente y se agitó durante 14 h. La mezcla se enfrió a 0°C y se trató secuencialmente con HCl 6M (35 mL), agua (30 mL), y MeOH (150 mL). La mezcla se agitó durante 8 horas y se concentró bajo presión reducida. El residuo crudo se trituró con MeOH, se concentró bajo presión reducida, y se colocó bajo

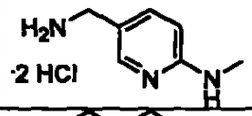
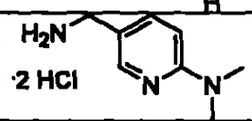
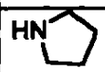
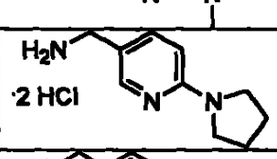
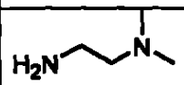
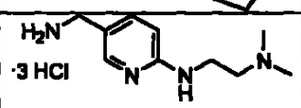
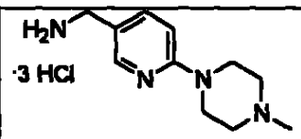
418
419

alto vacío para proporcionar 1,6 g (82%) de un sólido blanco en forma de la sal de diclorhidrato. M+H (base libre) = 182,0. Este material se uso crudo en el acoplamiento con los aductos 7-Cl.

EJEMPLOS PREPARATIVOS 207-211:

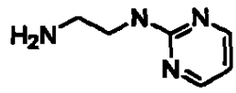
Esencialmente con el mismo procedimiento conocido indicado en el Ejemplo Preparativo 206 utilizando únicamente las aminas que se muestran en la Columna 2 de la Tabla 13 y las aminas que se muestran en la Columna 3 de la Tabla 13 se prepararon:

TABLA 13

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

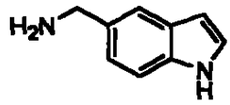
EJEMPLO PREPARATIVO 212:

-419
420



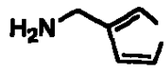
Se preparó el compuesto anterior de acuerdo con los métodos descriptos en la WO 91/18904.

EJEMPLO PREPARATIVO 213:



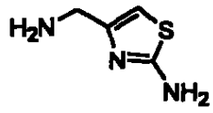
Se preparó el compuesto anterior de acuerdo con los métodos descriptos en la US 6,180,627 B1.

EJEMPLO PREPARATIVO 214:



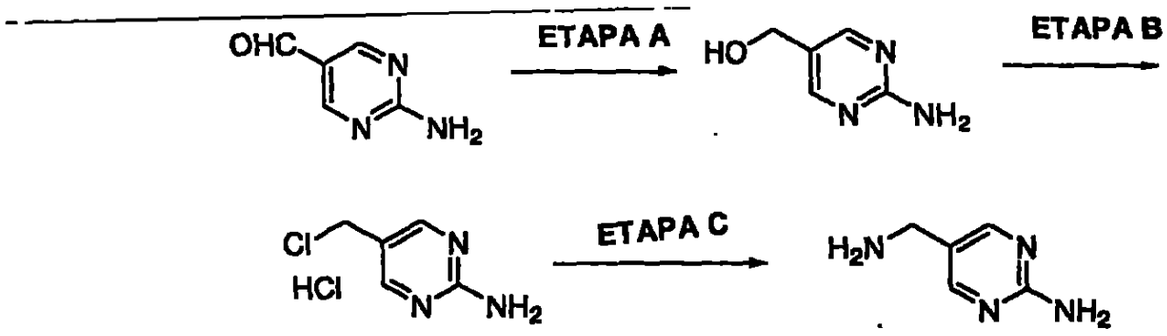
Se preparó la amina conocida tal como se describió en *J. Med. Chem.* (2001), *44*, 4505-4508.

EJEMPLO PREPARATIVO 215:



Se preparó la amina conocida tal como se ha descripto en *J. Med. Chem.* (1997), *40*, 3726-3733.

EJEMPLO PREPARATIVO 216:



ETAPA A:

Una solución de aldehido (50 g, 0,41 mol) [WO 0232893] e MeOH (300 mL) se enfrió a 0°C y se trató cuidadosamente con $NaBH_4$ (20g, 0,53 mol en 6 tandas) durante 20 minutos. Luego la reacción se dejó calentar a 20 °C y se agitó durante 4 horas. La mezcla se enfrió nuevamente a 0°C, se apagó cuidadosamente con NH_4Cl acuoso saturado, y se concentró. La cromatografía evaporativa (5–10% 7N NH_3-MeOH/CH_2Cl_2) proporcionó el alcohol primario (31g, 62%) en forma de un sólido como amarillo claro.

ETAPA B:

Una solución del alcohol (31 g, 0,25 mol) del Ejemplo Preparativo 216, Etapa A en CH_2Cl_2 (500 mL) se enfrió a 0°C y se trató lentamente con $SOCl_2$ (55 mL, 0,74 mol durante 30 minutos). La reacción se agitó luego durante la noche a 20°C. El material se concentró, se suspendió en acetona y luego se filtró. El sólido de color beige resultante se secó durante la noche al vacío (38,4g, 52%, sal de HCl).

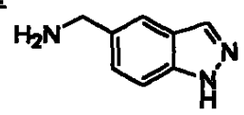
ETAPA C:

A un tubo bajo presión de 15 mL cargado con una barra agitadora se le agregó cloruro (150 mg, 0,83 mmol) del Ejemplo Preparativo 216, Etapa B seguido de 7 M NH_3/MeOH (10 mL). La solución resultante se agitó durante 48

421
422

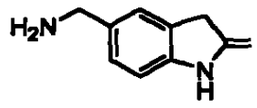
horas a temperatura ambiente con lo cual la mezcla se concentró bajo presión reducida para proporcionar un sólido de color amarillo claro (0,146 g, 83%). M+H (base libre) = 140.

EJEMPLO PREPARATIVO 217:



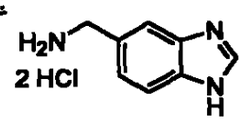
Se preparó el compuesto anterior de acuerdo con los métodos descriptos en WO 00/26210.

EJEMPLO PREPARATIVO 218:



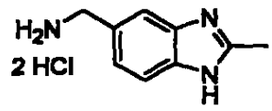
Se preparó el compuesto anterior de acuerdo con los métodos descriptos en WO 99/10325.

EJEMPLO PREPARATIVO 219:



Se preparó el diclorhidrato de amina conocido de acuerdo con los métodos descriptos en la WO 02/64211.

EJEMPLO PREPARATIVO 220:

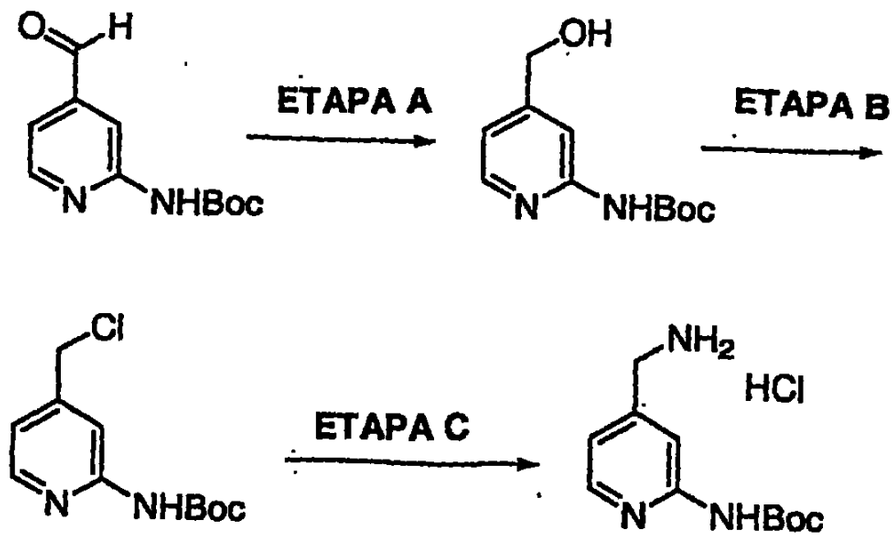


Se preparó el compuesto anterior de acuerdo con los métodos descriptos en la WO 02/64211.

EJEMPLO PREPARATIVO 221:

El alcohol primario conocido se preparó de acuerdo con la WO 00/37473 y se convirtió al diclorhidrato de amina deseado de manera análoga al Ejemplo Preparativo 220 de acuerdo con la WO 02/064211.

EJEMPLO PREPARATIVO 222:



ETAPA A:

A una solución del aldehido (WO 02/32893) (0,46 g, 2,07 mmol) en MeOH/THF (2 mL/2 mL) a 0°C se le agregó $NaBH_4$ (94 mg, 2,48 mmol) en una sola porción. La mezcla resultante se agitó durante 12 horas a temperatura ambiente y se diluyó con NH_4Cl acuoso saturado (3 mL). La mezcla se concentró bajo presión reducida y la capa acuosa resultante se extrajo con CH_2Cl_2 (3 x 5 mL). Las capas orgánicas se combinaron, se lavaron con salmuera (1 x 5 mL), se secaron (Na_2SO_4), y se filtraron. La capa orgánica se concentró bajo

presión reducida para proporcionar 417 mg (90% de rendimiento) de un sólido blanco. M+H = 225.

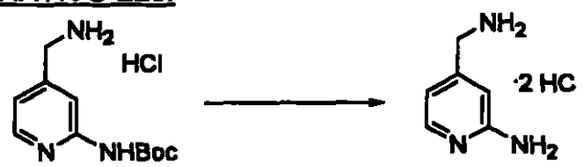
ETAPA B:

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

ETAPA C:

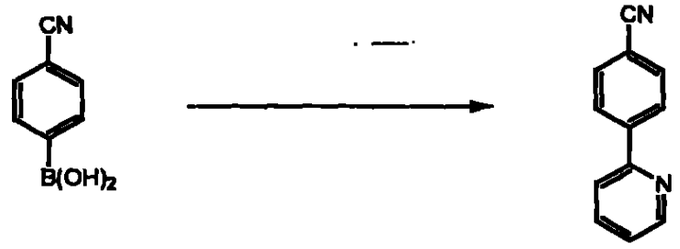
A una solución del cloruro crudo del Ejemplo Preparativo 222, Etapa B (0,33 g, 1,36 mmol) en un tubo bajo presión cargado con 7M NH_3/MeOH (35 mL) y la mezcla se agitó durante 72 horas. la mezcla se concentró bajo presión reducida para proporcionar 257 mg (85%) de un semisólido amarillo. M+H (base libre)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

EJEMPLO PREPARATIVO 223:



A un frasco de fondo redundo cargado con clorhidrato de amina (0,24 g, 1,1 mmol) del Ejemplo Preparativo 222, y con una barra agitadora se le agregó HCl 4N/dioxano (10 mL). La solución resultante se agitó durante 12 horas a temperatura ambiente, se concentró bajo presión reducida, y se trituró con CH_2Cl_2 (3 x 5 mL). El producto crudo se filtro, se lavó con Et2O (2 x 5mL), y se secó bajo alto vacío para proporcionar 0,19g (91%) de la sal de diclorhidrato. M+H (base libre) = 124.

EJEMPLO PREPARATIVO 224:



Se agregó $Pd(PPh_3)_4$ (0,404 g, 0,35 mmol) a una solución desgasificada de ácido 4-cianobenceno borónico (1,029 g, 7 mmol) y 2-bromopiridina (1,.11 g, 7 mmol) en 75 mL de acetonitrilo. Se agregó una solución de 0,4 M de carbonato de sodio (35 mL) a la mezcla de reacción y la solución resultante se reflujo a 90°C bajo Ar durante 24 horas (se monitoreó el progreso de la reacción mediante TLC). La mezcla de reacción se enfrió y se separó la capa acuosa. La capa orgánica que contenía el producto y el catalizador agotado se mezcló con gel de sílice (15 g) y se concentró hasta sequedad. Se aisló el 4-(2-piridil)-benzonitrilo por cromatografía en columna (0,850 g, 68%). LCMS: MH^+ = 181; ^1H RMN ($CDCl_3$) δ 8,85 (d, 1H), 8,7 (dd, 1H), 7,9 (dd, 1H), 7,75 (d, 2H), 7,7 (d, 2H), 7,4 (dd, 1H).

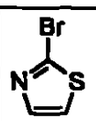
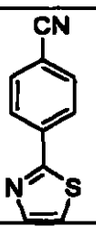
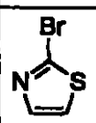
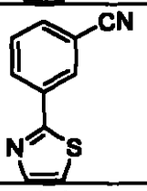
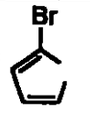
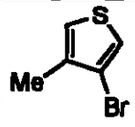
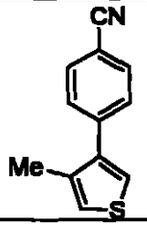
EJEMPLO PREPARATIVOS 225-228:

Siguiendo esencialmente el mismo procedimiento descripto en el Ejemplo Preparativo 224, sustituyendo únicamente los bromuros de la Columna 2 de la Tabla 14 se prepararon los compuestos de la Columna 3 de la Tabla 14.

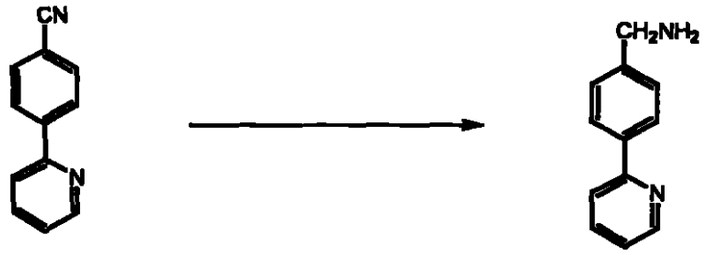
Tabla 14

Ej. Prep.	Columna 2	Columna 3	Columna 4

425
426

225			Rend. = 70% LCMS: MH^+ = 187
226			Rend. = 60% LCMS: MH^+ = 187
227			Rend. = 70% LCMS: MH^+ = 186
228			Rend. = 70% LCMS: MH^+ = 200

EJEMPLO PREPARATIVO 229:



Se agregó lentamente una solución de BH_3-THF (1 M, 24 mL, 5 eq) a una solución agitada de 4-(2-piridil)-benzonitrilo (0,85 g, 4,72 mmol) en THF anhidro (25 mL) bajo Ar, y la solución resultante se reflujo durante aproximadamente 12 horas. La solución se enfrió a 0°C usando agua helada. Se agregó por goteo metanol (15 mL) a la mezcla de reacción fría y se agitó durante 1 hora para destruir el exceso de BH_3. Se agregó lentamente HCl – metanol (1M, 10 mL) a la

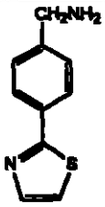
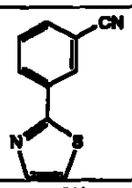
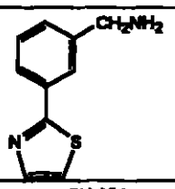
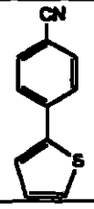
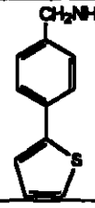
426
427

mezcla de reacción y se reflujo durante 5 horas. La solución se concentró hasta sequedad y el residuo se disolvió en 25 mL de agua y se extrajo con éter para remover cualquier material no reaccionado. La solución acuosa se neutralizó con carbonato de potasio sólido a pH 10-11. La amina libre, así formada se extrajo con éter, se secó sobre carbonato de potasio (0,45 g, 50%). LCMS: MH+ = 185; ^{1}H RMN ($CDCl_3$) δ 8,85 (d, 1H), 8,7 (dd, 1H), 7,9 (dd, 1H), 7,75 (d, 2H), 7,7 (d, 2H), 7,4 (dd, 1H), 3,7 (t, 2H), 1,7 (t, 2H).

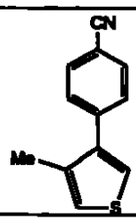
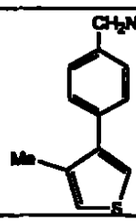
EJEMPLOS PREPARATIVOS 230-233:

Siguiendo esencialmente el mismo procedimiento indicado en el Ejemplo Preparativo 229, se prepararon los compuestos de la columna 3 de la Tabla 15.

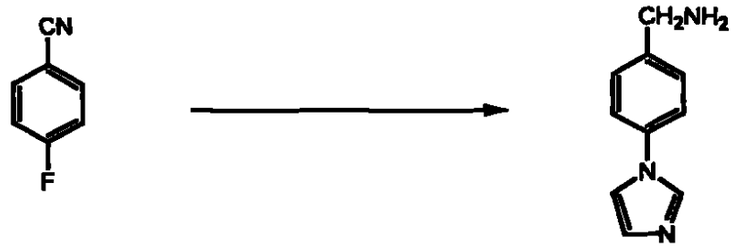
Tabla 15

Ej. Prep.	Columna 2	Columna 3	Columna 4
230			Rend. = 60% LCMS: MH^+ = 191
231			Rend. = 60% LCMS: MH^+ = 191
232			Rend. = 70% LCMS: MH^+ = 190

427
428

233			Rend.=70% LCMS: MH^+ = 204

EJEMPLO PREPARATIVO 234:



Etapa A:

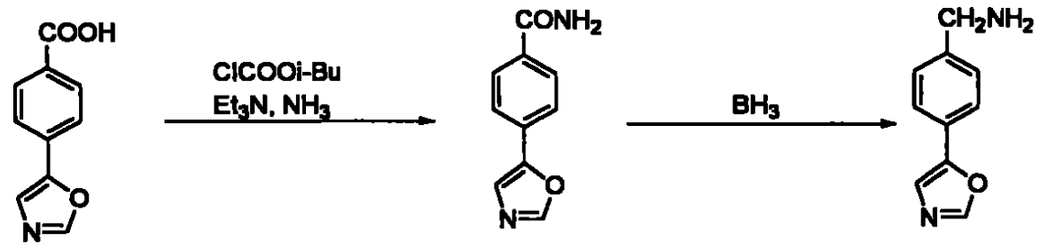
Una mezcla de 4-fluorbenzonitrilo (3 g, 25 mmol) e imidazolilo sodio (2,48 g, 27,5 mmol) en DMF (50 mL) se agitó a 80°C bajo Ar durante 12 horas. El progreso de la reacción se monitoreó por TLC. La mezcla de reacción se concentró *al vacío* y el residuo se diluyó con 50 mL de agua y se agitó. La mezcla acuosa se extrajo con EtOAc (2 x 50 mL). Los extractos de EtOAc combinados se secaron sobre MgSO4 anhidro, se concentraron, y se aisló el 4-(1-imidazolil)-benzonitrilo por cromatografía en columna (3,6 g, 78%). LCMS: MH^+ = 170; ^1H RMN ($CDCl_3$) δ 8,0 (s, 1H), 7,5 (d, 2H), 7,4 (m, 3H), 7,3 (d, 1H)

Etapa B:

Se disolvió 4-(1-imidazolil)-benzonitrilo (1g, 5,92 mmol) en THF anhidro (10 mL) y se agregó por goteo a una solución agitada de LAH –THF (1 M en THF, 18 mL) a temperatura ambiente. La mezcla de reacción se reflujo bajo Ar durante 2 horas y el progreso se monitoreó por TLC. La mezcla se enfrió a 0°C y se apagó por adición por goteo de una solución saturada de Na_2SO_4 – H_2O. La mezcla se agitó durante 1 hora y se filtró para remover las sales de litio. El filtrado se secó sobre $MgSO_4$ y se concentró para obtener 4-(1-imidazolil)-bencilamina (0,8 g, 80%). LCMS: MH^+ = 174.

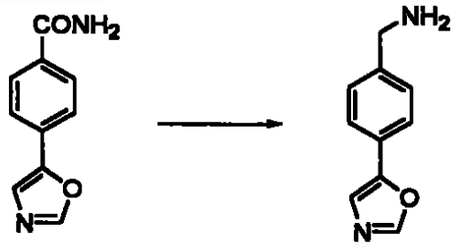
428
429

EJEMPLO PREPARATIVO 235:



Una mezcla de ácido 4-(5-oxazolil)benzoico (1,0 g, 5,46 mmol) y Et_3N (552 mg, 5,46 mmol) en 25 mL de THF se enfrió a 0 °C y se le agregó por goteo ClCOO*i*-Bu (745 mg, 5,46 mmol). Después de terminar la adición, la mezcla de reacción se agitó durante 5 minutos adicionales y luego se le agregó NH_4OH acuoso (0,63 mL de una solución al 28%, 10,46 mmol). Después de agitar durante la noche, el solvente se evaporó, se recogió el residuo en agua y se basificó a pH 9. Se filtró el sólido precipitado, se lavó con agua y se secó sobre P_2O_5 en un desecador al vacío para proporcionar 500 mg (48%) de la 4-(5-oxazolil)-benzamida: ^1H RMN (DMSO-d6) δ 8,50 (s, 1H), 8,20-7,80 (m, 5H).

EJEMPLO PREPARATIVO 236:



Una suspensión de 4-(5-oxazolil)benzamida (500 mg, 2,657 mmol) en 10 mL en THF seco se enfrío a 0°C y se agregaron 10 mL de 1 M BH_3.THF (10,00 mmol). El contenido se reflujo durante la noche y se destruyo el exceso de borano mediante adición por goteo de metanol. El solvente se evaporó y el residuo se trató con HCl metanólico para descomponer el complejo de amina-borano. Después de evaporación del metanol, el residuo se recogió en agua, se basificó a

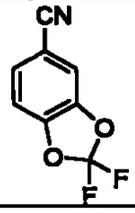
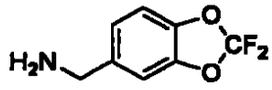
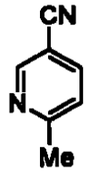
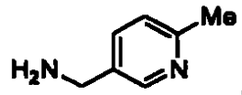
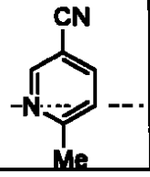
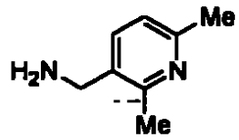
429
430

pH 10 y el producto se extrajo en DCM. La capa de DCM se secó (K_2CO_3) y el solvente se removió para proporcionar 150 mg (32%) de 4-(5-oxazolil)bencilamina: ^{1}H RMN ($CDCl_3$) δ 7,90 (s, 1H), 7,60 (d, 2H), 7,40 (d, 2H), 7,30 (s, 1H), 3,90 (s, 2H).

EJEMPLOS PREPARATIVOS 237-239:

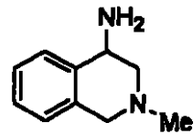
Esencialmente con los mismos procedimientos indicados más arriba, se redujeron los compuestos en la Columna 2 de la Tabla 16 usando el método indicado en la Columna 3 de la Tabla 16 para proporcionar la amina indicada en la Columna 4 de la Tabla 16.

Tabla 16

Ej. Prep.	Columna 2	Columna 3	Columna 4	COMP.
237		BH_3		^{1}H RMN ($CDCl_3$) δ 7,15-6,90 (m, 3H), 3,85 (s, 2H), 1,45 (s, 2H)
238		H_2		^{1}H RMN ($CDCl_3$) δ 8,40(s, 1H), 7,55 (dd, 1H), 7,10 (d, 1H), 3,85 (s, 2H), 2,50 (s, 3H), 1,70 (bs, 2 H)
239		BH_3		

EJEMPLO PREPARATIVO 240

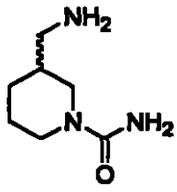
(480
43)



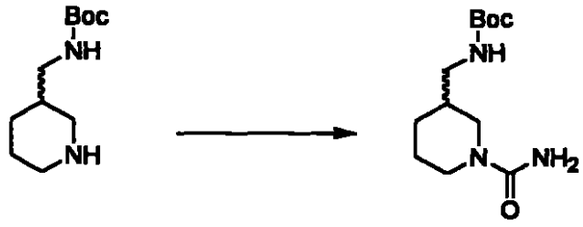
Se preparó por el procedimiento de la literatura (PCT Int. Appl, WO 0105783): ^{1}H RMN ($CDCl_3$) δ 7,35 (d, 1H), 7,24-7,10 (m, 2 H), 7,02 (d, 1H), 3,95 (t, 1H), 3,70 (d, 1H), 3,37 (d, 1H), 2,65 (m, 2H), 2,45 (s, 3H), 1,90 (bs, 2H)

EJEMPLO PREPARATIVO 241:

3-(AMINOMETIL)PIPERIDINA-1-CARBOXAMIDA



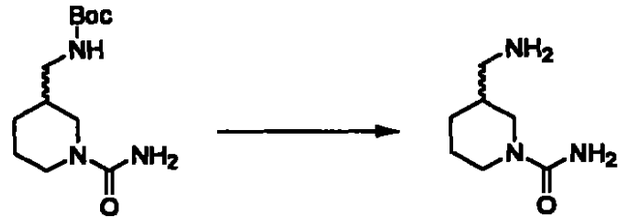
A. 3-(*ter*-BUTOXICARBONILAMINOMETIL)PIPERIDINA-1-CARBOXAMIDA



Se disolvió 3(R/S)-(*ter*-Butoxicarbonilaminometil)piperidina (3g, 14,0 mmoles) en diclorometano anhidro (50 mL) y se agregó isocianato de trimetilsililo (9,68g, 11,4 mL, 84,0 mmoles). La mezcla se agitó bajo argón a 25°C durante 68 horas. Se agregó isocianato de trimetilsililo adicional (4,84g, 5,7 mL, 42,0 mmoles) y la mezcla se agitó a 25°C por un total de 90 horas. La mezcla se evaporó hasta sequedad y se cromatografió sobre una columna de gel de sílice (30x5cm) usando 2% (10% de hidróxido de amonio concentrado en metanol)-

diclorometano como eluyente para proporcionar 3-(*ter*-butoxicarbonilaminometil) piperidina-1-carboxamida (3,05g, 85%): FABMS: m/z 258,1 (MH^+); HRFABMS: m/z 258,1816 (MH^+). Calc. para $C_{12}H_{24}O_3N_3$: m/z 258,1818; δ_H ($CDCl_3$) 1,22 91H, m, CH_2), 1,42 (9H, s, -COOC($C\underline{H}_3$)$_3$), 1,48 (1H, m, CH_2), 1,67 (2H, m, CH_2), 1,78 (1H, m, CH), 2,80 (1H, m, CH_2), 2,99, 3H, m, CH_2), 3,59 (1H, m, $CH_2$0 3,69 (1H, m, CH_2), 4,76 (2H, bm, $CONH_2$) y 4,98ppm (1H, bm, NH); δ_C ($CDCl_3$) CH_3: 28,5, 28,5, 28,5; CH_2: 24,0, 28,3, 43,2, 45,1, 47,8; CH: 36,5; C: 79,4, 156,3, 158,5.

B. 3-(AMINOMETIL)PIPERIDINA-1-CARBOXAMIDA



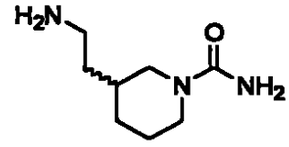
3-(*ter*-Butoxicarbonilaminometil)piperidina-1-carboxamida (150mg, 0,583 mmoles) (preparada tal como se describió en el Ejemplo Preparativo 241, Etapa A anterior) se disolvió en metanol (3 mL). Se agregó 10% de ácido sulfúrico concentrado en 1,4-dioxano (7,9 mL) y la mezcla se agitó a 25°C durante 1 hora. La mezcla se diluyó con metanol y se agregó resina BioRad AG1-X8 (forma OH^-) hasta que el pH fue básico. La resina se separó por filtración, se lavó con metanol, se evaporó hasta sequedad, y se cromatografió sobre una columna de gel de sílice (15x2cm) usando diclorometano seguido de 15% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente para proporcionar 3-(aminometil)piperidina-1-carboxamida (80mg, 87%): FABMS: m/z 158,1 (MH^+); HRFABMS: m/z 158,1294 (MH^+). Calc. para $C_7H_{16}N_3O$: m/z 158,1293; δ_H ($CDCl_3$ + gota CD_3OD) 1,20 (1H, m, CH_2), 1,48 (1H, m, CH_2), 1,60 (1H, m, CH), 1,68 (1H, m, CH_2), 1,83 (1H, m, CH_2), 2,64 (bm, 2H, -$CH_2N\underline{H}_2$), 2,82 (1H, m, CH_2), 3,02 (1H, m, CH_2), 2,98 (2H, m, CH_2), 3,70 (1H, m, -$C\underline{H}_2NH_2$), 3,78 (1H, m, -$C\underline{H}_2NH_2$) y 5,24 ppm (1H, bs, NH); δ_C ($CDCl_3$ + gota CD_3OD) CH_2: 24,1,

432
433

28,6, 44,0, 44,8, 47,9; CH: 38,3; C: 159,0.

EJEMPLO PREPARATIVO 242:

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

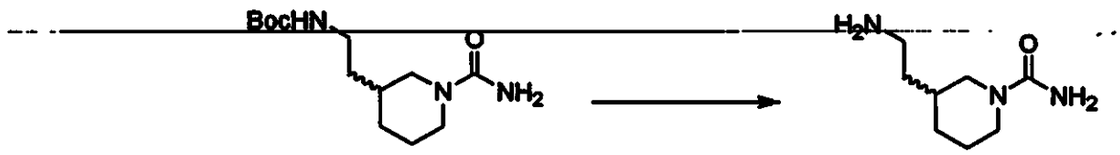


A. 3-(2-ter-BUTOXICARBONILAMINOETIL)PIPERIDINA-1-CARBOXAMIDA

Se disolvió 3-(2-*ter*-Butoxicarbonilaminoetil)piperidina (500mg, 2,19 mmoles) en diclorometano anhidro (10 mL) y se agregó isocianato de trimetilsililo (2,96 mL, 21,9 mmoles). La mezcla se agitó bajo argón a 25°C durante 3,35 horas. La mezcla se diluyó con diclorometano y se lavó con bicarbonato de sodio acuoso saturado. La capa orgánica se secó ($MgSO_4$), se filtró, se evaporó hasta sequedad y se cromatografió sobre una columna de gel de sílice (15x5cm) usando 5% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente para proporcionar 3-(2-*ter*-butoxicarbonilaminoetil)piperidina-1-carboxamida (417,7mg, 70%): FABMS: m/z 272,0 (MH^+); HRFABMS: m/z 272,1979 (MH^+). Calc. para $C_{13}H_{26}O_3$: m/z 272,1974; δ_H ($CDCl_3$) 1,16 (1H, m, CH_2), 1-30-1,60 (5H, m, CH/CH_2), 1,46 (9H, s, -COOC($C\underline{H_3}$)$_3$), 1,68 (1H, m, CH_2), 1,84 (1H, m, CH_2), 2,54 (1H, dd, CH_2), 2,73 (1H, m, CH_2), 3,08 (1H, m, CH_2), 3,42 (1H, m, CH_2), 4,02 (1H, m, CH_2), 4,10 (1H, m, CH_2), 4,84 (1H, m, NH) y 4,96 ppm (2H, bm, $CONH_2$); δ_C ($CDCl_3$) CH_3: 28,5, 28,5, 28,5; CH_2: 25,2, 31,7, 34,9, 37,3, 44,6, 50,3; CH: 32,9; C: 79,5, 156,4, 158,2.

B. 3-(2-AMINOETIL)PIPERIDINA-1-CARBOXAMIDA

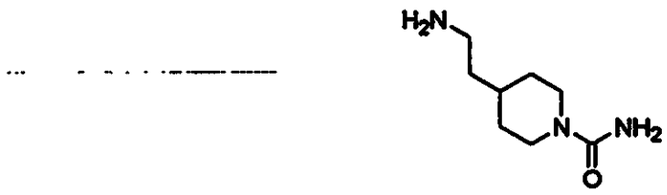
433
434



3-(2-*ter*-Butoxicarbonilaminoetil)piperidina-1-carboxamida (392,7mg, 1,45 mmoles) (preparada tal como se describió en el Ejemplo Preparativo 242, Etapa A anterior) se disolvió en metanol (7,5 mL) y se agregó 10% de ácido sulfúrico concentrado en 1,4-dioxano (19,5 mL). La mezcla se agitó a 25°C durante 1,25 horas. La mezcla se diluyó con metanol y se agregó resina BioRad AG1-X8 (forma OH^-) hasta que el pH fue básico. La resina se separó por filtración, se lavó con metanol, se evaporó hasta sequedad y se cromatografió sobre una columna de gel de sílice (30x2,5cm) usando 15% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente para proporcionar 3-(2-aminoetil)piperidina-1-carboxamida (233 mg, 94%): FABMS: m/z 172,1 (MH^+); HRFABMS: m/z 172,1444(MH^+). Calc. para $C_8H_{18}N_3O$ requiere: m/z 172,1450; δ_H ($CDCl_3$ + 3% CD_3OD) 1,14 (1H, m, CH_2), 1,40 (2H, m, CH_2), 1,49 (1H, m, CH), 1,58 (1H, m, CH_2), 1,69 (1H, m, CH_2), 1,85 (1H, m, CH_2), 2,55 (1H, m, CH_2), 2,67 (5H, m, CH_2/NH_2), 2,76 (1H, bm, CH_2), 2,84 (1H, m, CH_2) y 3,82 ppm (2H, m, $CONH_2$); δ_C ($CDCl_3$ + 3% CD_3OD) CH_2: 24,8, 30,9, 36,.6, 38,9, 44,9, 50,0; CH: 33,4.

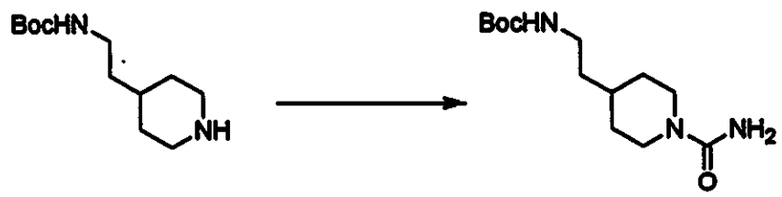
<u>EJEMPLO PREPARATIVO 243:</u>

4-(2-AMINOETIL)PIPERIDINA-1-CARBOXAMIDA



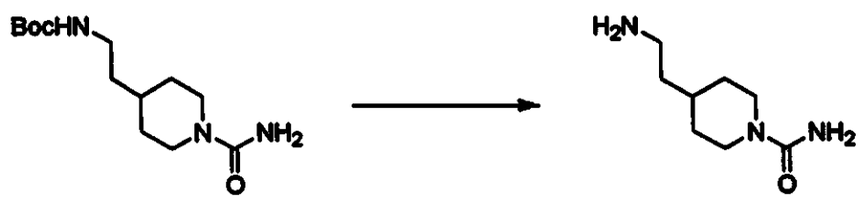
A. 4-(2-ter-BUTOXICARBONILAMINOETIL)PIPERIDINA-1-CARBOXAMIDA

435



4-(2-*ter*-Butoxicarbonilaminoetil)piperidina (500 mg, 2,19 mmoles) se disolvió en diclorometano anhidro (10 mL) y se agregó isocianato de trimetilsililo (2,96 mL, 21,9 mmoles). La mezcla se agitó bajo argón a 25°C durante 3,25 horas. Luego la mezcla se diluyó con diclorometano y se lavó con bicarbonato de sodio acuoso saturado. La capa orgánica se secó ($MgSO_4$), se filtró, se evaporó hasta sequedad y se cromatografió sobre una columna de gel de sílice (15x5cm) usando 5% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente para proporcionar 4-(2-*ter*-butoxicarbonilaminoetil)piperidina-1-carboxamida (308,2mg, 52%): FABMS: m/z 272,0 (MH^+); HRFABMS: m/z 272,1965 (MH^+). Calc. para $C_{13}H_{26}O_3N_3$: m/z 272,1974; δ_H ($CDCl_3$) 1,20 (2H, m, CH_2), 1,47 (9H, s, -COOC($C\underline{H}_3$)$_3$), 1,45-1,55 (3H, m, CH/CH_2), 1,75 (2H, m, CH_2), 2,82 (2H, m, CH_2), 3,19 (2H, m, CH_2), 3,96 (2H, m, CH_2), 4,64 (2H, m, CH_2) y 4,70 ppm (1H, bm, NH); δ_C ($CDCl_3$) CH_3: 28,5, 28,5, 28,5; CH_2: 31,8, 31,8, 36,7, 38,0, 44,5, 44,5; CH: 33,4; C: 79,2, 156,7, 158,1.

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

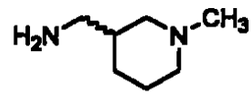


4-(2-*ter*-Butoxicarbonilaminoetil)piperidina-1-carboxamida (283,3mg, 1,04 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 243, Etapa A anterior) se disolvió en metanol (5,4 mL) y se agregó 10% de ácido

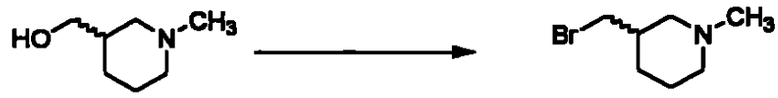
sulfúrico concentrado en 1,4-dioxano (14,2 mL) y la mezcla se agitó a 25°C durante 1,25 horas. La mezcla se diluyó con metanol y se agregó resina BioRad AG1-X8 (forma OH^-) hasta que el pH fue básico. La resina se separó por filtración, se lavó con metanol, se evaporó hasta sequedad y se cromatografió sobre una columna de gel de sílice (30x2.5cm) usando 15% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente para proporcionar la 3-(2-aminoetil)piperidina-1-carboxamida (170mg, 95%): FABMS: m/z 172,1 (MH^+); HRFABMS: m/z 172,1442. Calc. para $C_8H_{18}N_3O$ requiere: m/z 172,1450; δ_H ($CDCl_3$ + 3% CD_3OD) 1,16 (2H, m, CH_2), 1,43 (2H, m, CH_2), 1,52 (1H, m, CH), 1,70 (2H, m, CH_2), 2,70-2,85 (8H, m, CH_2) y 3,92 ppm (2H, m, $CONH_2$); δ_C ($CDCl_3$ + 3% CD_3OD) CH_2: 31,9, 31,9, 39,0, 39,7, 44,4, 44,4; CH: 33,5; C: 158,7.

EJEMPLO PREPARATIVO 244:

3-(AMINOMETIL)-1-METILPIPERIDINA



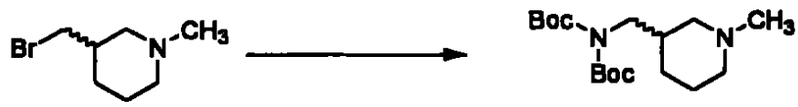
A. 3-(BROMOMETIL)-1-METILPIPERIDINA



Se disolvió 3-(hidroximetil)-1-metilpiperidina (2g, 15,5 mmoles) en acetonitrilo anhidro (32 mL) y se agregó piridina anhidro (2,02 mL, 24,8 mmoles) y la solución se enfrió a 0°C. Se agregó dibromotrifenilfosforano (8,49g, 20,2 mmoles) a 0°C y la mezcla se dejó calentar a 25°C y se agitó durante 94 horas. La mezcla se evaporó hasta sequedad y el residuo se cromatografió sobre una columna de gel de sílice (30x5cm) usando elución gradiente con diclorometano, 35% de éter dietílico en diclorometano y 5-10% de metanol en diclorometano como eluyente

para proporcionar 3-(bromometil)-1-metilpiperidina (3,13g, 100%): FABMS: m/z 192,1 (MH^+); δ_H ($CDCl_3$) 1,52 (1H, m, CH_2), 1,99 (2H, m, CH_2), 2,43 (1H, m, CH_2), 2,75 (2H, m, CH_2), 2,82 (1H, m, CH), 2,86/2,88 (3H, s, NCH_3), 3,42/3,49 (2H, dd, -$C\underline{H}_2$Br) y 3,56 ppm (2H, m, CH_2); δ_C ($CDCl_3$) CH_3: 44,3; CH_2: 22,1, 26,6, 35,4, 54,8, 58,2; CH: 34,6.

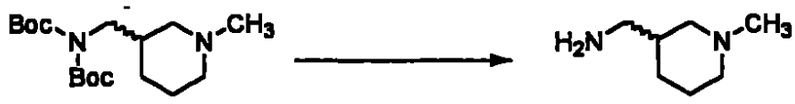
A. 3-(Di-ter-BUTOXICARBONILAMINOMETIL)-1-METILPIPERIDINA



3-(Bromometil)-1-metilpiperidina (1,5g, 7,81 mmoles) (del Ejemplo Preparativo 244, Etapa A anterior) y di-*ter*-butiliminodicarboxilato (1,697g, 7,81 mmoles) se disolvieron en acetonitrilo anhidro (25 mL). 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 20 horas. La mezcla se evaporó hasta sequedad y el residuo se dividió entre diclorometano y bicarbonato de sodio acuoso saturado. La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó hasta sequedad. El residuo se cromatografió sobre una columna de gel de sílice (30x5cm) usando 3% de metanol en diclorometano como eluyente para proporcionar 3-(di-*ter*-butoxicarbonilamino)-1-metilpiperidina (1,331g, 52%): FABMS: m/z 329,2 (MH^+); HRFABMS: m/z 329,2438 (MH^+). Calc. para $C_{17}H_{33}N_2O_4$: m/z 329,2440; δ_H ($CDCl_3$) 1,10 (1H, m, CH_2), 1,54 (18H, s, -$COOC(CH_3)_3$), 1,86 (2H, m, CH_2), 2,01 (1H, m, CH_2), 2,19 (1H m, CH), 2,34 (2H, bm, CH_2), 2,59 (3H, -NCH_3), 3,19 (2H, m, CH_2) y 3,52/3,52 ppm (2H, -CH_2N-); δ_C ($CDCl_3$) CH_3: 28,5, 28,5, 28,5, 28,5, 28,5, 28,5, 47,2; CH_2: 25,4, 28,3, 50,4, 56,8, 60,8; CH: 37,2; C: 83,0, 83,0,153,5, 153,5.

A. 3-(AMINOMETIL)-1-METILPIPERIDINA

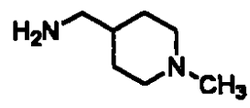
437
438



3-(Di-*ter*-butoxicarbonilamino)-1-metilpiperidina (500mg, 1,52 mmoles) (del Ejemplo Preparativo 244, Etapa B anterior) se disolvió en metanol (7,5 mL) y se agregó 10% (v/v) de ácido sulfúrico concentrado en 1,4-dioxano (19,75 mL). La solución se agitó a 25°C durante 0,5 horas. Se agregó metanol (300 mL) seguido de resina BioRad AG1-X8 (forma OH^-) hasta que el pH fue de ~10. La resina se separó por filtración y se lavó con metanol (2x200 mL). Los eluatos combinados se evaporaron hasta sequedad y el residuo se cromatografió sobre una columna de gel de sílice (30x2,5cm) usando 10% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente para proporcionar 3-(aminometil)-1-metilpiperidina (69,2mg, 35%): FABMS: m/z 129,1 (MH^+); HRFABMS: m/z 129,1392 (MH^+). Calc. para $C_7H_{17}N_2$: m/z 129,1392; δ_H ($CDCl_3$) 0,90 (2H, m, CH_2), 1,65 (2H, m, CH_2), 1,72 (1H, m, CH), 1,79 (1H, m, CH_2), 1,91 (1H, m, CH_2), 2,30 (3H, s, $-NCH_3$), 2,64 (2H, m, CH_2), 2,82 (1H, m, $-C\underline{H_2}NH_2$) 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.

EJEMPLO PREPARATIVO 245:

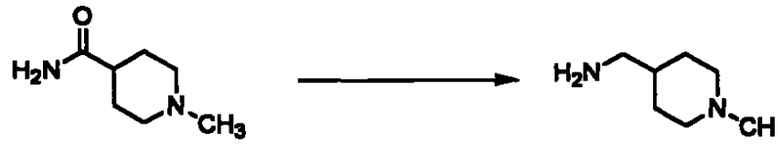
4-(AMINOMETIL)-1-METILPIPERIDINA



A. 1-METILISONIPECOTAMIDA

Se disolvió isonipecotamida (10g, 78,0 mmoles) en agua destilada (100 mL) y se agregó 37% de formaldehido acuoso (7,6 mL, equivalente a 2,81g de HCHO, 93,6 mmoles). Se agregó Pd-C húmedo al 10% (8 cucharadas) bajo argón y la mezcla se hidrogenó a 25°C y a 50psi durante 43 horas. El catalizador se separó por filtración a través de Celite y éste último se lavó con agua y metanol. Los filtrados combinados se evaporaron hasta sequedad y el residuo se cromatografió en una columna de gel de sílice (60x5cm) usando 8%-10%-20% (hidróxido de amonio concentrado al 10% en metanol)-diclorometano como eluyente para proporcionar 1-metilisonipecotamida (7,15g, 64%): FABMS: m/z 143,1 (MH^+); HRFABMS: m/z 143,1184 (MH^+). Calc. para $C_7H_{15}N_2O$: m/z 143,1184; δ_H (d_6-DMSO) 1,50/1,57 (4H, m, CH_2), 1,76/1,94 (4H, m, CH_2), 2,10 (3H, s, -NCH_3), 2,72 (1H, m, CH) y 6,68/7,18 ppm (2H, m, $CONH_2$); δ_C (d_6-DMSO) CH_3: 41,2; CH_2: 28,5, 28,5, 54,9, 54,9; CH: 46,2; C: 176,7.

B. 4-(AMINOMETIL)-1-METILPIPERIDINA



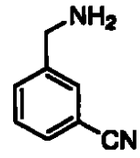
1-Metilisonipecotamida (6,75g, 47,5 mmoles) (preparada tal como se describió en el Ejemplo Preparativo 245, Etapa A anterior) se disolvió en THF anhidro (350 mL) y la mezcla resultante se agregó en porciones a una suspensión agitada de hidruro de litio aluminio (1,8g, 47,5 mmoles) en THF anhidro (100 mL) a 0°C bajo nitrógeno.

439
440

La mezcla se agitó a 0°C durante 30 minutos y luego se calentó a 66°C durante 25 horas bajo nitrógeno. Se agregó por goteo agua destilada (1,88 ml) a la mezcla agitada a 0°C, seguido de 20% de hidróxido de sodio acuoso (1,42 ml) y luego agua destilada (6,75 ml) y la mezcla se agitó durante 15 minutos. La mezcla se filtró y los sólidos se lavaron con THF y diclorometano. Los filtrados combinados se evaporaron hasta sequedad y se cromatografiaron sobre una columna de gel de sílice (30x5 cm) usando 15%-20% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente para proporcionar 4-(aminometil)-1-metilpiperidina (0,678 g, 11%): FABEM: m/z 129,1 (MH^+); HRFABEM: m/z 129,1389 (MH^+). Calc. para $C_7H_{17}N_2$: m/z 129.1392; δ_H (d_6-DEMO): 2,08 ppm (3H, s, $-NCH_3$); δ_C (d_6-DEMO): CH_3: bajo picos de DEMO; CH_2: 29,6, 29,6, 46,7, 55,2, 55,2; CH: 46,2.

EJEMPLO PREPARATIVO 246:

3-(AMINOMETIL)BENZONITRILO

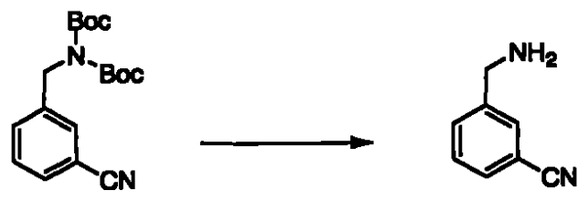


A. 3-(Di-*ter*-BUTOXICARBONILAMINO)BENZONITRILO

3-(Bromometil)benzonitrilo (5 g, 25,5 mmoles) y di-ter-butiliminodicarboxilato (5,54 g, 25,5 mmoles) se disolvieron en THF anhidro (50 ml) y se agregaron carbonato de cesio (16,62 g, 25,5 mmoles) y yoduro de litio

(170,5 mg, 1,275 mmoles). La mezcla se agitó a 70°C durante 22 horas y la reacción se elaboró tal como se describió en el Ejemplo Preparativo 89, Etapa B anterior. El residuo se cromatografió sobre una columna de gel de sílice (60x5cm) usando 5% de acetato de etilo en hexano como eluyente para proporcionar 3-(di-*ter*-butoxicarbonilamino)benzonitrilo (7,39 g, 87%): FABEM: m/z 333,2 (MH^+); HRFABEM: m/z 333,1815 (MH^+); Calc. para $C_{18}H_{25}N_2O_4$: m/z 333,1814; δ_H ($CDCl_3$) 1,52 (18H, s, $-COOC(CH_3)_3$), 4,84 (2H, s, CH_2), 7,48 (1H, m, Ar-H), 7,60 (2H, m, Ar-H) y 7,65 ppm (1H, m, Ar-H); δ_C ($CDCl_3$) CH_3: 28,1, 28,1, 28,1, 28,1, 28,1, 28,1; CH_2: 48,4; CH: 129,2, 131,0, 131,0, 131,9; C: 83,2, 83,2, 112,5, 118,8, 140,1, 152,5, 152,5.

B. 3-(AMINOMETIL)BENZONITRILO



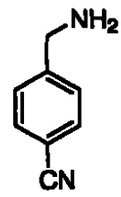
3-(Di-*ter*-butoxicarbonilamino)benzonitrilo (2 g, 6,0 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 246, Etapa A anterior) se disolvió en metanol (30 ml) y se agregó 10% (v/v) (10% de ácido sulfúrico concentrado en 1,4-dioxano) (79 ml). La solución se agitó a 25°C durante 0,25 horas y se elaboró tal como se describió en el Ejemplo Preparativo 89, Etapa C anterior). El residuo se cromatografió sobre una columna de gel de sílice (15x5cm) usando 3% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente para proporcionar el compuesto del título (651,4 mg, 82%): FABEM: m/z 133,1 (MH^+); HRFABEM: m/z 133,0762 (MH^+). Calc. para $C_8H_9N_2$: m/z 133,0766; δ_H ($CDCl_3$) 2,57 (2H, s, $-CH_2\underline{N}H_2$), 3,92 (2H, s, $-C\underline{H}_2NH_2$), 7,46 (1H, m, Ar-H), 7,57

441
442

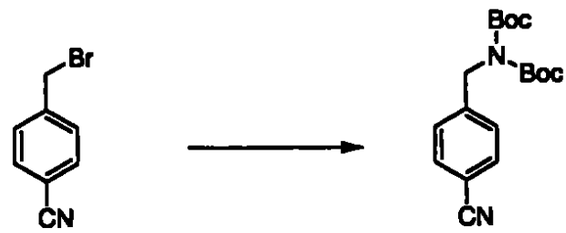
(2H, m, Ar-H) y 7,64 ppm (1H, m, Ar-H); δ_C ($CDCl_3$) CH_2: 45,2; CH: 129,4, 130,7, 130,7, 131,8; C: 112,4, 118,8, 143,8.

EJEMPLO PREPARATIVO 247

4-(AMINOMETIL)BENZONITRILO



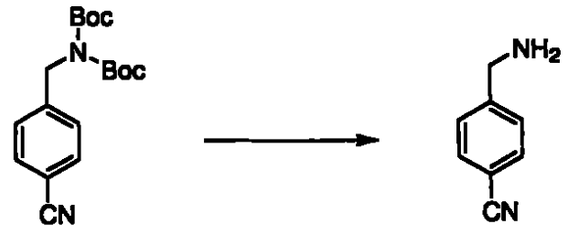
A. 3-(Di-*ter*-BUTOXICARBONILAMINOMETIL)BENZONITRILO



4-(Bromometil)benzonitrilo (5 g, 25,5 mmoles) y di-ter-butiliminodicarboxilato (5,54 g, 25,5 mmoles) se disolvieron en THF anhidro (50 ml) y se agregaron carbonato de cesio (16,62 g, 25,5 mmoles) y yoduro de litio (170,5 mg, 1,275 mmoles). La mezcla se agitó a 70°C durante 23 horas y la reacción se elaboró tal como se describió en el Ejemplo Preparativo 244, Etapa B anterior. El residuo se cromatografió sobre una columna de gel de sílice (50x5cm) usando 5% de acetato de etilo en hexano como eluyente para proporcionar 4-(di-*ter*-butoxicarbonilaminometil)benzonitrilo (7,07 g, 83%): FABEM: m/z 333,2 (MH^+); HRFABEM: m/z 333,1816 (MH^+). Calc. para $C_{18}H_{25}N_2O_4$: m/z 333,1814; δ_H ($CDCl_3$) 1,45 (18H, s, $-COOC(CH_3)_3$), 4,81 (2H, s, CH_2), 7,37 (2H, d, Ar-H) y 7,62 ppm (2H, d, Ar-H); δ_C ($CDCl_3$) CH_3: 28,1, 28,1, 28,1, 28,1, 28,1, 28,1; 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.

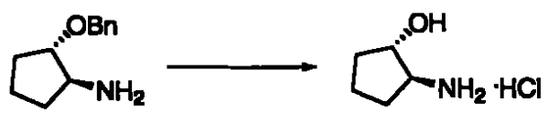
1442
1443

B. 4-(AMINOMETIL)BENZONITRILO



4-(Di-*ter*-butoxicarbonilaminometil)benzonitrilo (2 g, 6,0 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 247, Etapa A anterior) se disolvió en TFA (4 ml) y la solución se agitó a 25°C durante 0,25 horas. La mezcla de reacción se diluyó con diclorometano y se extrajo con hidróxido de sodio 1N. La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó hasta sequedad. El residuo se cromatografió sobre una columna de gel de sílice (15x5 cm) usando 3% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente para proporcionar 4-(aminometil)benzonitrilo (108 mg, 68%): FABEM: m/z 133,1 (MH^+); HRFABEM: m/z 133,0764 (MH^+). Calc. para $C_8H_9N_2$: m/z 133,0766; δ_H ($CDCl_3$) 2,04 (2H, s, -$CH_2N\underline{H_2}$), 3,89 (2H, s, -$C\underline{H_2}NH_2$), 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 le agregó 10% de Pd/C (50% húmedo 1,0 g) seguido de adición por goteo de HCl concentrado (0,7 ml). La mezcla se agitó bajo un balón de H_2 durante 14 horas y el catalizador se separó por filtración a través de una almohadilla de Celite. La almohadilla de Celite se

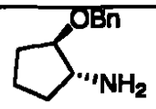
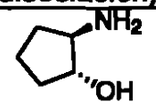
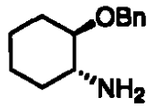
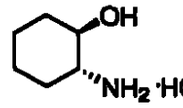
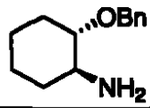
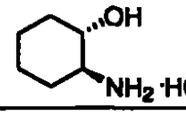
443
444

lavó con MeOH (2 x 10 ml) y el filtrado resultante se concentró bajo presión reducida para proporcionar 0,97 g (90%) de un semisólido amarillo; M+H (base libre) = 102.

EJEMPLOS PREPARATIVOS 249-251

De manera análoga al Ejemplo Preparativo 248, las cicloalquil aminas protegidas con bencilo (Columna 2) se convirtieron a los derivados del clorhidrato de aminocicloalcanol deseados (Columna 3) tal como se indica en la Tabla 17.

TABLA 17

Ej.	Columna 2 (Amina)	Columna 3 (Método de disociación)	COMP. M+H
249			M+H = 102 (base libre)
250			M+H = 116 (base libre)
251			M+H = 116 (base libre)

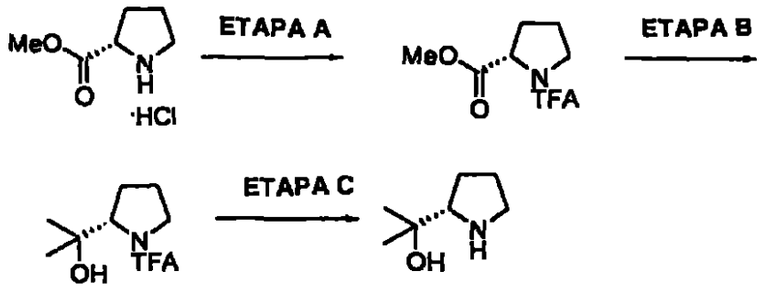
EJEMPLO PREPARATIVO 252

A una solución de éster (preparada de acuerdo con *J. Org. Chem.* (1999), *64*, 330) (0,5 g, 2,43 mmol) en THF (8 ml) a 0°C se le agregó $LiAlH_4$ (0,37 g, 9,74

444
445

mmol) en una sola porción. La mezcla resultante se calentó a reflujo durante 12 horas y se enfrió 0°C. La mezcla se trató secuencialmente con H_2O (1 ml), 1 M NaOH (1 ml), y H_2O (3 ml). Se agregó CH_2Cl_2 (10 ml) a la mezcla la cual se agitó vigorosamente durante 30 minutos. La mezcla se filtró a través de una almohadilla de Celite la cual se lavó generosamente con CH_2Cl_2 (3 x 5 ml). El filtrado resultante se concentró bajo presión reducida para proporcionar 0,41 g (85%) de un sólido de color amarillo/anaranjado. M+H = 142.

EJEMPLO PREPARATIVO 253



ETAPA A:

A una solución de clorhidrato de éster metílico de *L*-prolina (0,50 g, 3,0 mmol) en CH_2Cl_2 (15 ml) a 0°C se le agregó Et_3N (1,1 ml, 7,55 mmol) seguido de TFAA (0,56 ml, 3,92 mmol). La mezcla se agitó durante 12 horas a temperatura ambiente y se agregó HCl 1N (25 ml). Las capas se separaron y la capa orgánica se lavó secuencialmente con $NaHCO_3$ acuoso saturado (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 proporcionar 0,72 g (100%) de un aceite de color amarillo. M+H = 226. El material crudo se recogió en la Etapa B sin purificación adicional.

ETAPA B:

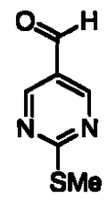
445
446

A una solución del compuesto preparado en el Ejemplo Preparativo 253, Etapa A (0,68 g, 3,0 mmol) en THF (20 ml) a 0°C se le agregó MeMgI (5,1 ml, 3,0M en Et_2O) por goteo durante 10 minutos. La solución resultante se agitó durante 16 horas a temperatura ambiente después de lo cual la mezcla se apagó mediante adición de NH_4Cl acuoso saturado. La mezcla se concentró hasta sequedad y el residuo resultante se agitó con EtOAc (100 ml) durante 45 minutos y se filtró. El filtrado se concentró bajo presión reducida para proporcionar 0,68 g (100%) de un aceite de color amarillo/anaranjado. M+H = 226. El material crudo se recogió en la Etapa C sin purificación adicional.

ETAPA C:

A una solución del compuesto preparado en el Ejemplo Preparativo 253, Etapa B (0,68 g, 3,0 mmol) en MeOH (5 ml) se le agregó una solución de KOH (0,68 g, 12,1 mmoles) en MeOH (5 ml). La mezcla se agitó a reflujo durante 12 horas y a temperatura ambiente durante 72 horas después de lo cual la mezcla se concentró hasta sequedad. El residuo crudo se suspendió en EtOAc (50 ml) y se agitó vigorosamente durante 30 minutos y luego se filtró. Este procedimiento se repitió 2 veces más y el filtrado resultante se concentró bajo presión reducida para proporcionar 128 mg (33%) de un aceite marrón/anaranjado. M+H = 130. Este material se usó sin purificación en la etapa de acoplamiento subsiguiente.

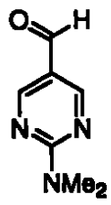
EJEMPLO PREPARATIVO 254:



El aldehído se preparó de acuerdo con el procedimiento de Gupton (*J. Heterocyclic Chem.* (1991), *28*, 1281).

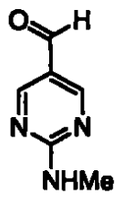
2446
447

EJEMPLO PREPARATIVO 255



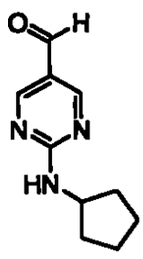
Usando el aldehído del Ejemplo Preparativo 254, se empleó el procedimiento de Gupton (*J. Heterocyclic Chem.* (1991), *28*, 1281) para preparar el aldehído del título.

EJEMPLO PREPARATIVO 256



El aldehído del título se preparó de acuerdo con el procedimiento de Ragan et. al *Synlett* (2000), *8*, 1172-1174.

EJEMPLO PREPARATIVO 257



La reacción de clorhidrato de ciclopentil guanidina conocida (*Org. Lett.* (2003), *5*, 1369-1372) bajo las condiciones de Ragan (*Synlett* (2000), *8*, 1172-1174) proporcionó el aldehído del título.

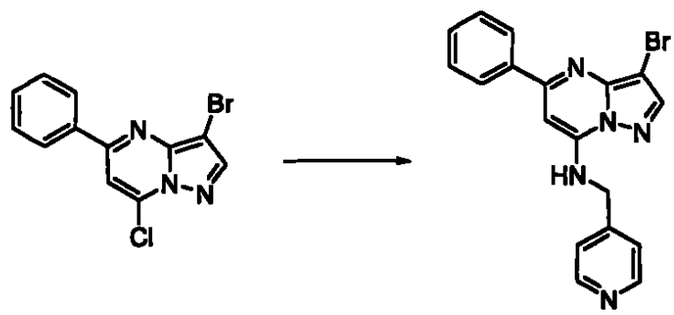
EJEMPLO PREPARATIVO

447
448

Se preparó el compuesto del título de acuerdo con la literatura conocida *Monatshefte fur Chemie* (1973), *104*, 1372-1382.

EJEMPLOS

EJEMPLO 1:



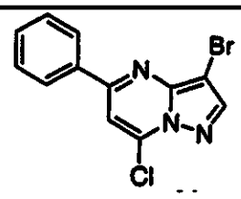
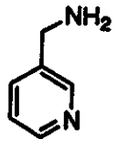
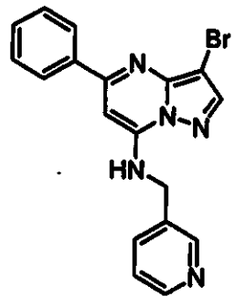
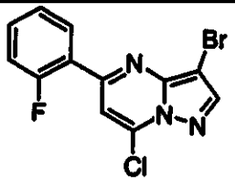
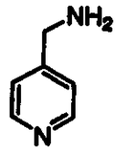
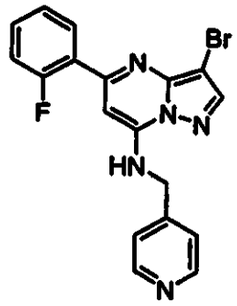
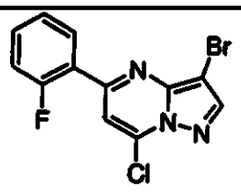
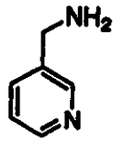
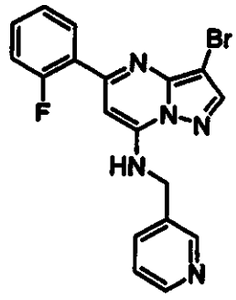
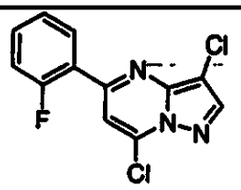
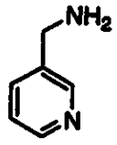
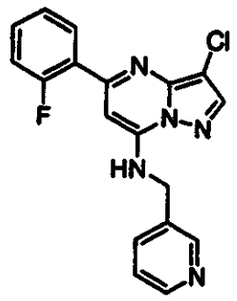
Una solución del producto del Ejemplo Preparativo 127 (0,27 g, 0,875 mmol), 4-aminometilpiridina (0,12 g, 1,3 eq.), y K_2CO_3 (0,24 g, 2 eq.) en CH_3CN (5 ml) se agitó a temperatura ambiente durante 48 horas. La mezcla de reacción se diluyó con H_2O y se extrajo con CH_2Cl_2. Los orgánicos combinados se secaron sobre Na_2SO_4, se filtraron y se concentraron. El producto crudo se purificó por cromatografía evaporativa usando una solución al 4% de MeOH en CH_2Cl_2 como eluyente (0,28 g, 93% de rendimiento). LCEM: MH^+ = 380; p.f. = >205°C (desc).

EJEMPLOS 2-210:

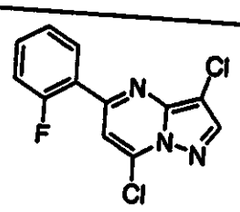
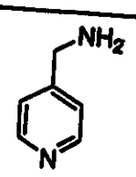
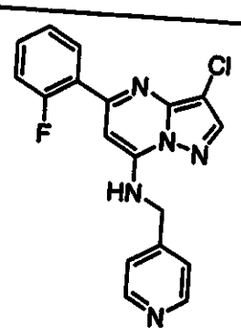
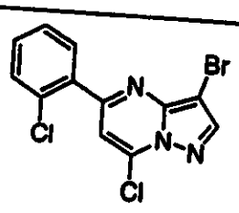
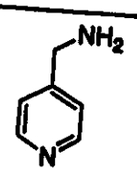
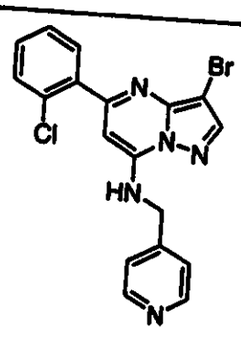
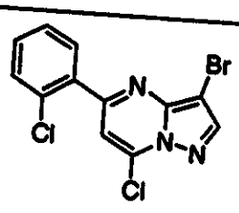
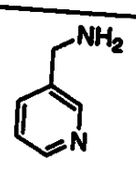
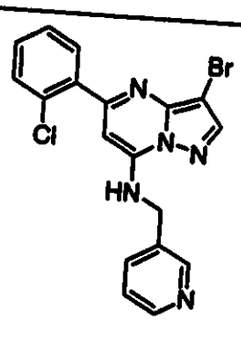
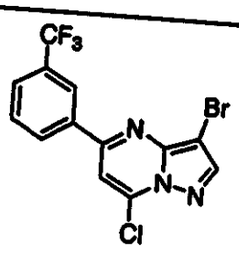
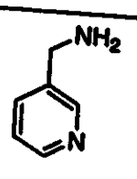
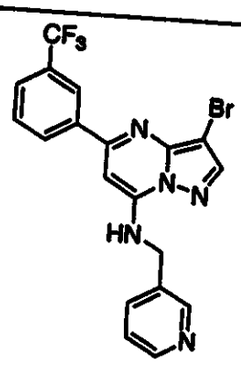
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo 1 sustituyendo únicamente los cloruros que se muestran en la Columna 2 de la Tabla 18 y las aminas que se muestran en la Columna 3 de la Tabla 18, se prepararon los compuestos de la Columna 4 de la Tabla 18:

448
449

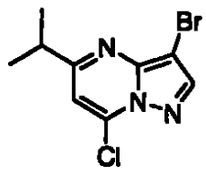
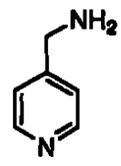
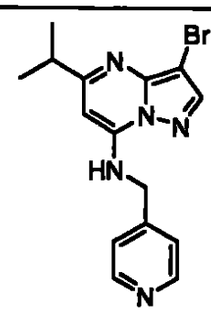
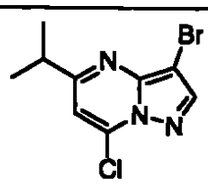
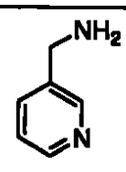
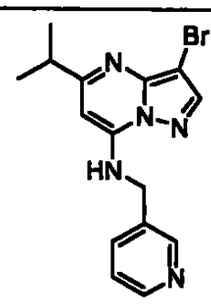
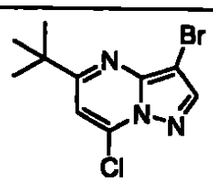
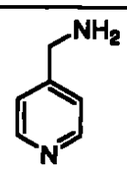
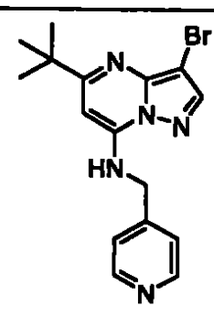
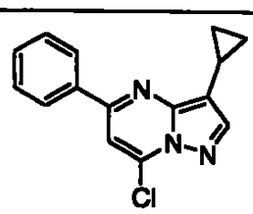
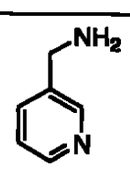
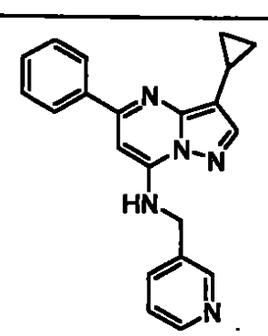
TABLA 18

Ej.	Columna 2	Columna 3	Columna 4	Datos
2				LCEM: MH^+ = 380; p.f.= 175-176°C
3				LCEM: MH^+ = 398; p.f.= 156-157°C
4				LCEM: MH^+ = 398; p.f.= 45-49°C
5				LCEM: MH^+ = 354; p.f.= 43-46°C

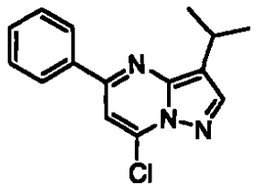
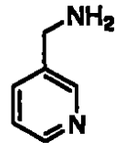
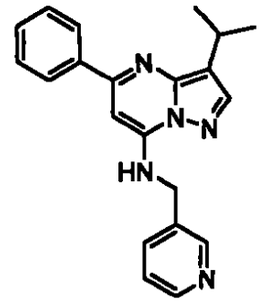
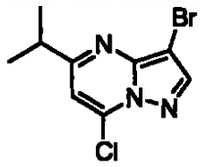
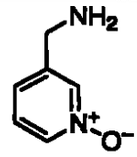
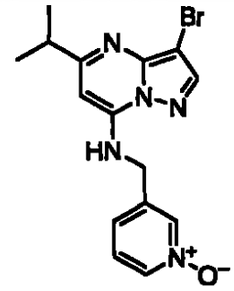
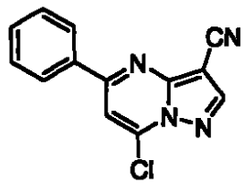
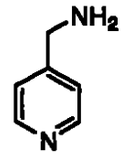
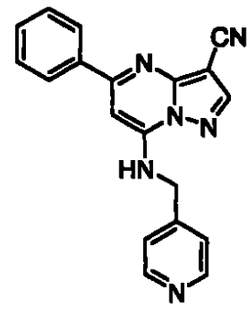
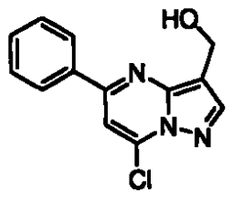
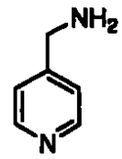
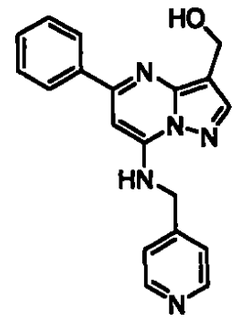
4019
450

6				LCEM: MH^+ = 354; p.f.= 149-150°C
7				LCEM: MH^+ = 414; p.f.= 86-92°C
8				LCEM: MH^+ = 414; p.f.= 185-186°C
9				LCEM: MH^+ = 448; p.f.= 167-168°C

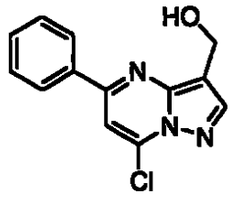
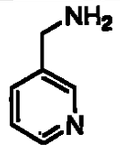
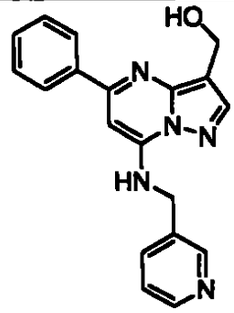
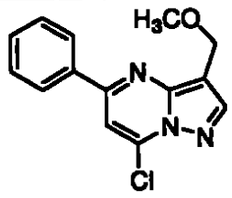
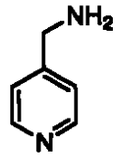
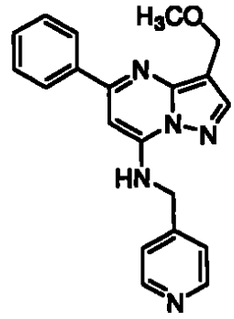
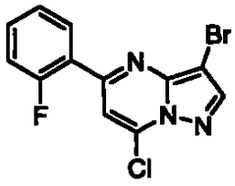
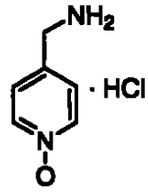
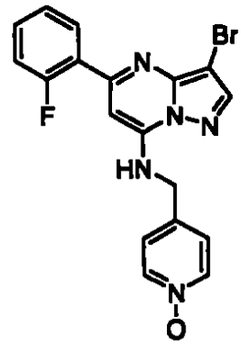
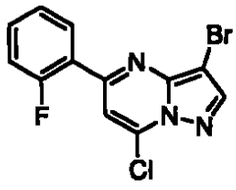
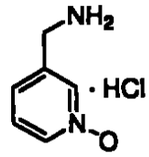
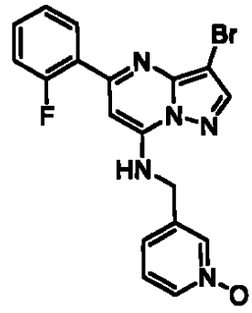
1450
451

10				LCEM: MH^+ = 346; p.f.= 57-58°C
11				LCEM: MH^+ = 347; p.f.= 122,9-125,3°C
12				LCEM: MH^+ = 360; p.f.= 127-128°C
13				LCEM: MH^+ = 342; p.f.= 133-135°C

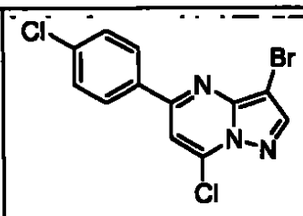
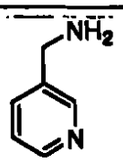
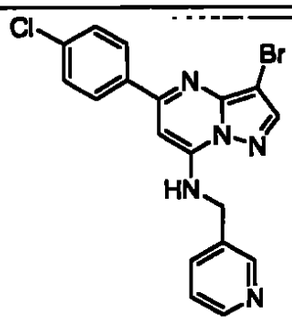
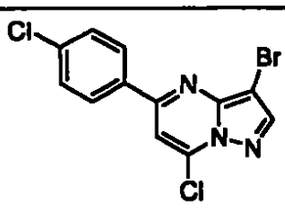
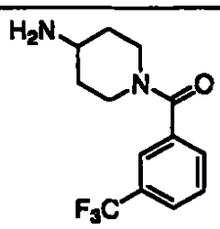
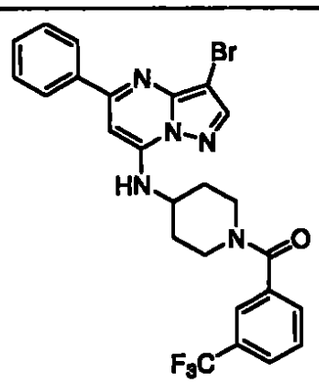
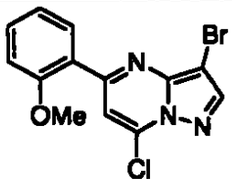
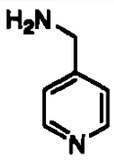
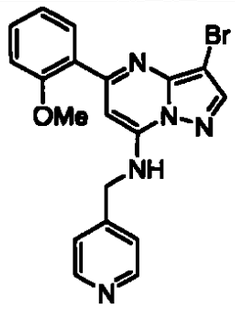
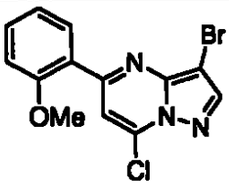
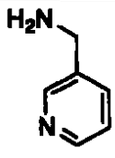
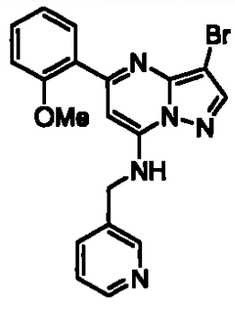
451
452

14				LCEM: MH^+ = 344; p.f.= 152-155°C
15				LCEM: MH^+ = 362; p.f.= 164-167°C
16				LCEM: MH^+ = 327; p.f.= 146-155°C
17				LCEM: MH^+ = 332; p.f.= 71-82°C

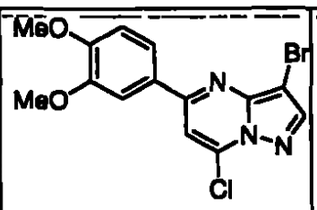
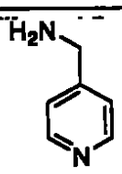
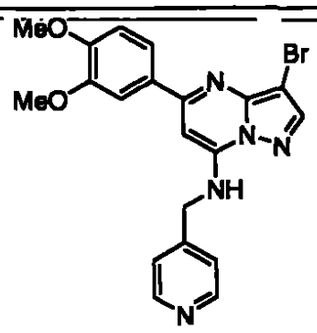
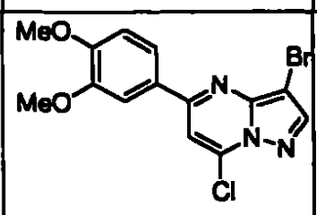
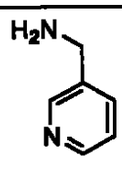
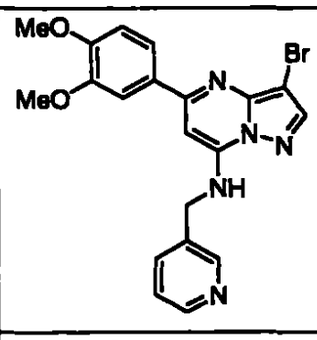
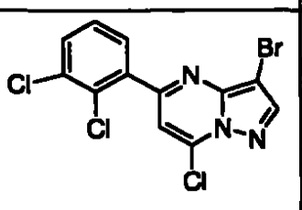
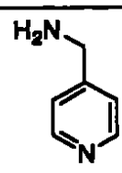
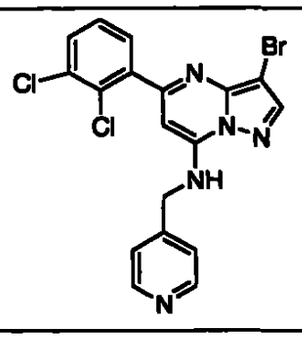
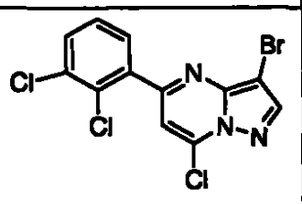
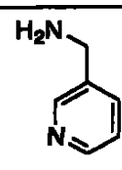
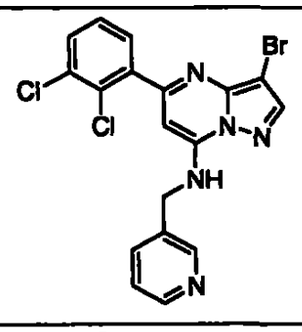
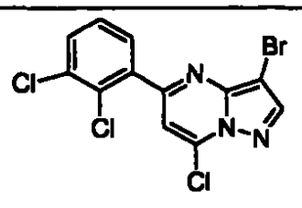
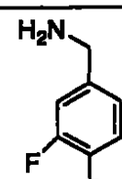
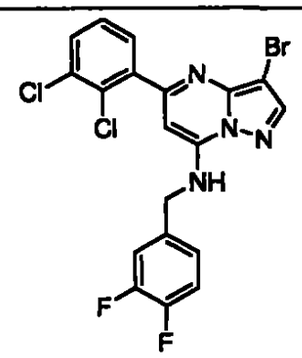
452
453

17. 1				EM: MH^+ = 332
18				LCEM: MH^+ = 346; p.f.= 58- 65°C
19				LCEM: MH^+ = 414; p.f.= 211- 213°C
20				LCEM: MH^+ = 414; p.f.= 194- 197°C

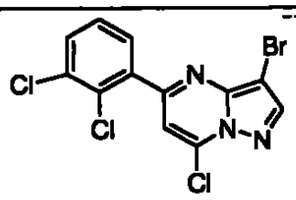
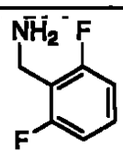
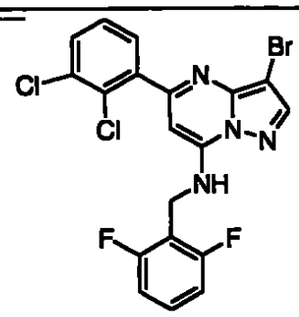
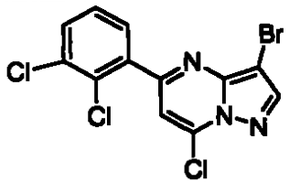
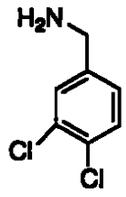
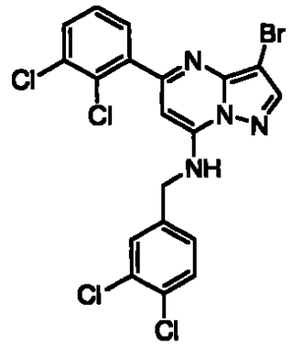
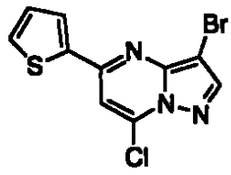
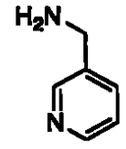
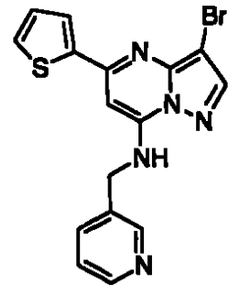
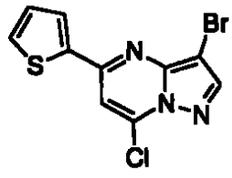
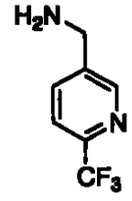
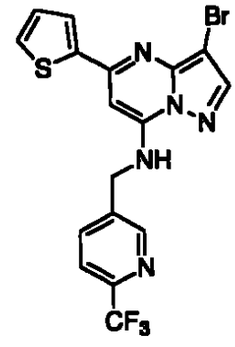
453
454

21				EM: MH^+ = 414 p.f. 211 – 216°C
22				LCEM: MH^+ = 544; p.f.= 104-107°C
23				Rend. = 83% LCEM: MH^+ = 410.
24				Rend. = 84% LCEM: MH^+ = 410

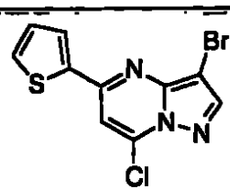
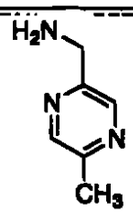
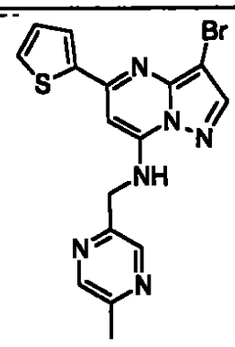
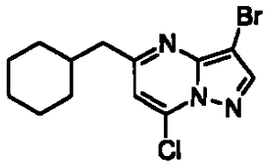
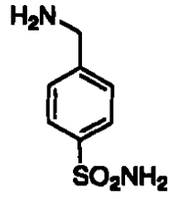
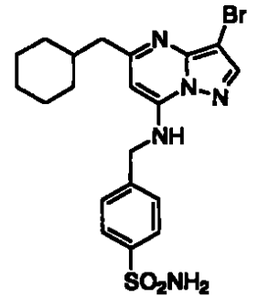
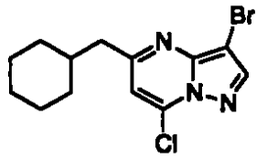
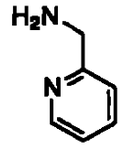
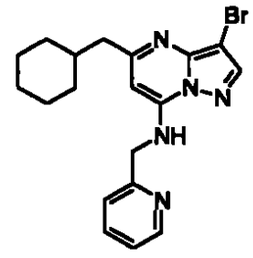
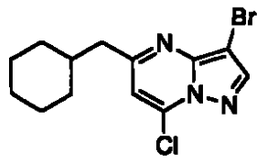
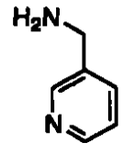
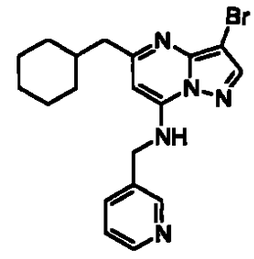
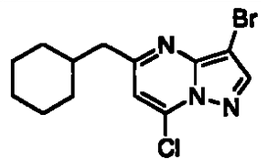
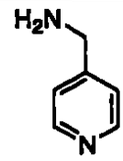
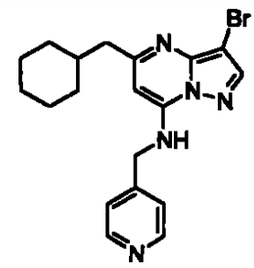
454
455

25				Rend. = 96% LCEM: MH^+ = 440.
26				Rend. = 99% LCEM: MH^+ = 440
27				Rend. = 89% LCEM: MH^+ = 448
28				Rend. = 78% LCEM: MH^+ = 448
30				Rend. = 96% LCEM: MH^+ = 483

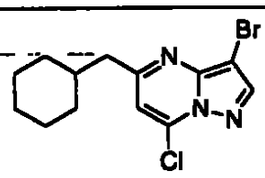
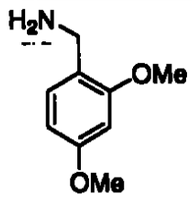
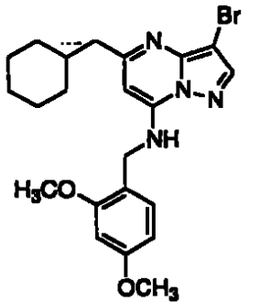
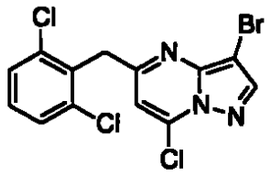
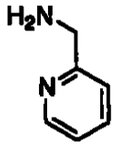
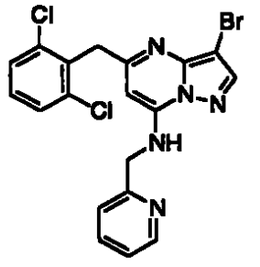
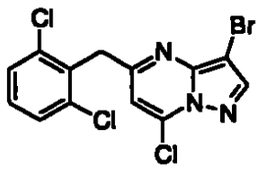
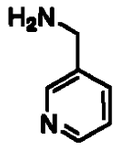
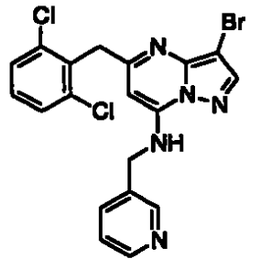
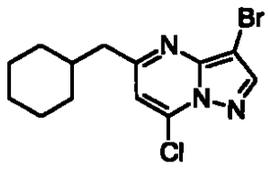
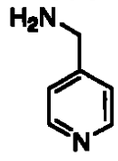
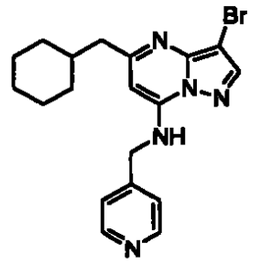
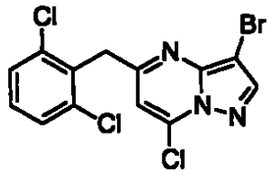
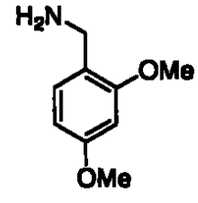
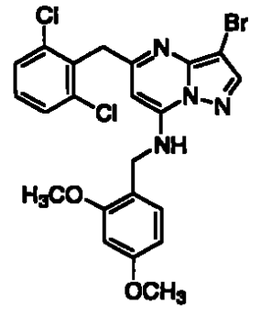
455
456

31				Rend. = 35% LCEM: MH^+ = 483
32				Rend. = 77% LCEM: MH^+ = 515
33				Rend. = 100% p.f. 179°C LCEM: MH^+ = 388
34				Rend. = 99% p.f. 186°C LCEM: MH^+ = 456

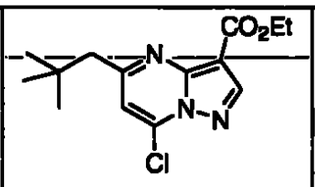
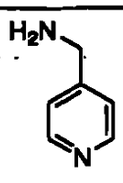
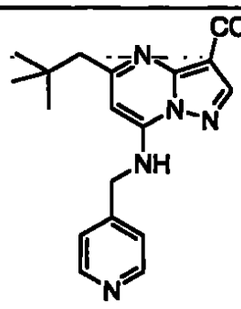
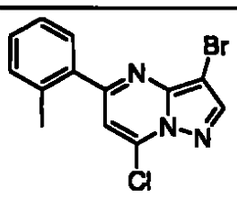
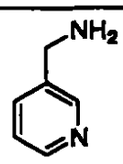
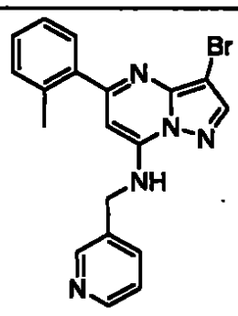
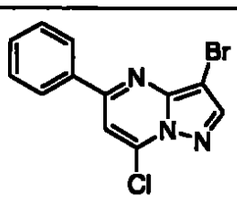
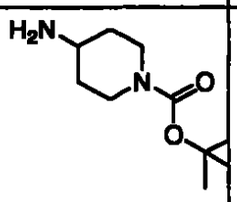
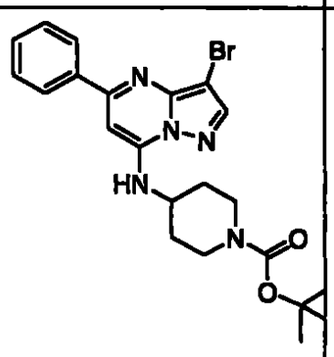
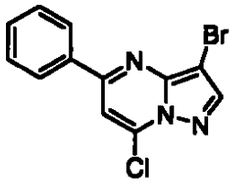
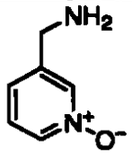
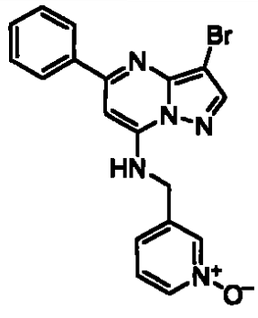
456
457

35				Rend. = 98% p.f. 181°C LCEM: MH^+ = 401
36				Rend. = 63% p.f. 192°C LCEM: MH^+ = 480
37				Rend. = 75% p.f. 126 – 127°C LCEM: MH^+ = 400
38				Rend. = 94% p.f. 132 -133°C LCEM: MH^+ = 400
39				Rend. = 95% p.f. 121 – 122°C LCEM: MH^+ = 400

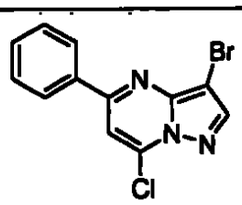
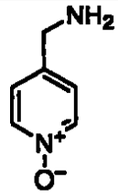
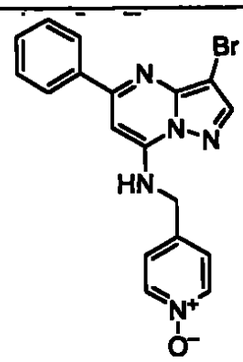
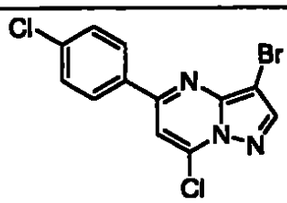
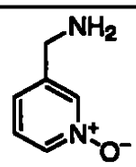
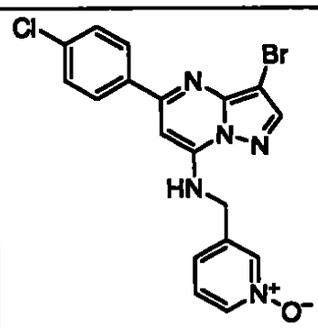
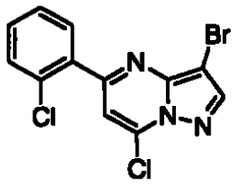
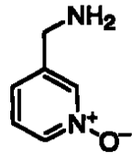
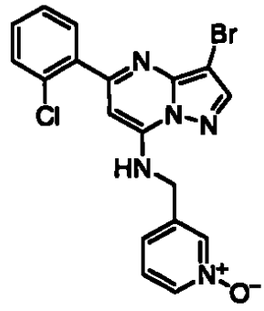
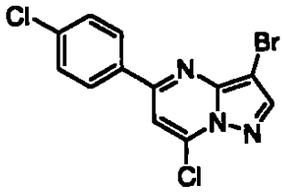
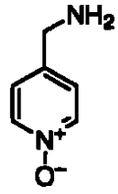
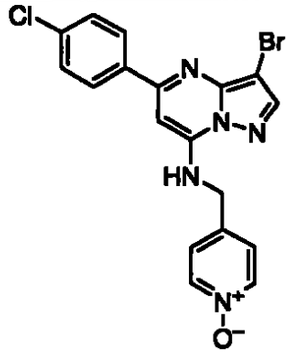
457
458

40				Rend. = 98% LCEM: MH^+ = 460
41				Rend. = 87% p.f. 170 - 171°C LCEM: MH^+ = 464
42				Rend. = 84% p.f. 216 -217°C LCEM: MH^+ = 464
43				Rend. = 96% p.f. 214°C LCEM: MH^+ = 464
44				Rend. = 95% p.f. 158°C LCEM: MH^+ = 522

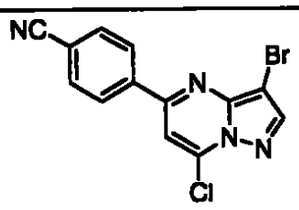
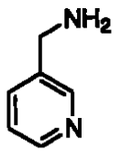
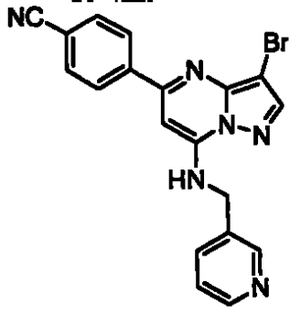
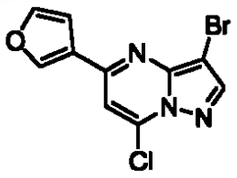
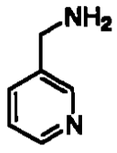
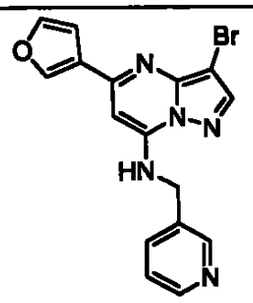
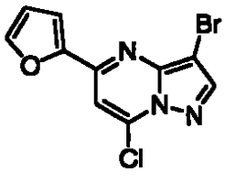
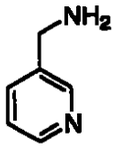
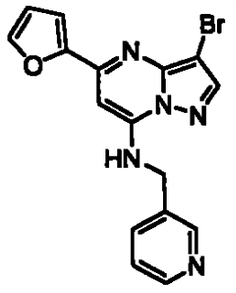
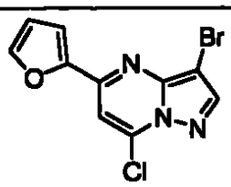
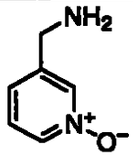
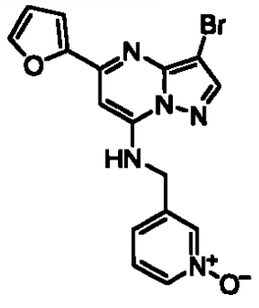
458
459

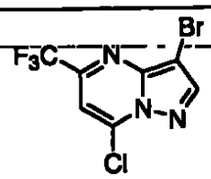
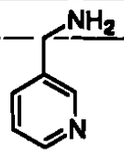
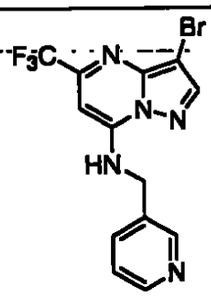
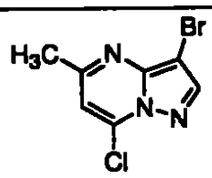
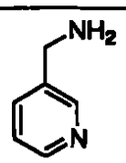
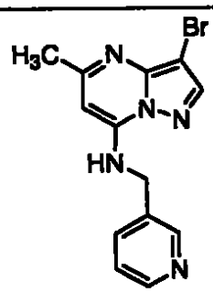
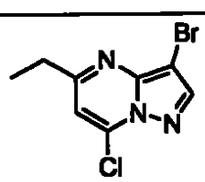
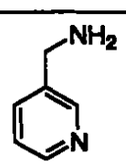
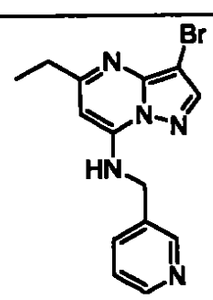
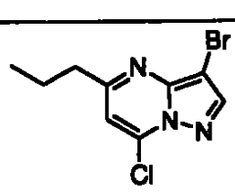
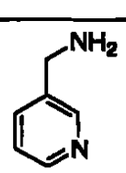
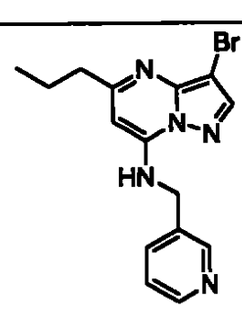
45				Rend. = 90% LCEM: MH^+ = 278
46				Rend. = 100%; LCEM: MH^+ = 394
47				LCEM: MH+ = 473 p.f. 84 - 87°C
48				EM: MH^+ = 396 p.f. 91,5 – 93,3°C

459
460

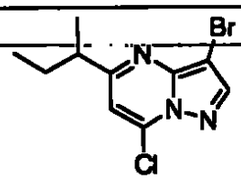
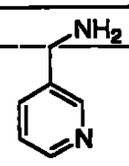
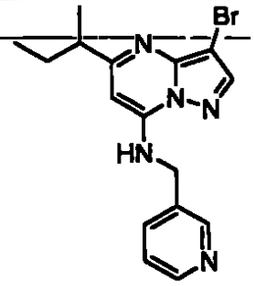
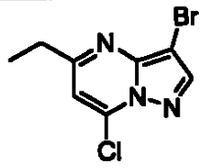
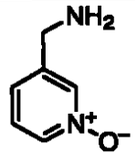
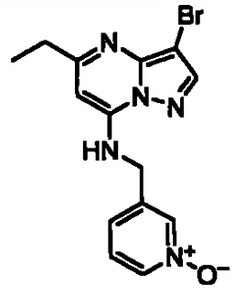
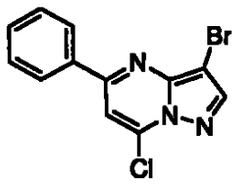
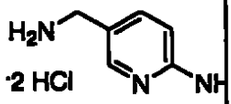
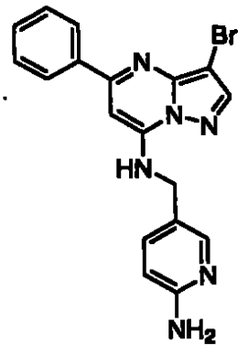
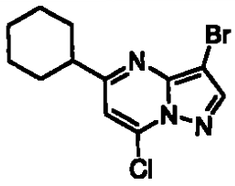
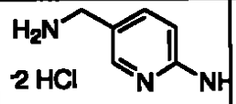
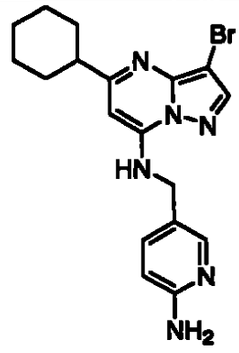
49				EM: MH^+ = 396 p.f. 196 – 199°C
50				EM: MH^+ = 430 p.f. 242 – 244°C
51				EM: MH^+ = 430 p.f. 218°C
52				EM: MH^+ = 430 p.f. 230 – 233°C

460-
461

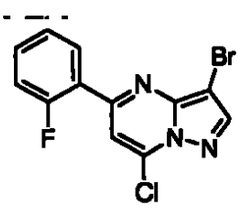
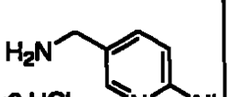
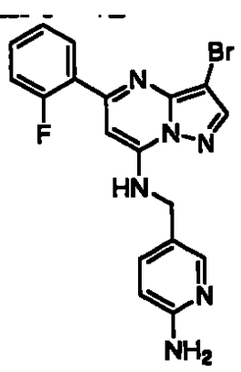
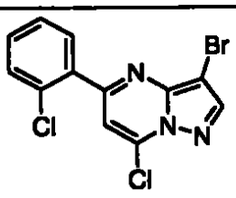
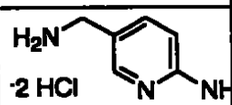
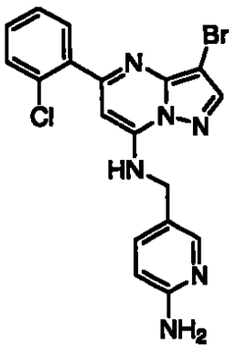
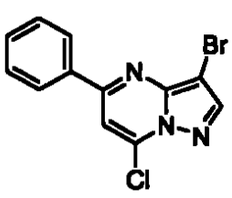
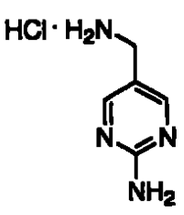
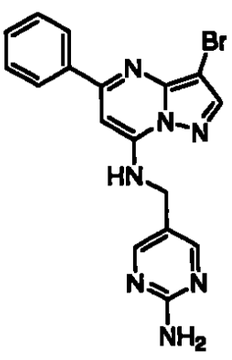
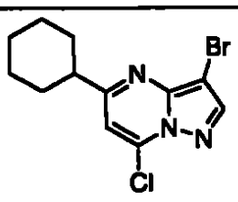
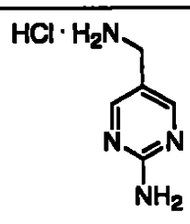
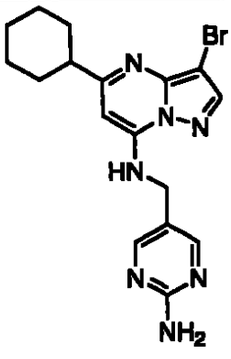
54				EM: MH^+ = 405 p.f. 185 – 188°C
55				EM: MH^+ = 370 p.f. 229 – 232°C
56				EM: MH^+ = 370 p.f. 85 – 90°C
57				EM: MH^+ = 386 p.f. 227 – 230°C

58				EM: MH^+ = 372 p.f. 212 – 215°C
59				EM: MH^+ = 318 p.f. 169 – 171°C
60				EM: MH^+ = 332 p.f. 170 – 173°C
61				EM: MH^+ = 346 p.f. 156 – 159°C

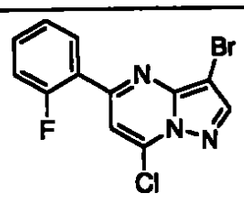
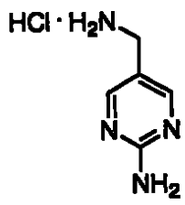
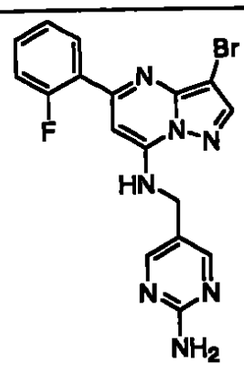
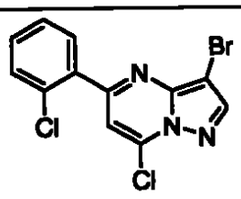
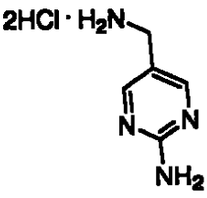
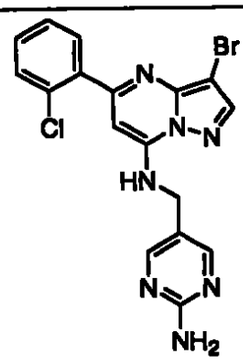
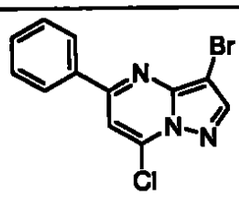
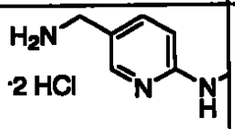
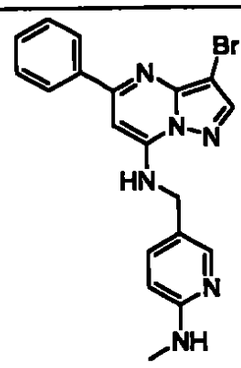
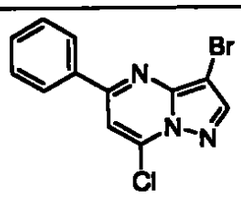
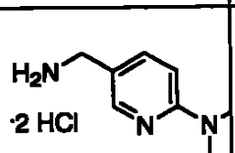
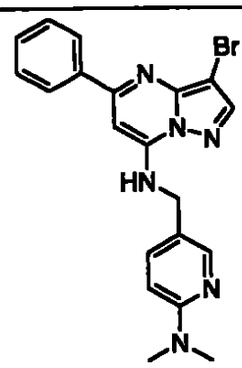
462
463

62				EM: MH^+ = 360 p.f. 114 – 116°C
63				EM: MH^+ = 348 p.f. 197 – 200°C
64				1. p.f. = 230-232 2. M+H = 396
65				1. p.f. = 205-207 2. M+H = 402

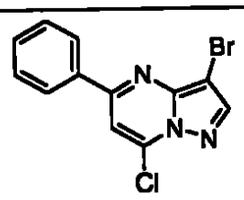
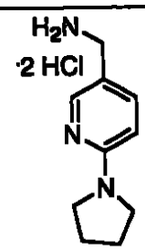
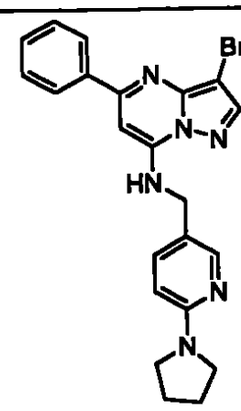
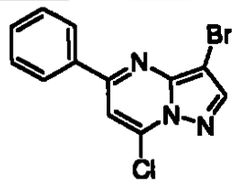
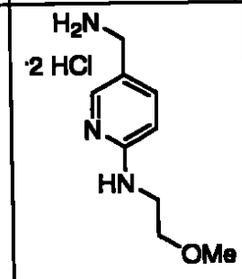
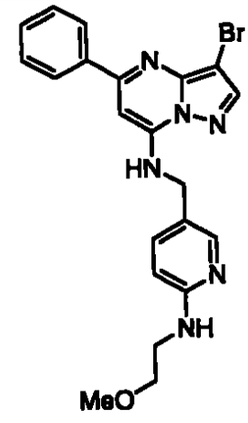
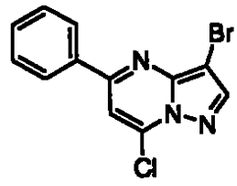
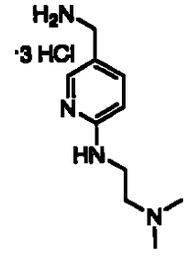
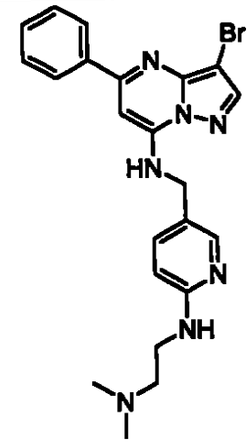
463
461

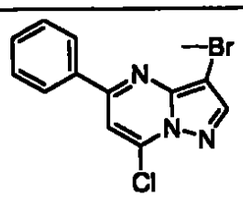
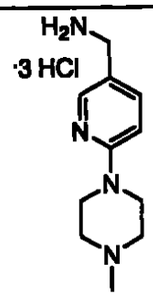
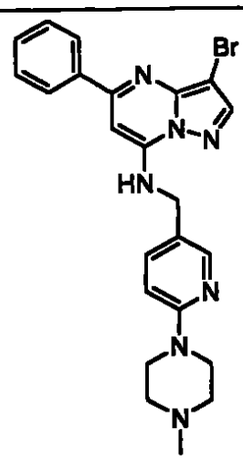
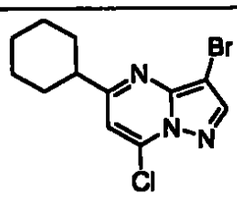
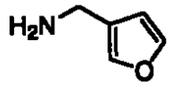
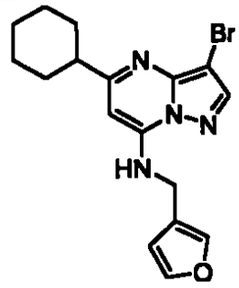
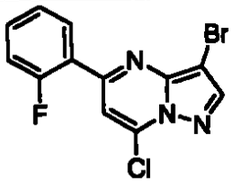
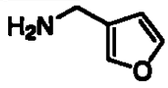
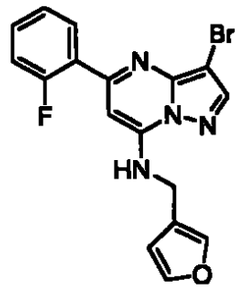
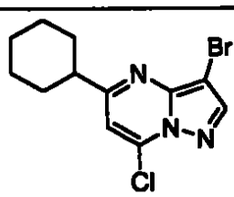
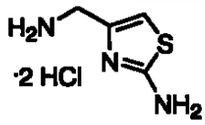
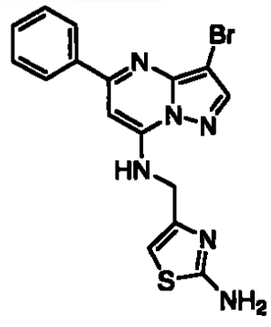
66				1. p.f. = 220-223 2. M+H = 414
67				1. p.f. = 191-193 2. M+H = 431
68				1. p.f. = 235-237 2. M+H = 397
69				1. p.f. = >250 2. M+H = 403

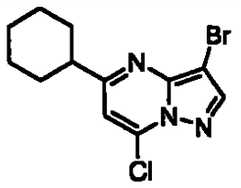
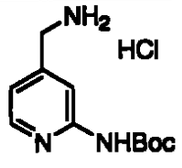
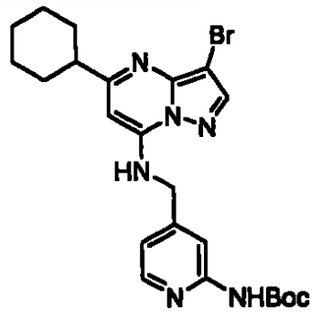
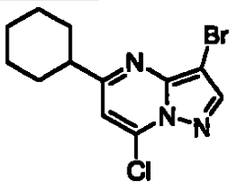
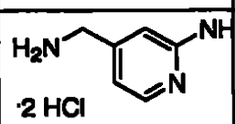
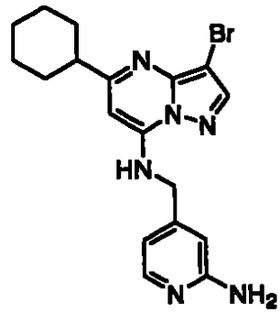
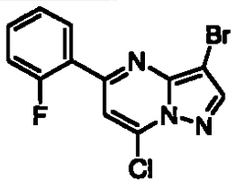
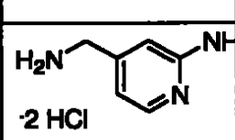
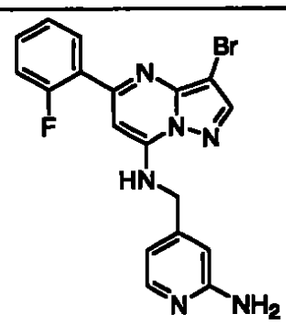
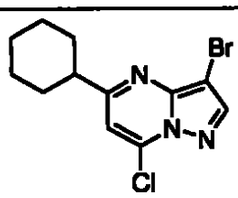
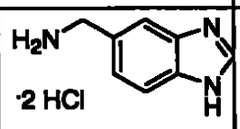
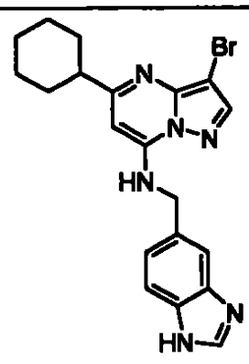
464
465

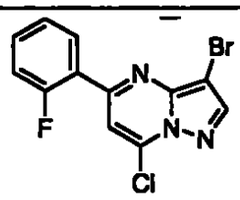
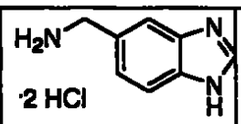
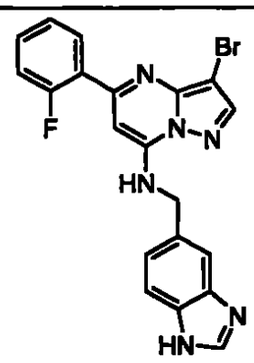
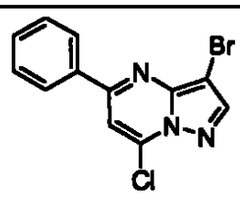
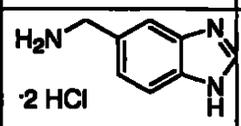
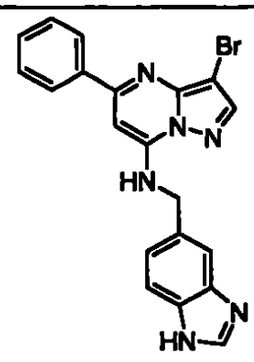
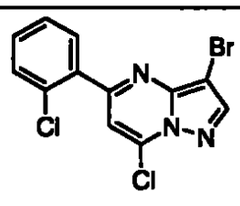
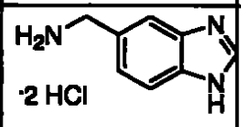
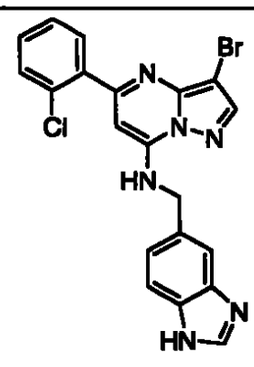
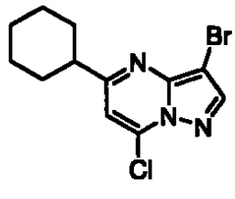
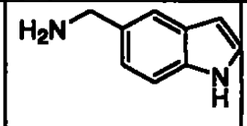
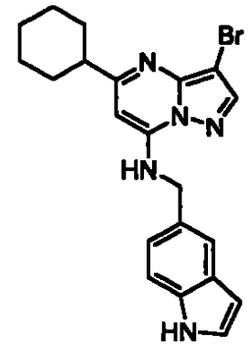
70				1. p.f. = 230-232 2. M+H = 415
71				1. p.f. = 235-238 2. M+H = 431
72				1. p.f. = 186-188 2. M+H = 410
73				1. p.f. = 136-138 2. M+H = 424

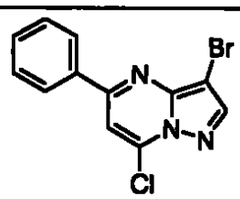
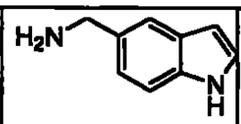
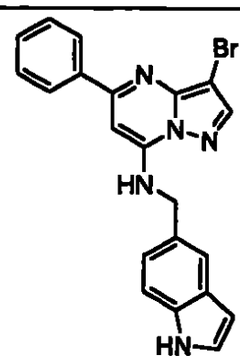
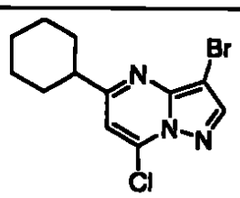
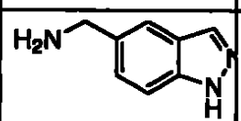
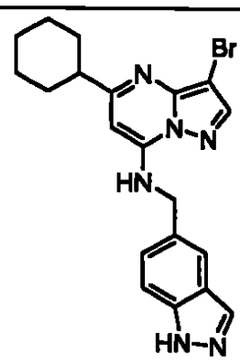
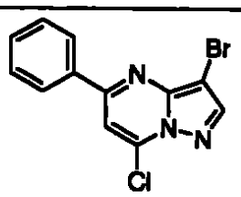
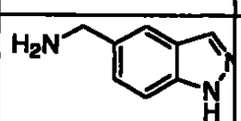
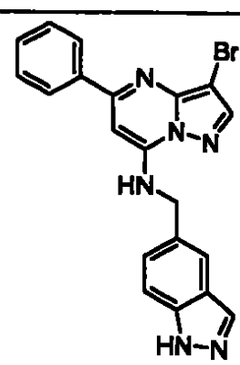
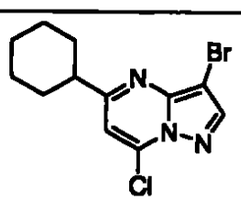
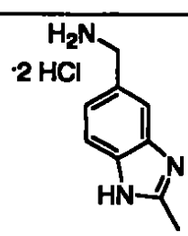
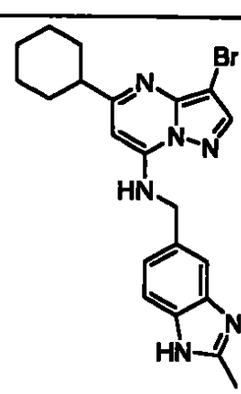
465
466

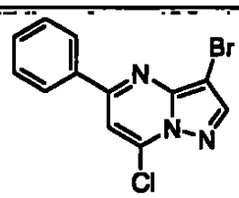
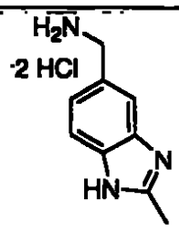
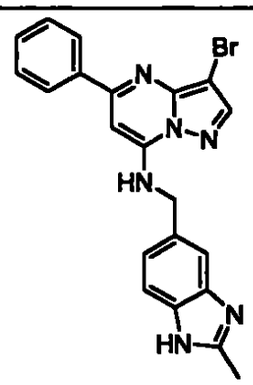
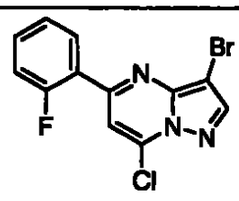
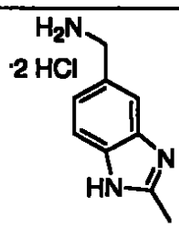
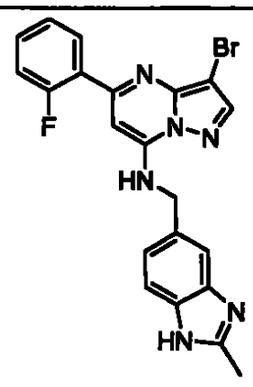
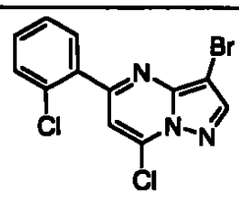
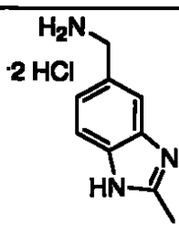
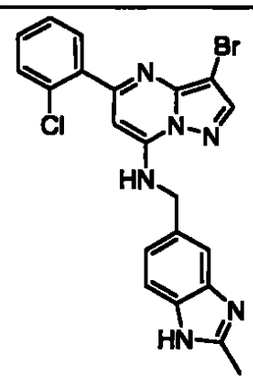
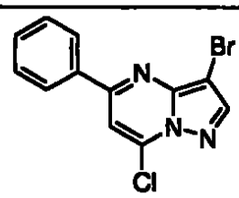
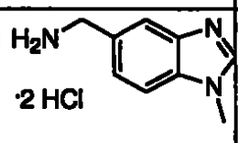
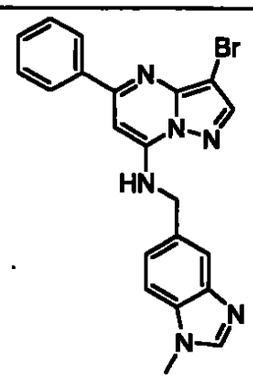
74				1. p.f. = 192-195 2. M+H = 450
75				1. p.f. = 88-90 2. M+H = 454
76				1. p.f. = 230-232 2. M+H = 467

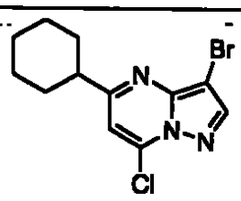
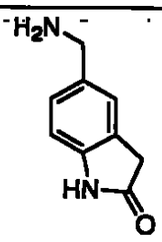
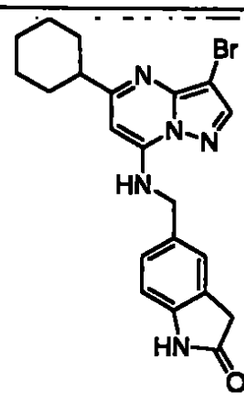
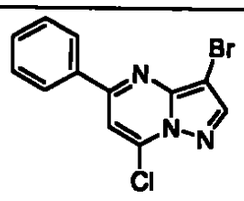
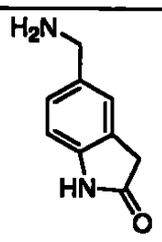
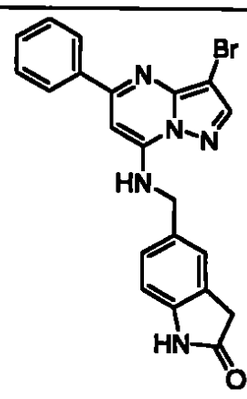
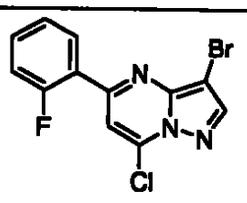
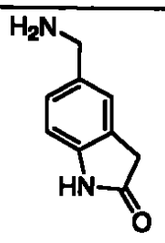
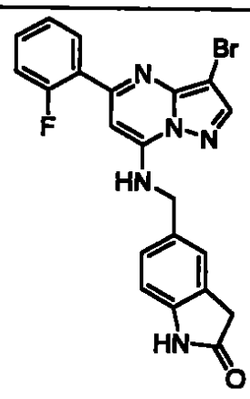
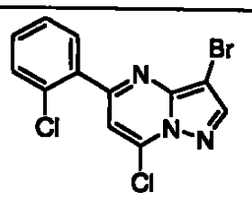
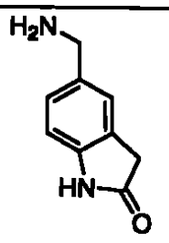
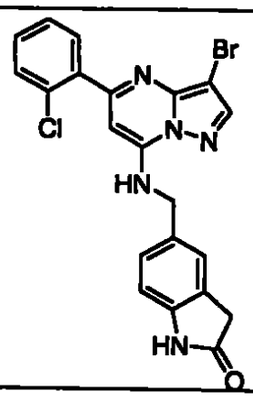
77				1. p.f. = 131-133 2. M+H = 479
78				1. p.f. = 85-88 2. M+H = 376
79				1. p.f. = 131-133 2. M+H = 388
80				1. p.f. = 206-208 2. M+H = 408

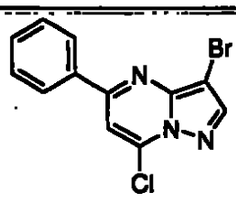
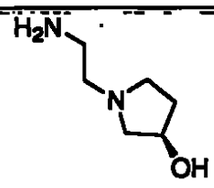
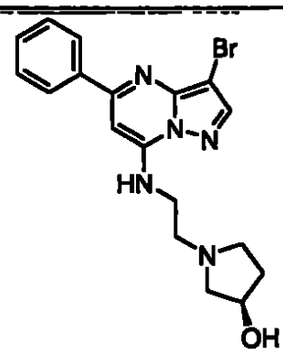
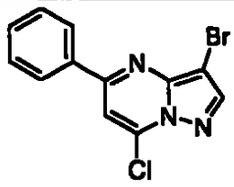
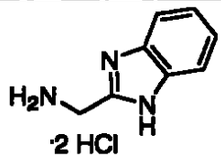
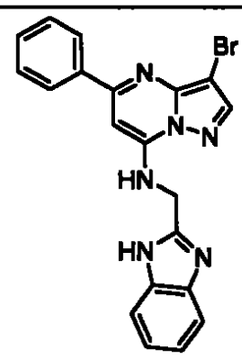
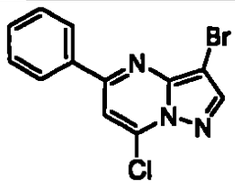
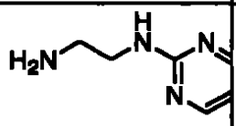
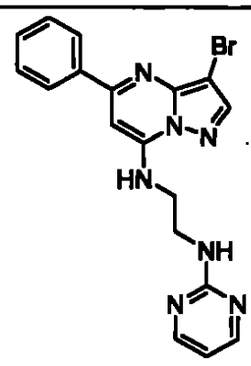
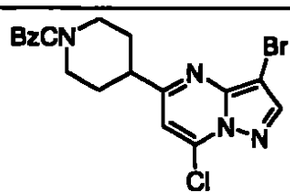
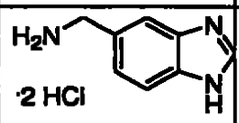
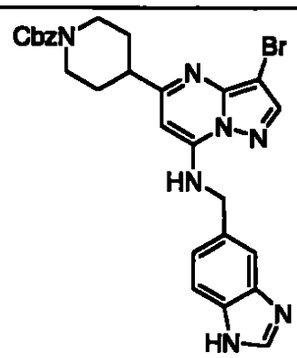
81				1. p.f. = 108-110 2. M+H = 502
82				1. p.f. = 83-85 2. M+H = 402
83				1. p.f. = 220 2. M+H = 414
84				1. p.f. = 154-156 2. M+H = 426

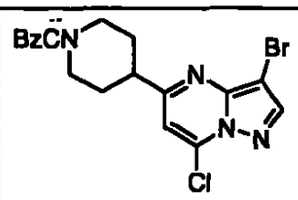
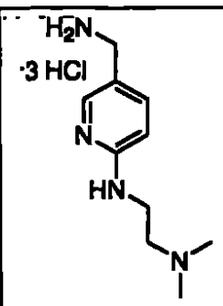
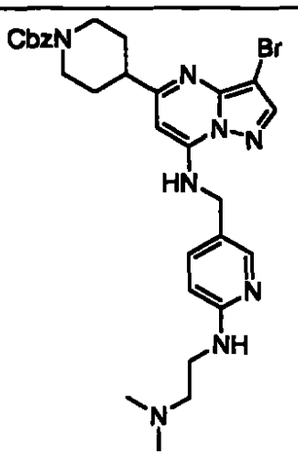
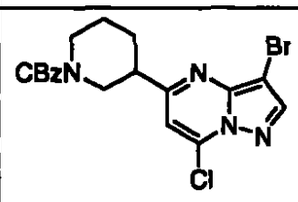
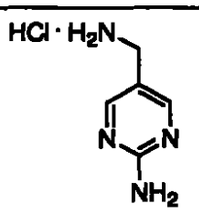
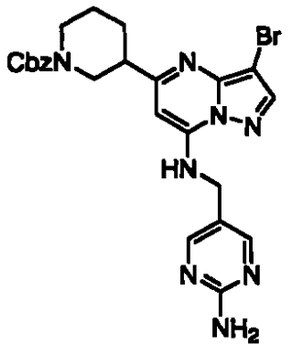
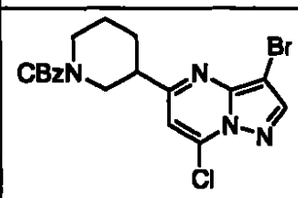
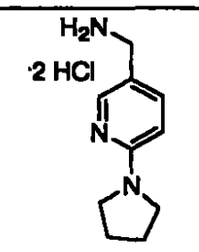
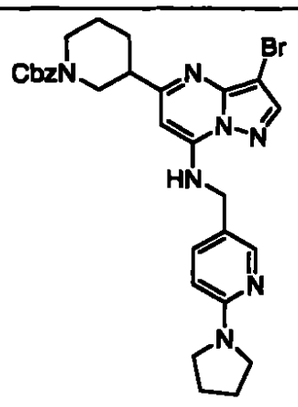
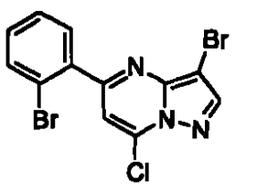
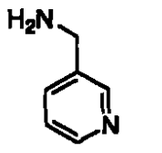
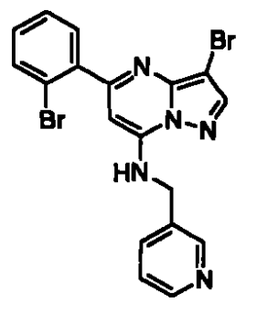
85		 ·2 HCl		1. p.f. = 152-153 2. M+H = 438
86		 ·2 HCl		1. p.f. = 159-161 2. M+H = 420
87		 ·2 HCl		1. p.f. = >220 2. M+H = 455
88				1. p.f. = 223-225 2. M+H = 425

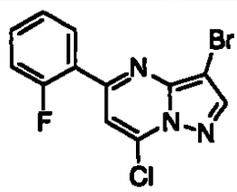
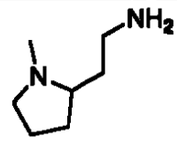
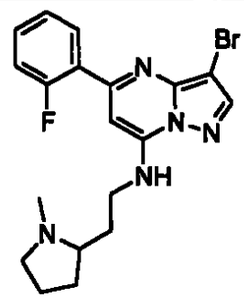
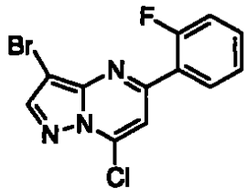
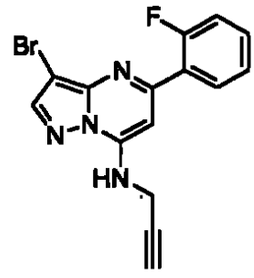
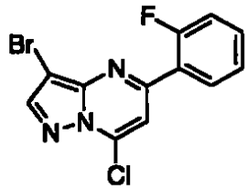
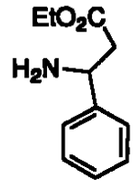
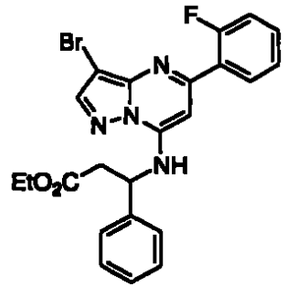
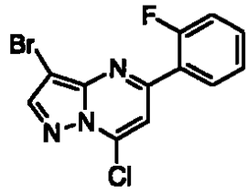
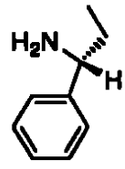
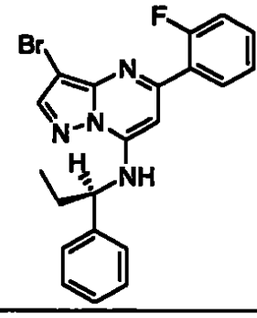
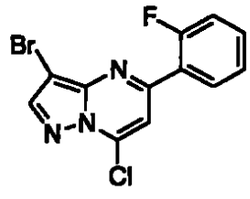
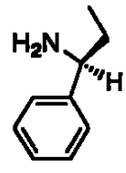
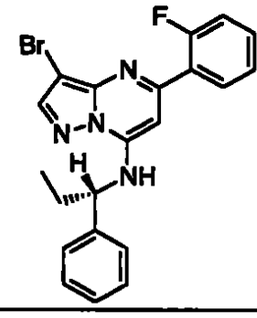
89				1. p.f. = 199-201 2. M+H = 419
90				1. p.f. = 184-186 2. M+H = 426
91				1. p.f. = 196-198 2. M+H = 420
92				1. p.f. = 156-159 2. M+H = 440

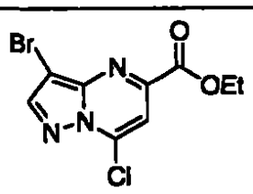
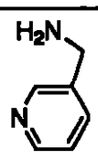
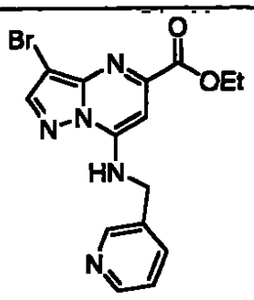
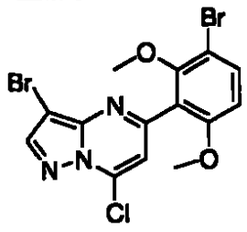
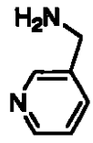
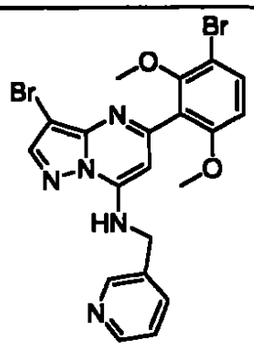
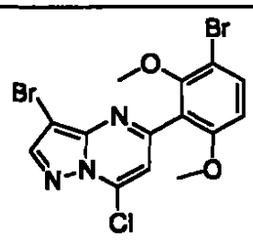
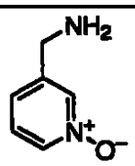
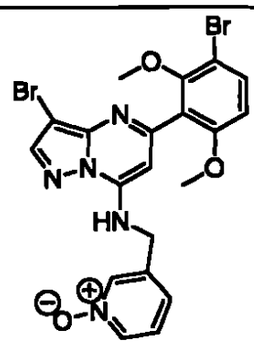
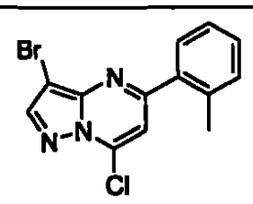
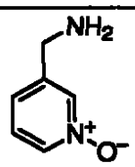
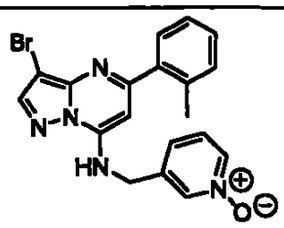
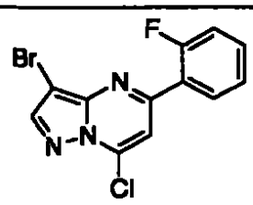
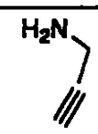
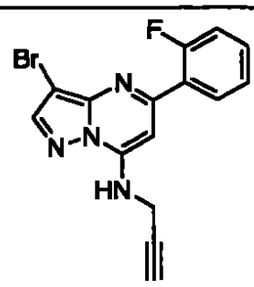
93				1. p.f. = 173-176 2. M+H = 434
94				1. p.f. = 173-175 2. M+H = 452
95				1. p.f. = 174-176 2. M+H = 469
96				1. p.f. = 230-234 2. M+H = 434

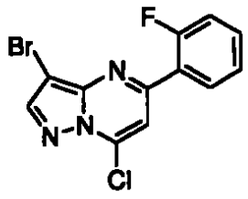
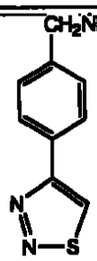
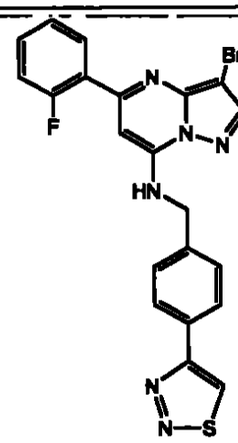
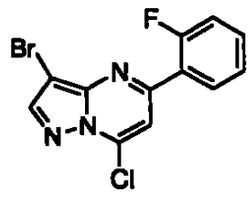
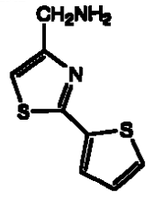
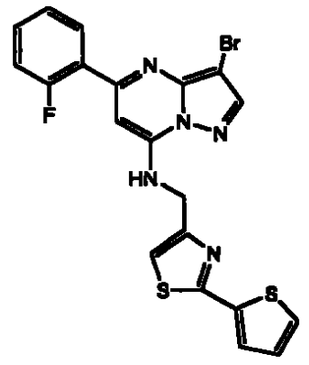
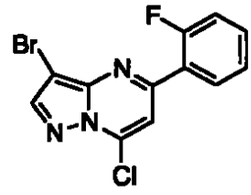
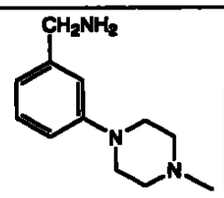
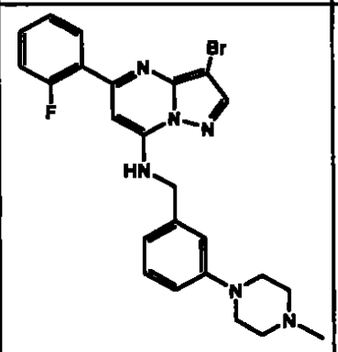
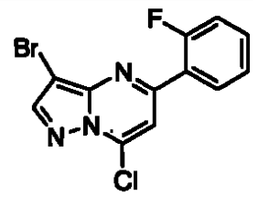
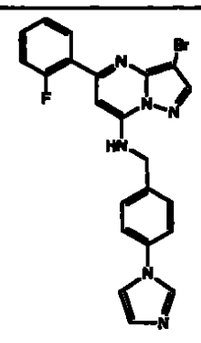
97				1. p.f. = 191-193 2. M+H = 441
98				1. p.f. = 202-205 2. M+H = 434
99				1. p.f. = 209-212 2. M+H = 453
100				1. p.f. = 219-221 2. M+H = 469

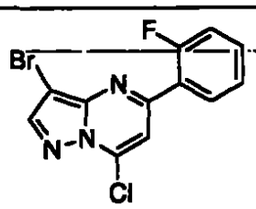
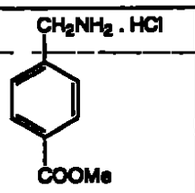
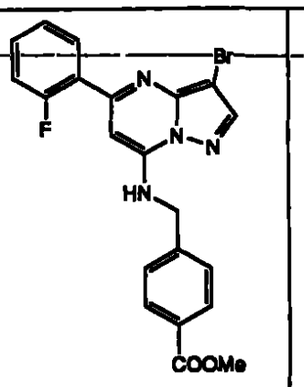
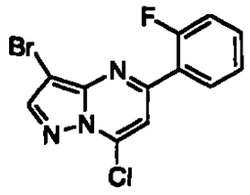
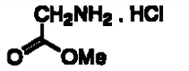
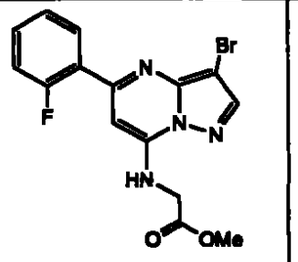
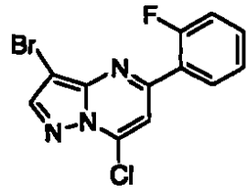
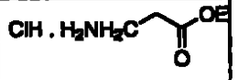
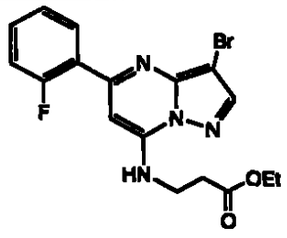
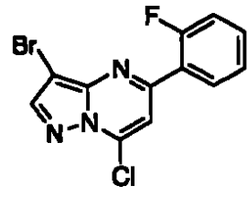
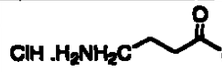
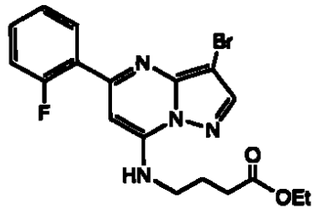
101				1. p.f. = 64-66 2. M+H = 403
102				1. p.f. = 168-170 2. M+H = 420
103				1. p.f. = 213-216 2. M+H = 411
104				1. p.f. = 98-100 2. M+H = 561

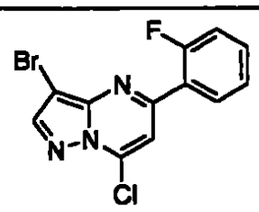
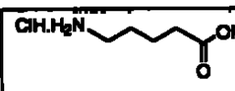
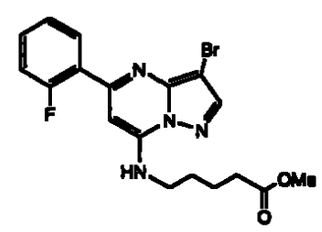
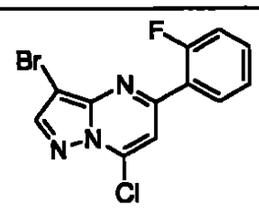
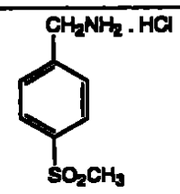
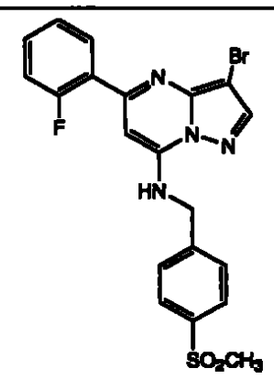
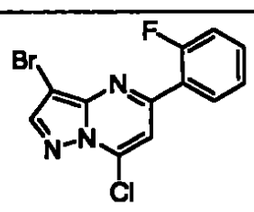
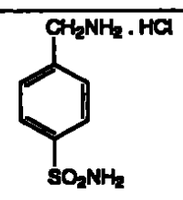
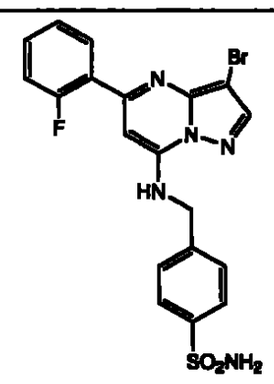
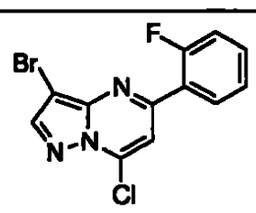
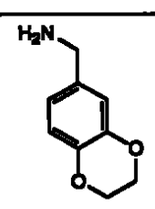
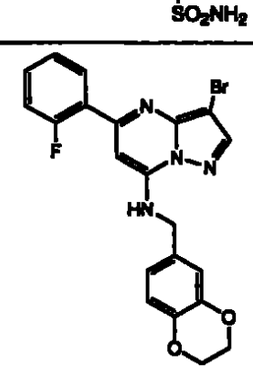
105				1. p.f. 70-72 2. M+H = 608
106				1. p.f. 168-170 2. M+H = 538
107				1. p.f. 189-191 2. M+H = 592
108				LCEM: MH^+ = 458;

109				Rend. = 89 LCEM: MH^+ = 418 p.f. = 131-132°C
110				Rend. = 95% LCEM: MH^+= 347
111				Rend. = 91% 3H); LCEM: MH^+= 484
112				Rend. = 87% LCEM: MH^+= 427
113				Rend. = 80% LCEM: MH^+ = 427

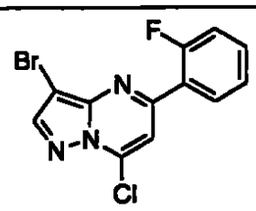
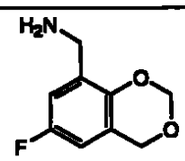
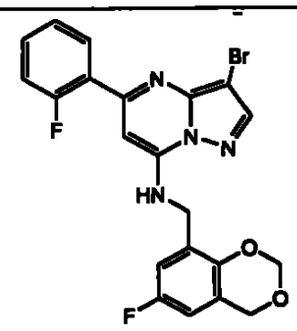
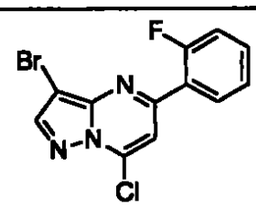
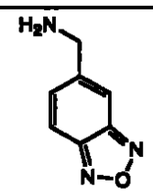
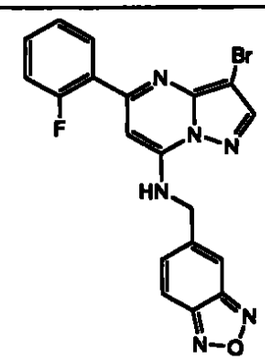
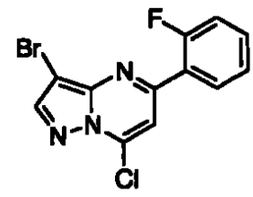
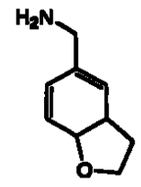
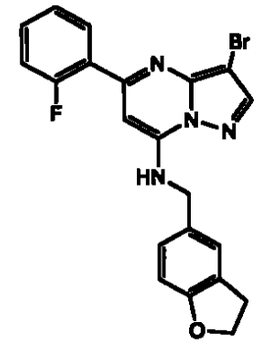
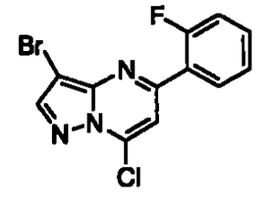
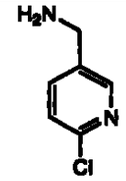
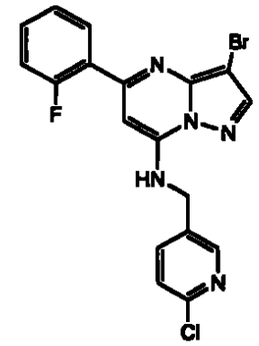
114				Rend. = 91% LCEM: MH^+ = 378
115				Rend. = 92%, 3H); LCEM: MH^+ = 520
116				Rend. = 98% LCEM: MH^+ = 536
117				Rend. = 82% LCEM: MH^+ = 410
118				Rend. = 95% LCEM: MH^+ = 347

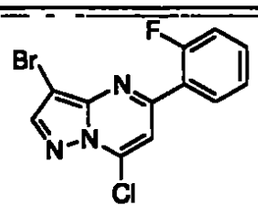
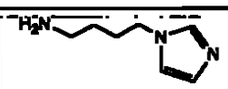
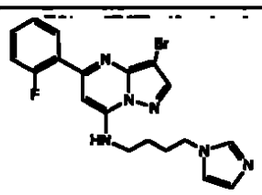
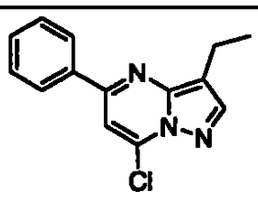
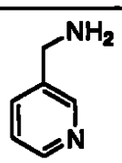
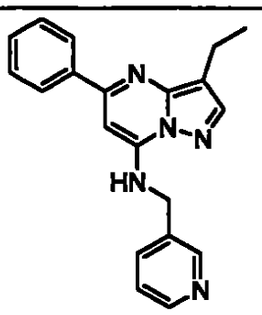
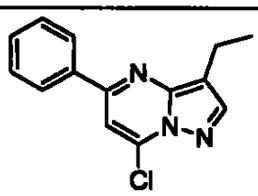
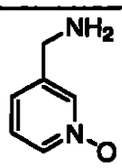
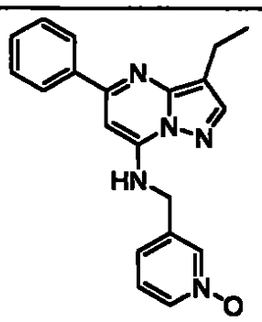
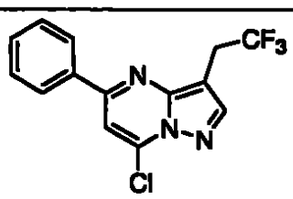
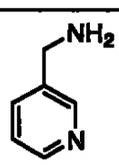
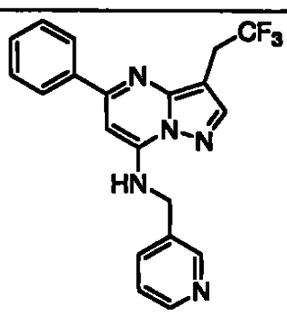
121				Rend. = 65% LCEM: MH^+ = 481,02
126				Rend. = 71% MH^+ = 486
127				Rend. = 71% MH^+ = 495,1
128				Rend. = 55% MH^+ = 463

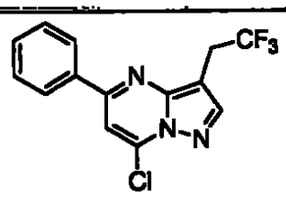
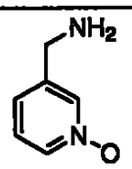
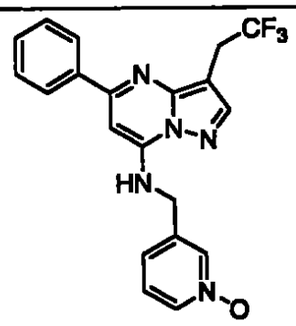
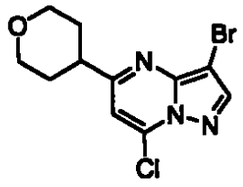
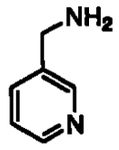
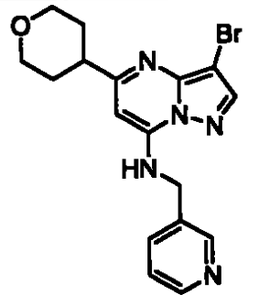
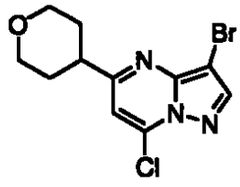
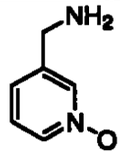
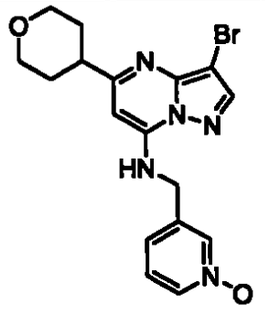
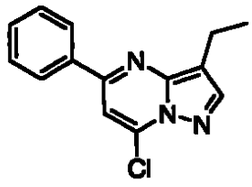
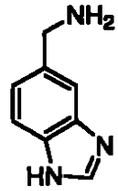
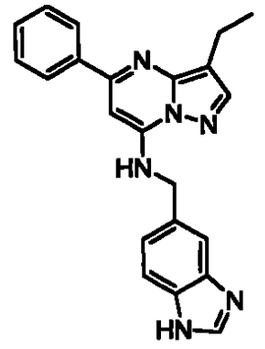
129				Rend. = 77% LCEM: MH^+ = 455
130				^1H RMN (Rend. = 75% LCEM: MH^+ = 379
131				Rend. = 75% LCEM: MH^+ = 407
132				Rend. = 75% LCEM: MH^+ = 421

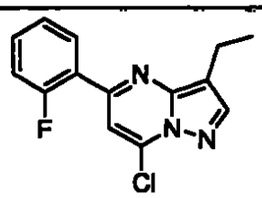
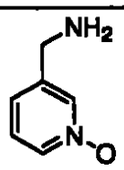
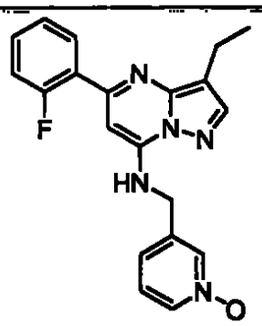
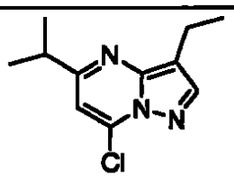
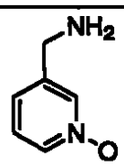
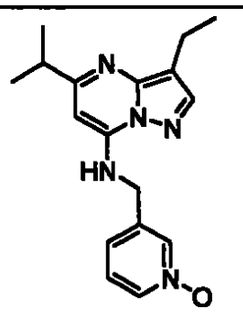
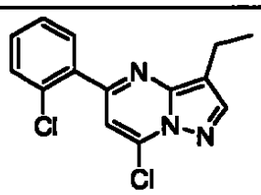
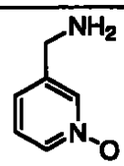
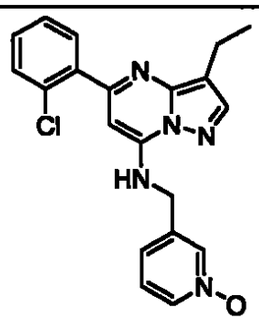
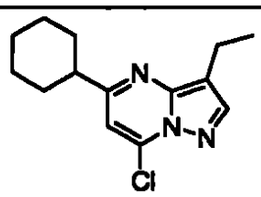
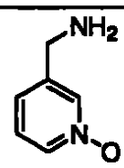
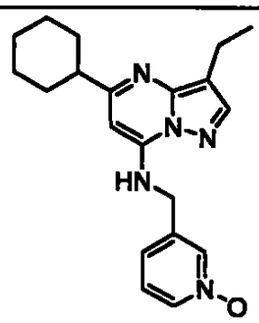
133				Rend. = 70% LCEM: MH^+ = 421
134				Rend. = 78% LCEM: MH^+ = 475
135				Rend. = 75% LCEM: MH^+ = 476
136				Rend. = 65% LCEM: MH^+ = 455

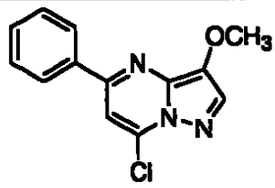
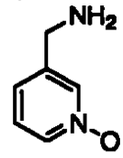
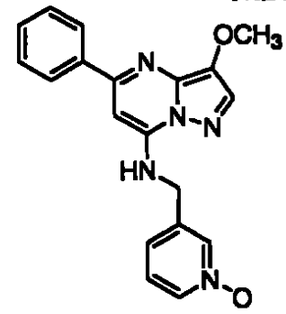
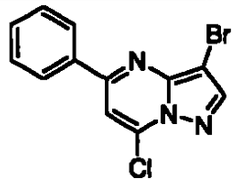
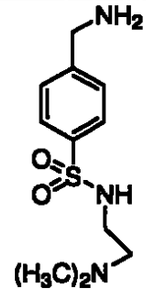
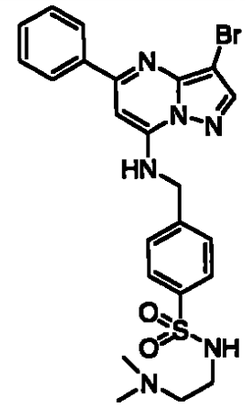
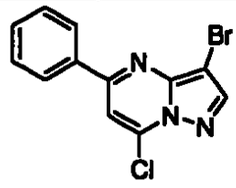
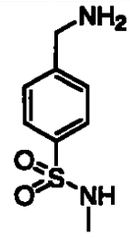
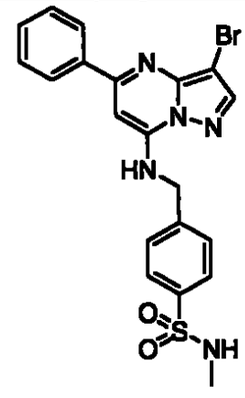
480

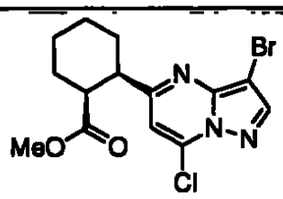
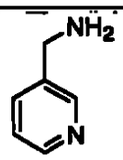
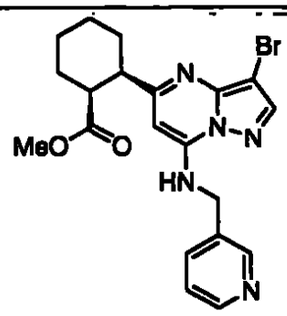
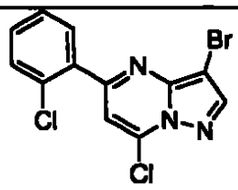
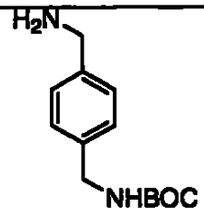
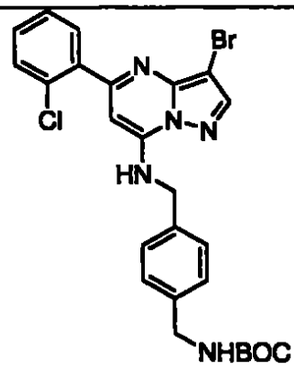
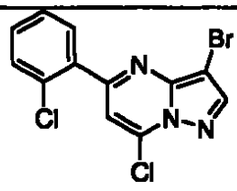
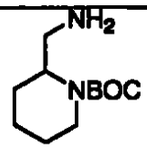
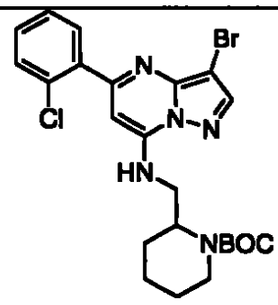
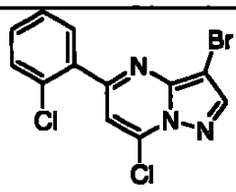
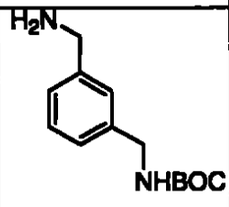
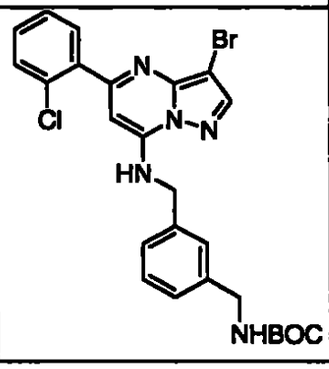
137				Rend. = 55% LCEM: MH^+ = 473
138				Rend. = 60% LCEM: MH^+ = 439
139				Rend. = 65% LCEM: MH^+ = 441
140				Rend. = 80% LCEM: MH^+ = 432

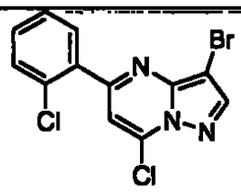
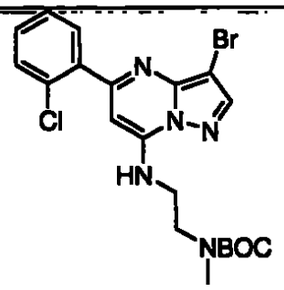
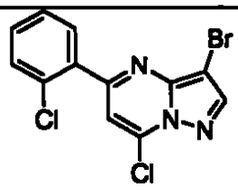
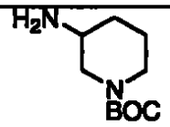
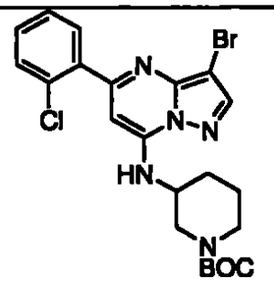
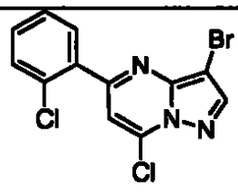
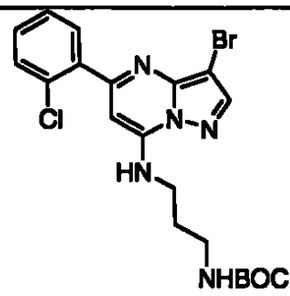
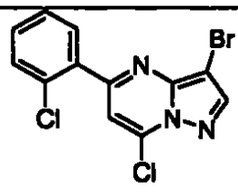
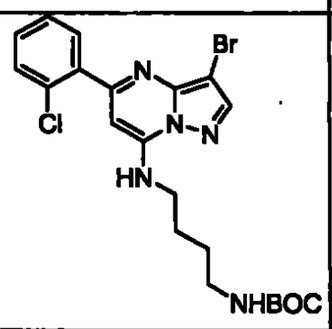
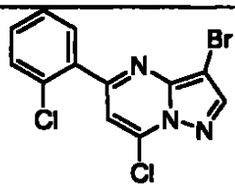
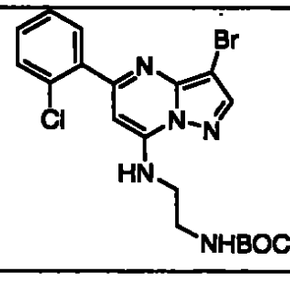
141				Rend. = 60% LCEM: MH^+ = 429
142				LCEM: MH^+ = 330; p.f.=109 -111°C
143				LCEM: MH^+ = 346; p.f.=186 -188°C
144				LCEM: MH^+ = 384; p.f.=148 -150°C

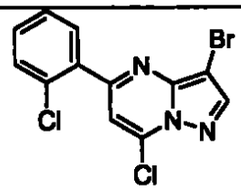
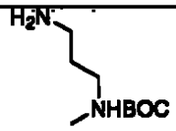
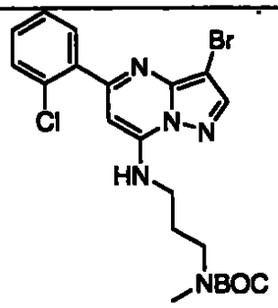
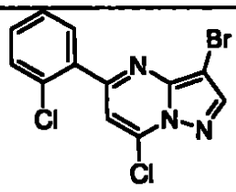
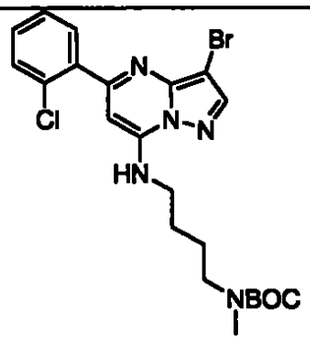
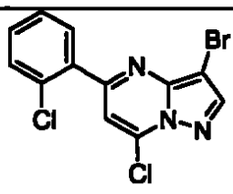
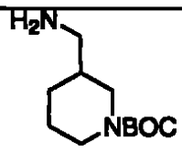
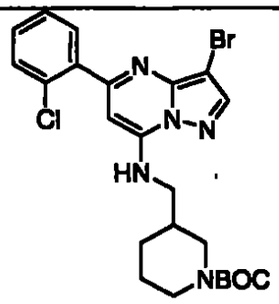
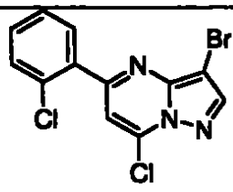
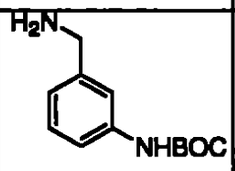
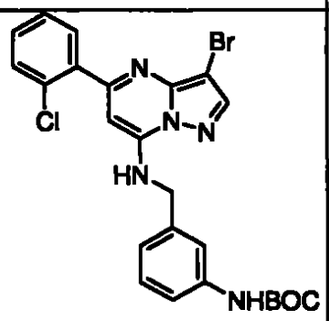
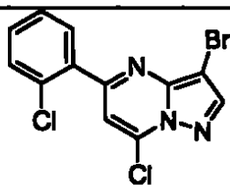
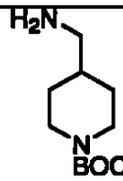
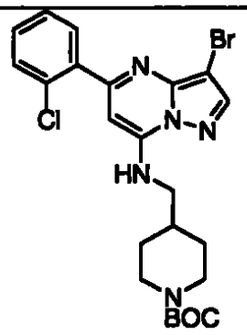
145				LCEM: MH^+ = 400; p.f.=186 -188°C
146				LCEM: $M2H^+$ = 390; p.f.=192 -194°C
147				LCEM: M^+ = 404; p.f.=220 -222°C
148				LCEM: MH^+ = 369; p.f. >230°C

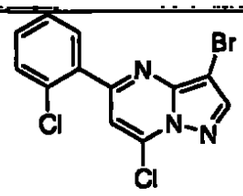
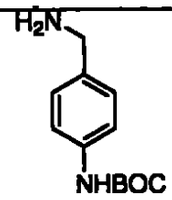
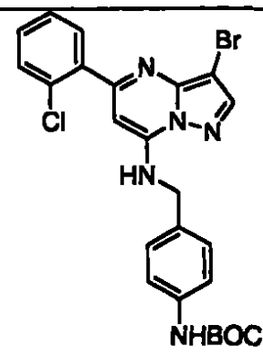
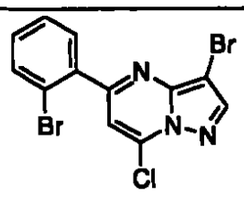
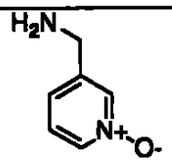
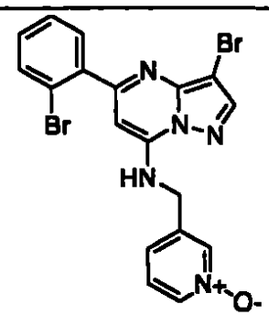
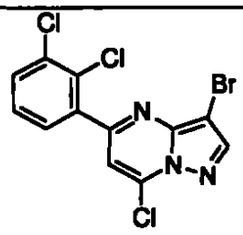
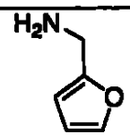
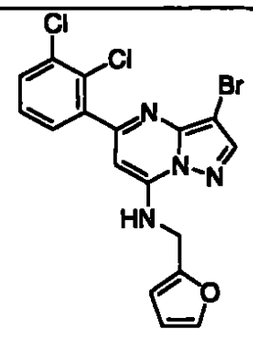
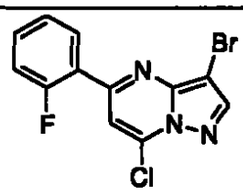
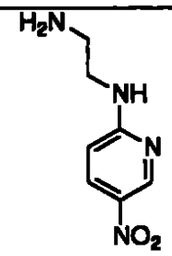
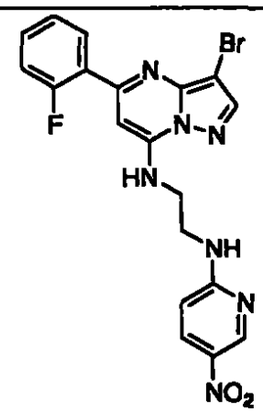
149				LCEM: MH^+ = 364; p.f.=186 -188°C
150				LCEM: MH^+ = 312; p.f.=138 -140°C
151				LCEM: M^+ = 380; p.f.=172 -174°C
152				LCEM: MH^+ = 352; p.f.=201 -203°C

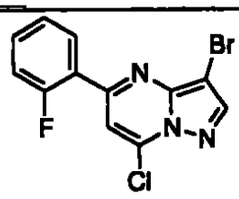
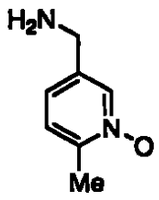
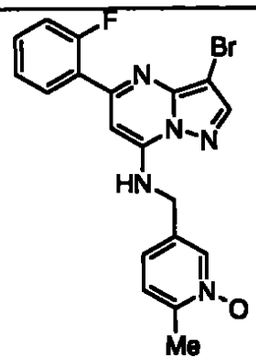
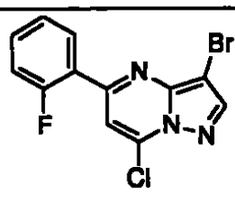
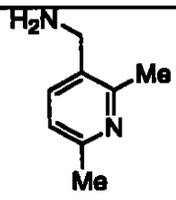
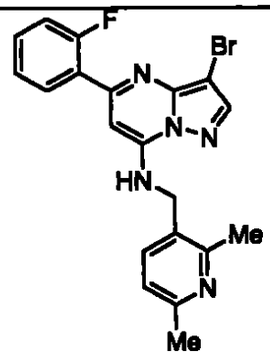
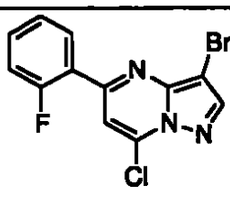
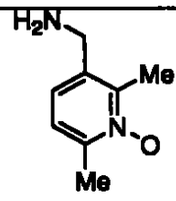
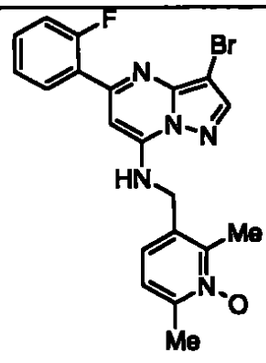
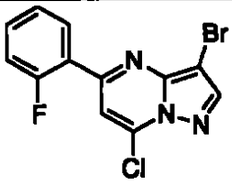
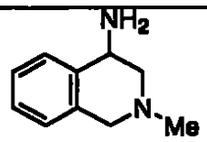
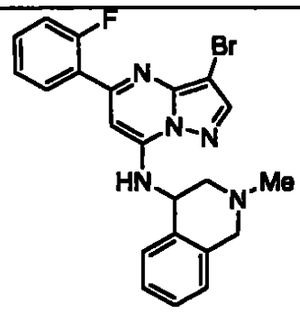
153				LCEM: MH^+ = 348; p.f.=166 -168°C
154				LCEM: $M2H^+$ = 531; p.f.=78-80°C
155				LCEM: $M2H^+$ = 474; p.f.=161 -163°C

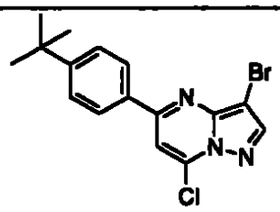
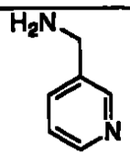
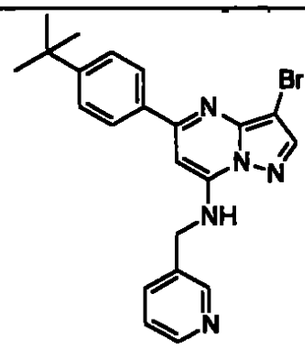
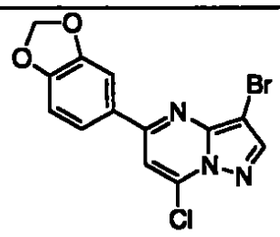
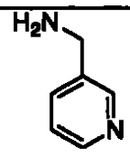
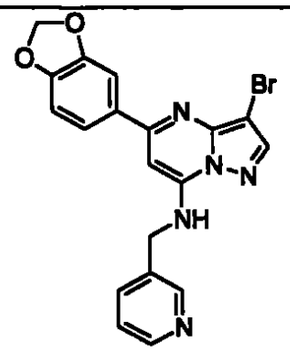
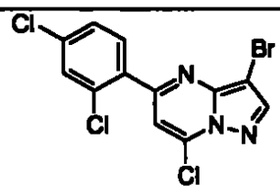
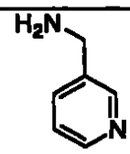
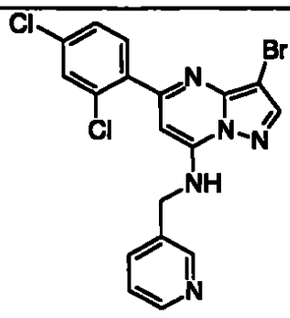
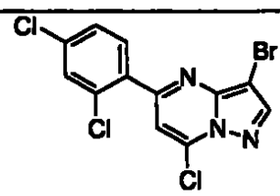
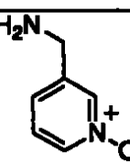
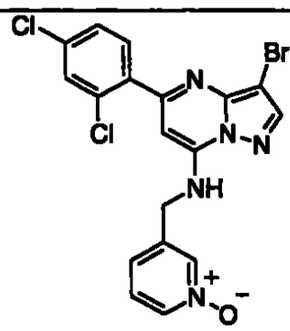
156				LCEM: M^+ = 444; p.f.=48-51°C
157				MH^+ = 542,1
158				MH^+ = 520,1
159				MH^+ = 542,1

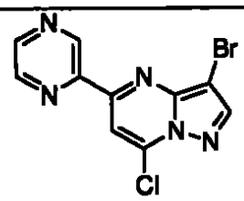
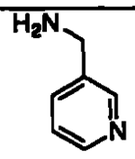
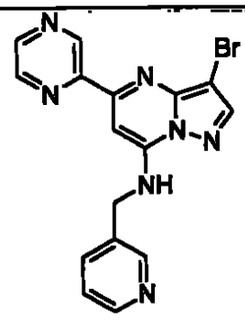
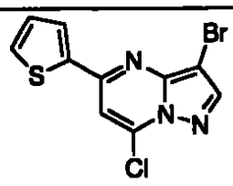
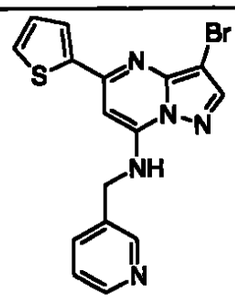
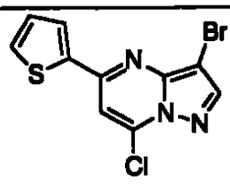
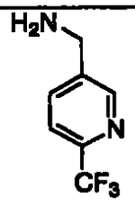
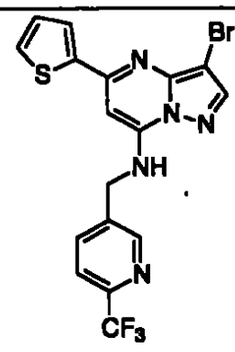
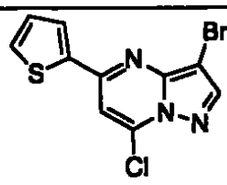
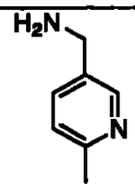
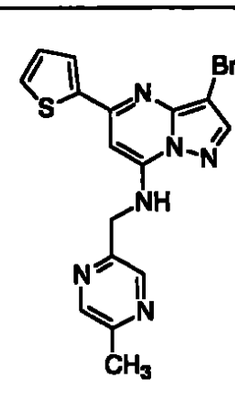
160				MH^+ = 480,1
161				MH^+ = 506,1
162				MH^+ = 480,1
163				MH^+ = 494,1
164				MH^+ = 466,1

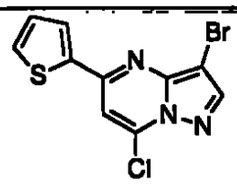
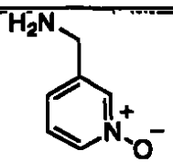
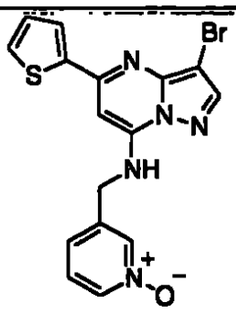
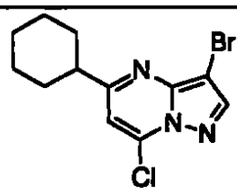
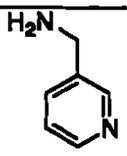
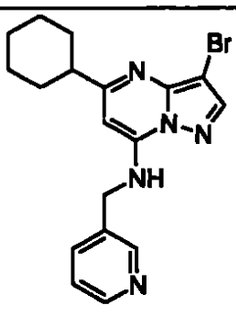
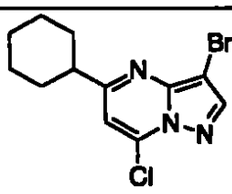
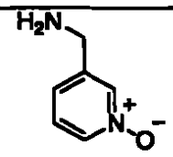
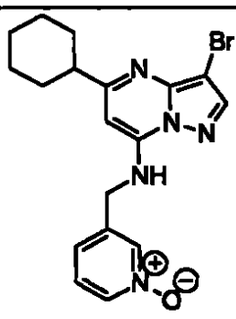
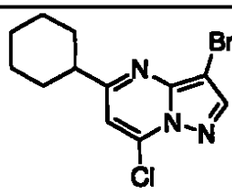
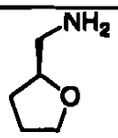
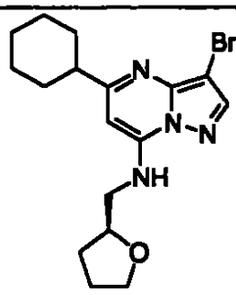
165				MH^+ = 494,1
166				MH^+ = 508,1
167				MH^+ = 520,1
168				MH^+ = 528,1
169				MH^+ = 520,1

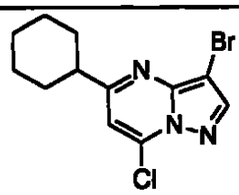
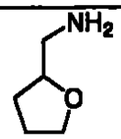
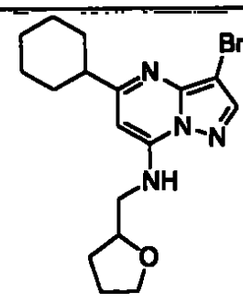
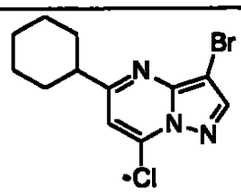
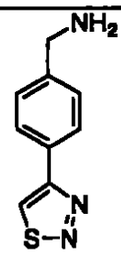
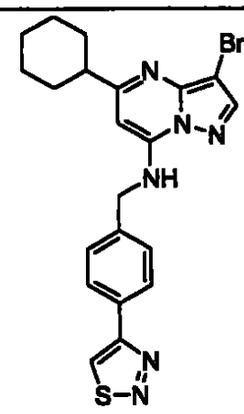
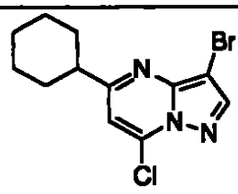
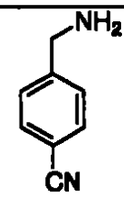
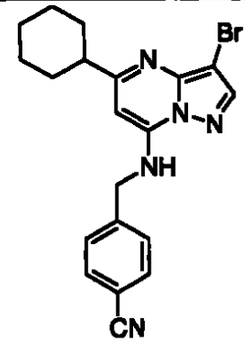
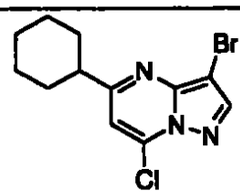
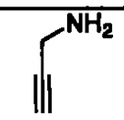
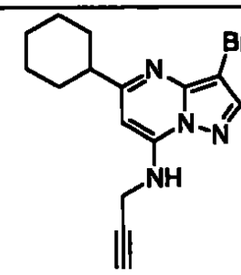
170				MH^+ = 528,1
171				LCEM: MH^+ = 474;
172				LCEM: MH^+ = 437;
173				LCEM: MH^+ = 472;

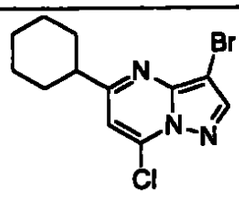
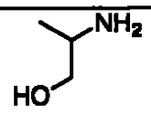
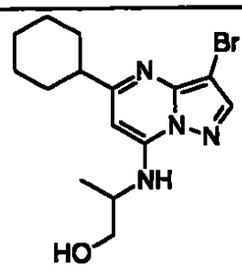
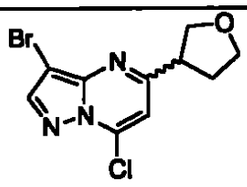
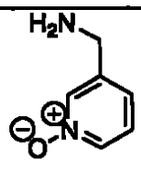
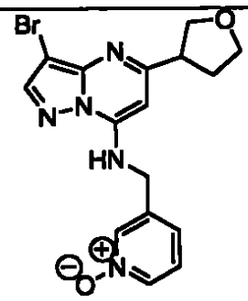
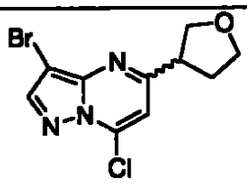
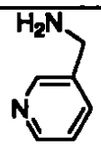
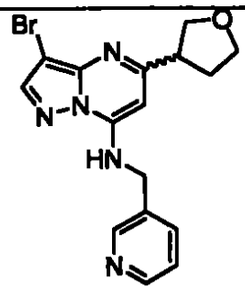
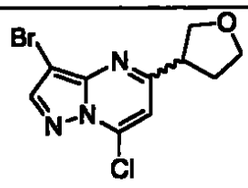
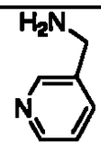
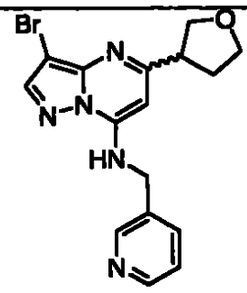
174				LCEM: MH^+ = 428.1
175				LCEM: MH^+ = 426,2
176				LCEM: MH^+ = 442,0
177				LCEM: MH^+ = 452,0

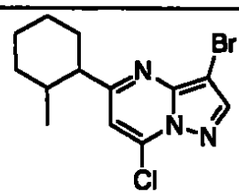
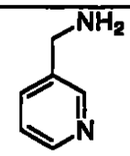
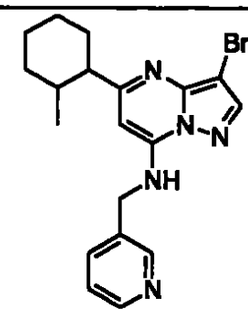
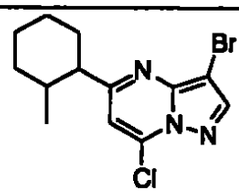
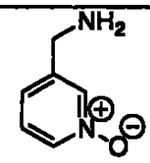
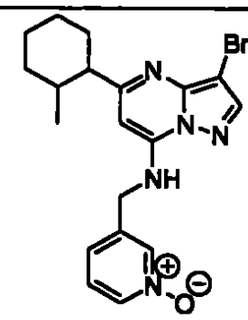
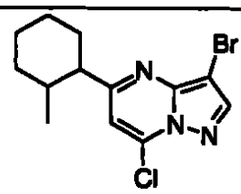
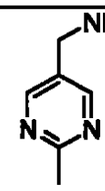
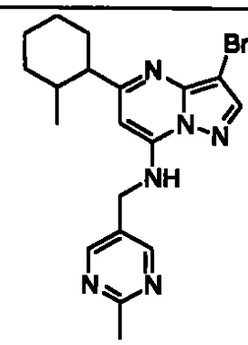
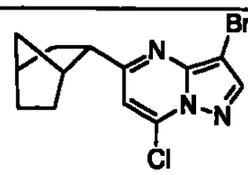
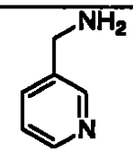
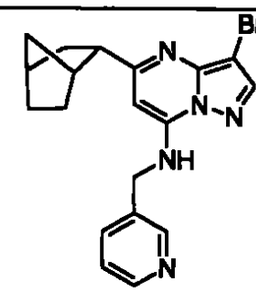
178				Rend. = 90 MH^+ = 436 p.f. = 89,1 °C
179				MH^+ = 424 p.f. = 188,2°C
180				MH^+ = 448 p.f. = 211,3°C
181				Rend. cuant. = MH^+ = 464

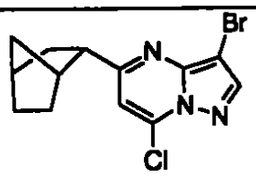
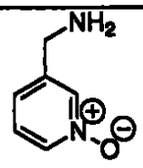
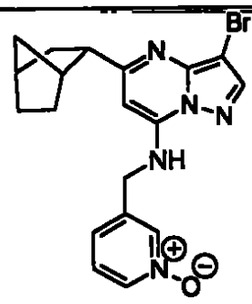
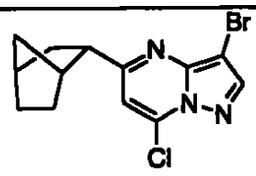
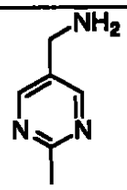
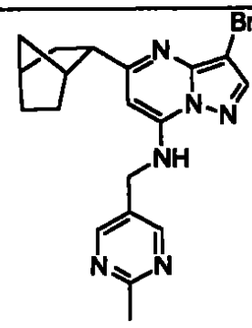
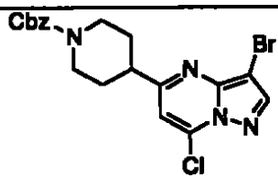
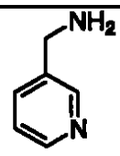
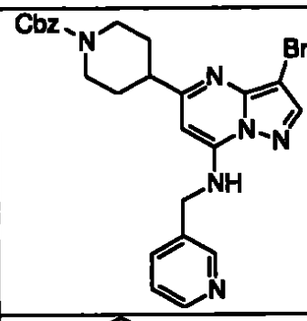
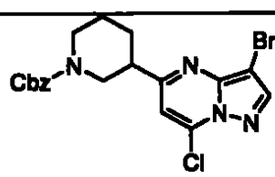
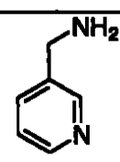
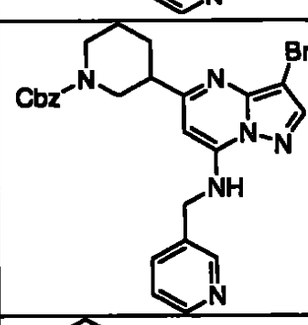
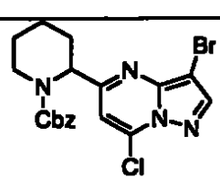
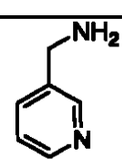
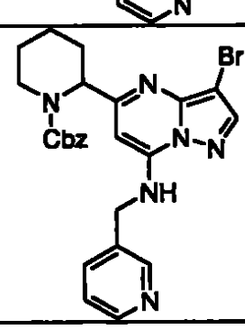
182				MH^+ = 382 p.f. = 185,8°C
183				MH^+ = 387 p.f. = 181 – 182°C
184				MH^+ = 453
185				MH^+ = 401 p.f. = 178,3°C

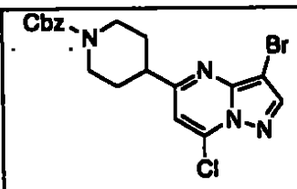
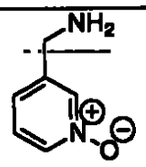
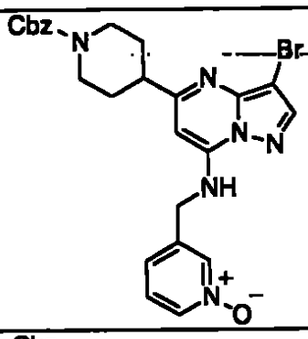
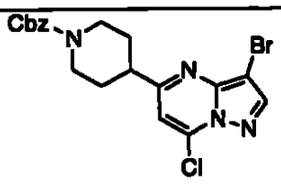
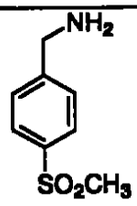
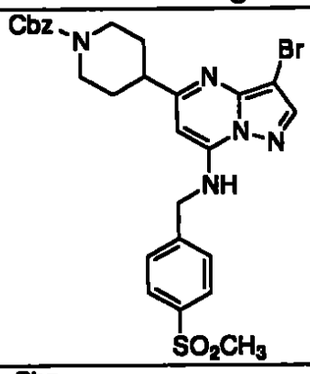
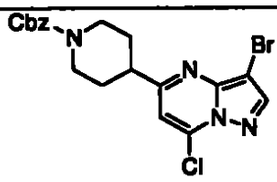
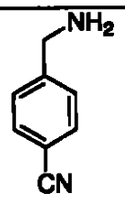
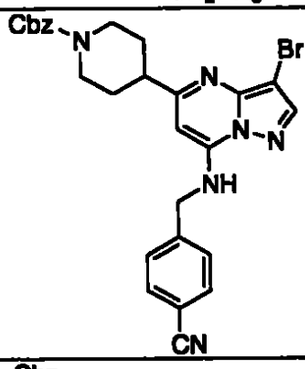
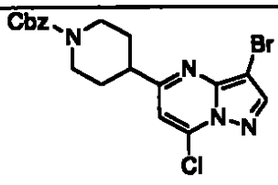
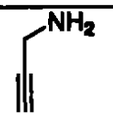
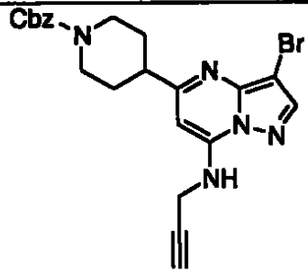
186				MH^+ = 402
187				Rend. = 91 MH^+ = 386 p.f. = 148,3°C
188				Rend. = 65 MH^+ = 402 p.f. = 174,5°C
189				MH^+ = 379 p.f. = 82 – 83°C

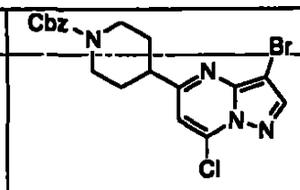
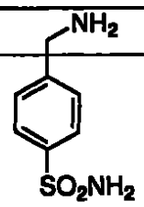
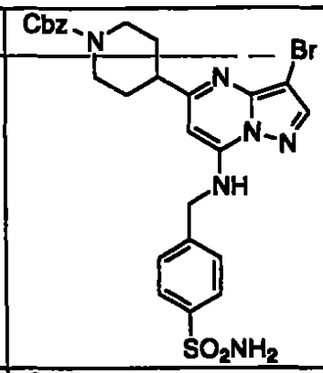
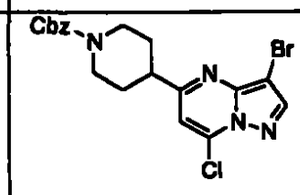
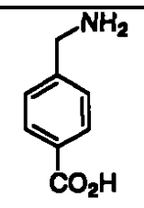
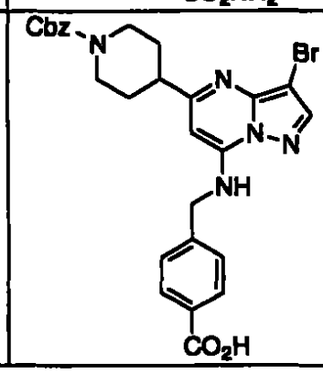
190				MH^+ = 379 p.f. = 50,7°C
191				Rend. = 89 MH^+ = 469 p.f. = 186,7°C
192				Rend. = 93 MH^+ = 410 p.f. = 86,7°C
193				Rend. = 76 MH^+ = 333 p.f. = 120,3°C

194				Rend. = 86 MH^+ = 353 p.f. = 188,9°C
195				Rend. = 11% LCEM: 374 MH^+ = 390
196				Rend. = 88% LCEM: 374 MH^+= 346
197				Rend. = 88% LCEM: 374 MH^+ = 346

198				Rend. = MH$^+$ = 400 p.f. = 111,5 – 112,2°C
199				MH$^+$ = 416
200				MH$^+$ = 415
201				MH$^+$ = 398 p.f. = 156,5°C

202				MH^+ = 414 p.f. = 89,5°C
203				MH^+ = 413
204				Rend. = 86 MH^+ = 521 p.f. = 79,9°C
204 .10				
204 .11				Rend. = 87 MH^+ = 521 p.f. = 128,6°C

205				Rend. = 99 MH^+ = 537 p.f. = 83,5°C
206				Rend. = 94 MH^+ = 598 p.f. = 110,8°C
207				Rend. cuant. = MH^+ = 545
208				Rend. = 96 MH^+ = 468 p.f. = 69,2°C

209				MH^+ = 498 p.f. = 226,5°C
210				MH^+ = 564 p.f. = 174,2°C

Los datos adicionales para los ejemplos seleccionados se dan a continuación.

Ejemplo 23: ^{1}H RMN (CD_3OD) δ 8,63 (d, J = 5,7 Hz, 2H), 8,18 (s, 1H), 7,81 (dd, J = 8,1 Hz, 2,1 Hz, 1H), 7,58 (d, J = 6,0 Hz, 2H), 7,48 (m, 1H), 7,15-7,10 (m, 2H), 6,50 (s, 1H), 4,86 (s, 2H), 3,70 (s, 3H)

Ejemplo 24: ^{1}H RMN ($CDCl_3$) δ 8,82 (s, 1H), 8,73 (d, J = 4,2 Hz, 1H), 8,11 (s, 1H), 8,06 (dd, J = 7,8 Hz, 1,8 Hz, 1H), 7,91 (d, J = 8,1 Hz, 1H), 7,53-7,47 (m, 2H), 7,20 (m, 1H), 7,08 (d, J = 8,1 Hz, 1H), 6,75 (s, 1H), 4,81 (d, J = 4,5 Hz, 2H), 3,86 (s, 3H)

Ejemplo 25: ^{1}H RMN ($CDCl_3$) δ 8,75 (d, J = 5,7 Hz, 2H), 8,12 (s, 1H), 7,81 (d, J = 2,1 Hz, 1H), 7,53 (dd, J = 8,4, 2,1 Hz, 1H), 7,45 (d, J = 6,0 Hz, 2H), 6,96 (t, J = 6,0 Hz, 2H), 6,33 (s, 1H), 4,85 (d, J = 6,0 Hz, 2H), 4,09 (s, 3H), 4,03 (s, 3H)

Ejemplo 26: ^{1}H RMN ($CDCl_3$) δ 8,82 (s, 1H), 8,72 (s, 1H), 8,09 (m, 1H), 7,87-7,83 (m, 2H), 7,60 (m, 1H), 7,45 (m, 1H), 7,03 (d, J = 8,4 Hz, 1H), 6,87 (s, 1H), 6,43 (s, 1H), 4,83 (d, J = 4,5 Hz, 2H), 4,11 (s, 3H), 4,04 (s, 3H)

Ejemplo 27: ^{1}H RMN ($CDCl_3$) δ 8,75 (d, J = 4,5 Hz, 2H), 8,19 (s, 1H), 7,63 (d, J = 7,8 Hz, 2H), 7,44-7,40 (m, 3H), 7,07 (m, 1H), 6,26 (s, 1H), 4,83 (d, J = 5,1 Hz, 2H)

Ejemplo 28: ^{1}H RMN ($CDCl_3$) δ 8,86 (s, 1H), 8,74 (m, 1H), 8,17 (s, 1H), 7,97 (m, 1H), 7,66-7,63 (m, 2H), 7,62 (m, 1H), 7,41 (m, 1H), 7,07 (m, 1H), 6,35 (s, 1H), 4,87 (d, J = 6,0 Hz, 2H)

Ejemplo 30: ^{1}H RMN ($CDCl_3$) δ 8,16 (s, 1H), 7,66-7,62 (m, 2H), 7,41 (m, 1H), 7,33-7,22 (m, 3H), 6,96 (t, J = 6,0 Hz, 1H), 6,33 (s, 1H), 4,73 (d, J = 6,0 Hz, 2H)

Ejemplo 31: ^{1}H RMN ($CDCl_3$) δ 8,13 (s, 1H), 7,66 (d, J = 7,8 Hz, 2H), 7,45-7,40 (m, 2H), 7,10-7,04 (m, 2H), 6,93 (t, J = 6,6 Hz, 1H), 6,60 (s, 1H), 4,84 (d, J = 6,6 Hz, 2H)

Ejemplo 32: ^{1}H RMN ($CDCl_3$) δ 8,16 (s, 1H), 7,66-7,62 (m, 2H), 7,57-7,55 (m, 2H), 7,41 (t, J = 7,8 Hz, 1H), 7,31 (dd, J = 7,8, 1,8 Hz, 1H), 6,99 (t, J = 6,0 Hz, 1H), 6,32 (s, 1H), 4,73 (d, J = 6,0 Hz, 2H)

Ejemplo 40: ^{1}H RMN ($CDCl_3$) δ 8,01 (s, 1H), 7,31 – 7,24 (d, J = 8,2 Hz, 1H), 6,72 – 6,64 (br t, J = 5,4 Hz, 1H), 6,62 – 6,52 (m, 2H), 6,05 – 6,01 (s, 1H), 5,56 – 4,64 (d, J = 6,0 Hz, 2H), 4,03 – 3,93 (s, 3H), 3,94 – 3,86 (s, 3H), 2,79 – 2,70 (d, J = 8,1 Hz, 2H), 2,02 – 1,66 (m, 6H), 1,43 – 1,22 (m, 3H), 1,20 – 1,02 (m, 2H)

Ejemplo 45: ^{1}H RMN ($CDCl_3$) δ 8,73 (d, 2H), 8,54 (s, 1H), 7,41 (d, 2H), 7,02 (br, 1H), 5,90 (s, 1H), 4,80 (s, 2H), 4,48 (q, 2H), 2,75 (s, 2H), 1,50 (t, 2H), 1,06 (s, 9H)

Ejemplo 46: ^{1}H RMN ($CDCl_3$) δ 8,79 (s, 1H), 8,72 (d, 1H), 8,14 (s, 1H), 7,84 (d, 1H), 7,54-7,33 (m, 4H), 6,97 (t, 1H), 6,18 (s, 1H), 4,79 (d, 2H), 2,47 (s, 3H)

Ejemplo 108: ^{1}H RMN ($CDCl_3$) δ 8,79 (s, 1H), 8,72 (d, J = 3,0 Hz, 1H), 8,16 (s, 1H), 7,84 (d, J = 7,8 Hz, 1H), 7,74 (d, J = 7,5 Hz, 2H), 7,55-7,35 (m, 3H), 6,92 (t, J = 6,3 Hz, 1H), 6,42 (s, 1H), 4,81 (d, J = 6,3 Hz, 2H)

Ejemplo 110: ^{1}H RMN ($CDCl_3$) δ 8,18 (t, 1H), 8,03 (s, 1H), 7,44 (m, 1H), 7,30 (t, 1H), 7,17 (q, 1H), 6,66 (s, 1H), 6,56 (br, 1H), 4,28 (d, 2H), 2,38 (s, 1H)

Ejemplo 111: ^{1}H RMN ($CDCl_3$) δ 8,72 (br, 1H), 8,59 (d, 1H), 8,11 (t, 1H), 8,06 (s, 1H), 7,73 (d, 1H), 7,44 (d, 1H), 7,42-7,21 (m, 3H), 7,07 (q, 1H), 6,39 (d, 1H), 5,21 (q, 1H), 4,16 (q, 2H), 3,08 (d, 2H), 1,22 (t, 3H)

Ejemplo 112: ^{1}H RMN ($CDCl_3$) δ 8,22 (t, 1H), 8,15 (s, 1H), 7,51-7,33 (m, 7H), 7,21 (q, 1H), 6,82 (d, 1H), 6,51 (s, 1H), 4,68 (q, 1H), 2,18 (m, 2H), 1,17 (t, 3H)

Ejemplo 113: ^{1}H RMN ($CDCl_3$) δ 8,22 (t, 1H), 8,14 (s, 1H), 7,51-7,33 (m, 7H), 7,21 (q, 1H), 6,82 (d, 1H), 6,51 (s, 1H), 4,68 (q, 1H), 2,18 (m, 2H), 1,17 (t, 3H)

Ejemplo 114: ^{1}H RMN ($CDCl_3$) δ 8,81 (s, 1H), 8,75 (d, 1H), 8,21 (s, 1H), 7,84 (d, 1H), 7,47 (q, 1H), 6,96 (s, 1H), 6,94 (t, 1H), 4,85 (d, 2H), 4,60 (q, 2H), 1,58 (t, 3H)

Ejemplo 115: ^{1}H RMN ($CDCl_3$) δ 8,77 (s, 1H), 8,72 (d, 1H), 8,14 (s, 1H), 7,83 (d, 1H), 7,65 (d, 1H), 7,44 (q, 1H), 7,80 (t, 1H), 7,6 (d, 1H), 6,18 (s, 1H), 4,75 (d, 2H), 3,91 (s, 3H), 3,81(s, 3H)

Ejemplo 116: ^{1}H RMN ($CDCl_3$) δ 8,67 (s, 1H), 8,55 (d, 1H), 8,50 (s, 1H), 7,92 (d, 1H), 7,90 (d, 1H), 7,78 (t, 1H), 7,10 (d, 1H), 6,97 (s, 1H), 5,11 (s, 2H), 3,77 (s, 6H)

Ejemplo 117: ^{1}H RMN ($CDCl_3$) δ 8,38 (s, 1H), 8,30 (d, 1H), 8,17 (s, 1H), 7,52-7,37 (m, 6H), 6,97 (t, 1H), 6,13 (s, 1H), 4,77 (d, 2H), 2,50 (s, 3H)

Ejemplo 118: ^{1}H RMN ($CDCl_3$) δ 8,18 (t, 1H), 8,03 (s, 1H), 7,44 (m, 1H), 7,30 (t, 1H), 7,17 (q, 1H), 6,66 (s, 1H), 6,56 (br, 1H), 4,28 (d, 2H), 2,38 (s, 1H);

Ejemplo 121: ^{1}H RMN ($CDCl_3$) δ 8,6 (S, 1H), 8,15 (dt,1H), 8,1 (s, 1H), 8,0 (d, 2H), 7,5 (d, 2H), 7,4 (dd, 1H), 7,2 (d, 1H), 7,15 (dd, 1H), 6,8 (t, 1H), 6,6 (s, 1H), 4,75 (d, 2H)

Ejemplo 126: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,5 (d, 1H), 7,42 – 7,35 (m, 2H), 7,3 – 7,2 (m, 2H), 7,15 (dd, 1H), 7,1 (dd, 1H), 7,0 (t, 1H), 6,6 (s, 1H), 4,8 (d, 2H).

Ejemplo 127: ^{1}H RMN ($CDCl_3$) δ 8,2 (dt, 1H), 8,0 (s,1H), 7,4 (dd, 1H), 7,3 - 7,25 (m, 3H), 7,1 (dd, 1H), 6,9 – 6,85 (m, 2H), 6,7 (t, 1H), 6,6 (s, 1H), 4,6 (d, 2H), 3,2 (m, 4H), 2,6 (m, 4H), 2,3 (s, 3H)

Ejemplo 128: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt,1H), 8,1 (s, 1H), 8,0 (d, 2H), 7,5 (d, 2H), 7,4 (m, 2H), 7,25 (d, 1H), 7,2 (s,1H), 7,15 (dd, 1H), 7,0 (s, 1H), 6,8 (t, 1H), 6,6 (s, 1H), 4,75 (d, 2H).

Ejemplo 129: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,05 (s, 1H), 8,0 (d, 2H), 7,5 (d, 2H), 7,4 (m, 1H), 7,3 (dd, 1H), 7,15 (dd, 1H), 6,9 (t, 1H), 6,5 (s, 1H), 4,75 (d, 2H), 3,85 (s, 3H)

Ejemplo 130: ^{1}H RMN ($CDCl_3$) δ 8,2 (dt,1H), 8,0 (s, 1H), 7,4 (dd, 1H), 7,3(dd, 1H), 7,15 (dd, 1H), 6,8 (t, 1H), 6,4 (s,1H), 4,2 (d, 2H), 3,8 (s, 3H).

Ejemplo 131: ^{1}H RMN ($CDCl_3$) δ 8,2 (dt, 1H), 8,0 (s,1H), 7,4 – 7,15 (m, 3H), 6,7 (t, 1H), 4,2 (q, 2H), 3,8 (dt, 2H), 2,8 (t, 2H), 1,2 (t, 3H)

Ejemplo 132: ^{1}H RMN ($CDCl_3$) δ 8,2 (dt, 1H), 8,0 (s,1H), 7,4 – 7,15 (m, 3H), 6,7 (t, 1H), 4,2 (q, 2H), 3,8 (dt, 2H), 2,8 (t, 2H), 2,05 (m, 2H), 1,2 (t, 3H)

Ejemplo 133: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s,1H), 7,4 (m, 1H), 7,3 (dd 1H), 7,2 (dd, 1H), 6,5 (s, 1H), 6,4 (t,1H), 3,7 (s, 3H), 3,5 (dd,2H),b 2,4 (t, 2H), 1,8 (m, 4H)

Ejemplo 134: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,95 (d, 2H), 7,6 (d, 2H), 7,4 (m, 1H), 7,25 (dd, 1H), 7,1 (dd, 1H), 6,9 (t, 1H), 6,5 (s, 1H), 4,8 (d, 2H), 3,0 (s, 3H)

Ejemplo 135: ^{1}H RMN (DMSO d6) δ 9,1 (bs, 2H), 8,4 (s,1H), 8,0 (t, 1H), 7,85 (d, 2H), 7,7 (d, 2H), 7,6 (m, 1H), 7,4 (m, 2H), 6,6 (s, 1H), 4,8 (bs, 2H)

Ejemplo 136: ^{1}H RMN ($CDCl_3$) δ 8,2 (dt, 1H), 8,0 (s,1H), 7,4 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 6,9 (m, 3H), 6,7 (t, 1H), 6,5 (s, 1H), 4,5 (d, 2H), 4,2 (s, 4H)

Ejemplo 137: ^{1}H RMN ($CDCl_3$) δ 8,2 (dt, 1H), 8,0 (s, 1H), 7,4 (m, 1H), 7,3 (dd, 1H), 7,2 (dd, 1H), 6,9 (dd, 1H), 6,8 (t, 1H), 6,7 (m, 1H), 6,6 (s, 1H), 5,3 (s, 2H), 4,85 (s, 2H), 4,6 (d, 2H)

Ejemplo 138: ^{1}H RMN ($CDCl_3$) δ 8,2 (dt, 1H), 8,0 (s, 1H), 7,9 (d,1H), 7,8 (d, 1H), 7,4 (m, 2H), 7,3 (dd, 1H), 7,1 (dd, 1H), 6,9 (t, 1H), 6,6 (s, 1H), 4,8 (d, 2H)

Ejemplo 139: ^{1}H RMN ($CDCl_3$) δ 8,2 (dt, 1H), 8,0 (s, 1H), 7,4 (m, 1H), 7,3 (m, 2H), 7,2 (dd, 1H), 7,1 (dd, 1H), 6,8 (d, 1H), 6,7 (t, 1H), 6,6 (s, 1H), 4,6 (m, 4H), 3,2 (t, 2H)

Ejemplo 140: ^{1}H RMN ($CDCl_3$) δ 8,45 (s, 1H), 8,2 (dt, 1H), 8,0 (s, 1H), 7,7 (dd, 1H), 7,4 – 7,3 (m, 3H), 7,15 (dd, 1H), 6,8 (t, 1H), 6,6 (s,1H), 4,7 (d, 2H)

Ejemplo 141: ^{1}H RMN ($CDCl_3$) δ 8,2 (dt, 1H), 8,0 (s, 1H), 7,45 – 7,1 (m, 7H), 6,6 (s, 1H), 4,4 (dt, 2H), 2,6 (t, 2H), 1,8 (m, 2H), 1,4 (m, 2H)

Ejemplo 171: ^{1}H RMN (CD_3OD) δ 8,41 (s, 1H), 8,25 (d, J = 6,3 Hz, 1H), 8,15 (s, 1H), 7,67 (d, J = 7,8 Hz, 2H), 7,55-7,48 (m, 2H), 7,45 (dd, J = 7,5, 1,2 Hz, 1H), 7,34 (dd, J = 7,5, 1,8 Hz, 1H), 6,28 (s, 1H), 4,79 (s, 2H)

Ejemplo 172: ^{1}H RMN ($CDCl_3$) δ 8,64 (s, 1H), 7,68-7,64 (m, 2H), 7,52 (m, 1H), 7,43 (t, J = 7,8 Hz, 1H), 6,89 (t, J = 6,0 Hz, 1H), 6,51 (s, 1H), 6,48 (m, 2H), 4,74 (d, J = 6,0 Hz, 2H)

Ejemplo 173: ^{1}H RMN (DMSO-d_6) δ 8,86 (s, 1H), 8,46 (s, 1H), 8,32-8,28 (m, 2H), 7,97 (m, 1H), 7,87 (m, 1H), 7,52 (m, 1H), 7,35-7,24 (m, 2H), 6,57 (s, 1H), 6,46 (m, 1H), 3,65 (m, 4H).

Ejemplo 174: ^{1}H RMN ($CDCl_3$) d 8,37 (s, 1H), 8,16 (t, J = 7,5 Hz, 1H), 7,45-7,35 (m, 1H), 7,32-7,20 (m, 3H), 7,17-7,07 (m, 1H), 6,92 (t, J = 6 Hz, 1H), 6,48 (s, 1H), 4,65 (d, 2H), 2,50 (s, 3H)

Ejemplo 175: ^{1}H RMN ($CDCl_3$) d 8,16 (t, J = 9 Hz, 1H), 8,00 (s, 1H), 7,49 (d, J= 9 Hz, 1H), 7,46 - 7,36 (m, 1H), 7,18 - 7,08 (m, 1H), 7,00 (d, J = 9 Hz, 1H), 6,62 – 6,50 (m, 2H), 2,60 (s, 3H), 2,55 (s, 3H).

Ejemplo 176: ^{1}H RMN ($CDCl_3$) d 8,15 (t, J = 9 Hz, 1H), 8,00 (s, 1H), 7,45-7,35 (m, 1H), 7,32-7,20 (m, 1H), 7,20-7,05 (m, 3H), 6,80 (t, 1H), 6,50 (s, 1H), 4,65 (d, 2H), 2,65 (s, 3H), 2,50 (s, 3H).

Ejemplo 177: ^{1}H RMN ($CDCl_3$) d 8,20 (t, 1H), 7,90 (s, 1H), 7,50 – 7,05 (m, 8H), 6,80 (s, 1H), 5,05 – 4,90 (m, 2H), 3,80 (d, 1H), 3,45 (d, 1H), 3,00 (dd, 1H), 2,90 (dd, 1H), 2,50 (s, 3H)

Ejemplo 181: ^{1}H RMN (300 MHz, $CDCl_3$) 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 (300 MHz, $CDCl_3$) 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 (300 MHz, $CDCl_3$) δ 8,96 – 8,90 (s, 1H), 8,08 (s, 1H), 8,44 (s, 1H), 8,27 – 8,24 (d, 1H), 8,02 (s, 1H), 7,78 – 7,76 (d, 1H), 7,73 – 7,70 (d, 1H), 7,58 – 7,51 (m, 2H), 7,13 – 7,08 (dd, 1H), 5,51 (s, 2H)

Ejemplo 195: ^{1}H RMN (CD_3OD) δ 8,40 (s, 1H), 8,27 (d, 1H), 8,03 (s, 1H), 7,75 –7,50 (m, 2H), 6,10 (s, 1H), 4,76 (s, 2H), 4,05 (m, 2H), 3,88 (m, 2H), 3,52 (m, 1H), 2,33 (m, 1H), 2,20 (m, 1H)

Ejemplo 196: ^{1}H RMN (CD_3OD) δ 8,73 (d, 1H), 8,58 (q, 1H), 8,12 (s, 1H), 8,00 (d, 1H), 7,54 (q, 1H), 6,19 (s, 1H), 4,86 (s, 2H), 4,22 – 4,08 (m, 2H), 4,03 – 3,93 (m, 2H), 3,63 (m, 1H), 2,50 – 2,39 (m, 1H), 2,32 – 2,21 (m, 1H)

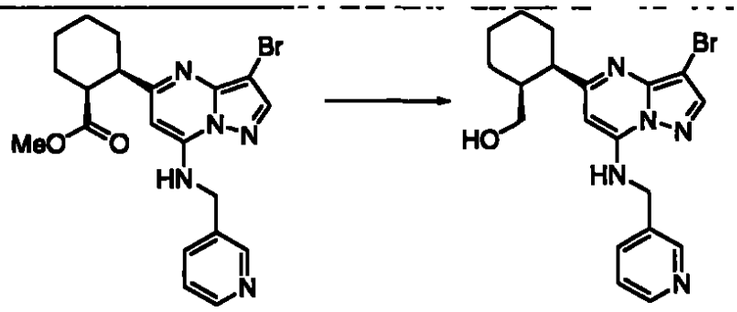
Ejemplo 197: ^{1}H RMN (CD_3OD) δ 8,73(d, 1H), 8,58(q, 1H), 8,12(s, 1H), 8,00(d, 1H), 7,54(q, 1H), 6,19(s, 1H), 4,86(s, 2H), 4,22-4,08(m, 2H), 4,03-3,93(m, 2H), 3,63(m, 1H), 2,50-2,39(m, 1H), 2,32-2,21(m, 1H).

Ejemplo 199: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,29 (s, 1H), 8,15 (br s, 1H), 7,95 (s, 1H), 7,28 (d, 1H), 7,05 - 6,95 (appt t, 1H), 5,70 (s, 1H), 4,62 (d, 2H), 2,90 (m, 1H), 2,30 (m, 1H), 1,9 – 1,2 (m, 8H), 0,65 (d, 3H).

Ejemplo 200: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,71 (s, 2H), 8,00 (s, 1H), 6,13 (s, 1H), 3,59 (s, 2H), 3,01 – 2,58 (m, 1H), 2,51 – 2,45 (m, 1H), 2,44 –2,30 (m,1H), 2,20 (s, 3H), 2,09 – 1,95 (m, 2H), 1,85 –1,70 (m, 2H), 0,80 – 0,76 (d, 3H).

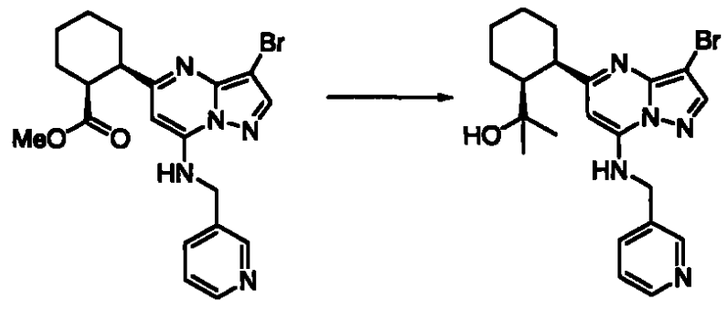
Ejemplo 203: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,10 (s, 1H), 8,08 (s, 1H), 6,27 (s, 2H), 4,95 (s, 2H), 3,00 – 2,90 (dd, 2H), 2,60 (m, 2H), 2,48 (br s, 1H), 2,39 (s, 3h), 2,25 m, 1H), 1,95 – 1,70 (m, 3H).

EJEMPLO 211:



A una solución del compuesto preparado en el Ejemplo 156 (100 mg, 0,23 mmol) en THF seco (4 mL) se le agregó $LiAlH_4$ (1,0 M en THF, 0,110 mL, 0,110 mmol) a 0°C bajo N_2. La mezcla se agitó a 0°C durante 1hora, se calentó a 25°C, y luego se agregó $LiAlH_4$ (1,0 M en THF, 0,400 mL) adicional, y la mezcla se agitó durante 20 minutos y luego se apagó con MeOH (2,0 mL). El solvente se evaporó y el producto crudo se purificó por cromatografía evaporativa usando 10:1 CH_2Cl_2:MeOH como eluyente. Se obtuvo un sólido blanco (46 mg, 49%). LCMS: M^+= 416. p.f. =71-72 °C.

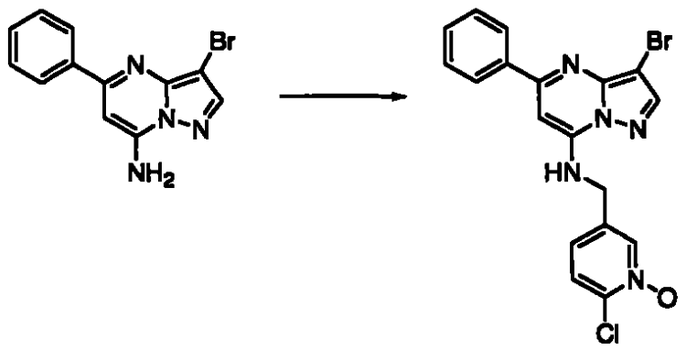
EJEMPLO 212:



A una solución del compuesto preparado en el Ejemplo 156 (70 mg, 0,16 mmol) en THF seco (3 mL) se le 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 minutos y luego se apagó con NH_4Cl acuoso saturado (5,0 mL) . La mezcla se vertió en NH_4Cl acuoso saturado (30 mL) y se extrajo con CH_2Cl_2 (3 x 20 mL). Los extractos se secaron

sobre Na_2SO_4 y se filtraron. El solvente se evaporó y el producto crudo se purificó por cromatografía evaporativa usando 20:1 CH_2Cl_2:MeOH como eluyente. Se obtuvo un sólido blando (25 mg, 36%). LCMS: M^+= 444. p.f.=76-80 °C.

EJEMPLO 213:

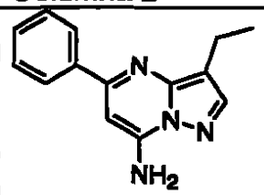
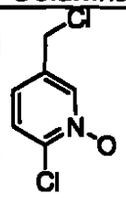
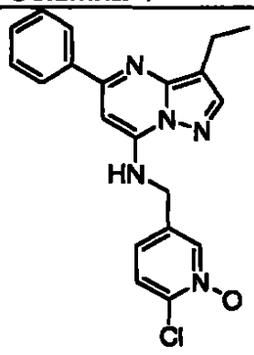
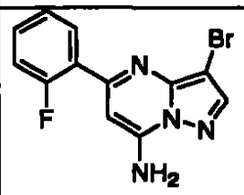
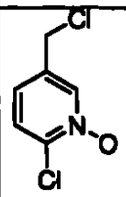
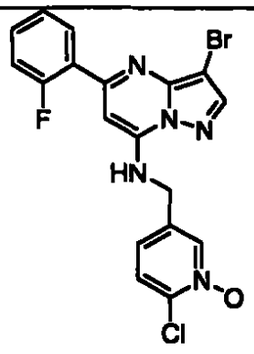
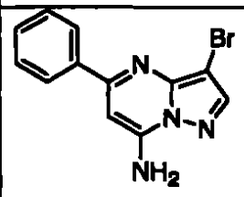
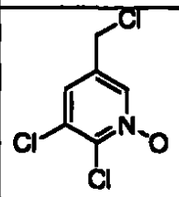
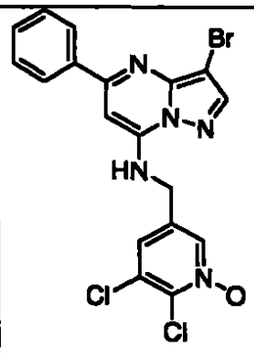
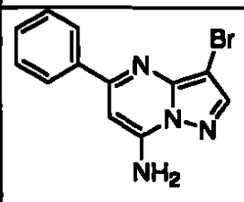
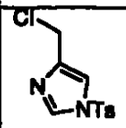
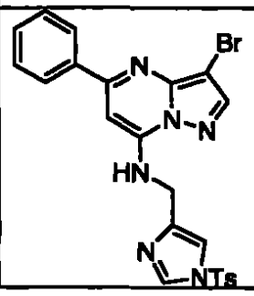


Se agregó DMF anhidro (40 mL) bajo N_2 al compuesto preparado en el Ejemplo Preparativo 174 (2.50 g, 8,65 mmol) y 60 % de NaHl en aceite mineral (346 mg, 8,65 mmol). La mezcla se agitó a 25°C durante 1 hora, y luego se agregó lentamente N-óxido de 2-cloro-5-clorometilpiridina (1,54 g, 8,65 mmol) en DMF anhidro (20 mL). La mezcla se agitó a 25°C durante 18 horas, el solvente se evaporó y el producto crudo se purificó por cromatografía evaporativa usando 30:1 de CH_2Cl_2:MeOH como eluyente. El sólido así obtenido se trituró con 50 mL de 1:1EtOAc:hexano. Se obtuvo un sólido de un color amarillo pálido (1,25 g, 34%).LCMS: MH^+=432. p.f. =224-226 °C.

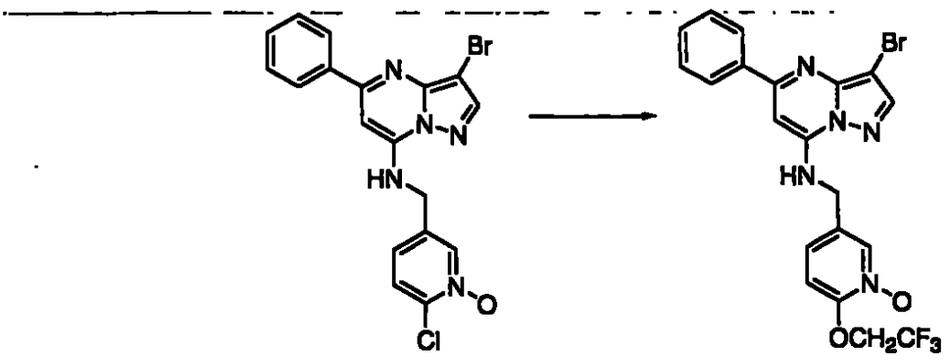
EJEMPLOS 214-217:

Esencialmente mediante el mismo procedimiento que se indica en el Ejemplo 213, combinando los compuestos que se muestran en la Columna 2 de la Tabla 19 con los compuestos de la Columna 3 de la Tabla 19, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 19.

TABLA 19

Ej.	Columna 2	Columna 3	Columna 4	COMP.
214				LCMS: MH^+=380; p.f.=°C
215				LCMS: MH^+=450; p.f.=218-222°C
216				LCMS: MH^+=466; p.f.=126-128°C
217				LCMS: M^+=523

EJEMPLO 218:

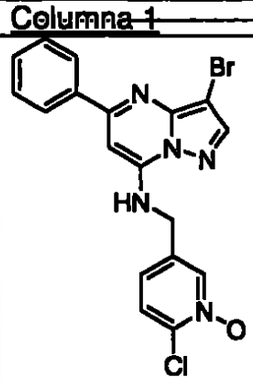
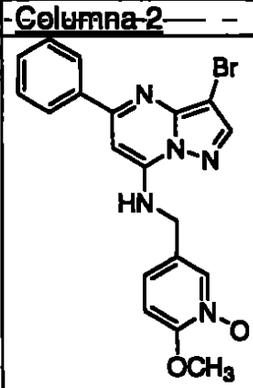
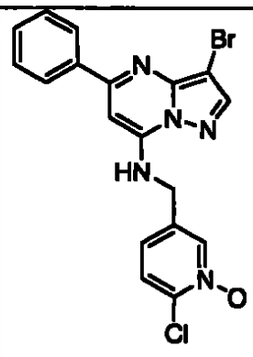
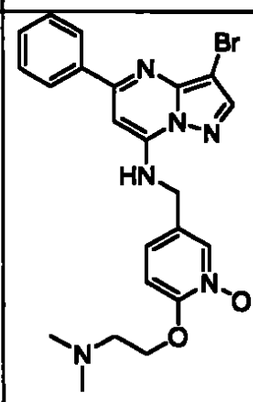
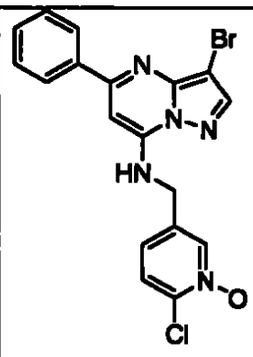
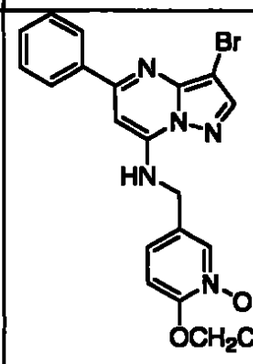
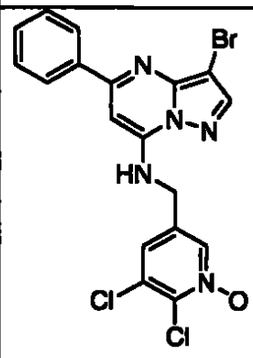
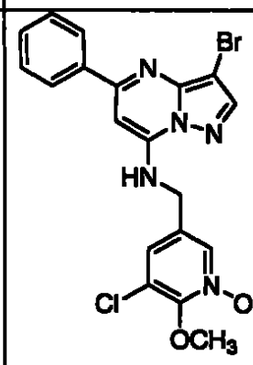


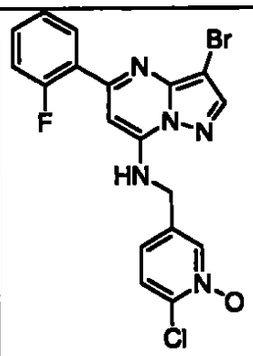
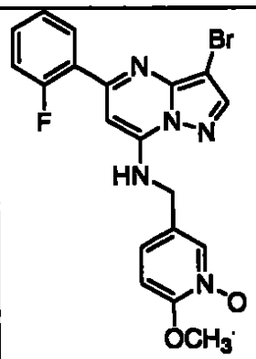
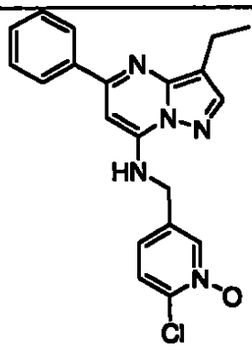
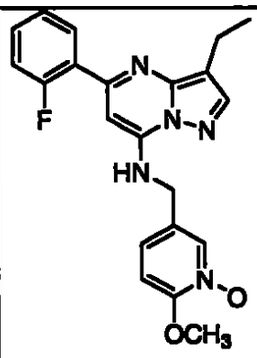
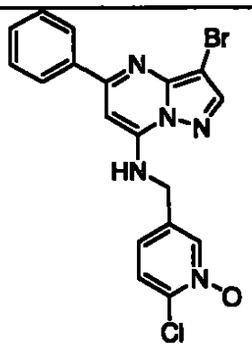
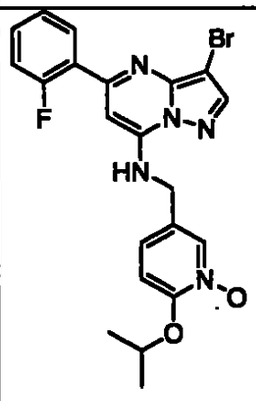
Se agregó CF_3CH_2OH (3,0 mL) bajo N_2 a 60% de NaH en aceite mineral (40 mg, 1,0 mmoles), la mezcla se agitó durante 20 minutos, y luego se agregó el producto preparado en el Ejemplo 213 (50 mg, 0,12 mmol). La mezcla se reflujó durante 20 horas, se evaporó el solvente, y el residuo se purificó por cromatografía evaporativa usando 20:1 CH_2Cl_2:MeOH como eluyente para propocionar un sólido de color amarillo pálido (35 mg, 61%). LCMS: $M2H^+$=496. p.f.=208-210 °C.

EJEMPLOS 219-225:

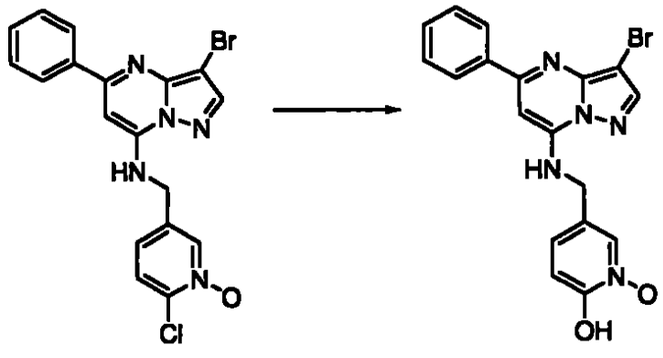
Esencialmente mediante el mismo procedimiento que se indica en el Ejemplo 218 combinando los compuestos que se muestran en la Columna 1 de la Tabla 20 con el alcohol apropiado, se prepararon los compuestos que se muestran en la Columna 2 de la Tabla 20.

TABLA 20

Ej.	Columna 1	Columna 2	Datos
219			LCMS: M^+=426; p.f.=126 -128°C
220			LCMS: M^+=483; p.f.=89-91°C
221			LCMS: $M2H^+$= 442; p.f.=112 -114°C
222			LCMS: MH^+=462; p.f.=121 -123°C

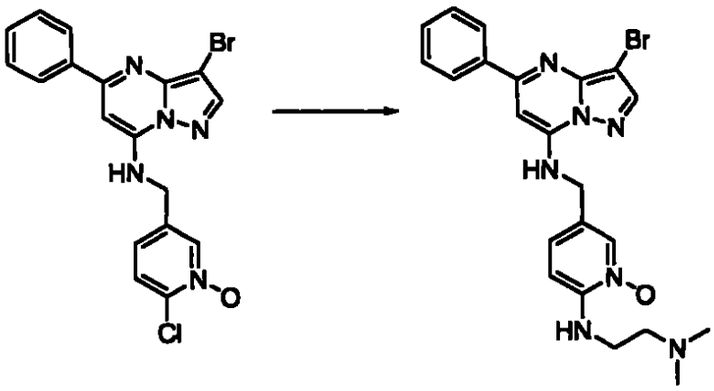
223			LCMS: MH^+=444; p.f.=112-114°C
224			LCMS: M^+=376; p.f.=°C
225			LCMS: MH^+=; p.f.=°C

EJEMPLO 226:



Una mezcla del producto preparado en el Ejemplo 213 (100 mg, 0,23 mmol) y KOH (95 mg, 1,70 mmol) en 1,2-dimetoxietano (3 mL) y H_2O (1,5 mL) se reflujó bajo N_2 durante 20 horas, se apagó con ácido acético (0,30 mL), y se evaporó el solvente. 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 al filtrado Et_2O (5 mL) y la mezcla se dejó en reposo durante la noche. El sólido se extrajo por filtración, se lavó con Et_2O y luego se disolvió en MeOH (5 mL). La solución se filtró y el solvente del filtrado se evaporó. Se obtuvo un sólido blancuzco (5 mg, 5%). LCMS: M^+=412. p.f.= 206-208°C.

EJEMPLO 227:



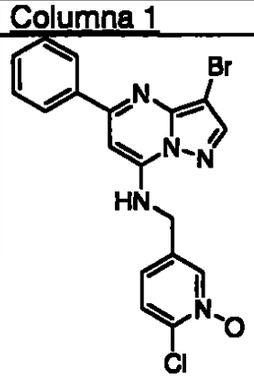
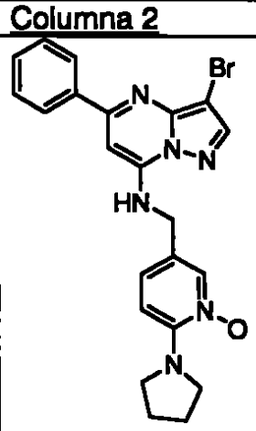
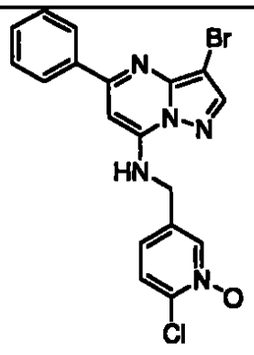
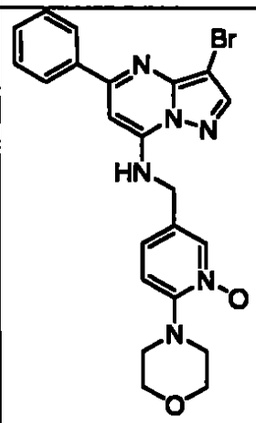
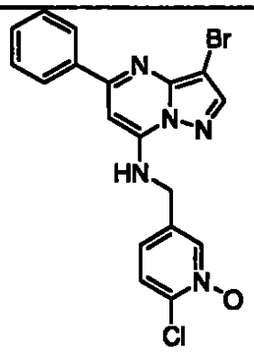
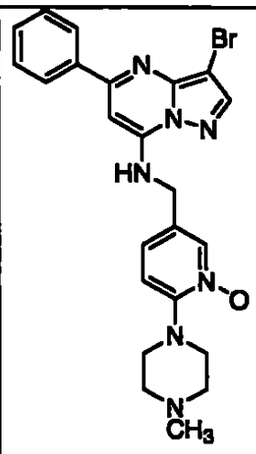
Una mezcla del producto preparado en el Ejemplo 213 (129 mg, 0,30 mmol), N,N-dimetiletilendiamina (0,165 mL, 1,50 mmol), y diisopropiletilamina (0,10 mL) en N-metilpirrolidinona anhidra (1,0 mL) se agitó a 100°C durante 24 hr. El solvente se evaporó, y el residuo se purificó por cromatografía evaporativa usando 20:1 CH_2Cl_2: 7N NH_3 en MeOH como eluyente para proporcionar un sólido de color amarillo pálido (110 mg, 76%). LCMS: M^+=482. p.f.=76-78 °C.

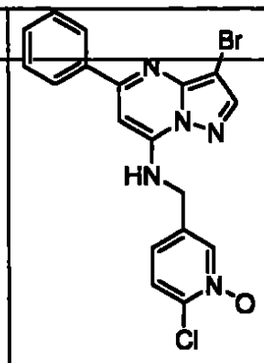
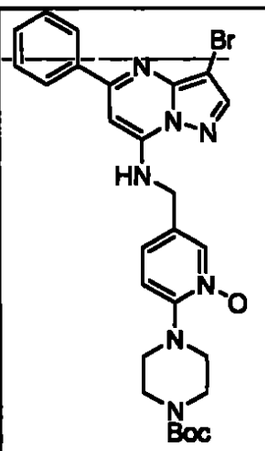
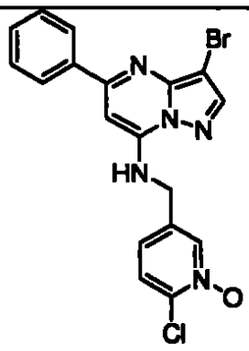
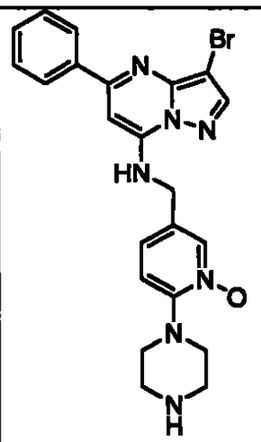
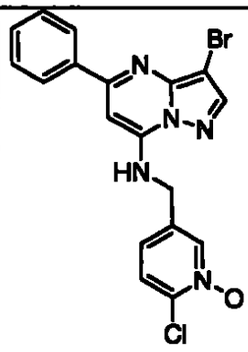
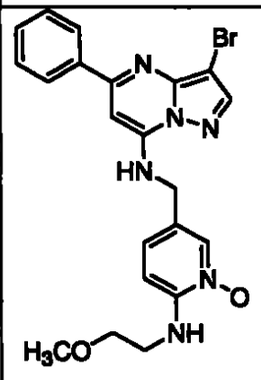
EJEMPLOS 228-233:

Esencialmente mediante el mismo procedimiento que se indica en el Ejemplo 227 combinando los compuestos que se muestran en la Columna 1 de la

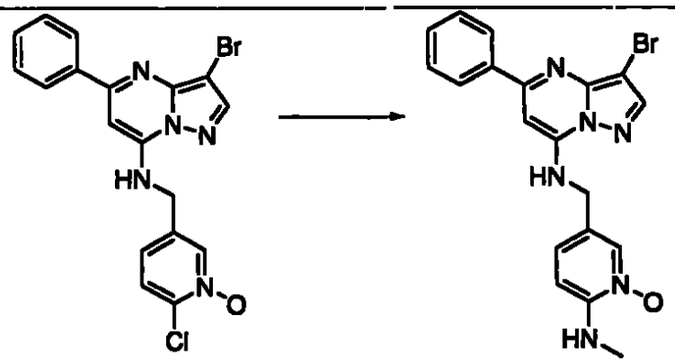
Tabla 21 con la amina apropiada, se prepararon los compuestos que se muestran en la Columna 2 de la Tabla 21.

TABLA 21

Ej.	Columna 1	Columna 2	Datos
228			LCMS: M2H$^+$= 467; p.f.126-128=°C
229			LCMS: M$^+$=481; p.f.=128 -130°C
230			LCMS: M$^+$=494; p.f.=108 -110°C

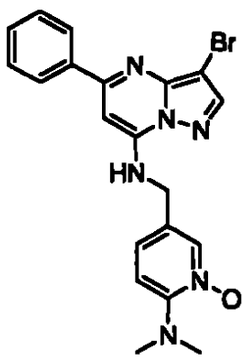
231			LCMS: $M2H^+$= 482; p.f.=129 -133°C
232			LCMS: $M2H^+$= 482; p.f.=124 -126°C
233			LCMS: $M2H^+$= 471; p.f.=88-90°C

EJEMPLO 234:



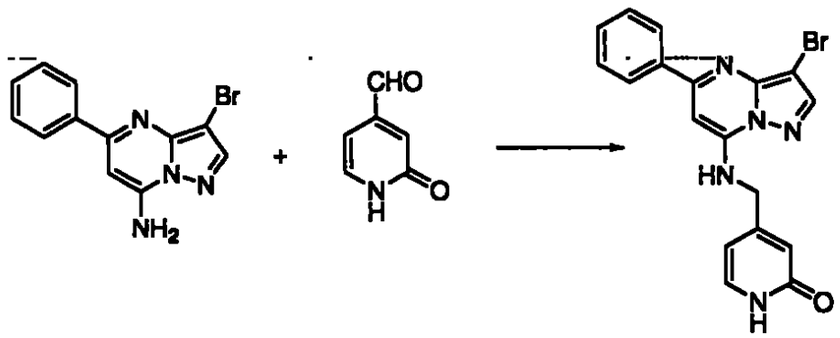
Una mezcla del producto preparado en el Ejemplo 213 (80 mg, 0,19 mmol) y 2.0 M metilamina en THF se agitaron en un recipiente cerrado bajo presión a 50ºC durante 72 horas. El solvente se evaporó, y el residuo se purificó por cromatografía evaporativa usando 10:1 CH_2Cl_2: MeOH como eluyente para proporcionar un sólido de color amarillo pálido (40 mg, 51%). LCMS: $M2H^+$=427. p.f.=217-219 °C.

EJEMPLO 235:



Esencialmente con el mismo procedimiento que se emplean en el Ejemplo 234, se preparó el compuesto que se muestra anteriormente. LCMS: $M2H^+$=441. p.f.=98-101 °C.

EJEMPLO 236:

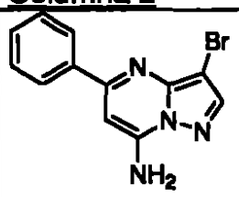
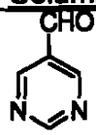
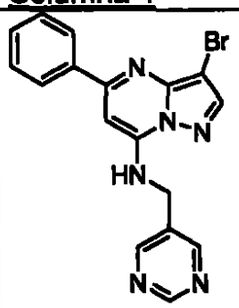
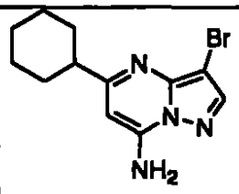
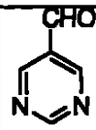
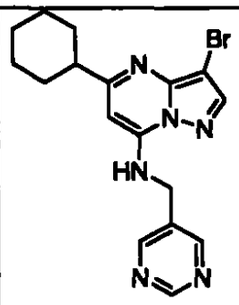
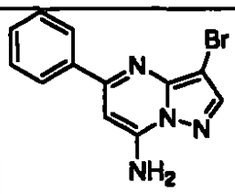
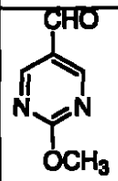
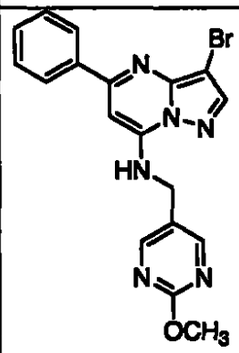
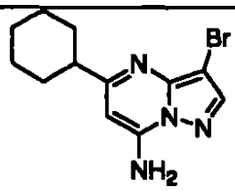
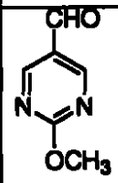
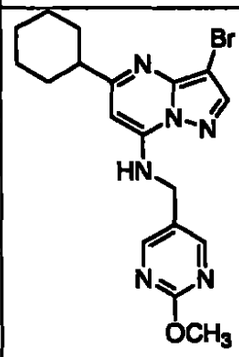


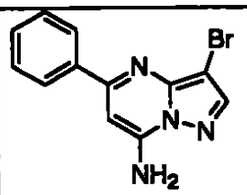
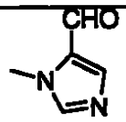
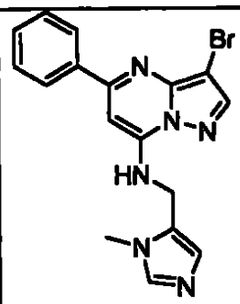
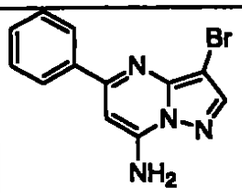
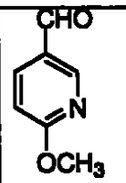
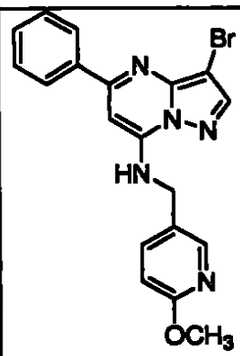
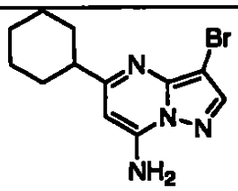
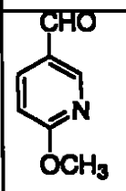
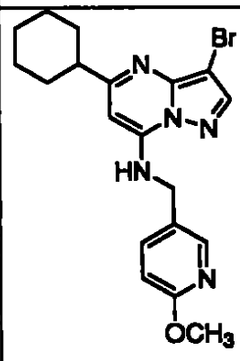
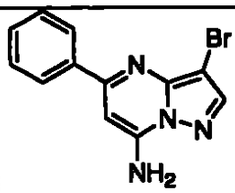
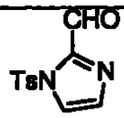
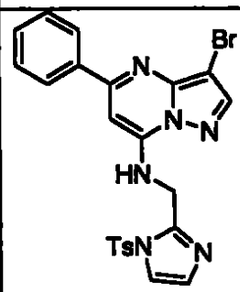
El compuesto preparado en el Ejemplo Preparativo 174 (140 mg, 0,48 mmol) y el aldehído (71 mg, 0,58 mmol) se agitaron en THF anhidro (4 mL) a 50°C bajo N_2. Se agregó $Ti(OiPr)_4$ (0,574 mL, 1,92 mmol), la mezcla se agitó a 50°C durante 3 horas, a 25°C. Se agregó $NaBH_3CN$ (181 mg, 2,88 mmol), la mezcla se agitó durante 2 horas más, y luego se vertió en 10 % de Na_2CO_3 acuoso (100 mL), y se extrajo con CH_2Cl_2 (3 x 50 mL). Los extractos combinados se secaron sobre Na_2SO_4, se filtraron, y el solvente se evaporó y se purificó por cromatografía evaporativa usando 15:1 CH_2Cl_2:MeOH como eluyente para proporcionar un sólido de color amarillo pálido (40 mg, 21%). LCMS: MH^+=398. p.f.> 230 °C.

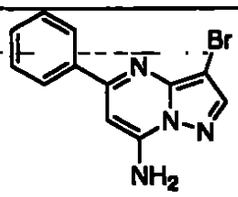
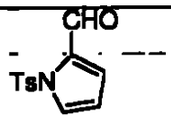
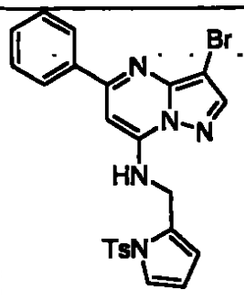
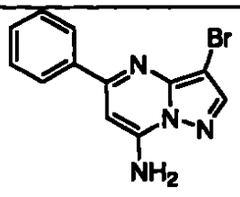
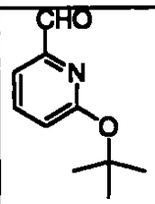
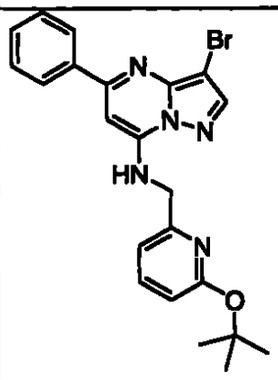
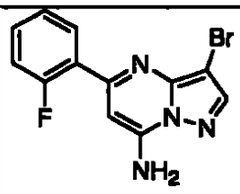
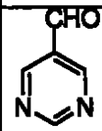
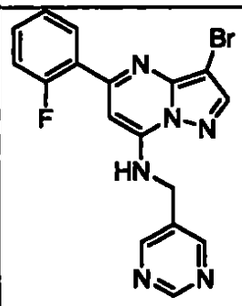
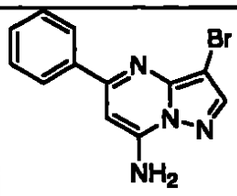
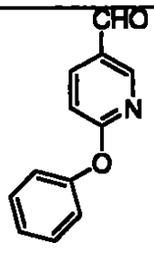
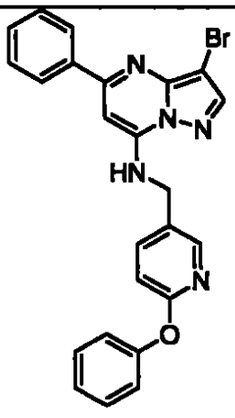
EJEMPLOS 237-256:

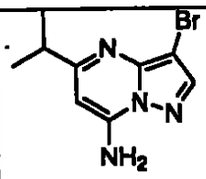
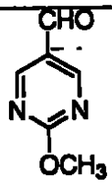
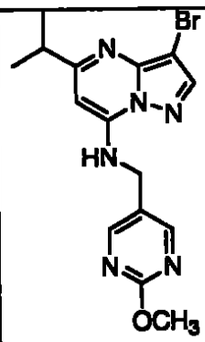
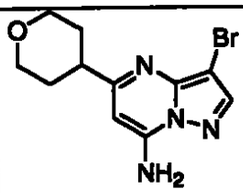
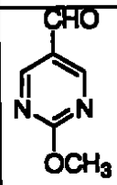
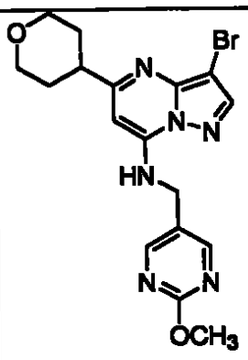
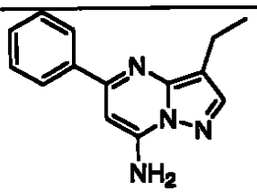
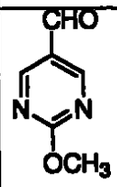
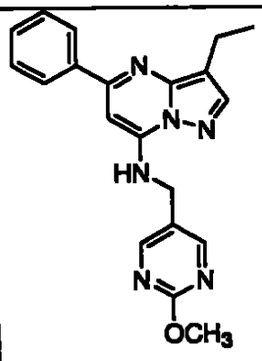
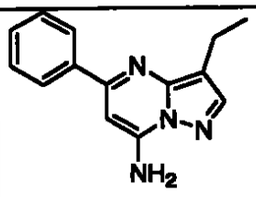
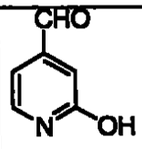
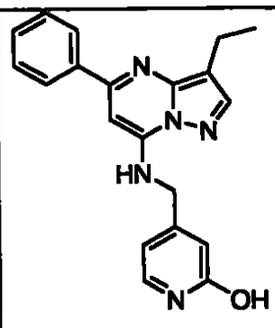
Esencialmente mediante el mismo procedimiento que se indica en el Ejemplo 236 combinando los compuestos que se muestran en las Columnas 2 y 3 de la Tabla 22, se prepararon los compuestos que se muestran en la Columna 4 de la Tabla 22.

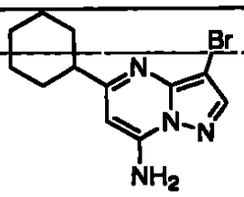
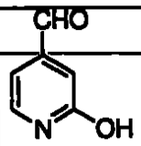
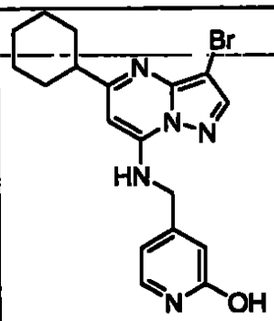
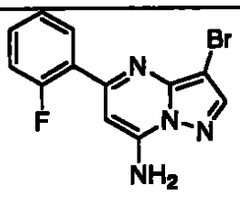
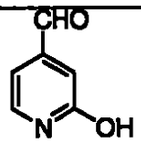
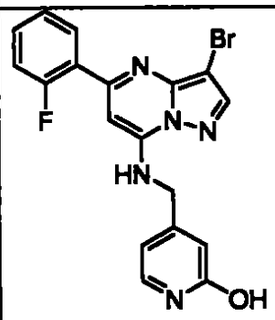
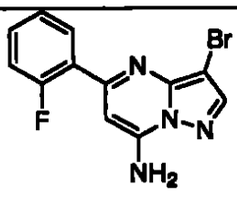
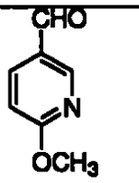
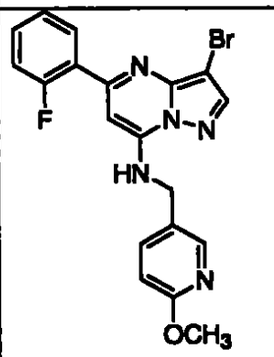
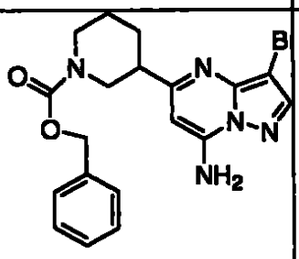
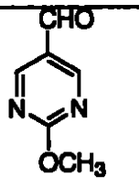
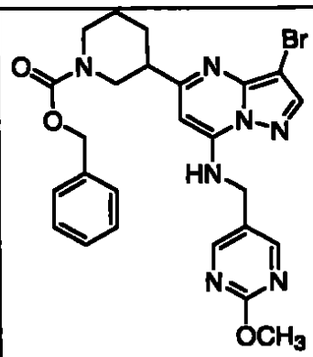
TABLA 22

Ej.	Columna 2	Columna 3	Columna 4	Datos
237				LCMS: M^+=381; p.f.>200 °C
238				LCMS: M^+=387; p.f.=°C
239				LCMS: MH^+=413; p.f.=157-159°C
240				LCMS: $M2H^+$= 419; p.f.=77-79°C

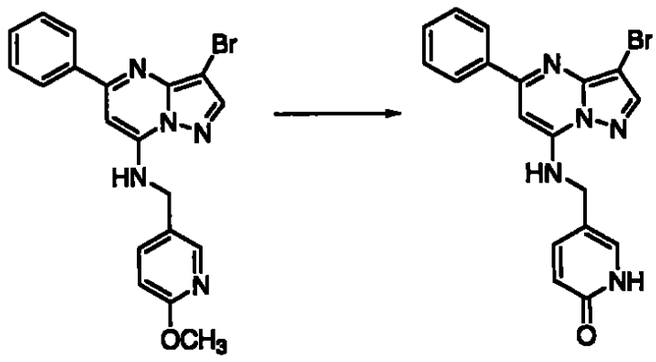
241				LCMS: $M2H^+$= 385; p.f.=214 -216°C
242				LCMS: MH^+=; p.f.=°C
243				LCMS: M^+=416; p.f.=80-82°C
244				

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

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

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

EJEMPLO 257:

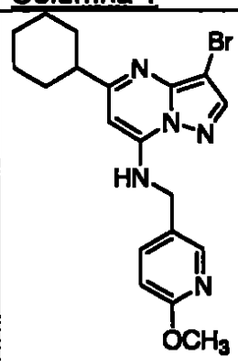
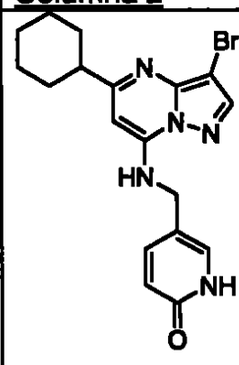
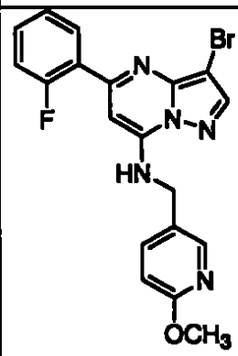
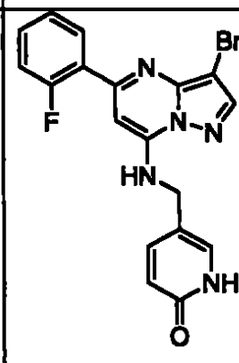
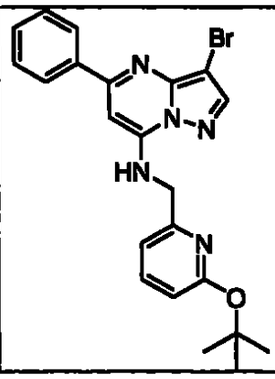
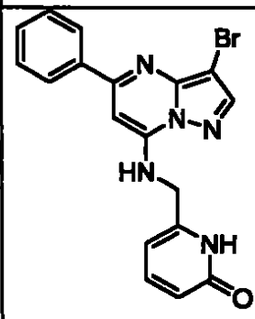


Una mezcla del compuesto preparado en el Ejemplo 242 (100 mg, 0,24 mmol), HCl acuoso concentrado (1,0 mL) y ácido acético (2,0 mL) se agitaron a 100°C bajo N_2 durante 2 horas, y luego se vertieron sobre Na_2CO_3 (15 g), y se extrajeron con 1:1 de acetona:CH_2Cl_2 (3 x 30 mL). Se filtraron los extractos combinados, y el solvente se evaporó. El residuo se purificó por cromatografía evaporativa usando 10:1 de CH_2Cl_2:MeOH como eluyente para proporcionar un sólido de color amarillo pálido (36 mg, 37%). LCMS: $M2H^+$=398.

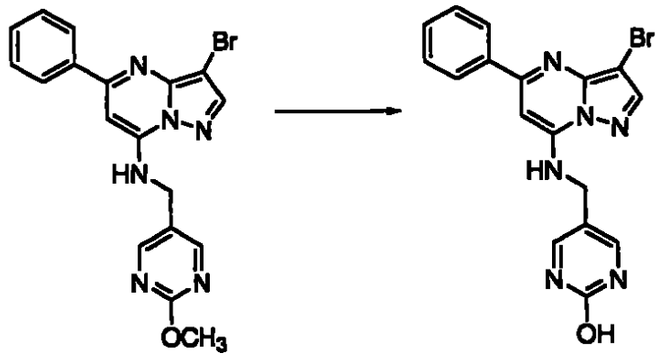
EJEMPLOS 258-260:

Esencialmente con el mismo procedimiento que se indica en el Ejemplo 257 a partir de los compuestos que se muestran en la Columna 1 de la Tabla 23, se prepararon los compuestos que se muestran en la Columna 2 de la Tabla 23.

TABLA 23

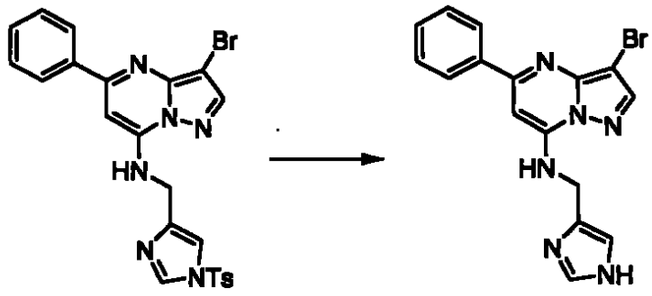
Ej.	Columna 1	Columna 2	Datos
258			LCMS: M^+=402; p.f.=229 -231°C
259			LCMS: MH^+=416; p.f.=215 -218°C
260			LCMS: $M2H^+$= 398; p.f.>230 °C

EJEMPLO 261:



A una solución agitada preparada en el Ejemplo 239 (41 mg, 0,10 mmol) en CH_2Cl_2 se le agregó 1,0 M de BBr_3 (0,30 mL, 0,30 mmol) en CH_2Cl_2 a -78°C. La mezcla se agitó a -78°C durante 5 minutos, luego a 24°C durante 3 horas, y luego se le agregó MeOH (2.0 mL) y la mezcla se agitó durante 10 minutos. El solvente se evaporó y el residuo se purificó por cromatografía evaporativa usando 5:1:0.1 de CH_2Cl_2:MeOH:conc. NH_4OH como eluyente para proporcionar un sólido blanco (39 mg, 99%). LCMS: M^+=397. p.f.>230 °C.

EJEMPLO 262:



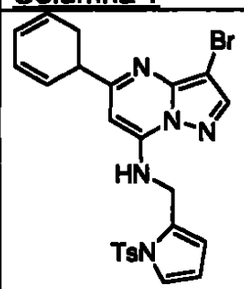
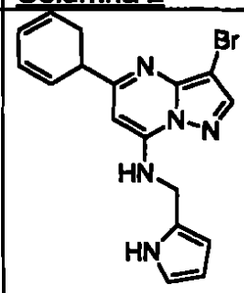
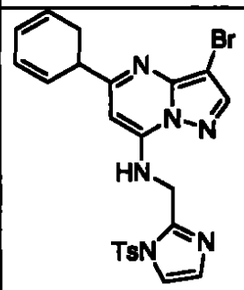
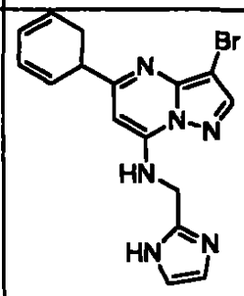
Una mezcla del producto preparado en el Ejemplo 217 (40 mg, 0,077 mmol) y 5.0 M de NaOH acuoso (0,8 mL) en MeOH (3.0 mL) se reflujó bajo N_2 durante 1 hora. Se agregó $NaHCO_3$ (700 mg), el solvente se evaporó, y el esiduo se purificó por cromatografía evaporativa usando 10:1:0.1 de CH_2Cl_2: MeOH:NH_4OH concentrado como eluyente para proporcionar un sólido blanco (10 mg, 35%). LCMS: $M2H^+$=371. p.f.=237-239 °C.

522-
523

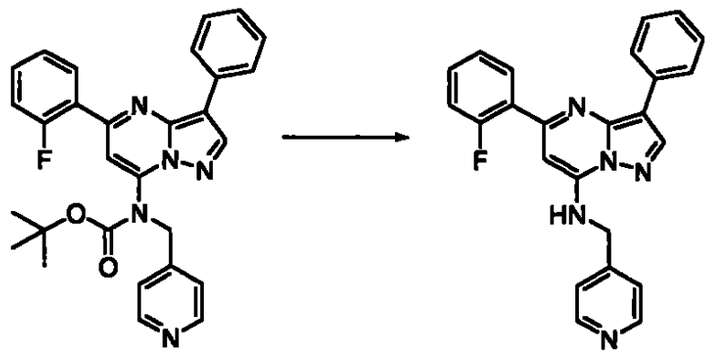
EJEMPLOS 263-264:

Esencialmente mediante el mismo procedimiento que se indica 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 1 de la Tabla 24.

TABLA 24

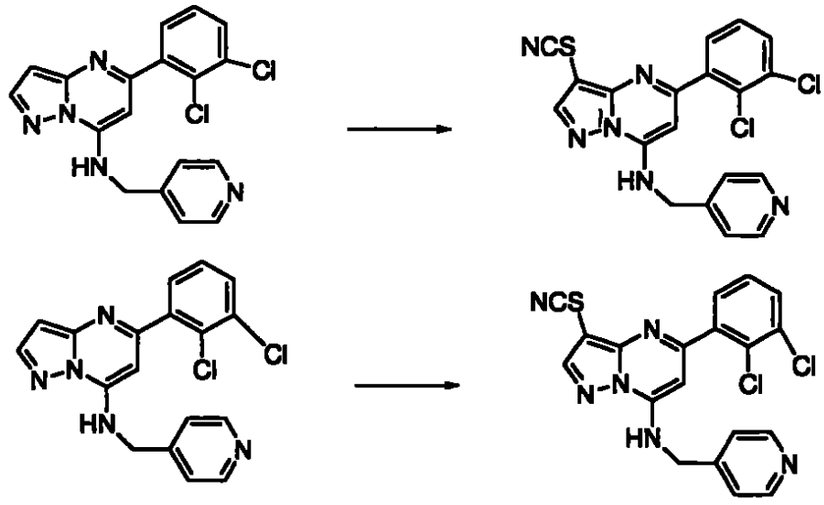
Ej.	Columna 1	Columna 2	Datos
263			LCMS: $M2H^+$= 370; p.f.=166 -168°C
264			LCMS: $M2H^+$= 371; p.f.=180 -182°C

EJEMPLO 265:



Se agregó TFA (0,5 mL) a una solución del compuesto preparado en el Ejemplo Preparativo 197 (0,08 g, 0,16 mmol) en CH_2Cl_2 (2,0 mL) a 0°C y la solución resultante se agitó durante 2.5 horas y se almacenó a 4°C durante la noche durante cuyo tiempo se agregó TFA adicional (0,5 mL). La solución resultante se agitó durante 4 horas y se concentro al vacío. El residuo se neutralizó con NaOH 1N y se extrajo con CH_2Cl_2. Se secaron los orgánicos combinados sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por cromatografía evaporativa usando una solución a 2,5% (10% NH_4OH en MeOH) en CH_2Cl_2 como eluyente (0,009 g, 15% de rendimiento). LCMS: MH^+=396; p.f. = 53-54°C.

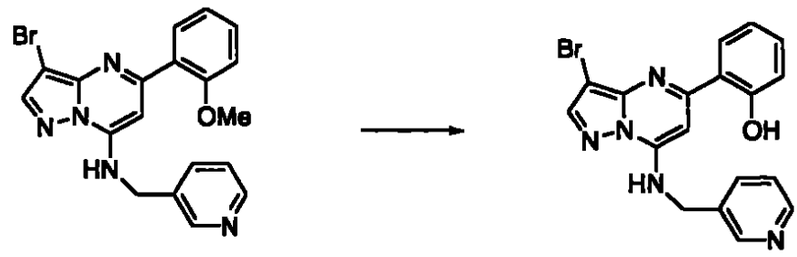
EJEMPLO 266:



Una solución del compuesto preparado en el Ejemplo Preparativo 182 (26 mg, 0,070 mmol) y tiocianato de potasio (13 mg, 0,14 mmol) en MeOH (1 mL) se enfrió en un baño de agua fría. A este baño se le agregó una solución de bromo (22 mg, 0,14 mmol) en MeOH (0,7 mL).por goteo. La mezcla de reacción resultante se agitó durante 4 horas a temperatura ambiente y se extrajeron los volátiles bajo presión reducida. El residuo obtenido se suspendió en una pequeña cantidad de CH_2Cl_2. Se separó por filtración bromuro de potasio y se ajustó el pH

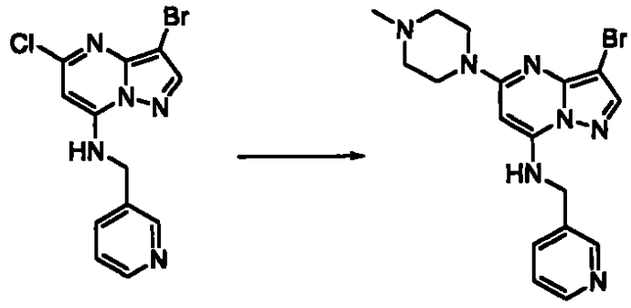
del filtrado hasta aproximadamente 7 mediante adición de amoníaco acuoso. Se concentró bajo presión reducida y el aceite residual se purificó mediante cromatografía de capa delgada preparativa usando 15% de MeOH en CH_2Cl_2 como eluyente (26 mg, 87% de rendimiento). ^1H RMN ($CDCl_3$) δ 8,75 (d, J = 4,2 Hz, 2H), 8,38 (s, 1H), 7,68-7,64 (m, 2H), 7,46-7,39 (m, 3H), 7,22 (t, J = 6,3 Hz, 1H), 6,43 (s, 1H), 4,84 (d, J = 6,3 Hz, 2H); LCMS: MH^+ = 427.

EJEMPLO 267:



Se agregó tribromuro de boro (1 M en CH_2Cl_2, 0,60 mL, 0,60 mmol) por goteo a una solución agitada enfriada con hielo del compuesto preparado en el Ejemplo 24 (50 mg, 0,12 mmol) en CH_2Cl_2 (1,5 mL) bajo atmósfera de argón. La mezcla de reacción resultante se agitó a 0°C durante 30 minutos, se dejó calentar a temperatura ambiente y se agitó durante la noche. La mezcla se apagó mediante adición de una pequeña cantidad de agua y se extrajo con CH_2Cl_2. La capa orgánica se secó sobre sulfato de magnesio y se concentró al vacío (45 mg, 94% de rendimiento). ^1H RMN (CD_3OD) δ 9,16 (s, 1H), 8,95 (s, 1H), 8,88 (d, J = 8,1 Hz, 1H), 8,24 (t, J = 6,9 Hz, 1H), 8,18 (s, 1H), 7,95 (d, J = 7,8 Hz, 1H), 7,40 (t, J = 7,8 Hz, 1H), 7,00-6,96 (m, 2H), 6,86 (s, 1H), 5,28 (s, 2H); LCMS: MH^+ = 396.

EJEMPLO 268:

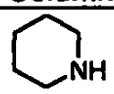
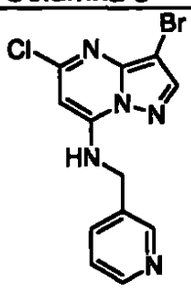
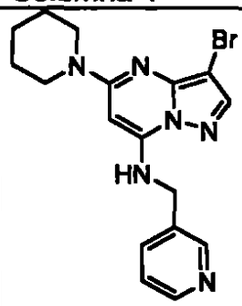
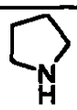
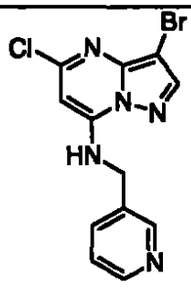
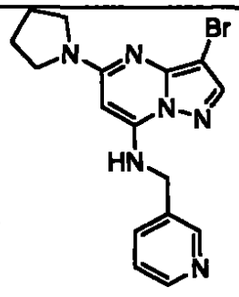
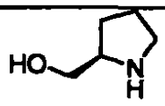
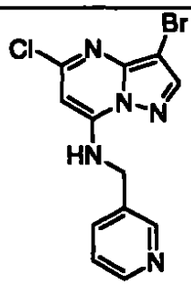
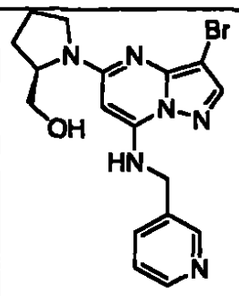
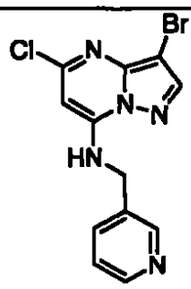
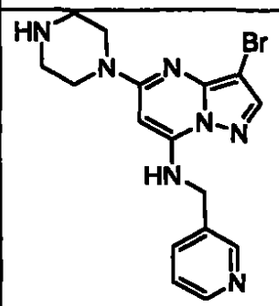


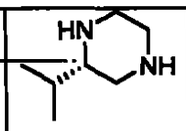
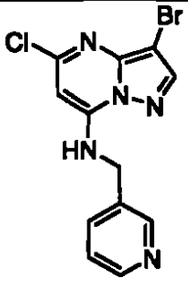
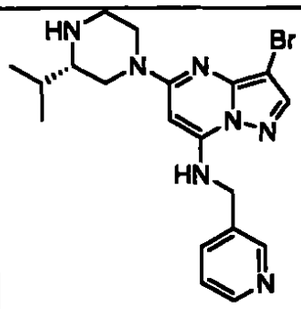
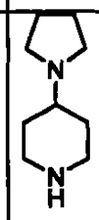
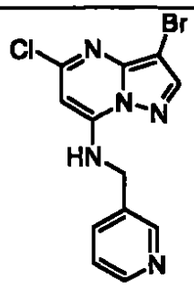
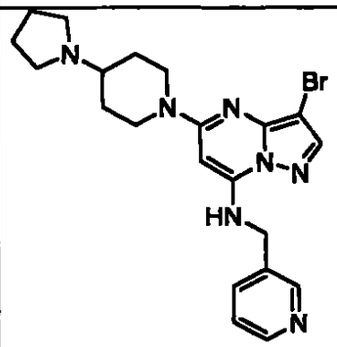
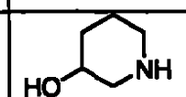
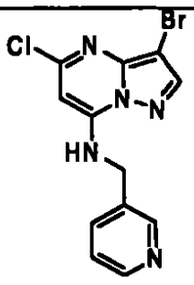
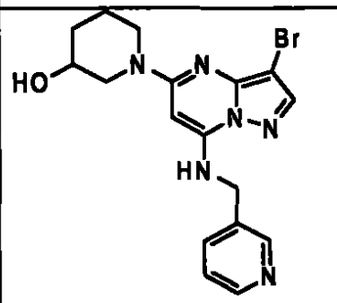
Una solución del compuesto del Ejemplo Preparativo 184 (0,05 g, 0,15 mmol), N-metilpiperazina (20 µL, 1,2 eq.) y iPr_2Et (52 µL, 2,0 eq.) en dioxano (1 mL) se calentó a 70 °C durante la noche. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con H_2O y con $NaHCO_3$.saturado. La mezcla resultante se extrajo con CH_2Cl_2, se secaron los orgánicos combinados sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por TLC Preparativa usando una solución al 5% (10% NH_4OH en MeOH) en CH_2Cl_2 como eluyente (0,028 g, 47% de rendimiento). EM: MH^+= 402. p.f. = 210 °C (desc.)

EJEMPLOS 269-275:

Siguiendo esencialmente con el mismo procedimiento que se indica en el Ejemplo 268 sustituyendo solamente la amina de 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.

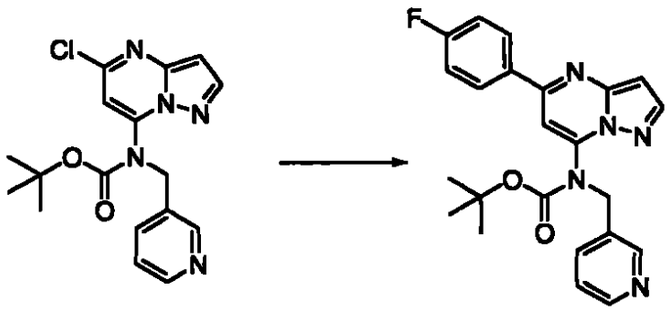
TABLA 25

Ej.	Columna 2	Columna 3	Columna 4	COMP.
269				EM: MH^+ = 387 p.f. 182 – 183°C
270				EM: MH^+ = 373 p.f.. 190 – 191 °C
271				EM: MH^+ = 403 p.f.. 227 – 230 °C
272				EM: MH^+ = 388 p.f.. 198 – 201 °C

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

EJEMPLO 276:

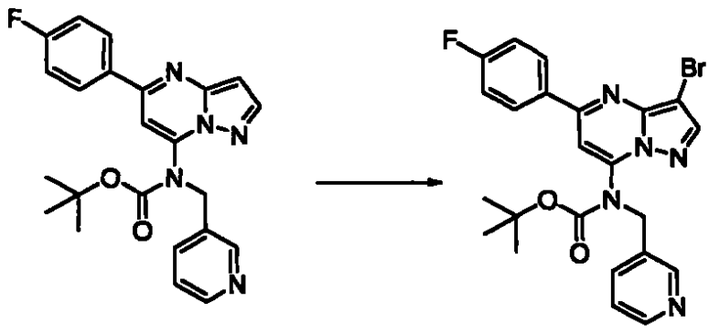
Etapa A:



Se agregó bromuro de 4-Fluorofenil magnesio (0,68 mL, 1,2 eq.) al compuesto preparado en el Ejemplo Preparativo 193 (0,20 g, 0,55 mmol) y

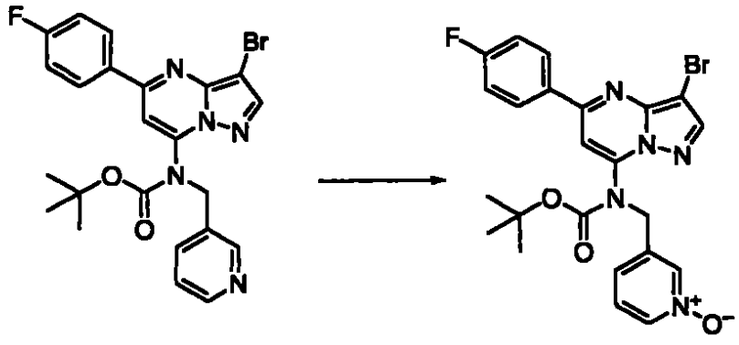
$PdCl_2(dppf)_2$ (0,037 g, 10 mol%) en THF y la solución resultante se agitó a temperatura ambiente durante 72 horas. La mezcla de reacción se diluyó con NH_4Cl saturado y se extrajo con EtOAc. Los orgánicos combinados se lavaron con NaCl saturado, se secaron sobre Na_2SO_4, se filtraron y se concentraron. El producto crudo se purificó por cromatografía evaporativa usando EtOAc neto como eluyente (0,15 g, 65% de rendimiento). EM: $MH^+ = 420$.

Etapa B:



Siguiendo esencialmente con el mismo procedimiento que se indica en el Ejemplo Preparativo 27 sustituyendo únicamente el compuesto preparado en el Ejemplo 276, Etapa A, se preparó el compuesto anterior (0,17 g, 94% de rendimiento).

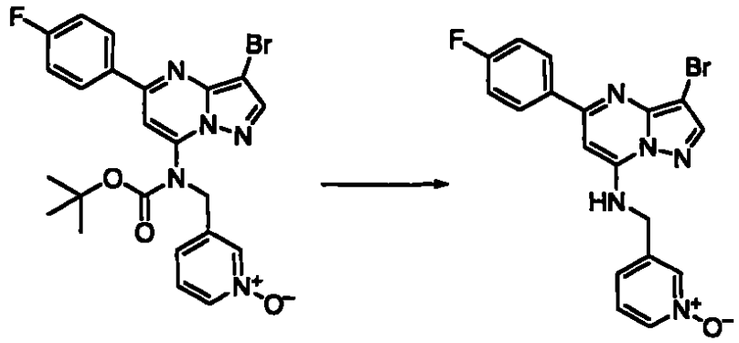
Etapa C:



Siguiendo esencialmente con el mismo procedimiento que se indica en el Ejemplo Preparativo 200 sustituyendo únicamente el compuesto preparado en el

Ejemplo 276, Etapa B, se preparó el compuesto anterior (0,1g, 100% de rendimiento).

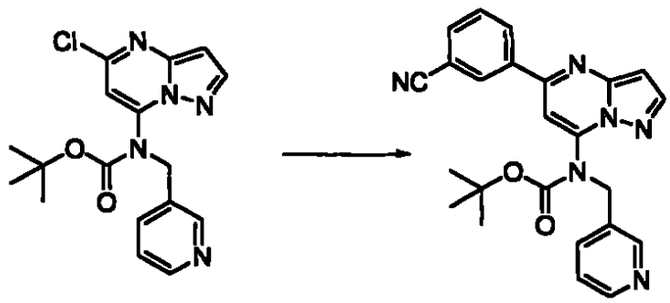
Step D:



Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo 265 sustituyendo únicamente el compuesto preparado en el Ejemplo 276, Etapa C, se preparó el compuesto anterior (0,049 g, 62% de rendimiento). EM: MH^+ = 414; p.f. = 110-115 °C.

EJEMPLO 277:

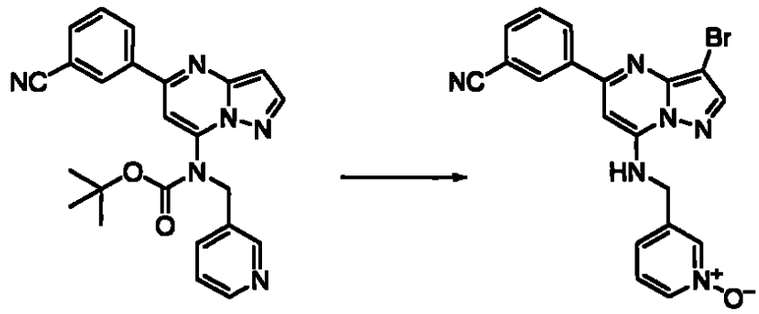
Step A:



Se agregó $Pd(PPh_3)_4$ (0,065 g, 10 mol %) a ioduro de 3-cianofenil zinc iodide (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 durante 144 horas. La mezcla de reacción se enfrió a temperatura ambiente, se diluyó con NH_4Cl saturado y se extrajo con EtOAc. Los orgánicos

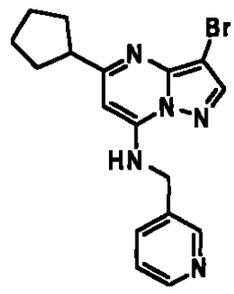
combinados se lavaron con H_2O y salmuera, se secaron sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por cromatografía evaporativa usando una solución de EtOAC neta como eluyente (0,07 g, 29% de rendimiento). EM: $MH^+ = 427$.

Etapa B hasta Etapa D:



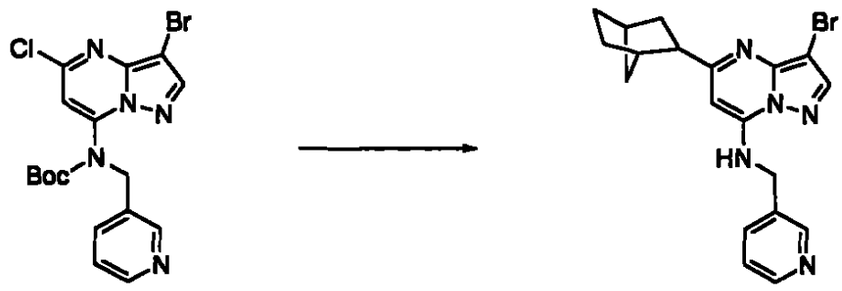
Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo 276, Etapa B hasta Etapa D, se preparó el compuesto anterior (0,023 g, 53% de rendimiento). EM: $MH^+ = 421$; mp = 230 °C (desc.)

EJEMPLO 278:



Siguiendo esencialmente el mismo procedimiento indicado en el Ejemplo 276 sustituyendo únicamente el bromuro de ciclopropilmagnesio apropiado en la Etapa A, se preparó el compuesto. EM: $MH^+ = 372$; p.f. = 96-98 °C.

EJEMPLO 279:

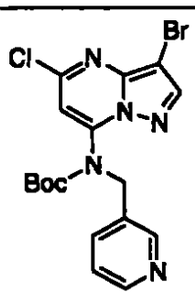
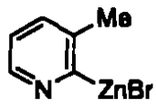
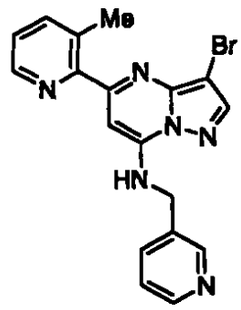
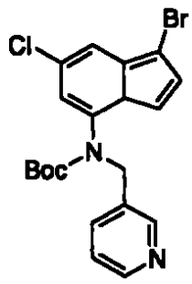
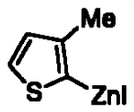
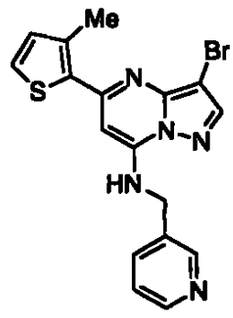
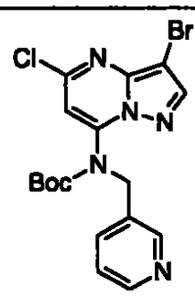
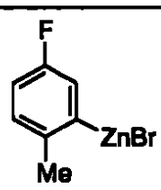
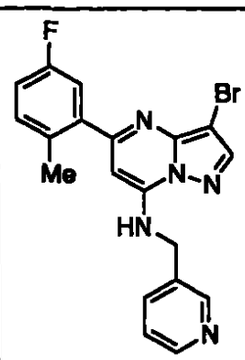


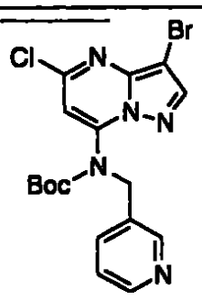
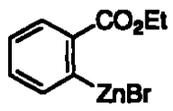
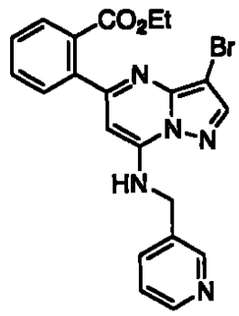
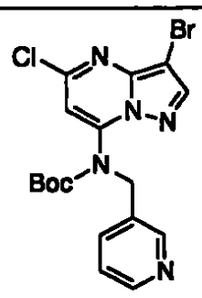
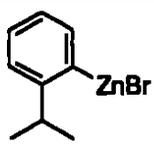
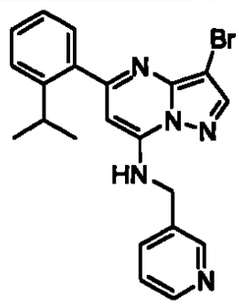
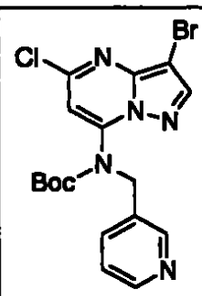
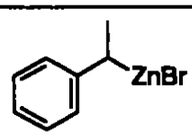
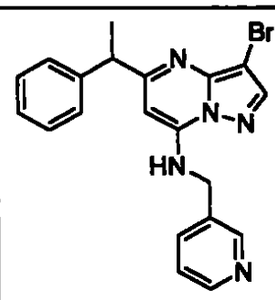
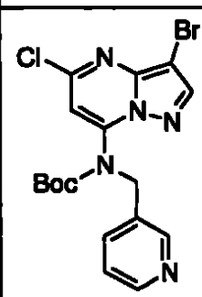
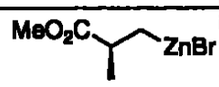
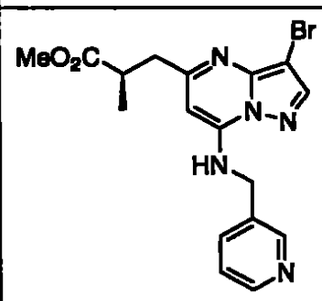
La reacción de acoplamiento entrecruzada de zinc catalizada por paladio se llevó a cabo de manera similar al procedimiento descripto en *J. Org. Chem.* (1999), 453. Una solución de la cloropirazolopirimidina (200 mg, 0,458 mmol), $Pd(PPh_3)_4$ (53 mg, 0,046 mmol), y bromuro de *exo*-2-norbonilzinc (0,5 M en THF, 0,95 mL, 0,47 mmol) en DMF (2 mL) reflujó a 100°C (temperatura del baño oleoso) durante la noche. La mezcla de reacción se apagó con NH_4Cl semi-saturado y se extrajo con CH_2Cl_2. La fase orgánica se secó sobre $MgSO_4$ y se concentró bajo presión reducida. El residuo se purificó por cromatografía evaporativa usando una solución al 50% de EtOAc ein hexanos como eluyente. Una solución del producto *N*-Boc-protegido (121 mg, 53% de rendimiento, LCMS: MH^+ = 498) y TFA (1 mL) en CH_2Cl_2 (2 mL) se agitó a temperatura ambiente durante 2 horas. Se extrajeron los volátiles bajo presión reducida. El residuo se disolvió en CH_2Cl_2, neutralizado con $NaHCO_3$ saturado, y se extrajo con CH_2Cl_2. La fase orgánica se secó sobre $MgSO_4$ y se concentró al vacío (96 mg, 99% de rendimiento). LCMS: MH^+ = 398; ^1H RMN ($CDCl_3$) δ 8,78 (s, 1H), 8,71 (d, J = 4,2 Hz, 1H), 8.04 (d, J = 3,9 Hz, 1H), 7,80 (d, J = 7,8 Hz, 1H), 7,44 (m, 1H), 6,73 (m, 1H), 5,98 (d, J = 7,5 Hz, 1H), 4,74 (d, J = 5,4 Hz, 2H), 3,40-1,00 (m, 11H).

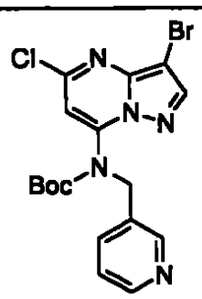
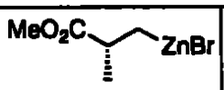
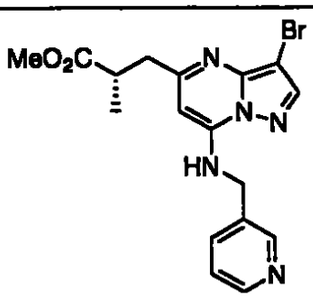
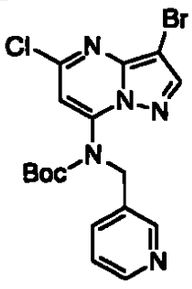
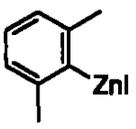
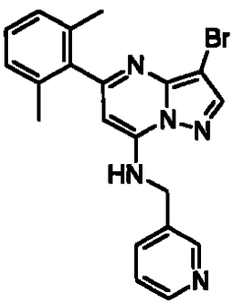
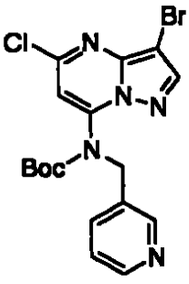
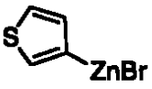
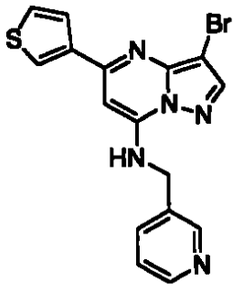
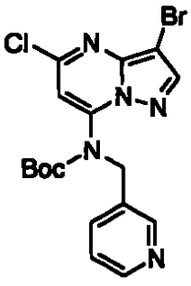
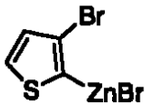
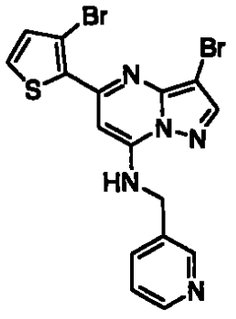
EJEMPLOS 280-294:

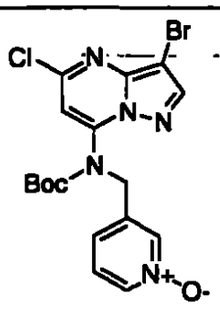
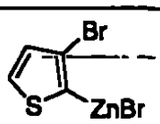
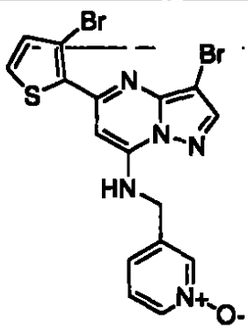
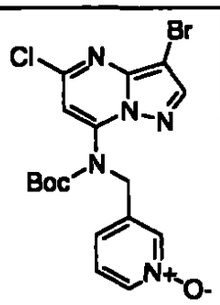
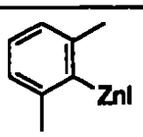
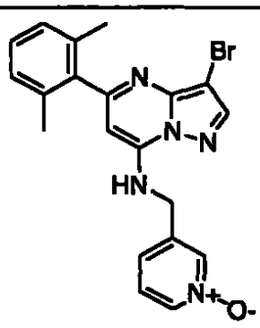
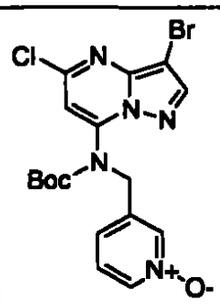
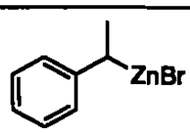
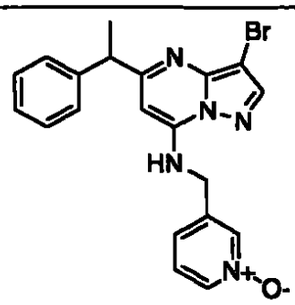
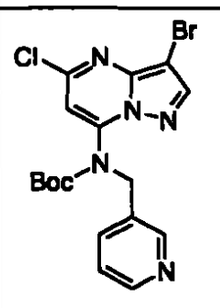
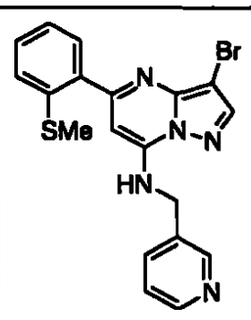
Siguiendo esencialmente el mismo procedimiento indicado en el Ejemplo 279 sustituyendo únicamente los cloruros que se muestran en la Columna 2 de la Tabla 26 y los reactivos de organozinc que se muestran en la Columna 3 de la Tabla 26, se prepararon los compuestos de la Columna 4 de la Tabla 26:

Tabla 26

Ej.	Columna 2	Columna 3	Columna 4	Datos
280				LCMS: MH^+ = 395
281				LCMS: MH^+ = 400
282				LCMS: MH^+ = 412

283				LCMS: MH^+ = 452
284				LCMS: MH^+ = 422
285				LCMS: MH^+ = 408
286				LCMS: MH^+ = 404

287				LCMS: MH^+ = 404
288				LCMS: MH^+ = 408
289				LCMS: MH^+ = 386
290				LCMS: MH^+ = 464

291				LCMS: MH^+ = 480
292				LCMS: MH^+ = 424
293				LCMS: MH^+ = 424
294				LCMS: MH^+ = 426

Los datos adicionales de los compuestos seleccionados se muestran a continuación.

EJEMPLO 280: ^{1}H RMN ($CDCl_3$) δ 8,65 (s, 1H), 8,57 (d, J = 4,2 Hz, 1H), 8,50 (d, J = 4,5 Hz, 1H), 8,01 (s, 1H), 7,69 (d, J = 7,5 Hz, 1H), 7,61 (d, J = 7,8 Hz, 1H), 7,31-7,22 (m, 2H), 6,77 (m, 2H), 4,71 (d, J = 5,4 Hz, 2H), 2,68 (s, 3H).

EJEMPLO 281: ^{1}H RMN ($CDCl_3$) δ 8,80 (s, 1H), 8,72 (d, J = 4,8 Hz, 1H), 8,08 (s, 1H), 7,85-7,40 (m, 3H), 7,02 (d, J = 5,1 Hz, 1H), 6,90 (t, J = 6,0 Hz, 1H), 6,29 (s, 1H), 4,79 (d, J = 6,0 Hz, 2H), 2,61 (s, 3H).

EJEMPLO 282: ^{1}H RMN ($CDCl_3$) δ 8,67 (s, 1H), 8,61 (d, J = 3,9 Hz, 1H), 8,03 (s, 1H), 7,72-7,31 (m, 3H), 7,22-7,00 (m, 2H), 6,81 (t, J = 6,0 Hz, 1H), 6,03 (s, 1H), 4,68 (d, J = 6,0 Hz, 2H), 2,28 (s, 3H).

EJEMPLO 283: ^{1}H RMN ($CDCl_3$) δ 8,68 (s, 1H), 8,63 (d, J = 4,0 Hz, 1H), 8,00 (s, 1H), 7,80-7,72 (m, 2H), 7,54-7,47 (m, 3H), 7,35 (m, 1H), 6,74 (t, J = 6,0 Hz, 1H), 6,19 (s, 1H), 4,67 (d, J = 6,0 Hz, 2H), 4,21 (q, J = 7,2 Hz, 2H), 1,13 (t, J = 7,2 Hz, 3H).

EJEMPLO 284: ^{1}H RMN ($CDCl_3$) δ 7,97 (s, 1H), 7,65 (d, J = 7,2 Hz, 1H), 7,33-7,15 (m, 5H), 6,73 (t, J = 5,4 Hz, 1H), 5,99 (s, 1H), 4,61 (d, J = 5,4 Hz, 2H), 3,09 (sept, J = 6,9 Hz, 1H), 1,11 (d, J = 6,9 Hz, 6H).

EJEMPLO 285: ^{1}H RMN ($CDCl_3$) δ 8,56-8,55 (m, 2H), 7,94 (s, 1H), 7,54 (m, 1H), 7,30-7,22 (m, 6H), 6,59 (t, J = 5,7 Hz, 1H), 5,66 (s, 1H), 4,47 (d, J = 5,7 Hz, 2H), 4,26 (q, J = 7,2 Hz, 1H), 1,68 (d, J = 7,2 Hz, 3H).

EJEMPLO 286: ^{1}H RMN ($CDCl_3$) δ 8,67 (m, 2H), 7,94 (s, 1H), 7,69 (d, J = 7,8 Hz, 1H), 7,34 (m, 1H), 6,63 (t, J = 5,7 Hz, 1H), 5,87 (s, 1H), 4,62 (d, J = 5,7 Hz, 2H), 3,64 (s, 3H), 3,13 (m, 2H), 2,82 (m, 1H), 1,22 (m, 3H).

EJEMPLO 287: ^{1}H RMN ($CDCl_3$) δ 8,66 (m, 2H), 7,94 (s, 1H), 7,68 (d, J = 7,8 Hz, 1H), 7,34 (m, 1H), 6,62 (t, J = 6,0 Hz, 1H), 5,87 (s, 1H), 4,62 (d, J = 6,0 Hz, 2H), 3,64 (s, 3H), 3,13 (m, 2H), 2,81 (m, 1H), 1,22 (m, 3H).

EJEMPLO 288: ^{1}H RMN ($CDCl_3$) δ 8,64 (s, 1H), 8,60 (d, J = 3,6 Hz, 1H), 8,04 (s, 1H), 7,68 (m, 1H), 7,31 (m, 1H), 7,16 (m, 1H), 7,07-7,05 (m, 2H), 6,80 (t, J = 6,3 Hz, 1H), 5,93 (s, 1H), 4,64 (d, J = 6,3 Hz, 2H), 2,08 (s, 6H).

EJEMPLO 289: ^{1}H RMN ($CDCl_3$) δ 8,72 (s, 1H), 8,62 (d, J = 4,8 Hz, 1H), 7,99-7,97 (m, 2H), 7,73-7,69 (m, 2H), 7,40-7,33 (m, 2H), 6,67 (t, J = 6,0 Hz, 1H), 6,29 (s, 1H), 4,71 (d, J = 6,0 Hz, 2H).

EJEMPLO 290: ^{1}H RMN ($CDCl_3$) δ 8,73 (s, 1H), 8,62 (d, J = 4,5 Hz, 1H), 8,01 (s, 1H), 7,76 (m, 1H), 7,41 (d, J = 5,1 Hz, 1H), 7,34 (dd, J = 8,1, 5,1 Hz, 1H), 7,05 (d, J = 5,1 Hz, 1H), 7,01 (s, 1H), 6,79 (t, J = 6,0 Hz, 1H), 4,74 (d, J = 6,0 Hz, 2H).

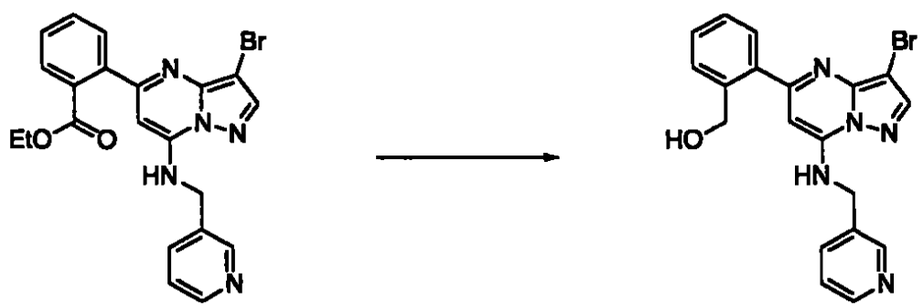
EJEMPLO 291: ^{1}H RMN (DMSO-d_6) δ 9,12 (s, 1H), 8,40 (s, 1H), 8,33 (s, 1H), 8,13 (m, 1H), 7,82 (d, J = 5,1 Hz, 1H), 7,40-7,39 (m, 2H), 7,22 (d, J = 5,1 Hz, 1H), 6,86 (s, 1H), 4,86 (s, 2H).

EJEMPLO 292: ^{1}H RMN ($CDCl_3$) δ 8,23 (s, 1H), 8,16 (d, J = 6,0 Hz, 1H), 8,06 (s, 1H), 7,31-7,05 (m, 5H), 6,86 (m, 1H), 5,87 (s, 1H), 4,62 (d, J = 6,3 Hz, 2H), 2,09 (s, 6H).

EJEMPLO 293: ^{1}H RMN ($CDCl_3$) δ 8,14 (s, 1H), 8,12 (d, J = 6,3 Hz, 1H), 7,94 (s, 1H), 7,29-7,16 (m, 6H), 7,07 (m, 1H), 6,78 (t, J = 6,0 Hz, 1H), 5,54 (s, 1H), 4,44 (d, J = 6,0 Hz, 2H), 4,24 (t, J = 7,2 Hz, 1H), 1,68 (d, J = 7,2 Hz, 3H).

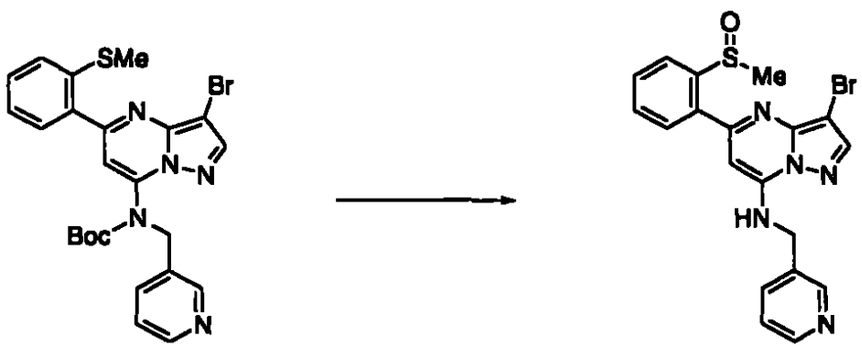
EJEMPLO 294: ^{1}H RMN ($CDCl_3$) δ 8,67 (s, 1H), 8,59 (d, J = 4,8 Hz, 1H), 8,01 (s, 1H), 7,71 (m, 1H), 7,52 (dd, J = 7,8, 1,8 Hz, 1H), 7,40-7,19 (m, 4H), 6,78 (t, J = 6,0 Hz, 1H), 6,32 (s, 1H), 4,67 (d, J = 6,0 Hz, 2H), 2,38 (s, 3H).

EJEMPLO 295:



A una suspensión de hidruro de litio aluminio (10 mg, 0,26 mmol) en THF anhidro (2 mL) a 0°C se le agregó por goteo una solución del compuesto preparado en el Ejemplo 283 (20 mg, 0,044 mmol) en THF anhidro (2 mL). La mezcla resultante se reflujó durante 1 hora y se agitó a temperatura ambiente durante la noche, se neutralizó con ácido sulfúrico diluido y se extrajo con EtOAc. La fase orgánica se secó sobre $MgSO_4$ y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía de capa delgada preparativa usando 5% MeOH en una solución de EtOAc como eluyentes (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).

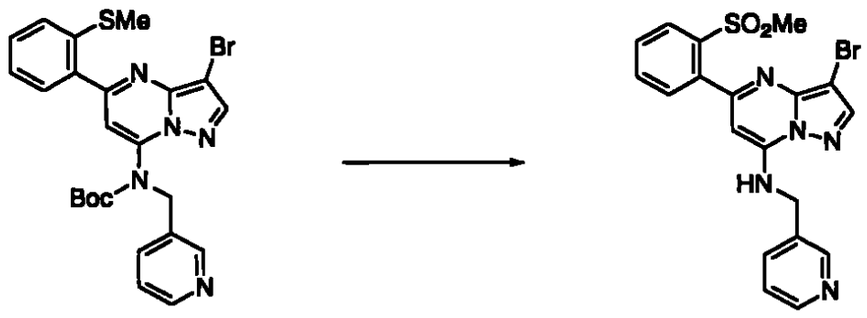
EJEMPLO 296:



A una solución del compuesto *N*-Boc-protegido preparado en el Ejemplo 294 (45 mg, 0,085 mmol) en CH_2Cl_2 (4 mL) a –50°C se agregó *m*-CPBA (18 mg, 0,10 mmol). Después de agitar durante 1 hora a –50°C se le agregó más *m*-CPBA (4 mg, 0,02 mmol). La mezcla se agitó durante 2 horas más, se diluyó con CH_2Cl_2 (20 mL), y se lavó con $NaHCO_3$ saturado (20 mL). La fase orgánica se secó sobre $MgSO_4$ y se concentró bajo presión reducida. El residuo se purificó por

cromatografía de capa delgada preparativa usando 2,5% MeOH en una solución CH_2Cl_2 como eluyente. Una solución del producto *N*-Boc-protegido (37 mg, 80% de rendimiento, LCMS: MH^+ = 542) y TFA (1 mL) en CH_2Cl_2 (2 mL) se agitó a temperatura ambiente durante 2 horas. Los volátiles se removieron bajo presión reducida. El residuo se disolvió en CH_2Cl_2, se neutralizó con $NaHCO_3$ saturado, y se extrajo con CH_2Cl_2. La fase orgánica se secó sobre $MgSO_4$ y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía de capa delgada preparativa usando 5% MeOH en una solución de EtOAc como eluyente (26 mg, 89% de rendimiento). LCMS: MH^+ = 442; ^1H RMN ($CDCl_3$) δ 8,71 (s, 1H), 8,64 (d, J = 3,9 Hz, 1H), 8,41 (m, 1H), 8,03 (s, 1H), 7,75-7,54 (m, 4H), 7,36 (dd, J = 8,1, 5,1 Hz, 1H), 6,81 (t, J = 6,0 Hz, 1H), 6,34 (s, 1H), 4,74 (d, J = 6,0 Hz, 2H), 3,25 (s, 3H).

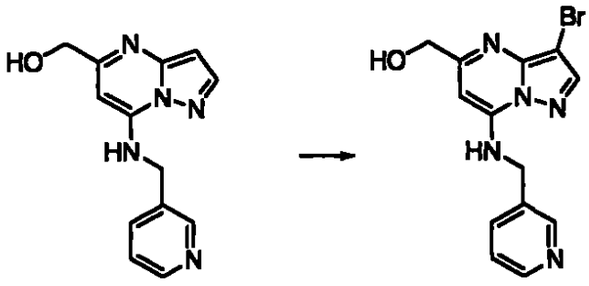
EJEMPLO 297:



A una solución del compuesto *N*-Boc-protegido preparado en el Ejemplo 294 (56 mg, 0,11 mmol) en CH_2Cl_2 (4 mL) a 0°C se agregó *m*-CPBA (42 mg, 0,24 mmol). Luego de agitar durante 2 horas a temperatura ambiente se le agregó más *m*-CPBA (13 mg, 0,075 mmol). La mezcla se agitó a temperatura ambiente durante la noche, se diluyó con CH_2Cl_2 (20 mL), y se lavó con $NaHCO_3$ saturado (20 mL). La fase orgánica se secó sobre $MgSO_4$ y se concentró bajo presión reducida. El residuo se purificó por cromatografía de capa delgada preparativa usando 2,5% de MeOH en una solución de EtOAc como eluyente. Una solución del producto *N*-Boc-

protegido obtenido (29 mg, 49% de rendimiento, LCMS: MH^+ = 558) y TFA (1 mL) en CH_2Cl_2 (2 mL) se agitó a temperatura ambiente durante 2 horas. Se extrajeron los volátiles bajo presión reducida. El residuo se disolvió en CH_2Cl_2, se neutralizó con $NaHCO_3$ saturado, y se extrajo con CH_2Cl_2. La fase orgánica se secó sobre $MgSO_4$ y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía de capa delgada preparativa usando 2.5% de MeOH en una solución de EtOAc como eluyente (21 mg, 90% de rendimiento). LCMS: MH^+ = 458; ^1H RMN ($CDCl_3$) δ 8,64 (s, 2H), 8,20 (m, 1H), 8,01 (s, 1H), 7,73-7,60 (m, 3H), 7,46 (m, 1H), 7,35 (s, 1H), 6,82 (t, J = 5,9 Hz, 1H), 6,17 (s, 1H), 4,65 (d, J = 5,7 Hz, 2H), 3,60 (s, 3H).

EJEMPLO 298

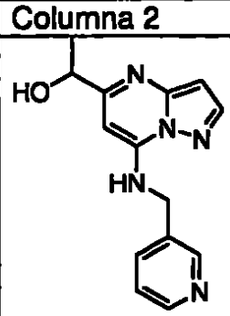
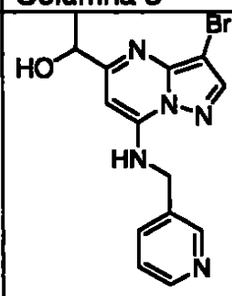
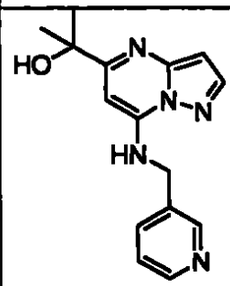
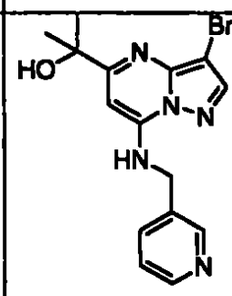


Siguiendo esencialmente el mismo procedimiento indicado en el Ejemplo Preparativo 127, únicamente sustituyendo el compuesto preparado en el Ejemplo Preparativo 189, se preparó el compuesto anterior. EM: MH^+ = 334; p.f. = 170-173 °C.

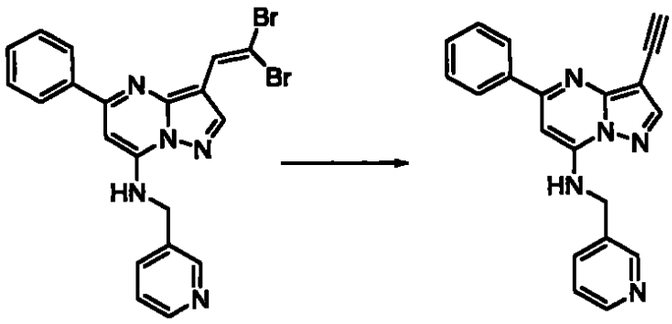
EJEMPLOS 299-300:

Siguiendo esencialmente el mismo procedimiento indicado en el Ejemplo 298, únicamente sustituyendo el compuesto que se muestra en la Tabla 27, Columna 2, se prepararon los compuestos que se muestran en la Tabla 27, Columna 3.

Tabla 27

Ej.	Columna 2	Columna 3	COMP
299			EM: MH^+ = 348 p.f.. = 73 – 83 °C
300			EM: MH^+ = 362 p.f.. = 165 – 175 °C

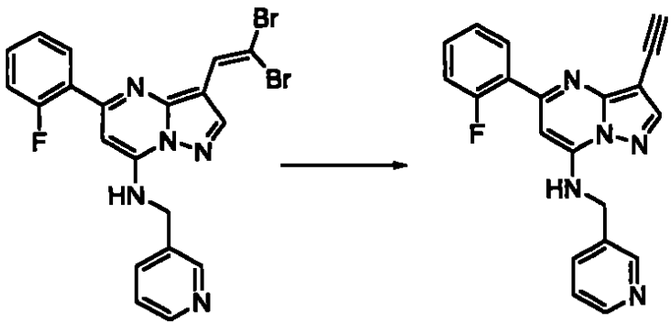
EJEMPLO 301:



A una solución del compuesto preparado en el Ejemplo Preparativo 186 (0,1 g, 0,21 mmol) en THF (4,0 mL) a -78 °C se le agregó nBuLi (0,57 mL, 2,16M en hexanos, 5,0 eq.) a -78 °C. La mezcla de reacción se agitó durante 2 horas a -78 °C, se apagó con H_2O, se calentó a temperatura ambiente y se extrajo con EtOAc. Se secaron los orgánicos combinados sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por TLC

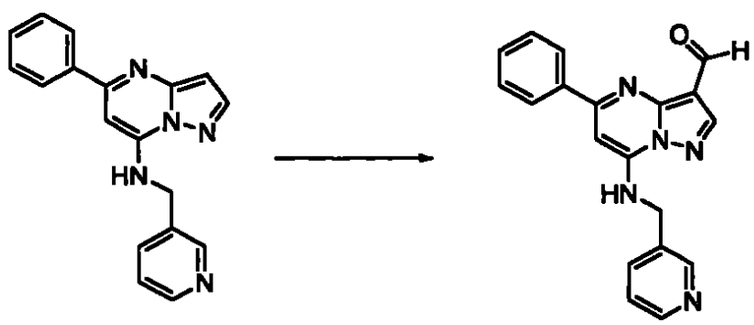
Preparativa usando una solución al 2.5% (10%NH_4OH en CH_3OH) en CH_2Cl_2 como eluyente (0,013 g, 20% de rendimiento). EM: MH^+ = 326; p.f. = 71-72 °C.

EJEMPLO 302:



Siguiendo esencialmente el mismo procedimiento indicado en el Ejemplo 301 únicamente sustituyendo el compuesto del Ejemplo Preparativo 187, se preparó el compuesto anterior (0.049 g, 68% de rendimiento). EM: MH^+ = 344; p.f. = 69-71 °C.

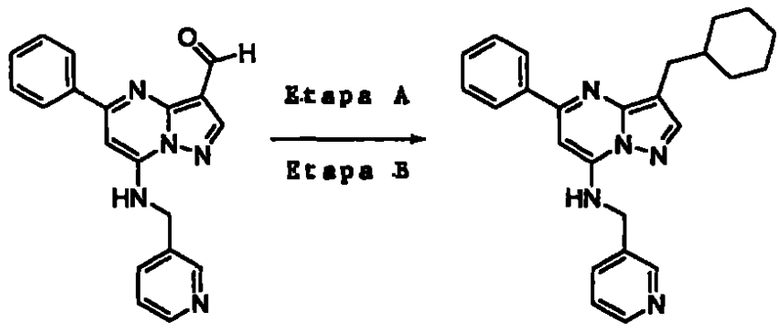
EJEMPLO 303:



A una solución del aducto 3-H del Ejemplo Preparativo 187.1 (0.70 g, 2,32 mmol) en DMF (4,2 mL) a 0 °C se le agregó por goteo $POCl_3$ (0,67 mL, 7,2 mmol). La mezcla se agitó durante 14 horas a temperatura ambiente, se enfrió a 0 °C, y se apagó por adición de hielo. Se agregó cuidadosamente NaOH 1 N para ajustar el pH a 8 y la mezcla se extrajo con CH_2Cl_2 (3 x 25 mL). Se combinaron las capas

orgánicas, se secaron (Na_2SO_4), se filtraron, y se concentraron bajo presión reducida. El producto crudo se recristalizó a partir de EtOAc para proporcionar 0,43 g (56%) de un sólido de color amarillo, p.f. 181-183 °C; M+H = 330.

EJEMPLO 304:



ETAPA A:

A una solución del aldehído (100 mg, 0,30 mmol) del Ejemplo 303 en THF (1 mL) a 0 °C se le agregó bromuro de ciclohexil magnesio (0.46 mL, 2,0M en Et_2O) por goteo durante 5 minutos. La mezcla resultante se agitó a 0 °C durante 2 horas y a temperatura ambiente durante 12 horas. La mezcla se enfrió a 0ºC y se trató con NH_4Cl acuoso saturado (3 mL) y con CH_2Cl_2 (5 mL). Se separaron las capas y las capas acuosas se extrajeron con CH_2Cl_2 (2 x 5 mL). Se combinaron las capas orgánicas, se lavaron con salmuera (1 x 5 mL), se secaron Na_2SO4), se filtraron y se concentraron bajo presión reducida para proporcionar 110 mg (89%) de un semisólido de color amarillo pálido. M+H = 414. Este material se llevó a la Etapa B en crudo sin purificación adicional.

544
545

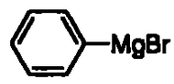
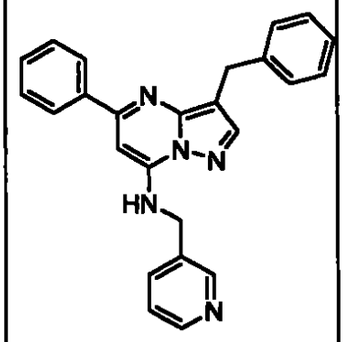
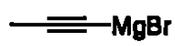
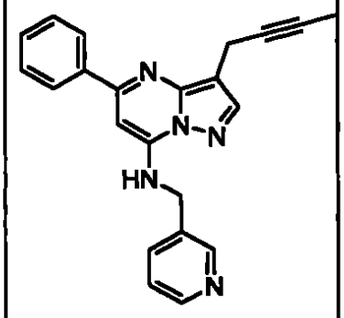
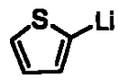
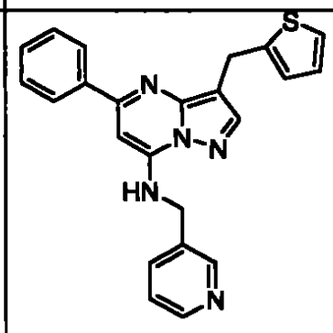
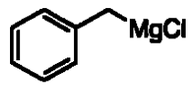
ETAPA B:

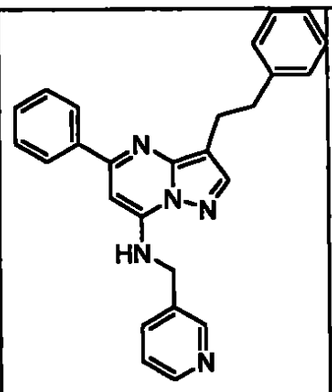
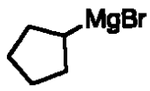
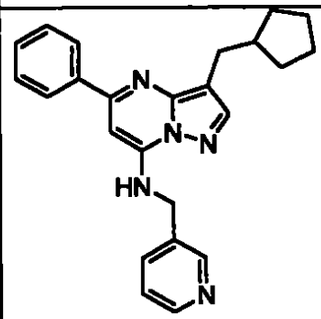
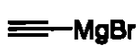
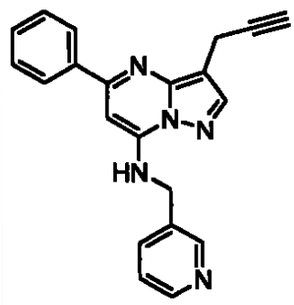
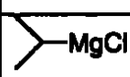
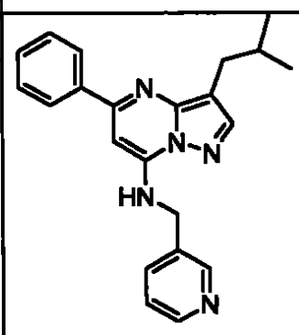
A una solución de alcohol (53 mg, 0,13 mmol) en CH_2Cl_2 (0.5 mL) a 0 °C se le agregó Et_3SiH (24 □L, 0,15 mmol) seguido de TFA (24 □L, 0.30 mmol). La mezcla se agitó durante 2 horas a 0 °C y a temperatura ambiente durante 2 horas después de lo cual se agregaron porciones adicionales de Et_3SiH (24 □L, 0,15 mmol) y TFA (24 □L, 0,30 mmol) y la mezcla se agitó durante 3 horas a temperatura ambiente (hasta completa según la TLC). La mezcla se concentró bajo presión reducida y el residuo crudo se dividió entre CH_2Cl_2 (5 mL) y $NaHCO_3$ acuoso saturado (2.5 mL). Las capas se separaron y se extrajo la capa acuosa con CH_2Cl_2 (2 x 5 mL). Se combinaron las capas orgánicas, se lavaron con salmuera (1 x 5 mL), se secaron (Na_2SO4), se filtraron y se concentraron bajo presión reducida. El producto crudo se purificó mediante TLC Preparativa (8 x 1000 mM) eluyendo con CH_2Cl_2/MeOH (22:1) para proporcionar 29 mg (56%) como un semisólido de color amarillo. M+H = 398.

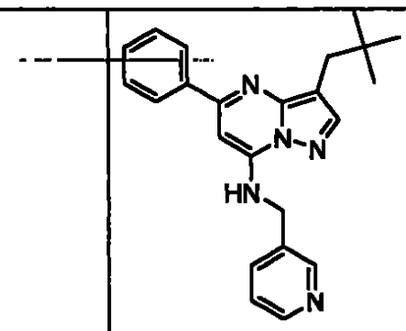
EJEMPLOS 305-312:

Esencialmente con el mismo procedimiento indicado en el Ejemplo 304, utilizando el aldehído del Ejemplo 303 y sustituyendo los reactivos de Grignard o de organolitio que se muestran en la Columna 2 de la Tabla 28, se prepararon los compuestos de la Columna 3 de la Tabla 28.

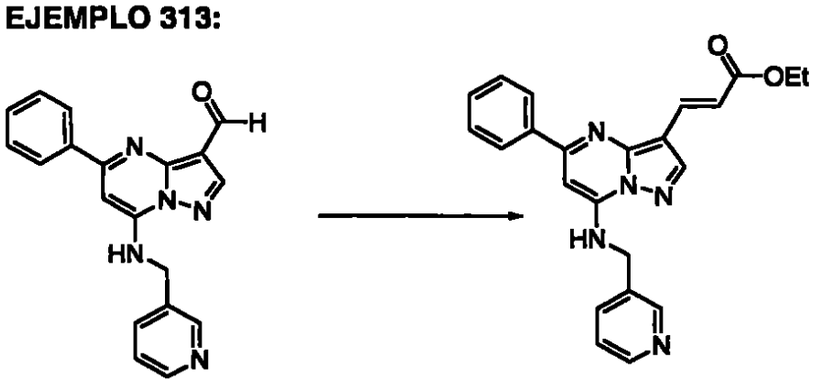
TABLA 28

Ej.	Columna 2 (Organometálico)	Columna 3 (Estructura final)	COMP 1. p.f. (°C) 2. M+H
305			1. aceite amarillo 2. M+H = 392
306			1.aceite rojo 2. M+H = 353
307			1. aceite rojo 2. M+H = 398
308			1. aceite amarillo 2. M+H = 406

			
309			1. semisólido marillo 2. M+H = 384
310			1.semisólido 2. M+H = 340
311			1. p.f. = 141-143 2. M+H = 358

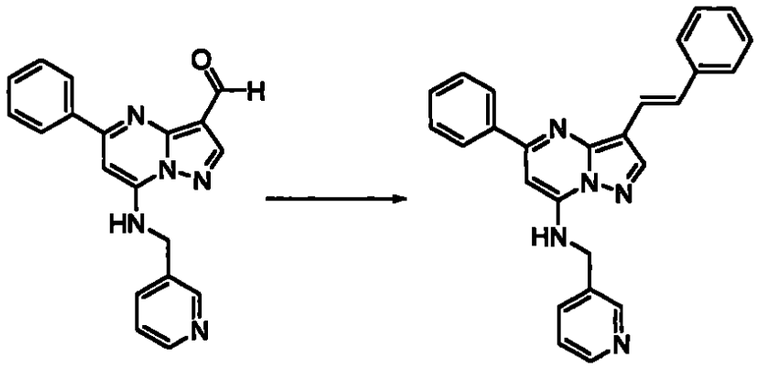
312			1. p.f. = 148-150 2. M+H = 372

EJEMPLO 313:



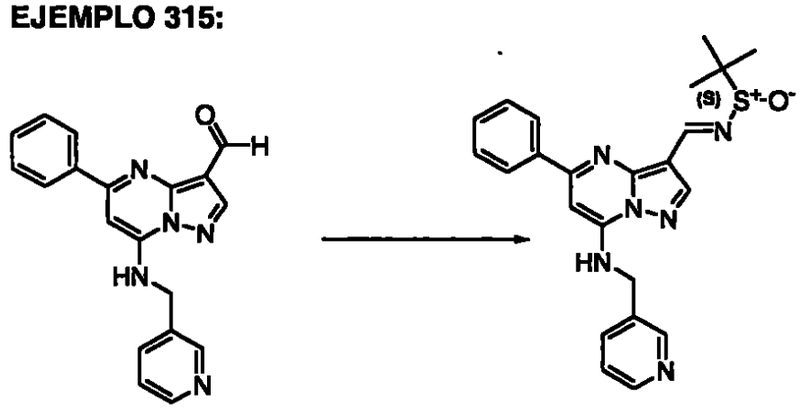
A una solución de aldehído (81 mg, 0,25 mmol) del Ejemplo 303 en benceno (2,5 mL) se le agregó carboetoximetileno trifenil fosforano (0.12 g, 0,33 mmol) en una sola porción.. La mezcla se calentó a reflujo durante 24 horas, se enfrió a temperatura ambiente, y se concentró bajo presión reducida. La mezcla se diluyó CH_2Cl_2 (5 mL), se agregó salmuera (2 mL) y las capas se separaron. Se extrajo la capa acuosa con CH_2Cl_2 (2 x 4 mL). Las capas orgánicas se combinaron, se secaron (Na_2SO_4), se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por TLC Preparativa (8 x 1000 □M) eluyendo con CH_2Cl_2/MeOH (20:1) para proporcionar 98 mg (100%) de un sólido blanco. p.f. 151-153 °C; M+H = 400.

EJEMPLO 314:



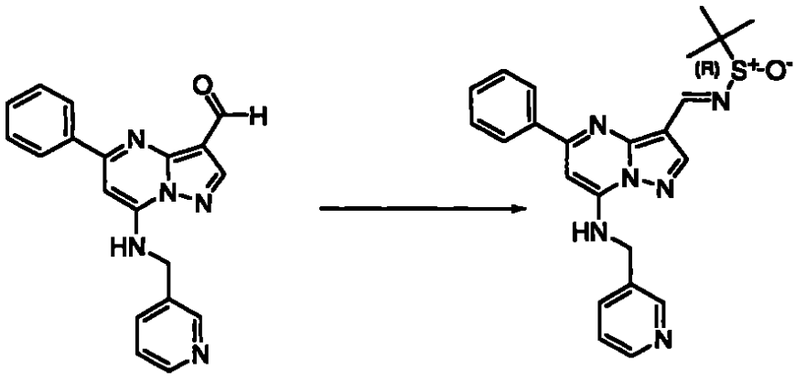
A una mezcla de bromuro de benciltrifenilfosfonio (0,59 g, 1,37 mmol) en THF (3 mL) se le agregó NaH (55 mg, 1,37 mmol) y la mezcla se agitó durante 30 minutos. El aldehído (0,15 g, 0,46 mmol) del Ejemplo 303 se agregó en una sola porción y la mezcla se calentó a reflujo durante 36 horas. La mezcla se enfrió a temperatura ambiente y se concentró bajo presión reducida. La mezcla se diluyó CH_2Cl_2 (5 mL), se agregó salmuera (2 mL), y se separaron las capas. La capa acuosa se extrajo con CH_2Cl_2 (2 x 4 mL). Se combinaron las capas orgánicas, se secaron (Na_2SO_4), se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por TLC Preparativa (8 x 1000 □M) eluyendo con CH_2Cl_2/MeOH (20:1) para proporcionar 58 mg (32%) de un sólido de color amarillo. p.f. 138-141°C; M+H = 404.

EJEMPLO 315:



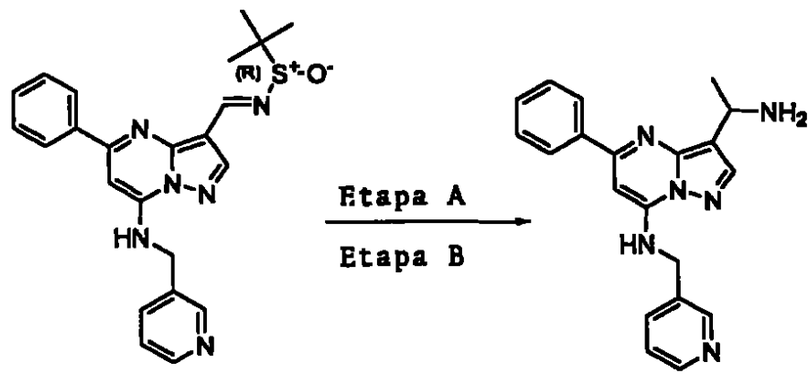
A una solución de aldehído (0.20 g, 0,60 mmol) del Ejemplo 303 en THF (3 mL) se le agregó Ti (i-OPr)$_4$ (0,36 mL, 1,21 mmol) por goteo seguido de adición de (S)-(-)-2-metil-2-propansulfinamida (74 mg, 0,61 mmol). La mezcla resultante se agitó durante 18 horas a reflujo y se enfrió a temperatura ambiente y se apagó con salmuera (2 mL). La mezcla se filtró a través de almohadilla de Celite la cual se lavó con EtOAc (2 x 2 mL). Las capas se separaron y la capa acuosa se extrajo con EtOAc (2 x 4 mL). Se combinaron las capas orgánicas, se secaron (Na_2SO_4), se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por TLC Preparativa TLC (8 x 1000 □M) eluyendo con CH_2Cl_2/MeOH (20:1) para proporcionar 0,21 g (80%) de un sólido de color amarillo. p.f. 108-110°C; M+H = 433.

EJEMPLO 316:



Se preparó de la misma manera que el Ejemplo 315 excepto que se sustituyó (R)-(-)-2-metil-2-propansulfinamida para proporcionar 0,25 g (94%) de un sólido de color amarillo. p.f. 107-109°C; M+H = 433.

EJEMPLO 317:



ETAPA A:

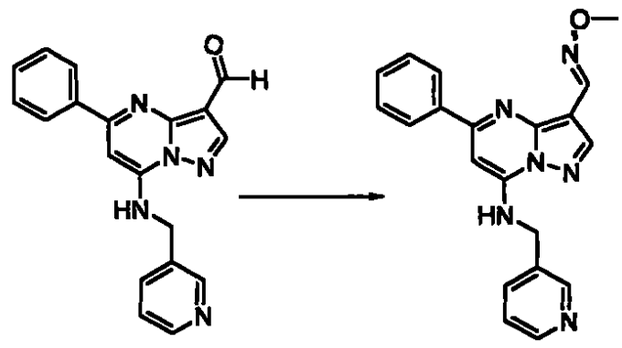
A una solución de sulfinimina (50 mg, 0,12 mmol) del Ejemplo 316 en CH_2Cl_2 (2,5 mL) a -40 °C se agregó MeMgBr (96 mL, 0,29 mmol) por goteo. La mezcla se agitó durante 5 horas a -40°C y se agitó a temperatura ambiente durante 12 horas. Se agregó una porción adicional de MeMgBr (96 mL, 0,29 mmol) y la mezcla se agitó durante 12 horas. Se agregó NH_4Cl acuoso saturado (2 mL) y la mezcla se extrajo con EtOAc (3 x 4 mL). Las capas orgánicas se combinaron, se secaron (Na_2SO_4), se filtraron, y se concentraron bajo presión reducida para proporcionar 30 mg (58%) del residuo crudo. Este material se recogió en la etapa siguiente sin purificación.

ETAPA B:

Al material crudo de la Etapa A (30 mg, 0,067 mmol) en MeOH (2 mL) se le agregó HCl concentrado (2 mL). La mezcla se agitó a temperatura ambiente durante 12 horas y la mezcla se concentró hasta sequedad. El material crudo se dividió entre CH_2Cl_2 (3 mL) y $NaHCO_3$ acuoso saturado (2 mL) y las capas se separaron. Se extrajo la capa acuosa con CH_2Cl_2 (2 x 3 mL) y se combinaron las

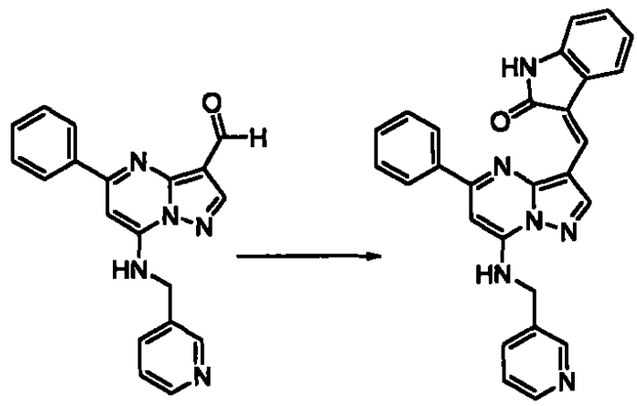
capas orgánicas. La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida para proporcionar 6 mg (24%) del compuesto del título en forma de un sólido de color amarillo claro. p.f. 100-102°C; M + H = 345.

EJEMPLO 318:



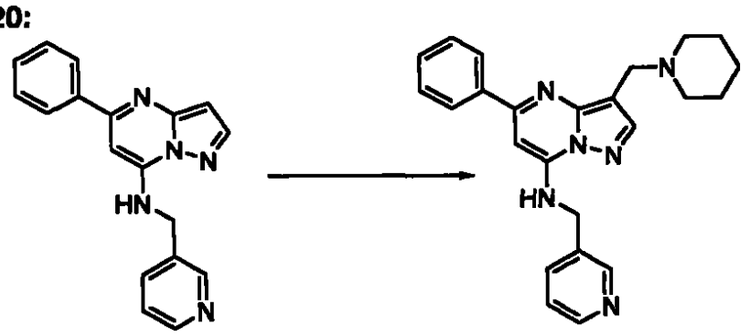
A una solución del aldehído (75 mg, 0,23 mmol) del Ejemplo 300 en THF/CH_2Cl_2 (5 mL/1mL) a temperatura ambiente se le agregó $MeONH_2$·HCl (38 mg, 0,46 mmol) seguido de adición por goteo de piridina (46 □L, 0,57 mmol). La mezcla se agitó durante 72 horas a temperatura ambiente después de lo cual la mezcla se concentró hasta sequedad. El material crudo se dividió entre CH_2Cl_2 (3 mL) y $NaHCO_3$ acuoso saturado (2 mL) y se separaron las capas. Se extrajo la capa acuosa con CH_2Cl_2 (2 x 3 mL) y se combinaron las capas orgánicas. La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida. El producto crudo se purificó por TLC Preparativa (3 x 1000 □M) eluyendo con CH_2Cl_2/MeOH (22:1) para proporcionar 90 mg (100%) de un sólido de color amarillo claro. p.f. 173-175°C ; M + H = 359.

EJEMPLO 319:



A una solución del aldehído (60 mg, 0,18 mmol) del Ejemplo 303 a EtOH (2,5 mL) se le agregó oxindol (48 mg, 0,37 mmol) seguido de piperidina (3 gotas). La mezcla se calentó a reflujo durante 14 horas, y luego la mezcla se enfrió a 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 proporcionar 81 mg (100%) del compuesto del título en forma de un sólido de color naranja/marrón. p.f. 182-185°C; M+H = 445.

EJEMPLO 320:



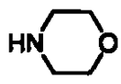
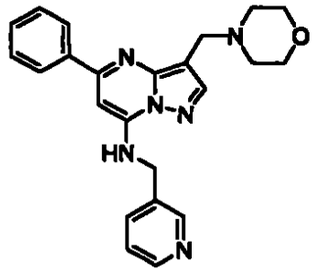
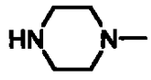
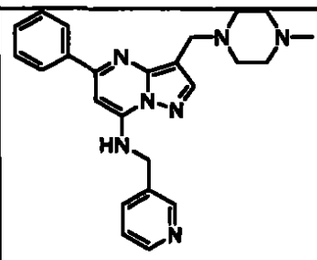
A una solución del análogo de 3-H (106 mg, 0,35 mmol) del Ejemplo Preparativo 187.10 en AcOH (2 mL) se le agregó 37% de formaldehído acuoso (1.5 ml; 1,40 mmol) seguido de piperidina (100 □L; 0,37 mmol). La mezcla resultante se agitó a temperatura ambiente durante 24 horas y se extrajo el AcOH

bajo presión reducida. La mezcla se diluyó con agua (2 mL) y se neutralizó con NaOH 2 M hasta pH = 8. La capa acuosa se extrajo con CH_2Cl_2 (3 x 7 mL) y se combinaron las capas orgánicas. La capa orgánica se lavó con salmuera (1 x 4 mL), se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida para proporcionar 96 mg (69%) de un sólido blancuzco. p.f. 88-90°C; M+H 399.

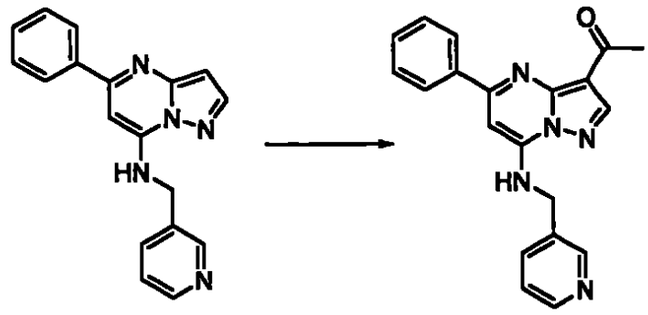
EJEMPLOS 321-322:

Esencialmente con el mismo procedimiento que se indica en el Ejemplo 320 únicamente sustituyendo las aminas de la Columna 2 de la Tabla 29 y empleando el aducto 3-H del Ejemplo Preparativo 187.10, se prepararon los compuestos de la Columna 3 de la Tabla 29.

TABLA 29

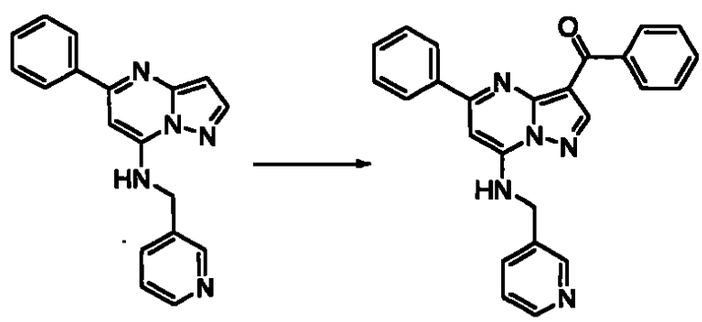
Ej.	Columna 2 (Amina)	Columna 3 (Estructura Final)	COMP 1. p.f. (°C) 2. M+H
321			1. p.f. = 178-180 2. M+H = 401
322			1. p.f. = 102-104 2. M+H = 414

EJEMPLO 323:



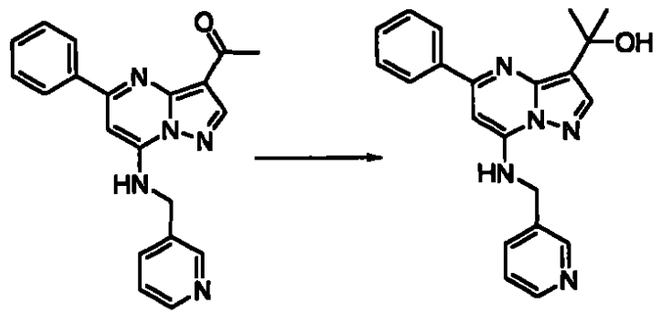
A una solución del análogo 3-H (113 mg, 0,38 mmol) del Ejemplo Preparativo 187.10 en CH_2Cl_2 (5 mL) a temperatura ambiente se le agregó $AlCl_3$ (215 mg, 1,61 mmol) seguido de AcCl (100 mL, 1,40 mmol). La mezcla se calentó a reflujo durante 12 horas y se enfrió a temperatura ambiente. La mezcla se trató secuencialmente con HCl 3M (3 mL) . seguido de. $NaHCO_3$ acuoso saturado (hasta pH = 8). Se separaron las capas y la capa acuosa se extrajo con CH_2Cl_2 (2 x 5 mL). Se combinaron las capas orgánicas, se secaron (Na_2SO_4), se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por TLC Preparativa (8 x 1000 mM) eluyendo con CH_2Cl_2/MeOH (20:1) para proporcionar 68 mg (52%) de un sólido blanco. p.f. 220-221°C; M+H = 344.

EJEMPLO 324:



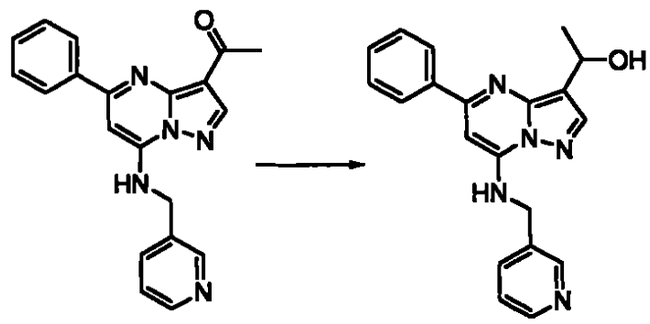
Utilizando el método descripto en el Ejemplo 323, excepto que se empleó cloruro de benzoílo, se preparó el compuesto del título con un rendimiento del 61% como un sólido blanco. p.f. 172-175°C; M+H = 406.

EJEMPLO 325:



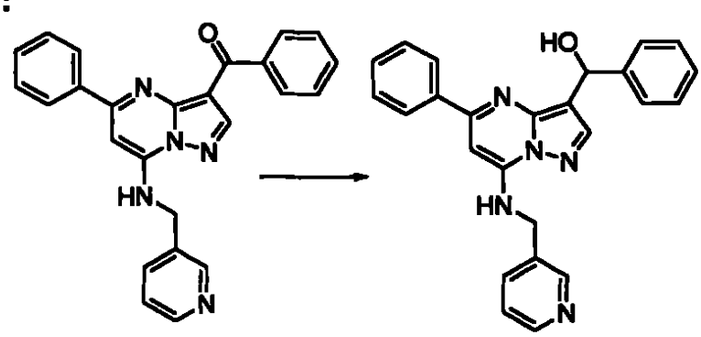
A una solución de cetona (100 mg, 0,29 mmol) del Ejemplo 323 en CH_2Cl_2 (2,5 mL) a 0 °C se le agregó MeMgBr (0,35 mL, 3,0M en Et_2O) por goteo. La mezcla resultante se agitó durante 18 horas a temperatura ambiente y se apagó cuidadosamente con adición de NH_4Cl acuoso saturado (2 mL) y se agregaron (2 mL) de CH_2Cl_2. Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (2 x 4 mL). Se combinaron las capas orgánicas, se secaron (Na_2SO_4), se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por TLC preparativa (8 x 1000 L:M) eluyendo con CH_2Cl_2/MeOH (10:1) para proporcionar 68 mg (52%) de un sólido amarillo. p.f. 160-162 °C; M+H = 360.

EJEMPLO 326:



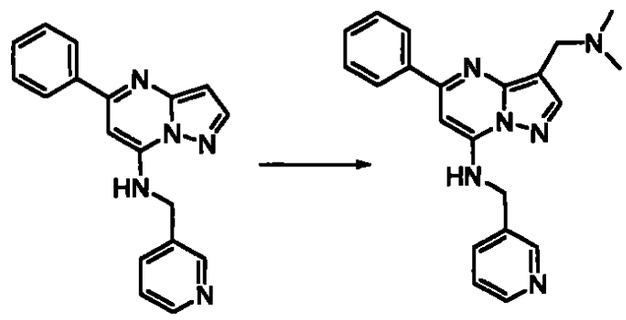
A una solución de cetona (84 mg, 0.24 mmol) del Ejemplo 323 en MeOH/THF (1,1; 2 mL total) a 0°C se le agregó $NaBH_4$ (12 mg, 0,30 mmol) en una porción. La mezcla resultante se agitó durante 18 horas a temperatura ambiente después de lo cual se agregó una porción adicional de $NaBH_4$ (12 mg, 0,30 mmol). La mezcla se agitó durante 12 horas después de lo cual la mezcla se apagó con hielo seguido de adición de NaOH 1N para ajustar el pH = 9. La mezcla se diluyó con CH_2Cl_2 (5 mL). Las capas se separaron y se extrajo la capa acuosa con CH_2Cl_2 (2 x 4 mL). Las capas orgánicas se combinaron, se secaron (Na_2SO_4), se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por TLC preparativa (8 x 1000 µM) eluyendo con CH_2Cl_2/MeOH (10:1) para proporcionar 25 mg (30%) de un sólido de color amarillo. p.f. 148-150 °C; M+H = 346.

EJEMPLO 327:



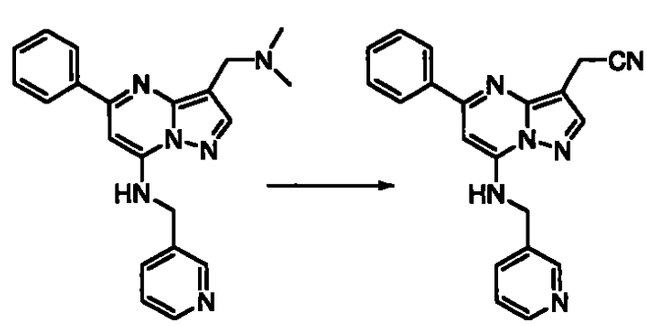
Usando el mismo procedimiento señalado en el Ejemplo 326, se convirtió la cetona (84 mg, 0,21 mmol) a 53 mg (62%) en forma de un sólido de color amarillo claro. p.f. 78-80 °C; M+H = 408.

EJEMPLO 328:



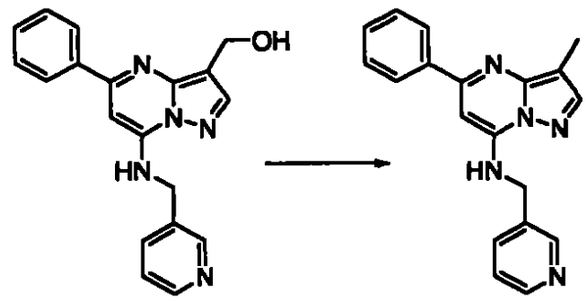
A una solución del aducto 3-H (1,3 g, 4,31 mmoles) del Ejemplo Preparativo 187,10 en CH_2Cl_2 (50 mL) Se le agregó sal de Eschenmoser (0,79 g, 4,31 mmoles) seguido de adición por goteo de TFA (0,56 mL, 7,33 mmol). La mezcla se agitó a temperatura ambiente durante 48 horas y luego se diluyó con CH_2Cl_2 (250 mL). La capa orgánica se lavó con $NaHCO_3$ acuoso saturado (2 x 125 mL) para proveer 1,41 h (92%) de un sólido amarillo. p.f. 231-233 °C; M+H = 359.

EJEMPLO 329:



A una solución del aducto de amina terciaria (100 mg, 0,28 mmol) del Ejemplo 328 en 50% de DMF acuoso (5 mL) en un tubo de presión se le agregó KCN (0,15 g, 2,32 mmoles). El tubo se tapó y se calentó a 100°C durante 96 horas. La mezcla se enfrió a temperatura ambiente y se diluyó con EtOAc (25 mL). La capa orgánica se lavó con salmuera (1 x 5 mL) y agua (1 x 5 mL). La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida. El producto crudo se purificó por TLC preparativa (4 x 1000 µM) eluyendo con EtOAc para proporcionar 21 mg (30%) de un sólido de color castaño. p.f. 152-155°C; M+H = 341.

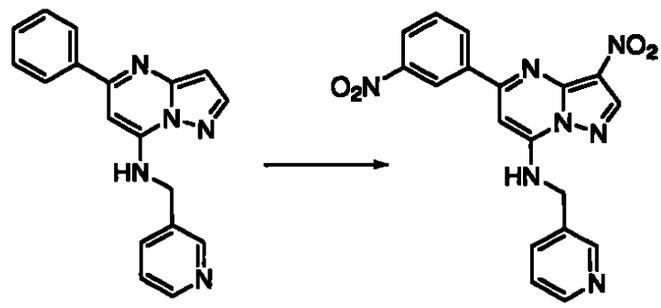
EJEMPLO 330:



A una solución de alcohol (45 mg, 0,14 mmol) del Ejemplo 17,10 in CH_2Cl_2 (0.7 mL) a 0 °C se le agregó Et_3SiH (26 µL, 0.16 mmol) seguido de TFA (25 µL, 0.33 mmol). La mezcla se agitó durante 2 horas a 0 °C y a temperatura ambiente durante 2 horas después de lo cual se agregaron porciones adicionales de Et_3SiH (26 µL, 0,16 mmol) y TFA (25 µL, 0,33 mmol) y la mezcla se agitó durante 4 horas a temperatura ambiente (hasta completarse de acuerdo a la TLC). La mezcla se concentró bajo presión reducida y el residuo crudo se dividió entre CH_2Cl_2 (3 mL) y $NaHCO_3$ acuoso saturado (1.5 mL). Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (2 x 4 mL). Las capas orgánicas se combinaron, se lavaron con salmuera (1 x 5 mL), se secaron (Na_2SO_4), se filtraron y se concentraron bajo

presión reducida. El producto crudo se purificó por TLC preparativa (4 x 1000 mM) eluyendo con CH_2Cl_2/MeOH (20:1) para proporcionar 21 mg (48%) de un sólido amarillo. p.f. 146-148°C; M+H = 316.

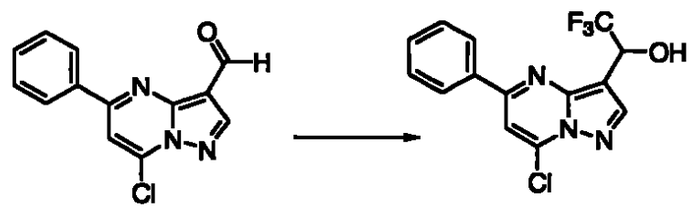
EJEMPLO 331:



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 le agregó HNO_3 fumante (30 µL, 0,72 mmol) por goteo. La mezcla resultante se agitó durante 1 hora a 0°C después de lo cual se agregó hielo (~1g) a la mezcla. El precipitado resultante se recogió y se lavó con agua (2 x 2 mL) y CH_2Cl_2 (2 x 2 mL). El producto crudo se secó bajo alto vacío para proporcionar 67 mg (60%) de la sal de monosulfato en forma de un sólido de color amarillo/anaranjado. p.f. 250°C; M+H (base libre) = 392.

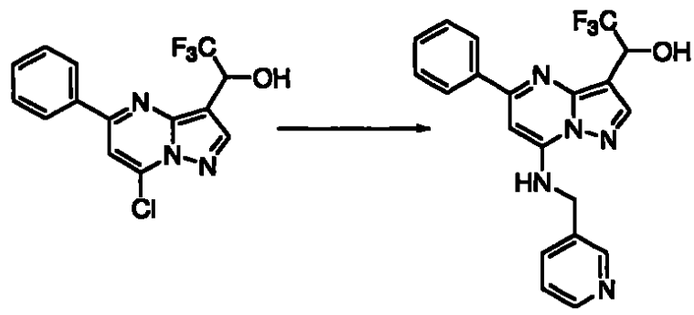
EJEMPLO 332:

Etapa A:



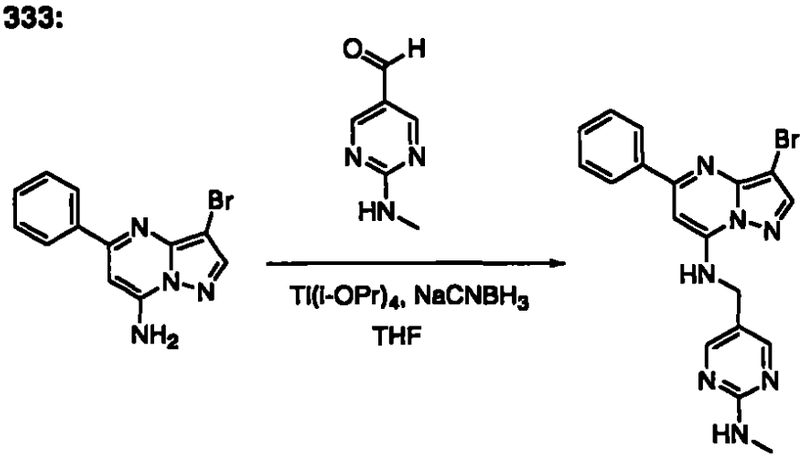
A una solución de aldehído (0,10 g, 0,39 mmol) del Ejemplo Preparativo 168 en THF (2.5 mL) a 0°C se le agregó CF_3TMS (64 mL, 0,43 mmol) seguido de CsF (10 mg). La mezcla resultante se agitó durante 2 horas a 0°C y 2 horas a temperatura ambiente. Se agregó HCl 1M (5 mL) y la mezcla se diluyó con CH_2Cl_2 (10 mL). Se separaron las capas, se extrajo la capa acuosa con CH_2Cl_2 (2 x 10 mL), y se combinaron las capas orgánicas. La capa orgánica se lavó con salmuera (1 x 10 mL), se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida para proporcionar 127 mg (99%) de un semisólido de color amarillo. M+H =328. El producto crudo se llevó sin purificación adicional.

Etapa B:



Utilizando el procedimiento general indicado en el Ejemplo 1, se hizo reaccionar el aducto 7-Cl (127 mg, 0,39 mmol) del Ejemplo 332, Etapa A con 3-(aminometil)piridina (73 µL, 0,43 mmol) para proporcionar 80 mg (51%) del compuesto del título en forma de un sólido de color amarillo claro. p.f. 68-72°C; M+H = 400.

EJEMPLO 333:

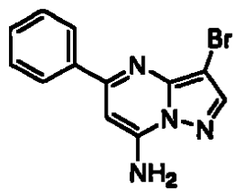
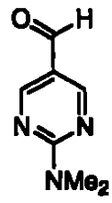
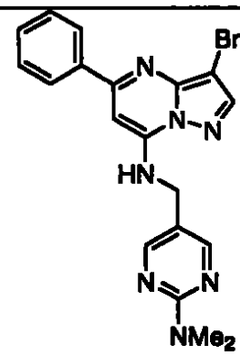
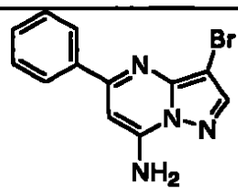
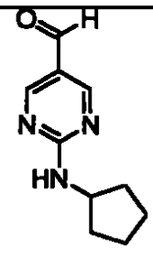
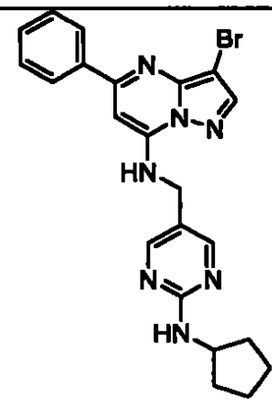
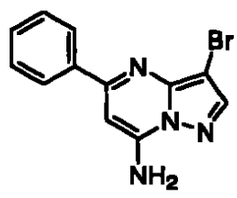
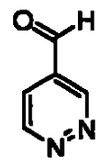
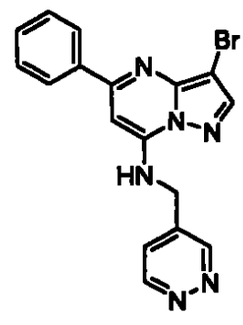


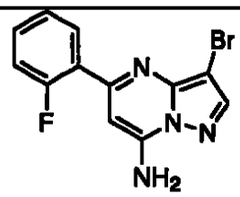
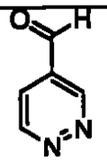
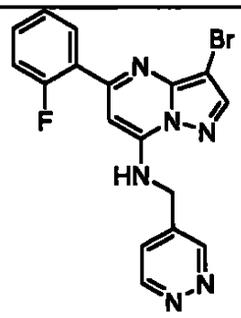
A una solución de anilina (200 mg, 0,69 mmol) del Ejemplo Preparativo 174 en THF (6 mL) a temperatura ambiente se le agregó aldehído (114 mg, 0,83 mmol) del Ejemplo Preparativo 256 seguido de adición por goteo de Ti(*i*-OPr)$_4$ (0,82 mL, 2,77 mmol). La mezcla se agitó a reflujo durante 4 horas y luego se enfrió a temperatura ambiente. Se agregó $NaCNBH_3$ (347 mg, 5,53 mmol) y la mezcla se agitó durante 2 horas a temperatura ambiente. La mezcla se enfrió a 0ºC, se trató con NaOH 1M (4 mL) y salmuera (1 mL) y se agitó durante 30 minutos. La mezcla se extrajo con CH_2Cl_2 (3 x 10 mL) y se combinaron las capas orgánicas. La capa orgánica se lavó con salmuera (1 x 7 mL), se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía de capa delgada preparativa (placas 8 x 1000 υM) eluyendo con CH_2Cl_2/MeOH (25:1) para proporcionar 89 mg (31%) del compuesto del título en forma de un sólido de color amarillo. p.f.210-213 °C ; M+H = 411.

EJEMPLOS 334-337:

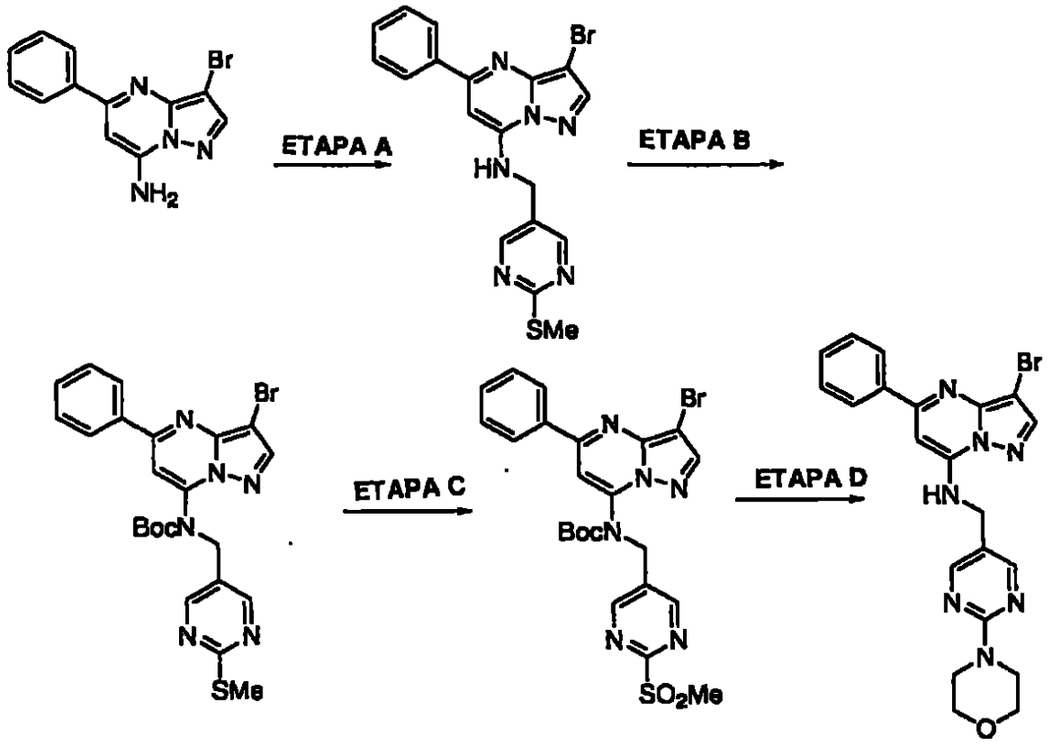
Esencialmente con el mismo procedimiento indicado en el Ejemplo 333, únicamente utilizando las anilinas que se muestran en la Columna 2 de la Tabla 30 y los aldehídos que se muestran en la Columna 3 de la Tabla 30, se prepararon los compuestos de la Columna 4 de la Tabla 30.

TABLA 30

Ej.	Columna 2 (Anilina)	Columna 3 (Aldehído)	Columna 4 (Estructura Final)	COMP 1. p.f. (°C) 2. M+H
334				1. mp = 85-87 2. M+H = 425
335				1. p.f. = 160-162 2. M+H = 451
336				1. p.f. = 117-119 2. M+H = 382

337				1. p.f. = 171-175 2. M+H = 400

EJEMPLO 338:



ETAPA A:

La reacción de anilina (0,20 g, 0,69 mmol) con aldehído (0,13 g, 0,83 mmol) bajo las condiciones de reacción descritas en el Ejemplo 333 proporcionó 70 mg (23%) del derivado tiometilo en forma de un sólido de color amarillo. M+H = 428.

ETAPA B:

A una solución del derivado tiometilo (60 mg, 0,14 mmol) del Ejemplo 338, Etapa A en dioxano (2 mL) se le agregó Boc_2O (61 mg, 0,28 mmol) seguido de DMAP (21 mg, 0.17 mmol). La mezcla se agitó durante 14h a temperatura ambiente y se concentró bajo presión reducida. El producto crudo se purificó por cromatografía de capa delgada preparativa (placas 6 x 1000 µM) eluyendo con hexanos/EtOAc (4:1) para proporcionar 61 mg (83%) el compuesto del título en forma de un sólido de color amarillo. M+H = 528.

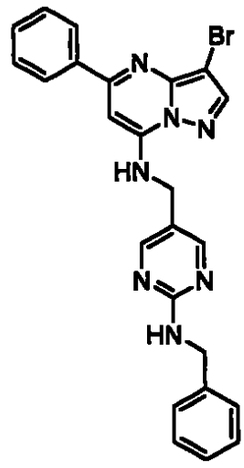
ETAPA C:

A una solución del derivado tiometilo del Ejemplo 338, Etapa B (41 mg, 0,078 mmol) en CH_2Cl_2 (2 mL) se le agregó MCPBA (33 mg, 0,19 mmol) en una porción. La mezcla resultante se agitó durante 3 horas a temperatura ambiente y la mezcla se diluyó con CH_2Cl_2 (5 mL) y $NaHCO_3$ acuoso saturado (2.5 mL). Las capas se separaron, se extrajo la capa acuosa con CH_2Cl_2 (2 x 5 mL), y se combinaron las capas orgánicas. La capa orgánica se secó (Na_2SO_4), se filtró, y se concentró bajo presión reducida para proporcionar 40 mg (92%) del aducto sulfona en forma de un sólido de color amarillo claro. M+H = 560.

ETAPA D:

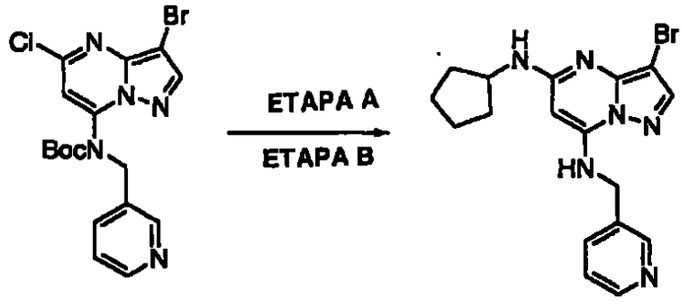
A un frascto cargado con sulfona del Ejemplo 338, Etapa C (75 mg, 0,13 mmol) y una barra agitadora se le agregó morfolina (2 ml; 22 mmol). La mezcla se calentó a reflujo durante 12 horas, se enfrió a temperatura ambiente, y se concentró hasta sequedad bajo alto vacío. El producto crudo se purificó por cromatografía de capa delgada preparativa (placa 6 x 1000 µM) eluyendo con CH_2Cl_2/MeOH (40:1) para proporcionar 41 mg (68%) el compuesto del título en forma de un sólido de color amarillo. p.f. 209-210°C; M+H = 466.

EJEMPLO 339:



Se preparó el compuesto del título de acuerdo con el procedimiento señalado en el Ejemplo 338 excepto que se usó bencil amina para obtener 12 mg (70%) de un sólido blanco. p.f. 194-196; M+H = 487.

EJEMPLO 340:



ETAPA A:

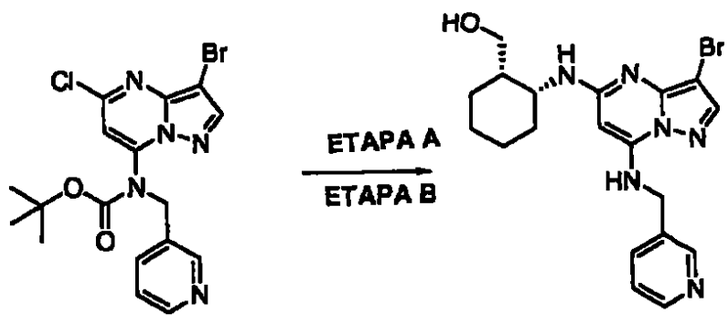
A una solución del aducto 5-cloro (0,15 g, 0,34 mmol) en dioxana/DIPEA (2,5mL/1,0mL) a temperatura ambiente se le agregó ciclopentilamina (0,041 µL, 0,41 mmol) por goteo. La solución resultante se agitó a reflujo durante 16 horas, se enfrió a temperatura ambiente, y se concentró bajo presión reducida. El material crudo se purificó por cromatografía de capa delgada preparativa (8 x

1000 µM) eluyendo con CH_2Cl_2/MeOH (25:1) para proporcionar 148 mg (89%) de un aceite de color amarillol. M+H = 489.

ETAPA B: Remoción del grupo protector t-butoxicarbonilo con TFA

A una solución del compuesto preparado en el Ejemplo 340, Etapa A (135 mg, 0,28 mmol) en CH_2Cl_2 (2 mL) a temperatura ambiente se le agregó TFA (0,54 mL, 7,0 mmol) por goteo. La solución resultante se agitó durante 18 horas a temperatura ambiente y luego se concentró bajo presión reducida. Se redisolvió el material crudo en CH_2Cl_2 (5 mL) y la capa orgánica se lavó sencuencialmente con $NaHCO_3$ acuoso saturado (2 x 2 mL) y salmuera (1 x 2 mL). Se secó la capa orgánica (Na_2SO_4), se filtró, y se concentró bajo presión reducida. El mateiral crudo se purificó por cromatografía de capa delgada preparativa (8 x 1000 µM) eluyendo con CH_2Cl_2/MeOH (20:1) para proporcionar 105 mg (97%) de un sólido blanco. p.f. 120-122 °C; M+H = 389.

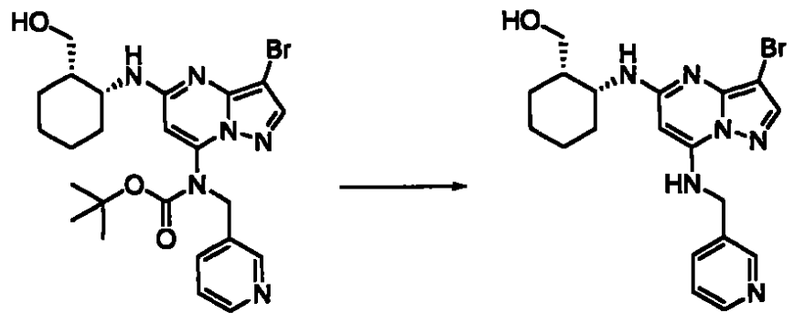
EJEMPLO 341:



Etapa A:

Con el mismo procedimiento indicado en el Ejemplo 340 únicamente sustituyendo la amina apropiada, se preparó el compuesto anterior. EM: MH^+= 431.

Etapa B: Remoción del grupo protector t-butoxicarbonilo con KOH.

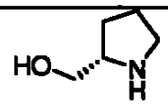
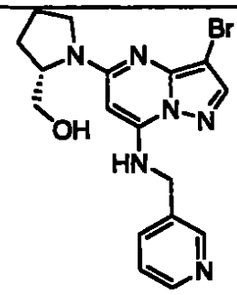
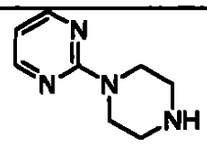
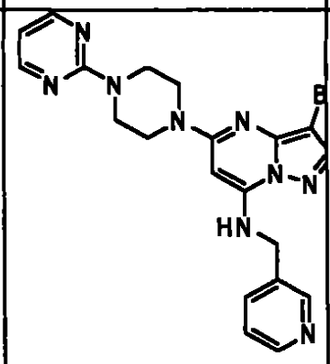
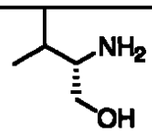
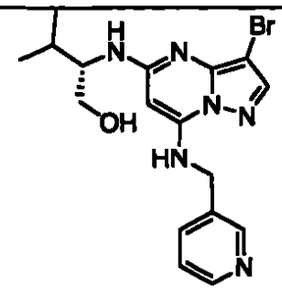
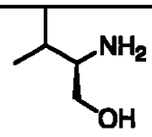
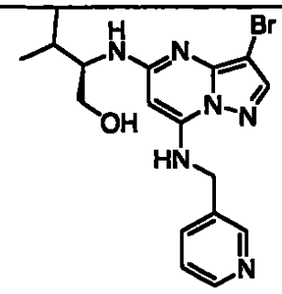


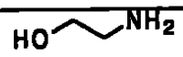
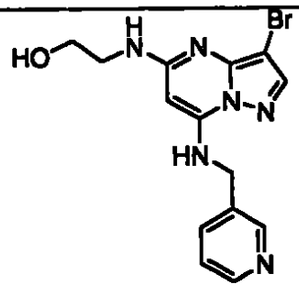
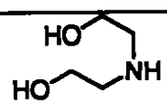
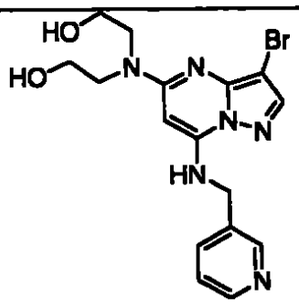
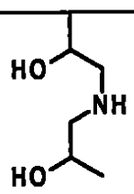
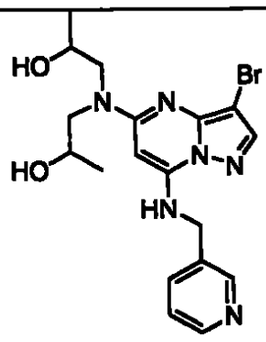
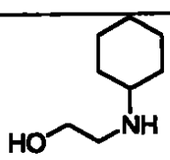
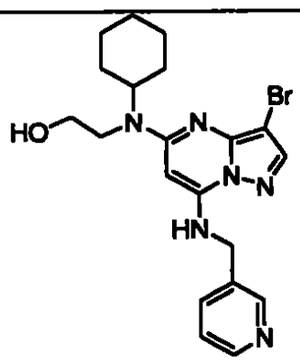
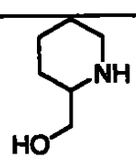
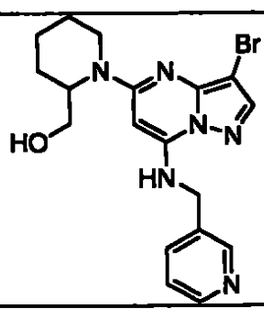
A una mezcla del compuesto preparado en el Ejemplo 341, Etapa A (0,14 g, 0,26 mmol) en EtOH : H_2O (3 mL, 2 : 1) se le agregó KOH (0.29 g, 20 eq.) en una sola porción. La solución resultante se agitó a reflujo durante 14 horas, se enfrió a temperatura ambiente, y se concentró bajo presión reducida. El residuo se recogió en CH_2Cl_2 (5 mL) y se diluyó con $NaHCO_3$ acuoso 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, y se secaron sobre Na_2SO_4, se filtraron, y se concentraron bajo presión reducida. El producto crudo se purificó por TLC preparativa (8 x 1000 µM) eluyendo con 5% MeOH en solución de CH_2Cl_2 (0,066 g, 59% de rendimiento). EM: MH^+ = 432; p.f. = 219-221°C.

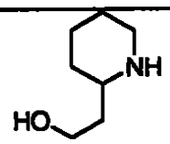
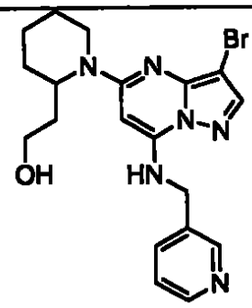
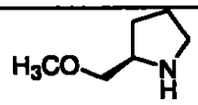
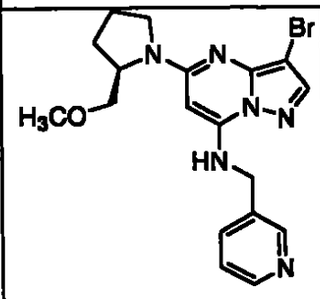
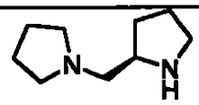
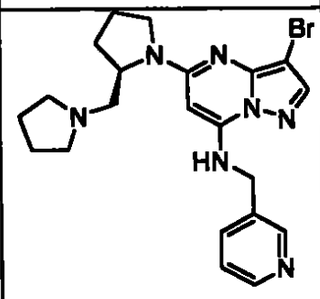
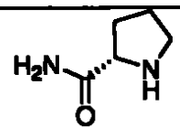
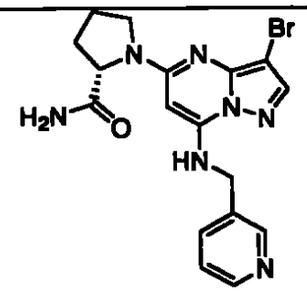
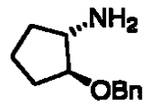
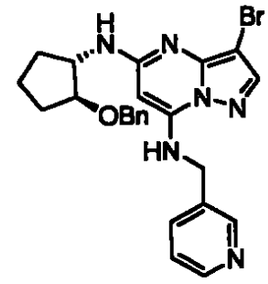
EJEMPLOS 342-397:

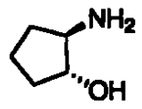
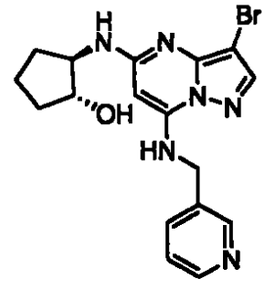
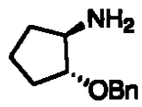
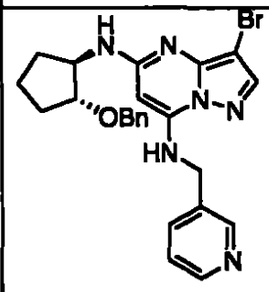
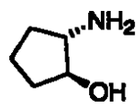
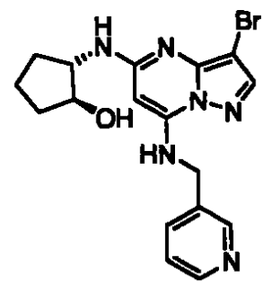
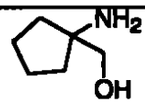
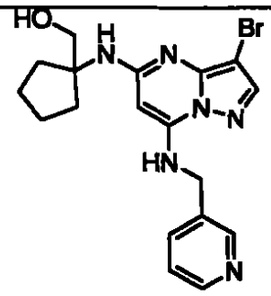
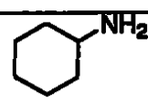
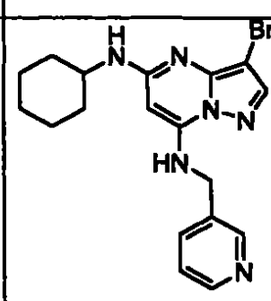
Esencialmente con el mismo procedimiento indicado en el Ejemplo 340 sustituyendo únicamente los cloruros de la Columna 2 de la Tabla 31 y removiendo el grupo protector t-butoxicarbonilo mediante le método que se muestra en la Columna 3 de la Tabla 31, se prepararon los compuestos que se muestran en la Columna 4 de la Tabla 31.

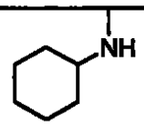
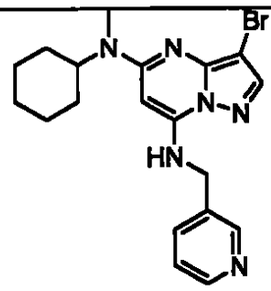
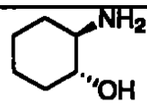
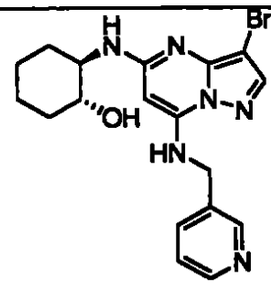
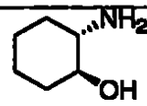
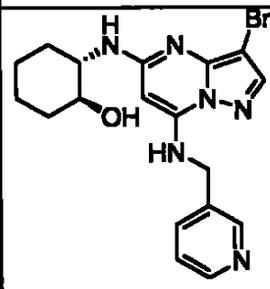
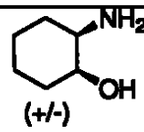
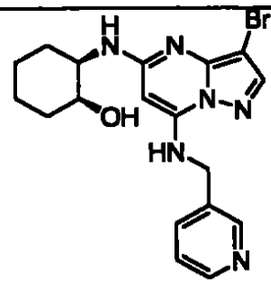
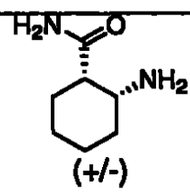
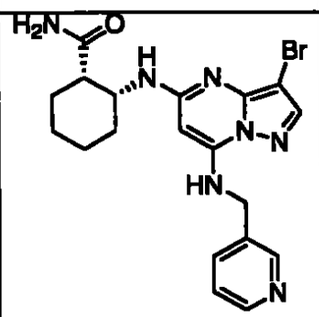
Tabla 31

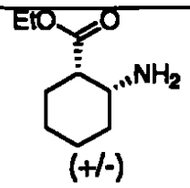
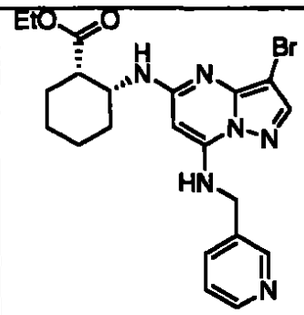
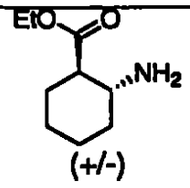
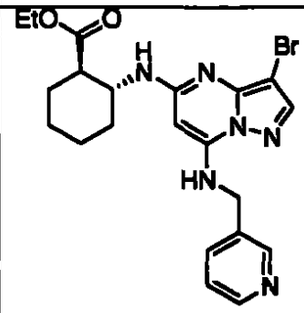
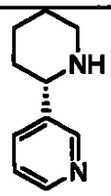
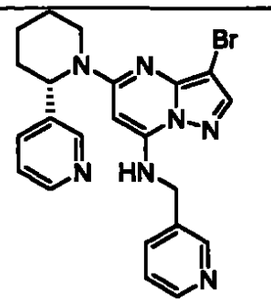
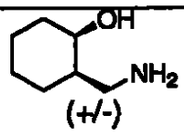
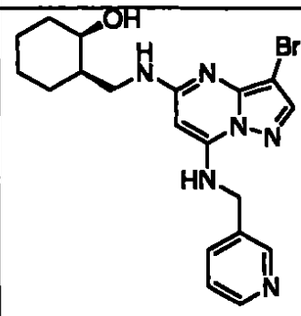
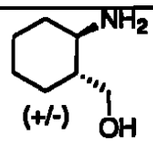
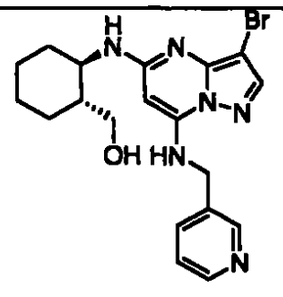
Ej.	Columna 2	Columna 3	Columna 4	COMP
342		HCl		EM: MH^+ = 403 p.f. 151 – 157 °C
343		HCl		EM: MH^+ = 466 p.f. 212 – 217 °C
344		HCl		MS: MH^+ = 405 p.f. 53 – 58 °C
345		HCl		EM: MH^+ = 405 p.f. 63 – 69 °C

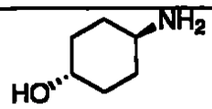
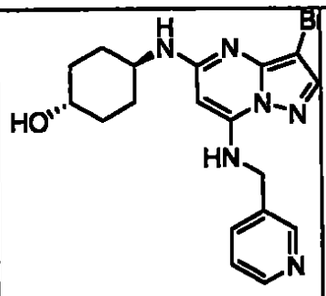
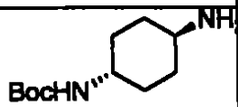
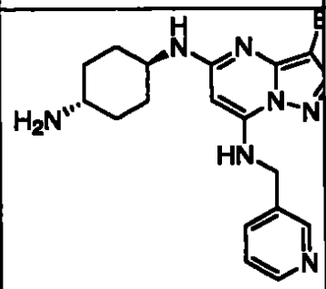
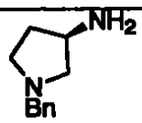
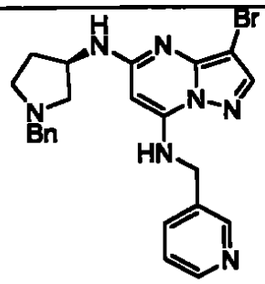
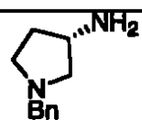
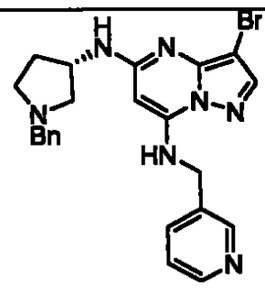
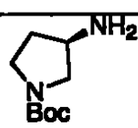
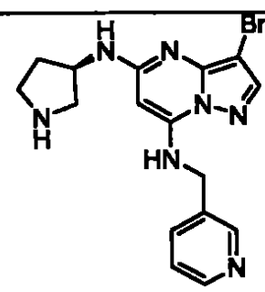
346		HCl		EM: MH^+ = 363 p.f. 170 – 171 °C
347		HCl		EM: MH^+ = 407 p.f. 148 – 151 °C
348		HCl		EM: MH^+ = 435 p.f. 56 – 59 °C
349		HCl		EM: MH^+ = 445 p.f. 66 – 68 °C
350		KOH		EM: MH^+ = 417 p.f. 149 – 151 °C

351		KOH		EM: MH^+ = 431 p.f. 111 – 114 °C
352		KOH		EM: MH^+ = 417 p.f. 53 – 58 °C
353		KOH		EM: MH^+ = 456 p.f. 186 – 189 °C
354		KOH		EM: MH^+ = 416 p.f. 210 – 213 °C
355		TFA		1. p.f. = 68-70 2. M+H = 494

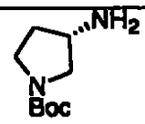
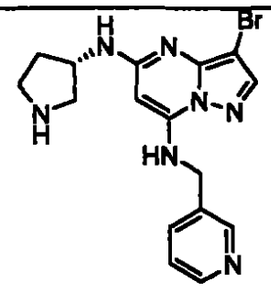
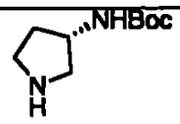
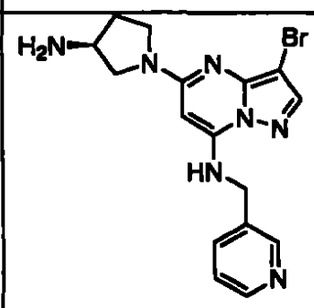
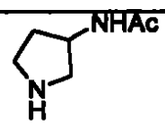
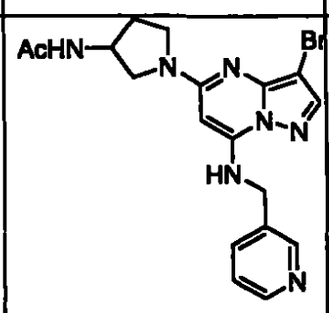
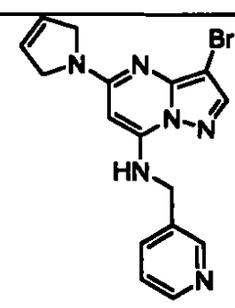
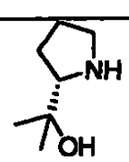
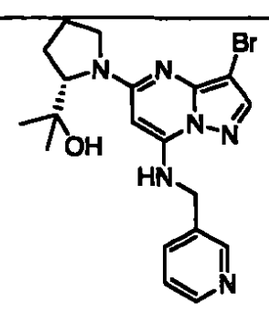
356		KOH		1. p.f. = 181-183 2. M+H = 404
357		TFA		1. p.f. = 69-71 2. M+H = 494
358		KOH		1. p.f. = 182-184 2. M+H = 404
359		KOH		1. p.f. = 202-204 2. M+H = 418
360		TFA		1. p.f. = 160-162 2. M+H = 402

361		TFA		1. p.f. = 151-153 2. M+H = 416
362		KOH		1. p.f. = 140-143 2. M+H = 418
363		KOH		1. p.f. = 139-142 2. M+H = 418
364	 (+/-)	KOH		1. p.f. = 115-117 2. M+H = 418
366	 (+/-)	TFA		1. p.f. = 102-104 2. M+H = 445

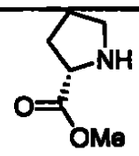
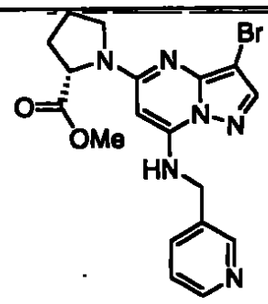
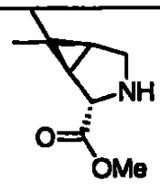
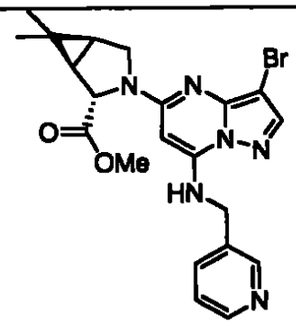
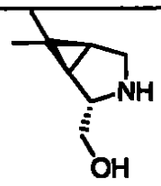
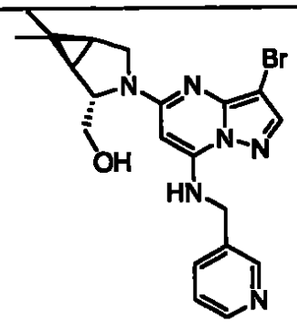
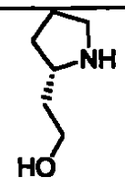
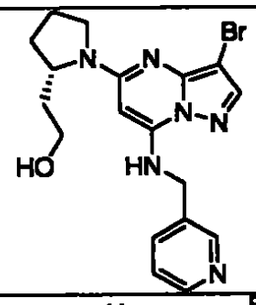
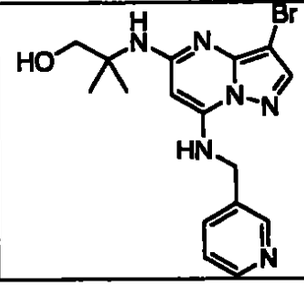
367		TFA		1. p.f. = 118-120 2. M+H = 474
368		TFA		1. p.f. = 106-108 2. M+H = 474
369		TFA		1. p.f. = 160-161 2. M+H = 464
370		TFA		1. p.f. = 93-95 2. M+H = 432
371		KOH		1. p.f. = 108-110 2. M+H = 432

372		KOH		1. p.f. = 180-182 2. M+H = 418
373		TFA		1. p.f. = 169-170 2. M+H = 417
374		TFA		1. p.f. = 77-79 2. M+H = 479
375		TFA		1. p.f. = 76-79 2. M+H = 479
376		TFA		1. p.f. = 105-107 2. M+H = 389

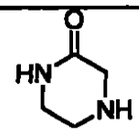
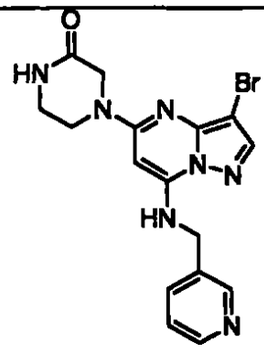
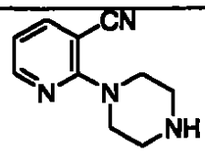
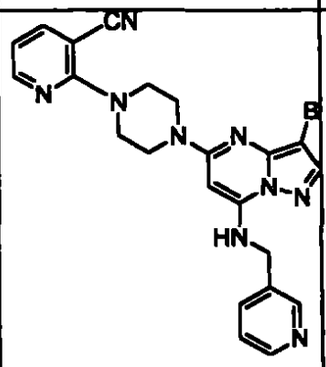
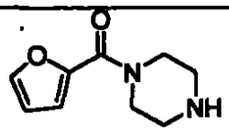
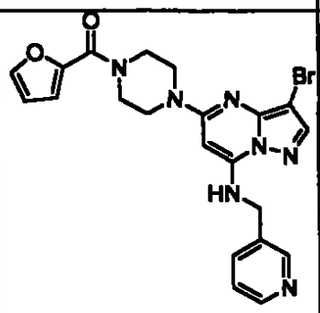
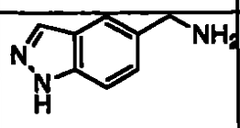
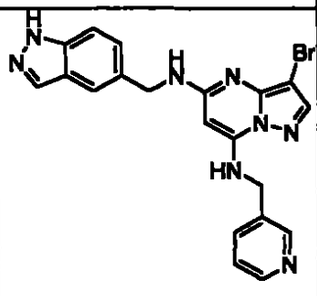
575
576

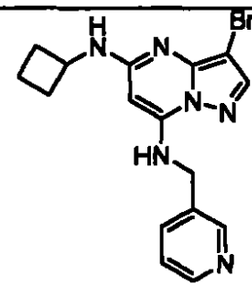
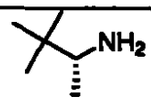
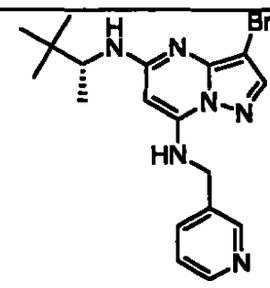
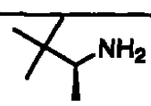
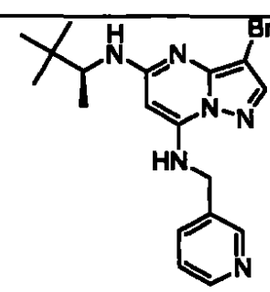
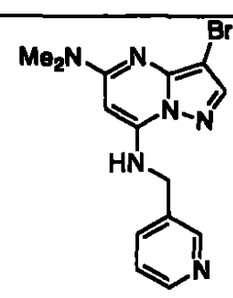
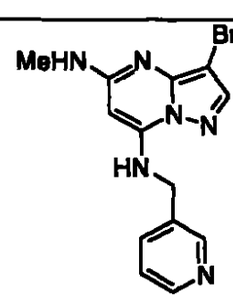
377		TFA		1. p.f. = 105-107 2. M+H = 389
378		TFA		1. p.f. = 130-133 2. M+H = 389
379		TFA		1. p.f. = 132-135 2. M+H = 431
380		TFA		1. p.f. = 135-137 2. M+H = 372
381		KOH		1. p.f. = 78-82 2. M+H = 432

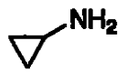
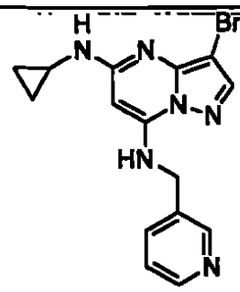
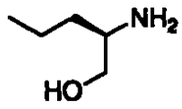
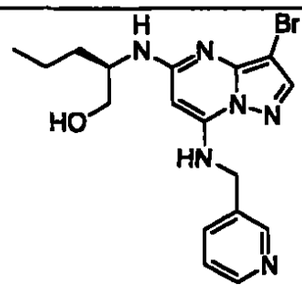
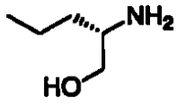
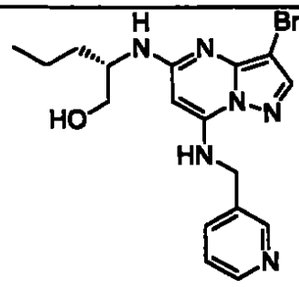
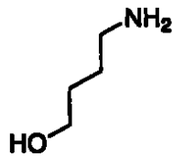
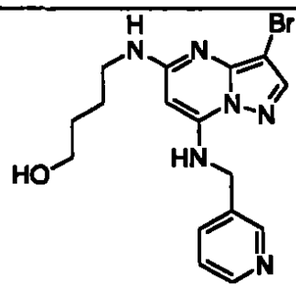
576
577

382		TFA		1. p.f. = 101-103 2. M+H = 432
383		TFA		1. p.f. = 92-95 2. M+H = 472
384		TFA		1. p.f. = 107-111 2. M+H = 444
384. 10		TFA		1. p.f. = 2. M+H = 417
384. 11		TFA		1. p.f. = 210-212 2. M+H = 391

577
578

385		TFA		1. p.f. = 122-124 2. M+H = 403
386		TFA		1. p.f. = 186-188 2. M+H = 491
387		TFA		1. p.f. = 173-175 2. M+H = 483
388		TFA		1. p.f. = 167-169 2. M+H = 450

389		TFA		1. p.f. = 90-92 2. M+H = 374
390		TFA		1. p.f. = 113-115 2. M+H = 404
391		TFA		1. p.f. = 114-116 2. M+H = 404
392	$HNMe_2$	TFA		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;

Los datos adicionales para los ejemplos seleccionados se muestran a continuación:

Ejemplo 392: ^{1}H RMN (DMSO-d_6) δ 8,65 (s, 1H), 8,46 (d, J = 3,3 Hz, 1H), 8,21 (t, J = 6,6 Hz, 1H), 7,90 (s, 1H), 7,80 (d, J = 7,8 Hz, 1H), 7,35 (dd, J = 7,8, 4,8 Hz, 1H), 5,46 (s, 1H), 4,61 (d, J = 6,9 Hz, 2H), 3,01 (s, 6H).

580 581

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.,6 (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 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).

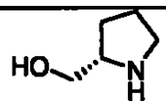
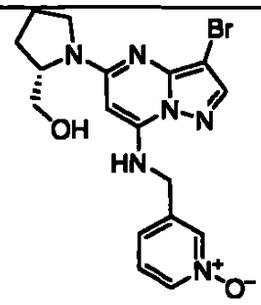
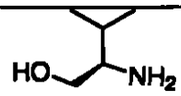
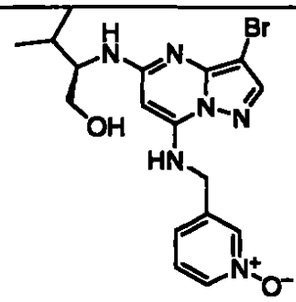
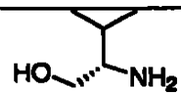
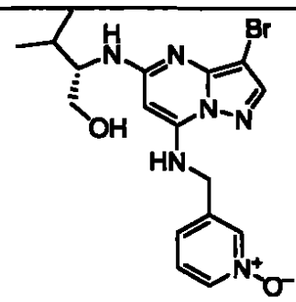
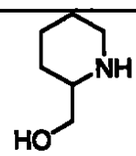
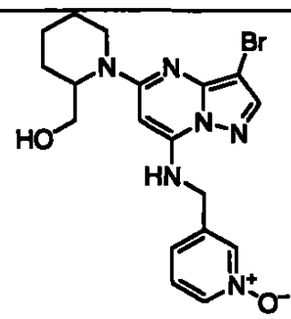
Ejemplo 397: ^{1}H RMN ($CDCl_3$) δ 8,65 (s, 1H), 8,59 (d, J = 4,5 Hz, 1H), 7,75 (s, 1H), 7,69 (m, 1H), 7,31 (m, 1H), 6,43 (t, J = 6.0 Hz, 1H), 5,06 (s, 1H), 4,88 (m, 1H), 4,55 (d, J = 6,0 Hz, 2H), 3,70 (m, 2H), 3,38 (m, 2H), 1,79-1,61 (m, 4H).

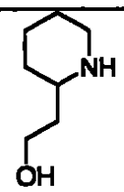
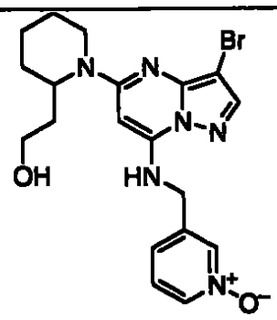
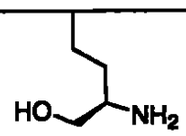
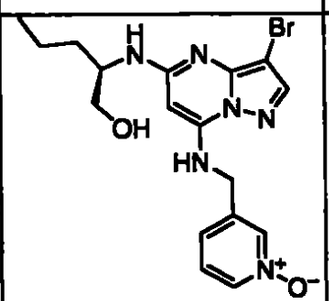
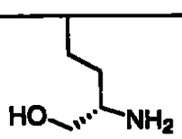
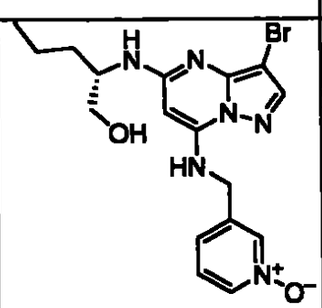
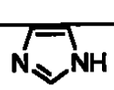
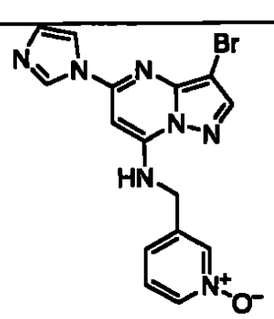
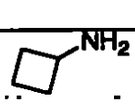
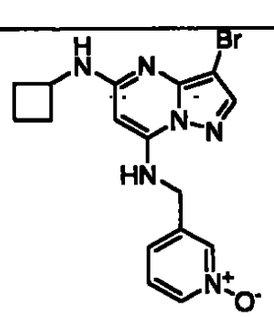
EJEMPLOS 398-416:

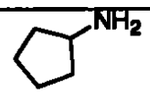
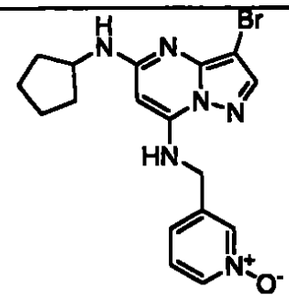
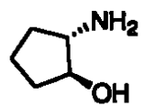
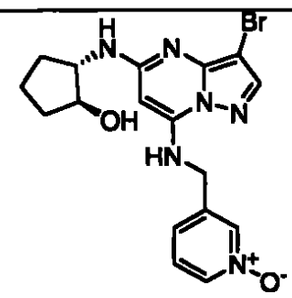
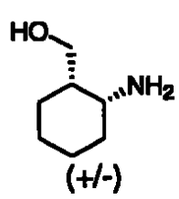
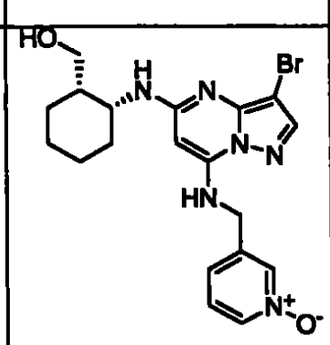
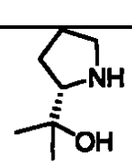
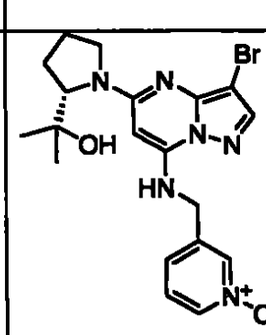
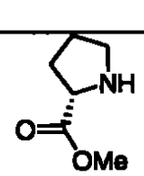
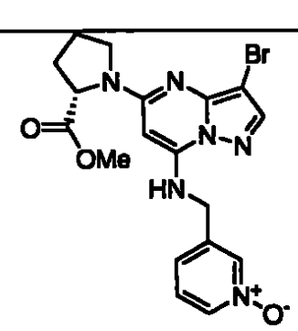
Esencialmente con las mismas condiciones indicadas en el Ejemplo 341, se prepararon únicamente sustituyendo los compuestos de las Etapa A y B en el Ejemplo Preparativo 193,10, se prepararon los compuestos de la Columna 4 de la Tabla 32.

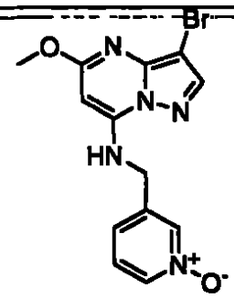
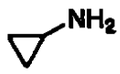
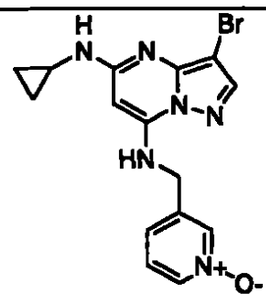
58.1
582

Tabla 32

Ej.	Columna 2	Columna 3	Columna 4	COMP
398				EM: MH^+ = 419 p.f.. 102 – 105 °C
399				EM: MH^+ = 421 p.f. 79 – 81 °C
400				EM: MH^+ = 421 p.f. 78 – 79 °C
401				EM: MH^+ = 433 p.f. 228-231 °C

402				EM: MH^+ = 447 p.f. 97-102 °C
403				EM: MH^+ = 421 p.f. °C
404				EM: MH^+ = 421 p.f. °C
405				ME: MH^+ = 386 p.f. °C
407		KOH		1. p.f. = 98-100 2. M+H = 390
408		TFA		1. p.f. = 170-173

				2. M+H = 404
409		KOH		1. p.f. = 219-221 2. M+H = 420
410		KOH		1. p.f. = 110-112 2. M+H = 448
411		TFA		1. p.f. = 81-83 2. M+H = 448
412		TFA		1. p.f. = 136-138 2. M+H = 448

413	NaOMe	KOH		1. p.f. = 107-110 2. M+H = 351
414				LCMS: MH^+ = 375;

Los datos adicionales para los ejemplos seleccionados 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).

Ejemplo 403: ^{1}H RMN (DMSO-d_6+$CDCl_3$) δ 8,08 (s, 1H), 7,90 (d, J = 6,3 Hz, 1H), 7,49 (s, 1H), 7,34 (t, J = 6,3 Hz, 1H), 7,16-7,09 (m, 2H), 5,65 (d, J = 6,6 Hz, 1H), 4,97 (s, 1H), 4,90 (s, 1H), 4,29 (d, J = 6,3 Hz, 2H), 3,70 (m, 1H), 3,46 (m, 1H), 3,34 (m, 1H), 1,35-1,17 (m, 4H), 0,71 (t, J = 7,2 Hz, 3H).

Ejemplo 404: ^{1}H RMN (DMSO-d_6) δ 8,21 (s, 1H), 8,12 (d, J = 6,6 Hz, 1H), 8,06 (m, 1H), 7,86 (s, 1H), 7,38 (t, J = 7,8 Hz, 1H), 7,30 (d, J = 7,5 Hz, 1H), 6,73 (d, J = 8,7 Hz, 1H), 5,28 (s, 1H), 4,70 (t, J = 5,1 Hz, 1H), 4,41 (d, J = 6,6 Hz, 2H), 4,00 (s, 1H), 3,39 (m, 1H), 1,53 (m, 1H), 1,36-1,25 (m, 3H), 0,86 (t, J = 7,0 Hz, 3H).

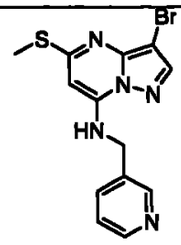
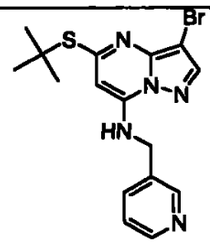
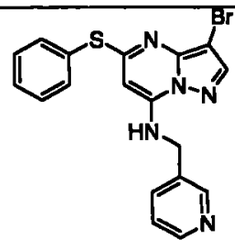
EJEMPLOS 417-421:

Mediante el procedimiento indicado en *Chem. Pharm. Bull.* **1999**, *47*, 928-

586

938. utilizando los nucleófilos de oxígeno o azufre que se muestran en la Columna 2 tal como se describe en la Tabla 33 y empleando el método de disociación enumerado en la Columna 3 de la Tabla 33, se prepararon los compuestos de la Columna 4 de la Tabla 33:

TABLA 33

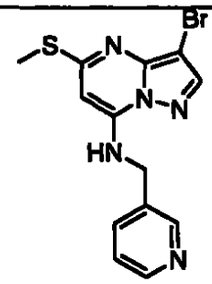
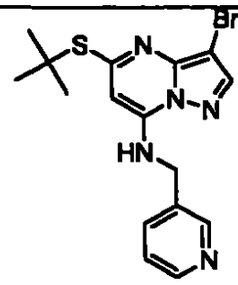
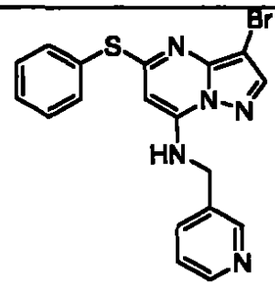
Ej.	Columna 2 (Nucleófilo)	Columna 3 (Método de disociación)	Columna 4 (Estructura Final)	COMP 1. p.f. 2. M+H
417	NaSMe	TFA		1. p.f. = 172-175 2. M+H = 351
418	NaSt-Bu	TFA		1. p.f. = 165-168 2. M+H = 392
419	NaSPh	TFA		1. p.f. = 154-156 2. M+H = 412
420	NaOMe	TFA		1. p.f. = 161-163 2. M+H = 335

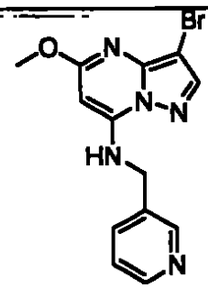
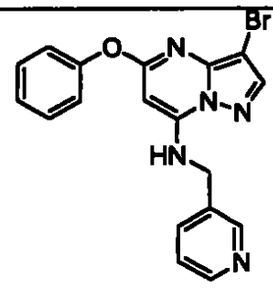
A una solución del compuesto amino (18 mg, 0,043 mmol) del Ejemplo 373 en CH_2Cl_2 (1 mL) a temperatura ambiente se le agregó DIPEA (10 µL, 0,056 mmol) seguido de $MeSO_2Cl$ (4 mL, 0,052 mmol). La mezcla de se agitó a temperatura ambiente durante 12 horas y luego se diluyó con CH_2Cl_2 (2 mL) y $NaHCO_3$ acuoso saturado (2 mL). Las capas se separaron y la capa orgánica se extrajo con salmuera (1 x 2 mL). Se secó la capa orgánica (Na_2SO_4), se filtró, y se concentró bajo presión reducida. El material crudo se purificó por cromatografía de capa delgada preparativa (4 x 1000 µM) eluyendo con CH_2Cl_2/MeOH (20:1) para proporcionar 16 mg (75%) de un sólido blanco. p.f. 152-154 °C; M+H = 495.

EJEMPLOS 423-424:

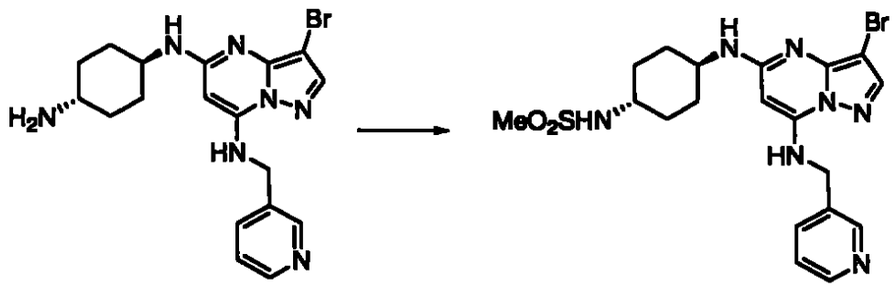
938. utilizando los nucleófilos de oxígeno o azufre que se muestran en la Columna 2 tal como se describe en la Tabla 33 y empleando el método de disociación enumerado en la Columna 3 de la Tabla 33, se prepararon los compuestos de la Columna 4 de la Tabla 33:

TABLA 33

Ej.	Columna 2 (Nucleófilo)	Columna 3 (Método de disociación)	Columna 4 (Estructura Final)	COMP 1. p.f. 2. M+H
417	NaSMe	TFA		1. p.f. = 172-175 2. M+H = 351
418	NaSt-Bu	TFA		1. p.f. = 165-168 2. M+H = 392
419	NaSPh	TFA		1. p.f. = 154-156 2. M+H = 412
420	NaOMe	TFA		1. p.f. = 161-163 2. M+H = 335

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

EJEMPLO 422:

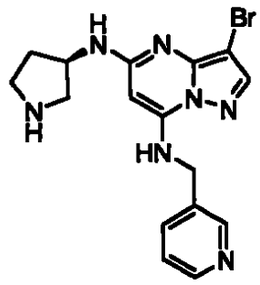
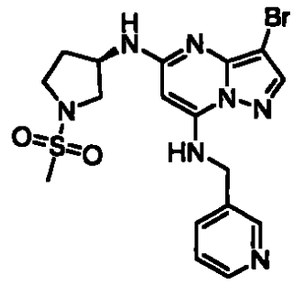
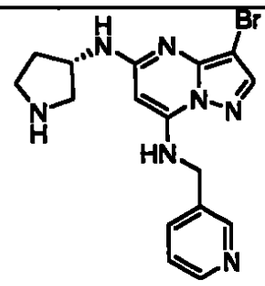
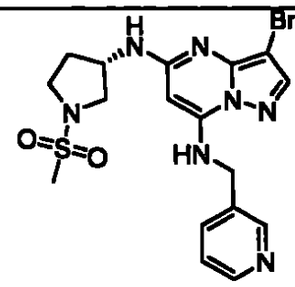


A una solución del compuesto amino (18 mg, 0,043 mmol) del Ejemplo 373 en CH_2Cl_2 (1 mL) a temperatura ambiente se le agregó DIPEA (10 µL, 0,056 mmol) seguido de $MeSO_2Cl$ (4 mL, 0,052 mmol). La mezcla de se agitó a temperatura ambiente durante 12 horas y luego se diluyó con CH_2Cl_2 (2 mL) y $NaHCO_3$ acuoso saturado (2 mL). Las capas se separaron y la capa orgánica se extrajo con salmuera (1 x 2 mL). Se secó la capa orgánica (Na_2SO_4), se filtró, y se concentró bajo presión reducida. El material crudo se purificó por cromatografía de capa delgada preparativa (4 x 1000 µM) eluyendo con CH_2Cl_2/MeOH (20:1) para proporcionar 16 mg (75%) de un sólido blanco. p.f. 152-154 °C; M+H = 495.

EJEMPLOS 423-424:

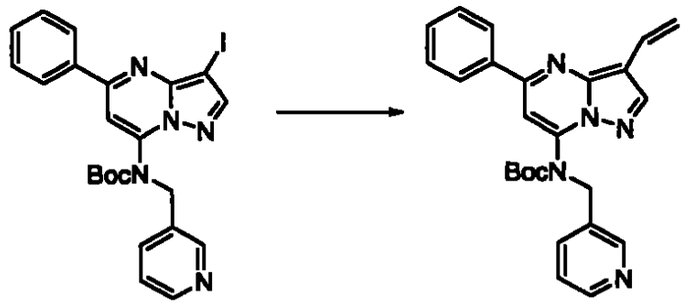
Utilizando el procedimiento señalado en el Ejemplo 422, se convirtieron los compuestos amino (Columna 2) a las correspondientes metilsulfonamidas (Columna 3) en la Tabla 34.

TABLA 34

Ej.	Columna 2 (Amina)	Columna 3 (Estructura Final)	COMP 1. p.f. 2. M+H
423			1. p.f. = 166-168 2. M+H = 467
424			1. p.f. = 165-168 2. M+H = 467

EJEMPLO 425:

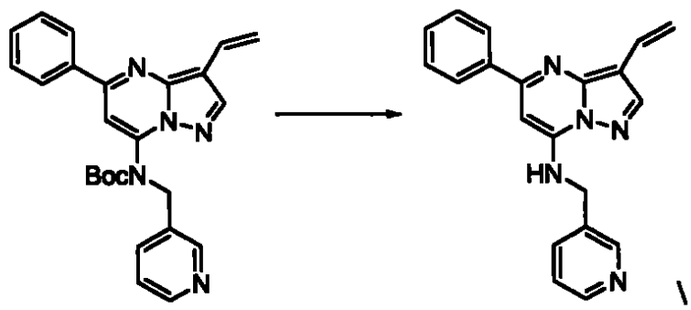
ETAPA A:



Una mezcla del compuesto preparado en el Ejemplo Preparativo 194 (132 mg, 0,25 mmol), tributilvinilestaño (95 mg, 0,30 mmol) y tetrakis(trifenilfosfina)

paladio (29 mg, 0,025 mmol) en dioxano anhidro (5 mL) se reflujó bajo N_2 durante 24 horas. El solvente se evaporó y el residuo se purificó por cromatografía evaporativa usando 2:1 CH_2Cl_2:EtOAc como eluyente para proporcionar un sólido ceroso de color amarillo (53 mg, 50%). LCMS: MH^+=428.

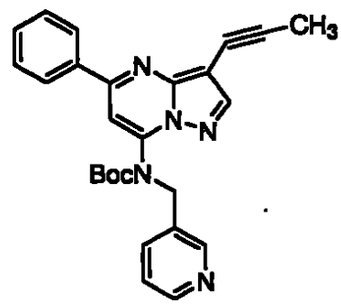
ETAPA B:



Una mezcla del compuesto preparado en el Ejemplo 425, Etapa 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 durante 24 horas. se agregaron $NaHCO_3$ (1,0 g), Na_2SO_4 (2,0g), y CH_2Cl_2 (20 mL), se agitó la mezcla y luego se filtró. El solvente se evaporó y el residuo se purificó por cromatografía evaporativa usando 20:1:0.1 CH_2Cl_2:MeOH: NH_4OH conoc. como eluyente para proporcionar un sólido ceroso de color amarillo (17 mg, 45%). LCMS: MH^+=328. P.f.=48-51 °C.

EJEMPLO 426:

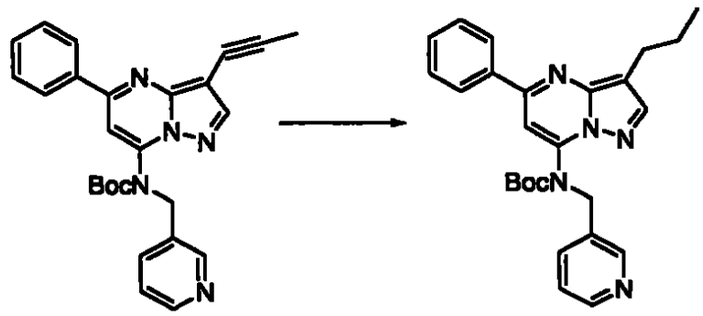
ETAPA A:



570

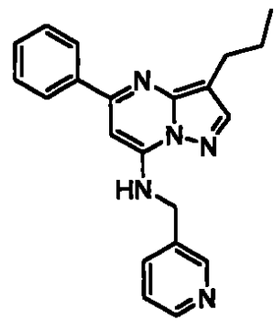
Esencialmente con el mismo procedimiento indicado en el Ejemplo 425, Etapa A únicamente usando tributilmetiletinilestaño, se preparó el compuesto que se muestra en lo que antecede.

ETAPA B:



Una mezcla del compuesto preparado en el Ejemplo 426, Etapa A (150 mg, 0,34 mmol) y PtO2 (30 mg, 0,13 mmol) en ácido acético glacial (5 mL) se agitó bajo una atmósfera de H_2 durante 20 horas. La mezcla se filtró, se agregó PtO2 (30 mg, 0,13 mmol) y la mezcla se agitó bajo una atmósfera de H_2 durante 2,5 horas. La mezcla se vertió sobre Na_2CO_3 (20 g) y H_2O (200 mL) y se extrajo con CH_2Cl_2 (4x20 mL). los extractos combinados se secaron Na_2SO_4 y se filtraron. El solvente se evaporó y el residuo se purificó por cromatografía evaporativa usando 1:1 CH_2Cl_2:EtOAc como eluyente para obtener un sólido ceroso de color amarillo (68 mg, 45%).

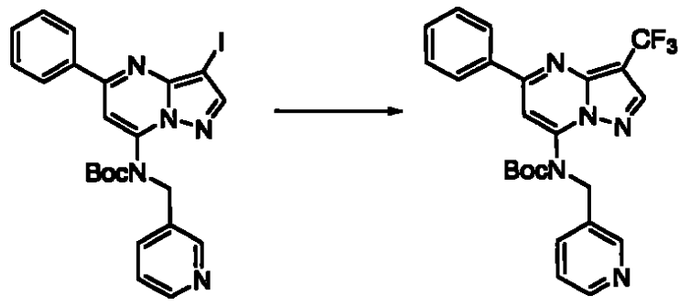
ETAPA C:



Siguiendo esencialmente el mismo procedimiento que se indica en el Ejemplo 425, Etapa B sustituyendo únicamente el compuesto preparado en el Ejemplo 426, Etapa B, se preparó el compuesto que se muestra anteriormente, EM: MH^+=344. P.f.=110-112 °C.

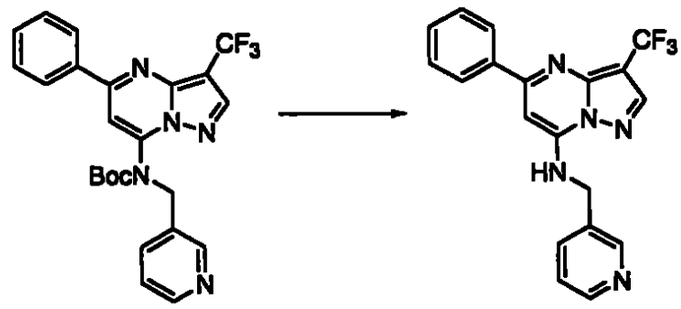
EJEMPLO 427:

ETAPA A:



Una mezcla del compuesto preparado en el Ejemplo Preparado 194 (527 mg, 1,00 mmol), trietil(trifluormetil)silano (666 mg, 3,60 mmol), fluoruro de potasio (210 mg, 3,60 mmol), y CuI (850 mg, 4,46 mmol) en DMF anhidro (4 mL) se agitó en un recipiente bajo presión cerrado a 80°C durante 72 horas. Se agregó CH2Cl2 (80 mL) y la mezcla se filtró a través de Celite. El solvente se evaporó y el residuo se purificó por cromatografía evaporativa usando 2:1 CH_2Cl_2: EtOAc como eluyente para proporcionar un sólido ceroso de color naranja pálido (70 mg, 15%). LCMS: M^+=470.

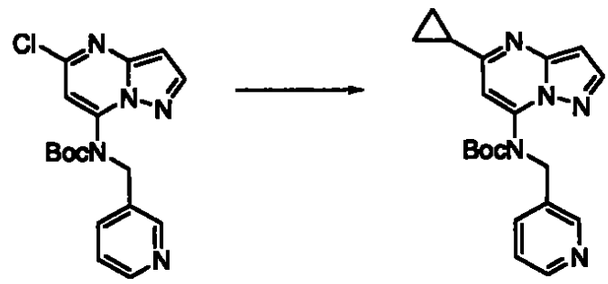
ETAPA B:



Se agregó TFA (0,70 ml) a 0°C bajo N_2 a una solución agitada del compuesto preparado en el Ejemplo 427, Etapa A (70 mg, 0,15 mmol), en CH_2Cl_2 anhidro (3 ml). La mezcla se agitó a 0°C durante 10 minutos, y luego a 25°C durante 2 horas. Se vertió Na_2CO_3 acuoso al 10% (50 ml), se extrajo con CH_2Cl_2 (3x15 ml), y se secó sobre Na_2SO_4, y se filtró. El solvente se evaporó y el residuo se purificó por cromatografía evaporativa usando EtOAc como eluyente para proporcionar un sólido blancuzco (40 mg, 73%). LCMS: M^+=370. P.f. =1 56-158°C.

EJEMPLO 428:

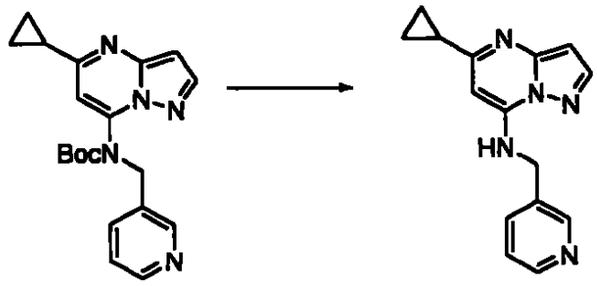
ETAPA A:



Una mezcla del compuesto preparado en el Ejemplo Preparativo 193 (100 mg, 0,28 mmol), tetraciclopropilestaño (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 anhidro (3 ml) se reflujó bajo N_2 durante 27 horas. El solvente se evaporó y el residuo se purificó por cromatografía evaporativa usando 1:1 CH_2Cl_2:EtOAc como eluyente para proporcionar un sólido ceroso incoloro (38 mg, 38%). LCMS: MH^+ = 366.

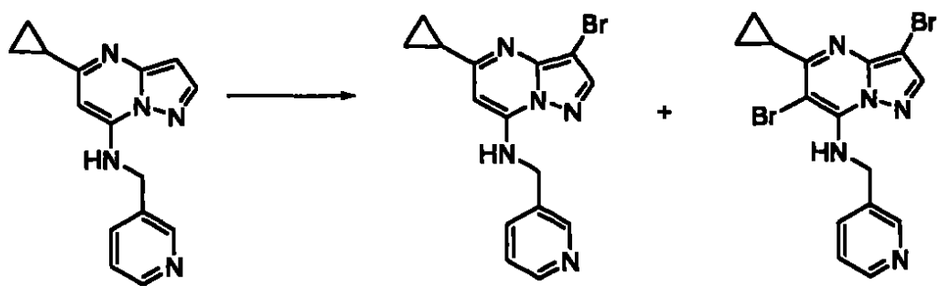
592 593

ETAPA B:



Una mezcla del compuesto preparado en el Ejemplo 428, Etapa A (36 mg, 0,10 mmol) y KOH (300 mg, 5,40 mmol) en etanol (3 ml), 1,2-dimetoxietano (3,0 ml y H_2O (0,8 ml) se reflujó bajo N_2 durante 4 horas. Se vertió en $NaHCO_3$ acuoso saturado (100 ml), se extrajo con CH_2Cl_2 (5x10 ml), se secó sobre Na_2SO_4, y se filtró. El solvente se evaporó y el residuo se purificó por cromatografía evaporativa usando 30:1 EtOAc:MeOH como eluyente para proporcionar un producto ceroso incoloro (18 mg, 69%). LCMS: $MH^+ = 266$.

ETAPA C:



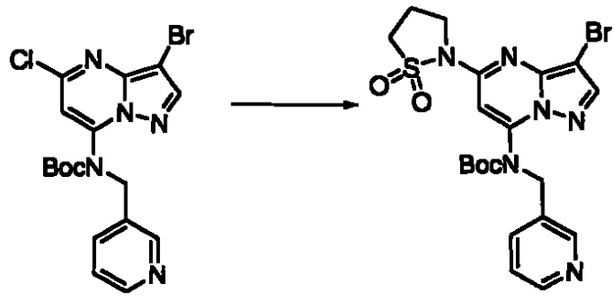
Se agregó N-bromosuccinimida (12 mg, 0,068 mmol) en CH_3CN anhidro (2 ml) bajo N_2 a una solución agitada del compuesto preparado en el Ejemplo 428, Etapa B (18 mg, 0,068 mmol), en CH_3CN anhidro (2 ml). La mezcla se agitó a 25°C durante 2 horas. El solvente se evaporó y el residuo se purificó por cromatografía evaporativa usando EtOAc como eluyente para obtener 5 mg (17%) del compuesto dibromo (sólido blanco, LCMS: $MH^+ = 370$, p.f. = 150-152°C) y 8

594

~~mg (34%)~~ del compuesto monobromo (sólido incoloro, LCMS: M^+= 344, p.f. = 196-198°C).

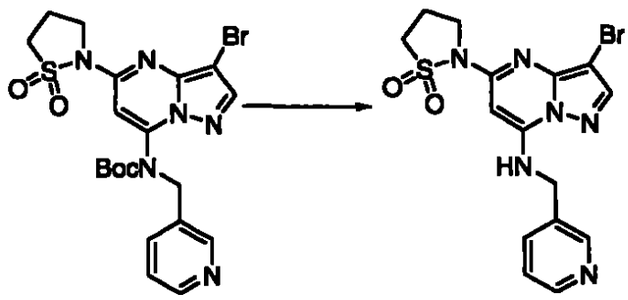
EJEMPLO 429:

ETAPA A:



Se agregó 1,3-propansultam (72 mg, 0,60 mmol) en DMF anhidro (3 ml) bajo N_2 a 60% de NaH en aceite mineral (36 mg, 0,90 mmol). La mezcla se agitó durante 20 minutos, y luego se agregó el compuesto preparado en el Ejemplo Preparativo 196 (200 mg, 0,46 mmol). La mezcla se agitó a 100°C durante 30 minutos, el solvente se evaporó y el residuo se purificó por cromatografía evaporativa usando EtOAc como eluyente para proporcionar un sólido incoloro (150 mg, 63%). LCMS: M^+ = 523.

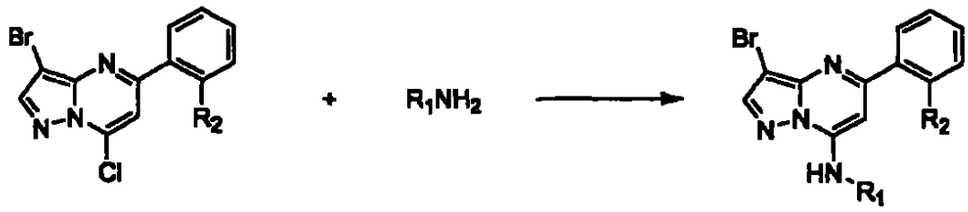
ETAPA B:



Se agregó TFA (1,5 ml) a 0°C bajo N_2 a una solución agitada del compuesto preparado en el Ejemplo Preparativo 196 (140 mg, 0,27 mmol), en CH_2Cl_2 anhidro (5 ml). La mezcla se agitó a 0°C durante 10 minutos, y luego a 25°C durante 2 horas. Se vertió sobre Na_2CO_3 (10 g), se extrajo con CH_2Cl_2 (3x50

ml), y se filtró. El solvente se evaporó y el residuo se purificó por cromatografía evaporativa usando 40:1 EtOAc:MeOH como eluyente para proporcionar un sólido blanco (32 mg, 28%). LCMS: $M^+ = 423$. P.f. = 218-220°C.

EJEMPLO 430:

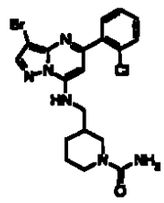
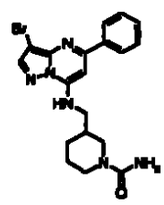
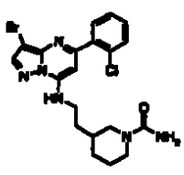
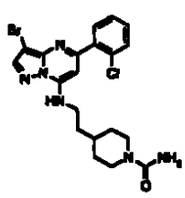
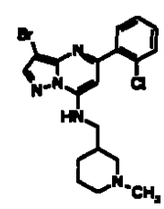


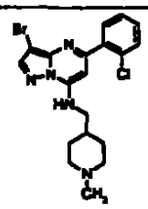
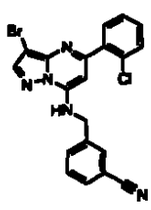
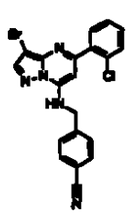
donde: R_2=H, o Cl

3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (1 equivalente) (preparado tal como se describió en el Ejemplo Preparativo 129), ó 3-bromo-7-cloro-5-fenilpirazolo[1,5-a]pirimidina (1 equivalente) (preparado tal como se describió en el Ejemplo Preparativo 127), R_1NH_2 (1,2 equivalentes) y diisopropil etilamina (2 equivalentes) se disolvieron en 1,4-dioxano anhidro y la mezcla se calentó a 75°C en el tiempo que se indica en la Tabla 97. La solución se evaporó hasta sequedad y el residuo se cromatografió sobre una columna de gel de sílice tal como se describió en la Tabla 97, para proporcionar el compuesto del título.

Usando los reactivos apropiados y esencialmente el mismo procedimiento descrito más arriba, se prepararon los productos de los Ejemplos 431 a 438. Las variaciones en las condiciones de reacción se indican en la Tabla 35.

TABLA35

Ej.	Estructura	PM	FABMS MH^+	Condiciones de Reacción	Rendimiento	Datos Cromatográficos
431		463,8	463,0	75°C / 26h	52%	15x2,5 cm 0,5-2% (10% de hidróxido de amonio conc. en metanol)-diclorometano
432		429,3	429,2	75°C / 26h 25°C / 39h	53%	15x5 cm Diclorometano; 1,5% (10% de hidróxido de amonio conc. en metanol)-diclorometano
433		477,8	477,1	75°C / 26h	48%	15x5 cm Diclorometano; 3,5-15% (10% de hidróxido de amonio conc. en metanol)-diclorometano
434		477,8	477,0	75°C / 26h	50%	15x5 cm Diclorometano; 3,5-15% (10% de hidróxido de amonio conc. en metanol)-diclorometano
435		434,8	434,1	75°C / 24h 25°C / 65h	53%	15x2,5 cm 3% (10% de hidróxido de amonio conc. en metanol)-diclorometano

436		434,8	434,2	75°C / 27h	31%	15x2,5 cm 3% (10% de hidróxido de amonio conc. en metanol)-diclorometano
437		438,7	438,1	75°C / 21h 25°C / 46h	97%	15x2,5 cm 0,25% (10% de hidróxido de amonio conc. en metanol)-diclorometano
438		438,7	438,1	75°C / 28h -20°C / 72h	95%	60x2,5 cm 20% de acetato de etilo en hexano

Los datos físicos adicionales para los compuestos se dan a continuación:

EJEMPLO 431: Reactivos: 3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (110 mg, 0,318 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 129); 3-(aminometil)piperidina-1-carboxamida (60 mg, 0,382 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 241 anterior); diisopropil etilamina (0,111 ml, 0,636 mmoles); 1,4-dioxano anhidro (2,5 ml). Propiedades físicas: HRFABMS: m/z 463,0628 (MH^+). Calc. para $C_{19}H_{21}N_6OBrCl$: m/z 463,0649: δ_H ($CDCl_3$) 1,38 (1H, m, CH_2), 1,52 (1H, m, CH_2), 1,73 (1H, m, CH), 1,93 (1H, m, CH_2), 2,02 (1H, m, CH_2), 2,98 (1H, m, CH_2), 3,06 (1H, m, CH_2), 3,37 (2H, m, CH_2), 3,58 (1H, m, CH_2), 3,82 (1H, m, CH_2), 4,87 (2H, bm, $CONH_2$), 6,28 (1H, s, H_6), 7,02 (1H, m, NH), 7,36 (2H, m, Ar-H), 7,45 (1H, m,

Ar-H), 7,68 (1H, m, Ar-H) y 8,00 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 23,7, 28,1, 44,6, 45,5, 47,2; CH: 35,2, 87,4, 127,2, 130,1, 130,3, 131,6, 143,9: C: 83,1, 132,1, 138,6, 145,5, 146,5, 158,0, 158,4.

EJEMPLO 432: Reactivos: 3-Bromo-7-cloro-5-fenilpirazolo[1,5-a]pirimidina (500 mg, 1,62 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 127); 3-(aminometil)piperidina-1-carboxamida (306 mg, 1,944 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 241 anterior); diisopropil etilamina (0,566 ml, 3,24 mmoles); 1,4-dioxano anhidro (13 ml). Propiedades físicas: HRFABMS: m/z 429,1031 (MH^+). Calc. para $C_{19}H_{22}N_6OBr$: m/z 429,1038; δ_H ($CDCl_3$) 1,44 (1H, m, CH_2), 1,59 (1H, m, CH_2), 1,79 (1H, m, CH), 2,01 (1H, m, CH_2), 2,08 (1H, m, CH_2), 3,03 (1H, m, CH_2), 3,13 (1H, m, CH_2), 3,39 (1H, m, CH_2), 3,47 (1H, m, CH_2), 3,63 (1H, m, CH_2), 3,90 (1H, m, CH_2), 4,88 (2H, bm, $CONH_2$), 6,40 (1H, s, H_8), 6,90 (1H, m, NH), 7,53 (2H, m, Ar-H), 8,02 (1H, s, H_2) y 8,12 (1H, m, Ar-H); δ_C ($CDCl_3$) CH_2: 23,7, 28,2, 44,7, 45,5, 47,3; CH: 35,2, 82,9, 127,5, 127,5, 128,7, 128,7, 130,0, 143,9; C: 83,0, 138,5, 145,8, 147,1, 158,3, 158,5.

EJEMPLO 433: Reactivos: 3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (347 mg, 1,01 mmoles) (preparada tal como se describió en el Ejemplo Preparativo 129); 3-(aminoetil)piperidina-1-carboxamida (208 mg, 1,21 mmoles) (preparada tal como se describió en el Ejemplo Preparativo 242 anterior); diisopropil etilamina (0,393 ml, 2,02 mmoles); 1,4-dioxano anhidro (9 ml). Propiedades físicas: δ_H ($CDCl_3$) 1,24 (1H, m, CH_2), 1,55 (1H, m, CH), 1,72 (4H, m, CH_2), 1,93 (1H, m, CH_2), 2,69 (1H, m, CH_2), 2,94 (1H, m, CH_2), 3,55 (2H, m, CH_2), 3,73 (1H, m, CH_2), 3,98 (1H, m, CH_2), 4,83 (2H, bm, $CONH_2$), 6,55 (1H, s, H_8), 6,78 (1H, m, NH), 7,41 (2H, m, Ar-H), 7,50 (1H, m, Ar-H), 7,75 (1H, m, Ar-H) y 8,04 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 24,6, 30,7, 32,6, 39,9, 45,3, 49,3; CH:

33,3, 87,5, 127,4, 130,1, 130,2, 131,6, 143,8; C: 83,2, 132,1, 138,8, 145,7, 146,2, 158,1, 158,1.

EJEMPLO 434: Reactivos: 3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (275 mg, 0,803 mmoles) (preparada tal como se describió en el Ejemplo Preparativo 129); 4-(aminoetil)piperidina-1-carboxamida (165 mg, 0,963 mmoles) (preparada tal como se describió en el Ejemplo Preparativo 243 anterior); diisopropil etilamina (0,311 ml, 0,963 mmoles); 1,4-dioxano anhidro (7,2 ml). Propiedades físicas: δ_H (d_6-DMSO) 1,00 (2H, m, CH_2), 1,50 (1H, m, CH), 1,59 (2H, m, CH_2), 1,67 (2H, m, CH_2), 2,60 (2H, m, CH_2), 3,48 (2H, m, CH_2), 3,70 (2H, m, CH_2), 5,84 (2H, bs, $CONH_2$), 6,43 (1H, s, H_6), 7,50 (2H, m, Ar-H), 7,62 (2H, m, Ar-H), 8,30 (1H, s, H_2) y 8,36 ppm (1H, m, NH); δ_C (d_6-DMSO) CH_2: 31,5, 31,5, 34,8, 43,5, 43,5, 43,5; CH: 32,8, 86,8, 127,1, 129,7, 130,3, 131,0, 143,3; CH: 81,3, 131,0, 138,7, 145,1, 146,4, 157,3, 157,8.

EJEMPLO 435: Reactivos: 3-Bromo-7-cloro-5-fenilpirazolo[1,5-a]pirimidina (174 mg, 0,507 mmoles) (preparada tal como se describió en el Ejemplo Preparativo 129) y 3-(aminometil)-1-metilpiperidina (65 mg, 0,507 mmoles) (preparada tal como se describió en el Ejemplo Preparativo 244 anterior); diisopropil etilamina (0,178 ml, 1,014 mmoles); 1,4-dioxano anhidro (2,5 ml). Propiedades físicas: HRFABMS: m/z 434,0742 (MH^+). Calc. para $C_{19}H_{22}N_5BrCl$: m/z 434,0747; δ_H ($CDCl_3$) 1,18 (1H, m, CH_2), 1,68 (1H, m, CH_2), 1,80 (1H, m, CH_2), 1,87 (1H, m, CH_2), 1,96 (1H, m, CH), 2,14 (2H, m, CH_2), 2,32 (3H, s, NCH_3), 2,75 (1H, m, CH_2), 2,29 (1H, m, CH_2), 3,42 (2H, m, -NHC$\underline{H_2}$CH), 6,36 (1H, s, H_6), 6,64 (1H, bm, NH), 7,41 (2H, m, Ar-H), 7,51 (1H, m, Ar-H), 7,74 (1H, m, Ar-H) y 8,06 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 46,6; CH_2: 24,4, 27,9, 46,1, 56,1, 59,6; CH: 36,0, 87,4, 127,1, 130,1, 130,2, 131,6, 143,8; C: 83,2, 132,1, 138,9, 145,6, 146,4, 158,2.

EJEMPLO 436: Reactivos: 3-Bromo-7-cloro-5-fenilpirazolo[1,5-a]pirimidina (111,4 mg, 0,325 mmoles) (preparada tal como se describió en el Ejemplo Preparativo 129); 4-(aminometil)-1-metilpiperidina (50 mg, 0,39 mmoles) (preparada tal como se describió en el Ejemplo Preparativo 245 anterior); diisopropil etilamina (0,1135 ml, 0,65 mmoles); 1,4-dioxano anhidro (1,5 ml). Datos físicos: HRFABMS: m/z 434,0735 (MH^+). Calc. para $C_{19}H_{22}N_5BrCl$: m/z 434,0747; δ_H ($CDCl_3$) 1,42 (2H, m, CH_2), 1,72 (1H, m, CH), 1,82 (2H, m, CH_2), 1,93 (2H, m, CH_2), 2,20 (3H, s, NCH_3), 2,89 (2H, m, CH_2), 3,34 (2H, m, -NHC$\underline{H_2}$CH), 6,31 (1H, s, H_6), 6,46 (1H, m, NH), 7,36 (2H, m, Ar-H), 7,46 (1H, m, Ar-H), 7,70 (1H, m, Ar-H) y 8,00 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 46,4; CH_2: 30,2, 30,2, 48,0, 55,3, 55,3; CH: 35,4, 87,5, 127,2, 130,2, 130,2, 131,6, 143,8; C: 83,3, 132,2, 138,9, 145,7, 146,4, 158,1.

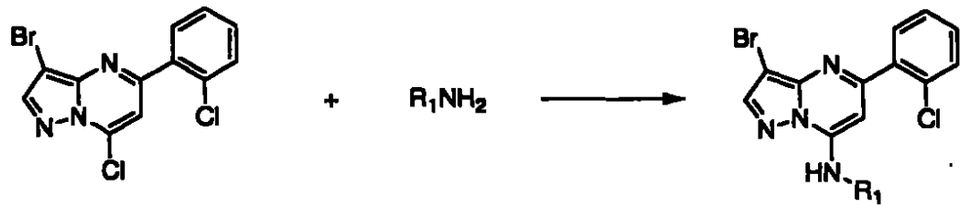
EJEMPLO 437: Reactivos: 3-Bromo-7-cloro-5-fenilpirazolo[1,5-a]pirimidina (191 mg, 0,557 mmoles) (preparada tal como se describió en el Ejemplo Preparativo 129); 3-(aminometil)benzonitrilo (88,3 mg, 0,668 mmoles) (preparado tal como se describió en el Ejemplo Preparativo 246 anterior); diisopropil etilamina (0,192 ml, 1,114 mmoles); 1,4-dioxano anhidro (4,5 ml). Datos físicos: HRFABMS: m/z 438,0125 (MH^+). Calc. para $C_{19}H_{12}N_5BrCl$: m/z 438,0121; δ_H ($CDCl_3$) 4,76 (2H, d, -C$\underline{H_2}$NH-), 6,32 (1H, s, H_6), 7,00 (1H, m, -CH_2N$\underline{H}$-), 7,40 (2H, m, Ar-H), 7,46 (1H, m, Ar-H), 7,55 (1H, m, Ar-H), 7,67 (2H, m, Ar-H), 7,71 (1H, m, Ar-H), 7,75 (1H, m Ar-H) y 8,10 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 45,5; CH: 88,2, 127,2, 130,0, 130,2, 130,4, 130,6, 131,4, 131,6, 131,9, 144,1; C: 83,8, 113,4, 118,3, 132,0, 137,8, 138,3, 145,6, 145,9, 158,0.

EJEMPLO 438: Reactivos: 3-Bromo-7-cloro-5-fenilpirazolo[1,5-a]pirimidina (233,5 mg, 0,681 mmoles) (preparada tal como se describió en el Ejemplo Preparativo 129); 4-(aminometil)benzonitrilo (108 mg, 0,817 mmoles) (preparado tal como se

601

~~descrito en el Ejemplo Preparativo 247 anterior);~~ diisopropil etilamina (0,235 ml, 1,362 mmoles); 1,4-dioxano anhidro (5,3 ml). Datos físicos: HRFABMS: m/z 438,0117 (MH^+) Calc. para $C_{20}H_{14}N_5BrCl$: m/z 438,0121; δ_H ($CDCl_3$) 4,80 (2H, d, CH_2), 6,30 (1H, s, H_6), 7,01 (1H, m, NH), 7,40 (2H, m, Ar-H), 7,47 (1H, m, Ar-H), 7,70 (2H, m, Ar-H), 7,72 (2H, m, Ar-H), 7,80 (1H, m, Ar-H) y 8,10 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 45,8; CH: 88,2, 127,2, 127,7, 127,7, 130,2, 130,4, 131,6, 132,9, 132,9, 144,1; C: 83,8, 112,2, 118,4, 132,0, 138,2, 141,5, 145,5, 146,0, 158,0.

EJEMPLO 439:

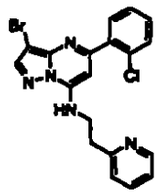
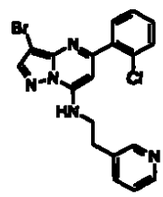
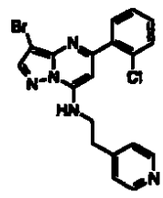
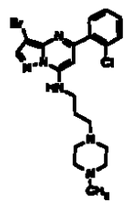


3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (50 mg, 0,146 mmoles) (preparada tal como se describió en el Ejemplo Preparativo 129) se disolvió en 1,4-dioxano anhidro (5 ml) en un tubo de reacción GeneVac Technologies carousel. Se agregó a cada uno de los tubos PS-resina de diisopropil etilamina (161 mg, 0,5828 mmoles). Una solución 1M recientemente preparada de la amina apropiada R_1NH_2 en 1,4-dioxano anhidro (0,2185 ml, 0,2185 mmoles) se agregó a cada uno de los tubos y los tubos se sellaron y se calentaron a 70°C durante 78 horas con agitación magnética en el bloque de reacción. Cada tubo se filtró y la resina se lavó con 1,4-dioxano anhidro y luego con diclorometano. Los filtrados individuales combinados se cada tubo se evaporaron hasta sequedad y los residuos fueron disueltos cada uno en 1,4-dioxano anhidro (5 ml) y se colocaron en tubos de reacción GeneVac. A cada uno de los tubos se le agregó PS-resina de isocianato (594 mg, 0,8742 mmoles) y PS-resina de trisamina (129 mg, 0,4371 mmoles) y los tubos se agitaron a 25°C

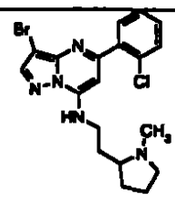
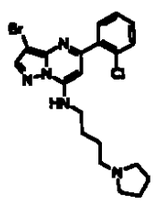
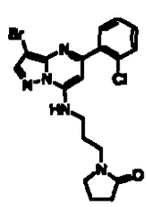
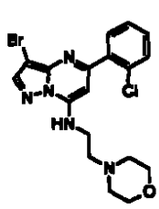
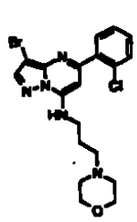
601 602

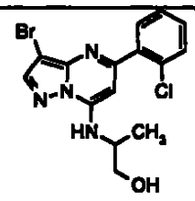
durante 20 horas en el bloque de reacción. Las resinas se separaron por filtración y se lavaron con 1,4-dioxano anhidro y diclorometano. Los filtrados de cada tubo se evaporaron hasta sequedad y cada uno de los residuos fue cromatografiado sobre una columna de gel de sílice usando el tamaño de columna y el eluyente que se muestran en la Tabla 36, para obtener los compuestos del título.

TABLA 36

Ej.	Estructura	PM	FABMS MH^+	Rendi-miento	Datos cromatográficos
440		428,7	428,0	81%	15x2,5 cm Diclorometano; 0,5% de metanol en diclorometano
441		428,7	428,0	48%	20x2 cm Diclorometano; 1,5% de metanol en diclorometano
442		428.7	428.0	24%	15x2,5 cm Diclorometano; 1,5% de metanol en diclorometano
443		463,8	463,0	44%	15x2,2 cm Diclorometano; 5% de metanol en diclorometano

603

444		434,8	434,1	63%	15x2,5 cm 5% de metanol en diclorometano
445		448,8	448,2	65%	15x2,5 cm 5% de metanol en diclorometano
446		448,8	448,1	40%	15x2,5 cm Diclorometano; 0,5% de metanol en diclorometano
447		436,7	436,1	72%	15x2,5 cm 0,5% de metanol en diclorometano
448		450,8	450,0	53%	20x2 cm Diclorometano; 0,5% de metanol en diclorometano

449		381,7	381,0	44%	20x2 cm 1,5% de metanol en diclorometano

Los datos físicos adicionales para los compuestos se dan a continuación:

EJEMPLO 440: Propiedades físicas: HRFABMS: m/z 428,0272 (MH^+). Calc. para $C_{19}H_{18}N_5BrCl$: m/z 428,0278; δ_H ($CDCl_3$) 3,28 (2H, dd, $C_5H_4NC\underline{H}_2CH_2NH$-), 3,94 (2H, ddd, $C_5H_4NCH_2C\underline{H}_2NH$-), 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) y 8,68 ppm (1H, NH); δ_C ($CDCl_3$) CH_2: 36,4, 41,5; CH: 87,3, 122,1, 123,6, 127,1, 130,1, 130,1, 131,6, 137,0, 143,8, 149,5; C: 83,1, 132,1, 138,9, 145,7, 146,3, 158,0, 158,1.

EJEMPLO 441: Propiedades físicas: HRFABMS: m/z 428,0272 (MH^+). Calc. para $C_{19}H_{18}N_5BrCl$: m/z 428,0278; δ_H ($CDCl_3$) 3,12 (2H, dd, $C_5H_4NC\underline{H}_2CH_2NH$-), 3,77 (2H, ddd, $C_5H_4NCH_2C\underline{H}_2NH$-), 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) y 8,63 ppm (1H, m, NH); δ_C ($CDCl_3$) CH_2: 32,7, 43,1; CH: 87,5, 127,2, 130,2, 130,3, 131,6, 136,4, 142,9, 148,3, 149,8; C: 83,5, 132,0, 138,6, 145,6, 145,9, 158,1.

EJEMPLO 442: Propiedades físicas: HRFABMS: m/z 428,0275 (MH^+). Calc. para $C_{19}H_{18}N_5BrCl$: m/z 428,0278; δ_H ($CDCl_3$) 3,13 (2H, dd, $C_5H_4NC\underline{H}_2CH_2NH$-), 3,80 (2H, ddd, $C_5H_4NCH_2C\underline{H}_2NH$-), 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) y 8,63 ppm (1H, m, NH); δ_C ($CDCl_3$) CH_2: 34,7, 42,5; CH: 87,4, 124,5, 124,5, 127,2, 130,2, 130,3, 131,6, 144,0, 150,2, 150,2; C: 83,5, 132,0, 138,6, 145,6, 145,9, 146,6, 158,1.

EJEMPLO 443: Propiedades físicas: HRFABMS: m/z 463,1003 (MH^+). Calc. para $C_{20}H_{25}N_6BrCl$: m/z 463,1013; δ_H ($CDCl_3$) 1,98 (2H, m, $=NCH_2C\underline{H_2}CH_2NH$-), 2,43 (3H, s, NCH_3), 2,67 (2H, m, $=NC\underline{H_2}CH_2CH_2NH$-), 2,70 (8H, piperazina CH_2), 3,58 (2H, m, $=NCH_2CH_2C\underline{H_2}NH$-), 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 8,60 ppm (1H, m, NH); δ_C ($CDCl_3$) CH_3: 46,1; CH_2: 24,1, 42,8, 53,3, 54,6, 54,6, 57,5, 57,5; CH: 87,1, 127,0, 130,0, 130,1, 131,5, 143,4; C: 82,7, 132,1, 139,2, 145,7, 146,7, 158,0.

EJEMPLO 444: Propiedades físicas: HRFABMS: m/z 434,0742 (MH^+). Calc. para $C_{18}H_{22}N_5BrCl$: m/z 434,0747; δ_H ($CDCl_3$) 1,72 (1H, m, CH/CH_2), 1,78-1,90 (2H, m, CH/CH_2), 2,02 (3H, m, CH/CH_2), 2,50 (1H, m, CH/CH_2), 2,45 (3H, s, NCH_3), 2,51 (1H, m, CH/CH_2), 3,23 (1H, m, CH/CH_2), 3,54 (1H, m, CH/CH_2), 3,60 (1H, m, CH/CH_2), 6,32 (1H, s, H_6), 7,38-7,44 (2H, m, Ar-H), 7,51 (1H, m, Ar-H), 7,75 (1H, m, Ar-H), 7,96 (1H, bm, NH) y 8,05 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 40,7; CH_2: 22,7, 29,3, 30,1, 39,4, 57,0; CH: 64,2, 87,1, 127,1, 130,0, 130,1, 131,6, 143,8; C: 82,8, 132,1, 139,1, 145,7, 146,4, 158,0.

EJEMPLO 445: Propiedades físicas: HRFABMS: m/z 448,0910 (MH^+). Calc. para $C_{20}H_{24}N_5BrCl$: m/z 448,0904; δ_H ($CDCl_3$) 1,90 (4H, m, CH_2), 2,00 (4H, m, CH_2), 2,84 (2H, m, CH_2), 2,95 (4H, m, CH_2), 3,51 (2H, m, CH_2), 6,32 (1H, s, H_6), 7,05 (1H, bm, NH), 7,37-7,43 (2H, m, Ar-H), 7,50 (1H, m, Ar-H), 7,73 (1H, m, Ar-H) y 8,04 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 23,4, 23,4, 24,8, 26,4, 41,8, 53,9, 53,9,

55,2; CH: 87,3, 127,1, 130,1, 130,2, 131,6, 143,7; C: 83,0, 132,0, 138,9, 145,7, 146,3, 158,1.

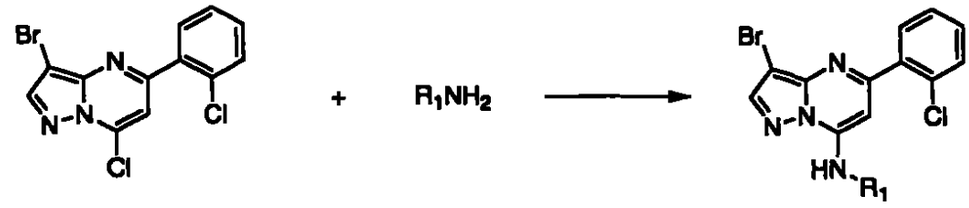
EJEMPLO 446: Propiedades físicas: HRFABMS: m/z 448,0548 (MH^+). Calc. para $C_{19}H_{20}N_5OBrCl$: m/z 448,0540; δ_H ($CDCl_3$) 1,94 (2H, m, CH_2), 2,09 (2H, m, CH_2), 2,49 (2H, m, CH_2), 3,45 (2H, m, CH_2), 3,51 (4H, m, CH_2), 6,32 (1H, s, H_6), 7,37-7,44 (3H, m, Ar-H/NH), 7,51 (1H, m, Ar-H), 7,75 (1H, m, Ar-H) y 8,10 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 18,0, 26,3, 30,8, 39,2, 39,9, 47,5; CH: 87,0, 127,1, 130,1, 130,1, 131,6, 144,1; C: 82,9, 132,1, 138,9, 145,6, 146,2, 157,9, 176,2.

EJEMPLO 447: Propiedades físicas: HRFABMS: m/z 436,0532 (MH^+). Calc. para $C_{18}H_{20}N_5OBrCl$: m/z 436,0540; δ_H ($CDCl_3$) 2,60 (4H, bm, -N($C\underline{H}_2CH_2)_2O$), 2,83 (2H, m, =$NC\underline{H}_2CH_2NH$-), 3,57 (2H, m, =$NCH_2C\underline{H}_2NH$-), 3,83 (4H, m, -$N(CH_2C\underline{H}_2)_2O$), 6,37 (1H, s, H_6), 6,99 (1H, bm, NH), 7,38-7,45 (2H, m, Ar-H), 7,51 (1H, m, Ar-H), 7,75 (1H, m, Ar-H) y 8,09 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 38,2, 53,3, 53,3, 56,2, 66,9, 66,9; CH: 87,6, 127,1, 130,1, 130,2, 131,6, 143,9; C; 83,1, 132,1, 138,9, 145,7, 146,2, 158,1.

EJEMPLO 448: Propiedades físicas: HRFABMS: m/z 450,0688 (MH^+). Calc. para $C_{19}H_{22}N_5OBrCl$: m/z 450,0696; δ_H ($CDCl_3$) 1,98 (2H, m, =$NCH_2C\underline{H}_2CH_2NH$-), 2,58 (4H, m, -$N(C\underline{H}_2CH_2)_2O$), 2,67 (2H,m, =$NC\underline{H}_2CH_2CH_2NH$-), 3,59 (2H, m, =$NCH_2CH_2C\underline{H}_2NH$-), 3,94 (4H, m, -$N(CH_2C\underline{H}_2)_2O$), 6,31 (1H, s, H_6), 7,37-7,44 (2H, Ar-H), 7,51 (1H, m, Ar-H), 7,78 (1H, m, Ar-H), 8,08 (1H, s, H_2) y 8,60 ppm (1H, bm, NH); δ_C ($CDCl_3$) CH_2: 23,7, 42,7, 52,9, 52,9, 58,0, 66,6, 66,6; CH: 87,0, 127,1, 130,0, 130,1, 131,5, 143,6; C: 82,8, 132,1, 139,1, 145,7, 146,7, 158,0.

~~EJEMPLO 449: Propiedades físicas: HRFABMS: m/z 381,0114 (MH^+).~~ Calc. para $C_{15}H_{15}N_4OBrCl$: m/z 381,0118; δ_H ($CDCl_3$) 1,39 (3H, d, $CHC\underline{H}_3$), 2,76 (1H, bm, -OH), 3,71 (1H, m, $=CHC\underline{H}_2OH$), 3,81 (1H, m, $=CHC\underline{H}_2OH$), 3,88 (1H, m, $=C\underline{H}CH_2OH$), 6,38 (1H, s, H_6), 7,38 (2H, m, Ar-H), 7,48 (1H, m, Ar-H), 7,68 (1H, m, Ar-H) y 8,02 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 16,9; CH_2: 65,0; CH: 50,0, 88,0, 127,1, 130,1, 130,3, 131,4, 143,8; C: 83,0, 132,0, 138,5, 145,6, 146,0, 158,2.

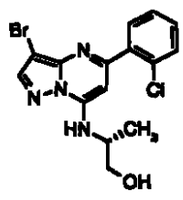
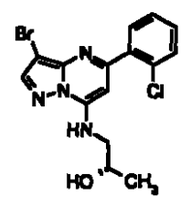
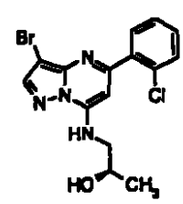
EJEMPLO 450:



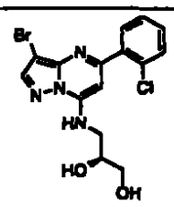
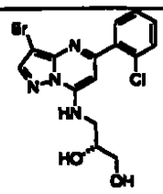
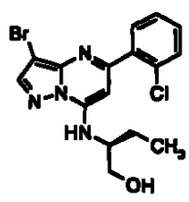
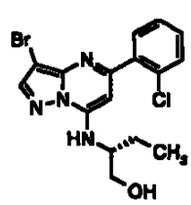
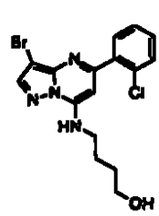
3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (50 mg, 0,146 mmoles) (preparada tal como se describió en el Ejemplo Preparativo 129) se disolvió en 1,4-dioxano anhidro (5 ml) en un tubo de reacción GeneVac Technologies carousel. Se agregó a cada uno de los tubos PS-resina de diisopropil etilamina (161 mg, 0,5828 mmoles). Se agregó a cada tubo una solución recientemente preparada de la amina apropiada R_1NH_2 (0,219 mmoles) en 1,4-dioxano anhidro (0,3 ml), con excepción del Ejemplo 99-5 en el cual la amina se disolvió en 10% de MeOH en 1,4-dioxano (0,3 ml), y los tubos se sellaron y calentaron a 70°C durante 74 horas con agitación magnética en el bloque de reacción. A cada tubo se filtró y la resina se lavó con 1,4-dioxano anhidro y luego con diclorometano. Los filtrados individuales combinados de cada tubo se evaporaron hasta sequedad y cada uno de los residuos fue re-disuelto en 1,4-dioxano anhidro (5 ml) y se colocó en tubos de reacción GeneVac. A cada uno de los tubos se le agregó PS-resina de isocianato (594 mg, 0,8742 mmoles) y PS-resina de trisamina (129 mg, 0,4371 mmoles) y los tubos se agitaron a 25°C

~~durante 20 horas en el bloque de reacción. Las resinas se separaron por filtración~~ y se lavaron con 1,4-dioxano anhidro y diclorometano. Los filtrados de cada tubo se evaporaron hasta sequedad y los residuos se cromatografiaron sobre una columna de gel de sílice usando el tamaño de columna y el eluyente que se muestran en la Tabla 37, para proporcionar los compuestos del título.

TABLA 37

Ej.	Estructura	PM	FABMS MH^+	Rendimiento	Datos cromatográficos
451		381,7	380,9	66%	15x2,5 cm; 0,5% de metanol en diclorometano
452		381,7	380,9	60%	20x2cm; 0,5% de metanol en diclorometano
453		381,7	380,9	69%	15x2,5 cm; 0,35% de metanol en diclorometano
454		381,7	380,9	75%	15x2,5 cm; 0,35% de metanol en diclorometano

609

455		397,7	397,2	84%	15x2,5 cm; 1,5% de metanol en diclorometano
456		397,7			
457		395,7	395,0	60%	15x2,5 cm; 0,35% de metanol en diclorometano
458		395,7	396,3	50%	15x2,5 cm; 0,35% de metanol en diclorometano
459		395,7	396,0	76%	15x2,5 cm; 0,35% de metanol en diclorometano

Los datos físicos adicionales para los compuestos se dan a continuación:

~~**EJEMPLO 451: Propiedades físicas: HRFABMS: m/z 381,0115 (MH^+).** Calc. para~~ $C_{15}H_{15}N_4OBrCl$: m/z 381,0118; $[\alpha]_D^{25°C}$ +1,4° (c=0,25 , MeOH); δ_H ($CDCl_3$) 1,44 (3H, d, -CHC<u>H</u>$_3$), 3,77, 3,89 (1H, dd, CHC<u>H</u>$_2$OH), (1H, dd, CHC<u>H</u>$_2$OH), 3,94 (1H, m, C<u>H</u>CH_2OH), 6,41 (1H, s, H_6), 6,58 (1H, d, NH), 7,41 (2H, m, Ar-H), 7,51 (1H, m, Ar-H), 7,74 (1H, m, Ar-H) y 8,04 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 17,1; CH_2: 65,5; CH: 49,9, 88,0, 127,1, 130,1, 130,2, 131,6, 143,8; C: 83,2, 132,1, 138,7, 145,6, 145,8, 158,1.

EJEMPLO 452: Propiedades físicas: HRFABMS: m/z 381,0115 (MH^+). Calc. para $C_{15}H_{15}N_4OBrCl$: m/z 381,0118; $[\alpha]_D^{25°C}$ +6,5° (c=0,32 , MeOH); δ_H ($CDCl_3$) 1,44 (3H, d, -CHC<u>H</u>$_3$), 3,78 (1H, dd, CHC<u>H</u>$_2$OH), 3,89 (1H, dd, CHC<u>H</u>$_2$OH), 3,96 (1H, m, C<u>H</u>CH_2OH), 6,41 (1H, s, H_6), 6,58 (1H, d, NH), 7,41 (2H, m, Ar-H), 7,51 (1H, m, Ar-H), 7,75 (1H, m, Ar-H) y 8,04 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 17,1; CH_2: 65,5; CH: 49,9, 88,0, 127,1, 130,1, 130,3, 131,6, 143,8; C: 83,2, 132,1, 138,6, 145,6, 145,8, 158,1.

EJEMPLO 453: Propiedades físicas: HRFABMS: m/z 381,0115 (MH^+). Calc. para $C_{15}H_{15}N_4OBrCl$: m/z 381,0118; $[\alpha]_D^{25°C}$ +9,4° (c=0,27, MeOH); δ_H ($CDCl_3$) 1,33 (3H, d, CH_3), 2,25 (1H, bs, OH), 3,37 (1H, dd, CH_2), 3,51 (1H, m, CH_2), 4,16 (1H, m, C<u>H</u>OH), 6,35 (1H, s, H_6), 6,93 (1H, m, NH), 7,40 (2H, m, Ar-H), 7,50 (1H, m, Ar-H), 7,70 (1H, m, Ar-H) y 8,04 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 20,8; CH_2: 49,2; CH: 65,7, 87,8, 127,1, 130,1, 130,2, 131,2, 143,9; C: 83,1, 132,1, 138,5, 145,6, 146,6, 158,3.

EJEMPLO 454: Propiedades físicas: HRFABMS: m/z 381,0112 (MH^+). Calc. para $C_{15}H_{15}N_4OBrCl$: m/z 381,0118; $[\alpha]_D^{25°C}$ –3,2° (c=0,29 , MeOH); δ_H ($CDCl_3$) 1,32 (3H, d, CH_3), 2,48 (1H, bs, OH), 3,35 (1H, dd, CH_2), 3,49 (1H, m, CH_2), 4,15 (1H,

m, C<u>H</u>OH), 6,34 (1H, s, H_6), 6,93 (1H, m, NH), 7,39 (2H, m, Ar-H), 7,49 (1H, m, Ar-H), 7,68 (1H, m, Ar-H) y 8,03 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 20,8; CH_2: 49,2; CH: 65,7, 87,7, 127,1, 130,1, 130,3, 131,4, 143,9; C: 83,0, 132,0, 138,6, 145,6, 146,6, 158,3.

EJEMPLO 455: Propiedades físicas: HRFABMS: m/z 397,0054 (MH^+). Calc. para $C_{15}H_{15}N_4O_2BrCl$: m/z 397,0067; $[\alpha]_D^{25°C}$ -9,5° (c= 0,28, MeOH); δ_H ($CDCl_3$) 3,18 (2H, bs, OH), 3,47 (1H, dd, CH_2), 3,58 (1H, dd, CH_2), 3,63 (1H, dd, C<u>H</u>$_2$OH), 3,70 (1H, dd, C<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); δ_C ($CDCl_3$) CH_2: 44,7, 64,0; CH: 69,7, 87,7, 127,0, 130,1, 130,3, 131,3, 143,9; C: 82,9, 132,0, 138,4, 145,4, 146,7, 158,3.

EJEMPLO 456: Este enantiómero puede prepararse esencialmente de la misma manera que se ha descrito anteriormente.

EJEMPLO 457: Propiedades físicas: HRFABMS: m/z 395,0260 (MH^+). Calc. para $C_{16}H_{17}N_4OBrCl$: m/z 395,0274; $[\alpha]_D^{25°C}$ –34,3° (c= 0,28, MeOH); δ_H ($CDCl_3$) 1,08 (3H, dd, CH_3), 1,78 (1H, m, CH_2), 1,86 (1H, m, CH_2), 2,35 (1H, bs, CH_2O<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^+). Calc. para $C_{16}H_{17}N_4OBrCl$: m/z 395,0274; $[\alpha]_D^{25°C}$ +27,5° (c= 0,25, MeOH); δ_H ($CDCl_3$) 1,05 (3H, dd, CH_3), 1,76 (1H, m, CH_2), 1,85 (1H, m, CH_2), 2,28 (1H, bs, CH_2O<u>H</u>), 3,67

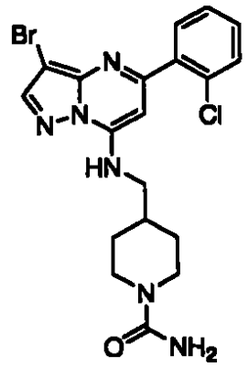
612

(1H, m, CHNH), 3,77 (1H, dd, CH_2OH), 3,84 (1H, dd, CH_2OH), 6,49 (1H, s, H_6), 6,66 (1H, m, NH), 7,39 (2H, m, Ar-H), 7,49 (1H, Ar-H), 7,71 (1H, m, Ar-H) y 8,04 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 10,5; CH_2: 24,3, 63,3; CH: 56,1, 88,0, 127,1, 130,1, 130,3, 131,5, 143,8; C: 83,0, 132,1, 138,6, 145,6, 146,3, 158,2.

EJEMPLO 459: Propiedades físicas: HRFABMS: m/z 395,0264 (MH^+). Calc. para $C_{16}H_{17}N_4OBrCl$: m/z 395,0274; δ_H ($CDCl_3$) 1,77 (2H, m, $-NHCH_2CH_2CH_2CH_2OH$), 1,90 (1H, bm, $-NHCH_2CH_2CH_2CH_2OH$), 1,93 (2H, m, $-NHCH_2CH_2CH_2CH_2OH$), 3,54 (2H, m, $-NHCH_2CH_2CH_2CH_2OH$), 3,77 (2H, m, $-NHCH_2CH_2CH_2CH_2OH$), 6,37 (1H, s, H_6), 6,72 (1H, m, $-NHCH_2CH_2CH_2CH_2OH$), 7,41 (2H, m, Ar-H), 7,51 (1H, m, Ar-H), 7,75 (1H, m, Ar-H) y 8,06 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 25,7, 29,7, 42,2, 62,2; CH: 87,4, 127,1, 130,1, 130,2, 131,6, 143,8; C: 83,1, 132,1, 138,8, 145,6, 146,3, 158,1.

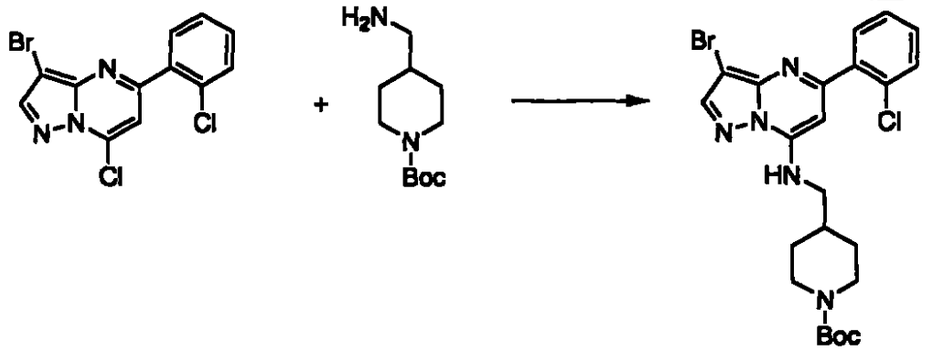
EJEMPLO 460:

AMIDA DE ÁCIDO 4-{[3-BROMO-5-(2-CLOROFENIL)PIRAZOLO[1,5-a]PIRIMIDIN-7-ILAMINO]METIL}PIPERIDINA-1-CARBOXÍLICO:



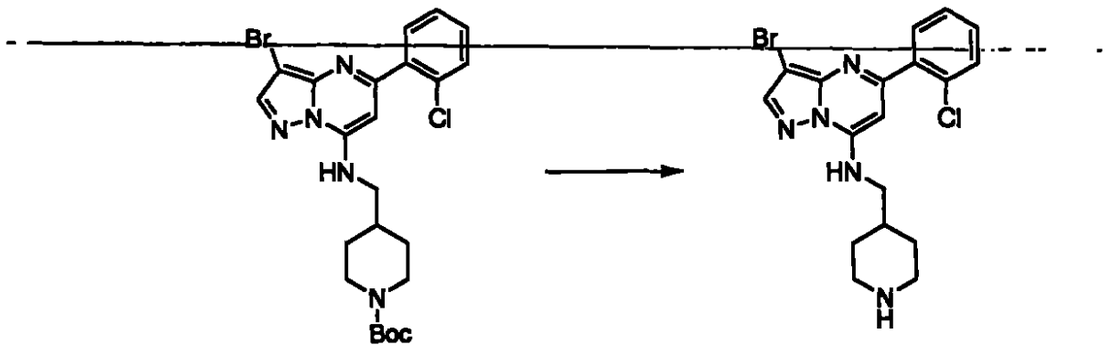
A. ÉSTER *ter*-BUTÍLICO DE ÁCIDO 4-{[3-BROMO-5-(2-CLOROFENIL)PIRAZOLO[1,5-a]PIRIMIDIN-7-ILAMINO]METIL}PIPERIDINA-1-CARBOXÍLICO:

613



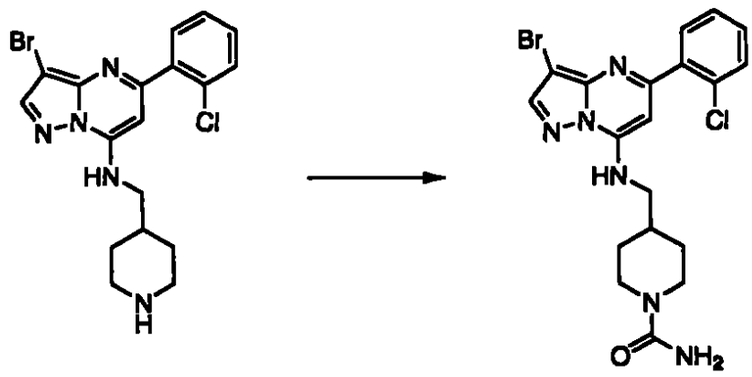
3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (300 mg, 0,875 mmoles) (preparada tal como se describió en el Ejemplo Preparativo 129) se disolvió en 1,4-dioxano anhidro (6,8 ml). Se agregaron éster *ter*-butílico de ácido 4-(aminometil)piperidina-1-carboxílico (225 mg, 1,05 mmoles) y diisopropil etilamina (0,3055 ml, 1,75 mmoles) y la mezcla se calentó a 75°C durante 24 horas. La solución se evaporó hasta sequedad y el residuo se cromatografió sobre una columna de gel de sílice (15x5 cm) usando diclorometano como eluyente para proporcionar éster *ter*-butílico de ácido 4-{[3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-ilamino]metil}piperidina-1-carboxílico (461,2 mg, 100%): FABMS: m/z 520,1 (MH^+); HRFABMS: m/z 520,1111 (MH^+). Calc. para $C_{23}H_{28}N_5O_2BrCl$: m/z 520,1115; δ_H ($CDCl_3$) 1,30 (2H, m, CH_2), 1,51 (9H, s, $-COOC(CH_3)_3$), 1,85 (2H, d, CH_2), 1,95 (1H, m , CH), 2,76 (2H, m, CH_2), 3,40 (2H, m, CH_2), 6,37 (1H, s, H_6), 6,55 (1H, m, NH), 7,42 (2H, m, Ar-H), 7,52 (1H, m, Ar-H), 7,76 (1H, m, Ar-H) y 8,07 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 28,5, 28,5, 28,5; CH_2: 29,1, 29,1, 43,5, 43,5, 47,9; CH: 36,3, 87,5, 127,2, 130,2, 130,3, 131,6, 143,9; C: 79,7, 83,3, 132,1, 138,6, 145,4, 146,3, 154,7, 158,1.

B. [3-BROMO-5-(2-CLOROFENIL)PIRAZOLO[1,5-a]PIRIMIDIN-7-IL]PIPERIDIN-4-ILMETILAMINA:



Éster *ter*-butílico de ácido 4-{[3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-ilamino]metil}piperidina-1-carboxílico (441 mg, 0,847 mmoles) (preparado tal como se describió en el Ejemplo 460, Etapa A anterior) se disolvió en metanol (4,5 ml) y se le agregó 10% (v/v) de ácido sulfúrico concentrado en 1,4-dioxano (11,46 ml). La mezcla se agitó a 25°C durante 0,5 horas. El producto se elaboró tal como se describió en el Ejemplo Preparativo 241, Etapa B y se cromatografió sobre una columna de gel de sílice (15x5 cm) usando 8% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente para proporcionar [3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-il]piperidin-4-ilmetil-amina (314,4 mg, 88%): FABMS: m/z 420,0 (MH^+); HRFABMS: m/z 420,0585 (MH^+). Calc. para $C_{18}H_{20}N_5BrCl$: m/z 420,0591; δ_H ($CDCl_3$) 1,34 (2H, m, CH_2), 1,86 (2H, m, CH_2), 1,91 (1H, m, CH), 2,10 (1H, bm, piperidina-NH), 2,67 (2H, m, CH_2), 3,18 (2H, m, CH_2), 3,38 (2H, m, CH_2), 6,37 (1H, s, H_6), 6,53 (1H, m, NH), 7,42 (2H, m, Ar-H), 7,52 (1H, m, Ar-H), 7,76 (1H, m, Ar-H) y 8,06 ppm (1H, s Ar-H); δ_C ($CDCl_3$) CH_2: 31,2, 31,2, 46,2, 46,2, 48,4; CH: 36,4, 89,5, 127,1, 130,1, 130,5, 131,6, 143,8; C: 83,2, 132,1, 138,9, 145,6, 146,4, 158,1.

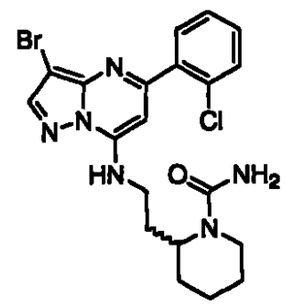
C. AMIDA DE ÁCIDO 4-{[3-BROMO-5-(2-CLOROFENIL)PIRAZOLO[1,5-a]PIRIMIDIN-7-ILAMINO]METIL}PIPERIDINA-1-CARBOXÍLICO



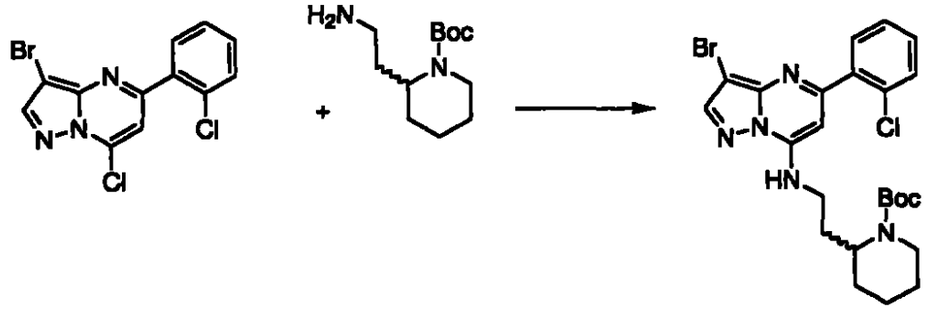
Se disolvió [3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-il]piperidin-4-ilmetilamina (57 mg, 0,136 mmoles) (preparada tal como se describió en el Ejemplo 460, Etapa B anterior) en diclorometano anhidro (1,2 ml) y se le agregó isocianato de trimetilsililo (0,091 ml, 0,679 mmoles). La mezcla se agitó a 25°C durante 2,5 horas. La mezcla se diluyó con diclorometano y se lavó con bicarbonato de sodio acuoso saturado. La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó hasta sequedad. El residuo se cromatografió sobre una columna de gel de sílice (30x2,5 cm) usando 3% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente para proporcionar amida de ácido 4-{[3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-ilamino]-metil}piperidina-1-carboxílico (53,7 mg, 86%): FABMS: m/z 463,1 (MH^+); HRFABMS: m/z 463,0647 (MH^+). Calc. para $C_{19}H_{21}N_6OBrCl$: m/z 463,0649; δ_H (d_6-DMSO) 1,09 (2H, m, CH_2), 1,63 (2H, m, CH_2), 1,87 (1H, m, CH), 2,60 (2H, m, CH_2), 3,53 (2H, bm, $CONH_2$), 3,91 (2H, d, CH_2), 6,52 (1H, s, H_6), 7,50 (2H, m, Ar-H), 7,62 (2H, m, Ar-H), 8,33 (1H, s, H_2) y 8,52 ppm (1H, m, NH); δ_C (d_6-DMSO) CH_2: 30,1, 30,1, 44,2, 44,2, 47,7; CH: 36,4, 88,2, 128,1, 130,7, 131,4, 132,1, 147,9; C: 82,1, 132,1, 139,4, 145,7, 147,9, 158,1, 158,8.

EJEMPLO 461:

AMIDA DE ÁCIDO 2-{2-[3-BROMO-5-(2-CLOROFENIL)PIRAZOLO[1,5-a]PIRIMIDIN-7-ILAMINO]ETIL}PIPERIDINA-1-CARBOXÍLICO



A. ÉSTER *ter*-BUTÍLICO DE ÁCIDO 2-{2-[3-BROMO-5-(2-CLOROFENIL)-PIRAZOLO[1,5-a]PIRIMIDIN-7-ILAMINO]ETIL}PIPERIDINA-1-CARBOXÍLICO

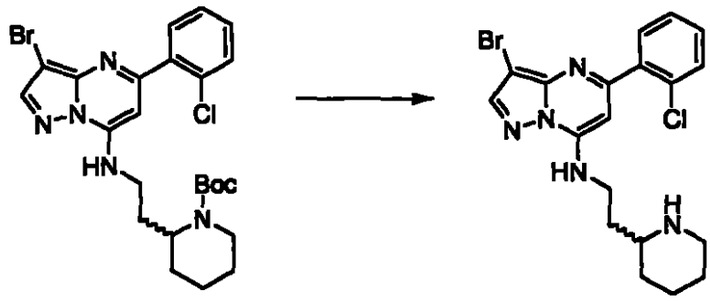


3-Bromo-7-cloro-5-(2-clorofenil)pirazolo[1,5-a]pirimidina (400 mg, 1,166 mmoles) (preparada tal como se describió en el Ejemplo Preparativo 129) se disolvió en 1,4-dioxano anhidro (5,7 ml). Se agregaron éster *ter*-butílico de ácido 2-aminoetilpiperidina-1-carboxílico (266 mg, 1,166 mmoles) y diisopropil etilamina (0,409 ml, 2,33 mmoles) y la mezcla se calentó a 75°C durante 48 horas. Se agregó diisopropil etilamina adicional (0,204 ml, 1,166 mmoles) y se prosiguió el calentamiento por un total de 58 horas. La solución se evaporó hasta sequedad y el residuo se cromatografió sobre una columna de gel de sílice (15x5 cm) usando diclorometano seguido de 0,3% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente para proporcionar éster *ter*-butílico de ácido 2-{[3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-ilamino]etil}piperidina-1-carboxílico (491,1mg, 79%): FABMS: m/z 534,1 (MH^+); HRESIMS: m/z 534,12797 (MH^+). Calc. para $C_{24}H_{30}N_5O_2BrCl$: m/z 534,12714; δ_H ($CDCl_3$) 1,50 (1H, m, CH_2), 1,51 (9H, s, $COOC(CH_3)_3$), 1,57 (2H, m, CH_2), 1,68 (2H, m, CH_2), 1,76 (2H, m,

617

CH_2), 2,24 (1H, brm, CH_2), 2,82/3,40/3,54/4,08/4,51 (5H, m, CH/CH_2), 6,34 (1H, s, H_8), 7,41 (2H, m, Ar-H), 7,51 (1H, m, Ar-H), 7,76 (1H, m, Ar-H) y 8,08 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_3: 28,5, 28,5, 28,5; CH_2: 19,2, 25,5, 29,2, 29,2, 39,2, 67,1; CH: ~47,4, 87,1, 127,1, 130,1, 130,1, 131,6, 143,9; C: 80,0, 83,0, 132,1, 138,9, 145,7, 146,2, 158,0.

B. [3-BROMO-5-(2-CLOROFENIL)PIRAZOLO[1,5-a]PIRIMIDIN-7-IL]-(2-PIPERIDIN-2-ILETIL)AMINA:

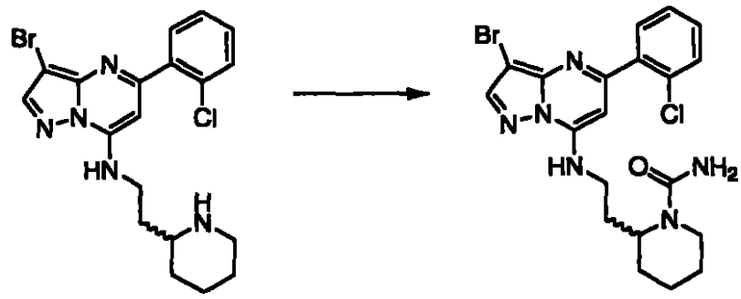


Éster *ter*-butílico de ácido 2-{[3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-ilamino]etil}piperidina-1-carboxílico (465 mg, 0,869 mmoles) (preparado tal como se describió en el Ejemplo 461, Etapa A anterior) se disolvió en metanol (4,5ml) y se agregó 10% (v/v) de ácido sulfúrico concentrado en 1,4-dioxano (11,76 ml). La mezcla se agitó a 25°C durante 1,5 horas. El producto se elaboró tal como se describió en el Ejemplo Preparativo 241, Etapa B y se cromatografió en una columna de gel de sílice (15x5 cm) usando 3,5% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente para proporcionar [3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-il]piperidin-2-iletil)-amina (365,6 mg, 97%): FABMS: *m/z* 434,1 (MH^+); HRFABMS: *m/z* 434,0726 (MH^+). Calc. para $C_{19}H_{22}N_5BrCl$: m/z 434,0747; δ_H ($CDCl_3$) 1,24.(1H, m, CH_2), 1,41 (1H, m, CH_2), 1,49 (1H, m, CH_2), 1,66 (1H, m, CH_2), 1,73 (1H, m, CH_2), 1,81 (1H, m, CH_2), 1,88 (2H, m, CH_2), 2,68 (1H, m, CH_2), 2,78 (1H, m, CH_2), 3,20 (1H, m,

618

CH), 3,55 (1H, m, CH_2), 3,60 (1H, m, CH_2), 6,32 (1H, s, H_6), 7,41 (2H, m, Ar-H), 7,51 (1H, m, Ar-H), 7,74 (1H, m, Ar-H), 7,78 (1H, m, NH) y 8,05 ppm (1H, s, H_2); δ_C ($CDCl_3$) CH_2: 24,7, 26,8, 33,1, 35,2, 40,3, 47,0; CH: 55,7, 87,2, 127,1, 130,0, 130,1, 131,5, 143,8; C: 82,9, 132,1, 139,0, 145,7, 146,5, 158,1.

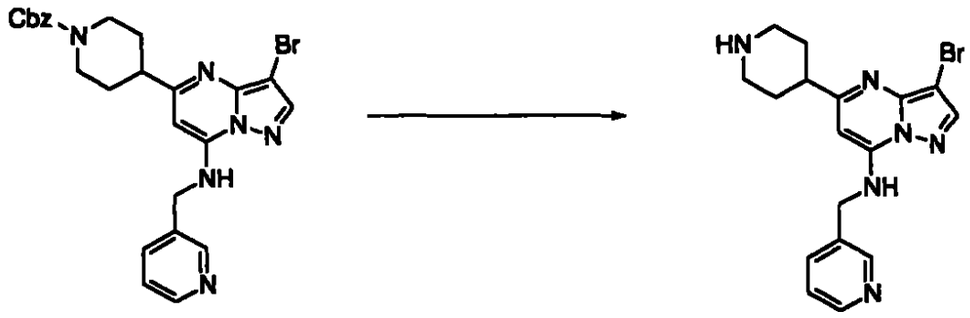
C. AMIDA DE ÁCIDO 2-{2-[3-BROMO-5-(2-CLOROFENIL)PIRAZOLO[1,5-a]PIRIMIDIN-7-ILAMINO]ETIL}PIPERIDINA-1-CARBOXÍLICO:



[3-Bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-il]piperidin-2-il)amina (200 mg, 0,46 mmoles) (preparada tal como se describió en el Ejemplo 461, Etapa B anterior) se disolvió en diclorometano anhidro (2 ml) y se agregó isocianato de trimetilsililo (0,31 ml, 2,3 mmoles). La mezcla se agitó a 25°C durante 1,25 horas. Se agregó isocianato de trimetilsililo adicional (0,155 ml, 1,15 mmoles) y la agitación se continuó por un total de 3 horas. La mezclas se diluyó con diclorometano y se lavó con bicarbonato de sodio acuoso saturado. La capa orgánica se secó ($MgSO_4$), se filtró y se evaporó hasta sequedad. El residuo se cromatografió en una columna de gel de sílice (30x2,5 cm) usando 2% (10% de hidróxido de amonio concentrado en metanol)-diclorometano como eluyente para proporcionar amida de ácido 2-{2-[3-bromo-5-(2-clorofenil)pirazolo[1,5-a]pirimidin-7-ilamino]etil}piperidina-1-carboxílico (106,3 mg, 48%): FABMS: m/z 477,0 (MH^+); HRFABMS: m/z 477,0804 (MH^+). Calc. para $C_{20}H_{23}N_6OBrCl$: m/z 477,0805; δ_H (d_6-DMSO) 1,29 (1H, m, CH_2), 1,52 (5H, m, CH_2), 1,72 (1H, m, CH_2), 2,05 (1H, m,

CH_2), 2,51 (2H, s, $CONH_2$), 2,79 (1H, dd, CH), 3,31 (1H, m, CH_2), 3,34 (1H, m, CH_2), 3,76 (1H, m, CH_2), 4,30 (1H, bm, CH_2), 6,42 (1H, s, H_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) y 8,38 ppm (1H, dd, NH); δ_C (d_6-DMSO) CH_2: 18,6, 25,2, 28,2, 38,4, 38,6, 54,8; CH: 46,7, 86,6, 127,1, 129,7, 130,3, 131,0, 143,4; C: 81,2, 131,0, 138,7, 145,1, 146,4, 158,2.

EJEMPLO 462:

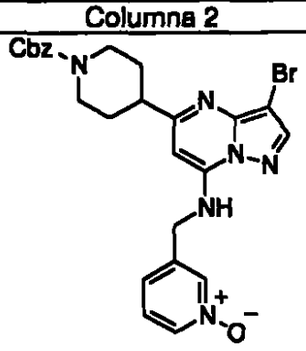
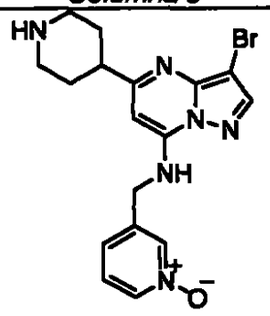
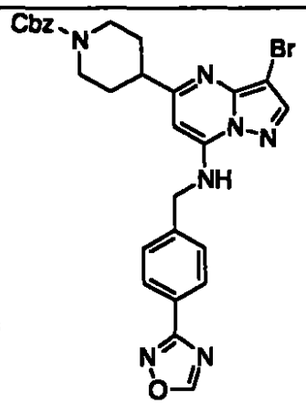
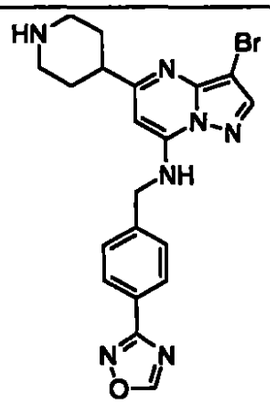
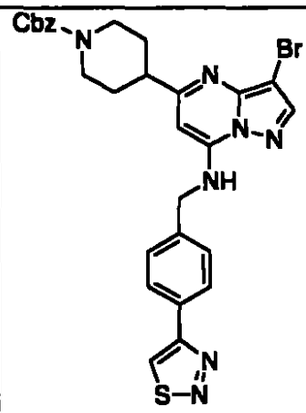
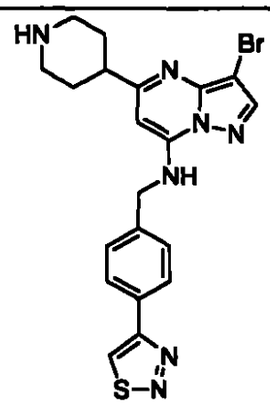


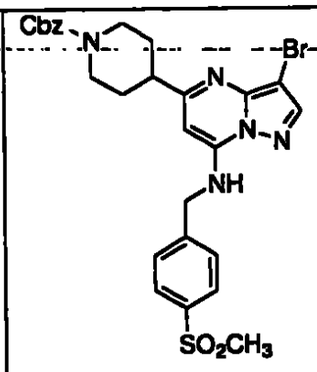
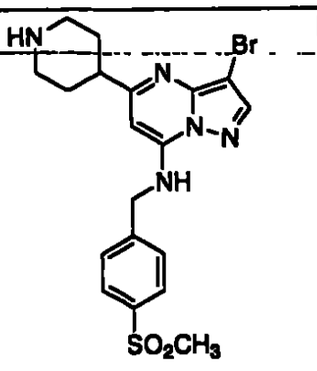
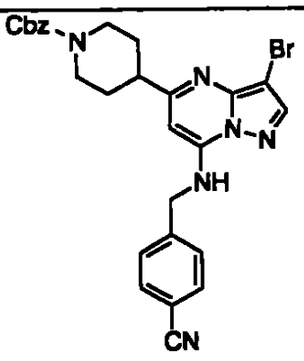
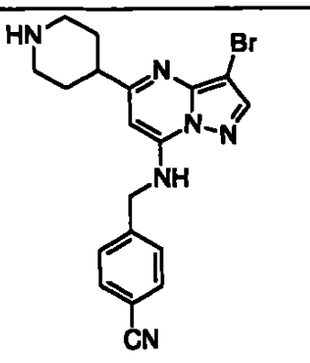
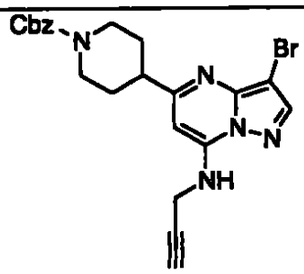
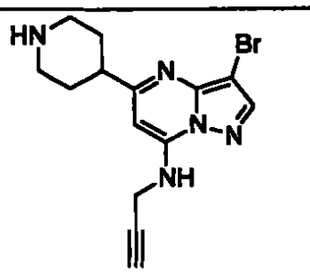
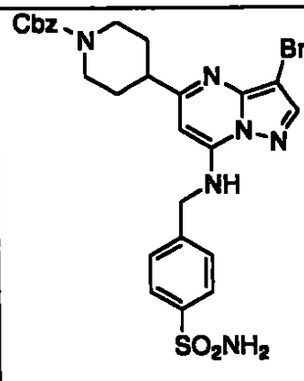
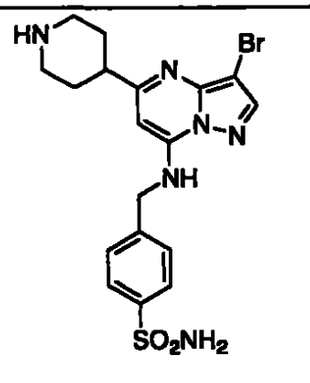
A una solución del compuesto preparado en el Ejemplo 204 (1,11 g, 2,12 mmol) en acetonitrilo anhidro (20 ml) se le agregó TMSI (1,70 g, 8,52 mmol), por goteo a temperatura ambiente. Después de 10 minutos, se extrajo el acetonitrilo al vacío. La espuma de color amarillo resultante se trató con una solución de HCl 2 N (7 ml) y luego se lavó inmediatamente con Et_2O (5X). El pH acuoso se ajustó a 10 con 50% de NaOH (acuoso) y el producto se aísla por saturación de la solución con NaCl (s) seguido de extracción con CH_2Cl_2 (5X) para proporcionar el producto cristalino (733 mg, 89% de rendimiento). MH^+ = 387; p.f. = 207,5°C

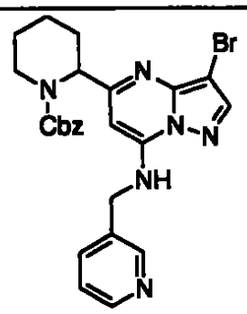
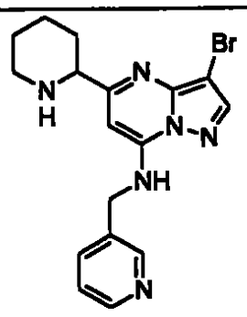
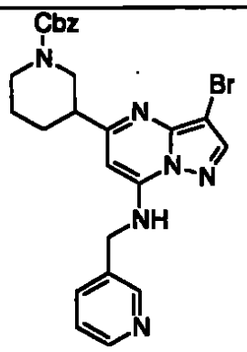
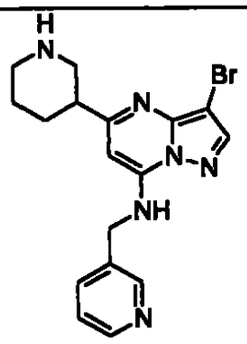
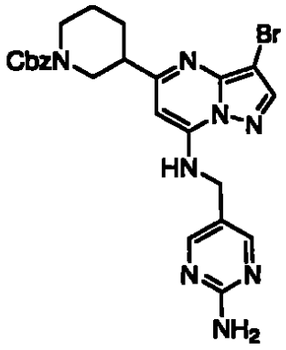
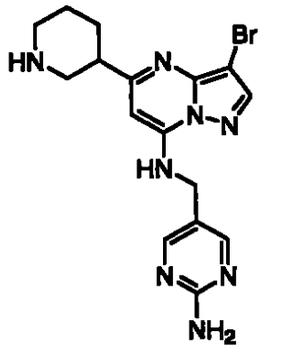
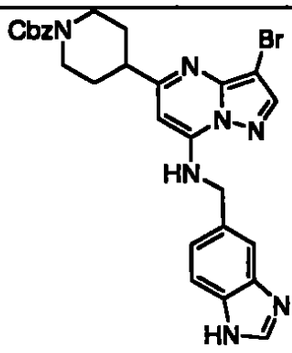
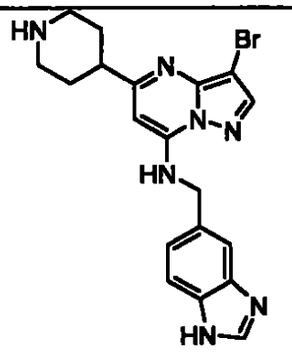
EJEMPLOS 463-472:

Esencialmente con el mismo procedimiento indicado en el Ejemplo 462 sustituyendo únicamente los compuestos que se muestran en la Columna 2 de la Tabla 38, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 38.

TABLA 38

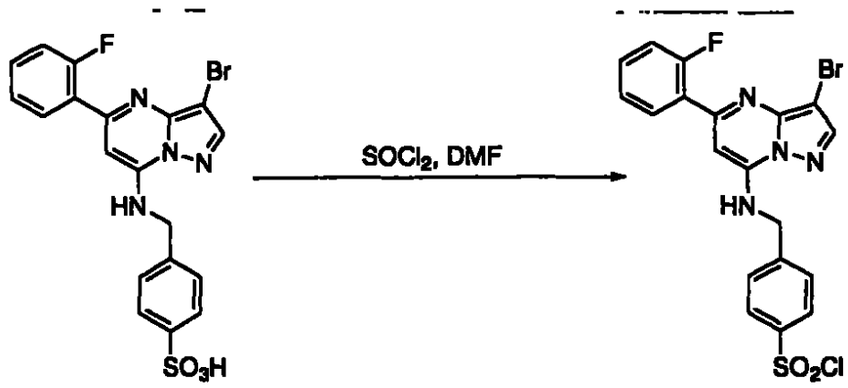
Ej.	Columna 2	Columna 3	COMP.
463			MH^+ = 403 ^{1}H RMN (300 MHz, $CDCl_3$) δ 8,52 (s, 1H), 8,38 (d, 1H), 8,04 (s, 1H), 7,78 (d, 1H), 7,65 (t, 1H), 6,18 (s, 1H), 4,89 (s, 2H), 3,26 – 3,21 (d, 2H), 2,96 – 2,70 (m, 3H), 2,05 – 1,78 (m, 4H).
464			MH^+ = 454 p.f. = 175,4 °C
465			Rend. = 87 MH^+ = 470 p.f. = 220°C p.f. (sal de clorhidrato) = 164,3°C

466			$MH^+ = 464$ p.f. = 206 °C
467			$MH^+ = 411$ p.f. = 169,5 °C
468			$MH^+ = 334$ p.f. = 176,2 °C
469			$MH^+ = 465$ p.f. = 250,4 °C

470			MH^+ = 387 p.f. = 68,5°C
471			MH^+ = 387 p.f. = 59,4°C
472			1. p.f. = 230-232 2. M+H = 396
472. 10			1. p.f. = 157-160 2. M+H = 427

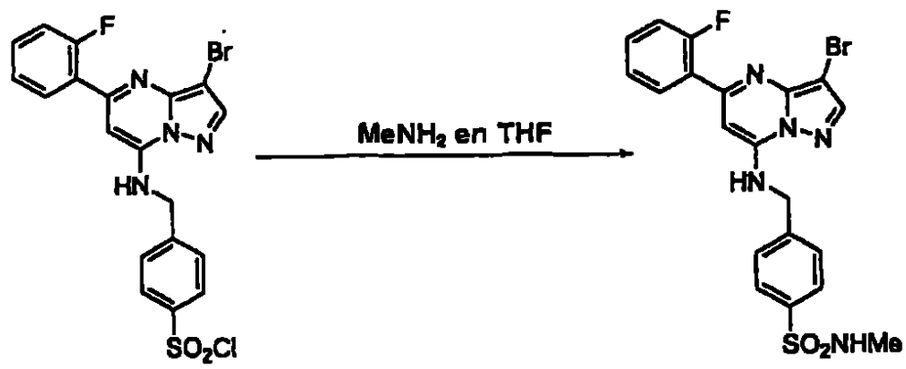
EJEMPLO 473:

<u>Etapa A:</u>



Una solución del ácido sulfónico (560 mg, 1,17 mmol) en 5 ml de DMF seco se enfrió a 0°C y se agregó $SOCl_2$ (278 mg, 2,34 mmol). La mezcla de reacción se llevó a temperatura ambiente y se agitó durante la noche. Al día siguiente se vertió el contenido sobre hielo y se ajustó el pH cuidadosamente a 8. El producto se extrajo en EtOAc y el solvente se extrajo después de secado (Na_2SO_4) para proporcionar 240 mg (41%) del cloruro de sulfonilo crudo el cual se usó para la Etapa siguiente 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).

Etapa B:

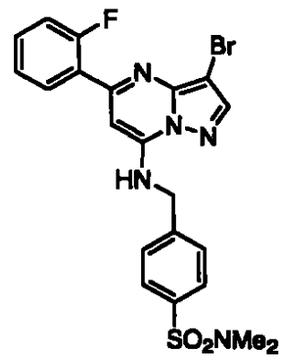


Una solución del compuesto preparado en el Ejemplo 473, Etapa A (120 mg, 0,24 mmol) en 10 ml de THF se trató con 2 ml de $MeNH_2$ 1 M (2,00 mmoles)

en THF a temperatura ambiente durante la noche. El solvente se extrajo y el residuo se purificó por cromatografía (sílice, hexano:EtOAc (4:1→1:1)) para proporcionar 56 mg (48%) de la sulfonamida. ^{1}H RMN (DMSO-d6) δ 9,05 (t, J = 9 Hz, 1H), 8,35 (s, 1H), 7,90 (t, J = 7,5 Hz, 1H), 7,75 (d, J = 9 Hz, 2H), 7,62 (d, J = 9 Hz, 2H), 7,55-7,46 (m, 1H), 7,45-7,38 (m, 1H), 7,38-7,25 (m, 1H), 6,50 (s, 1H), 4,80 (d, 2H), 3,30 (s, 3H)

LCMS: MH^+ = 492,1

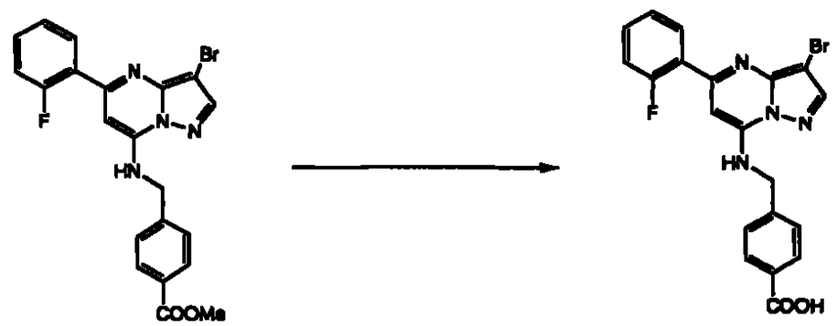
EJEMPLO 474:



Esencialmente con el mismo procedimiento indicado en el Ejemplo 473, sustituyendo únicamente dimetilamina, se preparó el compuesto anterior. ^{1}H RMN ($CDCl_3$) δ 8,14 (t, J = 9 Hz, 1H), 8,00 (s, 1H), 7,76 (d, J = 9 Hz, 2H), 7,54 (d, J = 9 Hz, 2H), 7,34-7,44 (m, 1H), 7,26 (t, J = 9 Hz, 1H), 7,14-7,04 (m, 1H), 6,93 (t, J= 6 Hz, 1H), 6,45 (s, 1H), 4,75 (d, 2H), 2,70 (s, 6H).

LCMS: MH^+ = 504,2

EJEMPLO 475:

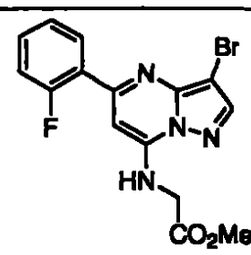
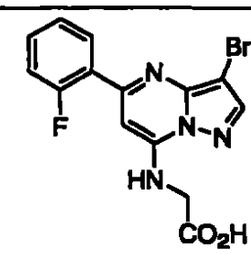
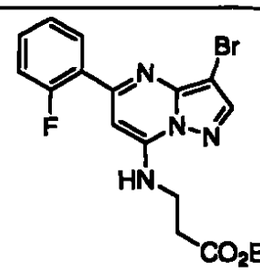
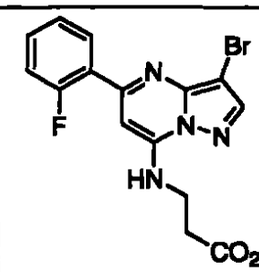


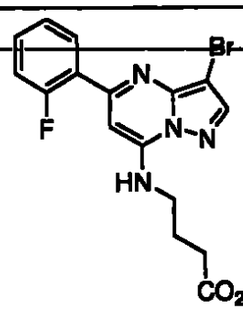
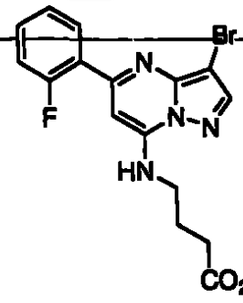
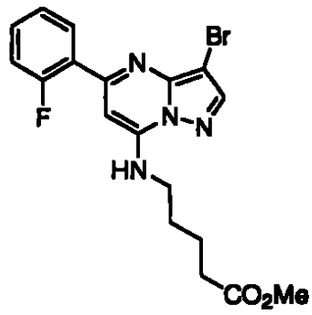
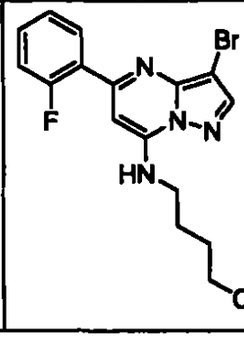
Una mezcla del compuesto preparado en el Ejemplo 129 (300 mg, 0,66 mmol), NaOH (5 g), CH_3OH -H_2O (100 ml, 90:10) se agitó a 25°C durante aproximadamente 15 horas. Se controló el progreso de la hidrólisis mediante TLC. La mezcla de reacción se concentró para remover el metanol. El concentrado se diluyó con 50 ml de agua, y se extrajo con éter para remover cualquier éster no reaccionado. La solución acuosa así obtenida se neutralizó con HCl 3 N a pH 4 para obtener el ácido libre, se filtró y se lavó repetidamente con agua. El ácido se secó al vacío (270 mg, 93%) y se usó sin purificación adicional.

EJEMPLO 476-479:

Esencialmente con el mismo procedimiento indicado en el Ejemplo 475 sustituyendo únicamente los compuestos de la Columna 2 de la Tabla 39, se prepararon los compuestos de la Columna 3 de la Tabla 39.

Tabla 39

Ej.	Columna 2	Columna 3	COMP.
476			Rend. = 82% LCMS: MH^+ = 365
477			Rend. = 82% LCMS: MH^+ = 379

478			Rend. = 72% LCMS: MH^+ = 393
479			Rend. = 70% LCMS: MH^+ = 407

Los datos adicionales para los ejemplos seleccionados se muestran a continuación:

Ejemplo 476: ^{1}H RMN ($CDCl_3$) δ 8,15 (m, 2H), 8,0 (m, 1H), 7,6 (m, 1H), 7,3 (m, 2H), 6,6 (s, 1H), 4,2 (d, 2H).

Ejemplo 477: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,4 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 7,0 (t, 1H), 6,5 (s, 1H), 3,8 (dt, 2H), 2,6 (t, 2H).

Ejemplo 479: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,4 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 6,8 (t, 1H), 3,5 (dt, 2H), 2,4 (t, 2H), 1,8 (m, 4H).

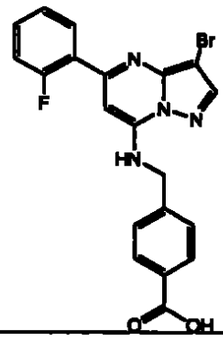
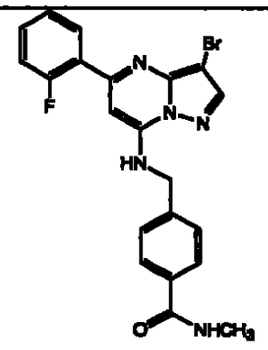
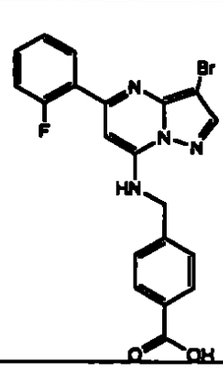
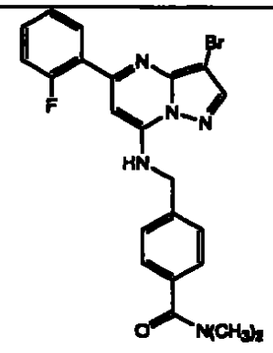
EJEMPLO 480:

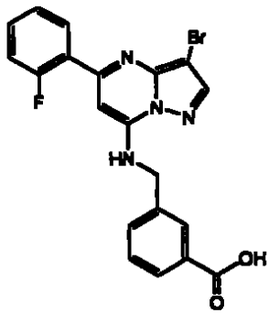
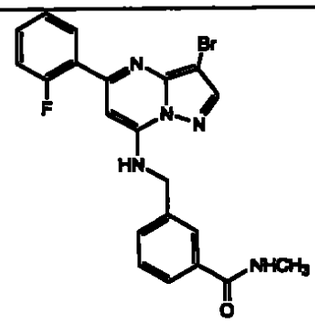
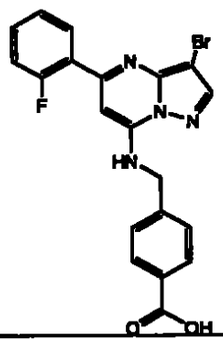
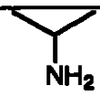
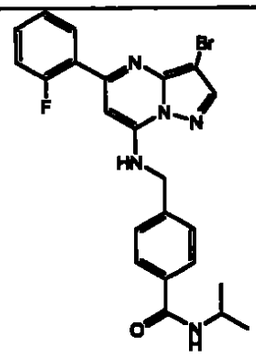
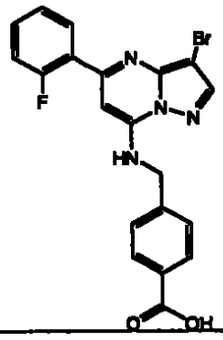
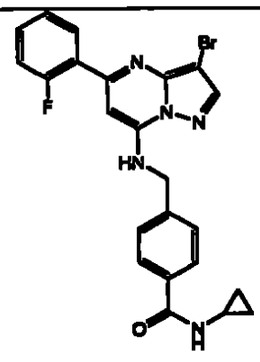
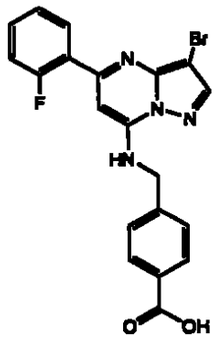
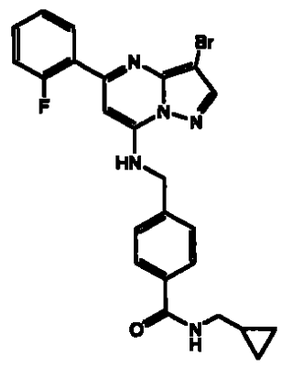
Una mezcla del ácido del Ejemplo 475 (85 mg, 0,193 mmol) y Et_3N (20 mg, 0,193 mmol) en THF (20 ml) se agitó a 25°C durante 15 minutos. Se agregó cloroformiato de isobutirilo (28 mg, 0,205 mmol) a la mezcla de reacción y se agitó durante 10 minutos seguido de adición de la solución de NH_4OH (0,5 ml). La mezcla de reacción se agitó durante 1 hora y se concentró hasta sequedad. La masa seca se purificó por cromatografía en columna.

EJEMPLOS 481-509:

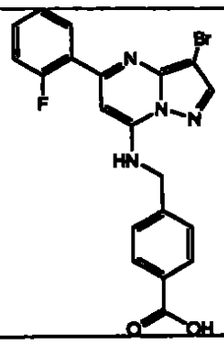
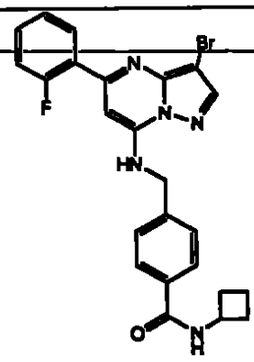
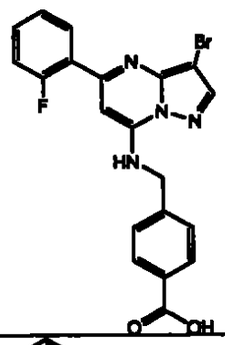
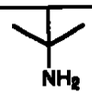
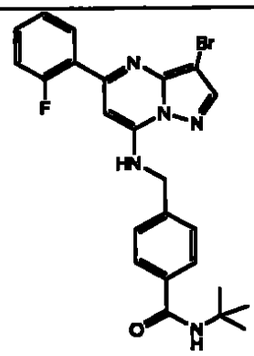
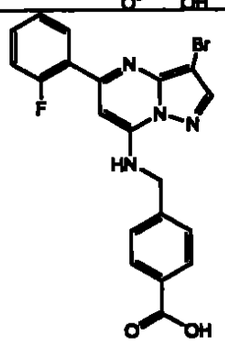
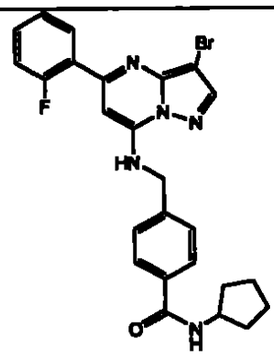
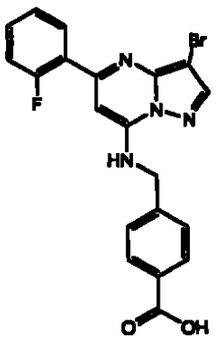
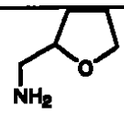
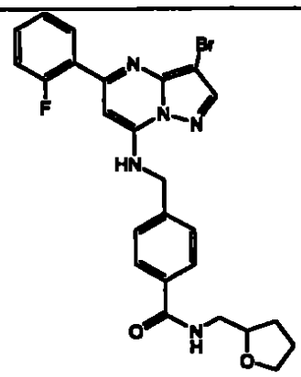
Esencialmente con el mismo procedimiento indicado en el Ejemplo 480 sustituyendo únicamente el ácido carboxílico que se muestra en la Columna 2 de la Tabla 40 y la amina que se muestra en la Columna 3 de la Tabla 40, se prepararon los compuestos que se muestran en la Columna 4 de la Tabla 40.

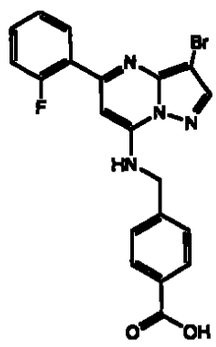
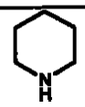
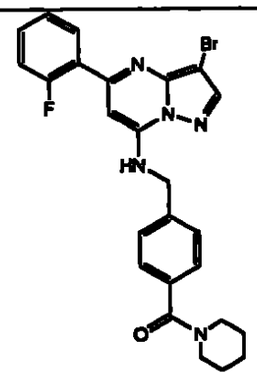
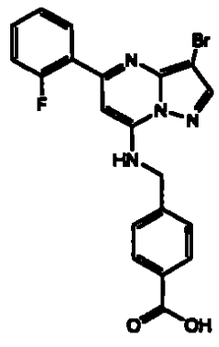
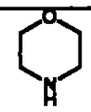
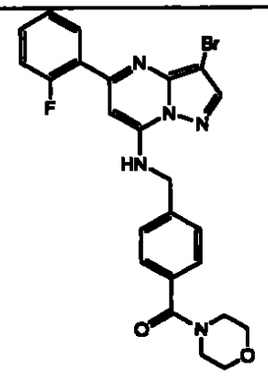
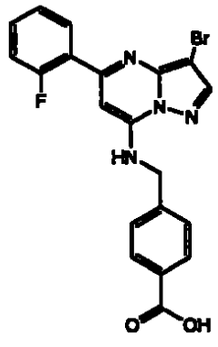
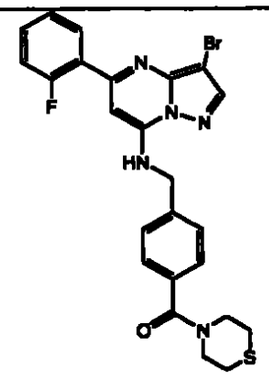
Tabla 40

Ej.	Columna 2	Columna 3	Columna 4	COMP.
481		CH_3NH_2		Rend. = 88% LCMS: MH^+ = 454
482		$(CH_3)_2NH$		Rend. = 80% LCMS MH^+ = 468

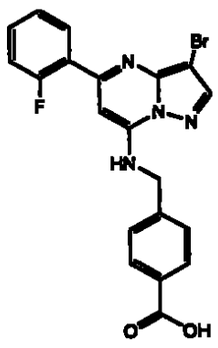
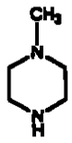
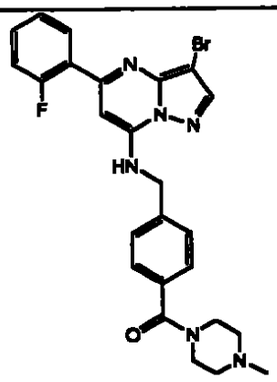
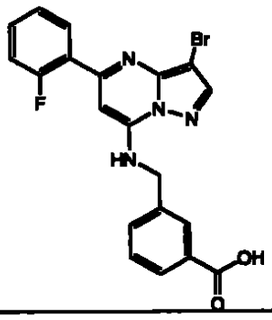
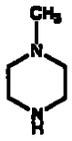
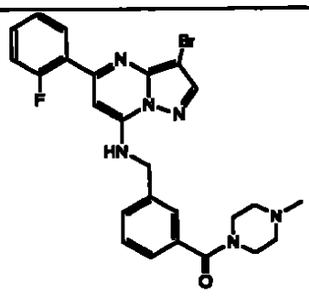
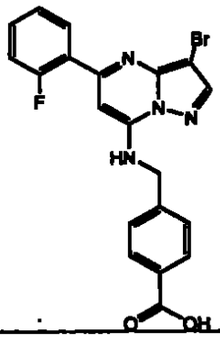
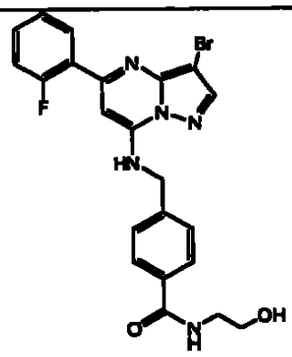
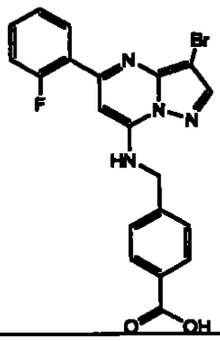
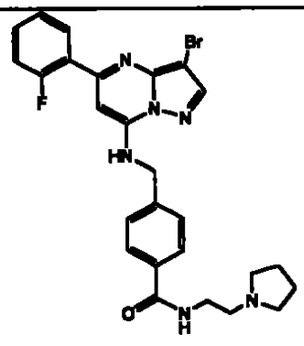
483		CH_3NH_2		Rend. = 70% LCMS MH^+ = 454
484				Rend. = 75% LCMS MH^+ = 482,1
485				Rend. = 71% LCMS MH^+ = 480,1
486				Rend. = 75% LCMS MH^+ = 494,1

626
629

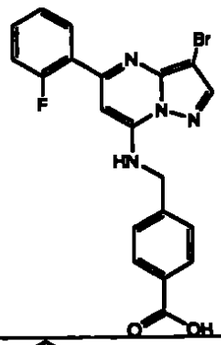
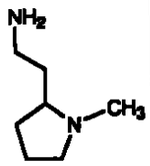
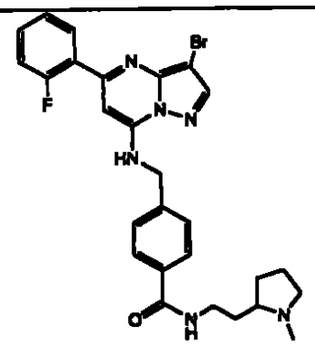
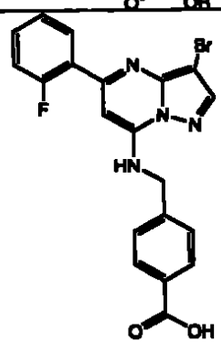
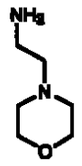
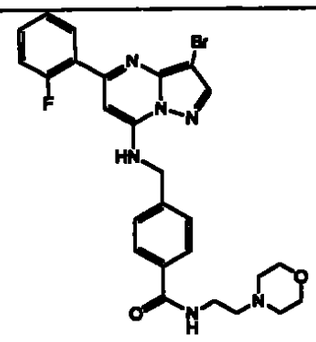
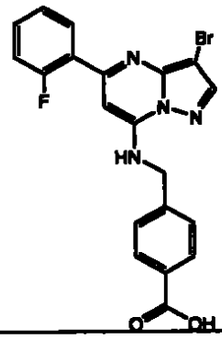
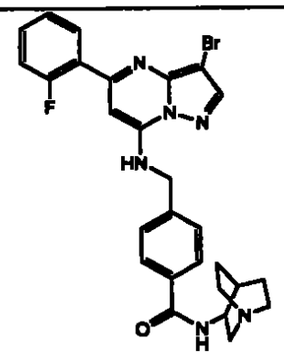
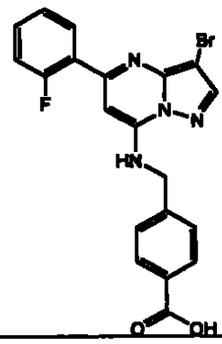
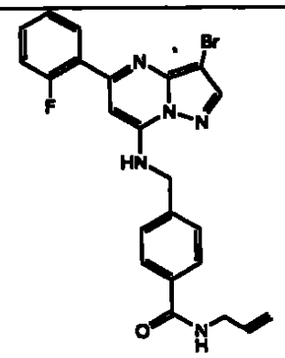
487				Rend. = 75% MH^+ = 494,1
488				Rend. = 75% MH^+ = 496,1
489				Rend. = 75% LCMS MH^+ = 508,1
490				Rend. = 78% LCMS MH^+ = 524,1

491				Rend. = 73% LCMS MH^+ = 508,1
492				Rend. = 73% LCMS MH^+ = 510,1
493				Rend. = 76% LCMS MH^+ = 526,1

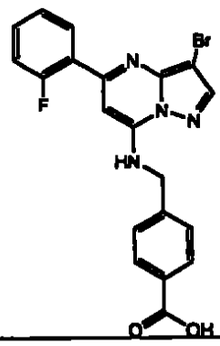
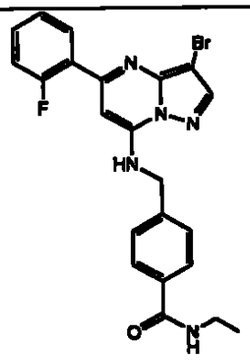
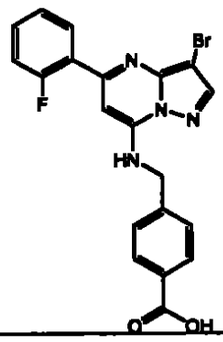
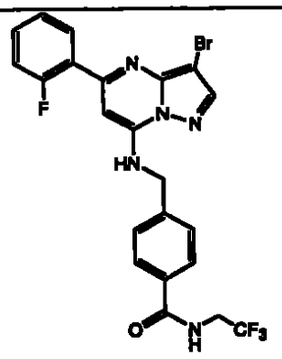
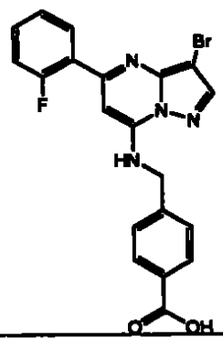
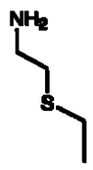
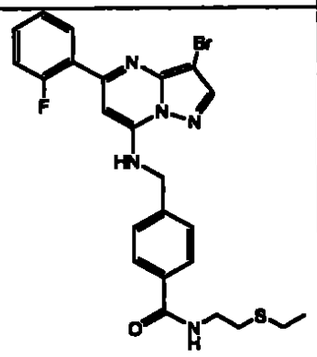
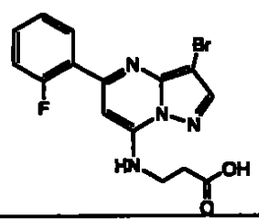
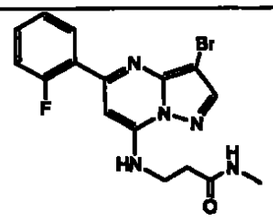
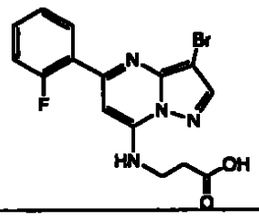
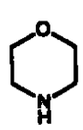
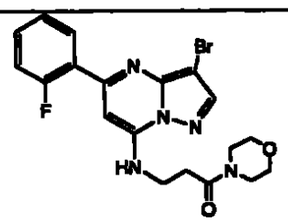
f98
0631

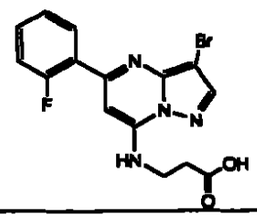
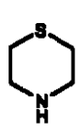
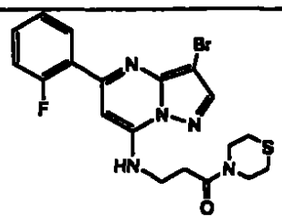
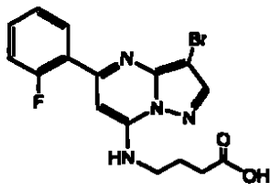
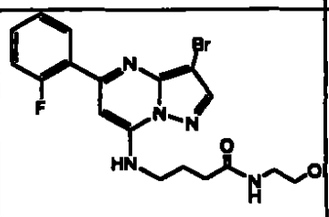
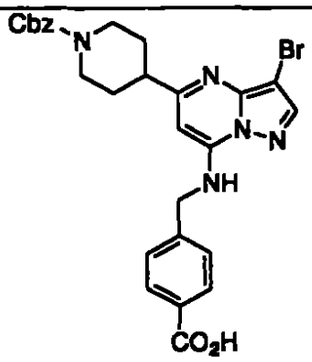
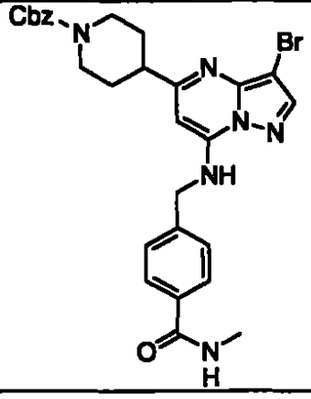
494				Rend. = 76% MH^+ = 523,1
495				Rend. = 76% MH^+ = 523,1
496				Rend. = 51% LCMS MH^+ = 484,1
497				Rend. = 66% MH^+ = 537,1

632

498				Rend. = 76% LCMS MH^+ = 551,2
499				Rend. = 79% LCMS MH^+ = 552,1
500				Rend. = 80% LCMS MH^+ = 549,1
501				Rend. = 80% LCMS MH^+ = 478,1

130
633

502				Rend. = 80% LCMH$^+$ = 468,1
503				Rend. = 80% MH$^+$ = 522,1
504				Rend. = 82% LCMS MH$^+$ = 528,1
505		CH_3NH_2		Rend. = 60% MH$^+$ = 392
506				Rend. = 60% LCMH$^+$ = 448,1

507				Rend. = 70% MH^+ = 464,1
508				Rend. = 50% LCMS MH^+ = 436,1
508.10		CH_3NH_2		Rend. = 92 MH^+ = 577

Los datos adicionales para los ejemplos seleccionados se proporcionan a continuación:

Ejemplo 481: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,7 (d, 2H), 7,4 (s, 1H), 7,35 (d, 2H), 7,25 (dd, 1H), 7,1 (dd, 1H), 6,95 (t, 1H), 6,5 (s, 1H), 6,25 (bs, 1H), 4,7 (d, 2H), 3,0 (d, 3H).

Ejemplo 482: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,45 – 7,35 (m, 4H), 7,25 (d, 2H), 7,15 (dd, 1H), 6,7 (t, 1H), 6,5 (s, 1H), 4,7 (d, 2H), 3,1 (s, 3H), 3,0 (s, 3H).

Ejemplo 483: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,8 (bs, 1H), 7,7 (d, 1H), 7,5 – 7,3 (m, 3H), 7,25 (d, 1H), 7,15 (dd, 1H), 6,75 (t, 1H), 6,5 (s, 1H), 6,2 (bs, 1H), 4,7 (d, 2H), 3,0 (d, 3H).

Ejemplo 484: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,7 (d, 2H), 7,4 (d, 2H), 7,35 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 6,8 (t, 1H), 6,5 (s, 1H), 6,0 bs, 1H), 4,7 (d, 2H), 4,25 (m, 1H), 1,2 (d, 6H).

Ejemplo 485: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,7 (d, 2H), 7,4 (d, 2H), 7,35 (s, 1H), 7,25 (dd, 1H), 7,1 (dd, 1H), 6,9 (t, 1H), 6,5 (s, 1H), 6,3 (t, 1H), 4,7 (d, 2H), 2,9 (m, 1H), 0,8 (bt, 2H), 0,6 (bt, 2H).

Ejemplo 486: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,8 (d, 2H), 7,4 (d, 2H), 7,35 (d, 1H), 7,25 (dd, 1H), 7,1 (dd, 1H), 6,9 (t, 1H), 6,5 (s, 1H), 6,2 (t, 1H), 4,7 (d, 2H), 3,3 (dd, 2H), 1,05 (m, 1H), 0,5 (m, 2H), 0,25 (m, 2H).

Ejemplo 487: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,7 (d, 2H), 7,4 (d, 2H), 7,35 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 6,85 (t, 1H), 6,5 (s, 1H), 6,2 (bs, 1H), 4,7 (d, 2H), 4,6 (m, 1H), 2,4 (m, 2H), 1,95 (m, 1H), 1,75 (m, 2H).

Ejemplo 488: ^{1}H RMN ($CDCl_3$) δ 8,5 (t, 1H), 8,15 (dt, 1H), 8,0 (s, 1H), 7,7 (d, 2H), 7,4 (d, 2H), 7,35 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 6,8 (t, 1H), 6,5 (s, 1H), 5,9 (bs, 1H), 4,7 (d, 2H), 1,4 (s, 9H).

Ejemplo 489: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,7 (d, 2H), 7,4 (d, 2H), 7,35 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 6,8 (t, 1H), 6,5 (s, 1H), 6,0 bs, 1H), 4,7 (d, 2H), 4,4 (m, 1H), 2,05 (m, 2H), 1,7 (m, 4H), 1,4 (m, 2H).

Ejemplo 490: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,7 (d, 2H), 7,4 (d, 2H), 7,35 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 6,8 (t, 1H), 6,5 (s, 1H), 6,5 (bs, 2H), 4,7 (d, 2H), 4,1 (m, 1H), 3,9 – 3,7 (m, 3H), 3,3 (m, 1H), 2,0 – 1,9 (m, 4H).

Ejemplo 491: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,45 – 7,35 (m, 5H), 7,25 (dd, 1H), 7,1 (dd, 1H), 6,8 (t, 1H), 6,5 (s, 1H), 4,7 (d, 2H), 3,7 (bs, 2H), 3,3 (bs, 2H), 1,7 (bs, 4H), 1,5 (bs, 2H).

Ejemplo 492: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,45 – 7,35 (m, 5H), 7,25 (dd, 1H), 7,1 (dd, 1H), 6,85 (t, 1H), 6,5 (s, 1H), 4,7 (d, 2H), 3,8 – 3,4 (bm, 8H).

~~**Ejemplo 493:** ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,45 – 7,35 (m, 5H),~~ 7,25 (dd, 1H), 7,1 (dd, 1H), 6,80 (t, 1H), 6,5 (s, 1H), 4,7 (d, 2H), 4,0 (m, 2H), 3,6 (m, 2H), 2,8 – 2,45 (m, 4H).

Ejemplo 494: ^{1}H RMN (CH3OD) δ 8,15 (s, 1H), 8,0 (dt, 1H), 7,45 – 7,35 (m, 5H), 7,25 (dd, 1H), 7,1 (dd, 1H), 6,80 (t, 1H), 6,5 (s, 1H), 4,7 (d, 2H), 3,7 (bs, 2H), 3,4 (bs, 2H), 2,5 – 2,4 (m, 4H), 2,2 (s, 3H).

Ejemplo 495: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,45 – 7,35 (m, 5H), 7,25 (dd, 1H), 7,1 (dd, 1H), 6,80 (t, 1H), 6,5 (s, 1H), 4,7 (d, 2H), 3,75 (bs, 2H), 3,35 (bs, 2H), 2,4 (bs, 2H), 2,3 (s, 3H), 2,2 (bs, 2H).

Ejemplo 496: ^{1}H RMN ($CDCl_3$) δ 7,95 (s, 1H), 7,9 (dt, 1H), 7,8 (t, 1H), 7,7 (d, 2H), 7,15 (m, 4H), 7,05 (dd,1H), 6,9 (dd, 1H), 6,2 (s,1H), 4,5 (d, 2H), 3,6 (t, 2H), 3,3 (dt, 2H).

Ejemplo 497: ^{1}H RMN (CH3OD) δ 8,1 (s, 1H), 7,9 (dt, 1H), 7,8 (d, 2H), 7,5 (d, 2H), 7,4 (m, 1H), 7,3 (dd, 1H), 7,2 (dd, 1H), 6,4 (s, 1H), 4,7 (d, 2H), 3,5 (t, 2H), 2,7 (m, 2H), 2,6 (bs, 4H), 1,8 (bs, 4H).

Ejemplo 498: ^{1}H RMN ($CDCl_3$) δ 8,5 (t, 1H), 8,15 (dt, 1H), 8,0 (s, 1H), 7,8 (d, 2H), 7,4 (d, 2H), 7,35 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 6,8 (t, 1H), 6,5 (s, 1H), 4,7 (d, 2H), 3,7 – 2,5 (m, 4H), 2,35 (s, 3H), 2,2 (m, 1H), 1,9 – 1,6 (m, 6H).

Ejemplo 499: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,8 (d, 2H), 7,4 (d, 2H), 7,35 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 6,8 (t, 1H), 6,5 (s, 1H), 4,7 (d, 2H), 3,7 (m, 4H), 3,5 (dt, 2H), 2,6 (t, 2H), 2,5 (m, 4H).

Ejemplo 500: ^{1}H RMN (CH3OD) δ 8,15 (s, 1H), 7,9 (dt, 1H), 7,8 (d, 2H), 7,45 (d, 2H), 7,4 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 6,4 (s, 1H), 4,75 (d, 2H), 4,2 (m, 1H), 3,4 – 2,8 (m, 7H), 1,9 – 1,6 (m, 4H).

Ejemplo 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).

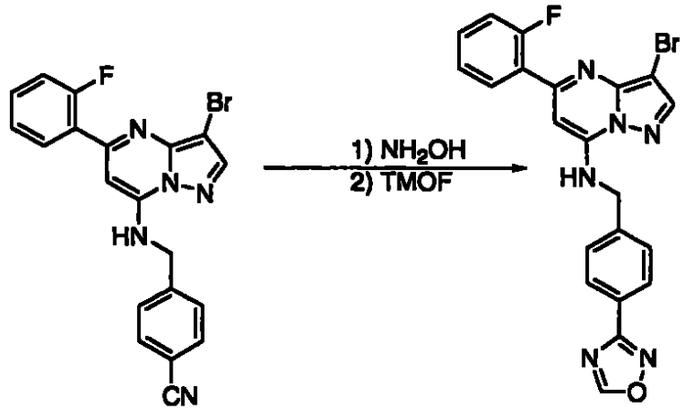
Ejemplo 505: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,4 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 7,0 (t, 1H), 6,5 (s, 1H), 3,8 (m, 2H), 2,7 (t, 2H), 3,0 (d, 3H).

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:



sustituyendo únicamente el compuesto preparado en el Ejemplo Preparativo 192, se preparó el compuesto anterior. Rendimiento = 75; MH^+ = 453; p.f. = 79,3°C.

Ejemplo 502: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,75 (d, 2H), 7,45 (s, 1H), 7,4 (d, 2H), 7,3 (dd, 1H), 7,1 (dd, 1H), 6,8 (t, 1H), 6,5 (s, 1H), 6,1 (bs, 1H), 4,7 (d, 2H), 3,5 (dq, 2H), 1,2 (t, 3H).

Ejemplo 503: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,8 (d, 2H), 7,4 (d, 2H), 7,35 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 6,9 (t, 1H), 6,5 (s, 1H), 6,4 (t, 1H), 4,75 (d, 2H), 4,1 (m, 2H).

Ejemplo 504: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,8 (d, 2H), 7,45 (d, 2H), 7,4 (m, 1H), 7,25 (dd, 1H), 7,1 (dd, 1H), 6,8 (t, 1H), 6,6 (t, 1H), 6,5 (s, 1H), 4,7 (d, 1H), 3,6 (m, 2H), 2,8 (t, 2H), 2,6 (q, 2H), 1,3 (t, 3H).

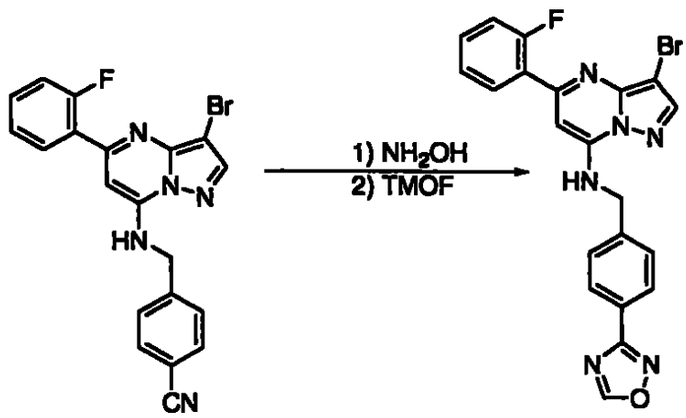
Ejemplo 505: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,4 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 7,0 (t, 1H), 6,5 (s, 1H), 3,8 (m, 2H), 2,7 (t, 2H), 3,0 (d, 3H).

Ejemplo 506: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,4 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 7,0 (t, 1H), 6,5 (s, 1H), 3,8 (m, 2H), 3,6 (m, 6H), 3,4 (m, 2H), 2,7 (t, 2H).

Ejemplo 507: ^{1}H RMN ($CDCl_3$) δ 8,15 (dt, 1H), 8,0 (s, 1H), 7,4 (m, 1H), 7,25 (dd, 1H), 7,15 (dd, 1H), 7,0 (t, 1H), 6,5 (s, 1H), 3,9 (t, 2H), 3,8 (dt, 2H), 3,7 (t, 2H), 2,7 (t, 2H), 2,6 (m, 4H).

Ejemplo 508: ^{1}H RMN (CH_3OD) δ 8,1 (s, 1H), 7,95 (dt, 1H), 7,5 (m, 1H), 7,35 – 7,2 (m, 2H), 6,5 (s, 1H), 3,6 (m, 4H), 3,25 (m, 4H), 2,4 (t, 2H), 2,05 (dt, 2H).

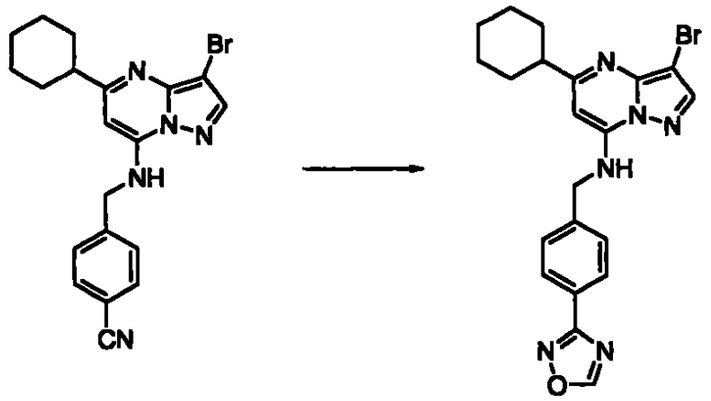
EJEMPLO 509:



Una solución de NaOH (59 mg, 1,47 mmol) en 1 ml de agua se agregó a una suspensión de $NH_2OH.HCl$ (102 mg, 1,47 mmol) en 10 ml de metanol a 0°C. Después de 5 minutos, se agregó el compuesto preparado en el Ejemplo 210.10 (208 mg, 0,49 mmol) y la mezcla de reacción se reflujó durante la noche. El solvente se extrajo al vacío y el residuo se dividió entre agua y EtOAc. La capa de EtOAc se secó (Na_2SO_4) y el solvente se evaporó. La amidoxima cruda resultante se suspendió en ortoformiato de trimetilo que contenía una cantidad catalítica de ácido PTS y se reflujó durante la noche. El solvente se extrajo y el residuo se recogió en EtOAc. Se lavó la capa de EtOAc con $NaHCO_3$ acuoso seguido de agua y salmuera. El solvente se evaporó y el residuo se purificó por cromatografía (sílice, hexano:EtOAc (1:1)) para proveer 80 mg (35%) del oxadiazol. ^1H RMN ($CDCl_3$) δ 8,75 (s, 1H), 8,20-8,10 (m, 3H), 8,03 (s, 1H), 7,53 (d, J = 9 Hz, 2H), 7,45-7,36 (m, 1H), 7,30-7,22 (m, 2H), 7,16-7,08 (m, 1H), 6,80 (t, J = 5 Hz, 1H), 6,56 (s, 1H).

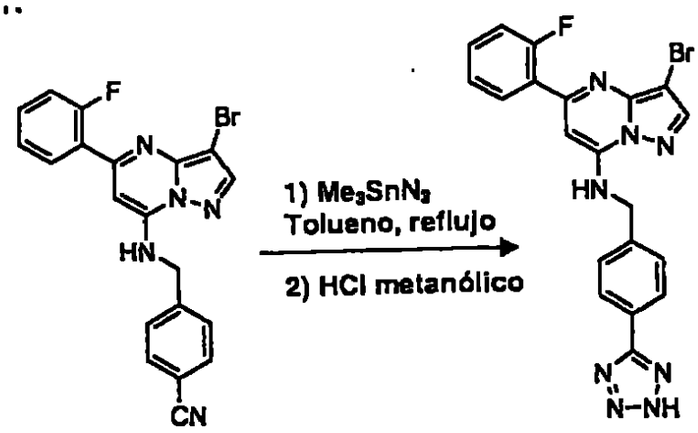
LCMS: MH^+ = 465,2

Ejemplo 510:



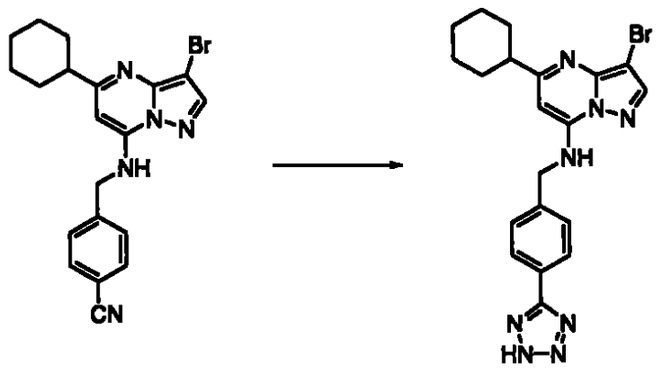
Esencialmente con el mismo procedimiento indicado en el Ejemplo 509 sustituyendo únicamente el compuesto preparado en el Ejemplo Preparativo 192, se preparó el compuesto anterior. Rendimiento = 75; MH^+ = 453; p.f. = 79,3°C.

EJEMPLO 511:



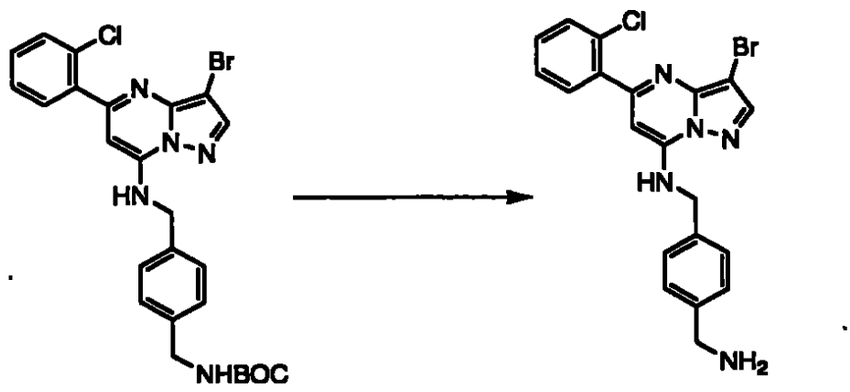
Una mezcla del nitrilo (235 mg, 0,56 mmol) y Me_3SnN_3 (343 mg, 1,67 mmol) en 20 ml de tolueno seco se reflujó durante 2 días bajo Ar. El solvente se extrajo al vacío y el residuo se disolvió en metanol seco. Se hizo burbujear gas HCl a través de la solución durante 15 minutos y la mezcla de reacción se dejó en reposo durante la noche a temperatura ambiente. Al día siguiente se extrajo el solvente, se recogió el residuo en agua y se ajustó el pH a 5. El producto precipitado se extrajo en EtOAc. La evaporación de la capa de EtOAc después del secado (Na_2SO_4) proporcionó el residuo el cual se purificó por cromatografía (sílice, DCM:MeOH (98:2→95:5)) para proporcionar 50 mg (19%) del tetrazol puro. ^1H RMN (CD_3OD) δ 8,10 (s, 1H), 8,00 (d, J = 9 Hz, 2H), 7,90 (t, J = 7 Hz, 1H), 7,65 (d, J = 9 Hz, 2H), 7,50-7,40 (m, 1H), 7,30-7,10 (m, 2H), 6,45 (s, 1H), 4,80 (s, 2H); LCMS: MH^+ = 465,0

EJEMPLO 512:



Esencialmente con el mismo procedimiento indicado en el Ejemplo 511 sustituyendo únicamente el compuesto preparado en el Ejemplo 192, se preparó el compuesto anterior. Rendimiento = 64; MH^+ = 453; p.f. = 238,9°C.

EJEMPLO 513:



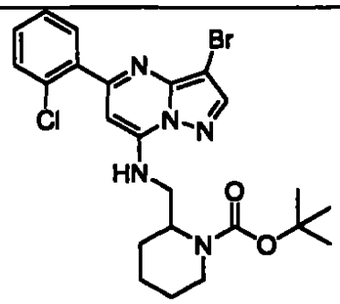
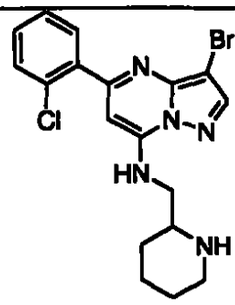
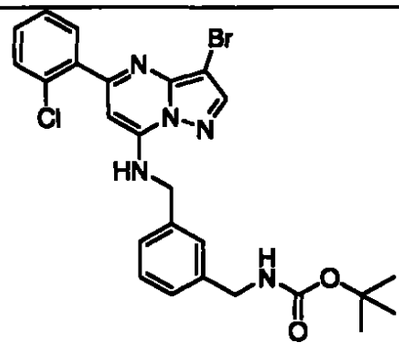
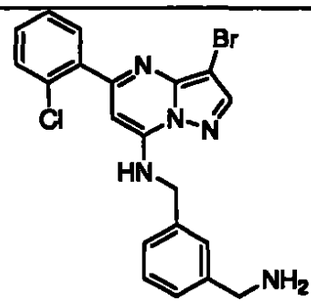
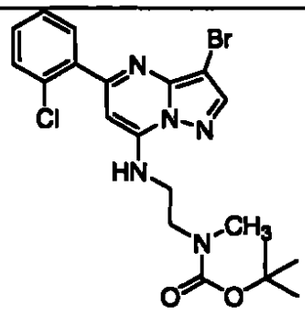
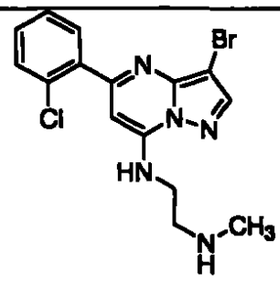
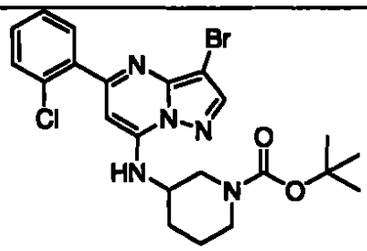
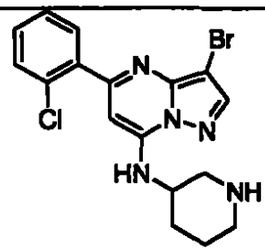
El compuesto preparado en el Ejemplo 157 se disolvió en dioxano (30 ml) y se le agregó una solución de HCl-dioxano (4 M, 30 ml). La mezcla de reacción se agitó a temperatura ambiente durante 4 horas. La mezcla de reacción se evaporó bajo presión reducida y se agregó acetato de etilo (200 ml). La solución orgánica se lavó con hidróxido de sodio 1 N seguido de salmuera saturada, La capa orgánica se secó sobre sulfato de sodio anhidro y se evaporó bajo presión reducida. MH^+ = 442,1

EJEMPLO 514-526:

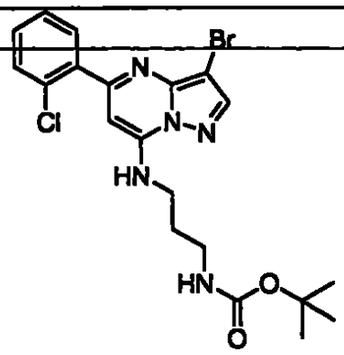
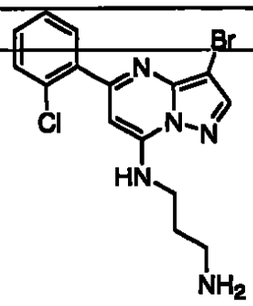
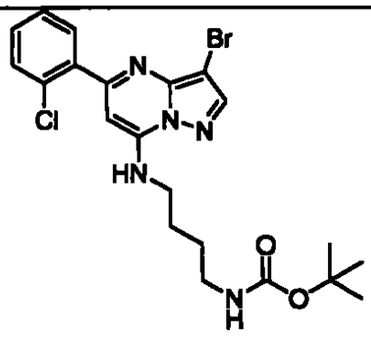
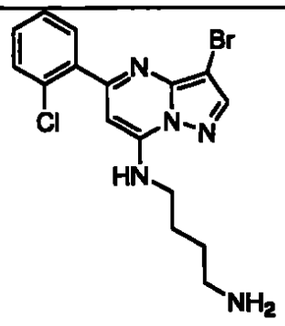
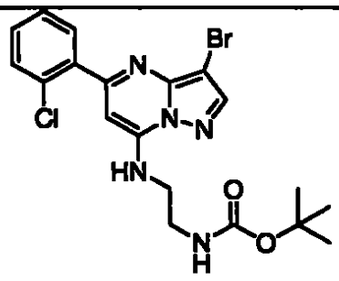
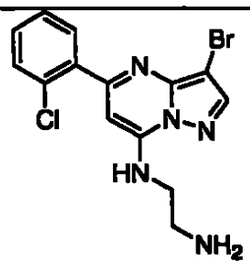
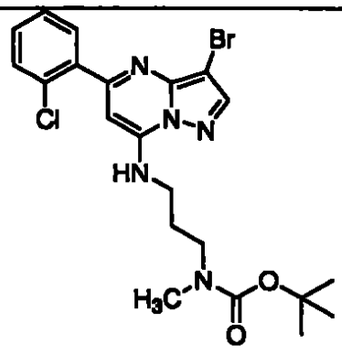
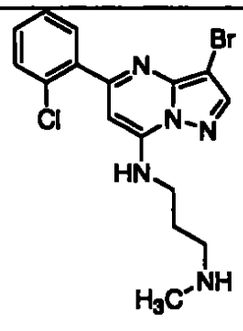
Esencialmente con el mismo procedimiento indicado en el Ejemplo 513, sustituyendo únicamente los compuestos que se muestran en la Columna 2 de la

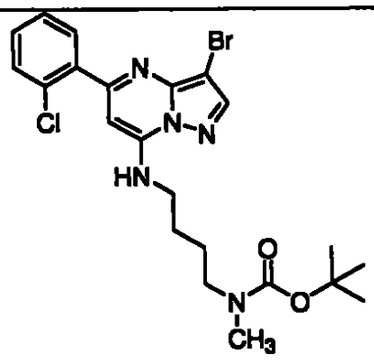
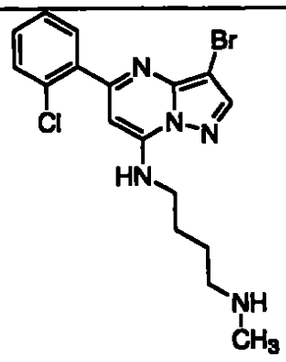
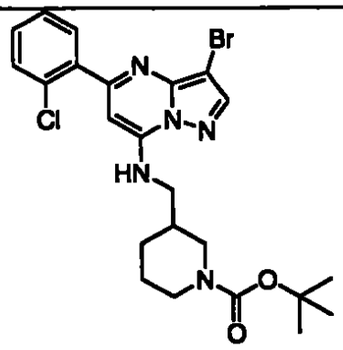
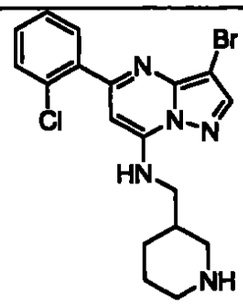
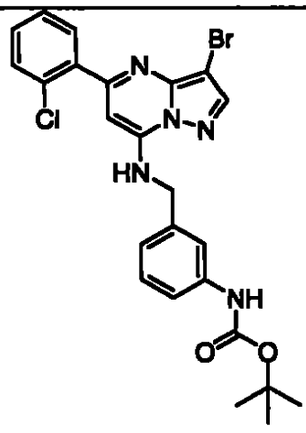
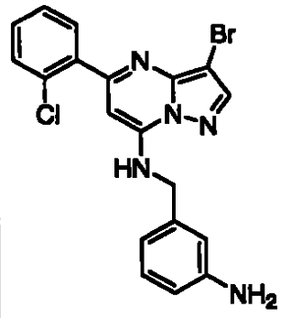
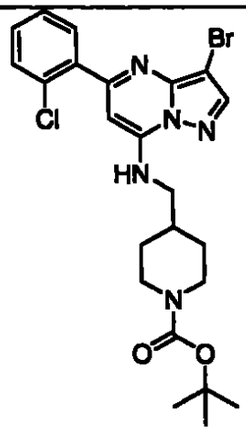
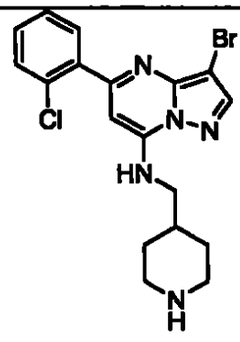
Tabla 41, se prepararon los compuestos que se muestran en la Columna 3 de la Tabla 41.

TABLA 41

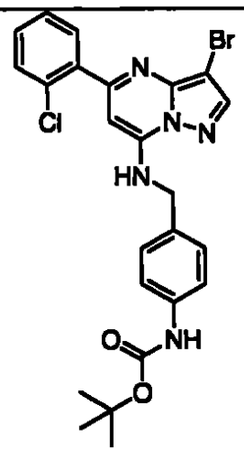
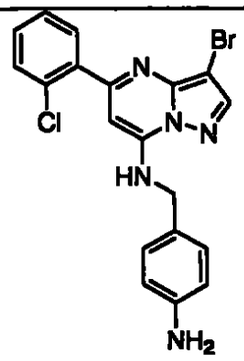
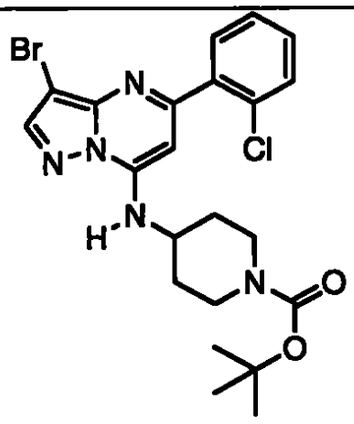
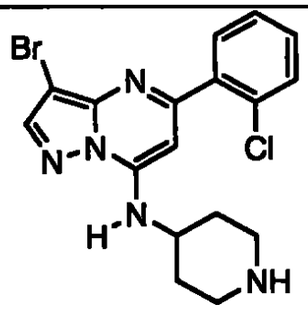
Ej.	Columna 2	Columna 3	COMP.
514			MH^+ = 420,1
515			MH^+ = 442,1
516			MH^+ = 380,1
517			MH^+ = 406,1

642

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

644

526			MH^+ = 428,1
526.10			

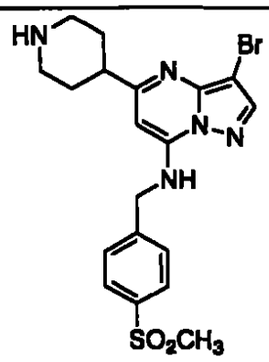
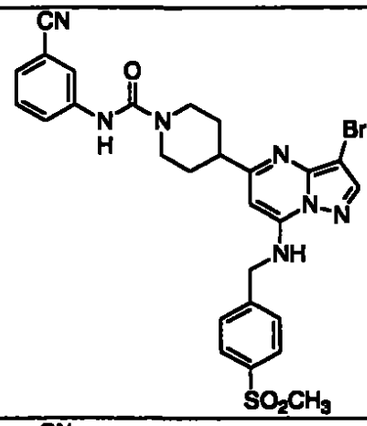
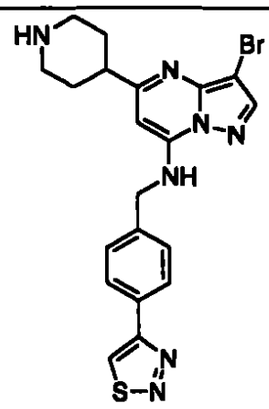
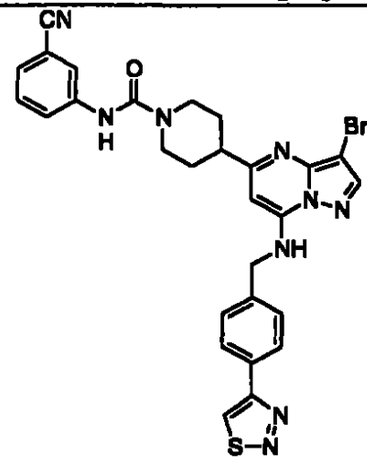
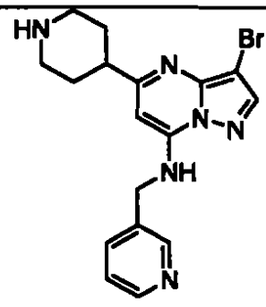
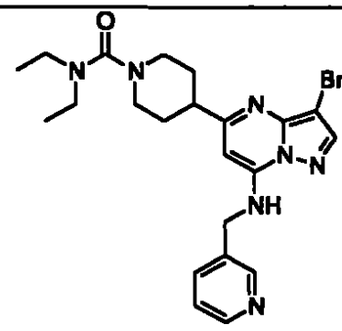
EJEMPLOS 528-564:

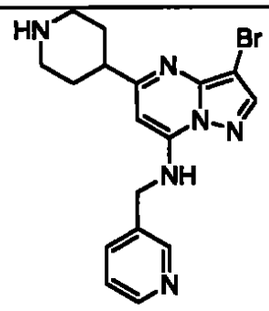
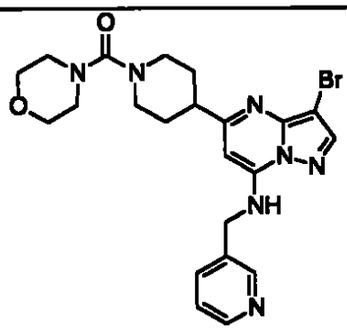
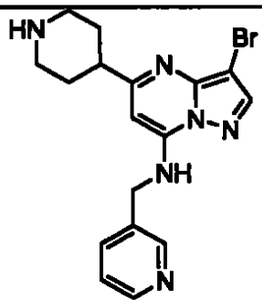
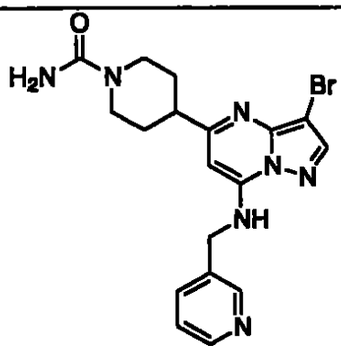
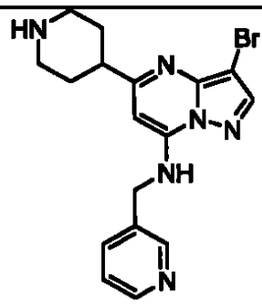
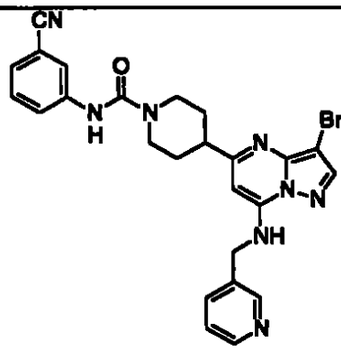
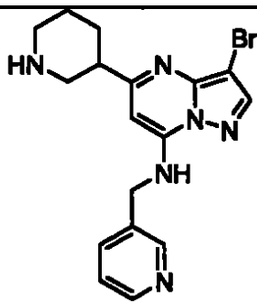
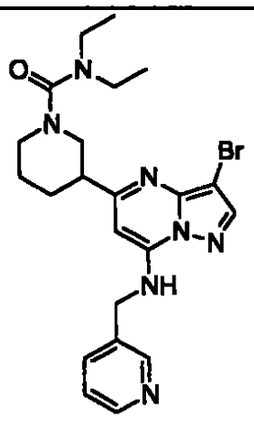
Procedimiento general para la formación de una colección paralela de 5-piperidinilo

A una mezcla del material de partida (80 mg, 0,21 mmol) que se muestra en la Columna 2 de la Tabla 42 en CH_2Cl_2 anhidro (1,5 ml) se le agregó DIPEA (75 µl, 0,42 mmol) y el reactivo de taponamiento apropiado (1,1 equiv., 0,23 mmol). Después de 1 a 2 horas, la mezcla de reacción se aplicó a una placa de TLC preparativa de 1000 micrones y subsiguientemente se reveló usando 8 - 10% de EtOH - CH_2Cl_2 como eluyente para proporcionar los compuestos que se muestran en la Columna 3 de la Tabla 42.

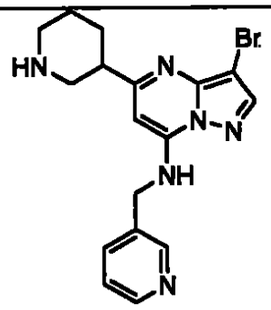
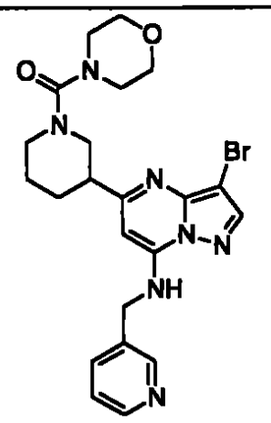
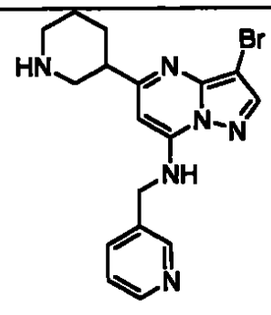
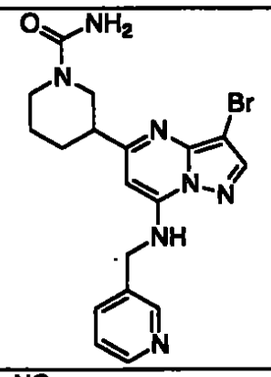
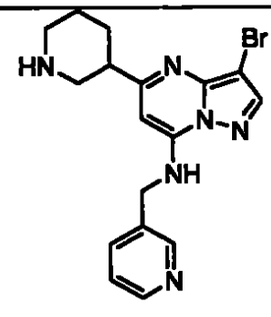
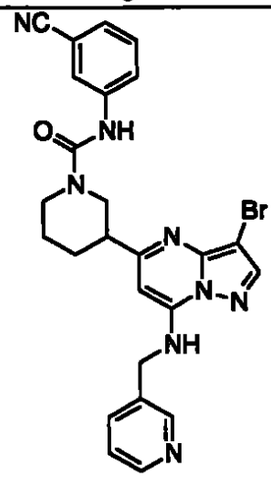
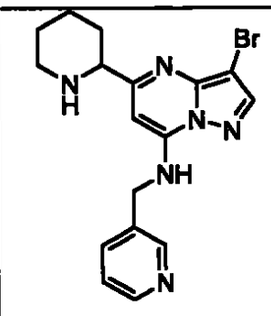
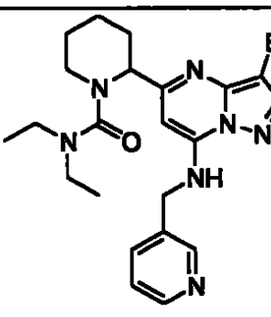
645

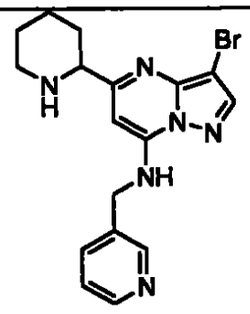
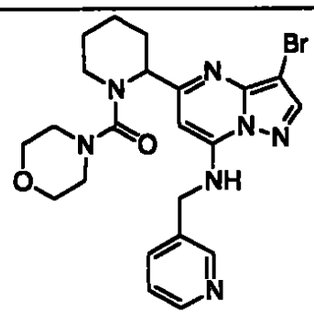
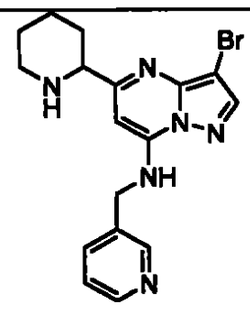
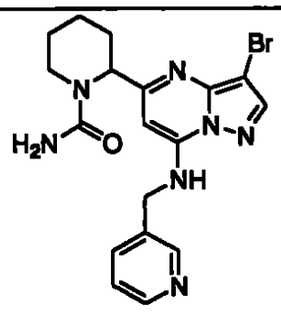
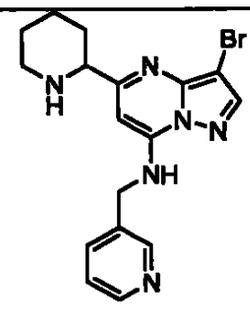
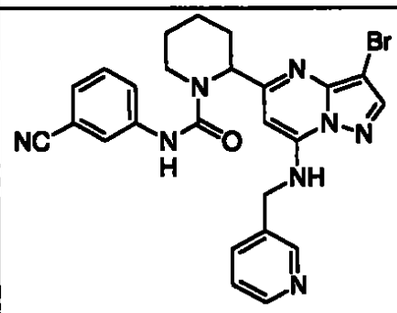
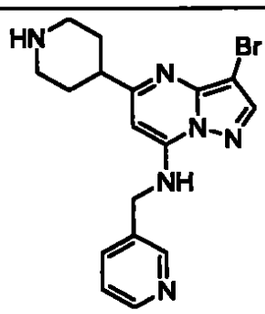
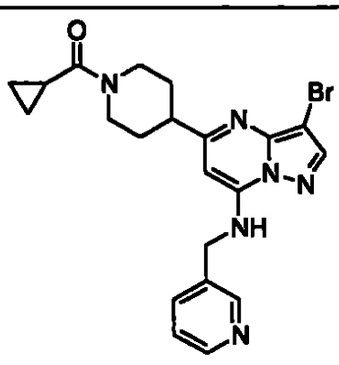
TABLA 42

Ej.	Columna 2	Columna 3	COMP.
528			MH^+ = 608 p.f. = 230,1°C
529			Rend. = 82 MH^+ = 614 p.f. = 235,4°C
530			MH^+ = 486 p.f. = 60,5°C

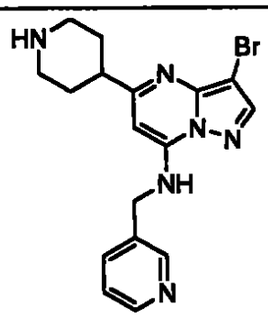
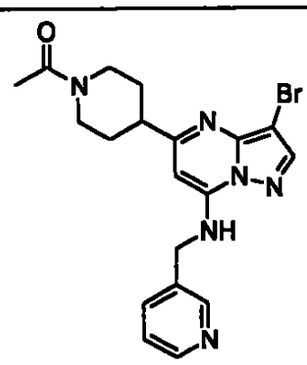
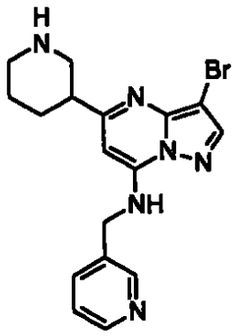
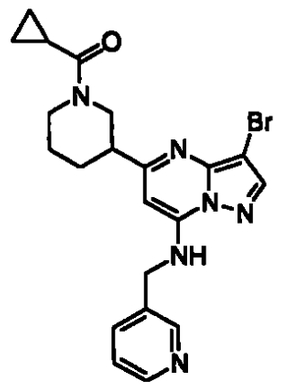
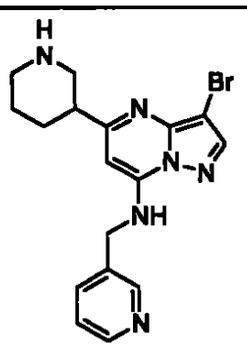
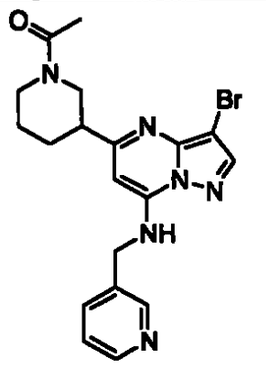
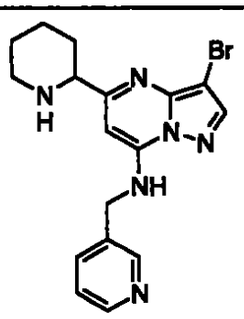
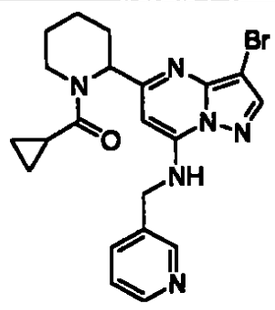
531			MH^+ = 500 p.f. = 113,6°C
532			MH^+ = 430 p.f. = 158,3 – 159,2°C
533			MH^+ = 531 p.f. =105,9°C
534			MH^+ = 486

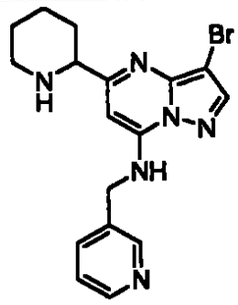
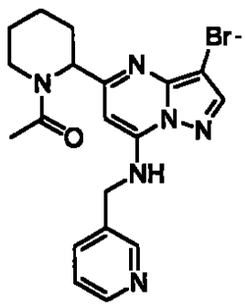
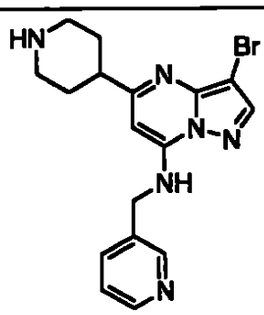
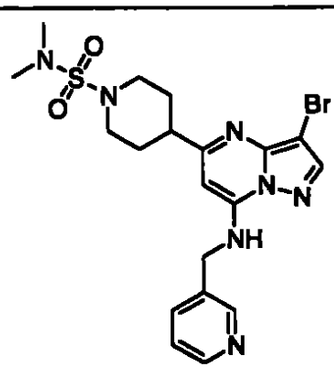
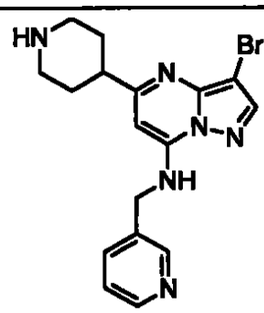
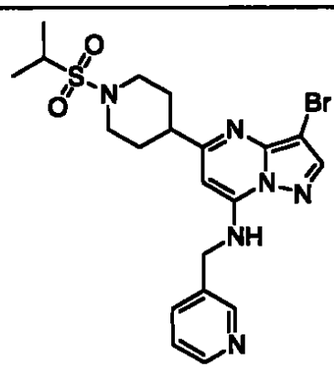
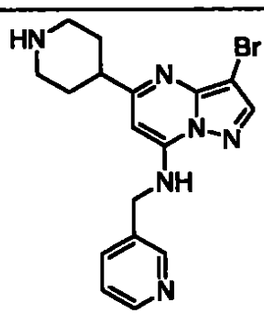
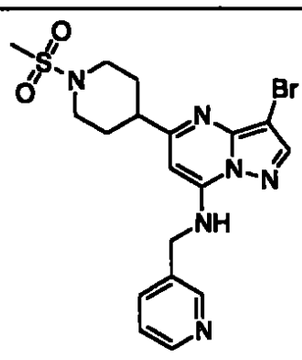
647

535			MH^+ = 500
536			MH^+ = 430
537			MH^+ = 531
538			MH^+ = 486 p.f. = 69,6°C

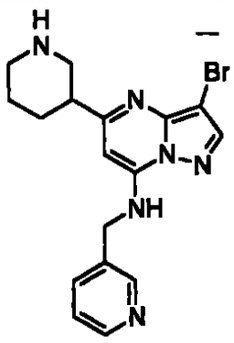
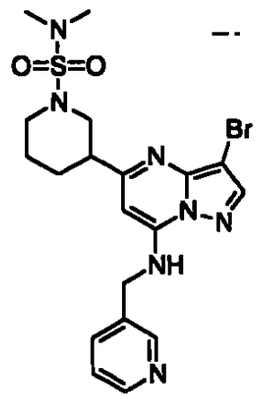
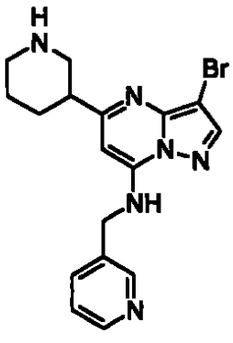
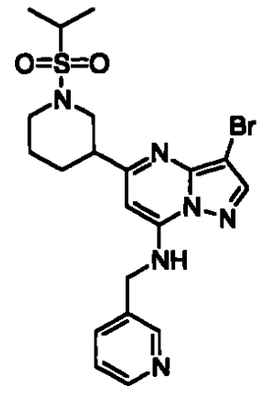
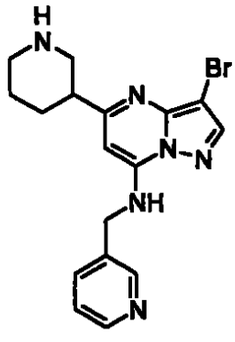
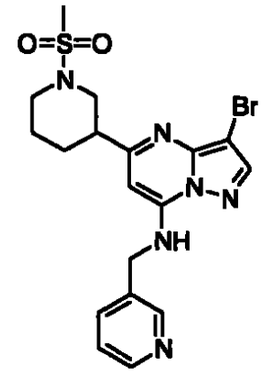
539			MH^+ = 500 p.f. = 82,3°C
540			MH^+ = 430 p.f. = 223,6°C
541			MH^+ = 531 p.f. = 118,1°C
542			MH^+ = 455 p.f. = 109 – 110°C

649

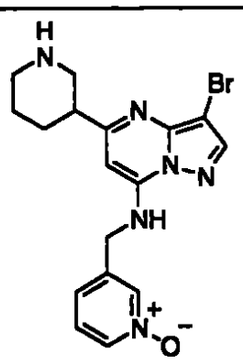
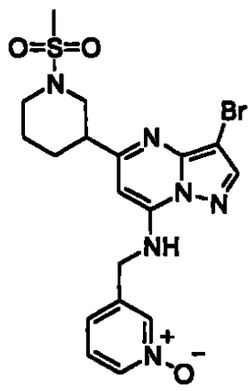
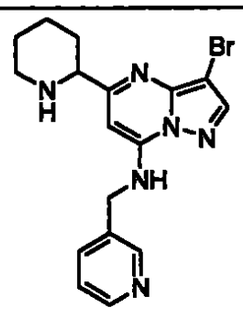
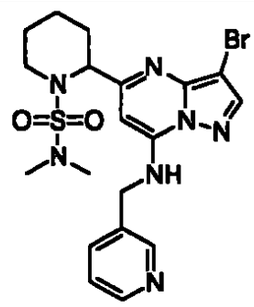
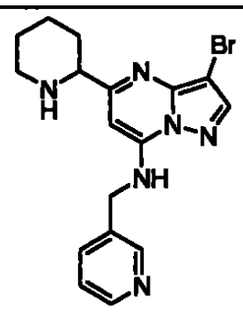
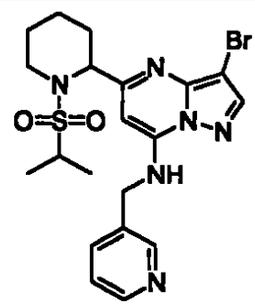
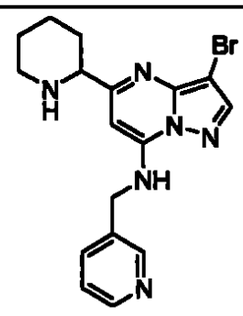
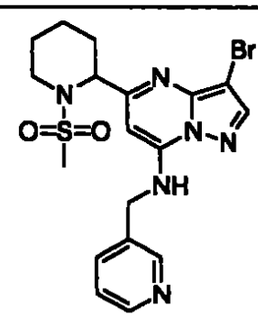
543			MH^+ = 429 p.f. = 111,5ºC
544			MH^+ = 455
545			MH^+ = 429
546			MH^+ = 455 p.f. = 80,1°C

547			MH^+ = 429 p.f. = 64,7°C
548			MH^+ = 494 p.f. = 76,5°C
549			MH^+ = 493 p.f. = 83,6°C
550			MH^+ = 465 p.f. = 207,5°C

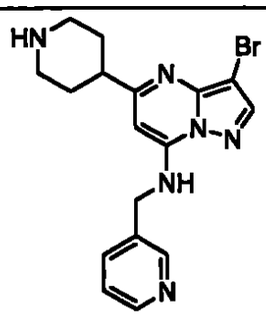
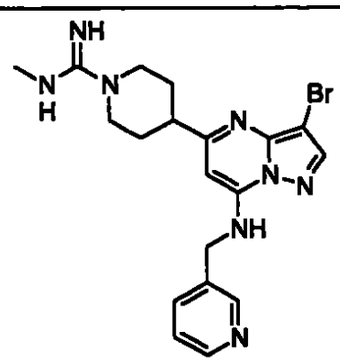
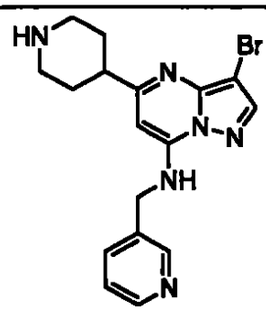
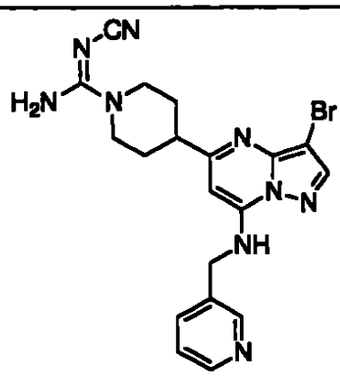
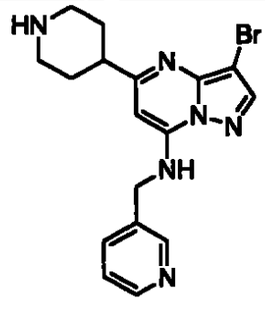
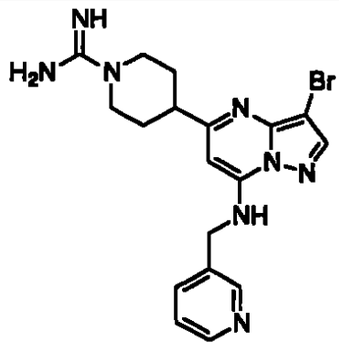
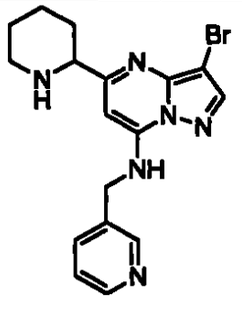
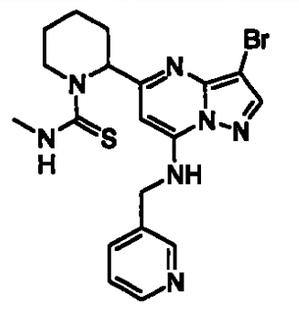
651

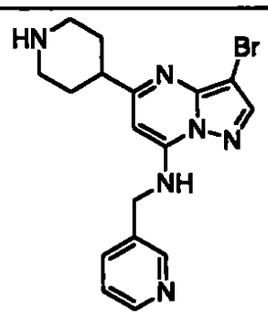
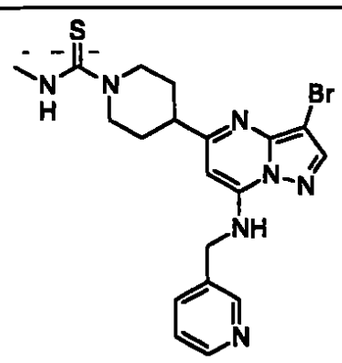
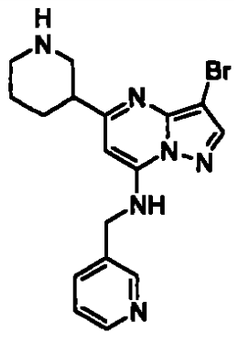
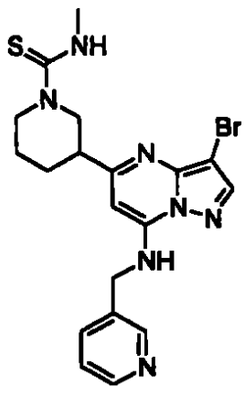
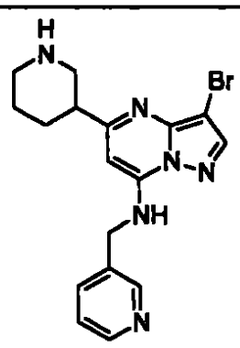
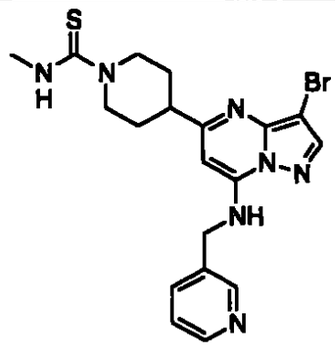
551			MH^+ = 494
552			MH^+ = 493
553			MH^+ = 465

649
652

554			MH^+ = 481 p.f. = 102,7°C
555			MH^+ = 494 p.f. = 85,3°C
556			MH^+ = 493 p.f. = 89,1°C
557			MH^+ = 465 p.f. = 83,8°C

650-653

558			Rend. cuant. = MH^+ = 443 p.f. = 98,3°C (sal de HCl)
559			MH^+ = 454
560			Rend. cuant. = MH^+ = 429 p.f. = 111,5 – 112, 6°C
561			MH^+ = 460 p.f. = 122,7°C

562			MH^+ = 460 p.f. = 95,4°C
563			MH^+ = 460
564			MH^+ = 460 p.f. = 95,4°C

Los datos adicionales para los ejemplos seleccionados se dan a continuación.

Ejemplo 534: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,66 – 8,62 (s, 1H), 8,62 – 8,58 (d, 1H), 7,95 (s, 1H), 7,72 – 7,68 (d, 1H), 7,36 – 7,31 (dd, 1H), 6,66 – 6,62 (t, 1H), 5,93 (s, 1H), 4,65 – 4,62 (d, 2H), 3,86 – 3,82 (d, 1H), 3,65 – 3,58 (m, 1H), 3,26 – 3,12 (dd, 4H), 3,02 – 2,80 (m, 3H), 2,10 – 2,00 (m, 1H), 1,67 – 1,57 (m, 3H).

Ejemplo 535: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,66 – 8,62 (s, 1H), 8,62 – 8,58 (d, 1H), 7,95 (s, 1H), 7,72 – 7,67 (d, 1H), 7,36 – 7,30 (dd, 1H), 6,70 – 6,64 (t, 1H), 5,90 (s, 1H), 4,63 – 4,61 (d, 2H), 3,93 – 3,86 (m, 1H), 3,69 – 3,61 (m, 4H), 3,27 – 3,23 (m, 4H), 3,10 – 3,01 (dd, 1H), 2,93 – 2,84 (m, 2H), 2,08 – 2,03 (m, 1H), 1,90 – 1,57 (m, 4H).

Ejemplo 536: ^{1}H RMN (300MHz, $CDCl_3$) δ 8,67 (s, 1H), 8,62 – 8,58 (d, 1H), 7,96 (s, 1H), 7,72 – 7,68 (d, 1H), 7,36 – 7,30 (dd, 1H), 6,79 – 6,72 (t, 1H), 5,96 (s, 1H), 4,86 (br s, 2H), 4,66 – 4,63 (d, 2H), 3,89 – 3,73 (m, 2H), 3,55 – 3,32 (m, 2H), 3,00 – 2,89 (m, 1H), 2,10 – 1,97 (m, 2H), 1,70 – 1,53 (m, 2H).

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).

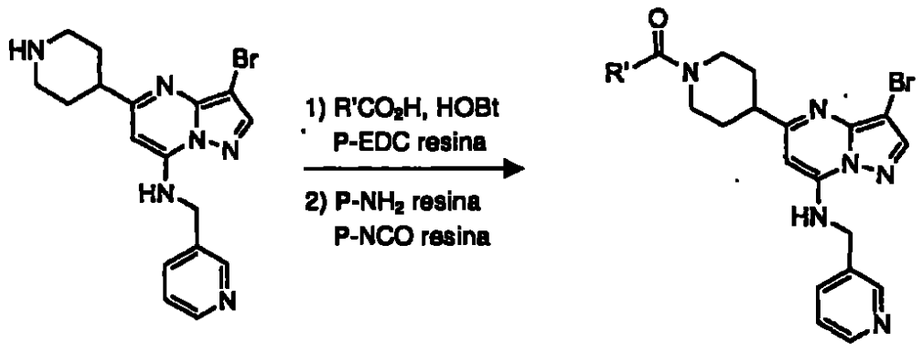
~~**Ejemplo 552:** ^{1}H RMN (300MHz, $CDCl_3$) δ 8,67 (s, 1H), 8,62 – 8,59 (d, 1H), 7,95 (s, 1H), 7,74 – 7,69 (d, 1H), 7,36 – 7,31 (dd, 1H), 6,67 – 6,60 (t, 1H), 5,98 (s, 1H), 4,67 – 4,63 (d, 2H), 3,92 – 3,86 (m, 1H), 3,85 – 3,75 (m, 1H), 3,40 – 3,30 (dd, 1H), 3,27 – 3,16 (m, 1H), 3,10 – 2,86 (m, 2H), 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 la síntesis paralela de formación de amida:

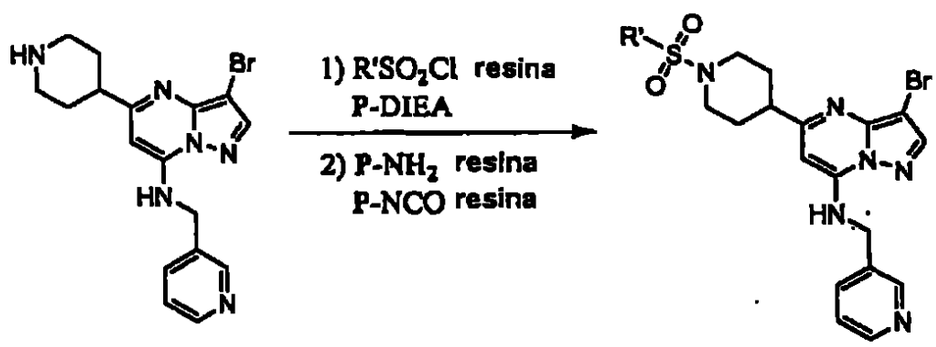


Se llevó a cabo una síntesis paralela en bloques de reacción de 96 receptáculos de polipropileno con un sello superior removible y un sello inferior

657

fijo. Cada reacción se ajustó con un fondo fritado de polipropileno de 20 micrones y el volumen máximo fue de 3 ml. El bloque de recolección no estaba previsto en un fondo fritado. A cada recipiente de reacción se le agregó una solución de amina (0,021 mmol) disuelta en una mezcla de DMF-THF-MeCN (4:3:3 v/v, 0,95 ml), resina EDC (P-EDC, Polymer Laboratories Ltd., 43 mg, 0,063 mmol), 1-hidroxibenzotriazol (HOBt, 5,67 mg, 0,042 mmol) y a 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 horas. La solución del producto crudo se filtró en un recipiente de reacción cargado con resina de trisamina (P-NH2, Argonaut Tech. Inc., 30 mg, 0,126 mmol) y resina de isocianato (P-NCO, Argonaut Tech. Inc., 35 mg, 0,063 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 horas y se filtró en un bloque de recolección. La solución del producto se evaporó bajo presión reducida para proporcionar el producto de amida deseado.

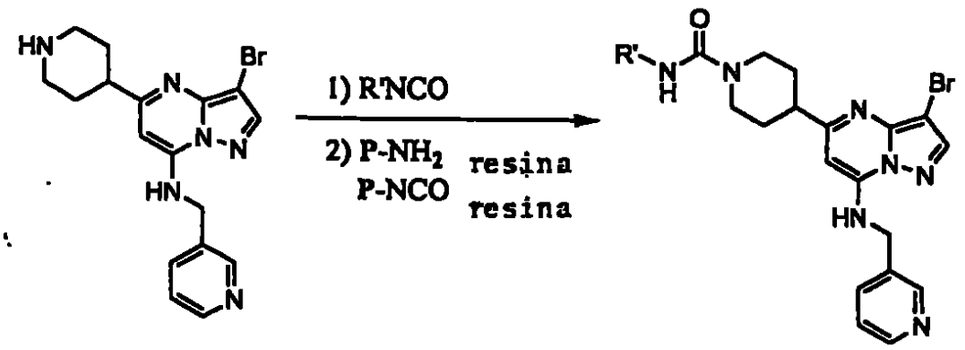
PROCEDIMIENTO GENERAL 2: Procedimiento para la síntesis paralela de formación de sulfonamida



Se llevó a cabo una síntesis paralela en bloques de reacción de 96 receptáculos de polipropileno con un sello superior removible y un sello inferior fijo. Cada reacción se ajustó con un fondo fritado de polipropileno de 20 micrones y el volumen máximo fue de 3 ml. El bloque de recolección no estaba previsto en

un fondo fritado. A cada receptáculo de reacción se le 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 DIEA (P-DIEA, Argonaut Tech. Inc., 18 mg, 0,063 mmol) y una solución de cloruro de sulfonilo en dimetilformamida (1 M, 0,0315 ml, 0,0315 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 horas. La solución del producto crudo se filtró en un recipiente de reacción cargado con resina de trisamina (P-NH2, Argonaut Tech. Inc., 30 mg, 0,126 mmol) y resina de isocianato (P-NCO, Argonaut Tech. Inc., 35 mg, 0,063 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 horas y se filtró en el bloque de recolección. La solución del producto se evaporó bajo presión reducida para proporcionar el producto de sulfonamida deseado.

PROCEDIMIENTO GENERAL 3: Procedimiento para la síntesis paralela de formación de urea

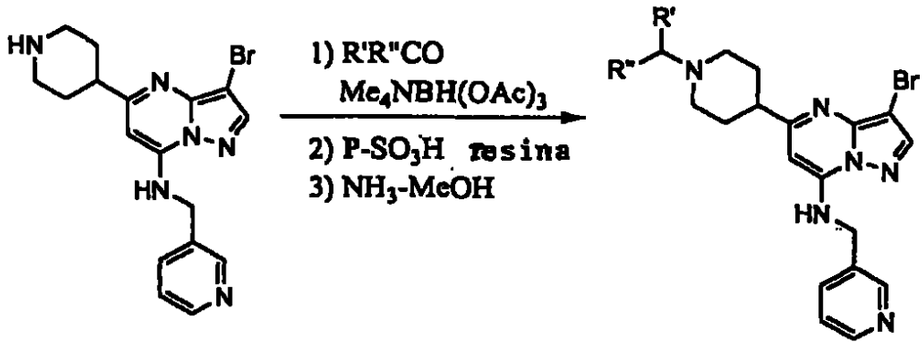


Se llevó a cabo la síntesis paralela en bloques de reacción de 96-receptáculos de polipropileno con sello superior removible y sello inferior fijo. Cada recipiente de reacción estaba provisto de un fondo fritado de polipropileno

659

~~20 micrones y el volumen máximo fue de 3 mL. El bloque de recolección~~ no estaba provisto de fondo fritado. A cada uno de los receptáculos de reacción se le 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 de diclorometano (0,33 M, 0,126 mL, 0,042 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 horas. La solución de producto crudo se filtró en un receptáculo de reacción cargado con resina de trisamina (P-NH2, Argonaut Tech. Inc., 30 mg, 0,126 mmol) y resina de isocianato (P-NCO, Argonaut Tech. Inc., 35 mg, 0,063 mmol). La mezcla de reacción se agitó a temperatura ambiente durante 16 horas y se filtró en el bloque de recolección. La solución del producto se evaporó bajo presión reducida para proporcionar el producto de urea deseado.

PROCEDIMIENTO GENERAL 4: Procedimiento para la síntesis paralela de alquilación reductiva

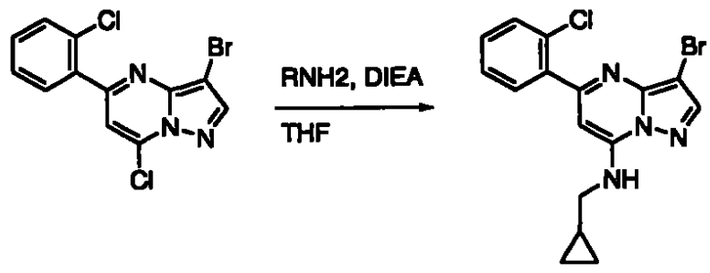


Se llevó a cabo la síntesis paralela en bloques de reacción de 96-receptáculos de polipropileno con sello superior removible y sello inferior fijo. Cada receptáculo de reacción estaba provisto de un fondo fritado de polipropileno de 20 micrones y el volumen máximo era de 3 mL. El bloque de recolección no estaba provisto de fondo fritado. A cada receptáculo de reacción se le agregó una

666

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) disuelto en una mezcla de AcOH-DCE 1:99 v/v, 0, mL). La mezcla de reacción se agitó a temperatura ambiente durante 3 días. La solución del producto crudo se filtró en un recipiente 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 horas y se decantó. El producto de resina Lanterns se lavó con metanol (1 mL) tres veces. Se agregó una solución de amonfaco en metanol (2 M, 1,2 mL). Se agitó la mezcla de reacción a temperatura ambiente durante 30 minutos, y se filtró en el bloque de recolección. La solución del producto se evaporó bajo presión reducida para proporcionar el producto de amina terciaria deseado.

PROCEDIMIENTO GENERAL 5: Procedimiento para la síntesis paralela de 7,N-sususstituido pirazolo[1,5a]pirimidinas



3-bromo-7-cloro-5-(2-cloro-fenil)-pirazolo[1,5-a]pirimidina (9,0 mg, 0,03 mmol) en tetrahidrofurano se le agregó di-iso-propiletilamina (12 µL, 0.07), seguido de ciclopropilmetilamina (70 µL, .07 mmol; solución 1M en DMF). La mezcla de reacción se calentó a 70°C durante 36 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

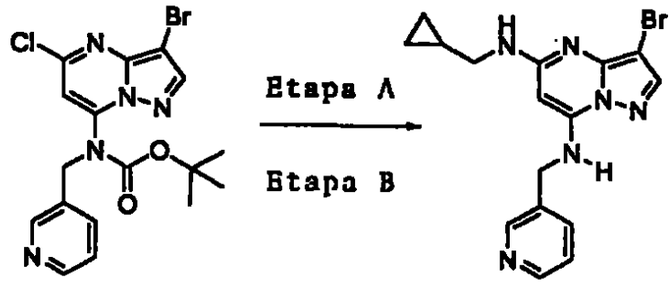
661

temperatura ambiente durante 12-18 horas. La solución se filtró y evaporó hasta sequedad para proveer el producto. m/z observado 375,21.

PROCEDIMIENTO GENERAL 6: Procedimiento para la síntesis parelala de 5,N-sustituido pirazolo[1,5a]pirimidinas

Protocolos Generales:

Se llevó a cabo una síntesis paralela en bloques de polipropileno de 96 receptáculos tal como se ha descrito anteriormente. En el caso de ser necesario calentamiento, las reacciones se llevaron a cabo en tubos de vidrio de 2,5 mL individualmente sellados con una esterilla de polipropileno y el calentamiento se logró mediante un bloque de transferencia de calor de 96 receptáculos.



ETAPA A:

A la 3-bromo-5-cloro-7-N-Boc-alquilamino-pirazolo[1,5-a]pirimidina (17 mg, 0,04 mmol) en p-dioxanose le agregó DIEA (9 µL, 0,05), seguido de ciclopropil-metilamina (80 µL, 0,08 mmol; solución 1M en isopropanol). La mezcla de reacción se calentó a 90ºc duratne 36 horas y luego se enfrió a temperatura ambiente. La mezcla se trató con P-NCO (Argonaut Tech. Inc. 70 mg, 0,12 mmol) yP-CO_3^- (Argonaut Tech. Inc. 70 mg, 0,24 mmol) y se agitó a temperatura ambiente duratne 12-18 horas. La solución se filtró y evaporó hasta sequedad para proporcionar el producto.

ESA 662

ETAPA B (ácido):

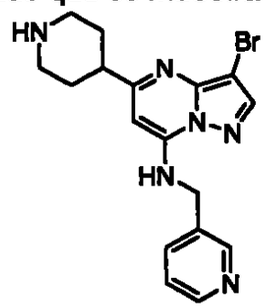
El producto de la ETAPA A se recogió en 35% de TFA/DCM y se agitó durante 4 horas seguido de concentración bajo alto vacío. El residuo se trató con 10% de HCl(acuoso) en MeOH agitado durante 2 horas y luego se concentró para proporcionar el producto deseado. m/z observado 375,21.

ETAPA B (básica):

El producto de la etapa A se recogió en EtOH y se trató con una resina de intercambio iónico Ambersep® 900-OH (Acros, 100mg), calentada a reflujo durante 48 horas con suave agitación. La mezcla de reacción se enfrió a temperatura ambiente, se filtró y se concentró para proporcionar el producto deseado.

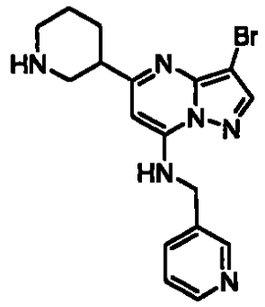
EJEMPLO 565:

Utilizando el procedimiento que se indica en el Procedimiento General 1 y el compuesto del Ejemplo 462 que se muestra a continuación, se prepararon los compuestos con el m/z observado que se muestra en la Tabla 43.



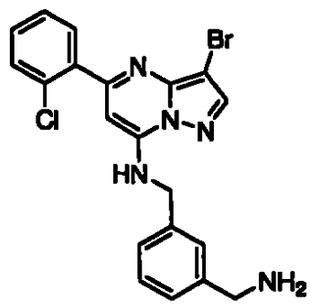
EJEMPLO 566:

Utilizando el procedimiento que se establece en el Procedimiento General 1 y el compuesto del Ejemplo 471 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 44 con el m/z observado.



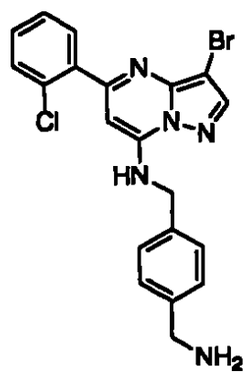
EJEMPLO 567:

Utilizando el procedimiento que se establece en el Procedimiento General 1 y el compuesto del Ejemplo 515 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 45 con el m/z observado.



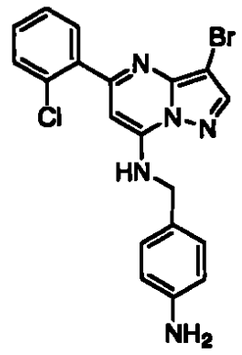
EJEMPLO 568:

Utilizando el procedimiento que se establece en el Procedimiento General 1 y el compuesto del Ejemplo 513 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 46 con el m/z observado.



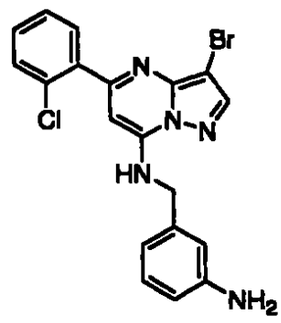
EXAMPLE 569:

Utilizando el procedimiento que se establece en el Procedimiento General 1 y el compuesto del Ejemplo 526 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 47 con el m/z observado.



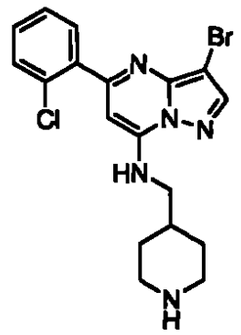
EJEMPLO 570:

Utilizando el procedimiento que se establece en el Procedimiento General 1 y el compuesto del Ejemplo 524 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 48 con el m/z observado.



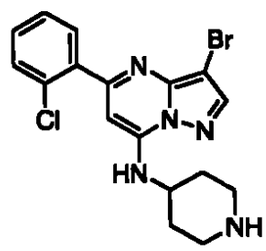
EJEMPLO 571:

Utilizando el procedimiento que se establece en el Procedimiento General 1 y el compuesto del Ejemplo 525 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 49 con el m/z observado.



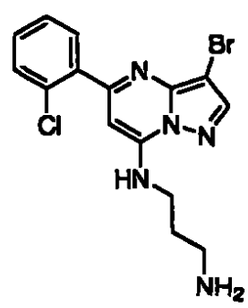
EJEMPLO 572:

Utilizando el procedimiento que se establece en el Procedimiento General 1 y el compuesto del Ejemplo 526.10 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 50 con el m/z observado.



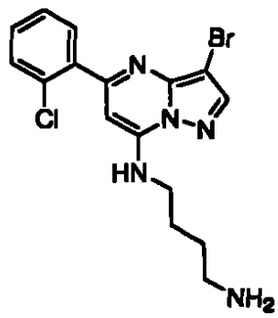
EJEMPLO 573:

Utilizando el procedimiento que se establece en el Procedimiento General 1 y el compuesto del Ejemplo 518 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 51 con el m/z observado.



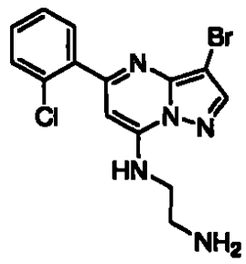
EJEMPLO 574:

Utilizando el procedimiento que se establece en el Procedimiento General 1 y el compuesto del Ejemplo 519 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 52 con el m/z observado.



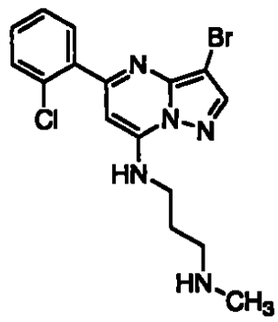
EJEMPLO 575:

Utilizando el procedimiento que se establece en el Procedimiento General 1 y el compuesto del Ejemplo 520 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 53 con el m/z observado.



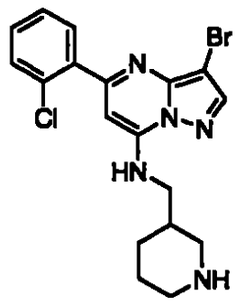
EJEMPLO 576:

Utilizando el procedimiento que se establece en el Procedimiento General 1 y el compuesto del Ejemplo 522 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 54 con el m/z observado.



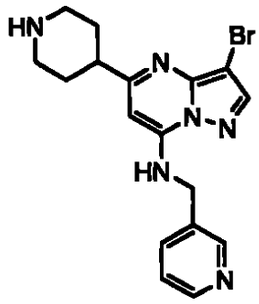
EJEMPLO 577:

Utilizando el procedimiento que se establece en el Procedimiento General 1 y el compuesto del Ejemplo 523 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 55 con el m/z observado.



EJEMPLO 578:

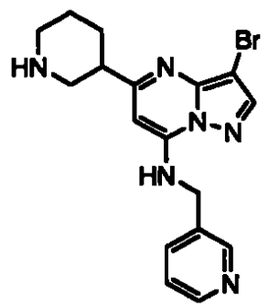
Utilizando el procedimiento que se establece en el Procedimiento General 2 y el compuesto del Ejemplo 462 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 56 con el m/z observado.



665
668

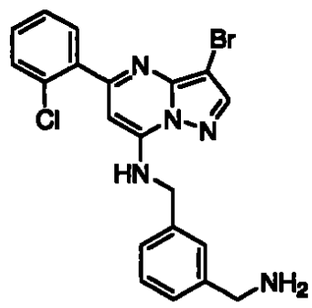
EJEMPLO 579:

Utilizando el procedimiento que se establece en el Procedimiento General 2 y el compuesto del Ejemplo 471 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 57 con el m/z observado.



EJEMPLO 580:

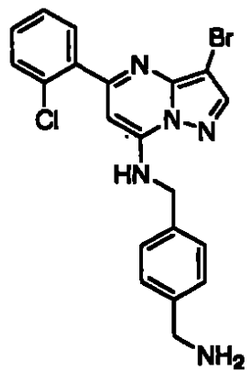
Utilizando el procedimiento que se establece en el Procedimiento General 2 y el compuesto del Ejemplo 515 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 58 con el m/z observado.



EJEMPLO 581:

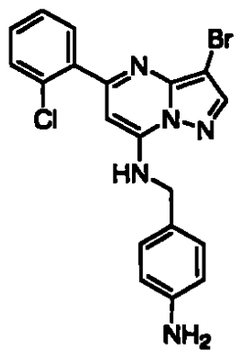
Utilizando el procedimiento que se establece en el Procedimiento General 2 y el compuesto del Ejemplo 513 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 59 con el m/z observado.

669



EJEMPLO 582:

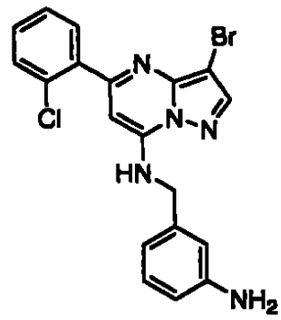
Utilizando el procedimiento que se establece en el Procedimiento General 2 y el compuesto del Ejemplo 513 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 60 con el m/z observado.



EJEMPLO 583:

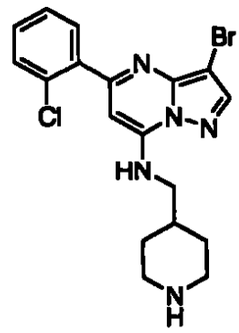
Utilizando el procedimiento que se establece en el Procedimiento General 2 y el compuesto del Ejemplo 524 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 61 con el m/z observado.

667
670



EJEMPLO 584:

Utilizando el procedimiento que se establece en el Procedimiento General 2 y el compuesto del Ejemplo 525 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 62 con el m/z observado.

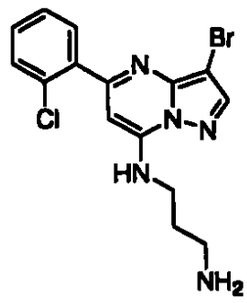


EJEMPLO 585:

Utilizando el procedimiento que se establece en el Procedimiento General 2 y el compuesto del Ejemplo 526.10 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 63 con el m/z observado.

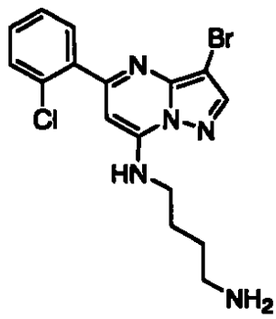
EJEMPLO 586:

Utilizando el procedimiento que se establece en el Procedimiento General 2 y el compuesto del Ejemplo 518 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 64 con el m/z observado.



EJEMPLO 587:

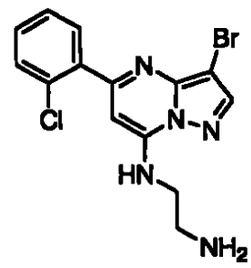
Utilizando el procedimiento que se establece en el Procedimiento General 2 y el compuesto del Ejemplo 519 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 65 con el m/z observado.



EJEMPLO 588:

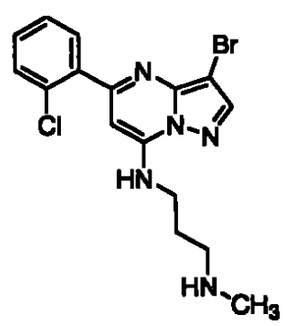
Utilizando el procedimiento que se establece en el Procedimiento General 2 y el compuesto del Ejemplo 520 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 67 con el m/z observado.

661
672



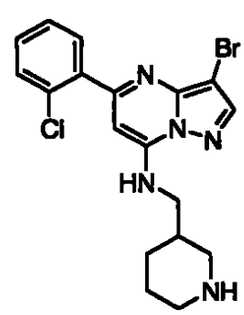
EJEMPLO 589:

Utilizando el procedimiento que se establece en el Procedimiento General 2 y el compuesto del Ejemplo 521 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 68 con el m/z observado.



EJEMPLO 590:

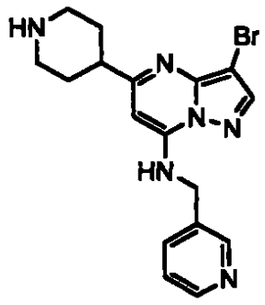
Utilizando el procedimiento que se establece en el Procedimiento General 2 y el compuesto del Ejemplo 523 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 69 con el m/z observado.



620
073

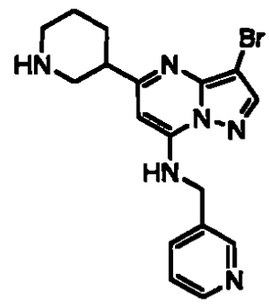
EJEMPLO 591:

Utilizando el procedimiento que se establece en el Procedimiento General 3 y el compuesto del Ejemplo 462 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 70 con el m/z observado.



EJEMPLO 592:

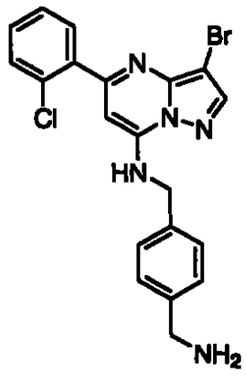
Utilizando el procedimiento que se establece en el Procedimiento General 3 y el compuesto del Ejemplo 471 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 71 con el m/z observado.



EJEMPLO 593:

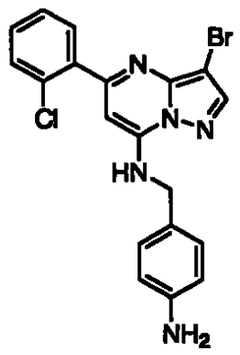
Utilizando el procedimiento que se establece en el Procedimiento General 3 y el compuesto del Ejemplo 513 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 72 con el m/z observado.

671
674



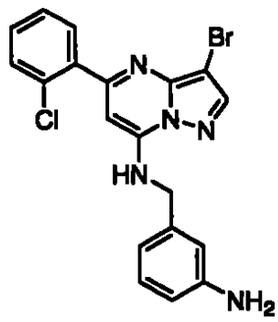
EJEMPLO 594:

Utilizando el procedimiento que se establece en el Procedimiento General 3 y el compuesto del Ejemplo 524 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 73 con el m/z observado.



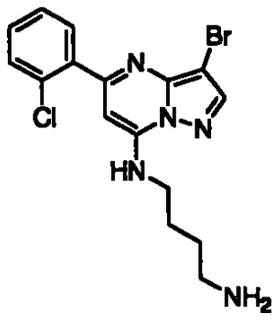
EJEMPLO 595:

Utilizando el procedimiento que se establece en el Procedimiento General 3 y el compuesto del Ejemplo 524 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 74 con el m/z observado.



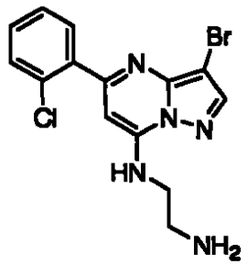
EJEMPLO 596:

Utilizando el procedimiento que se establece en el Procedimiento General 3 y el compuesto del Ejemplo 519 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 75 con el m/z observado.



EJEMPLO 597:

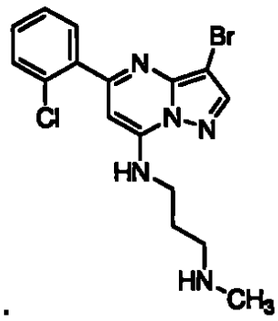
Utilizando el procedimiento que se establece en el Procedimiento General 3 y el compuesto del Ejemplo 520 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 76 con el m/z observado.



676

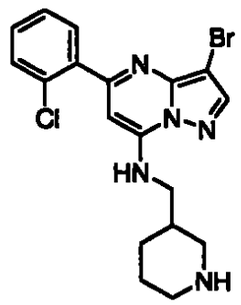
EJEMPLO 598:

Utilizando el procedimiento que se establece en el Procedimiento General 3 y el compuesto del Ejemplo 521 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 77 con el m/z observado.



EJEMPLO 599:

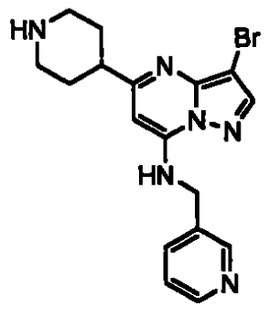
Utilizando el procedimiento que se establece en el Procedimiento General 3 y el compuesto del Ejemplo 523 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 78 con el m/z observado.



EJEMPLO 600:

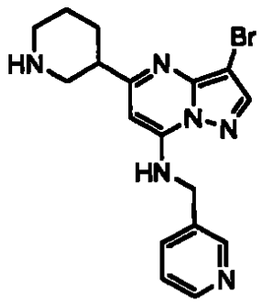
Utilizando el procedimiento que se establece en el Procedimiento General 4 y el compuesto del Ejemplo 462 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 79 con el m/z observado.

677



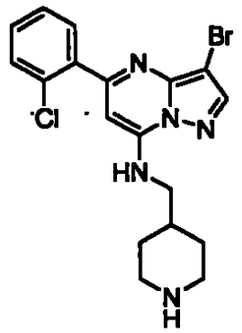
EJEMPLO 601:

Utilizando el procedimiento que se establece en el Procedimiento General 4 y el compuesto del Ejemplo 471 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 80 con el m/z observado.



EJEMPLO 602:

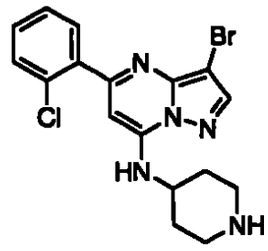
Utilizando el procedimiento que se establece en el Procedimiento General 4 y el compuesto del Ejemplo 525 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 81 con el m/z observado.



678

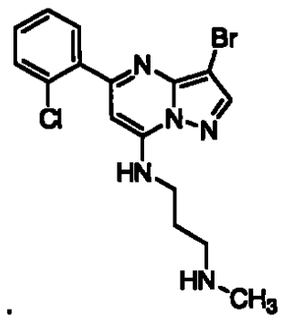
EXAMPLE 603:

Utilizando el procedimiento que se establece en el Procedimiento General 4 y el compuesto del Ejemplo 526.10 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 82 con el m/z observado.



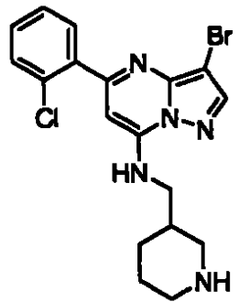
EJEMPLO 604:

Utilizando el procedimiento que se establece en el Procedimiento General 4 y el compuesto del Ejemplo 521 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 83 con el m/z observado.



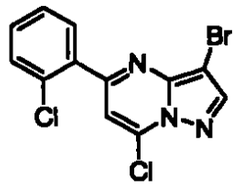
EJEMPLO 605:

Utilizando el procedimiento que se establece en el Procedimiento General 4 y el compuesto del Ejemplo 523 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 84 con el m/z observado.



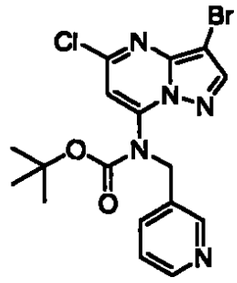
EJEMPLO 606:

Utilizando el procedimiento que se establece en el Procedimiento General 5 y el compuesto del Ejemplo 81 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 85 con el m/z observado.



EJEMPLO 607:

Utilizando el procedimiento que se establece en el Procedimiento General 6 y el compuesto del Ejemplo 196 que se muestra a continuación, se prepararon los compuestos que se muestran en la Tabla 86 con el m/z observado.



680

ENSAYO:

CONSTRUCCIONES DE BACULOVIRUS: Se clonaron las ciclinas A y E en pFASTBAC (Invitrogen) por PCR, con adición de una secuencia GluTAG (EYMPME) en el extremo amino-terminal para permitir la purificación en las columnas de afinidad anti-GluTAG. Las proteínas expresadas fueron de un tamaño de aproximadamente 46kDa (ciclina E) y de 50kDa (ciclina A) .También se clonó la CDK2 en pFASTBAC por PCR, con adición del epitopo de hemaglutinina tag en el extremo carboxi-terminal (YDVPDYAS). La proteína expresada fue de un tamaño de aproximadamente 34kDa.

PRODUCCION DE LAS ENZIMAS: Baculovirus recombinantes que expresan las ciclinas A, E y CDK2 fueron infectados en células de SF9 a una multiplicidad de infección (MOI) de 5, durante 48 horas. Las células se consecharon por centrifugación a 1000 RPM durante 10 minutos. Los gránulos que contienen ciclina- (E o A) se combinaron con gránulos de células que contenían CDK2 y se lisaron sobre hielo durante 30 minutos en cinco veces el volumen de los gránulos del buffer de lisis que contenía 50mM de Tris pH 8,0, 0,5% NP40, 1mM DTT e inhibidores de proteasa/fosfatasa (Roche Diagnostics GmbH, Mannheim, Alemania). Las mezclas se agitaron durante 30-60 minutos para promover la formación del complejo de ciclina-CDK2. Los lisados mixtos fueron luego centrifugados a 15000 RPM durante 10 minutos y se retuvo el sobrenadante. Luego se usaron 5ml de perlas anti-GluTAG (para un litro de células SF9) para capturar los complejos de ciclina-CDK2. Las perlas adheridas se lavaron tres veces en un buffer de lisis. Las proteínas se eluyeron competitivamente con el buffer de lisis que contenía 100-200ug/mL del péptido GluTAG. El eluido fue dializado durante la noche en 2 litros de buffer de quinasa que contenía 50mM de

128
681

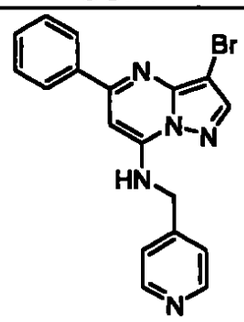
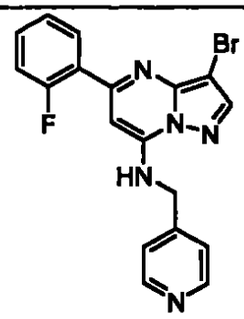
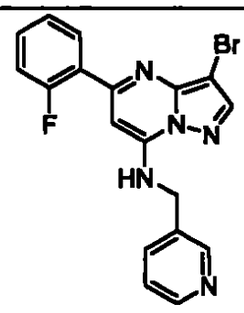
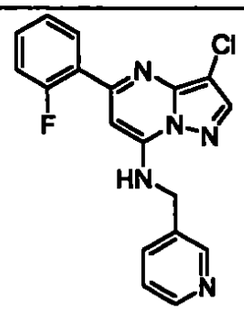
Tris pH 8,0, 1mM DTT, 10mM de MgCl2, 100uM de ortovanadato de sodio y 20% de glicerol. La enzima se almacenó en alícuotas a -70°C.

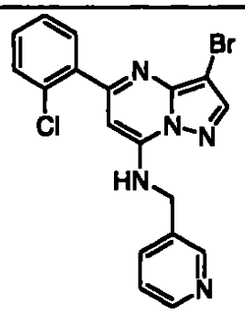
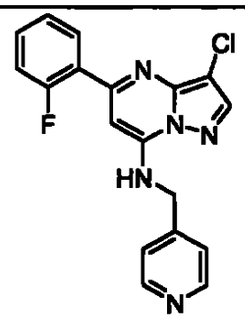
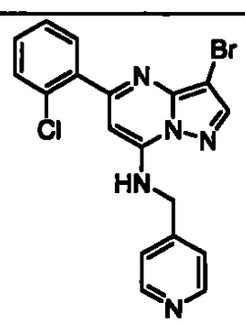
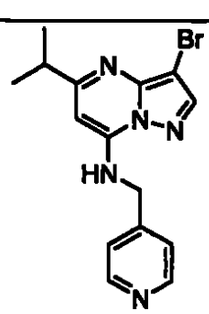
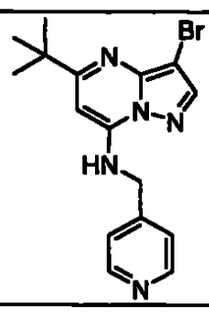
ENSAYO DE QUINASA IN VITRO: Los ensayos de quinasa CDK2 (dependientes de ciclina A o bien E) se efectuaron en placas de 96 receptáculos de baja adhesión de proteína (Corning Inc, Corning, New York). La enzima se diluyó hasta una concentración final de 50 ug/ml en el buffer de quinasa que contenía 50mM de Tris pH 8,0, 10mM de $MgCl_2$, 1mM de DTT, y 0.1mM de ortovanadato de sodio. El sustrato usado en estas reacciones fue un péptido biotinilado derivado de Histona H1 (de Amersham, UK). El sustrato se descongeló en hielo y se diluyó a 2 uM en buffer de quinasa. Los compuestos se diluyeron en 10% de DMSO a concentraciones deseables. Para cada reacción de quinasa, 20 ul de la solución de enzima de 50 ug/ml (1 ug de enzime) y 20 ul de la solución del sustrato de un 1 uM se mezclaron, luego se combinaron con 10 ul de compuesto diluido en cada receptáculo para ensayo. La reacción de quinasa se inició por adición de 50 ul de 4 uM ATP y 1 uCi de 33P-ATP (de Amersham, UK).La reacción se dejó transcurrir durante 1 hora a temperatura ambiente. La reacción se interrumpió mediante agregado de 200 ul de buffer de stop que contenía 0.1% de Triton X-100, 1mM de ATP, 5mM de EDTA, y 5 mg/ml de gránulos de SPA recubiertos con estreptavidina (de Amersham, UK) durante 15 minutos. Las perlas de SPA fueron luego capturadas en una placa de filtro GF/B de 96 receptáculos (Packard/Perkin Elmer Life Sciences) usando una cosechadora universal Filtermate (Packard/Perkin Elmer Life Sciences.). Se eliminaron señales no específicas lavando dos veces las perlas con NaCl 2M, luego dos veces con NaCl 2M con ácido fosfórico al 1%. Luego se midió la señal radioactiva usando un contador de centelleo líquido de 96 receptáculos TopCount 96 (de Packard/Perkin Elmer Life Sciences).

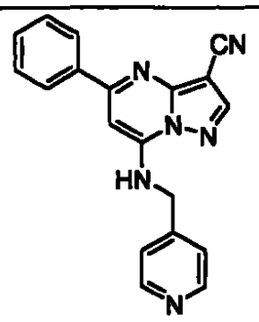
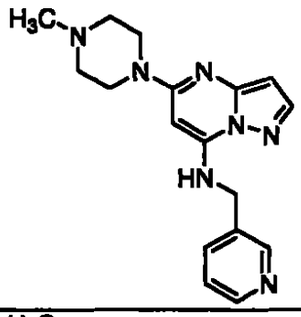
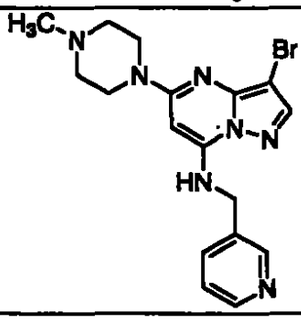
682

DETERMINACION DELA CI_{50}: Se graficaron las curvas de respuesta a la dosis a partir de los datos de inhibición generados, cada uno por duplicado, desde diluciones seriadas de 8 puntos de los compuestos inhibidores. La concentración del compuesto se graficó contra el porcentaje de actividad de quinasa, calculado mediante el CPM de las muestras tratadas dividido por el CPM de las muestras no tratadas. Para generar los valores de la CI_{50}, las curvas de respuesta a la dosis fueron luego ajustadas a una curva sigmoidal estándar y se derivaron los valores de la CI_{50} mediante análisis de regresión no lineal. Los valores de CI_{50} así obtenidos 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 previamente descripto.

Tabla 87

COMP	Ejemplo	CI_{50} (μM)
	1	0.,20 0,029
	3	0,032 0,024
	4	0,011
	5	0,021

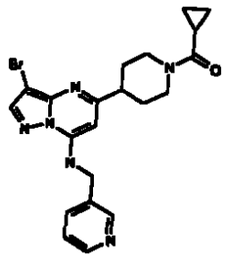
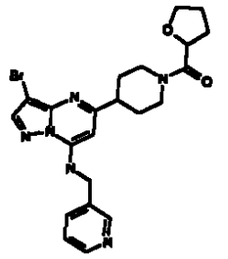
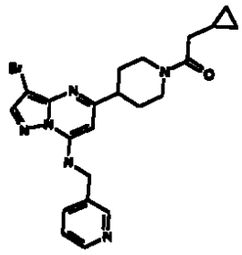
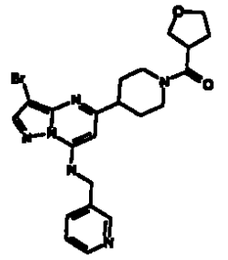
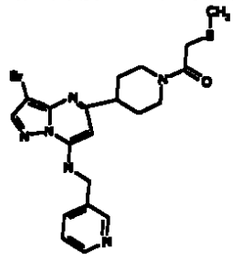
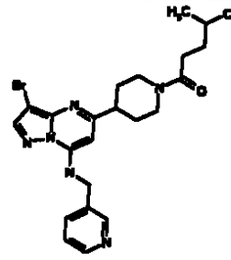
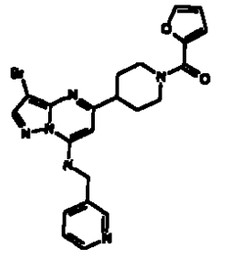
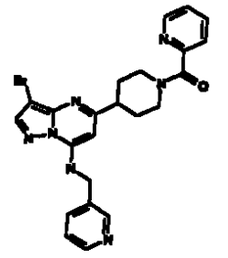
	8	0.003
	6	0,064 0,029
	7	0,01 0,006
	10	0,042
	12	0,17

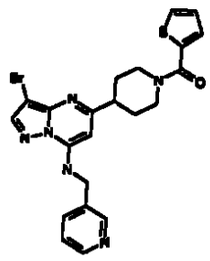
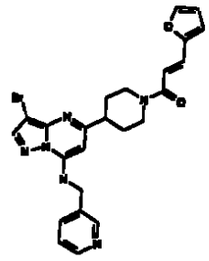
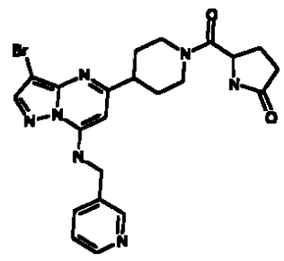
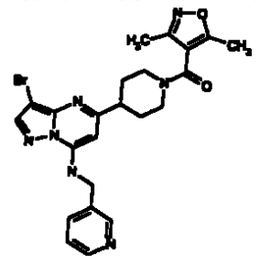
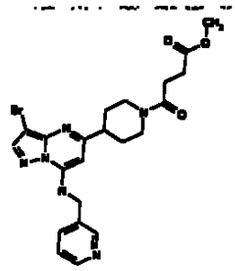
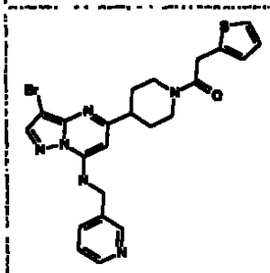
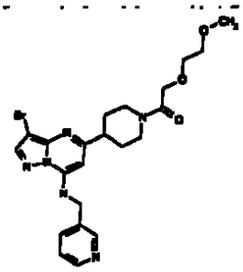
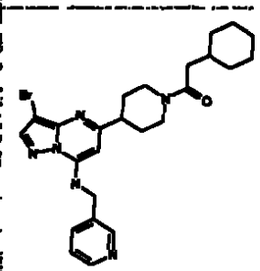
	16	0,62
	1	5,6
	3	0,14

Tal como se demostró más arriba mediante los valores de ensayo, los compuestos de la presente invención exhiben excelentes propiedades inhibidoras de CDK.

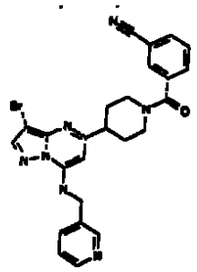
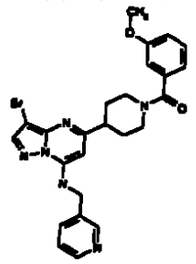
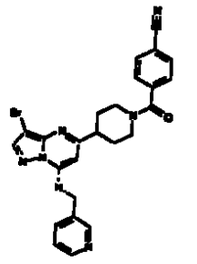
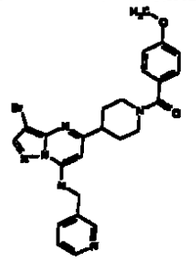
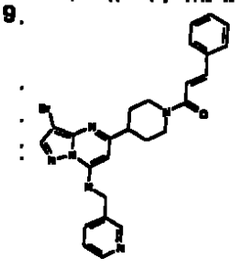
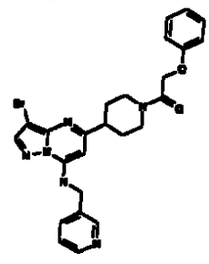
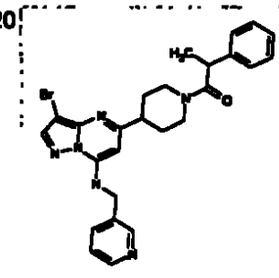
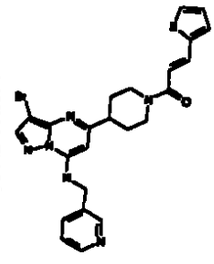
Aunque la presente invención ha sido descripta conjuntamente con las realizaciones específicas que se indican en lo que antecede, muchas alternativas, modificaciones y otras variaciones de las mismas resultarán aparentes para los expertos en la materia. Todas dichas alternativas, modificaciones y variaciones entran dentro del espíritu y alcance de la presente invención.

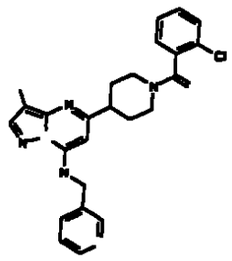
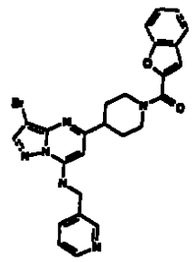
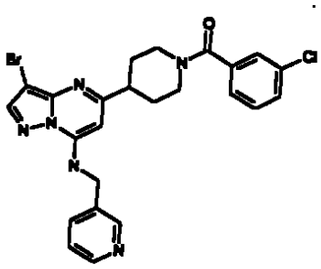
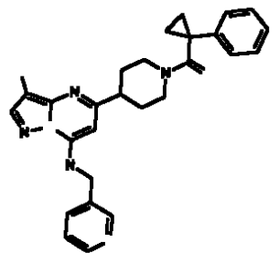
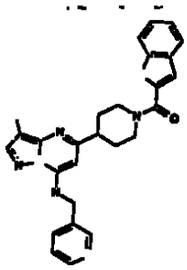
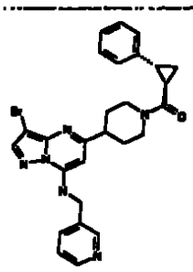
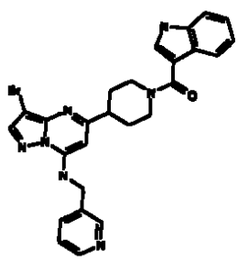
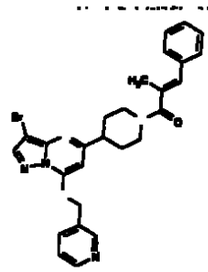
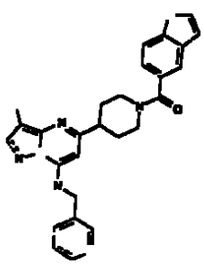
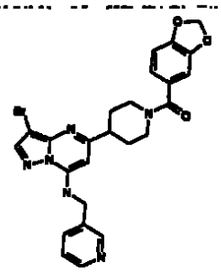
TABLA 43

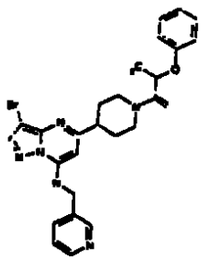
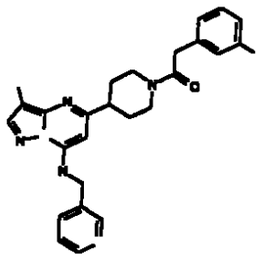
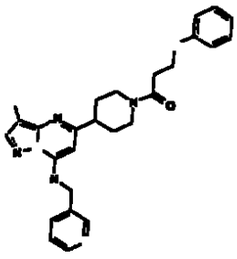
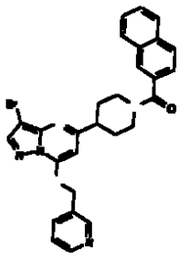
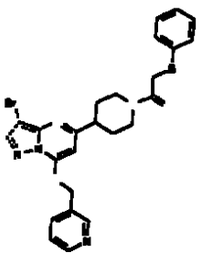
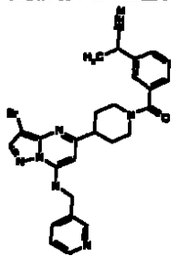
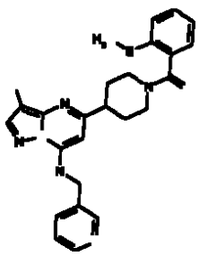
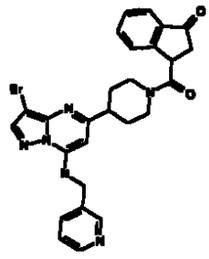
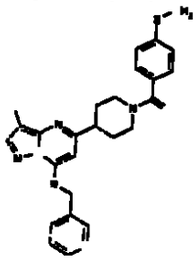
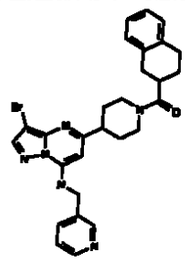
Ej.	Compuesto	m/z	Ej.	Compuesto	m/z
4301		457.25	4305		487.27
4302		471.26	4306		487.27
4303		477.26	4307		487.27
4304		483.27	4308		494.27

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

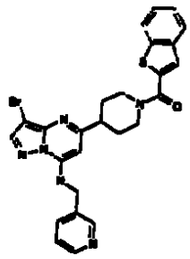
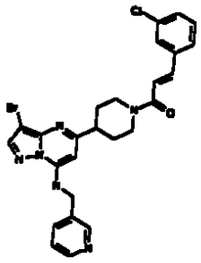
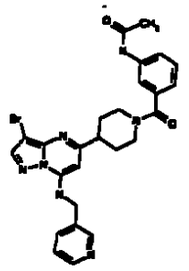
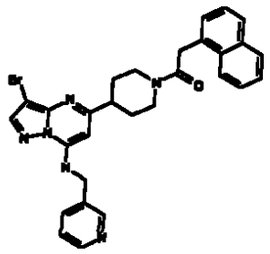
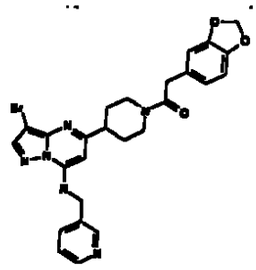
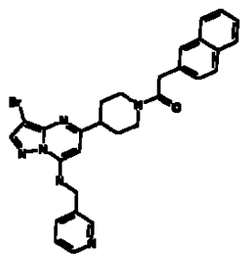
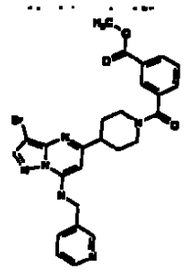
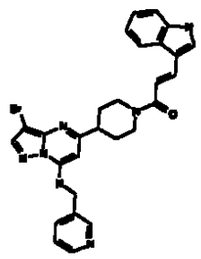
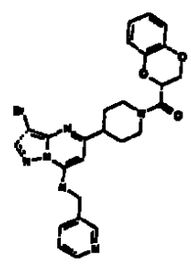
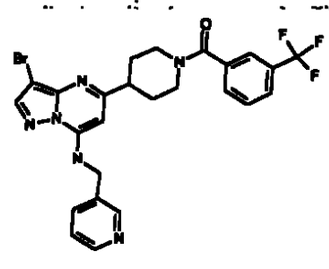
688

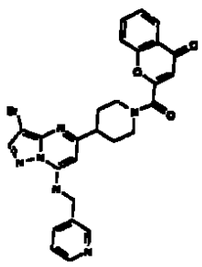
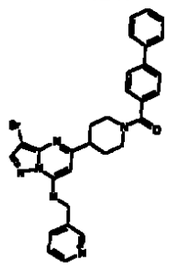
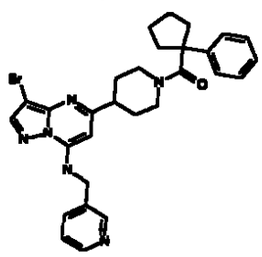
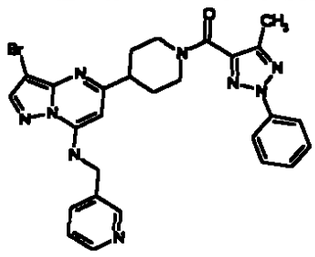
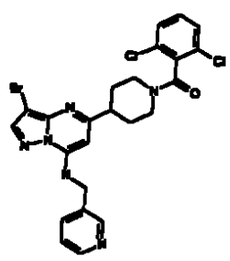
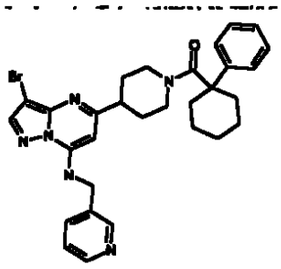
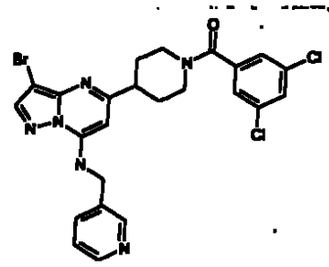
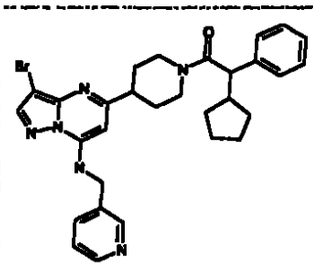
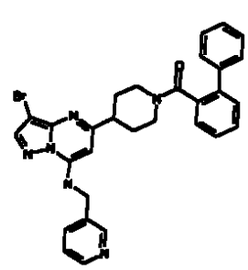
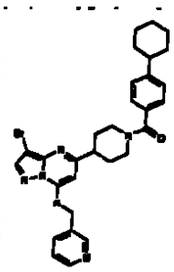
Ej.	Producto	m/z	Ej.	Producto	m/z
4317		518.28	4321		523.29
4318		518.28	4322		523.29
4319		519.29	4323		523.29
4320		521.29	4324		525.29

Producto	1.Ej. 2. m/z	Producto	1. Ej. 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

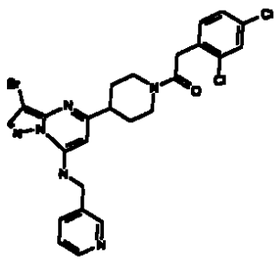
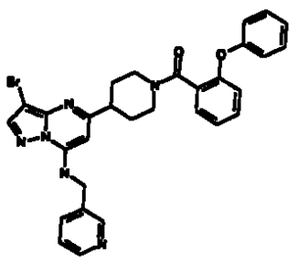
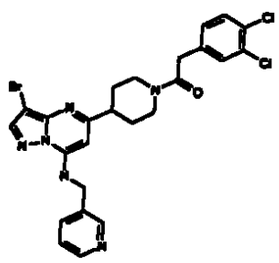
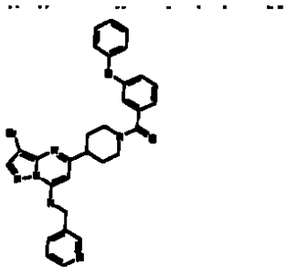
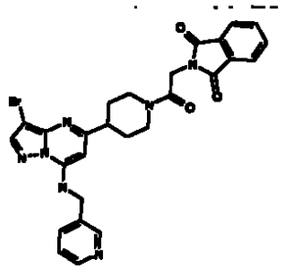
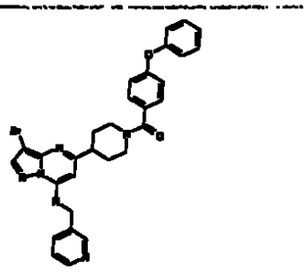
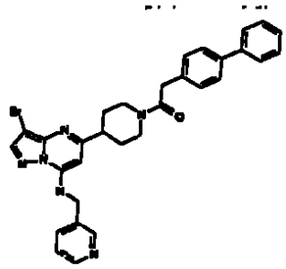
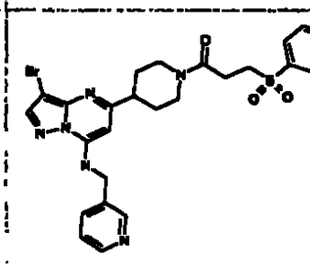
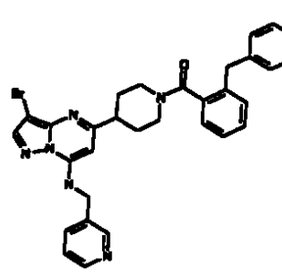
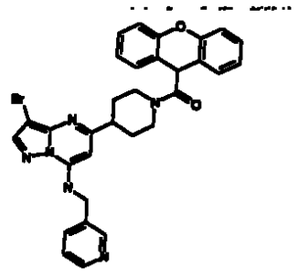
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4335 2.537.3		1. 4340 2. 541.3
	1.4336 2. 537.3		1. 4341 2. 543.3
	1. 4337 2. 539.3		1. 4342 2. 548.3
	1. 4338 2. 539.3		1. 4343 2. 547.3
	1. 4339 2. 539.3		1. 4344 2. 547.3

691

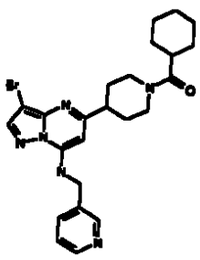
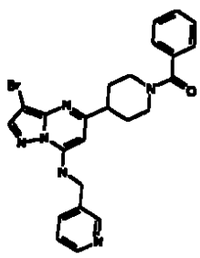
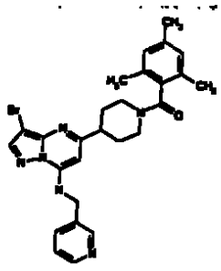
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4345 2. 549.3		1. 4350 2. 553.3
	1. 4346 2. 550.3		1. 4351 2. 557.31
	1. 4347 2. 551.3		1. 4352 2. 557.31
	1. 4348 2. 551.3		1. 4353 2. 558.31
	1. 4349 2. 551.3		1. 4354 2. 561.31

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4355 2. 561.31		1. 4360 2. 569.31
	1. 4356 2. 561.31		1. 4361 2. 574.32
	1. 4357 2. 561.31		1. 4362 2. 573.32
	1. 4358 2. 561.31		1. 4363 2. 573.32
	1. 4359 2. 569.31		1. 4364 2. 575.32

693

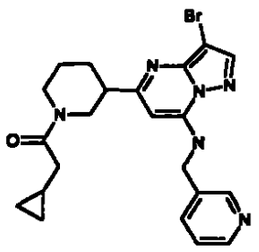
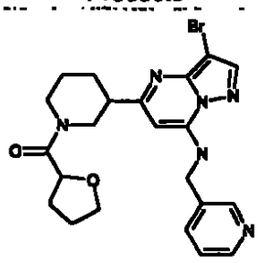
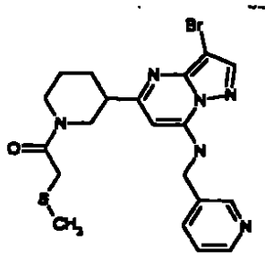
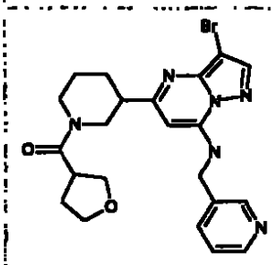
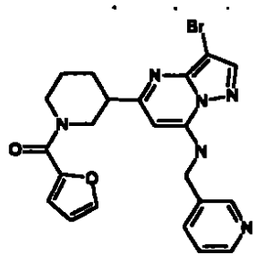
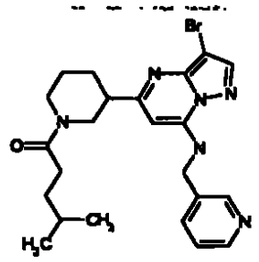
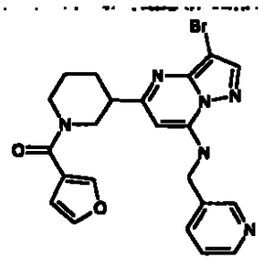
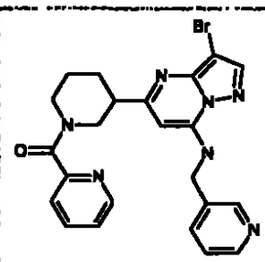
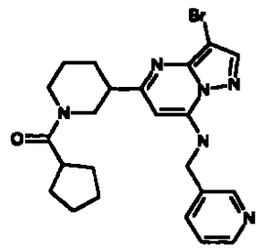
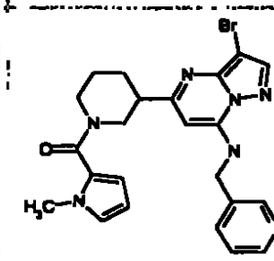
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4365 2. 575.32		1. 43700 2. 585.32
	1. 43666 2. 575.32		1. 4371 2. 583.32
	1. 4367 2. 574.32		1. 4372 2. 585.32
	1. 43688 2. 583.32		1. 4373 2. 585.32
	1. 4369 2. 583.32		1. 4374 2. 597.33

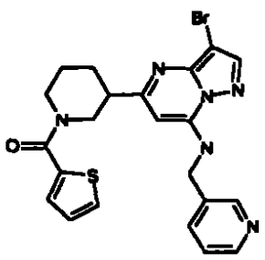
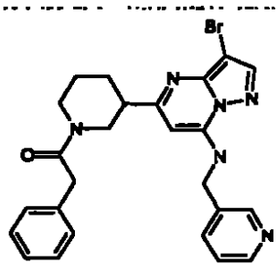
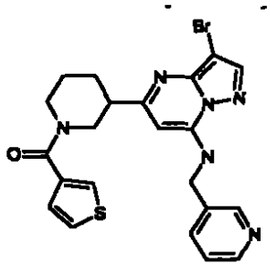
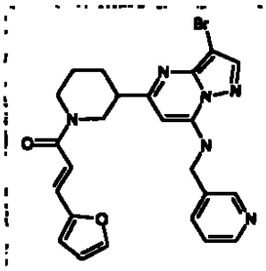
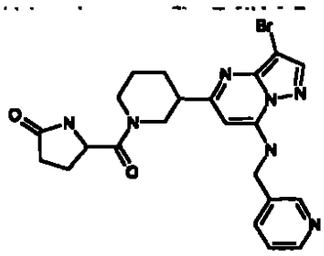
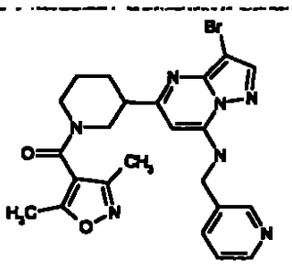
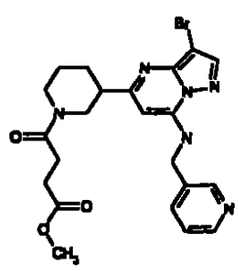
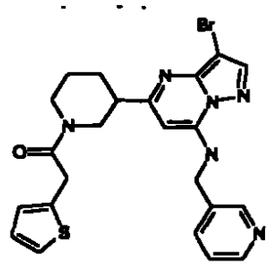
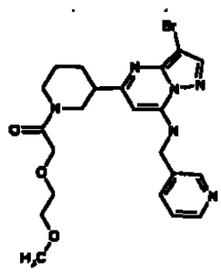
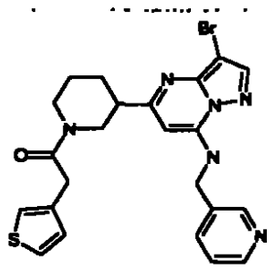
694

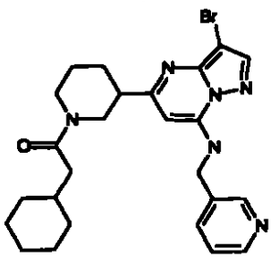
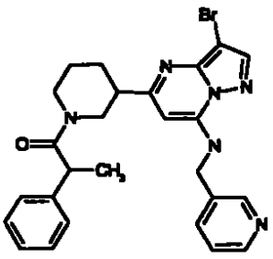
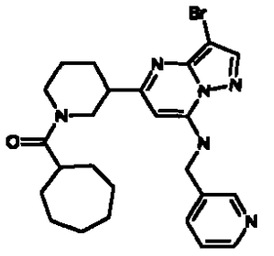
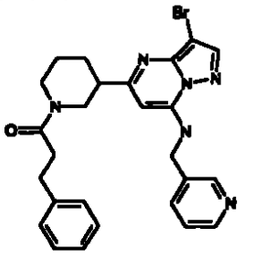
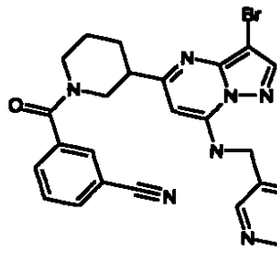
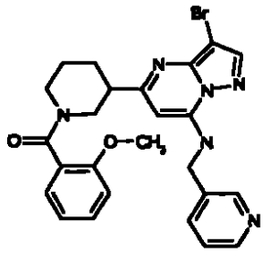
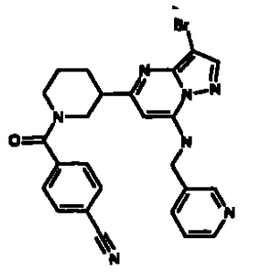
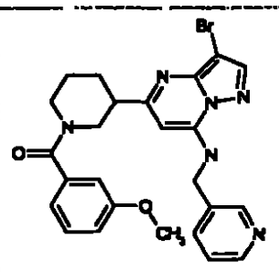
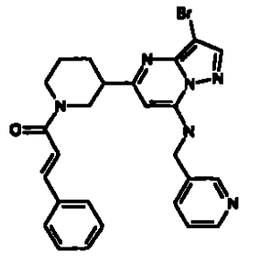
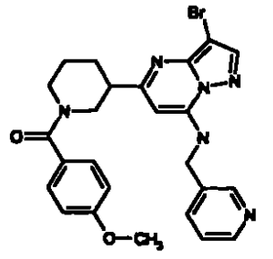
Producto	1. Ej. 2. m/z
	1. 4375 2. 499.27
	1. 4376 2. 493.27
	1. 4377 2. 535.29

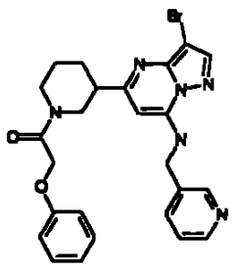
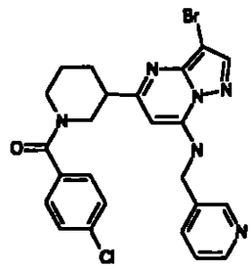
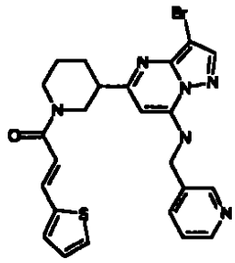
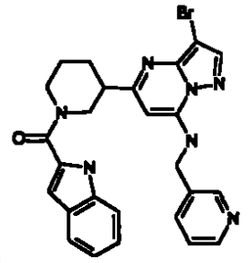
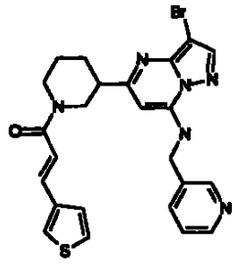
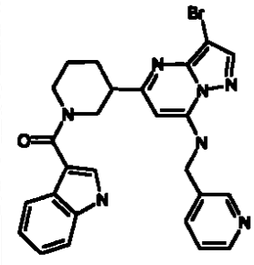
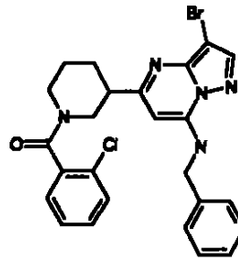
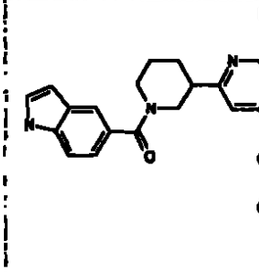
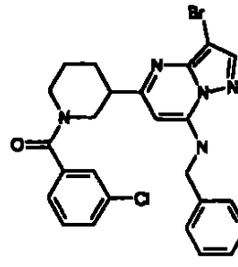
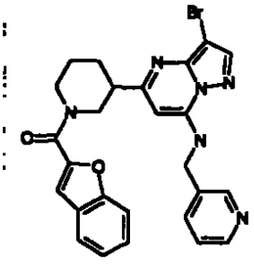
642
695

TABLA 44

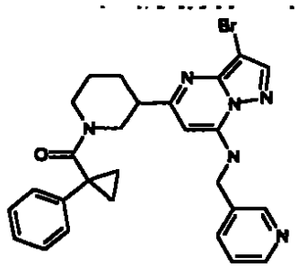
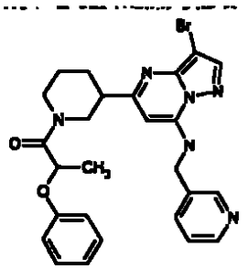
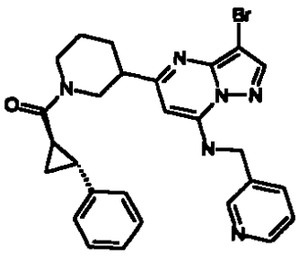
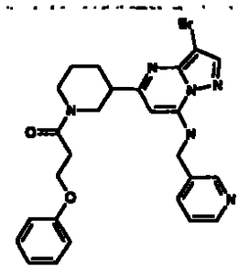
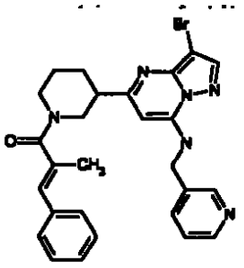
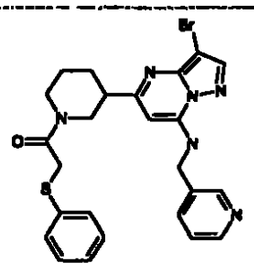
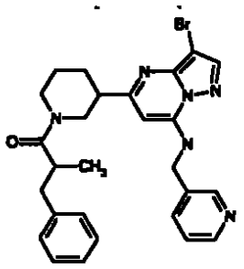
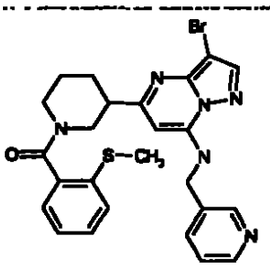
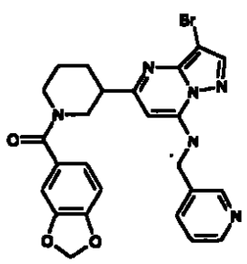
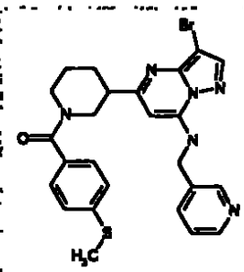
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4401 2. 471.3		1. 4406 2. 487.27
	1. 4402 2. 475.26		1. 4407 2. 487.27
	1. 4403 2. 483.27		1. 4408 2. 487.27
	1. 4404 2. 481.26		1. 4409 2. 494.3
	1. 4405 2. 485.27		1. 4410 2. 496.27

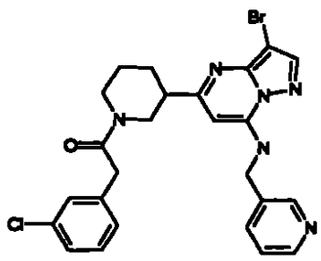
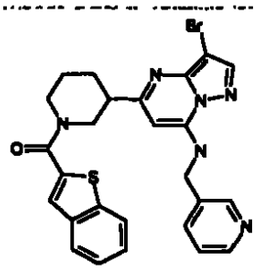
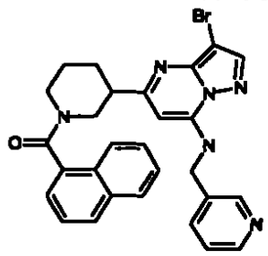
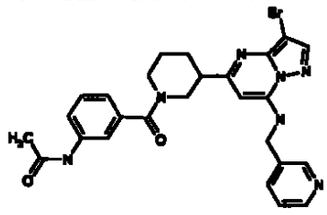
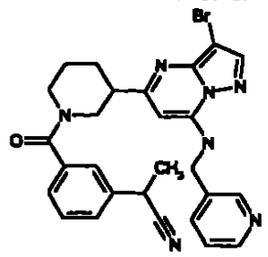
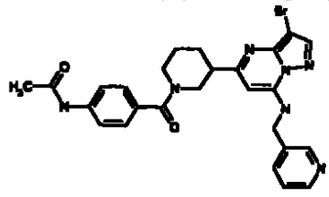
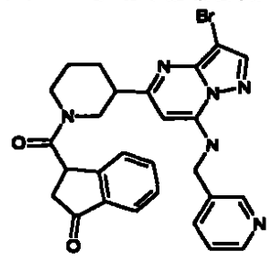
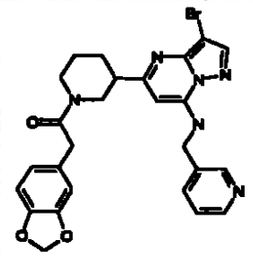
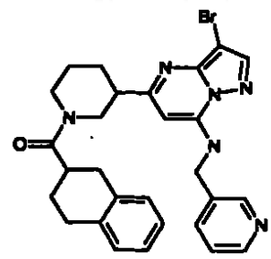
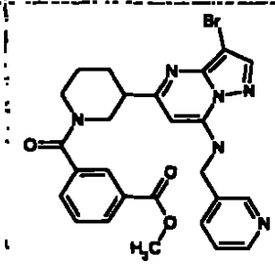
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4411 2. 499.27		1. 4416 2. 507.28
	2. 4412 2. 499.27		1. 4417 2. 509.3
	1. 4413 2. 500.27		1. 4418 2. 512.28
	1. 4414 2. 503.28		1. 4419 2. 513.28
	1. 4415 2. 505.28		1. 4420 2. 513.28

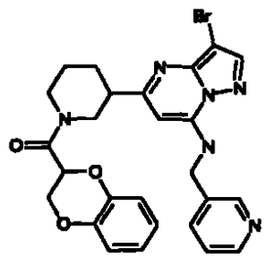
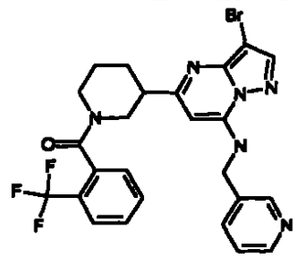
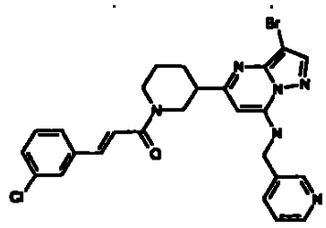
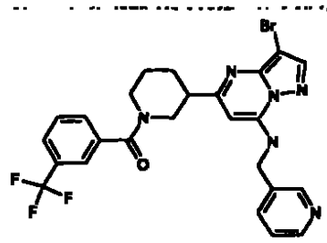
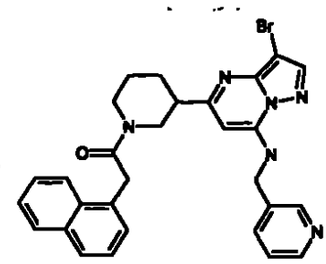
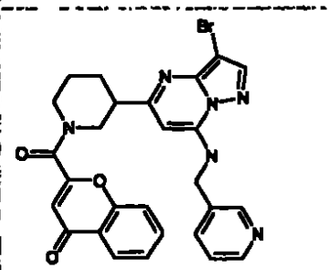
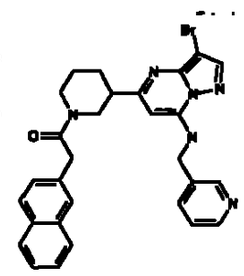
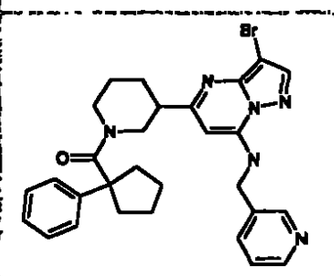
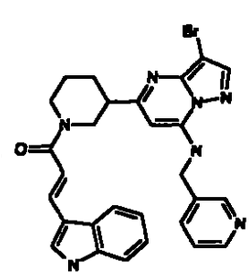
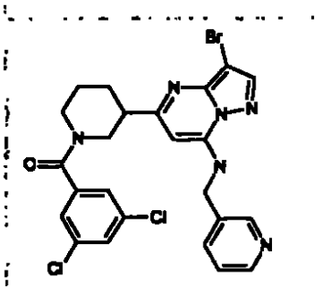
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4421 2. 513.28		1. 4426 2. 521.29
	1. 4422 2. 513.28		1. 4428 2. 521.29
	1. 4423 2. 516.28		1. 4428 2. 523.29
	1. 4424 2. 516.28		1. 4429 2. 523.29
	1. 4425 2. 519.3		1. 4430 2.523.29

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4431 2. 523.29		1. 4436 2. 527.29
	1. 4432 2. 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

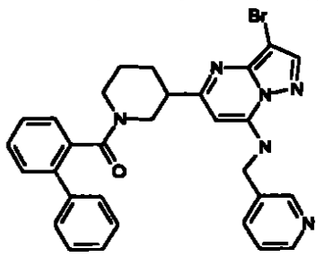
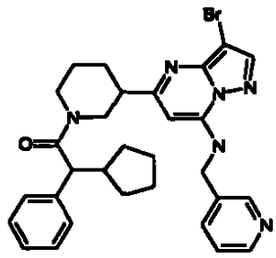
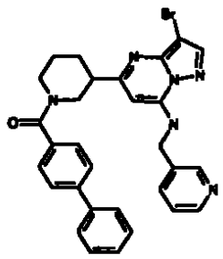
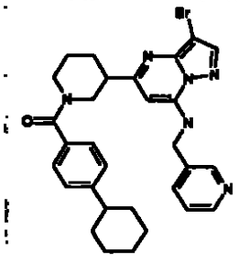
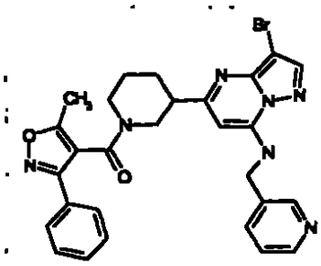
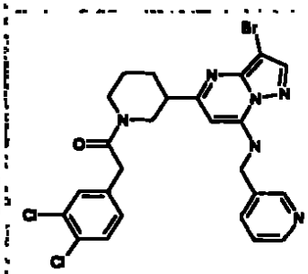
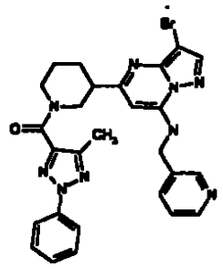
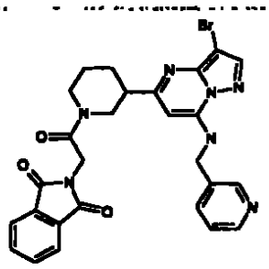
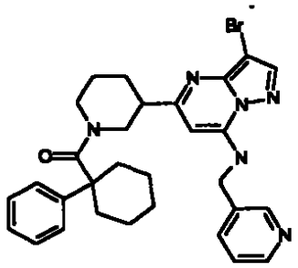
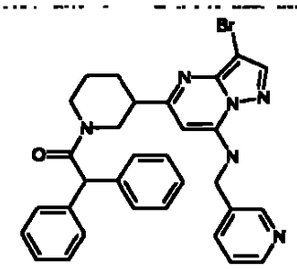
~~696~~ 699

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4441 2. 533.3		1. 4446 2. 537.3
	1. 4442 2. 531.29		1. 4447 2. 537.3
	1. 4443 2. 533.29		1. 4448 2. 539.3
	1. 4444 2. 535.29		1. 4449 2.539.3
	1. 4445 2. 537.3		1. 4450 2.539.3

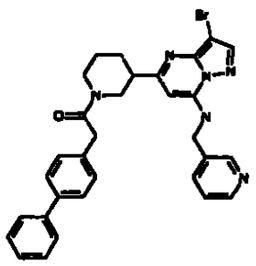
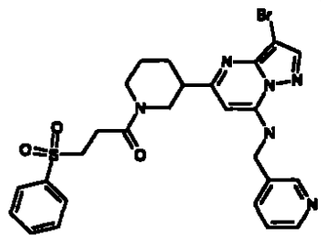
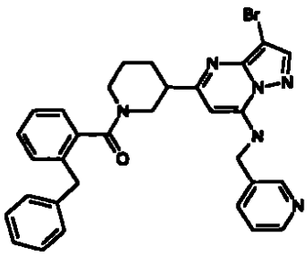
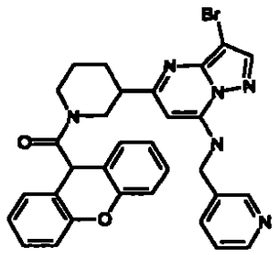
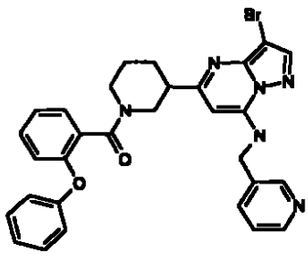
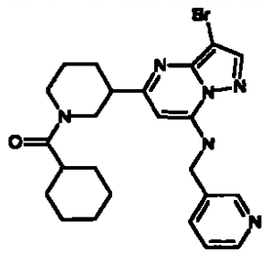
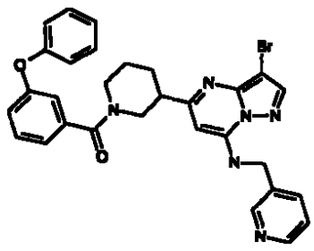
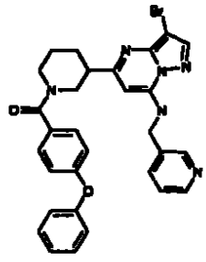
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4451 2. 541.3		1. 4456 2. 549.3
	1. 4451 2. 543.3		1. 4457 2. 550.3
	1. 4453 2. 546.3		1. 4458 2. 550.3
	1. 4454 2.547.3		1. 4459 2. 551.3
	1. 4455 2.547.3		1. 4460 2. 551.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4461 2. 549.3		1. 4466 2. 561.31
	1. 4462 2. 553.3		1. 4467 2. 561.31
	1. 4463 2. 557.3		1. 4468 2. 561.31
	1. 4464 2. 557.31		1. 4469 2. 561.31
	1. 4465 2. 558.31		1. 4470 2. 562.3

604
702

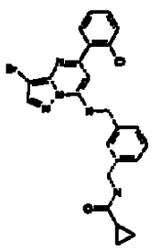
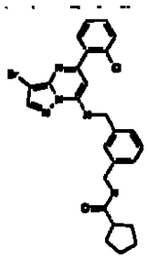
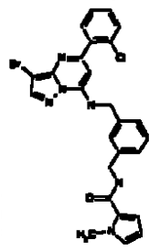
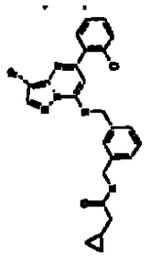
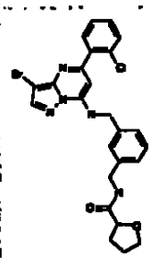
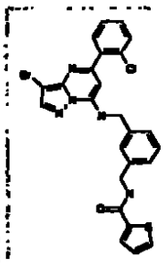
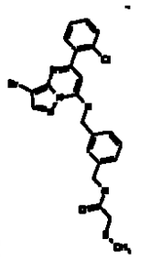
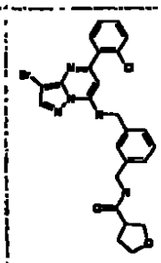
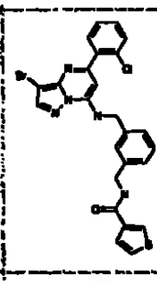
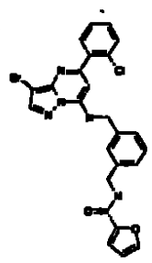
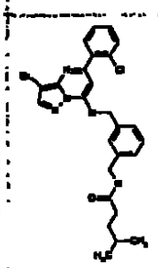
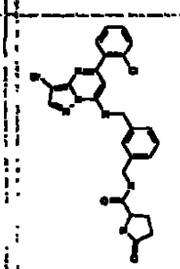
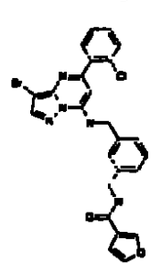
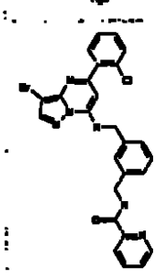
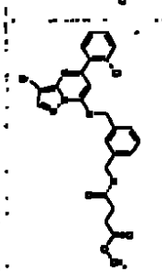
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4471 2. 569.31		1. 4476 2.572.31
	1. 4472 2. 569.31		1. 4477 2. 573.32
	1. 4473 2. 572.31		1. 4478 2. 574.32
	1. 4474 2. 572.31		1. 4479 2. 576.32
	1. 4475 2. 575.32		1. 4480 2. 583.32

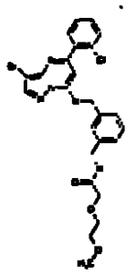
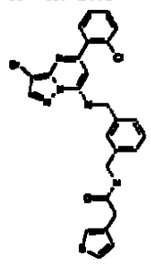
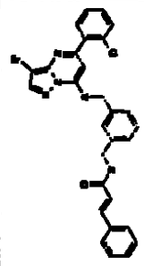
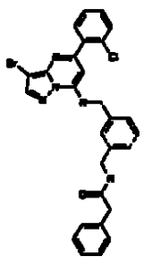
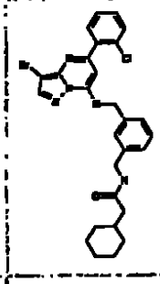
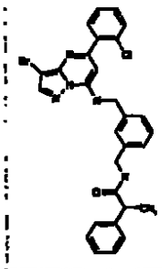
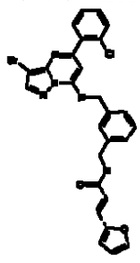
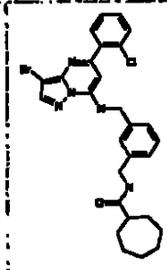
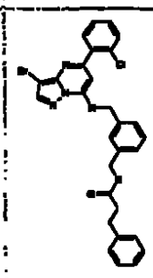
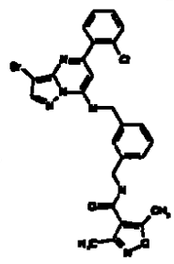
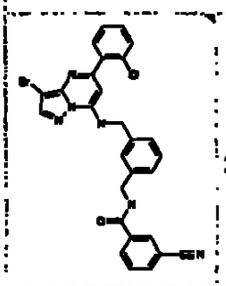
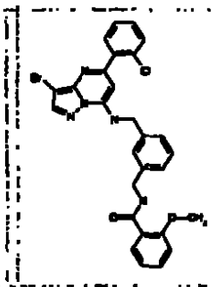
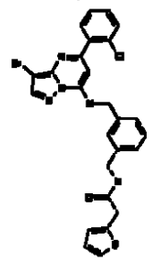
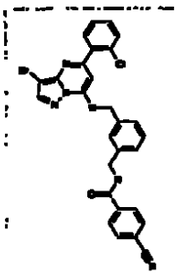
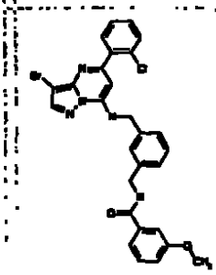
700
703

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4481 2. 583.32		1. 4486 2. 585.32
	1. 4482 2. 583.32		1. 4487 2. 597.33
	1. 4483 2. 585.32		1. 4488 2. 499.27
	1. 4484 2. 585.32		
	1. 4485 2. 585.3		

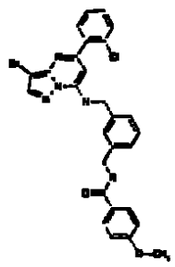
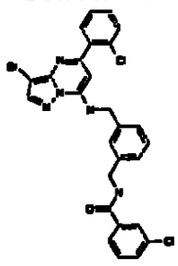
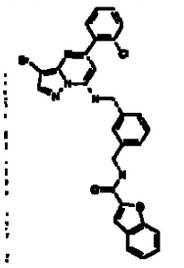
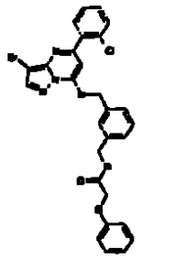
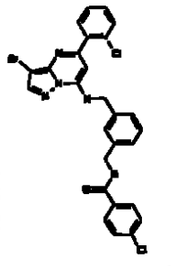
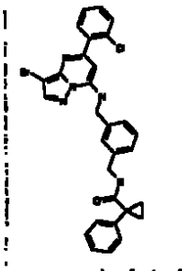
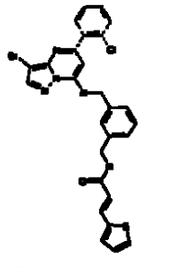
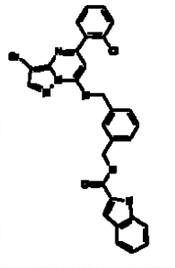
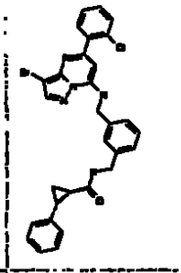
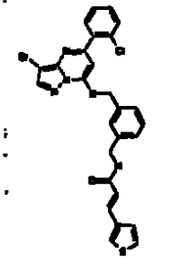
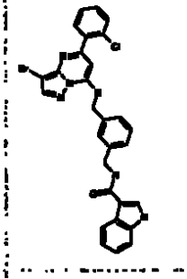
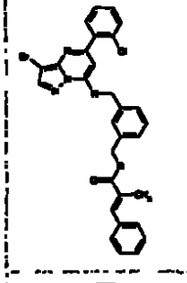
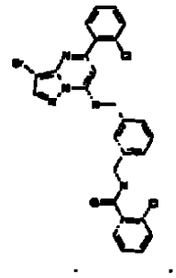
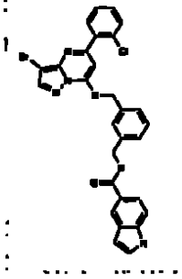
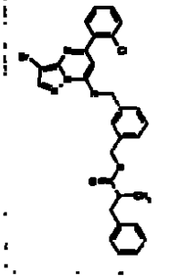
701
704

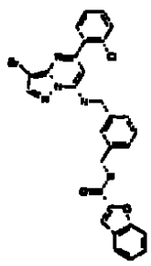
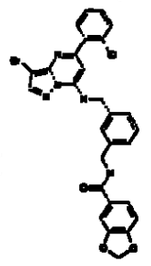
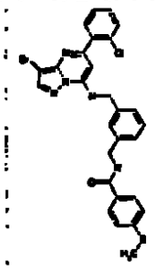
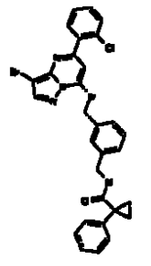
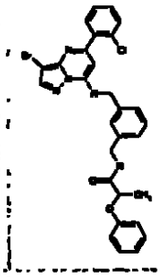
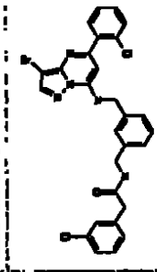
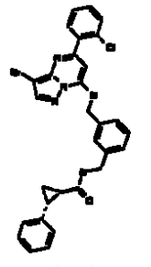
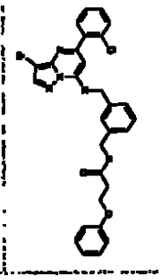
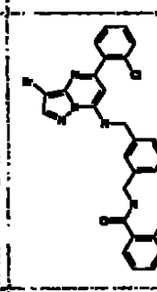
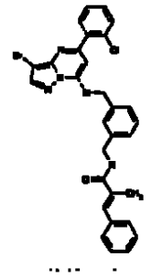
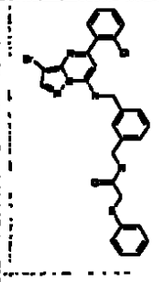
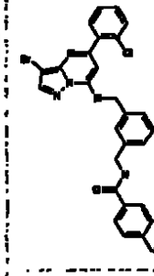
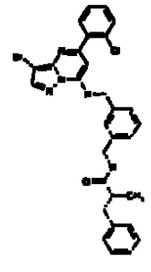
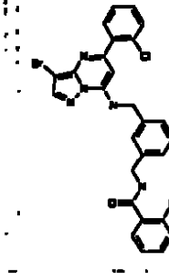
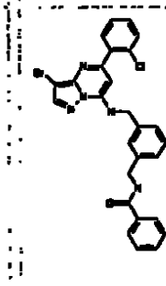
TABLA 45

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4501 2. 512.28		1. 4506 2. 540.3		1. 4511 2. 551.3
	1. 4502 2. 526.29		1. 4507 2. 542.3		1. 4512 2. 554.3
	1. 4503 2. 532.29		1. 4508 2. 542.3		1. 4513 2. 554.3
	1. 4504 2. 538.3		1. 4509 2. 542.3		1. 4514. 2. 555.31
	1. 4505 2. 538.3		1. 4510 2. 549.3		1. 4515 2. 558.31

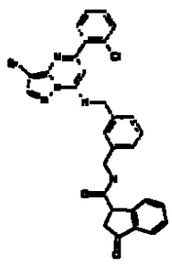
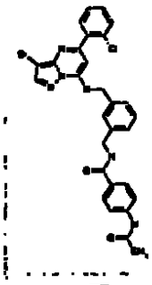
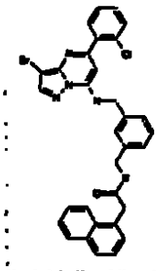
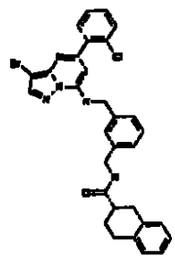
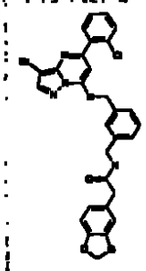
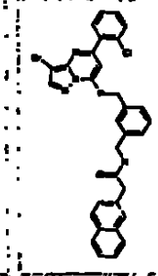
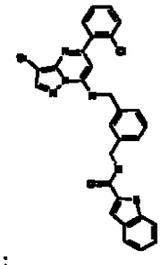
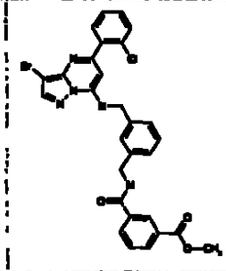
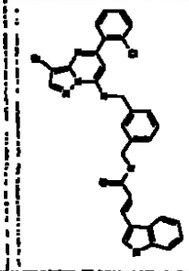
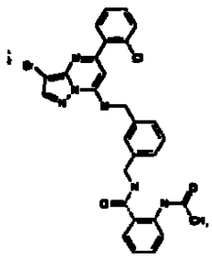
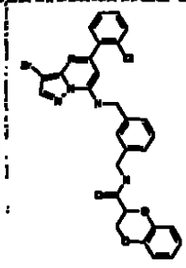
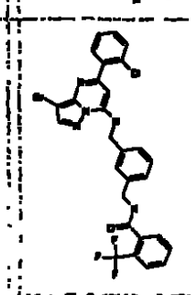
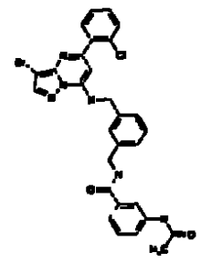
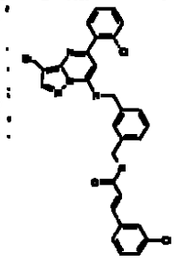
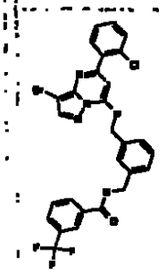
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4516 2. 560.31		1. 4521 2. 568.31		1. 4526 2. 574.32
	1. 4517 2. 562.31		1. 4522 2. 568.31		1. 4527 2. 576.32
	1. 4518 2. 564.31		1. 4523 2. 568.31		1. 4528 2. 576.32
	1. 4519 2. 567.31		1. 4524 2. 573.32		1. 4529 2. 578.32
	1. 4520 2. 568.31		1. 4525 2. 573.32		1. 4530 2. 578.32

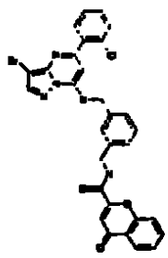
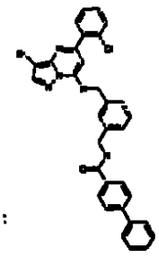
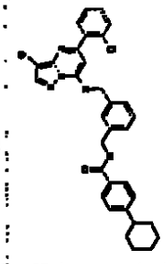
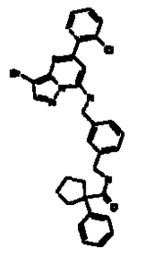
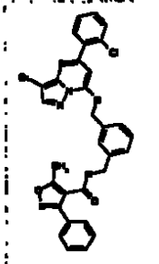
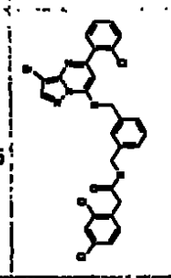
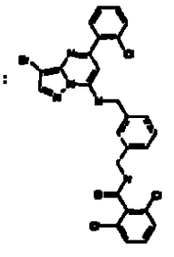
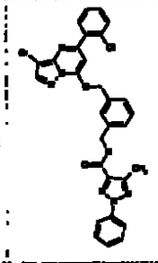
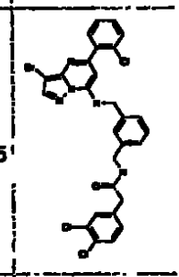
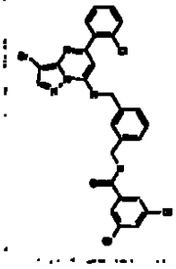
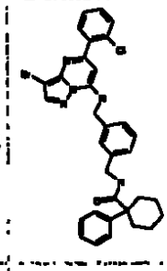
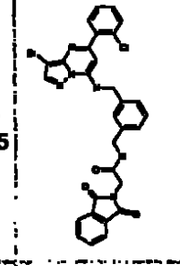
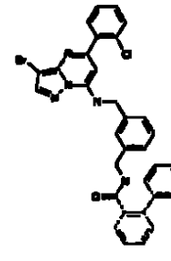
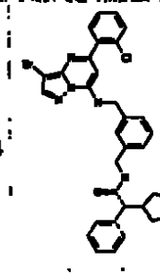
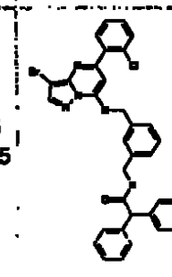
766

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4531 2. 578.32		1. 4536 2. 582.32		1. 4541 2. 588.32
	1. 4532 2. 578.32		1. 4537 2. 582.32		1. 4542 2. 588.32
	1. 4533 2. 580.32		1. 4538 2. 587.32		1. 4543 2. 588.32
	1. 4534 2. 580.32		1. 4539 2. 587.32		1. 4544 2. 588.32
	1. 4535 2. 582.32		1. 4540 2. 587.32		1. 4545 2. 590.32

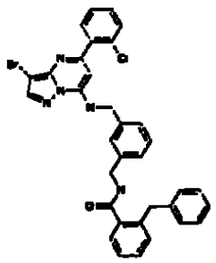
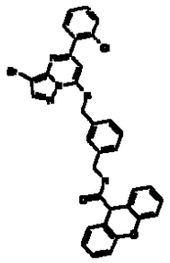
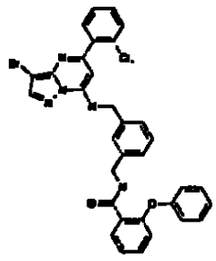
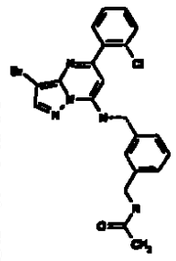
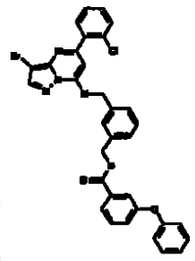
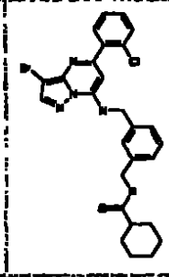
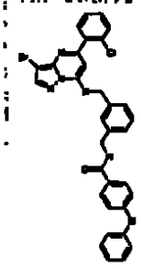
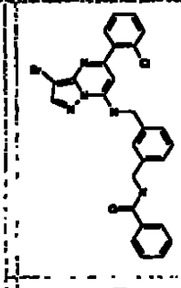
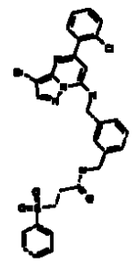
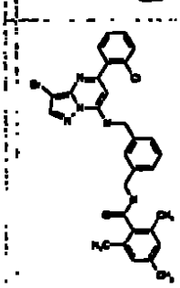
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4546 2. 588.32		1. 4551 2. 592.33		1. 4556 2. 593.33
	1. 4547 2. 588.32		1. 4552 2. 592.33		1. 4557 2. 596.33
	1. 4548 2. 588.32		1. 4553 2. 592.33		1. 4558 2. 596.33
	1. 4549 2. 588.32		1. 4554 2. 594.33		1. 4559 2. 598.33
	1. 4550 2. 590.32		1. 4555 2. 594.33		1. 4560 2. 601.33

708

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4561 2. 602.33		1. 4665 2. 605.33		1. 4571 2. 612.34
	1. 4562 2. 602.33		1. 4567 2. 606.33		1. 4572 2. 612.34
	1. 4563 2. 604.33		1. 4568 2. 606.33		1. 4573 2. 613.34
	1. 4564 2. 603.3		1. 4569 2. 606.33		1. 4574 2. 616.34
	1. 4565 2. 605.33		1. 4570 2. 608.33		1. 4575 2. 616.34

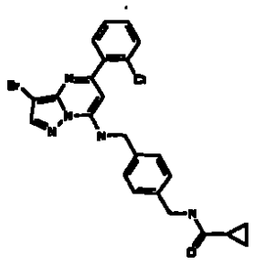
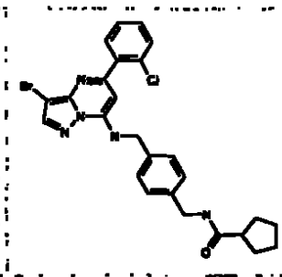
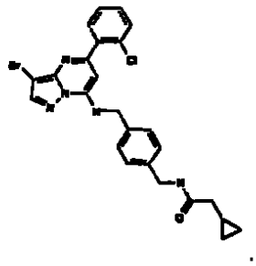
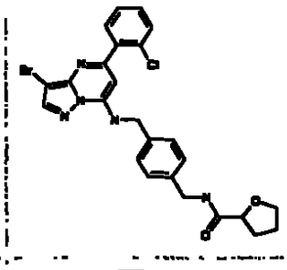
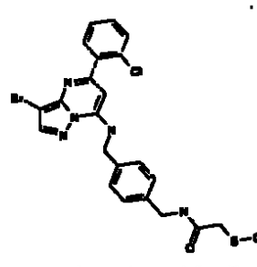
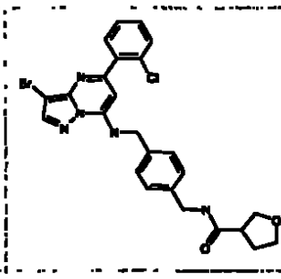
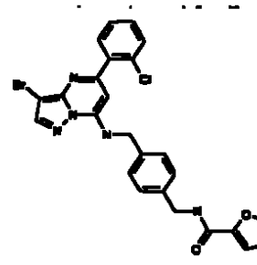
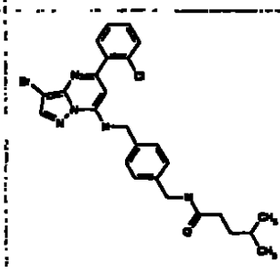
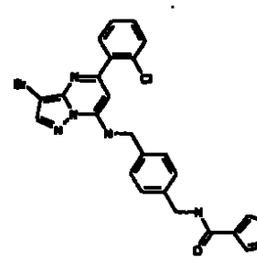
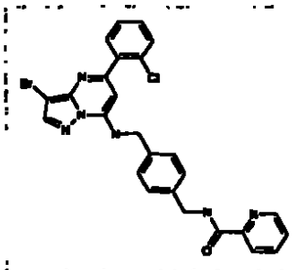
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4576 2. 616.34		1. 4581 2. 624.34		1. 4586 2. 630.35
	1. 4577 2. 616.34		1. 4582 2. 629.35		1. 4587 2. 630.35
	1. 4578 2. 616.34		1. 4583 2. 629.35		1. 4588 2. 630.35
	1. 4579 2. 616.34		1. 4584 2. 630.35		1. 4589 2. 631.35
	1. 4580 2. 624.34		1. 4585 2. 630.35		1. 4590 2. 638.35

710

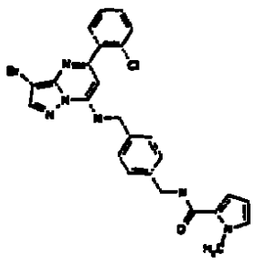
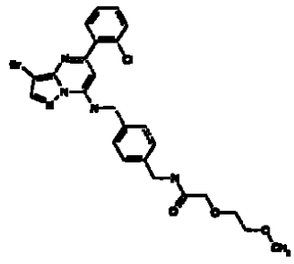
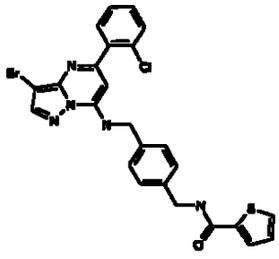
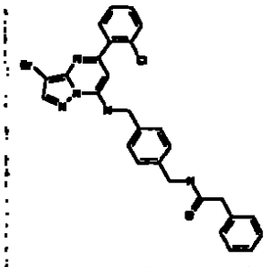
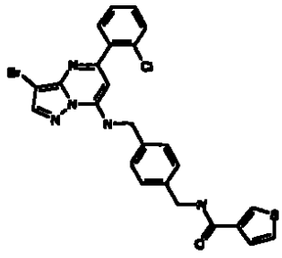
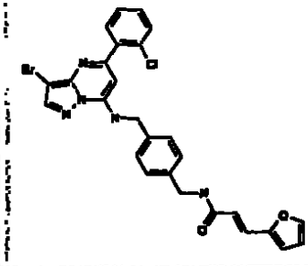
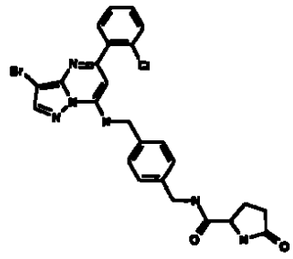
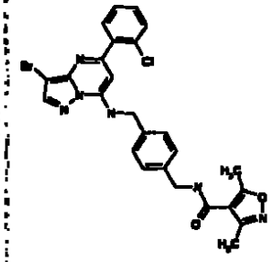
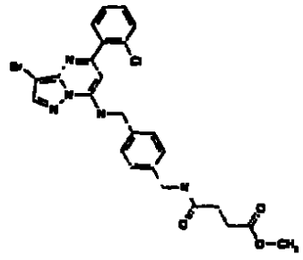
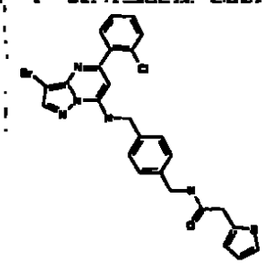
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4591 2. 638.35		1. 4596 2. 652.36
	1. 4592 2. 640.35		1. 4597 2. 486.27
	1. 4593 2. 640.35		1. 4598 2. 554.3
	1. 4594 2. 640.35		1. 4599 2. 548.3
	1. 4595 2. 640.35		1. 45100 2.

711

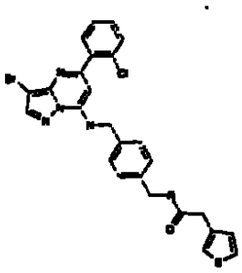
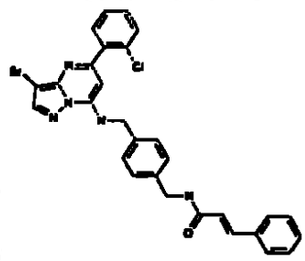
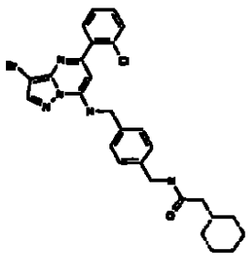
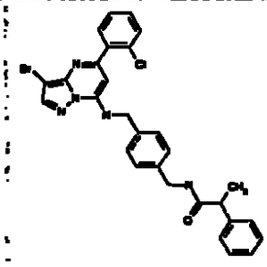
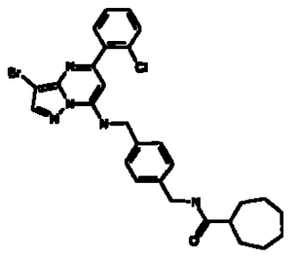
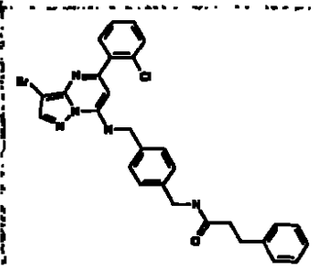
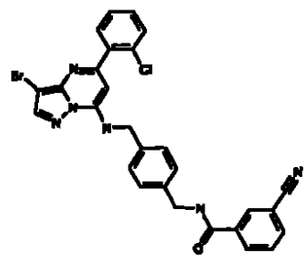
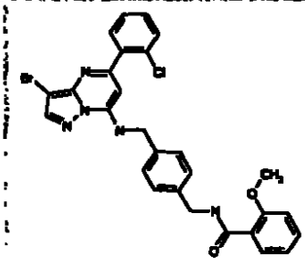
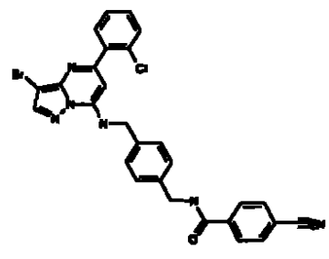
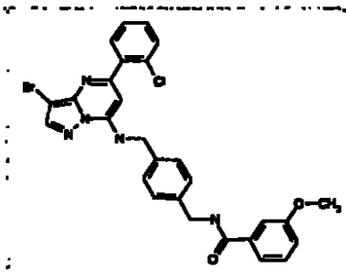
TABLA 46

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4601 2. 512.28		1. 4606 2. 540.3
	1. 4602 2. 526.29		1. 4607 2. 542.3
	1. 4603 2. 532.29		1. 4608 2. 542.3
	1. 4604 2. 538.3		1. 4609 2. 542.3
	1. 4605 2. 536.3		1. 4610 2. 547.3

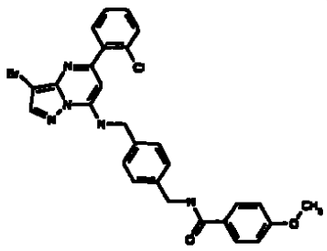
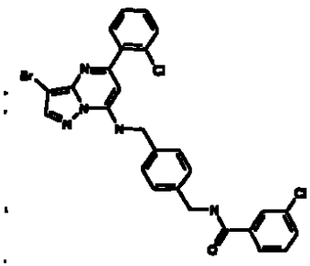
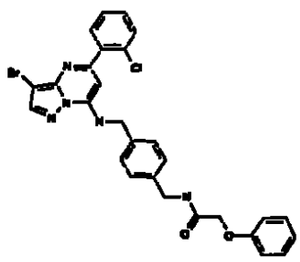
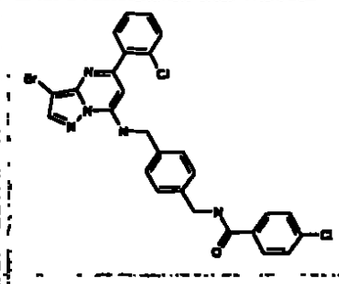
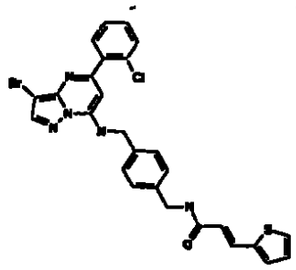
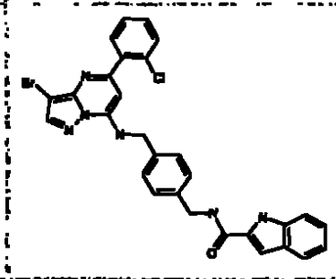
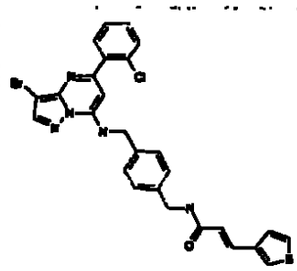
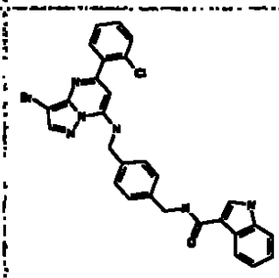
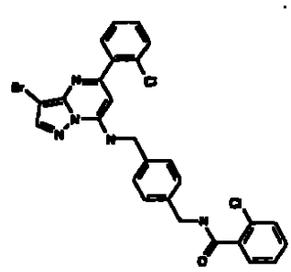
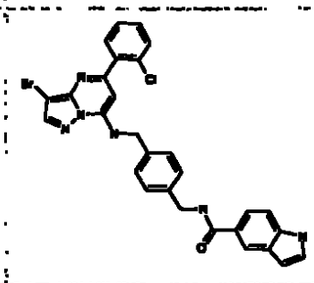
712

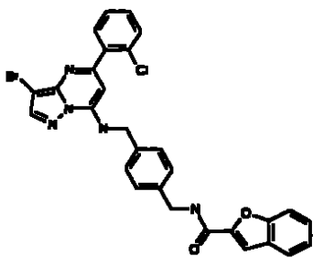
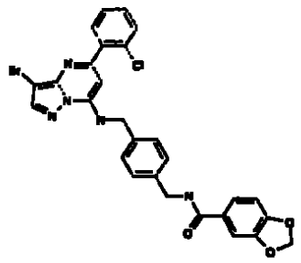
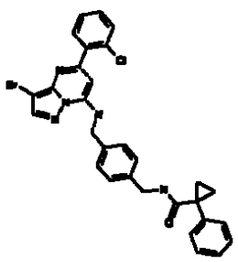
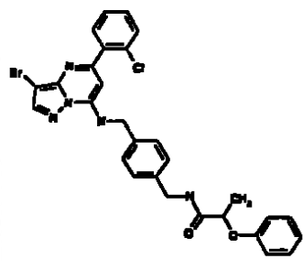
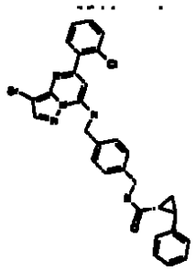
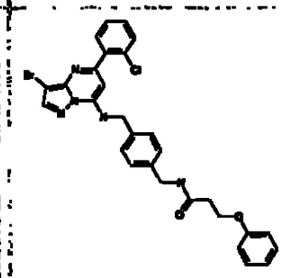
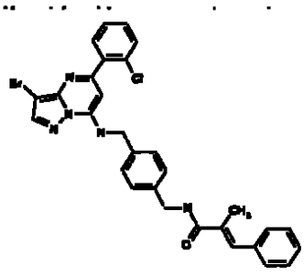
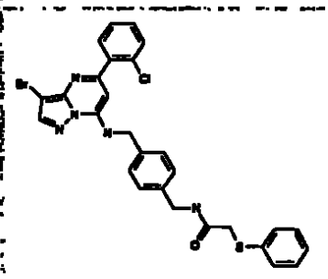
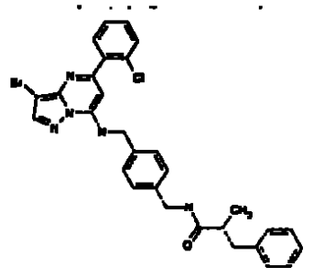
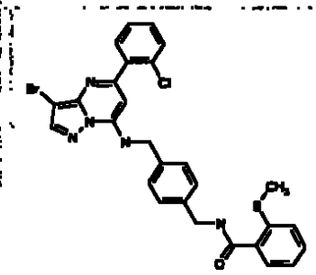
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4611 2. 551.3		1. 4616 2. 560.31
	1. 4612 2. 552.3		1. 4617 2. 562.31
	1. 4613 2. 552.3		1. 4618 2. 562.3
	1. 4614 2. 555.31		1. 4619 2. 567.31
	1. 4615 2. 558.31		1. 4620 2. 568.31

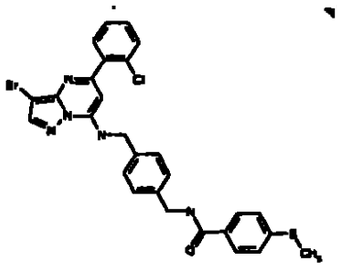
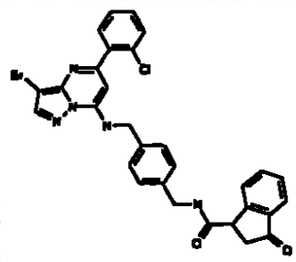
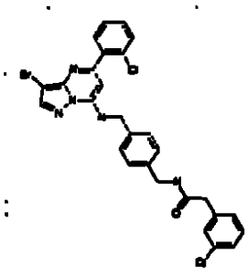
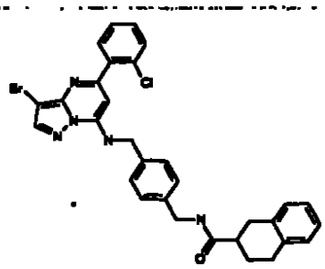
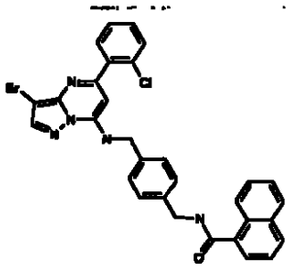
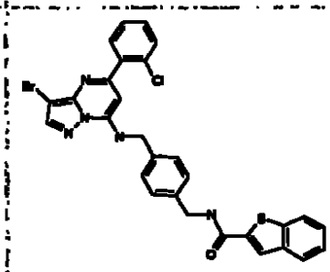
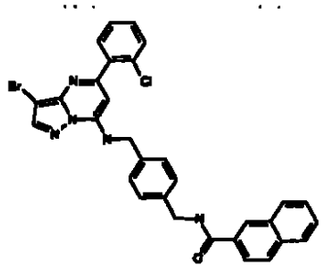
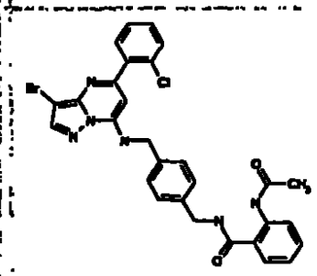
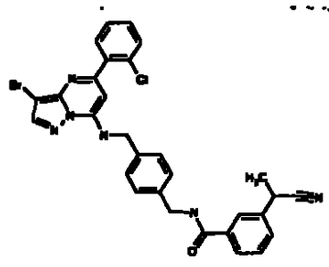
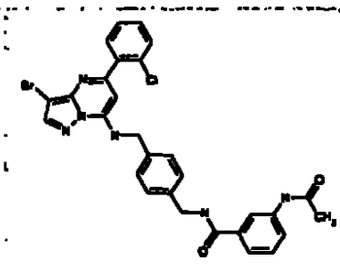
713

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4621 2. 568.31		1. 4626 2. 574.32
	1. 4622 2. 568.31		1. 4627 2. 576.32
	1. 4623 2. 568.31		1. 4628 2. 576.32
	1. 4624 2. 573.32		1. 4629 2. 578.32
	1. 4625 2. 573.32		1. 4630 2. 578.32

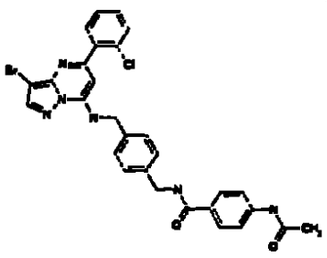
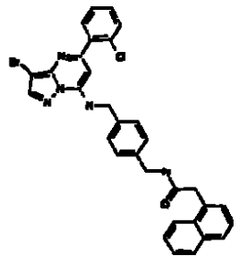
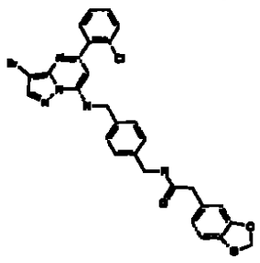
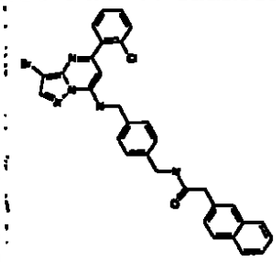
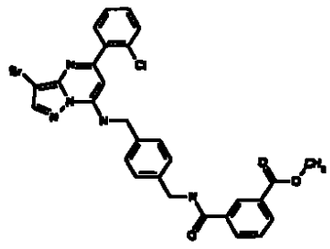
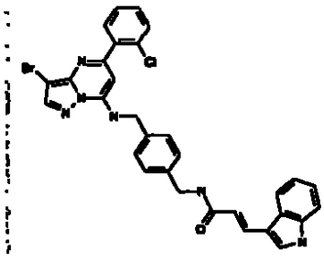
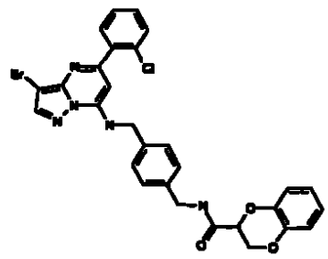
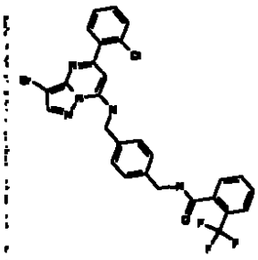
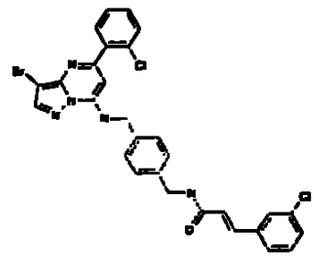
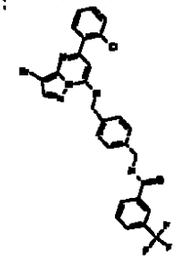
714

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4631 2. 578.32		1. 4636 2. 582.32
	1. 4632 2. 578.32		1. 4637 2. 582.32
	1. 4633 2. 580.32		1. 4638 2. 587.32
	1. 4634 2. 580.32		1. 4639 2. 585.3
	1. 4635 2. 582.32		1. 4640 2. 585.3

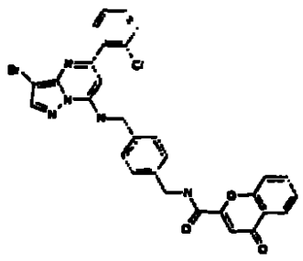
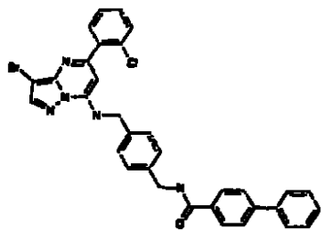
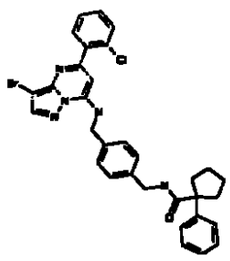
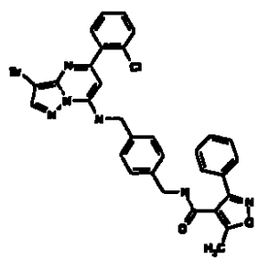
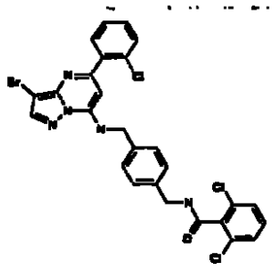
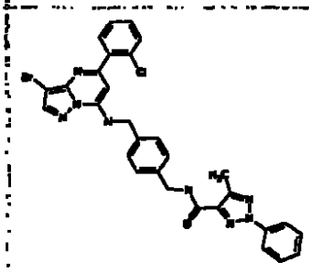
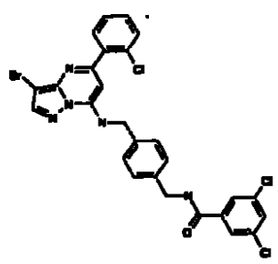
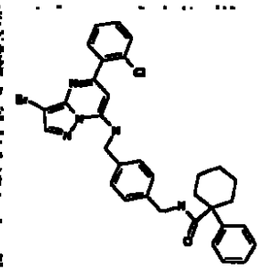
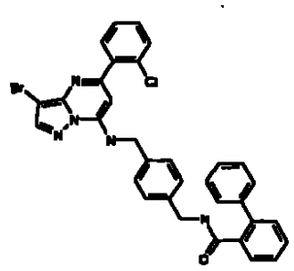
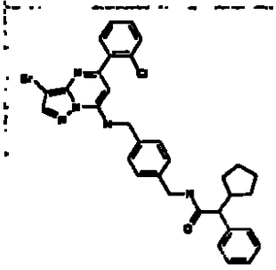
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4641 2. 588.32		1. 4646 2. 592.33
	1. 4642 2. 588.32		1. 4647 2. 592.33
	1. 4643 2. 588.32		1. 4648 2. 592.33
	1. 4644 2,. 588.32		1. 4649 2.
	1. 4645 2. 590.32		1. 4650 2. 594.33

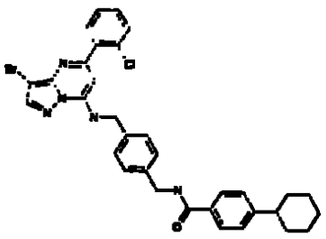
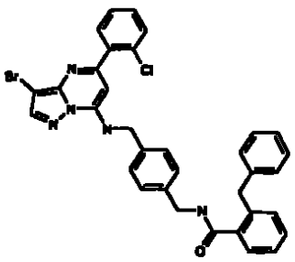
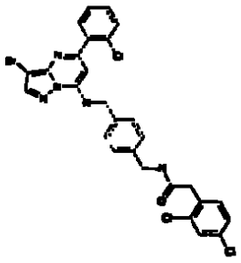
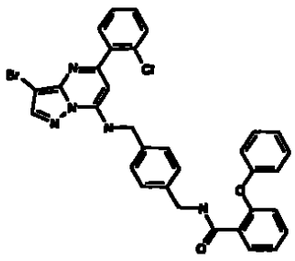
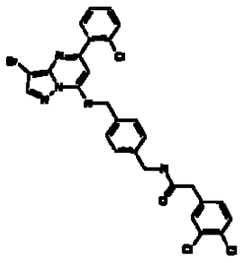
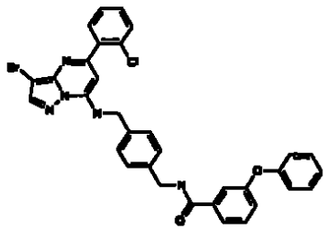
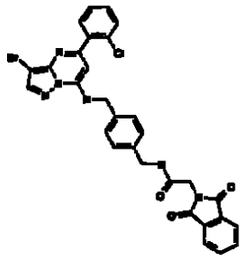
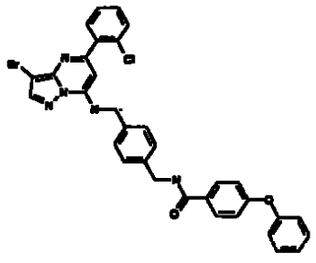
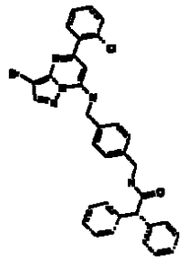
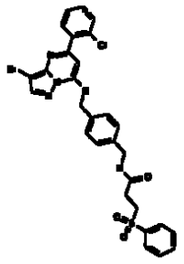
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4651 2. 594.33		1. 4656 2. 602.33
	1. 4652 2. 596.33		1. 4657 2. 602.33
	1. 4653 2. 596.3		1. 4658 2. 604.33
	1. 4654 2. 598.33		1. 4659 2. 603.3
	1. 4655 2. 601.33		1. 4660 2. 605.33

- 714.
717

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4661 2. 605.33		1. 4666 2. 612.34
	1. 4662 2. 606.33		1. 4667 2. 612.34
	1. 4663 2. 606.33		1. 4668 2. 613.34
	1. 4664 2. 606.33		1. 4669 2. 616.34
	1. 4665 2. 608.33		1. 4670 2. 616.34

718

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4671 2. 616.34		1. 4676 2. 624.34
	1. 4672 2. 616.34		1. 4677 2. 629.35
	1. 4673 2. 616.34		1. 4678 2. 629.35
	1. 4674 2. 616.34		1. 4679 2. 630.35
	1. 4675 2. 624.34		1. 4680 2. 630.35

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4681 2. 630.35		1. 4686 2. 638.35
	1. 4682 2. 630.35		1. 4687 2. 640.35
	1. 4683 2. 630.35		1. 4688 2. 640.35
	1. 4684 2. 631.35		4689 2.
	1. 4685 2. 638.35		1. 4690 2. 640.35

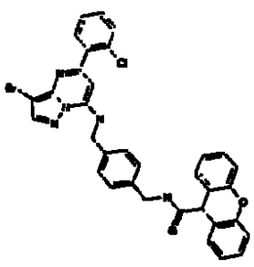
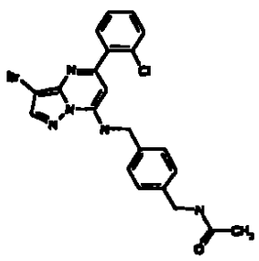
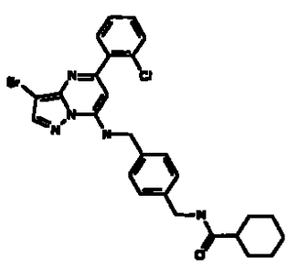
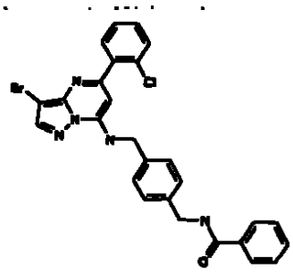
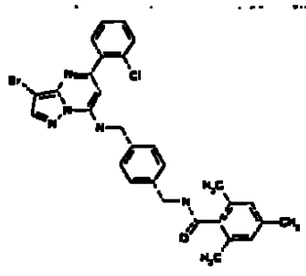
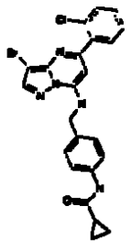
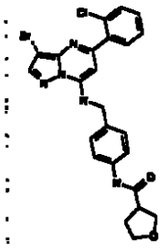
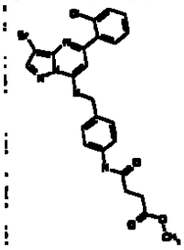
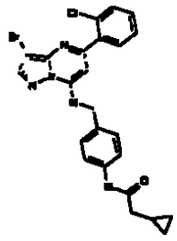
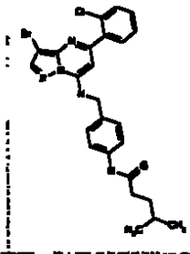
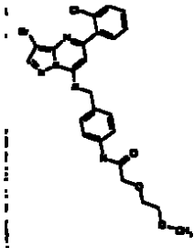
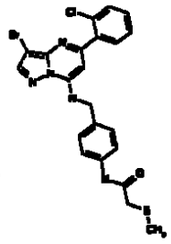
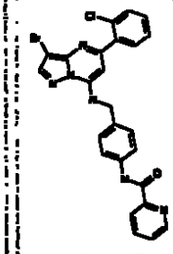
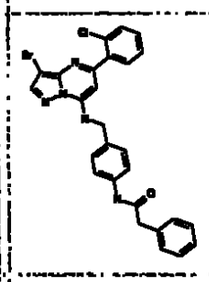
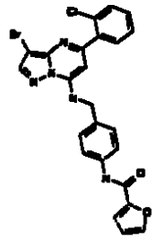
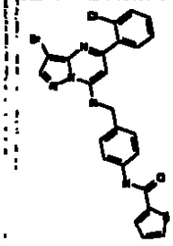
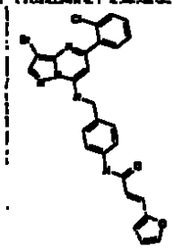
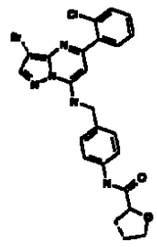
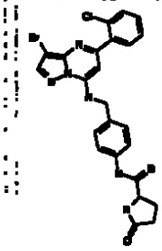
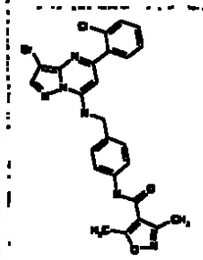
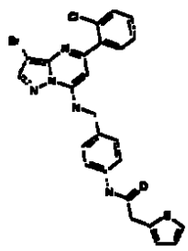
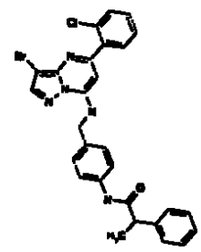
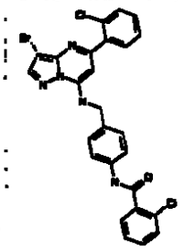
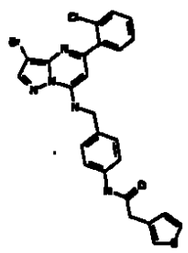
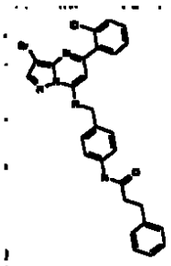
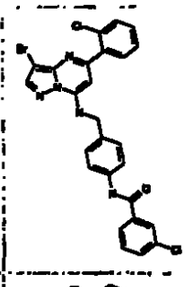
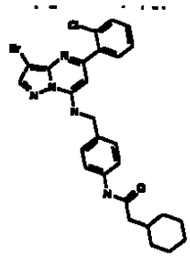
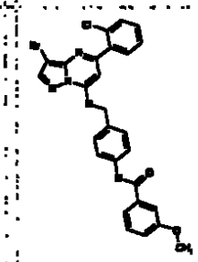
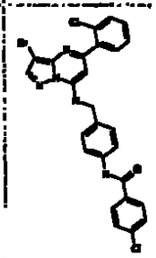
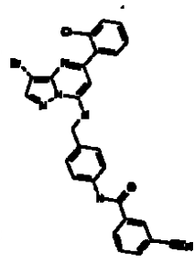
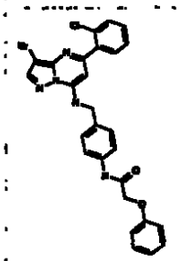
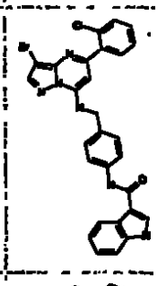
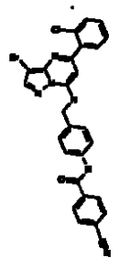
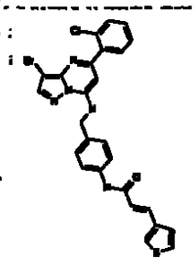
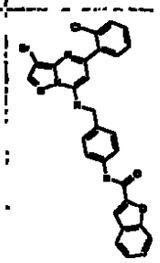
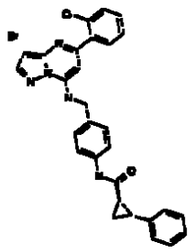
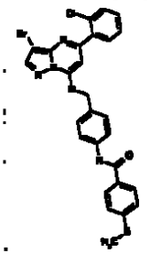
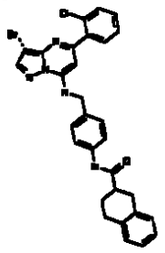
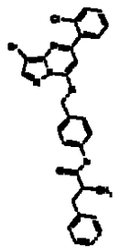
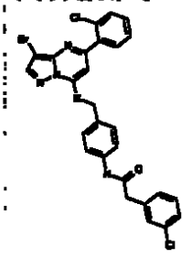
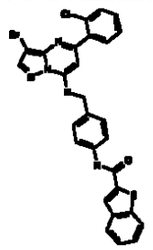
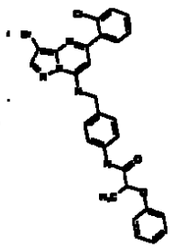
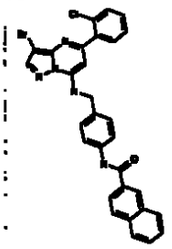
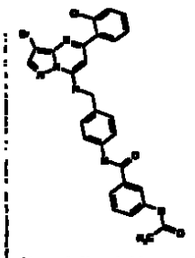
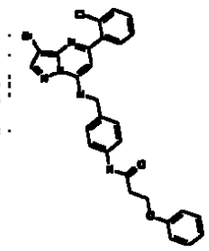
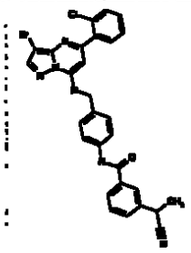
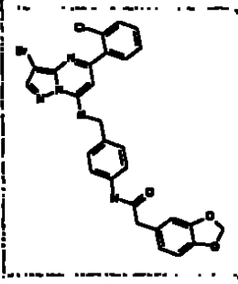
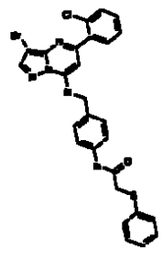
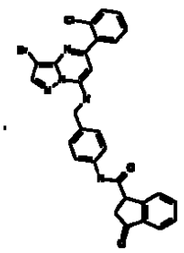
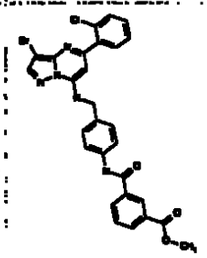
Producto	1. Ej. 2. m/z
	1. 4691 2. 652.36
	1. 4692 2. 484.3
	1. 4693 2. 554.3
	1. 4694 2. 548.3
	1. 4695 2. 590.32

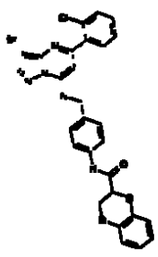
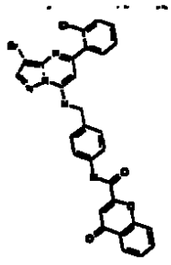
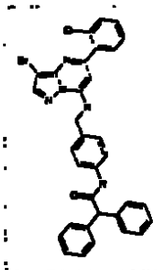
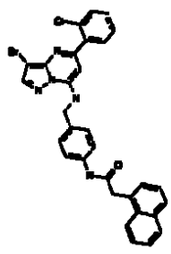
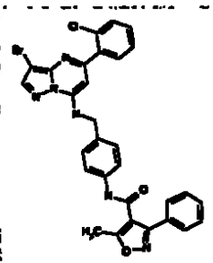
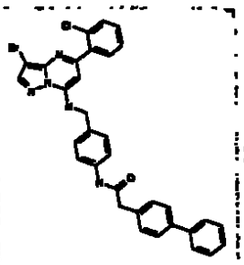
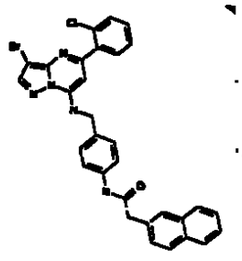
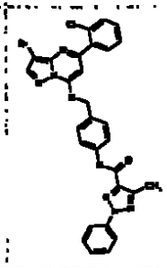
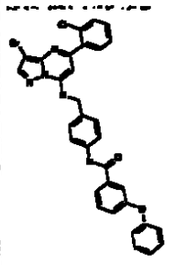
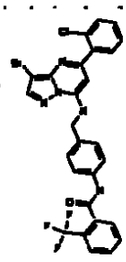
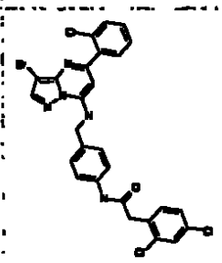
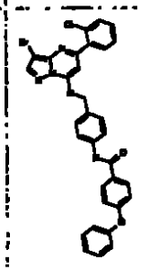
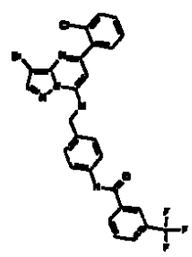
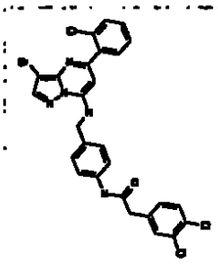
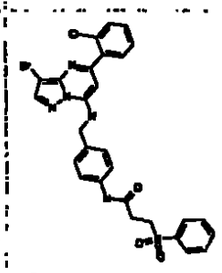
TABLA 47

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4701 2. 498.27		1. 4706 2. 528.29		1. 4711 2. 544.3
	1. 4702 2. 512.28		1. 4707 2. 528.29		1. 4712 2. 546.3
	1. 4703 2. 518.28		1. 4708 2. 535.29		1. 4713 2. 548.3
	1. 4704 2. 524.29		1. 4709 2. 540.3		1. 4714 2. 550.3
	1. 4705 2. 528.29		1. 4710 2. 541.3		1. 4715 2. 553.3

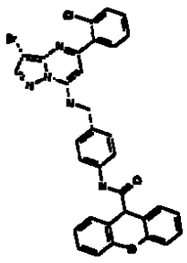
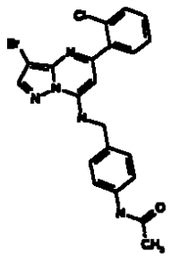
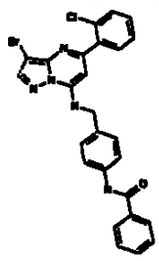
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4716 2. 554.3		1. 4721 2. 562.31		1. 4726 2. 568.31
	1. 4717 2. 554.3		1. 4722 2. 582.31		1. 4727 2. 568.31
	1. 4718 2. 554.3		1. 4723. 2 564.31		1. 4728 2. 568.31
	1. 4719 2. 559.31		1. 4724 2. 564.31		1. 4729 2. 573.32
	1. 4720 2. 559.31		1. 4725 2. 586.31		1. 4730 2. 574.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4731 2. 574.32		1. 4736 2. 580.32		1. 4741 2. 588.32
	1. 4732 2. 576.32		1. 4737 2. 582.32		1. 4742 2. 590.32
	1. 4733 2. 578.32		1. 4738 2. 584.32		1. 4743 2. 591.33
	1. 4734 2. 578.32		1. 4739 2. 585.32		1. 4744 2. 592.33
	1. 4735 2. 580.32		1. 4740 2. 588.32		1. 4745 2. 592.33

724

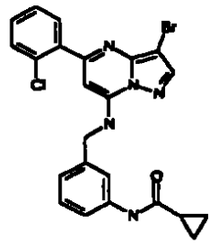
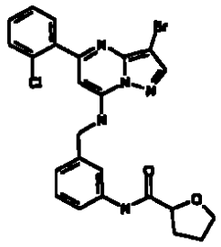
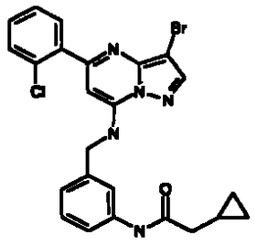
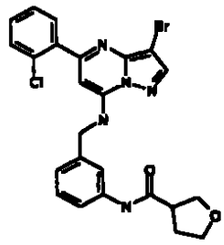
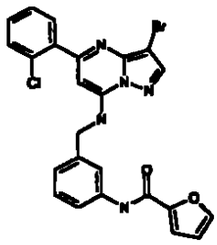
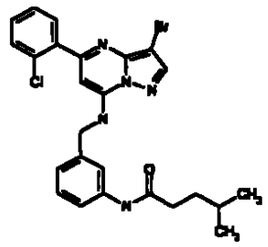
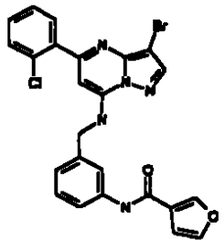
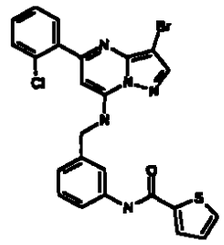
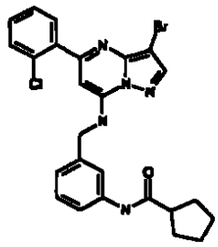
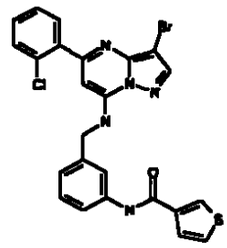
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4746 2. 592.33		1. 4751 2. 602.33		1. 4756 2. 624.34
	1. 4747 2. 598.33		1. 4752 2. 615.34		1. 4757 2. 624.34
	1. 4748 2. 598.33		1. 4753 2. 615.34		1. 4758 2. 626.34
	1. 4749 2. 602.33		1. 4754 2. 616.34		1. 4759 2. 624.34
	1. 4750 2. 602.33		1. 4755 2. 616.34		1. 4760 2. 626.34

725

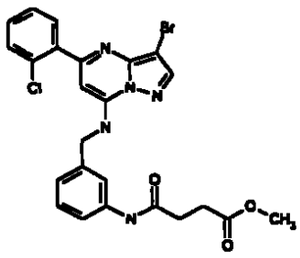
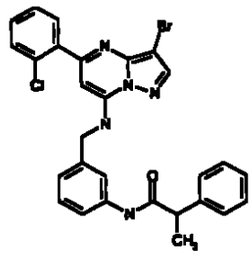
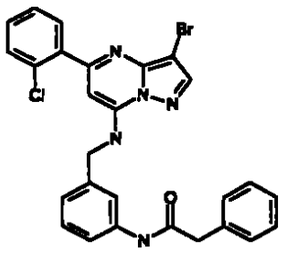
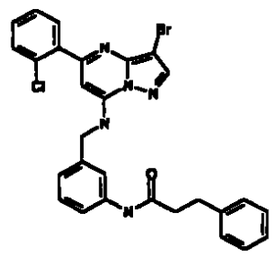
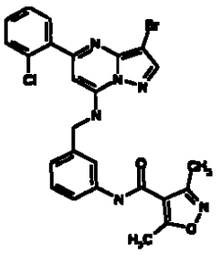
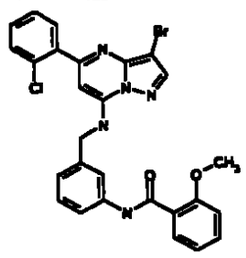
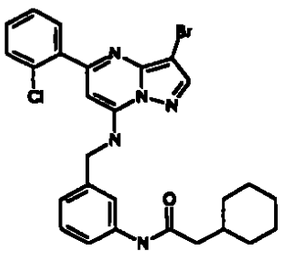
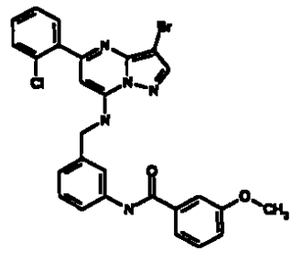
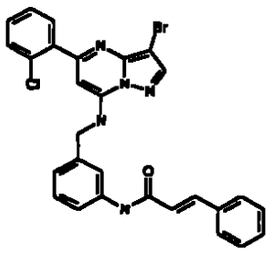
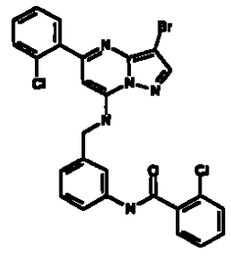
Producto	1. Ej. 2. m/z
	1. 4761 2. 638.35
	1. 4762 2. 472.26
	1. 4763 2. 534.29

223 726

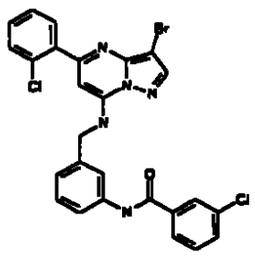
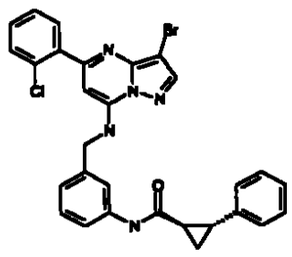
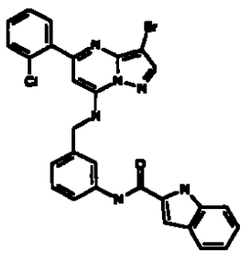
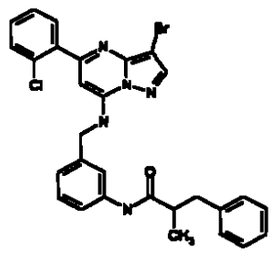
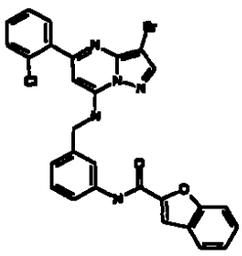
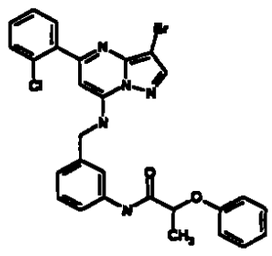
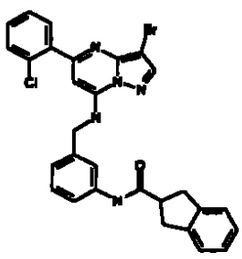
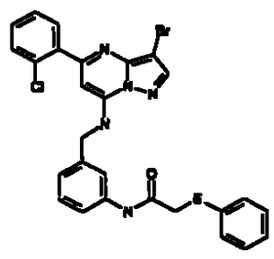
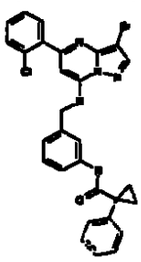
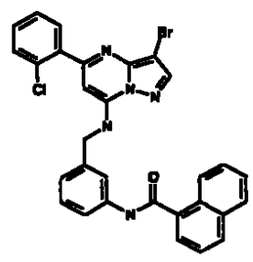
TABLA 48

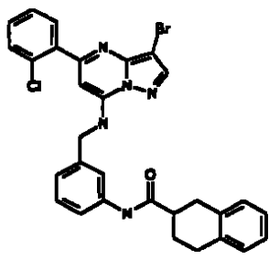
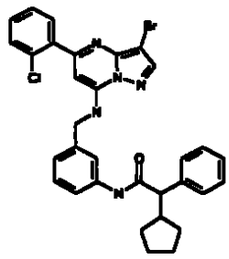
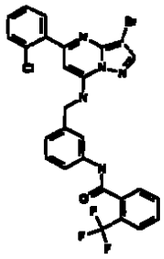
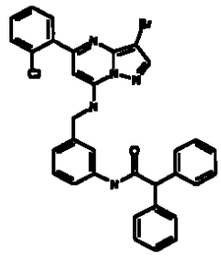
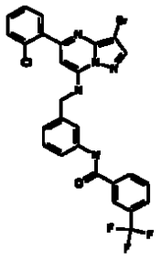
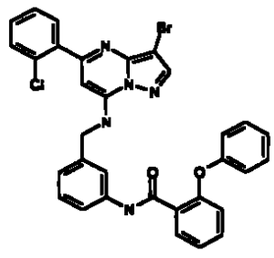
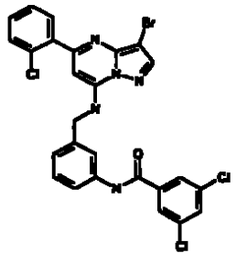
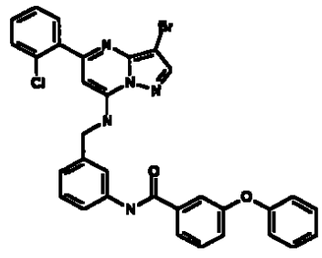
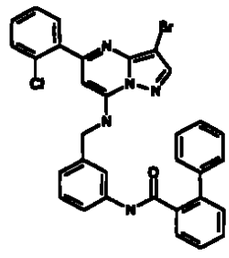
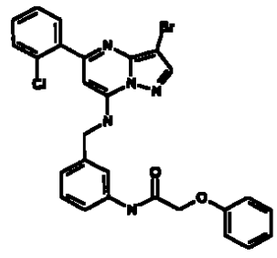
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4801 2. 498.27		1.4808 2. 528.29
	1. 4802 2. 512.28		1.. 4807 2. 528.29
	1. 4803 2. 524.29		1. 4808 2. 528.29
	1. 4804 2. 524.29		1. 4809 2. 540.3
	1. 4805 2. 526.29		1. 4810 2. 540.3

824
727

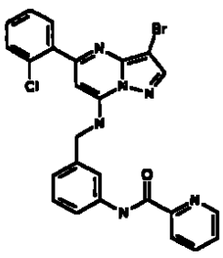
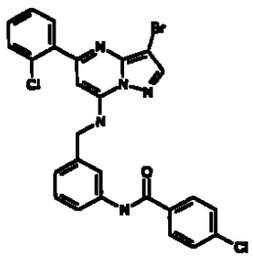
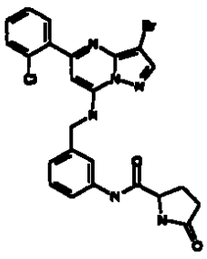
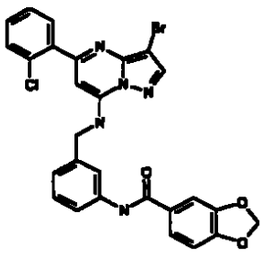
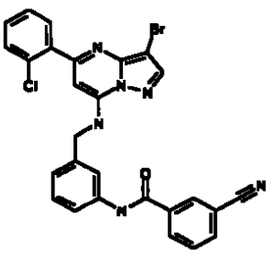
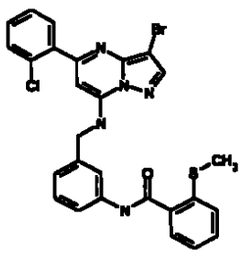
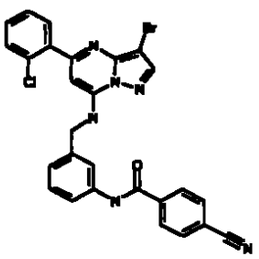
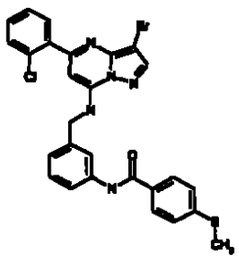
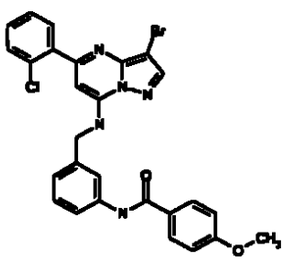
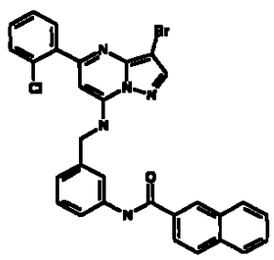
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4811 2. 544.3		1. 4816 2. 562.31
	1. 4812 2. 548.3		1. 4817 2. 562.31
	1. 4813 2. 553.3		1. 4818 2. 564.31
	1. 4814 2. 554.3		1. 4819 2. 564.31
	1. 4815 2. 560.31		1. 4820 2. 568.31

728

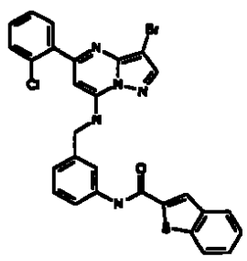
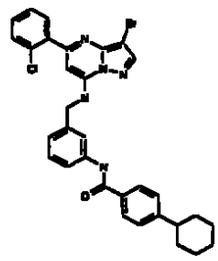
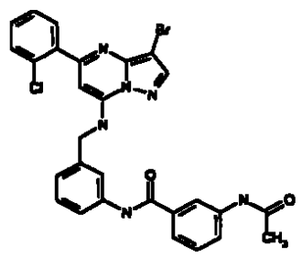
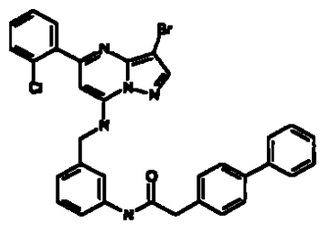
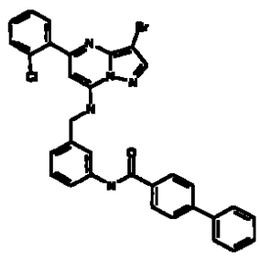
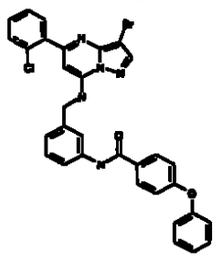
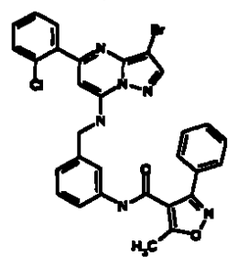
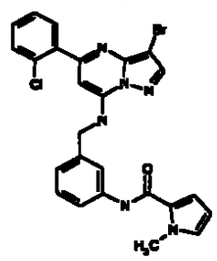
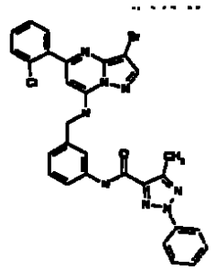
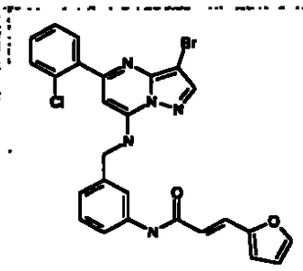
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4821 2. 568.31		1. 4826 2. 574.32
	1. 4822 2. 573.32		1. 4828 2. 576.32
	1. 4821 2. 574.32		1. 4829 2. 578.32
	1. 4824 2. 574.32		1. 4829 2. 580.32
	1. 4825 2. 574.32		1. 4830 2. 584.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4831 2. 588.32		1. 4836 2. 616.34
	1. 4832 2. 602.33		1. 4837 2. 624.34
	1. 4833 2. 602.33		1. 4838 2. 626.34
	1. 4834 2. 602.33		1. 4839 2. 626.34
	1. 4835 2. 610.34		1. 4840 2. 564.31

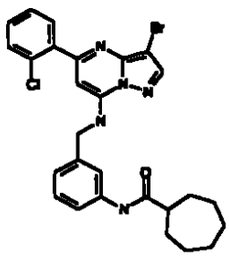
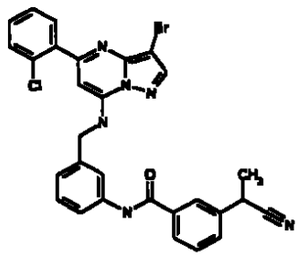
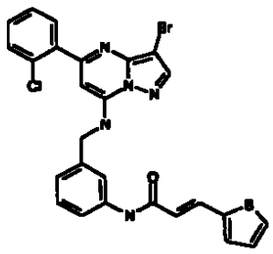
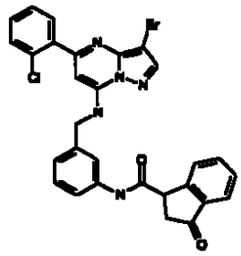
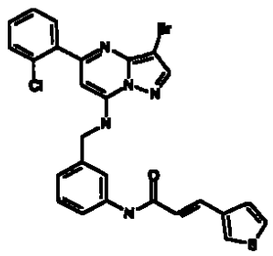
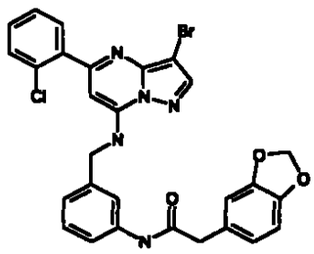
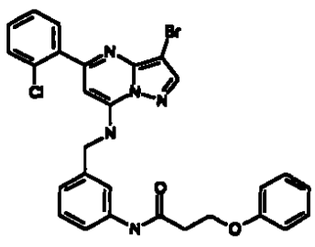
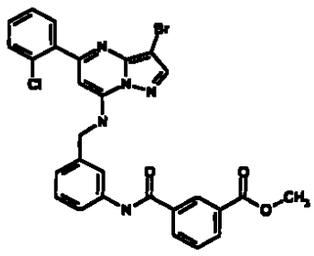
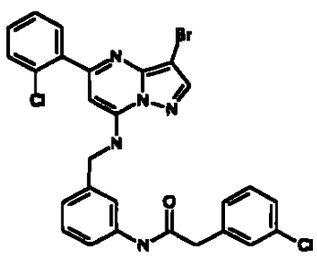
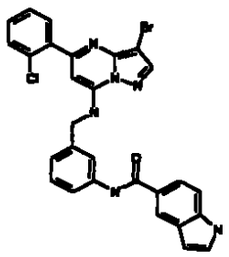
727 730

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4841 2. 535.29		1. 4846 2. 568.31
	1. 4842 2. 541.3		1. 4847 2. 578.32
	1. 4843 2. 559.31		1. 4848 2. 580.32
	1. 4844 2. 559.31		1. 4849 2. 580.32
	1. 4845 2. 564.31		1. 4850 2. 584.32

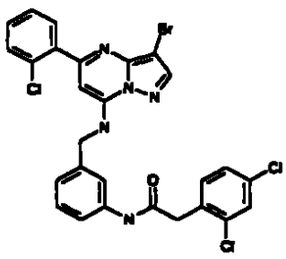
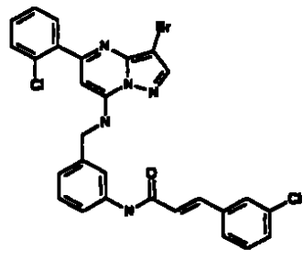
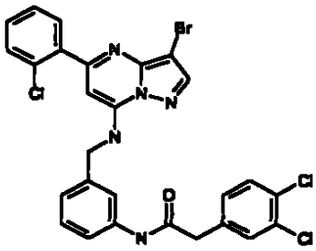
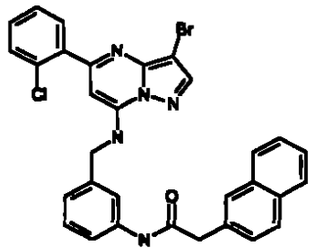
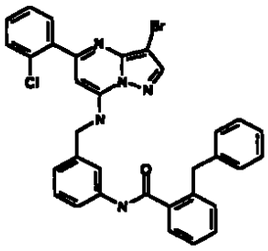
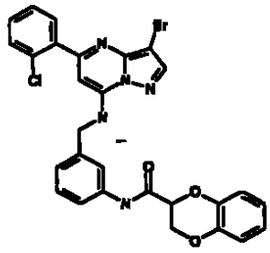
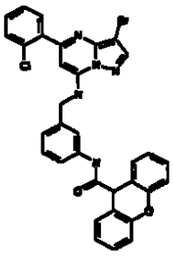
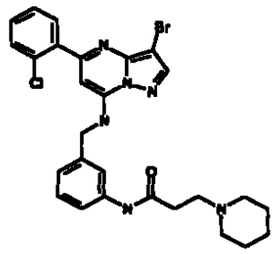
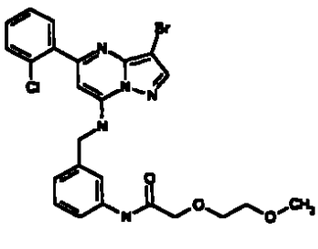
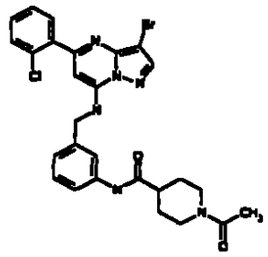
728
731

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4851 2. 590.32		1. 4856 2. 616.34
	1. 4852 2. 591.33		1. 4857 2. 624.34
	1. 4853 2. 610.34		1. 4858 2. 626.34
	1. 4854 2. 615.34		1. 4859 2. 537.3
	1. 4855 2. 615.34		1. 4860 2. 550.3

732

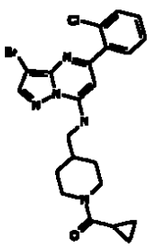
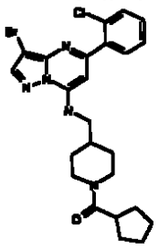
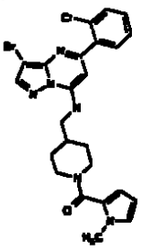
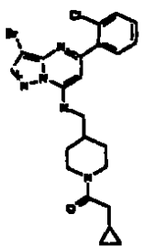
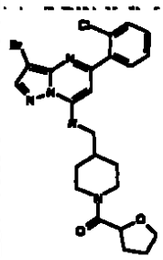
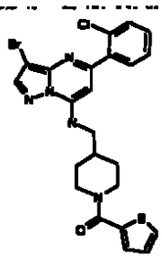
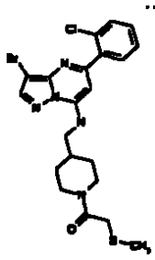
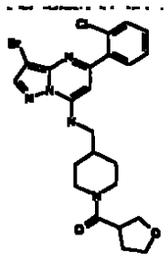
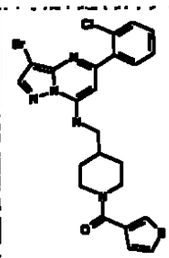
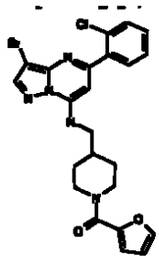
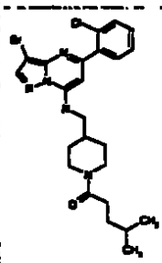
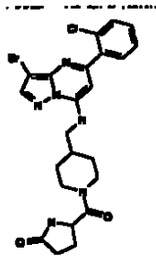
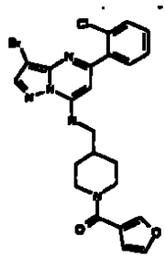
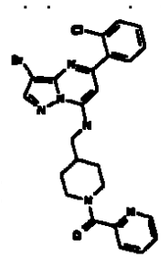
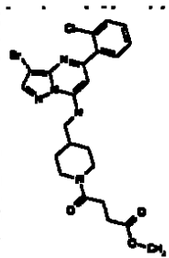
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4861 2. 554.3		1. 4866 2. 587.32
	1. 4862 2. 566.31		1. 4867 2. 588.32
	1. 4863 2. 566.31		1. 4868 2. 592.33
	1. 4864 2. 578.32		1. 4869 2. 592.33
	1. 4865 2. 582.32		1. 4870 2. 573.32

733

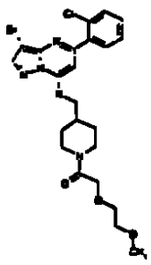
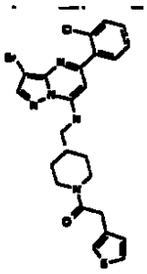
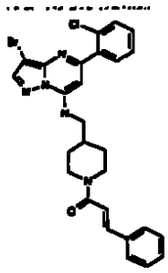
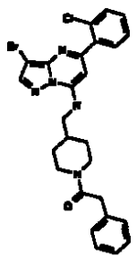
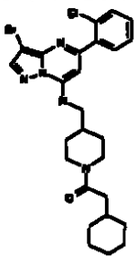
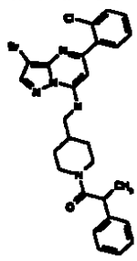
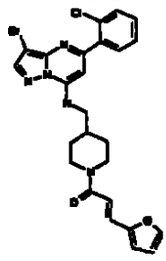
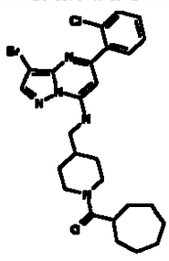
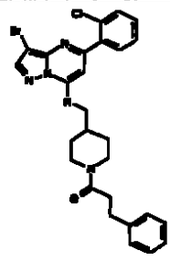
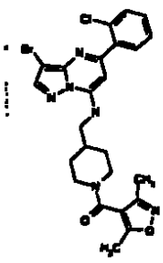
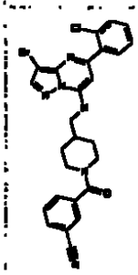
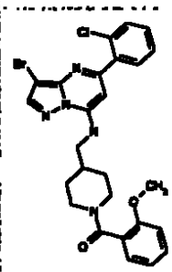
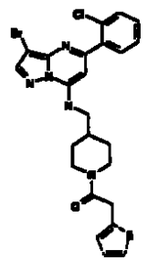
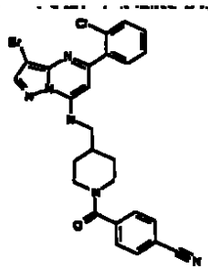
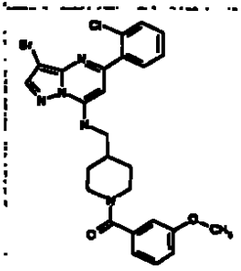
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4871 2. 616.34		1. 4876 2. 594.33
	1. 4872 2. 616.34		1. 4877 2. 598.33
	1. 4873 2. 624.34		1. 4878 2. 592.33
	1. 4874 2. 638.35		1. 4879 2. 569.31
	1. 4875 2. 546.3		1. 4880 2. 583.32

734

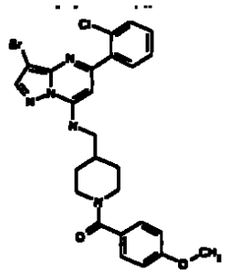
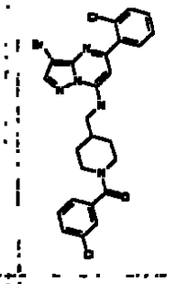
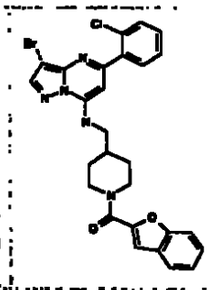
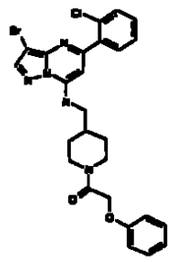
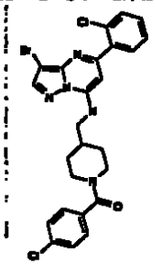
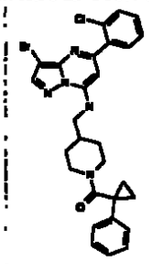
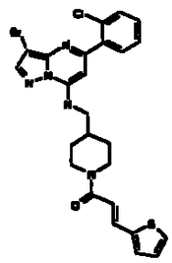
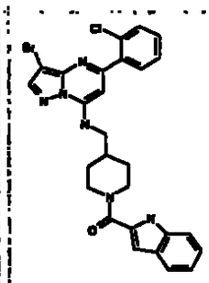
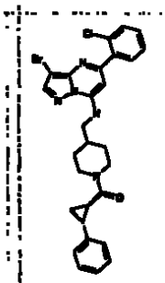
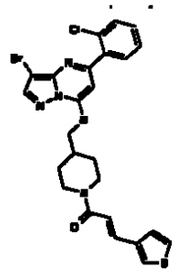
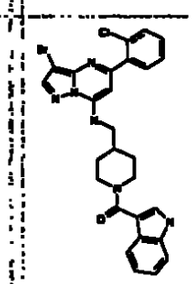
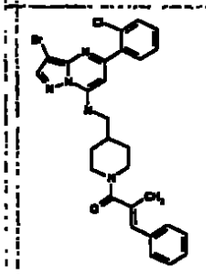
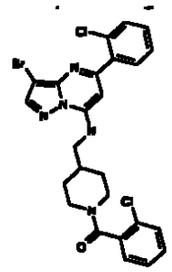
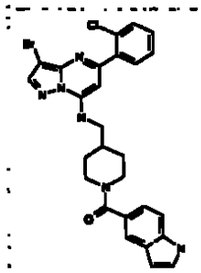
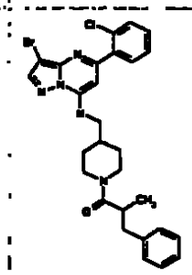
TABLA 49

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4901 2. 490.27		1. 4906 2. 518.28		1. 4911 2. 529.29
	1. 4902 2. 504.28		1. 4907 2. 520.29		1. 4912 2. 532.29
	1. 4903 2. 510.28		1. 4908 2. 520.29		1. 4913 2. 532.29
	1. 4904 2. 516.28		1. 4909 2. 520.29		1. 4914 2. 533.29
	1. 4905 2. 516.28		1. 4910 2. 527.29		1. 4915 2. 536.29

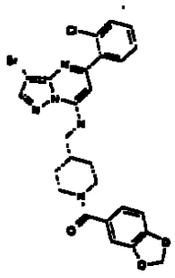
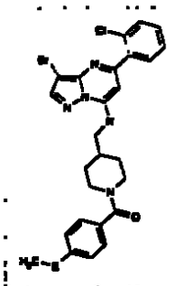
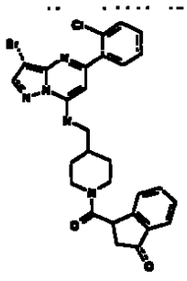
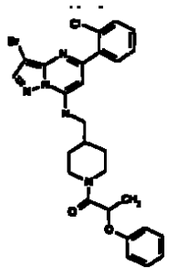
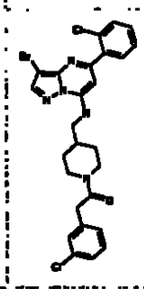
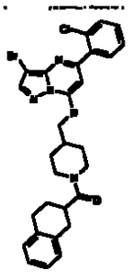
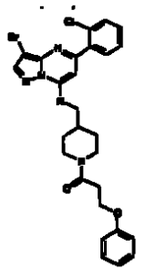
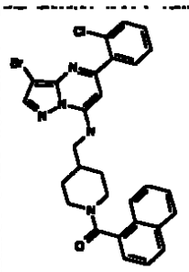
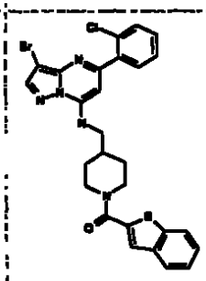
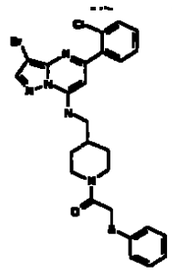
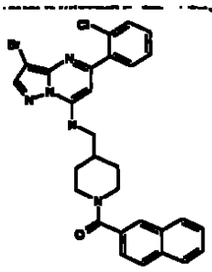
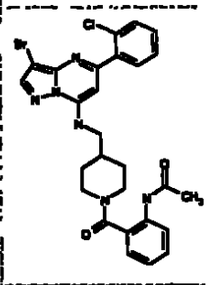
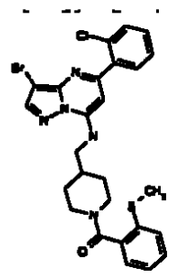
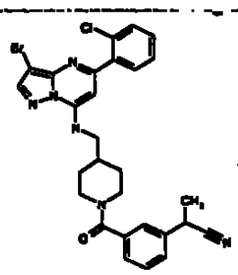
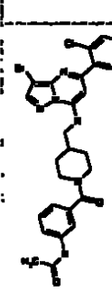
735

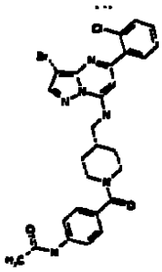
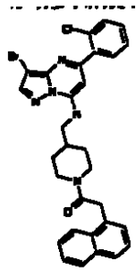
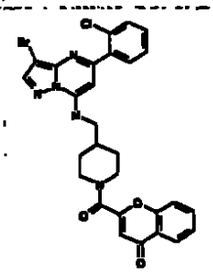
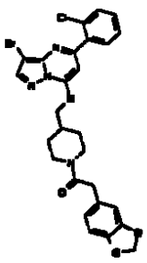
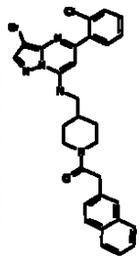
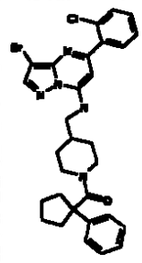
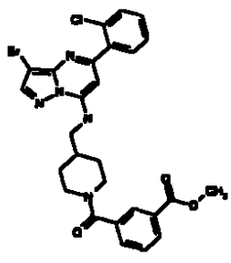
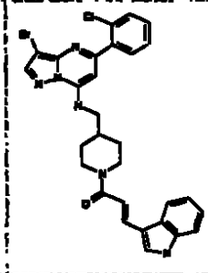
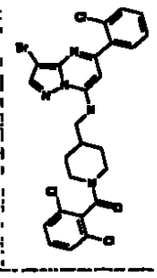
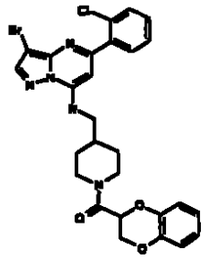
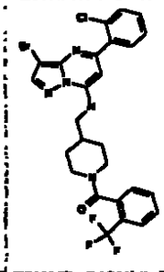
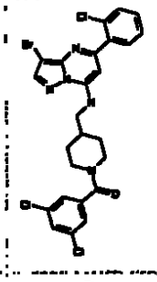
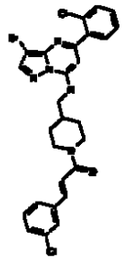
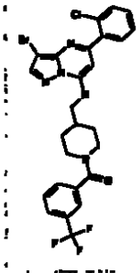
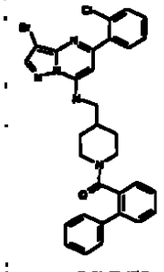
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4916 2. 538.3		1. 4921 2. 546.3		1. 4926 2. 552.3
	1. 4917 2 .540.3		1. 4922 2. 546.3		1. 4927 2. 554.3
	1. 4918 2. 542.3		1. 4923 2. 546.3		1. 4928 2. 554.3
	1. 4919 2. 545.3		1. 4924 2. 551.3		1. 4929 2. 556.31
	1. 4920 2. 546.3		1. 4925 2. 551.3		1. 4930 2. 556.31

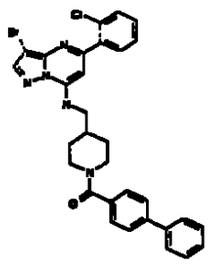
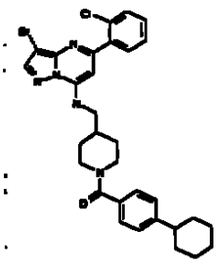
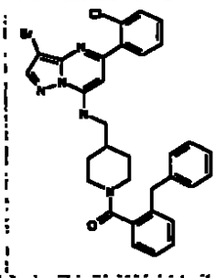
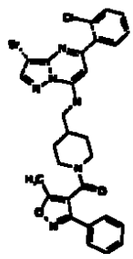
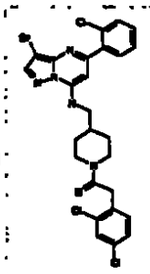
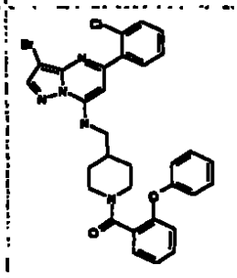
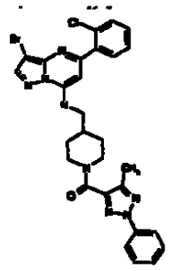
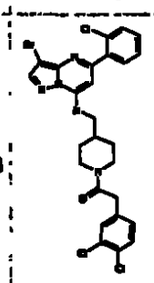
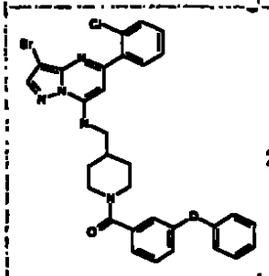
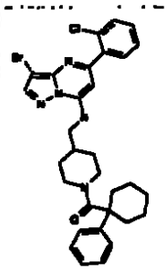
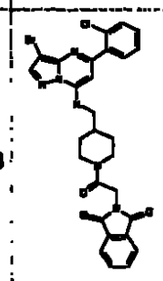
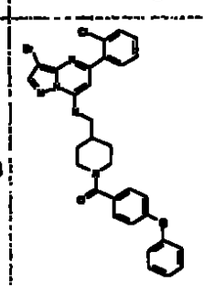
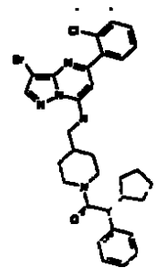
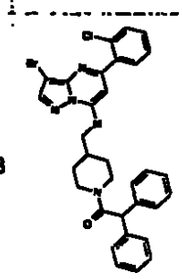
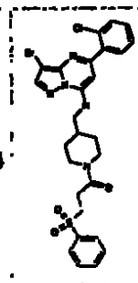
736

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4931 2. 556.31		1. 4936 2. 560.31		1. 4941 2. 566.31
	1. 4932 2. 556.31		1. 4937 2. 560.31		1. 4942 2. 566.31
	1. 4933 2. 558.31		1. 4938 2. 565.31		1. 4943 2. 566.31
	1. 4934 3. 558.31		1. 4939 2. 565.3		1. 4944 2. 566.31
	1. 4935 2. 560.31		1. 4940 2. 565.31		1. 4945 2. 568.31

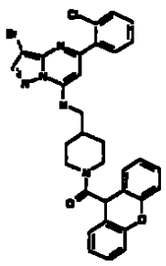
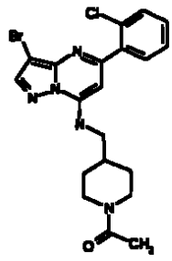
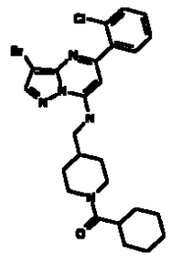
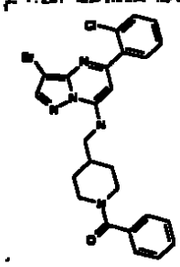
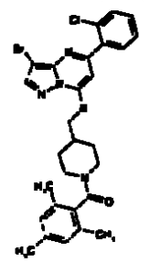
234
737

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4946 2. 570.31		1. 4951 2. 571.31		1. 4956 2. 580.32
	1. 4947 2. 570.31		1. 4952 2. 574.32		1. 4957 2. 580.32
	1. 4948 2. 570.31		1. 4953 2. 576.32		1. 4958 2. 582.32
	1. 4949 2. 572.31		1. 4954 2. 576.32		1. 4959 2. 583.32
	1. 4950 2. 572.31		1. 4955 2. 579.32		1. 4960 2. 583.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4961 2. 583.32		1. 4966 2. 590.32		1. 4971 2. 594.33
	1. 4962 2. 584.32		1. 4967 2. 590.32		1. 4972 2. 594.33
	1. 4963 2. 584.32		1. 4968 2. 591.3		1. 4973 2. 594.33
	1. 4964 2. 584.32		1. 4969 2. 594.33		1. 4974 2. 594.33
	1. 4965 2. 586.32		1. 4970 2. 594.33		1. 4975 2. 602.33

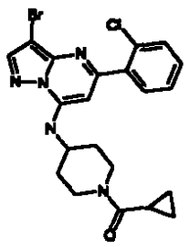
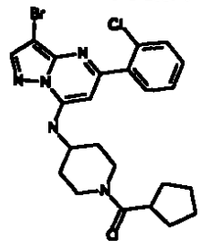
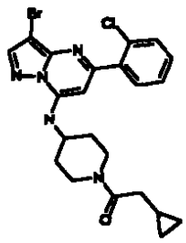
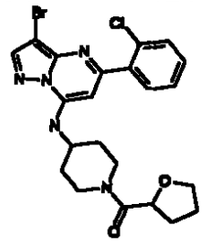
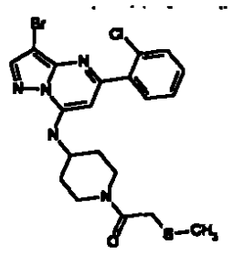
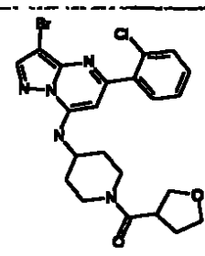
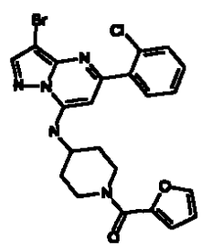
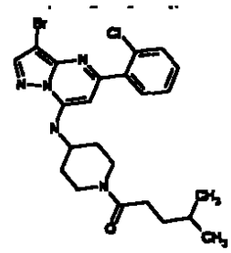
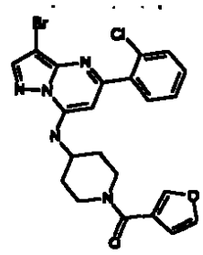
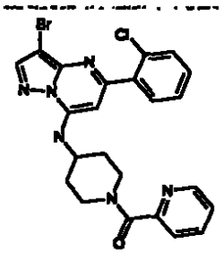
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 4976 2. 602.33		1. 4981 2. 608.33		1. 4986 2. 616.34
	1. 4977 2. 607.33		1. 4982 2. 608.33		1. 4987 2. 618.34
	1. 4978 2. 607.33		1. 4983 2. 608.33		1. 4988 2. 618.34
	1. 4979 2. 605.33		1. 4984 2. 609.33		1. 4089 2. 618.34
	1. 4980 2. 608.33		1. 4985 2. 616.34		1. 4990 2. 618.34

740

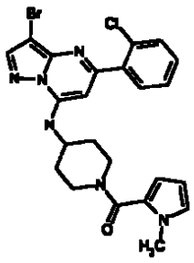
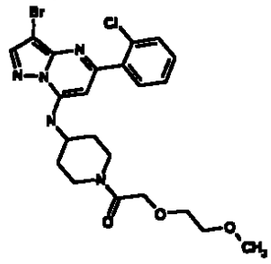
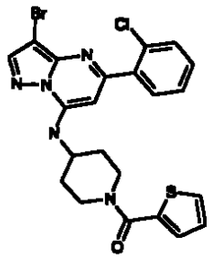
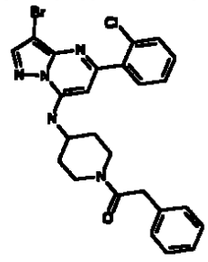
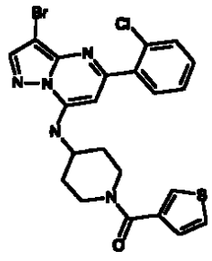
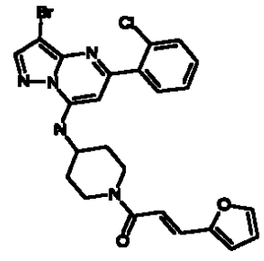
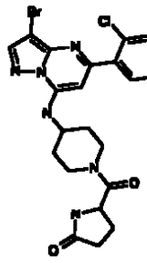
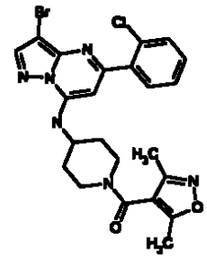
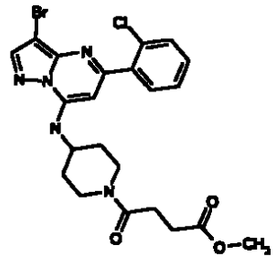
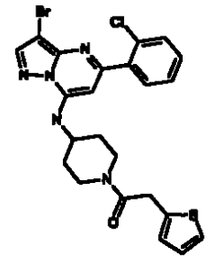
Producto	1. Ej. 2. m/z
	1. 4991 2. 630.35
	1. 4992 2. 464.26
	1. 4993 2. 532.29
	1. 4994 2. 526.29
	1. 4995 2. 568.31

741

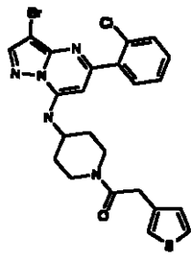
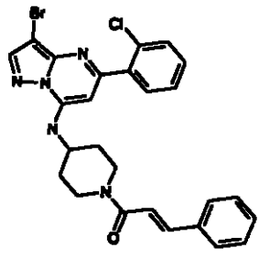
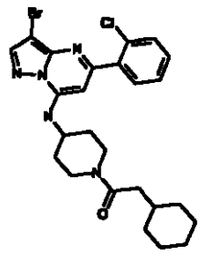
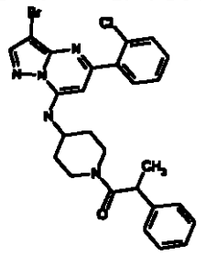
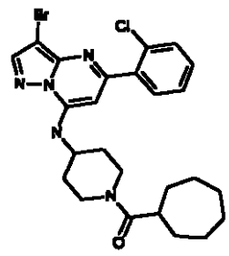
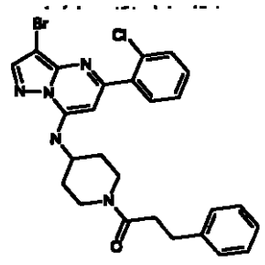
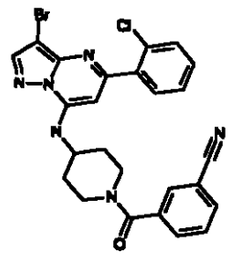
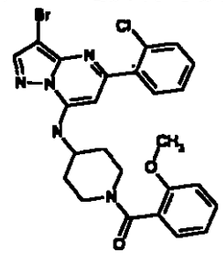
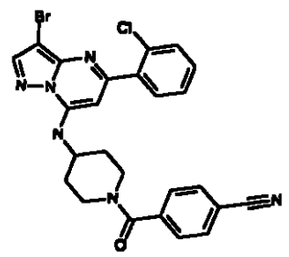
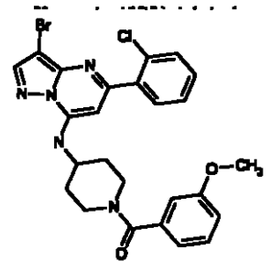
TABLA 50

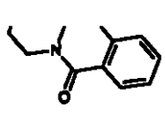
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2.m/z
	1. 5001 2.476.26		1. 5006 2. 504.28
	1. 5002 2. 490.27		1. 5007 2. 506.28
	1. 5003 2. 496.27		1. 5008 2. 506.28
	1. 5004 2. 502.28		1. 5009 2. 506.28
	1. 5005 2. 502.28		1. 5010 2. 513.28

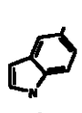
742

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5011 2. 515.28		1. 5016 2. 524.29
	1. 5012 2. 518.28		1. 5017 2. 526.29
	1. 5013 2. 518.28		1. 5018 2. 528.29
	1. 5014 2. 519.29		1. 5019 2. 531.29
	1. 5015 2. 522.29		1. 5020 2. 532.29

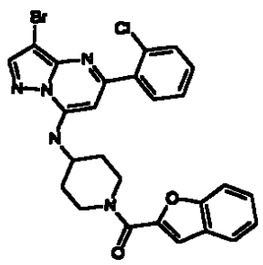
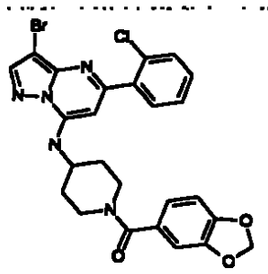
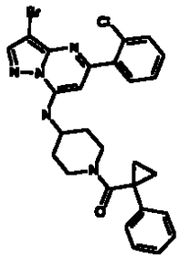
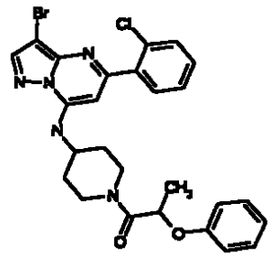
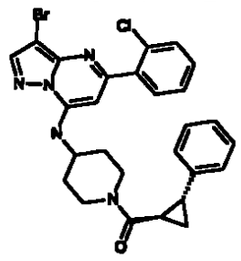
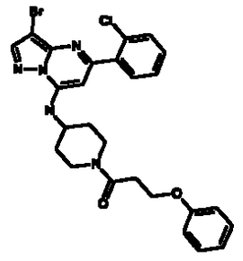
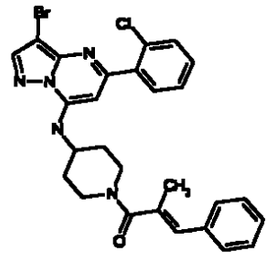
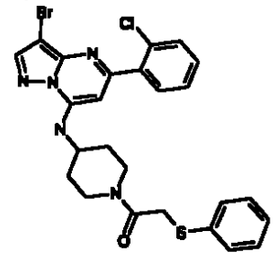
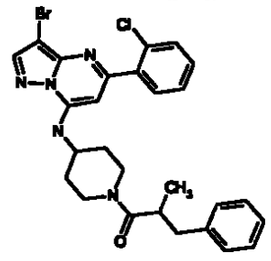
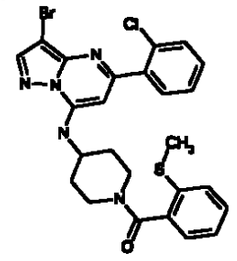
743

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5021 2. 532.29		1. 5026 2. 538.3
	1. 5022 2. 532.29		1. 5027 2. 540.3
	1. 5023 2. 532.29		1. 5028 2. 540.3
	1. 5024 2. 537.3		1. 5029 2. 542.3
	1. 5025 2. 537.3		1. 5030 2. 542.3

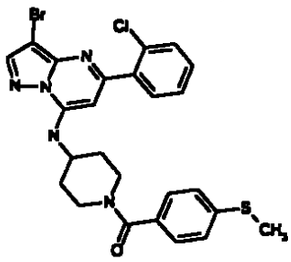
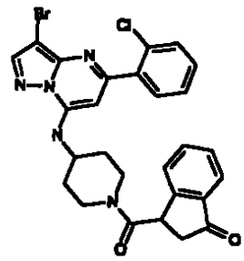
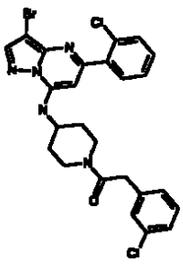
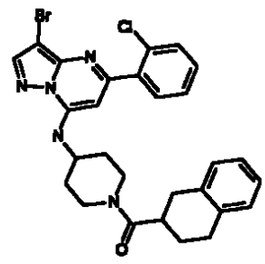
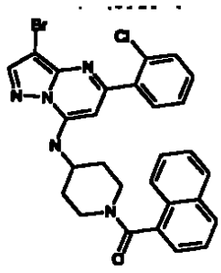
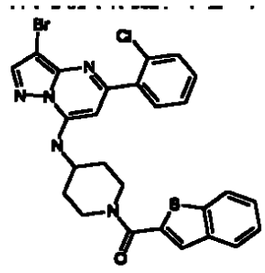
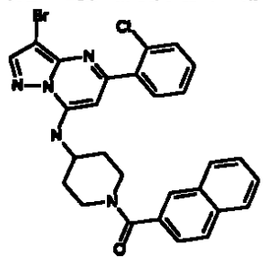
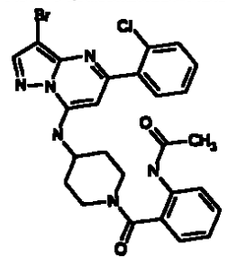
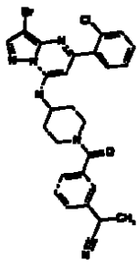
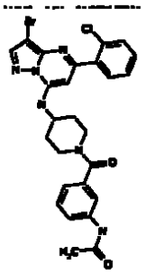




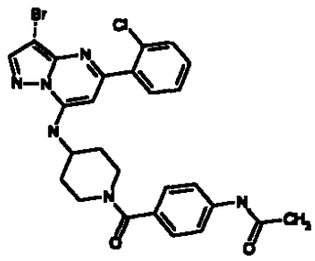
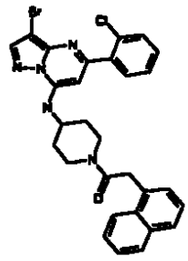
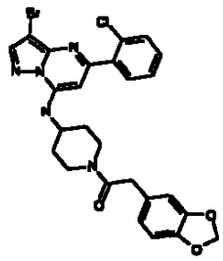
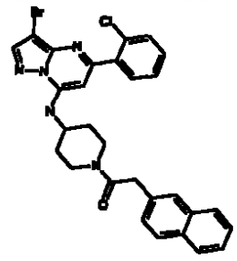
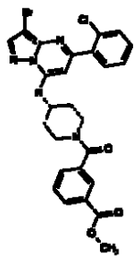
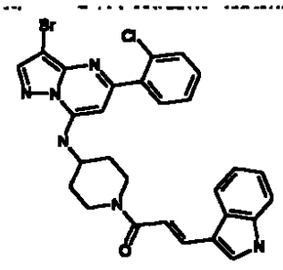
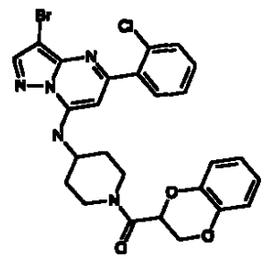
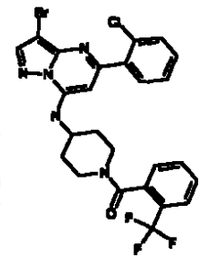
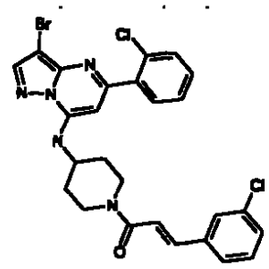
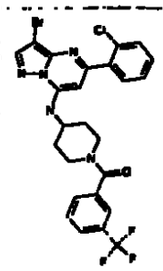
745

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

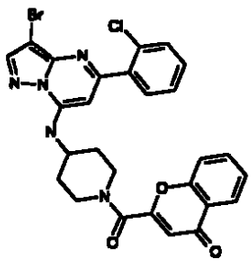
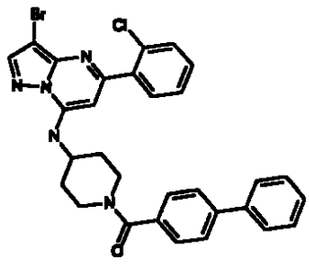
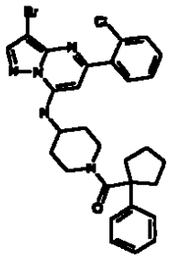
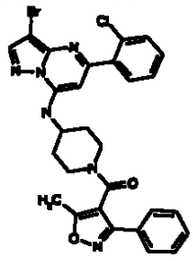
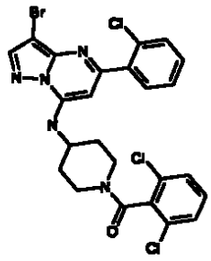
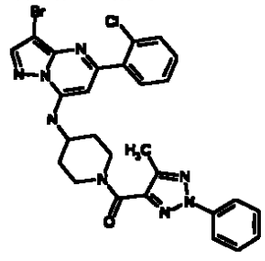
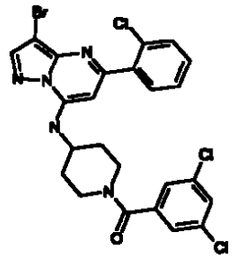
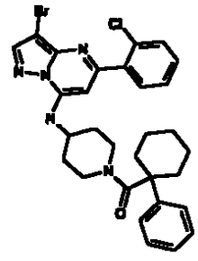
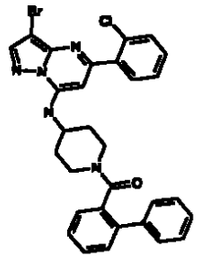
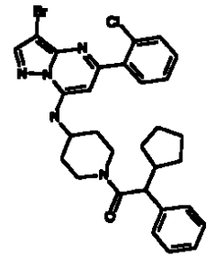
746

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5051 2. 558.31		1. 5056 2. 566.31
	1. 5052 2. 560.31		1. 5057 2. 566.31
	1. 5053 2. 562.31		1. 5058 2. 568.31
	1. 5054 2. 562.31		1. 5059 2. 569.31
	1. 5055 2. 565.31		1. 5060 2. 569.31

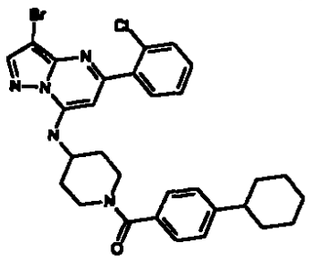
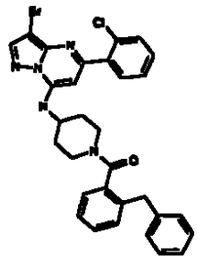
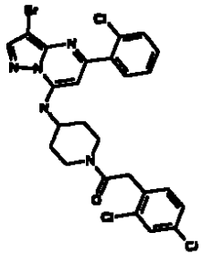
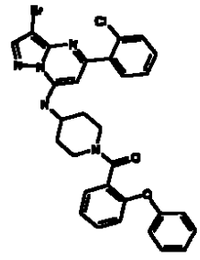
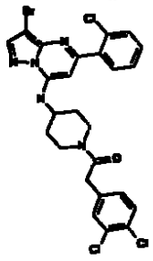
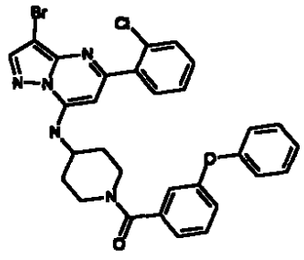
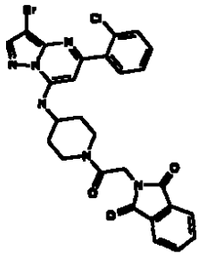
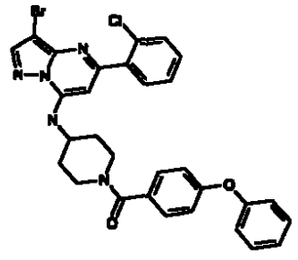
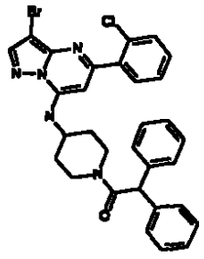
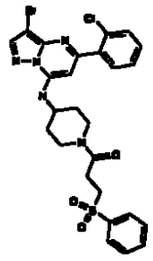
747

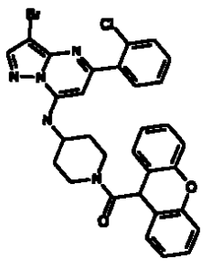
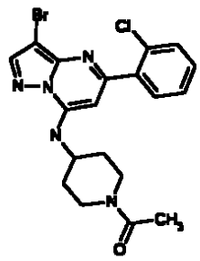
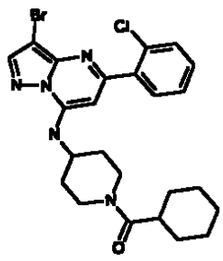
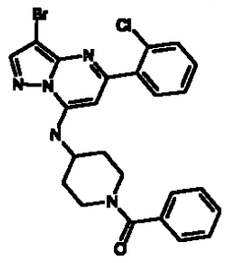
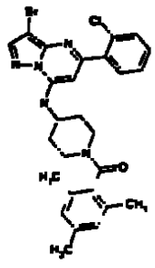
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5061		1. 5066 2. 576.32
	1. 5062 2. 570.31		1. 5067 2. 576.32
	1. 5063 2. 570.31		1. 5068 2. 577.32
	1. 5064 2. 570.31		1. 5069 2. 580.32
	1. 5065 572.31		1. 5070 2. 580.32

745
748

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5071 2. 580.32		1 5076 2. 588.32
	1. 5072 2. 580.32		1. 5077 2. 593.33
	1 5073 2. 580.32		1 5078 2. 593.33
	1 5074 2. 580.32		1. 5079 2. 594.33
	1 5075 2. 588.32		1. 5080 2. 594.33

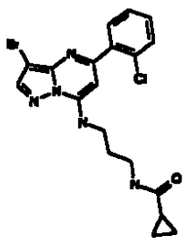
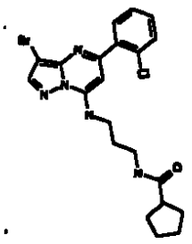
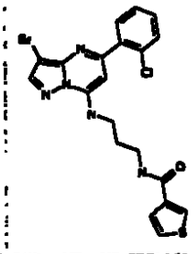
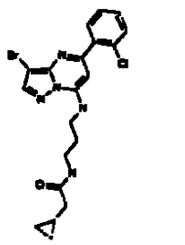
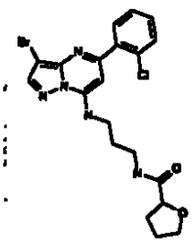
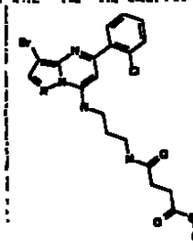
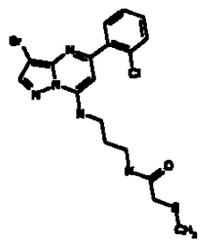
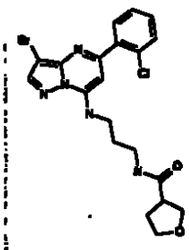
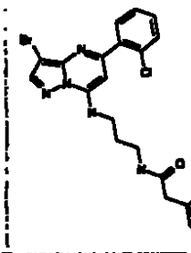
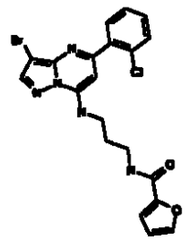
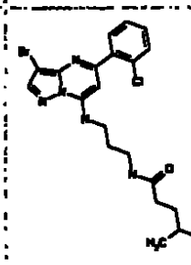
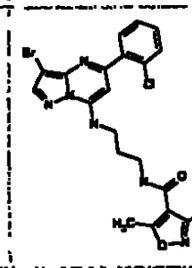
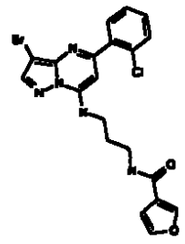
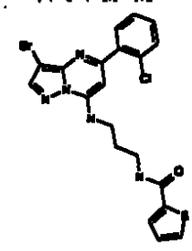
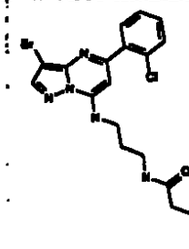
746
749

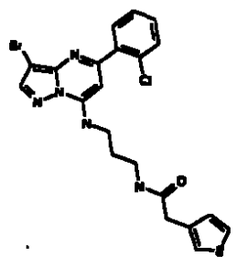
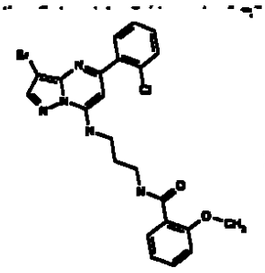
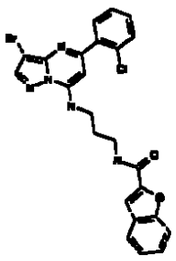
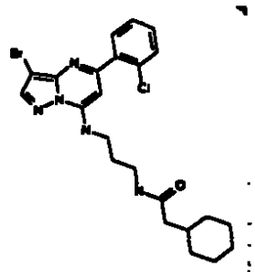
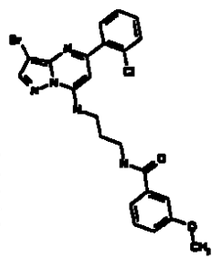
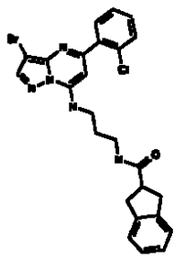
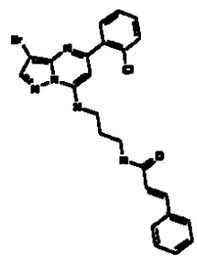
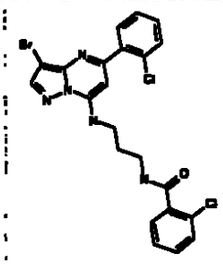
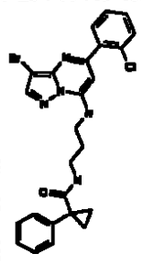
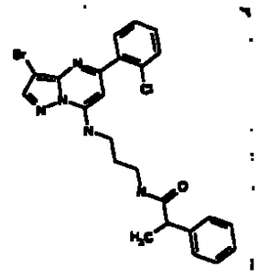
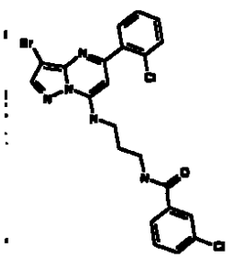
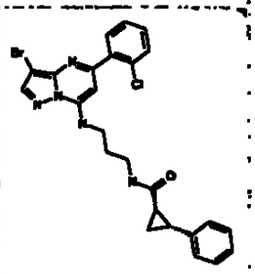
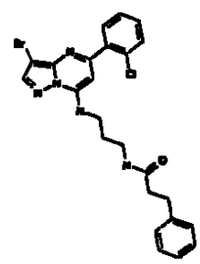
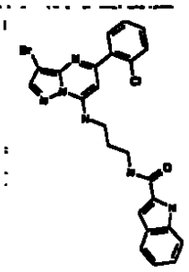
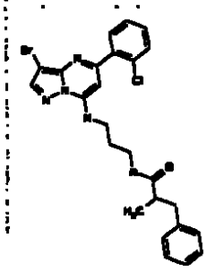
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2.m/z
	1. 5081 2. 594.33		1. 5086 2. 602.33
	1. 5082 2. 594.33		1.5087 2. 604.33
	1. 5083 2. 594.33		1. 5088 2. 604.33
	1. 5084 2. 595.33		1. 5089 2. 604.33
	1.5085 2. 602.33		1. 5090 2. 604.33

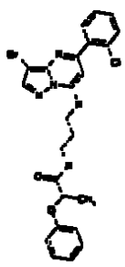
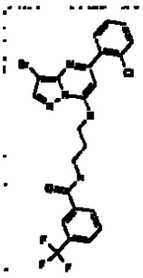
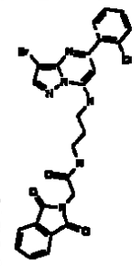
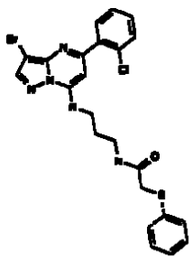
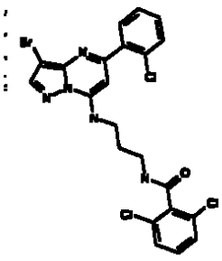
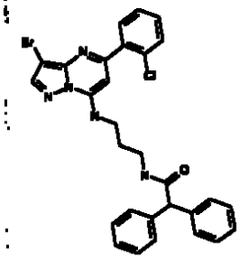
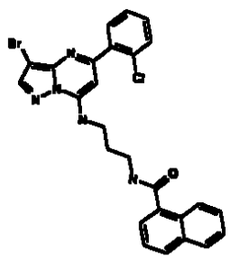
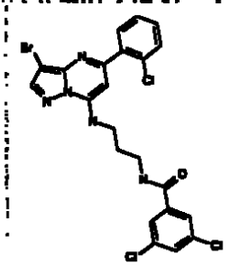
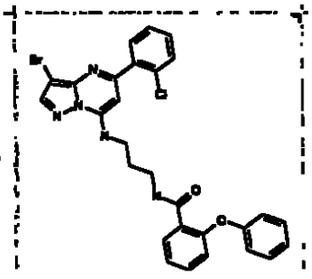
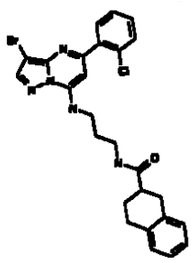
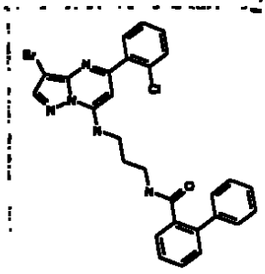
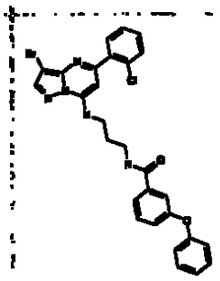
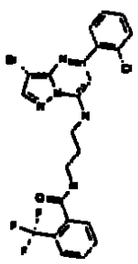
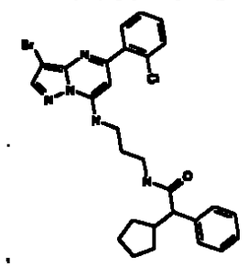
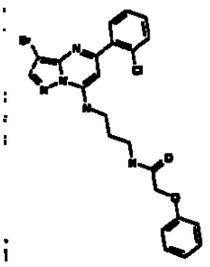
Producto	1. Ej. 2. m/z
	1. 5091 2. 616.34
	1. 5092 2. 450.25
	1. 5093 2. 518.28
	1. 5094 2. 512.28
	1. 5095 2.554.3

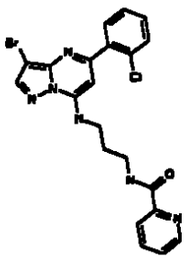
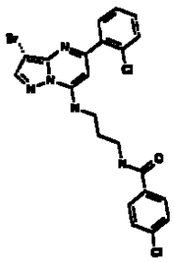
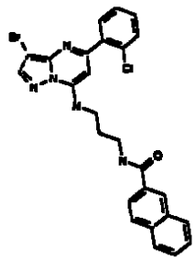
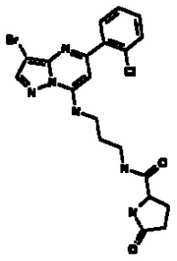
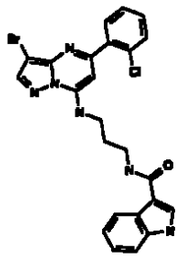
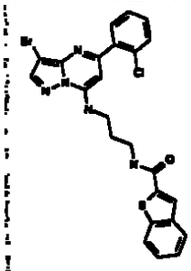
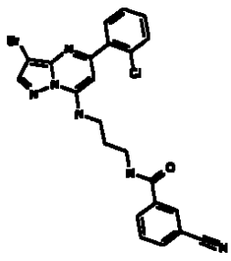
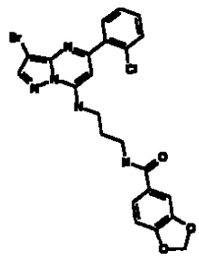
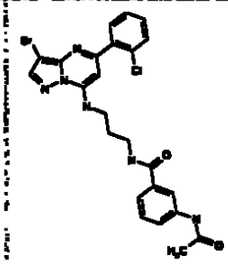
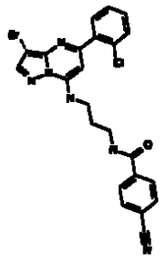
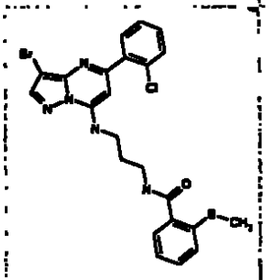
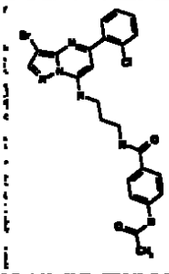
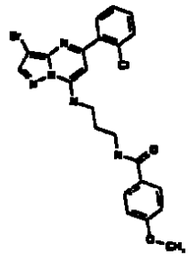
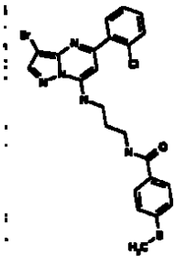
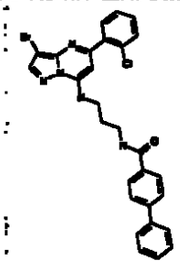
751

TABLA 51

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5101 2. 448.8		1. 5106 2. 476.8		1. 5111 2. 490.8
	1. 5102 2. 462.8		1. 5107 2. 478.8		1. 5112 2. 494.8
	1. 5103 2. 468.8		1. 5108 2. 478.8		1. 5113 2. 498.8
	1. 5104 2. 474.7		1. 5109 2. 478.8		1. 5114 2. 503.8
	1. 5105 2. 474.7		1. 5110 2. 490.8		1. 5115 2. 504.8

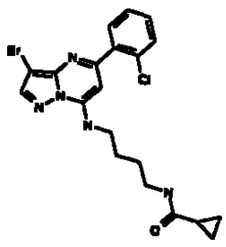
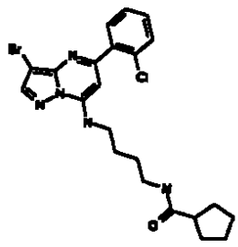
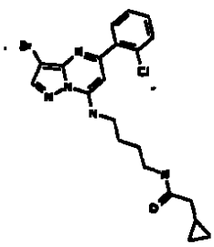
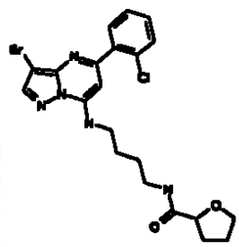
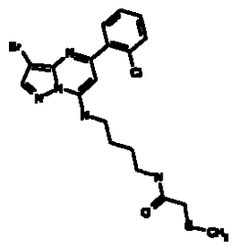
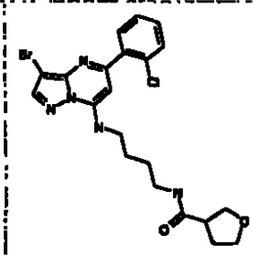
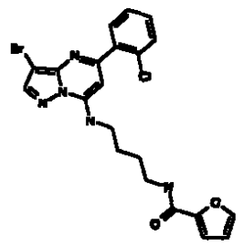
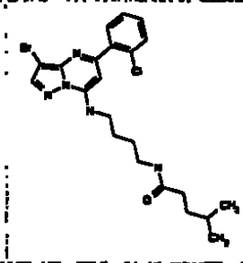
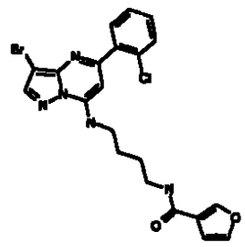
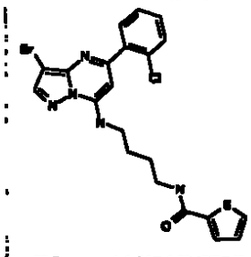
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5116 2. 504.8		1. 5121 2. 514.8		1. 5126 2. 524.8
	1. 5117 2. 504.9		1. 5122 2. 514.8		1. 5127 2. 524.9
	1. 5118 2. 510.8		1. 5123 2. 519.2		1. 5128 2 . 524.9
	1. 5119 2. 512.8		1. 5124 2. 519.2		1. 5129 2. 524.9
	1. 5120 2. 512.8		1. 5125 2. 523.8		1. 5130 2. 526.9

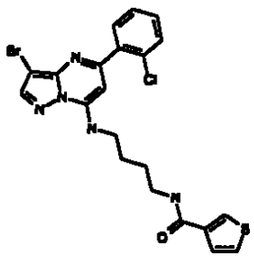
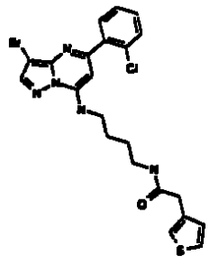
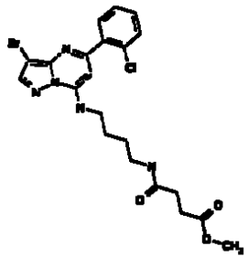
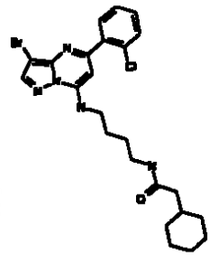
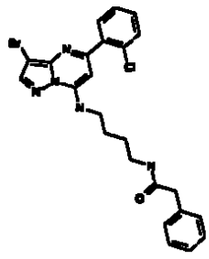
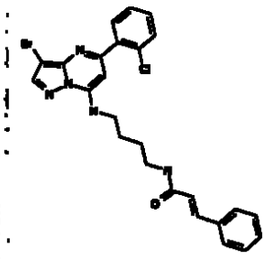
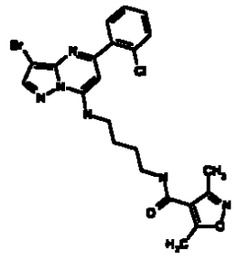
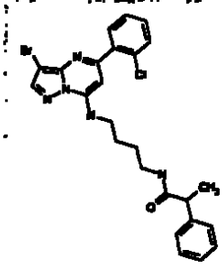
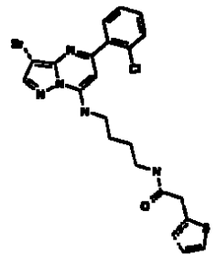
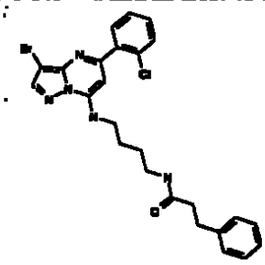
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5131 2. 528.8		1. 5136 2. 552.8		1. 5141 2. 567.8
	1. 5132 2. 530.9		1. 5137 2. 553.7		1. 5142 2. 574.9
	1. 5133 2. 534.8		1. 5138 2. 553.7		1. 5143 2. 576.9
	1. 5134 2. 538.9		1. 5139 2. 560.9		1. 5144 2. 576.9
	1. 5135 2. 552.8		1. 5140 2. 566.9		1. 5145 2. 514.8

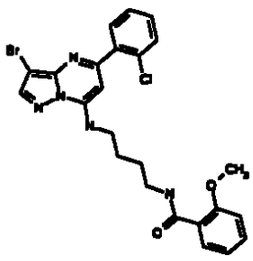
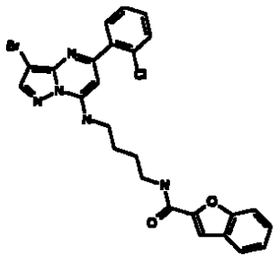
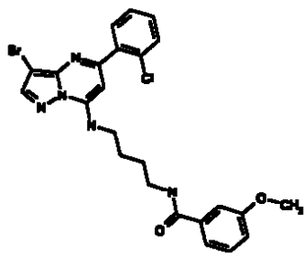
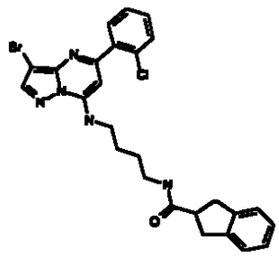
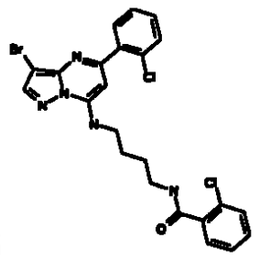
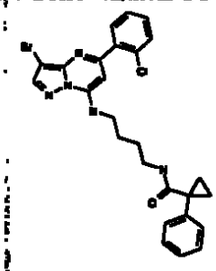
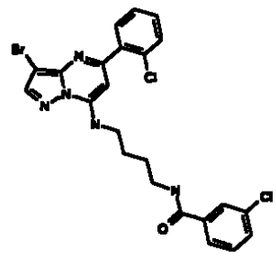
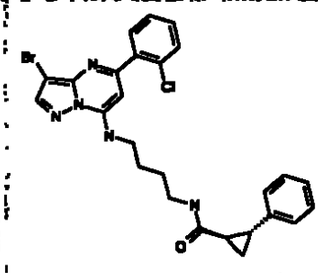
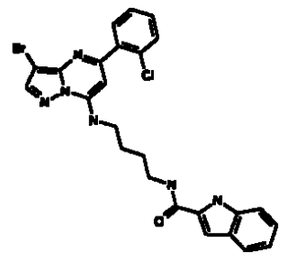
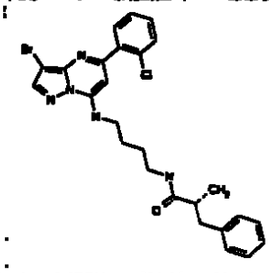
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5146 2. 485.8		1. 5151 2. 519.2		1. 5156 2. 534.8
	1. 5147 2. 491.8		1. 5152 2. 523.8		1. 5157 2. 540.9
	1. 5148 2. 509.8		1. 5153 2. 528.8		1. 5158 2. 541.8
	1. 5149 2. 509.8		1. 5154 2. 530.9		1. 5159 2. 541.8
	1. 5150 2. 514.8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

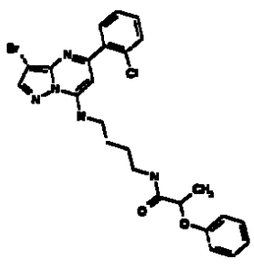
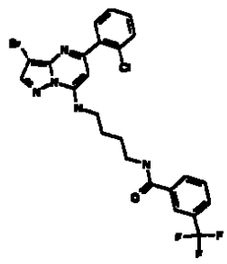
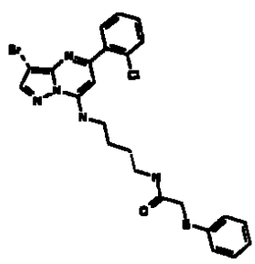
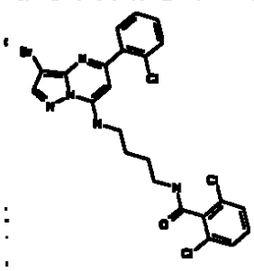
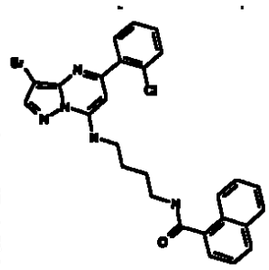
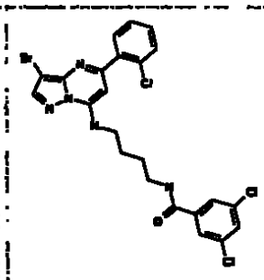
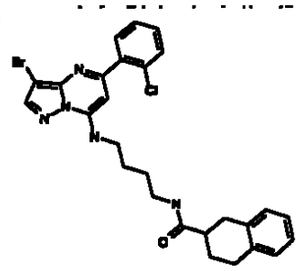
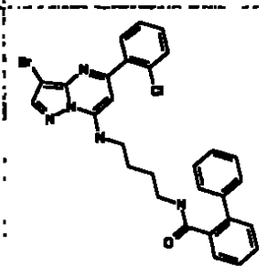
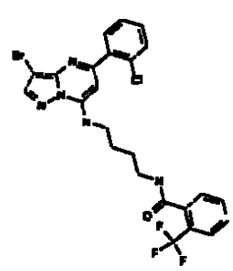
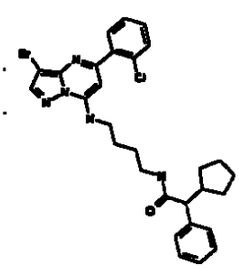
755

TABLA 52

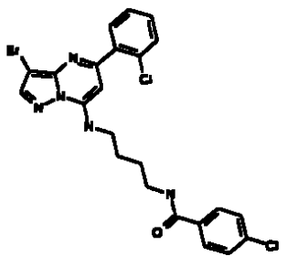
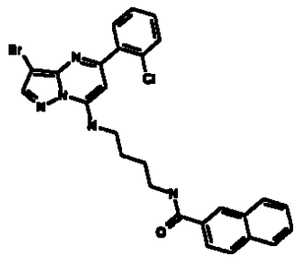
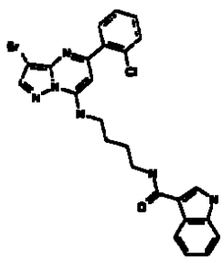
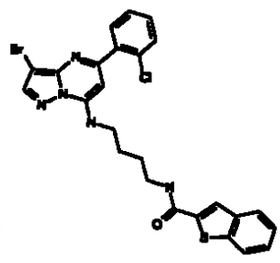
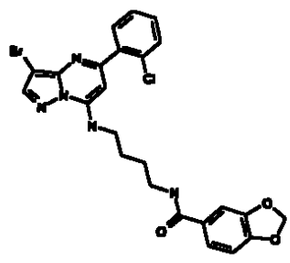
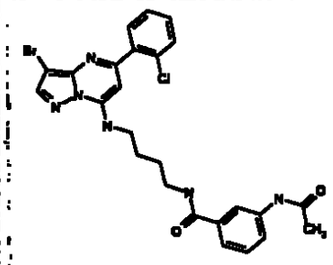
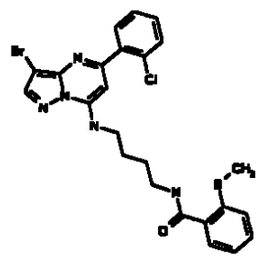
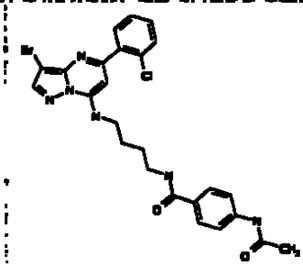
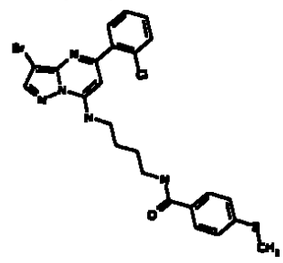
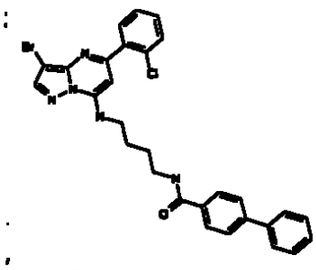
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5201 2. 482.8		1. 5206 2. 490.8
	1. 5202 2. 476.8		1. 5207 2. 492.8
	1. 5203 2. 482.8		1. 5208 2. 492.8
	1. 5204 2. 488.8		1. 52009 2. 492.9
	1. 5205 2. 488.8		1. 5210 2. 504.8

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5211 2. 504.8		1. 5216 2. 518.9
	2. 5212 2. 508.8		1. 5217 2. 518.9
	1. 5213 2. 512.8		1. 5218 2. 524.9
	1. 5214 2. 517.8		1. 5219 2. 526.9
	1. 5215 2. 518.9		1. 5220 2. 526.9

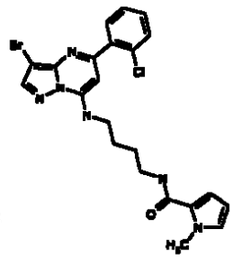
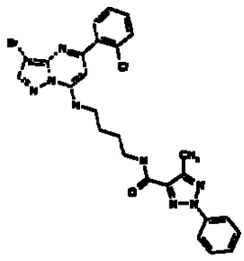
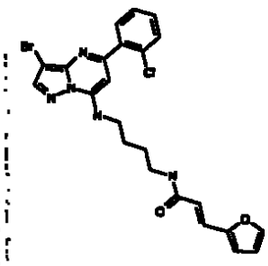
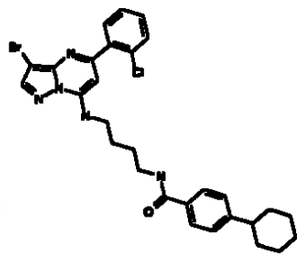
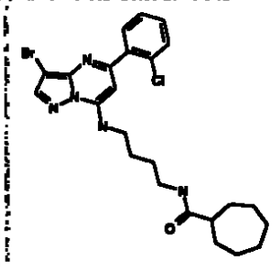
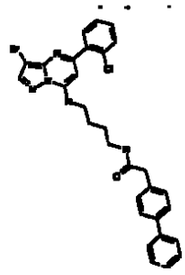
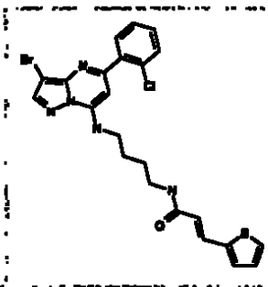
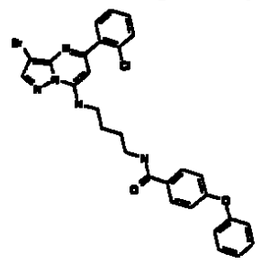
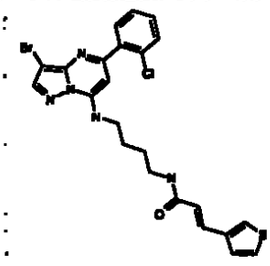
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5221 2. 528.8		1. 5226 2. 538.8
	1. 5222 2. 528.8		1. 5227 2. 538.9
	1. 5223 2. 533.3		1. 5228 2. 538.9
	1. 5224 2. 533.3		1. 5229 2. 538.9
	1. 5225 2. 537.9		1. 5230 2. 540.9

Producto	1. Ej. 2. m/z	Producto	1. Ej. 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

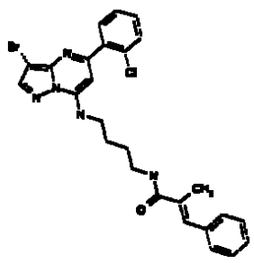
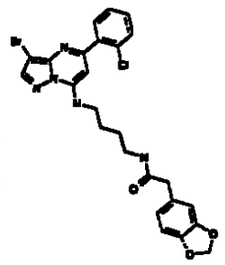
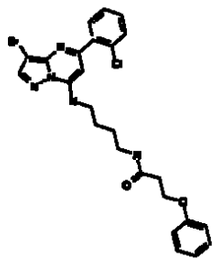
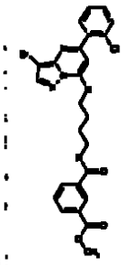
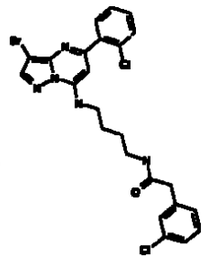
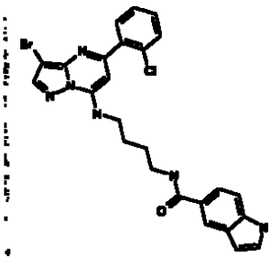
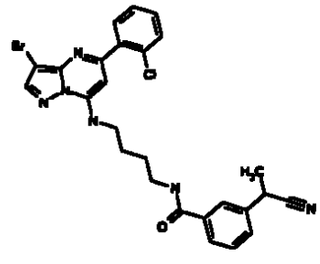
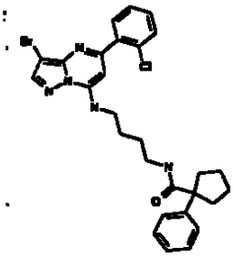
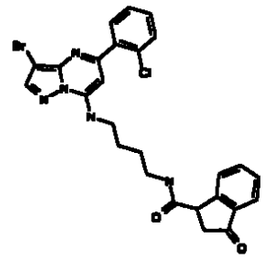
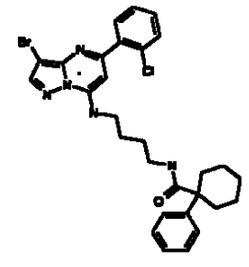
759

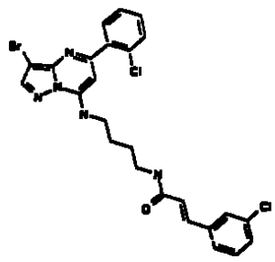
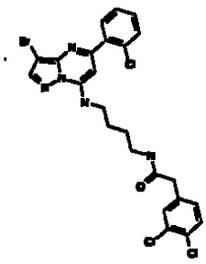
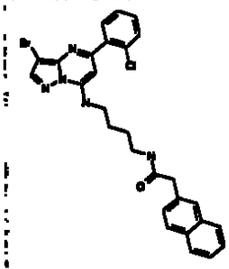
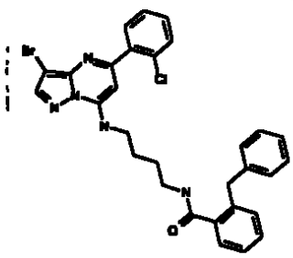
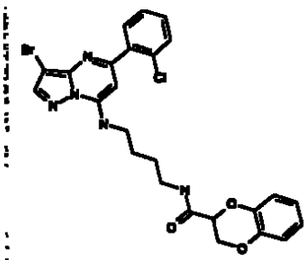
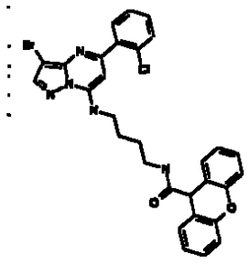
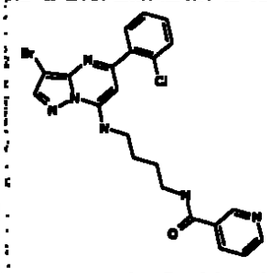
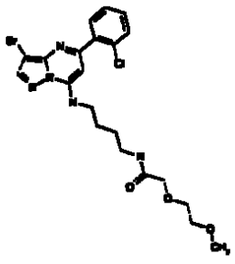
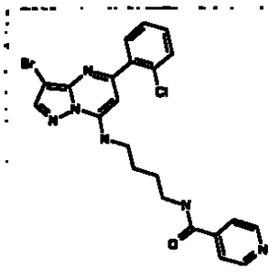
Producto	1. Ej. 2.m/z	Producto	1. Ej. 2. m/z
	1. 5241 2. 533.3		1. 5246 2. 548.9
	1. 5242 2. 537.9		1. 5247 2. 554.9
	1. 5243 2. 542.8		1. 5248 2. 555.9
	1. 5244 2. 544.9		1. 5249 2. 555.9
	1. 5245 2. 544.9		1. 5250 2. 574.9

760

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

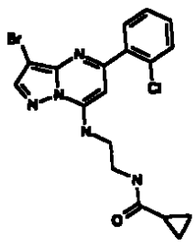
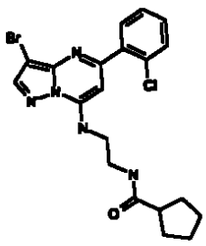
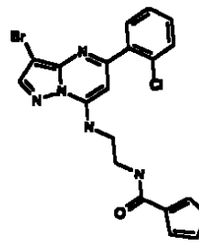
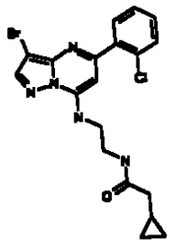
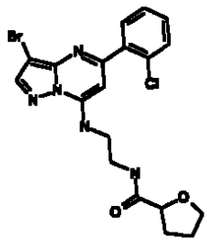
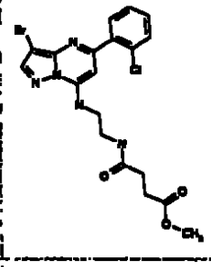
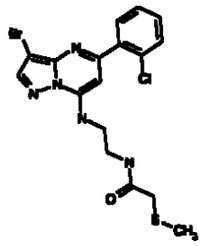
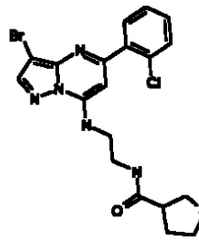
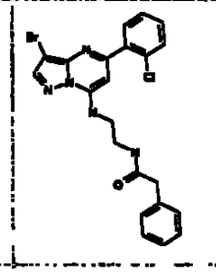
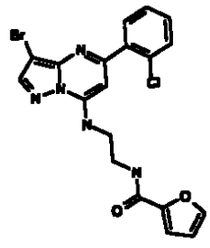
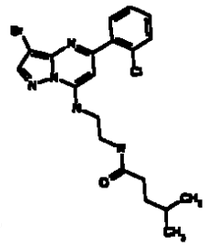
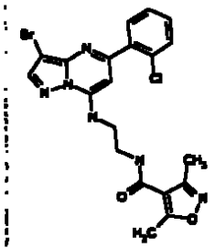
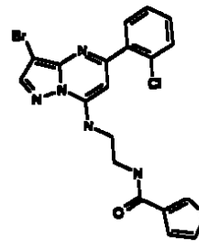
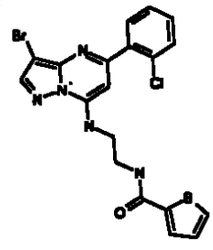
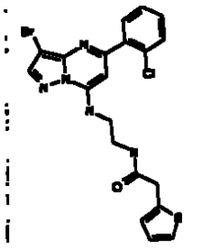
761

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5261 2. 538.9		1. 5266 2. 556.9
	1. 5262 2. 542.9		1. 5267 2. 556.9
	1. 5263 2. 547.3		1. 5268 2. 537.9
	1. 5264 2. 551.9		1. 5269 2. 566.9
	1. 5265 2. 552.9		1. 5270 2. 581

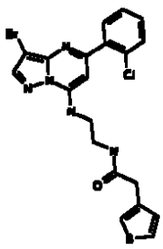
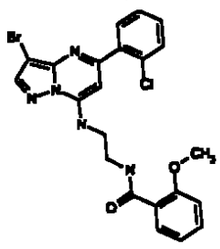
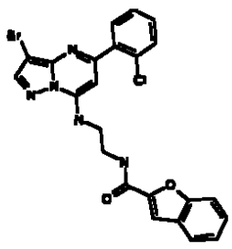
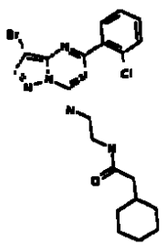
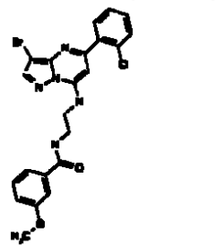
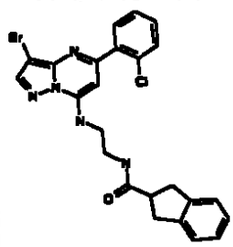
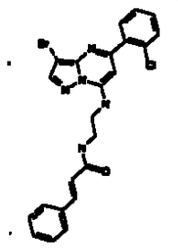
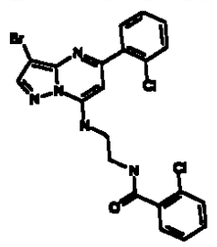
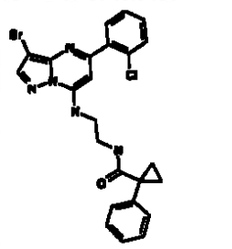
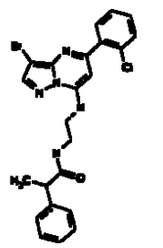
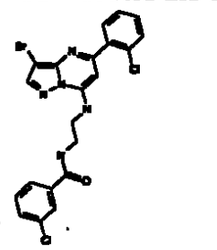
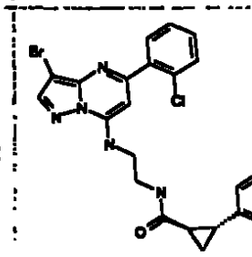
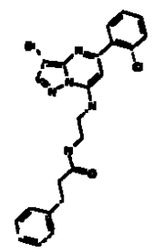
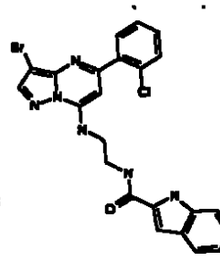
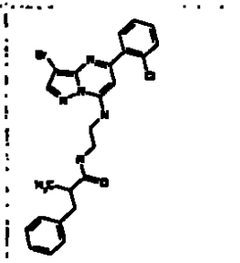
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5271 2. 581.7		1. 5276 2. 559.3
	1. 5272 2. 581.7		1. 5277 2. 562.9
	1. 5273 2. 588.9		1. 5278 2. 556.9
	1. 5274 2. 602.9		1. 5279 2. 499.8
	1. 5275 2. 510.8		1. 5280 2. 499.8

763

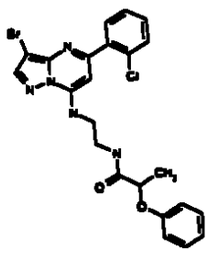
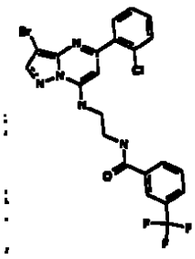
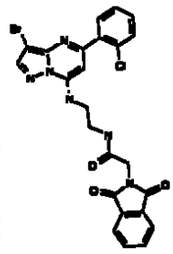
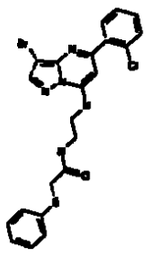
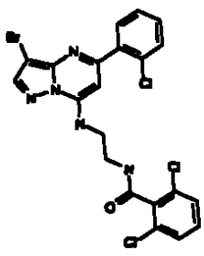
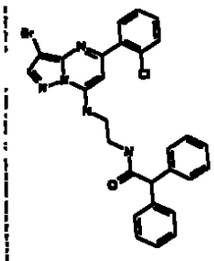
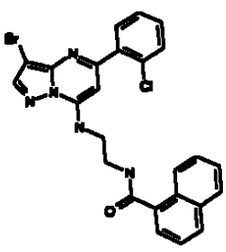
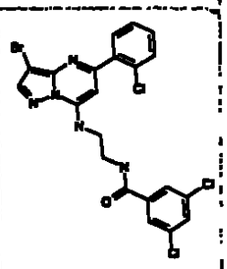
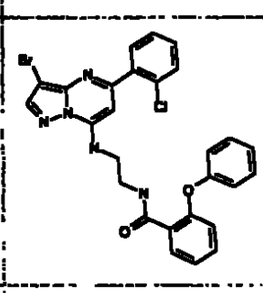
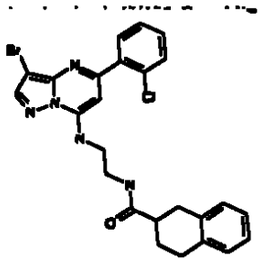
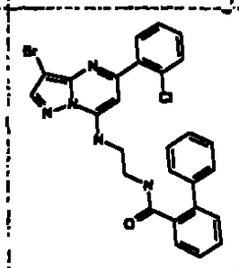
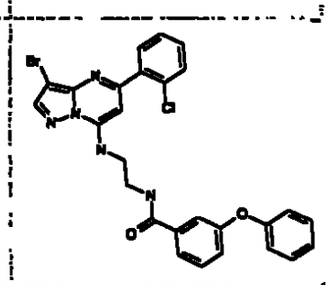
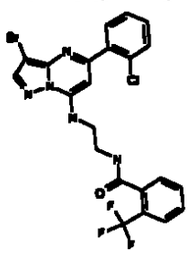
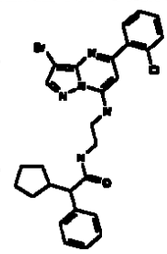
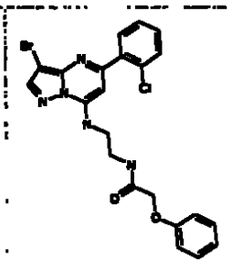
TABLA 53

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5301 2. 434.7		1. 5306 2. 462.8		1. 5311 2. 476.8
	1. 5302 2. 448.8		1. 5307 2. 464.8		1. 5312 2. 480.8
	1. 5303 2. 454.8		1. 5308 2. 464.8		1. 5313 2. 484.8
	1. 5304 2. 460.7		1. 5309 2. 464.8		1. 5314 2. 489.8
	1. 5305 2. 460.7		1. 5310 2. 476.8		1. 5315 2. 490.8

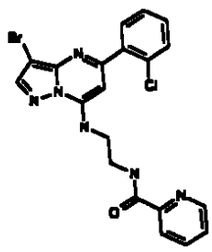
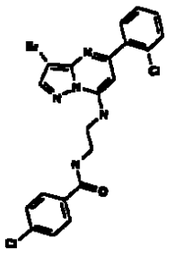
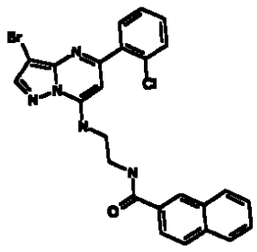
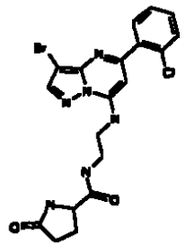
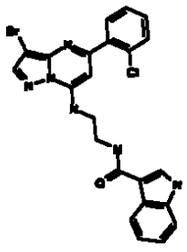
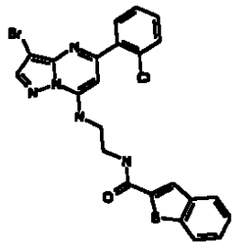
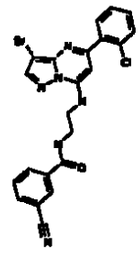
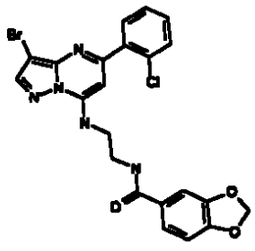
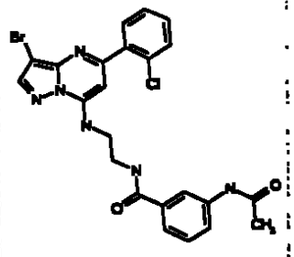
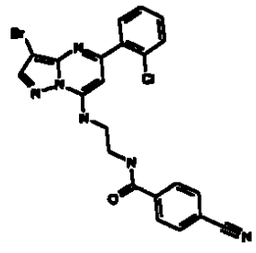
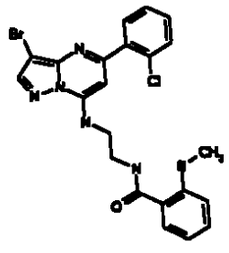
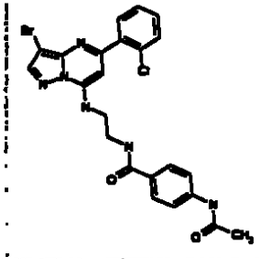
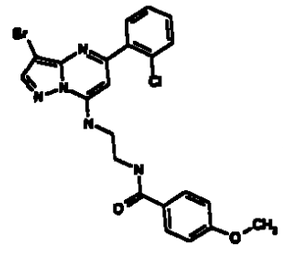
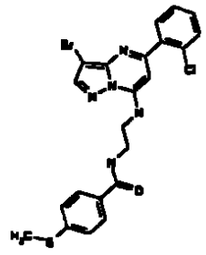
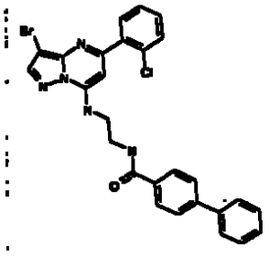
764

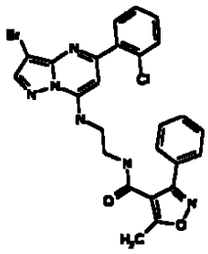
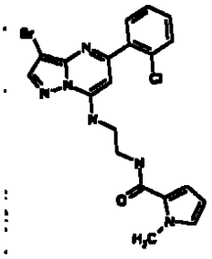
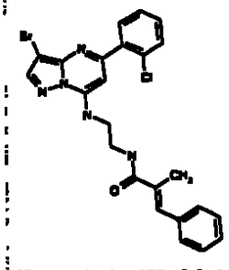
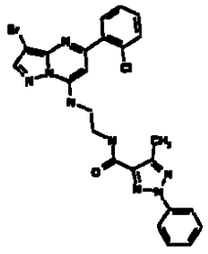
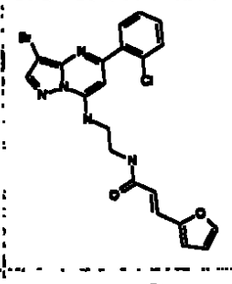
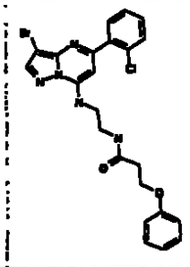
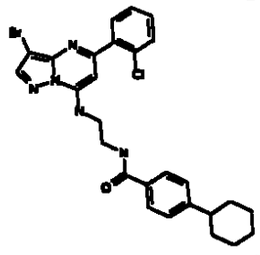
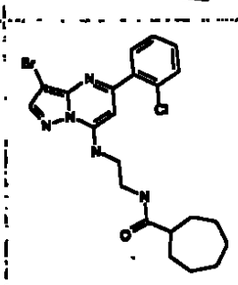
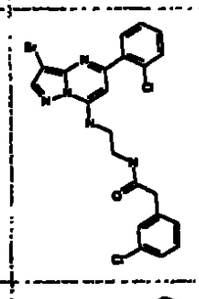
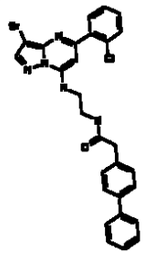
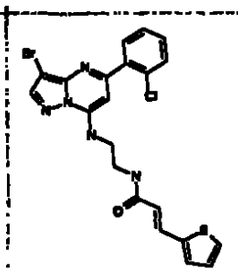
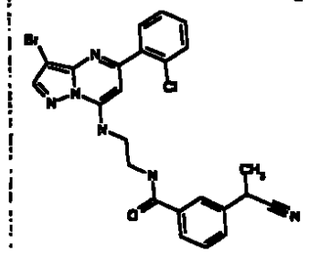
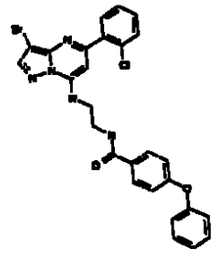
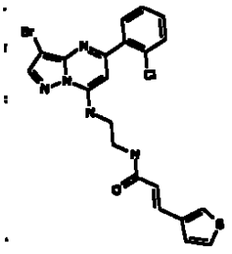
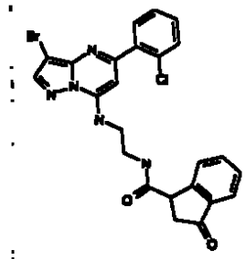
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5316 2. 490.8		1. 5321 2. 500.8		1. 5326 2. 510.8
	1. 5317 2. 490.8		1. 5322 2. 500.8		1. 5327 2. 510.8
	1. 5318 2. 496.8		1. 5323 2. 505.2		1. 5328 2. 510.8
	1. 5319 2. 498.8		1. 5324 2. 505.2		1. 5329 2. 510.8
	1. 5320 2. 498.8		1. 5325 2. 509.8		1. 5330 2. 512.8

765

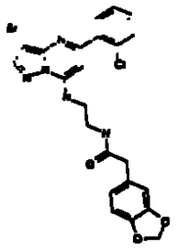
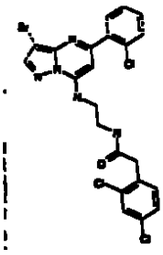
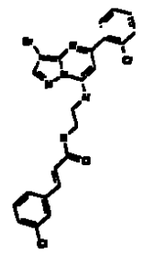
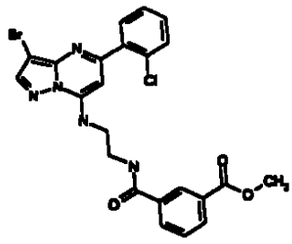
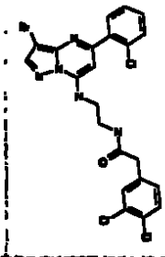
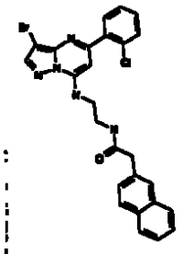
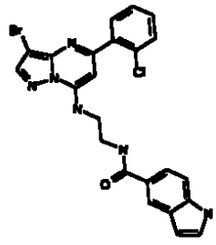
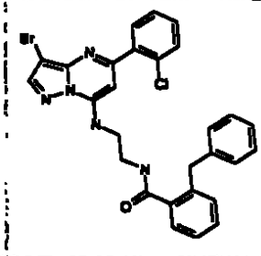
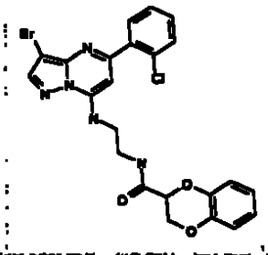
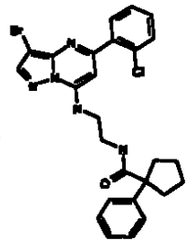
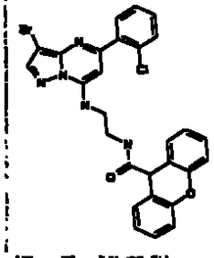
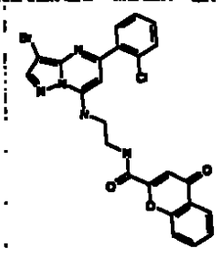
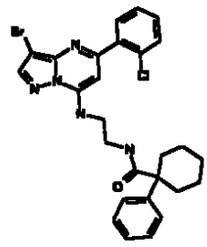
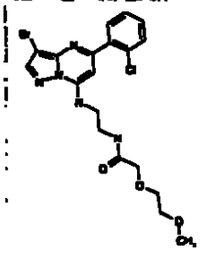
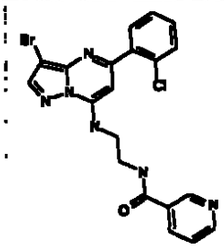
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5331 2. 514.8		1. 5336 2. 538.8		1. 5341 2. 553.8
	1. 5332 2. 516.9		1. 5337 2. 539.6		1. 5342 2. 560.9
	1. 5333 2. 520.8		1. 5338 2. 539.6		1. 5343 2. 562.9
	1. 5334 2. 524.9		1. 5339 2. 546.9		1. 5344 2. 562.9
	1. 5335 2. 538.8		1.5340 2. 552.9		1. 5345 2. 500.8

766

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5346 2. 471.7		1. 5351 2. 505.2		1. 5356 2. 520.8
	1. 5347 2. 477.8		1. 5352 2. 509.8		1. 5357 2. 526.8
	1. 5348 2. 495.8		1. 5353 2. 514.8		1. 5358 2. 527.8
	1. 5349 2. 495.8		1. 5355 2. 516.9		1. 5359 2. 527.8
	. 5350 . 500.8		1. 5356 2. 516.9		1. 5360 2. 546.9

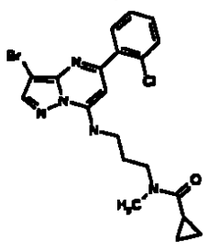
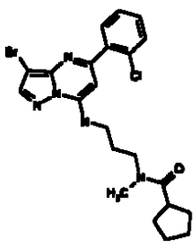
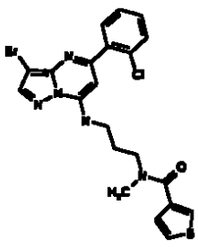
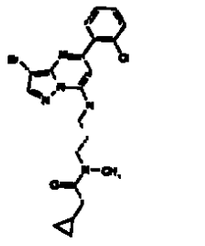
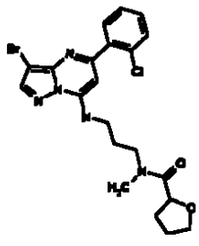
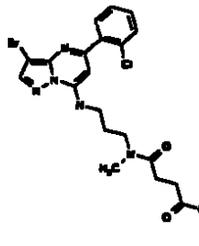
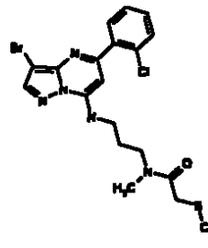
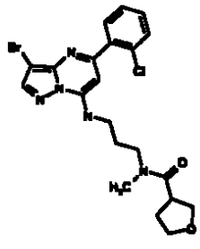
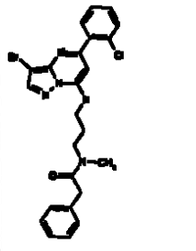
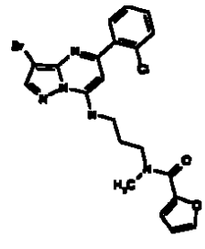
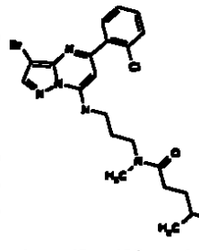
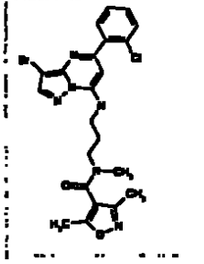
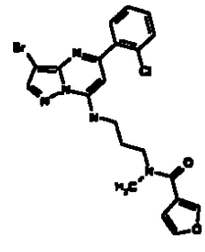
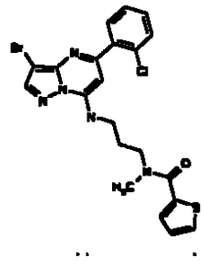
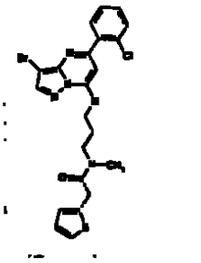
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5361 2. 551.8		1. 5366 2. 473.8		1. 5371 2.510.8
	1. 5362 2. 551.8		1. 5367 2. 486.8		1. 5372 2. 514.8
	1. 5363 2. 552.9		1. 5368 2. 490.8		1. 5373 2. 519.2
	1. 5364 2. 560.9		1. 5369 2. 502.8		1. 5374 2. 523.8
	1. 5365 2. 562.9		1. 5370 2. 502.8		1. 5375 2. 524.8

768

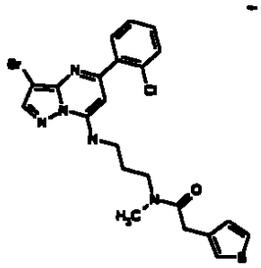
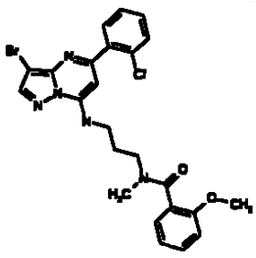
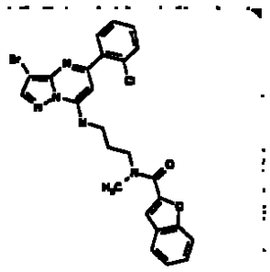
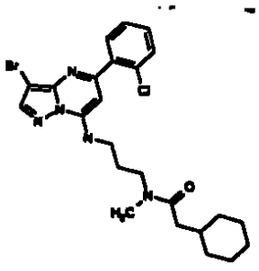
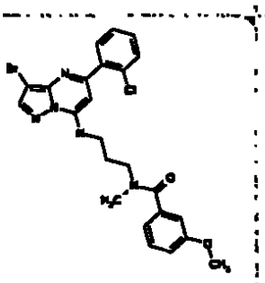
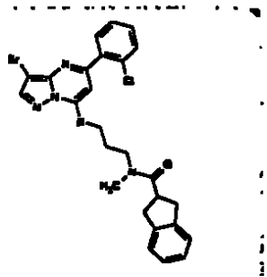
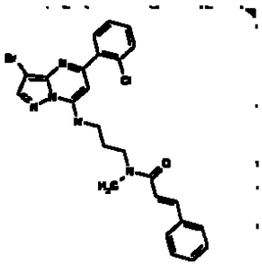
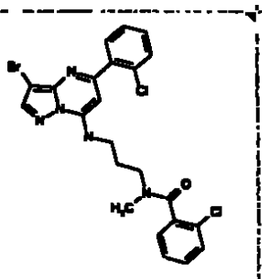
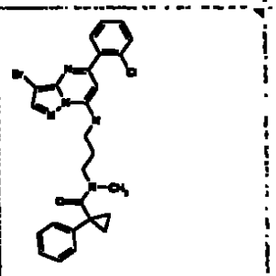
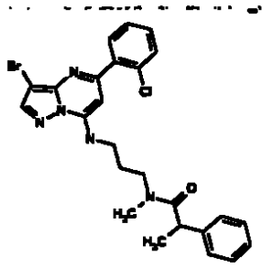
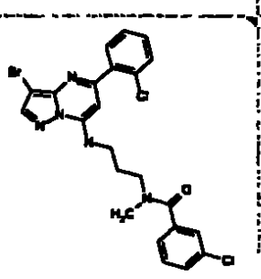
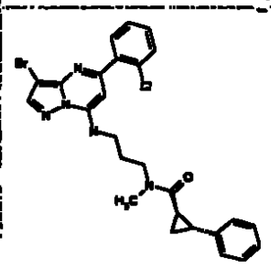
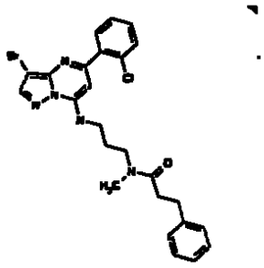
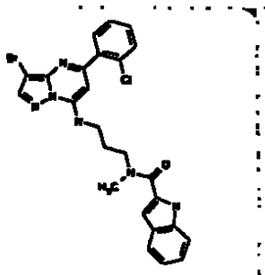
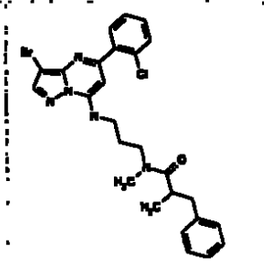
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5376 2. 528.8		1. 5381 2. 553.7		1. 5386 2. 531.2
	1. 5377 2. 528.8		1. 5382 2. 553.7		1. 5387 2. 534.8
	1. 5378 2. 509.8		1. 5383 2. 560.9		1. 5388 2. 528.8
	1. 5379 2. 538.9		1. 5384 2. 574.9		1. 5389 2. 538.8
	1. 5380 2. 552.9		1. 5385 2. 482.8		1. 5390 2. 471.7

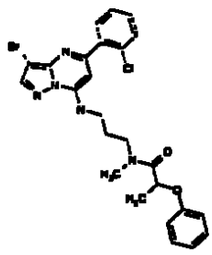
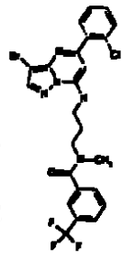
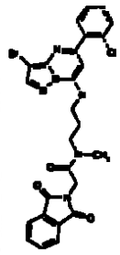
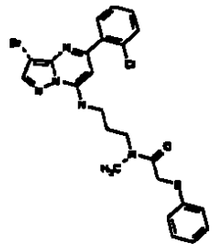
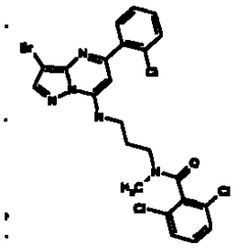
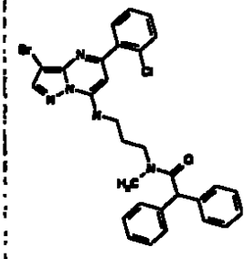
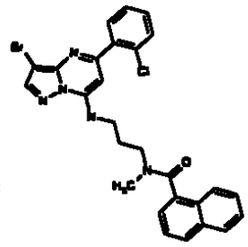
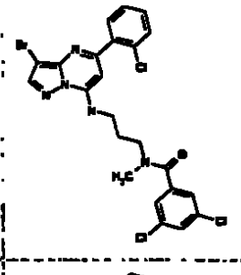
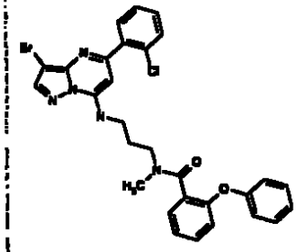
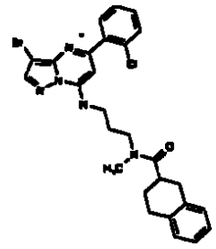
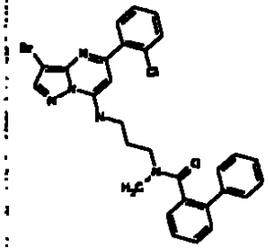
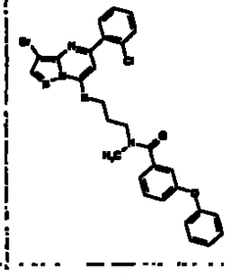
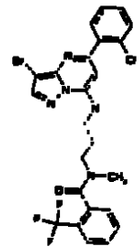
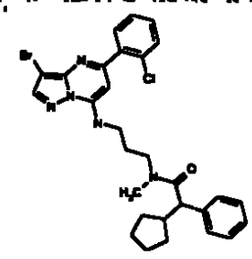
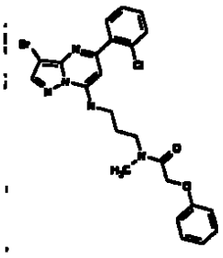
769

TABLA 54

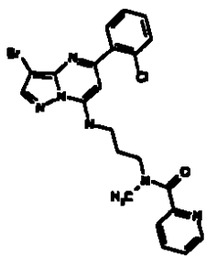
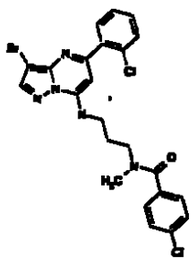
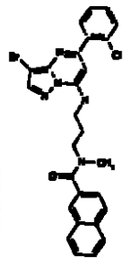
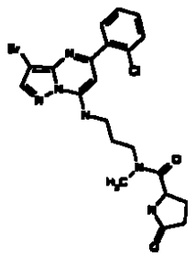
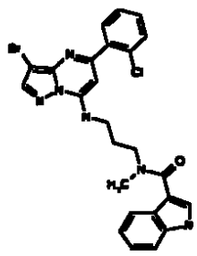
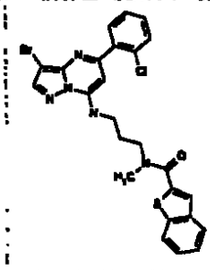
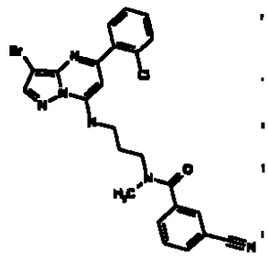
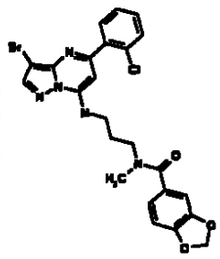
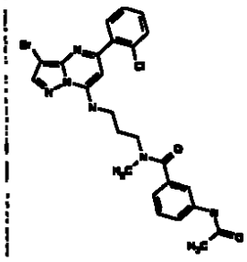
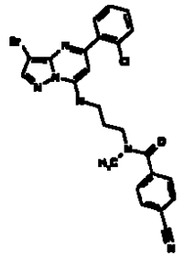
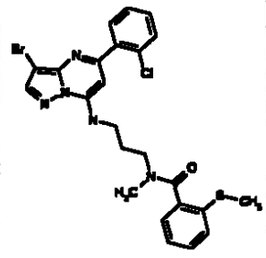
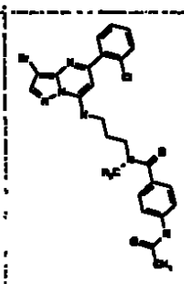
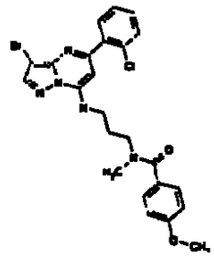
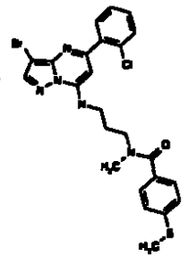
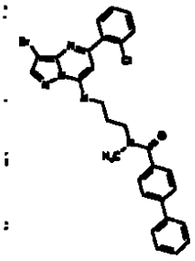
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5401 2. 483.3		1. 5406 2. 491.3		1. 5411 2. 505.3
	1. 5402 2. 477.3		1. 5407 2. 493.3		1. 5412 2. 509.3
	1. 5403 2. 483.3		1. 5408 2. 493.3		1. 5413 2. 513.3
	1. 5404 2. 489.3		1. 5409 2. 493.3		1. 5414 2. 518.3
	1. 5405 2. 489.3		1. 5410 2. 505.3		1. 5415 2. 519.3

770

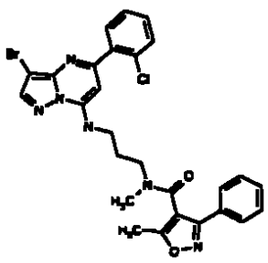
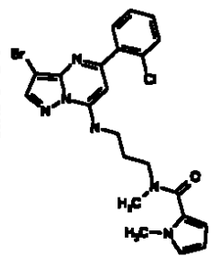
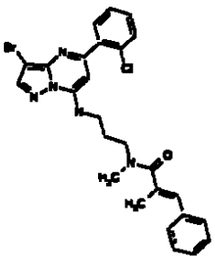
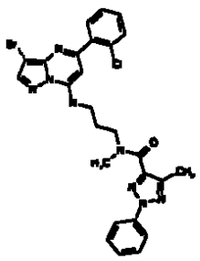
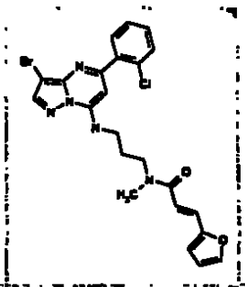
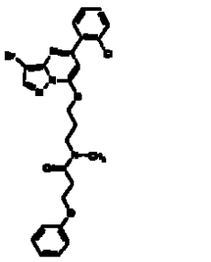
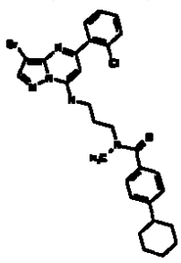
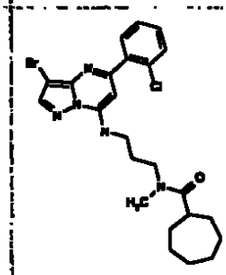
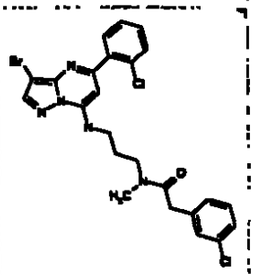
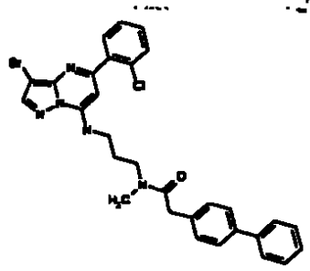
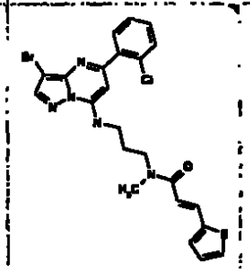
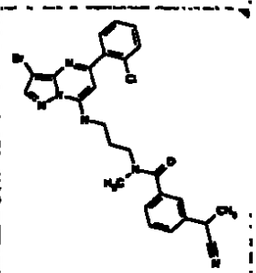
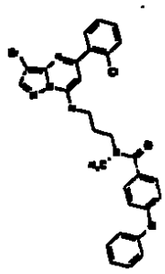
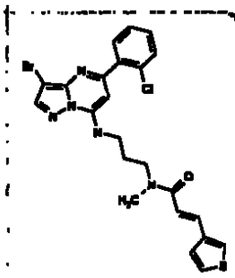
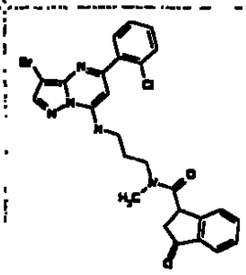
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5416 2. 519.3		1. 5121 2. 529.3		1. 5426 2. 539.3
	1. 5417 2. 519.3		1. 5422 2. 529.3		1. 5427 2. 539.3
	1. 5418 2. 525.3		1. 5423 2. 533.3		1. 5428 2. 539.3
	1. 5419 2. 527.3		1. 5424 2. 533.3		1. 5429 2. 539.3
	1. 5420 2. 527.3		1. 5425 2. 536.3		1. 5430 2. 541.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2.m/z	Producto	1. Ej. 2. m/z
	1. 5431 2. 543.3		1. 5436 2. 567.3		1. 5441 2. 582.3
	1. 5432 2. 545.3		1. 5437 2. 567.3		1. 5442 2. 589.3
	1. 5433 2. 549.3		1. 5438 2. 567.3		1. 5443 2. 591.3
	1. 5434 2. 553.3		1. 5439 2. 575.3		1. 5444 2. 591.3
	1. 5435 2. 567.3		1. 5440 2. 581.3		1. 5445 2. 529.3

772

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2.m/z
	1. 5446 2. 500.3		1. 5451 2. 533.3		1. 5456 2. 549.3
	1. 5447 2. 830.5		1. 54525 2. 719.4		1. 5457 2. 555.3
	1. 5448 2. 524.3		1. 5453 2. 543.3		1. 5458 2. 556.3
	1. 5449 2. 524.3		1. 5454 2. 545.3		1.5459 2. 556.3
	1. 5450 2. 529.3		1. 5455 2. 545.3		1. 5460 2. 575.3

773

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5461 2. 580.3		1. 5466 2. 502.3		1. 5471 2. 539.3
	1. 5462 2. 580.3		1. 5467 2. 515.3		1. 5472 2. 543.3
	1. 5463 2. 581.3		1. 5468 2. 519.3		1. 5473 2. 547.3
	1. 5464 2. 589.3		1. 5469 2. 531.3		1. 5474 2. 552.3
	1. 5465 2. 591.3		1. 5470 2. 531.3		1. 5475 2. 553.3

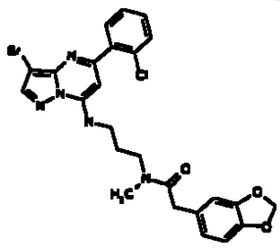
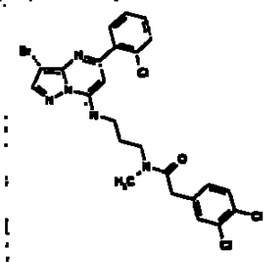
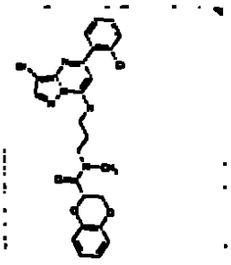
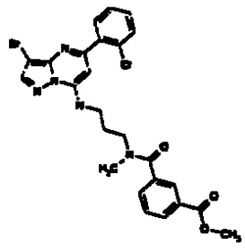
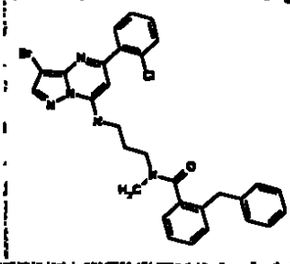
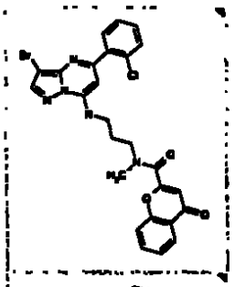
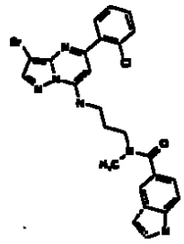
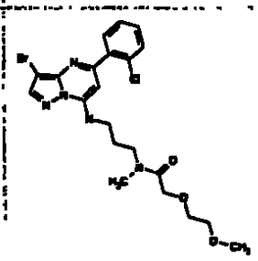
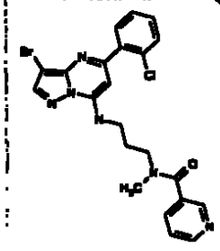
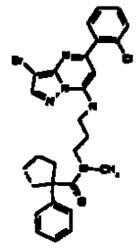
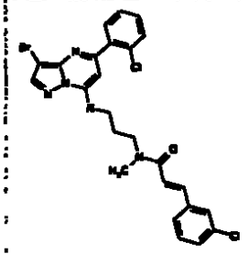
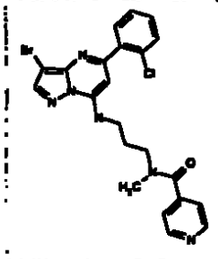
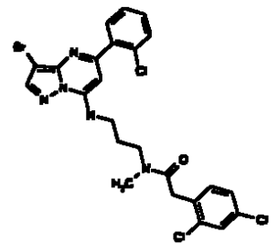
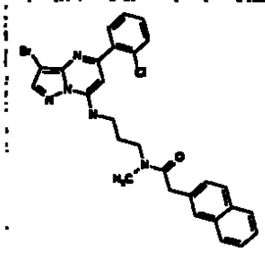
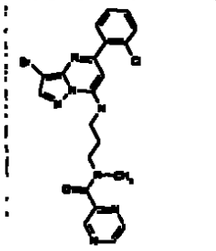
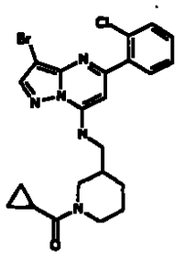
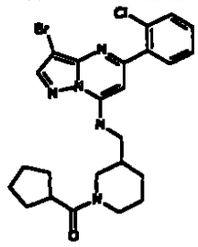
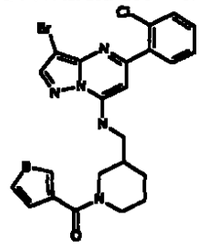
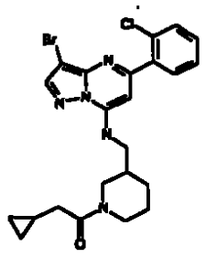
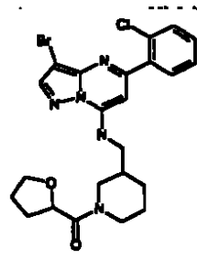
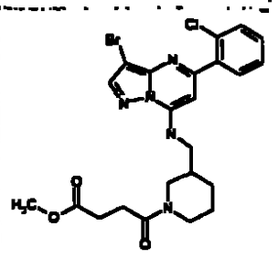
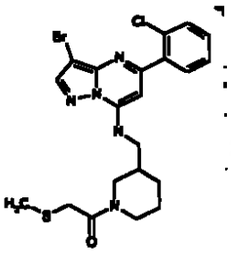
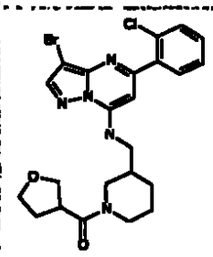
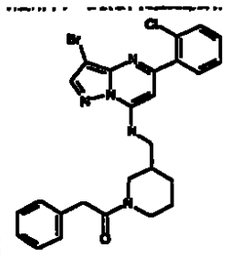
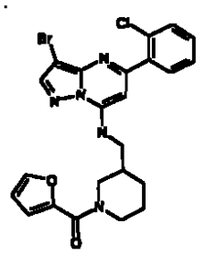
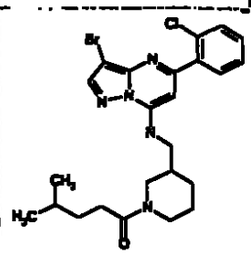
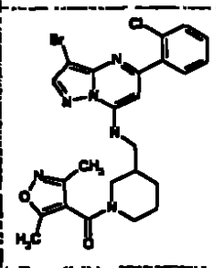
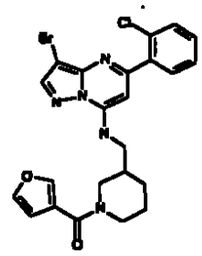
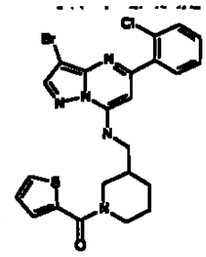
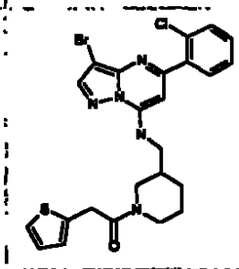
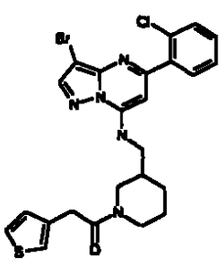
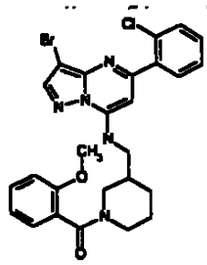
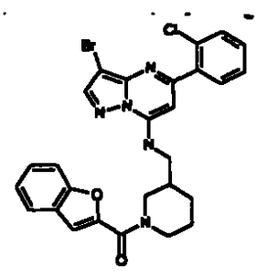
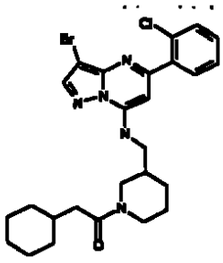
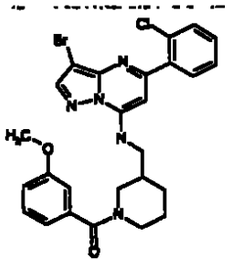
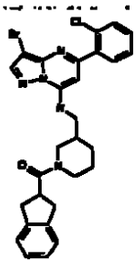
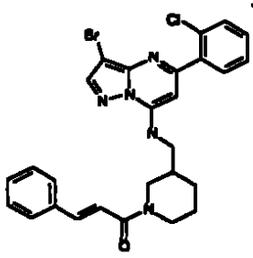
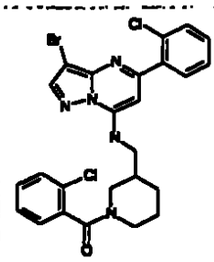
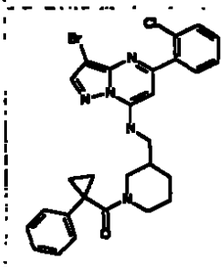
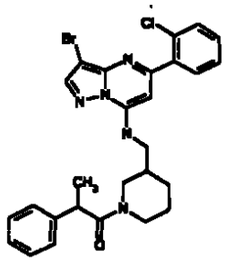
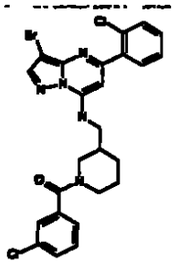
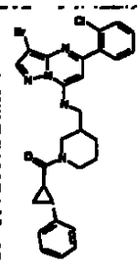
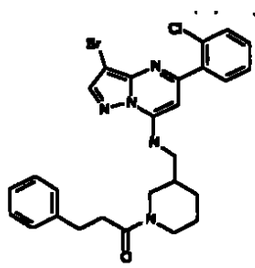
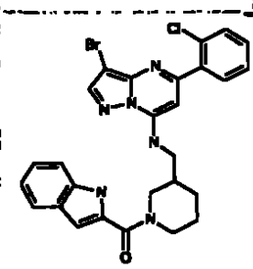
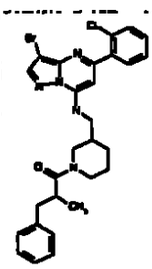
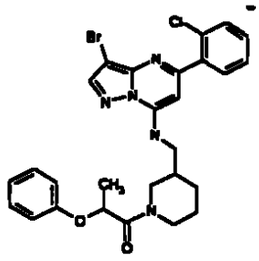
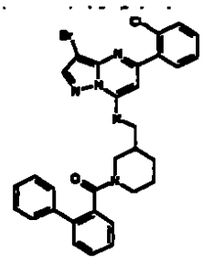
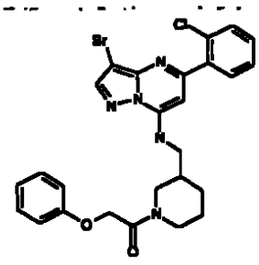
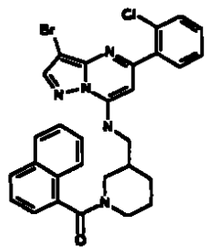
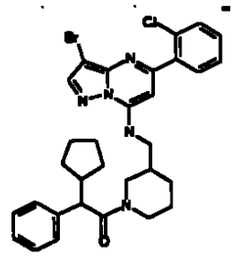
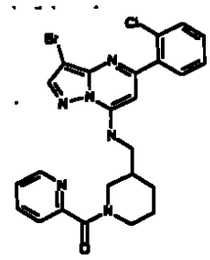
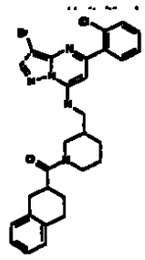
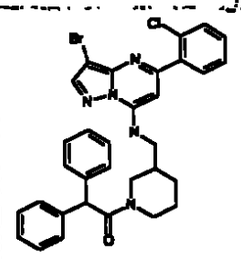
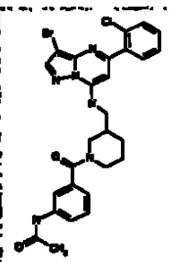
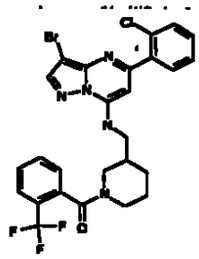
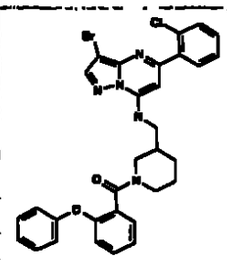
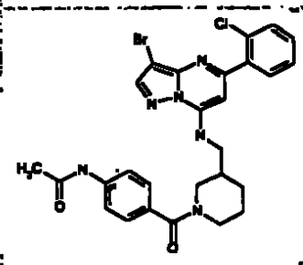
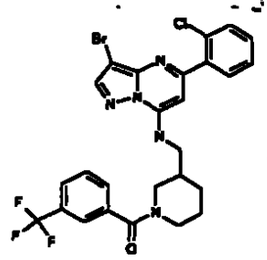
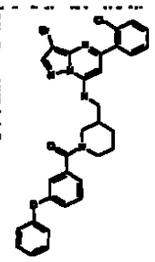
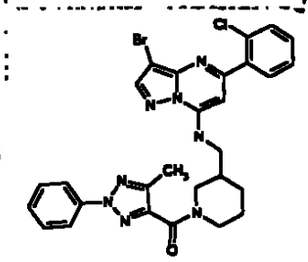
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5476 2. 557.3		1. 5481 2. 581.3		. 5486 2.
	1. 5477 2. 557.3		1. 5482 2. 589.3		1. 5487 2. 691.5
	1. 5478 2. 538.3		1. 5483 2. 511.3		1. 5488 2. 500.3
	1. 5479 2. 567.3		1. 5484 2. 559.3		1. 5489 2. 500.3
	1. 5480 2. 581.3		1. 5485 2. 583.3		1. 5490 2. 501.3

TABLA55

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5501 2. 488.81		1. 5506 2. 516.87		1. 5511 2. 530.87
	1. 5502 2. 502.84		1. 5507 2. 518.84		1. 5512 2. 534.84
	1. 5503 2. 508.87		1. 5508 2. 518.84		1. 5513 2. 538.87
	1. 5504 2. 514.81		1. 5509 2. 518.88		1. 5514 2. 543.85
	1. 5505 2. 514.81		1. 5510 2. 530.87		1. 5515 2. 544.9

776

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5516 2. 544.9		1. 5521 2. 554.87		1. 5526 2. 564.87
	1. 5517 2. 544.92		1. 5522 2. 554.87		1. 5527 2. 564.91
	1. 5518 2. 550.89		1. 5523 2. 559.29		1. 5528 2. 564.91
	1. 5519 2. 552.9		1. 5524 2. 559.29		1. 5529 2. 564.91
	1. 5520 2. 552.9		1. 5525 2. 563.88		1. 5530 2. 566.93

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5531 2. 568.9		1. 5536 2. 600.95		1. 5541
	1. 5532 2. 574.91		1. 5537 2. 606.99		1. 5542 2. 525.83
	1. 5533 2. 578.94		1. 5538 2. 614.97		1. 5543 2. 581.9
	1. 5534 2. 592.85		1. 5539 2. 616.95		1. 5544 2. 581.9
	1. 5535 2. 592.85		1. 5540 2. 616.95		1. 5545 2. 605.92

778

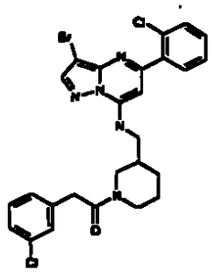
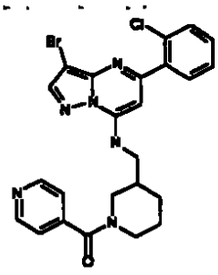
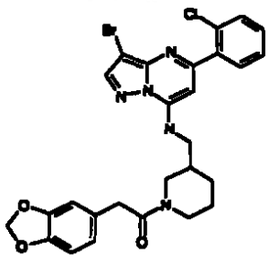
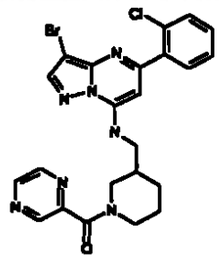
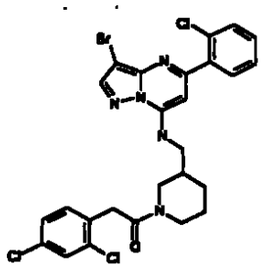
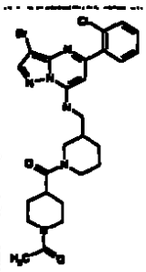
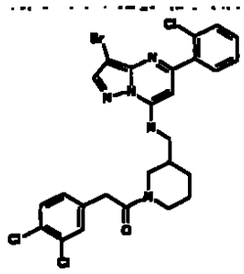
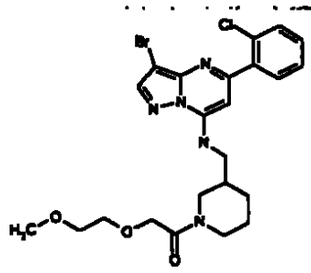
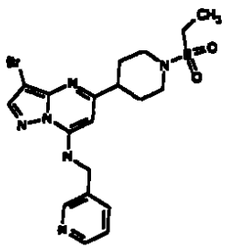
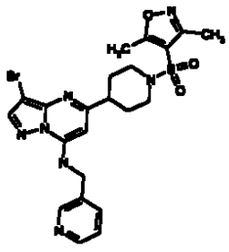
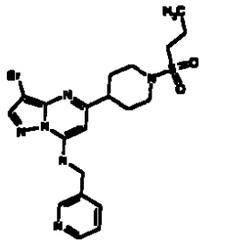
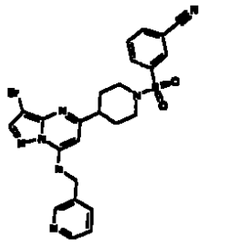
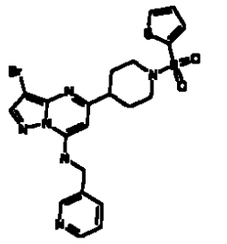
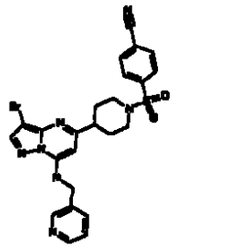
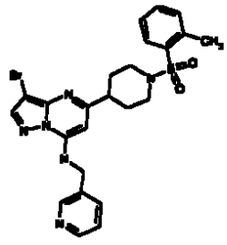
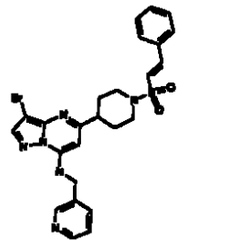
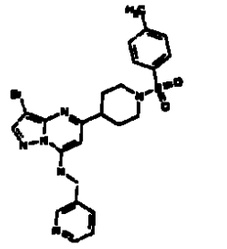
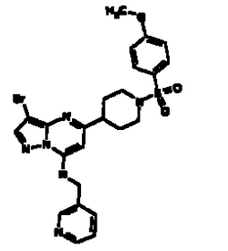
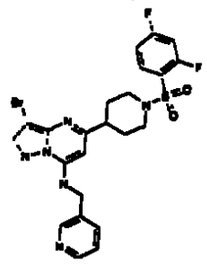
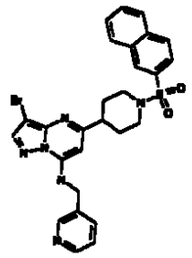
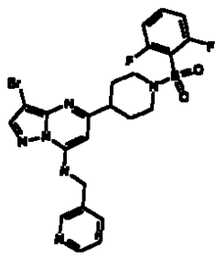
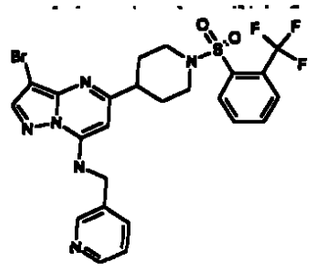
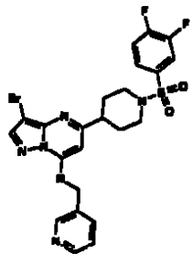
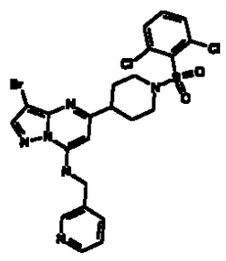
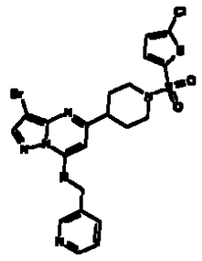
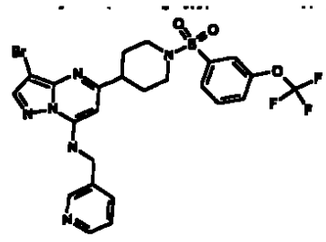
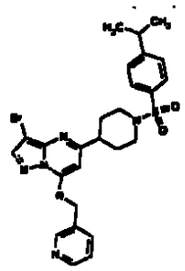
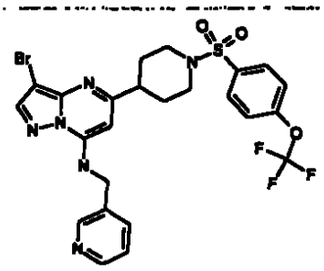
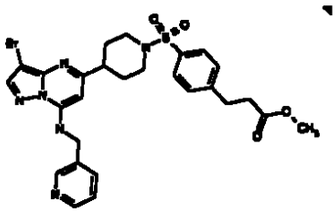
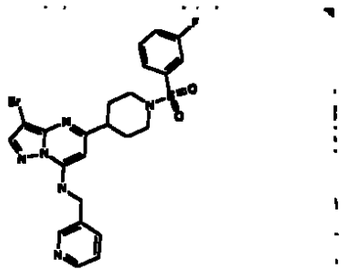
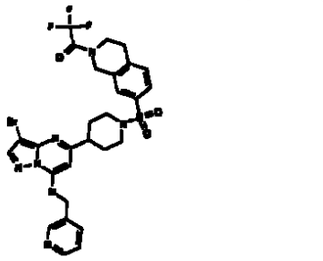
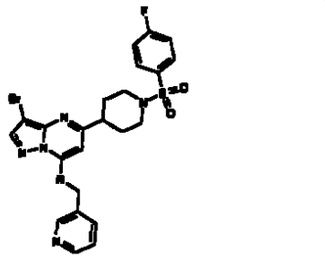
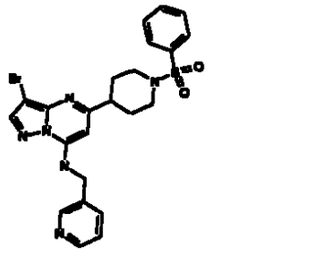
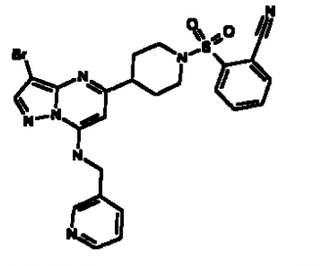
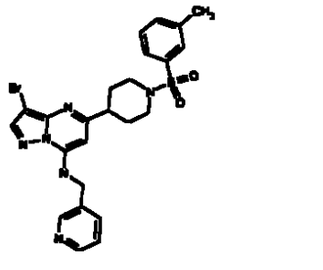
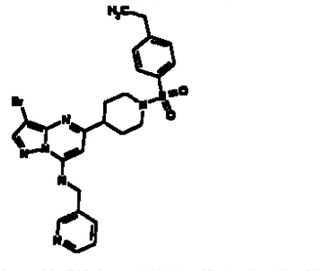
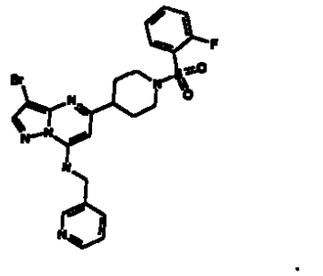
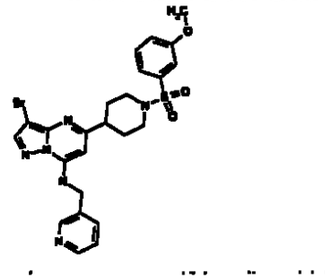
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5546 2. 573.32		1. 5551 2. 525.83
	1. 5547 2. 582.88		1. 5552 2. 526.82
	1. 5548 2. 607.76		1. 5553 2. 573.92
	1. 5549 2. 607.76		
	1. 5550 2. 536.86		

TABLA 56

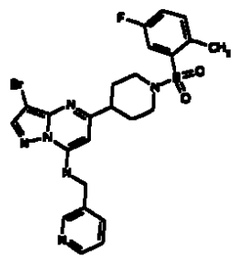
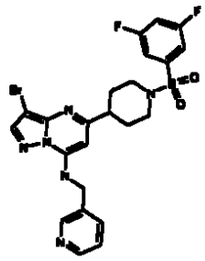
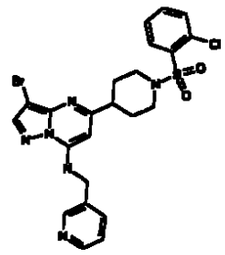
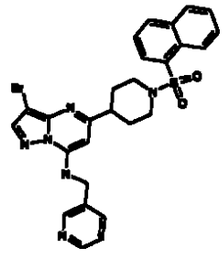
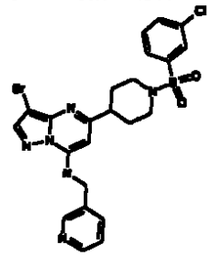
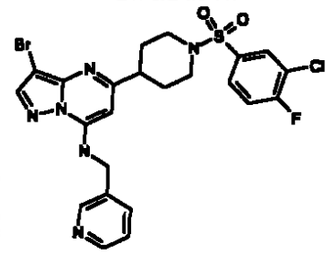
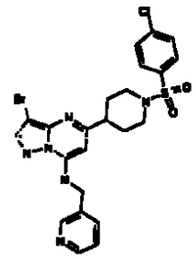
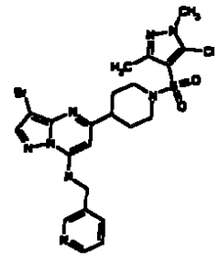
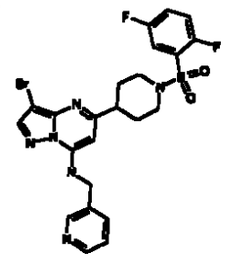
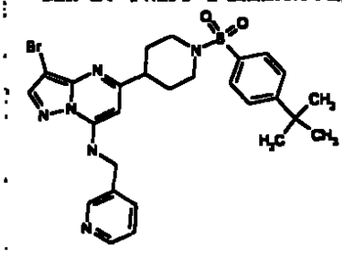
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5601 2. 481.26		1. 5606 2. 548.3
	1. 5602 2. 495.27		1. 5607 2. 554.3
	1. 5603 2. 535.29		1. 5608 2. 554.3
	1. 5604 2. 543.3		1. 5609 2. 555.31
	1. 5605 2. 543.3		1. 5610 2. 559.31

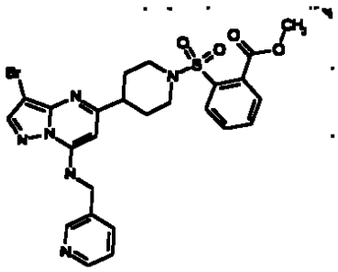
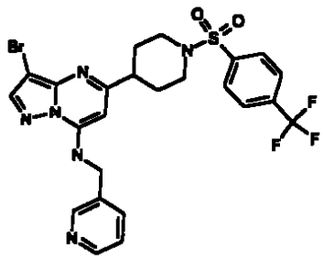
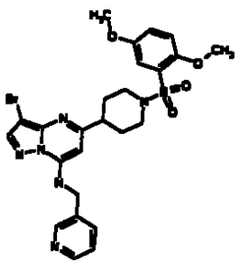
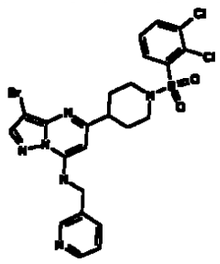
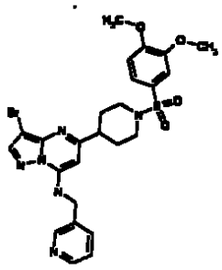
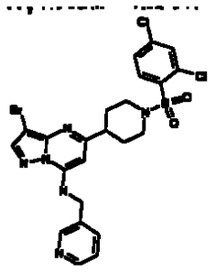
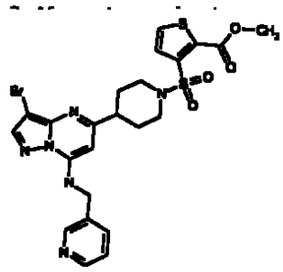
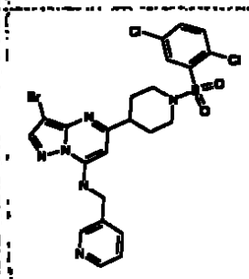
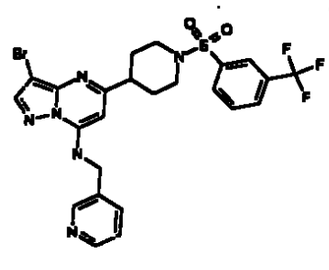
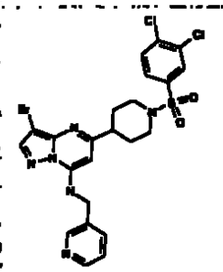
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5611 2. 565.31		1 .5616 2. 579.32
	1. 5612 2. 565.31		1. 5617
	1. 5613 2. 565.31		1. 5618
	1. 5614 2. 569.31		1. 5619
	1. 5615 2. 571.31		1. 5620

781

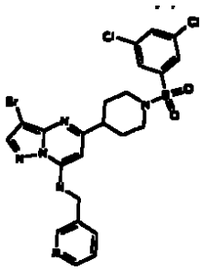
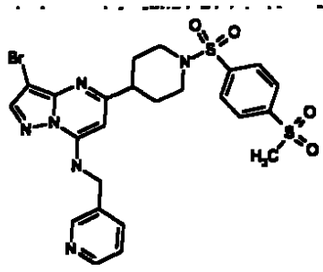
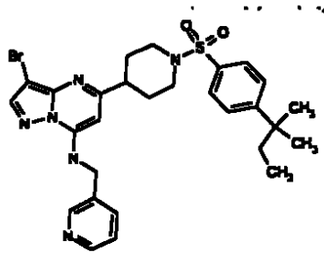
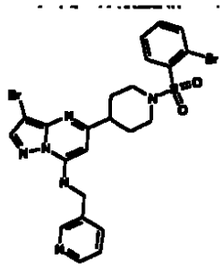
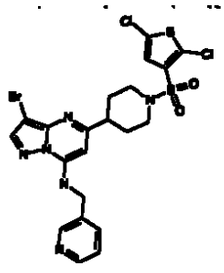
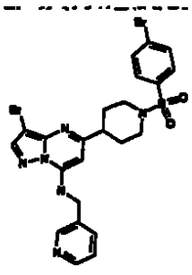
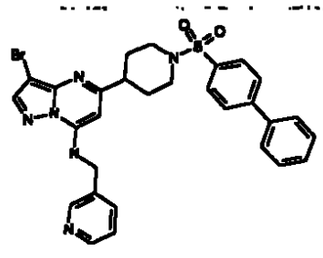
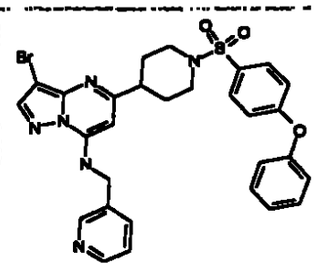
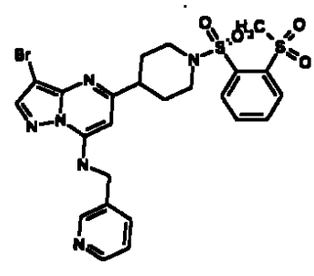
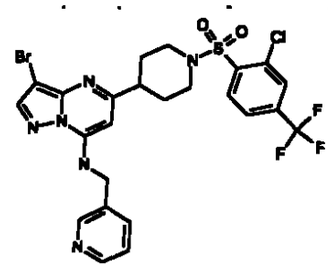
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5621 2. 615.34		1. 5626 2. 547.3
	2. 5622 2. 680.37		1. 5627 2. 547.3
	1. 5623 2. 529.29		1. 5628 2. 554.3
	1. 5624 2. 543.3		1. 5629 2. 555.31
	1. 5625 2. 547.3		1. 5630 2. 559.31

782

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5631 2. 561.31		1. 5636 2. 565.31
	1. 5632 2. 563.31		1. 5637 2. 579.32
	1. 5633 2. 563.31		1. 5638 2. 581.32
	1. 5634 2. 563.31		1. 5639 2. 581.32
	1. 5635 2. 563.31		1. 5640 2. 585.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5641 2. 587.32		1. 5646
	1. 5642 2. 589.32		1. 5647 2. 597.33
	1. 5643 2. 589.32		1. 5648 2. 597.33
	1. 5644 2. 593.33		1. 5649 2. 597.33
	1. 5645 2. 597.33		1. 5650 2. 597.33

784

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5651 2. 597.33		1. 5656 2. 607.33
	1. 5652 2. 599.33		1. 5657 2. 607.33
	1. 5653 2. 603.33		1. 5658 2. 607.33
	1. 5654 2. 605.33		1. 5659 2. 621.34
	1. 5655 2. 607.33		1. 5660 2. 631.35

785

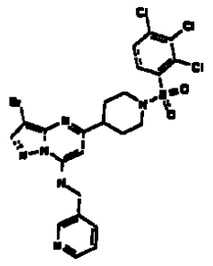
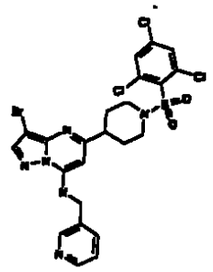
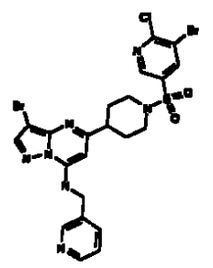
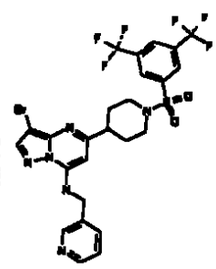
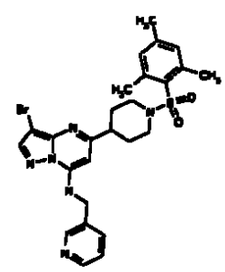
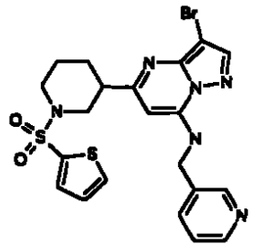
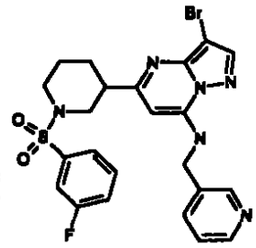
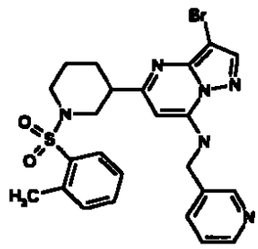
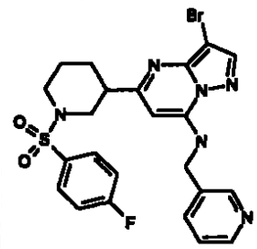
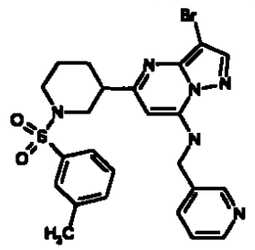
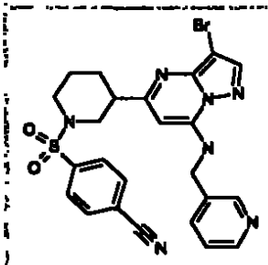
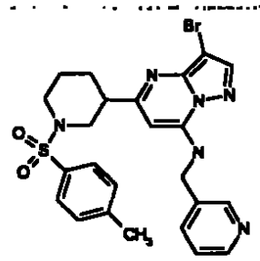
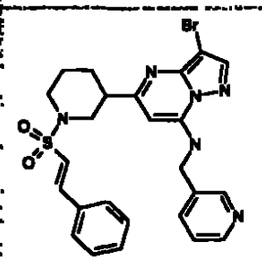
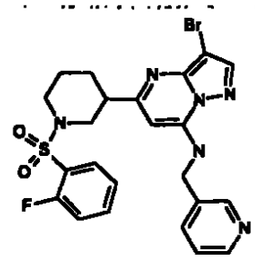
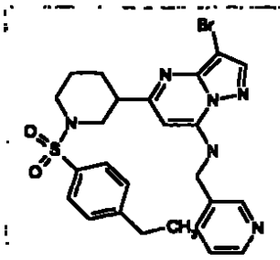
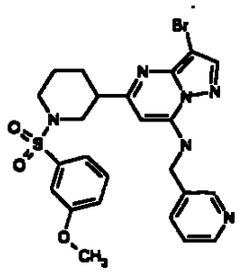
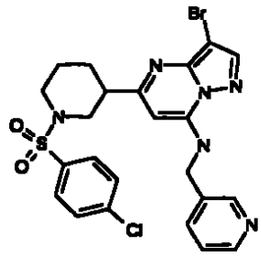
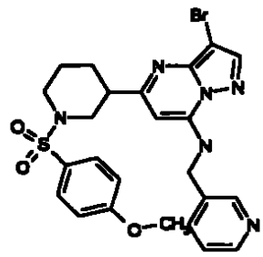
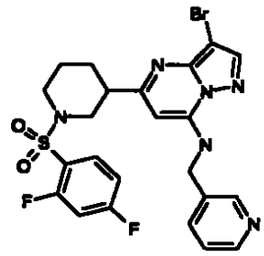
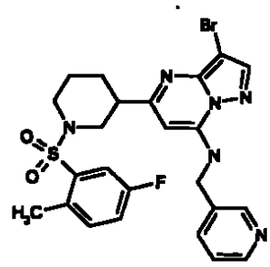
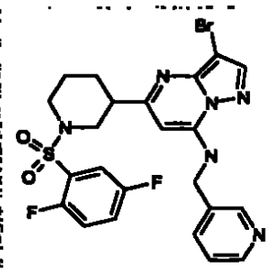
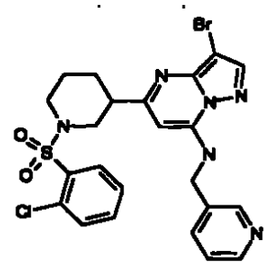
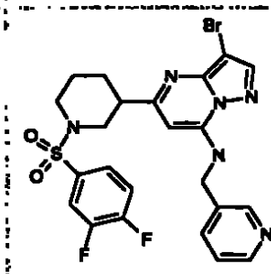
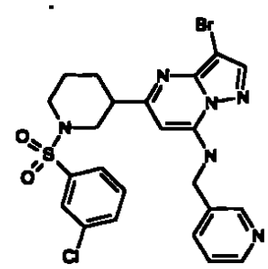
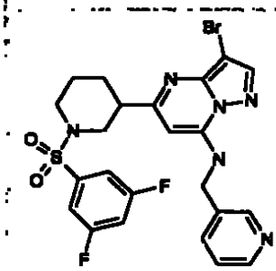
Producto	1. Ej. 2. m/z
	1. 5661 2. 631.35
	1. 5662 2. 631.35
	1. 5663 2. 642.35
	1. 5664 2. 665.37
	1. 5665 2. 571.31

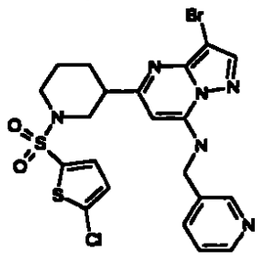
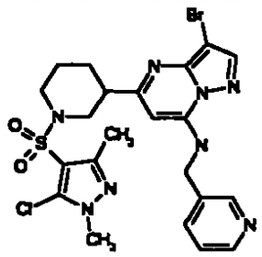
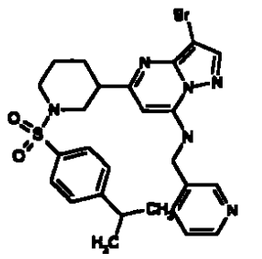
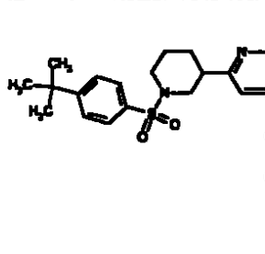
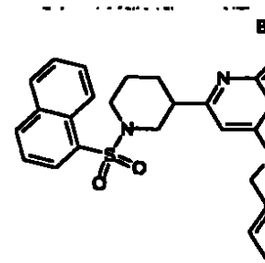
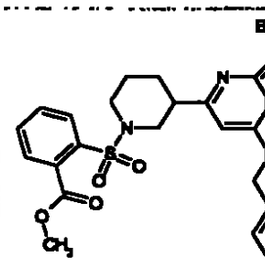
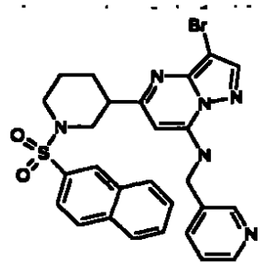
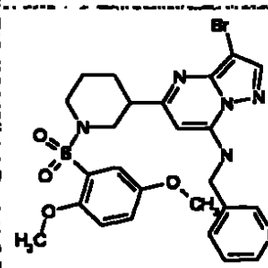
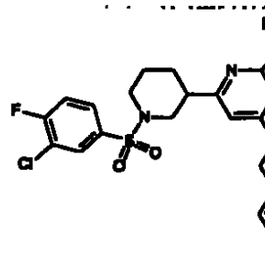
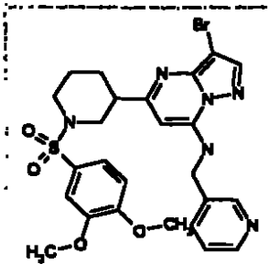
TABLA 57

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5701 2. 535.29		1. 5706 2. 547.3
	1. 5702 2. 540.3		1. 5707 2. 547.3
	1. 5703 2. 543.3		1. 5708 2. 554.3
	1. 5704 2. 543.3		1. 5709 2. 555.31
	1. 5705 2. 547.3		1. 5710 2. 555.31

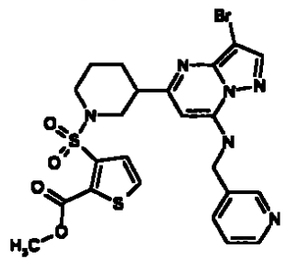
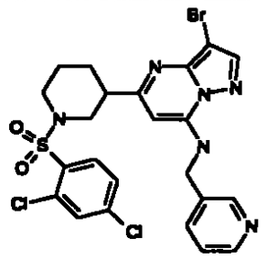
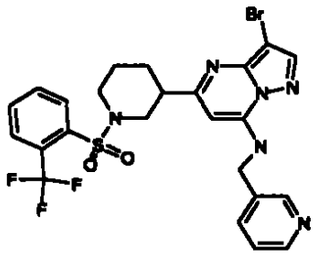
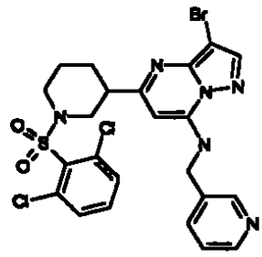
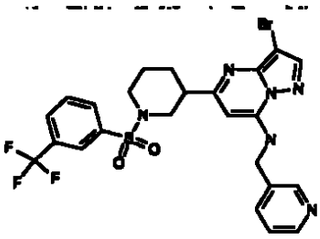
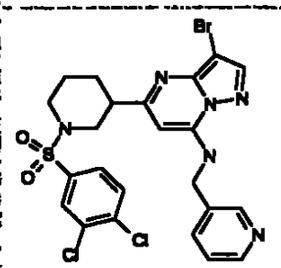
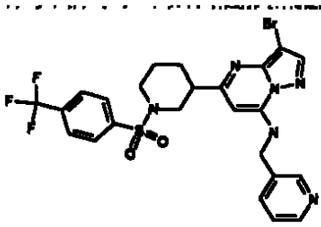
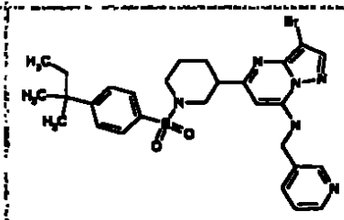
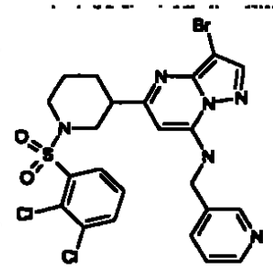
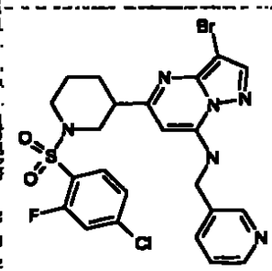
57

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5711 2. 559.31		1. 5716 2. 563.31
	1. 5712 2. 559.31		1. 5717 2. 565.31
	1. 5713 2. 561.31		1. 5718 2. 565.31
	1. 5714 2. 562.31		1. 5719 2. 565.31
	1. 5715 2. 563.31		1. 5720 2. 565.31

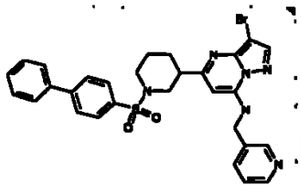
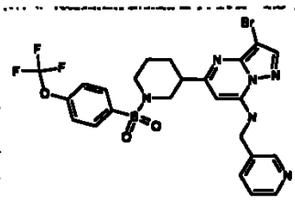
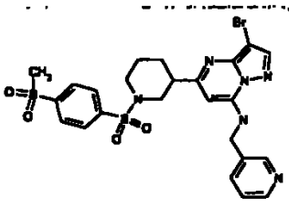
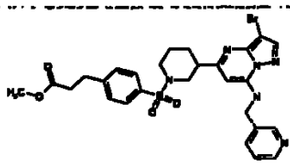
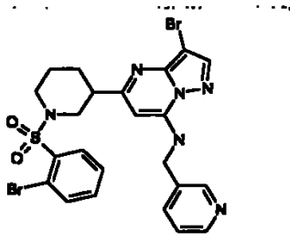
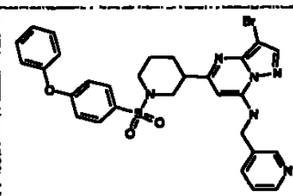
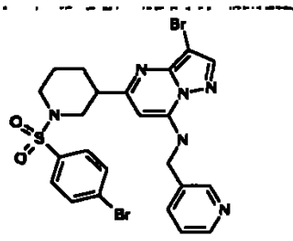
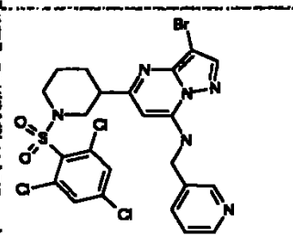
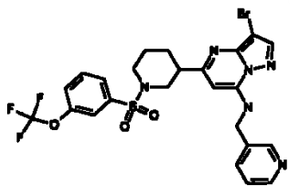
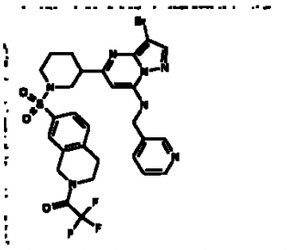
788

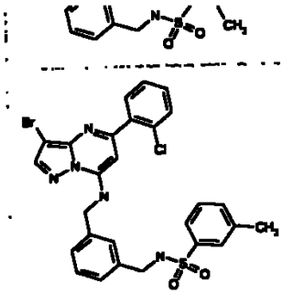
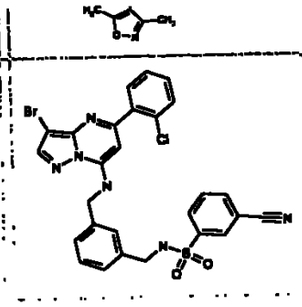
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5721 2. 589.31		1. 5726 2. 581.32
	1. 5722 2. 571.31		1. 5727 2. 585.32
	1. 5723 2. 579.32		1. 5728 2. 587.32
	1. 5724 2. 579.32		1. 5729 2. 589.32
	1. 5725 2. 581.32		1. 5730 2. 589.32

789

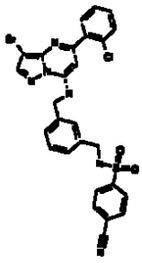
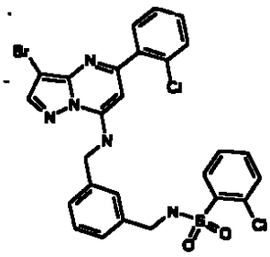
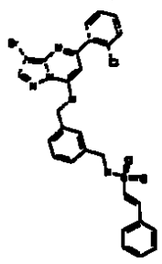
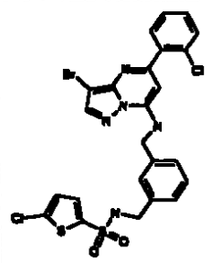
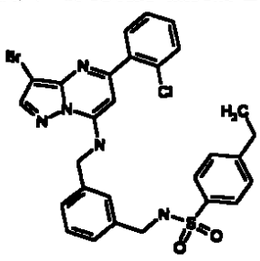
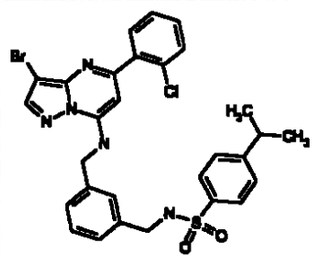
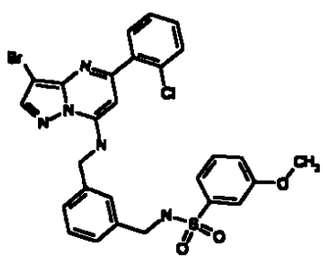
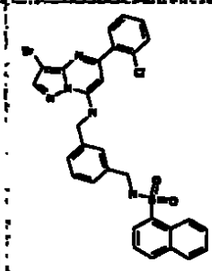
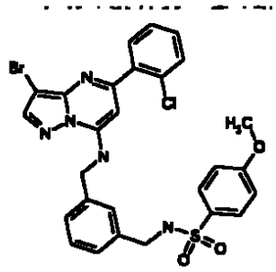
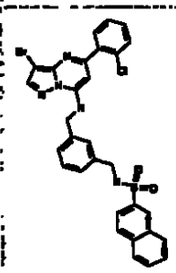
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5731 2. 591.33		1. 5736 2. 597.33
	1. 5732 2. 597.33		1. 5737 2. 597.33
	1. 5733 2. 595.33		1. 5738 2. 596.33
	1. 5734 2. 597.33		1. 5739 2. 597.33
	1. 5735 2. 597.33		1. 5740 2. 581.32

790

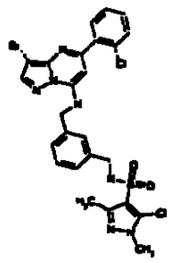
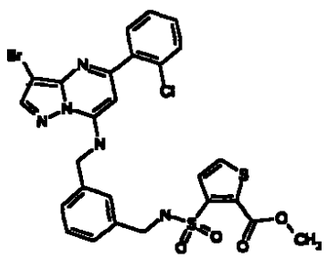
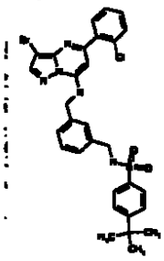
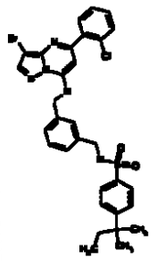
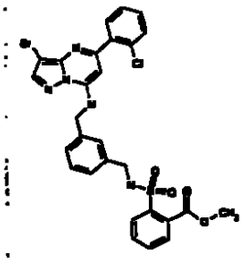
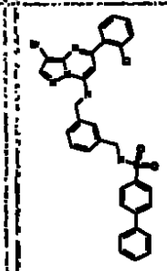
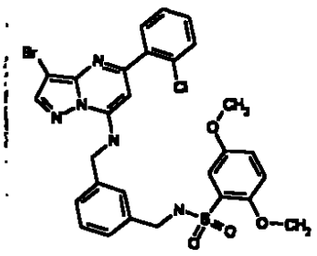
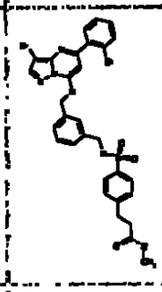
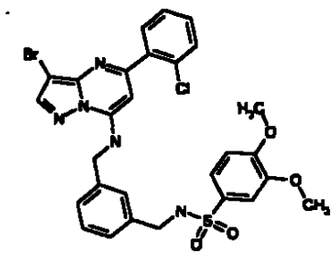
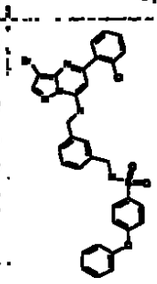
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5741 2. 605.33		1. 5746 2. 613.34
	1. 5742 2. 607.33		1. 5747 2. 615.34
	1. 5743 2. 607.33		1. 5748 2. 621.34
	1. 5744 2. 607.33		1. 5749 2. 631.35
	1. 57454 2. 613.34		1. 5750 2. 680.37

	1. 5805 2. 598.33		1. 5810 2. 609.33

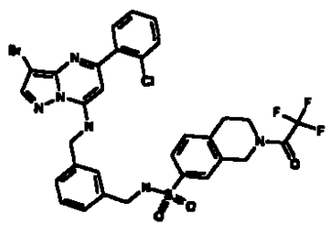
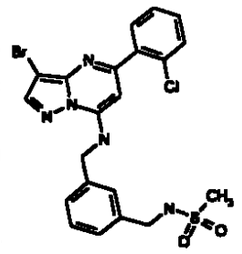
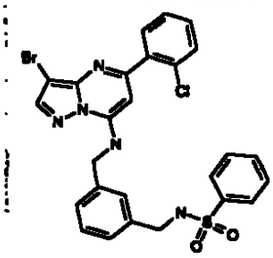
792

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5811 2. 609.33		1. 5816 2. 618.34
	1. 5812 2. 610.34		1. 5817 2. 624.34
	1. 5813 2. 612.34		1. 5818 2. 626.34
	1. 5814 2. 614.34		1. 5819 2. 634.35
	1. 5815 2. 614.34		1. 5820 2. 632.35

793

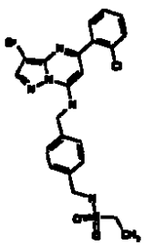
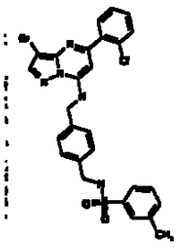
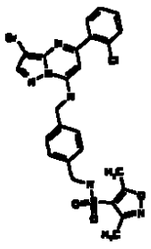
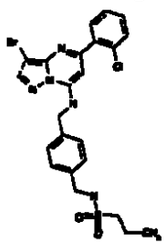
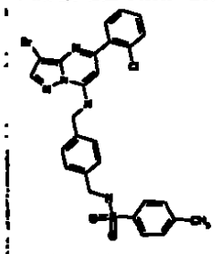
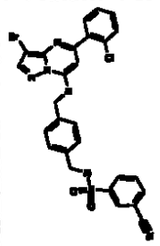
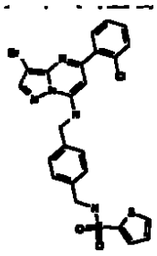
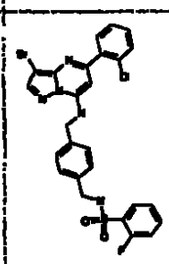
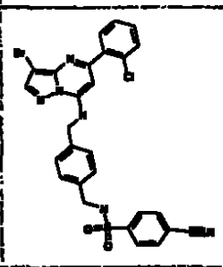
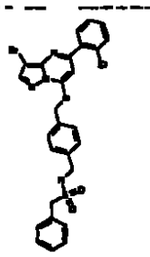
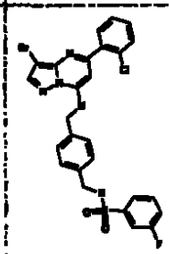
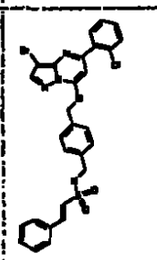
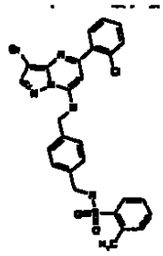
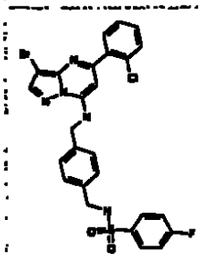
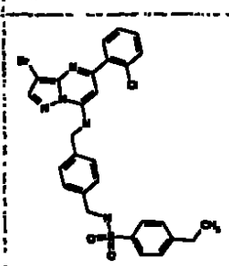
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5821 2. 636.35		1. 5826 2. 648.36
	1. 5822 2. 640.35		1. 5827 2. 654.36
	1. 5823 2. 642.35		1. 5828 2. 660.36
	1. 5824 2. 644.35		1. 5829 2. 670.37
	1. 5825 2. 644.35		1. 5830 2. 676.37

794

Producto	1. Ej. 2. m/z
	1. 5831 2. 735.4
	1. 5832 2. 522.29
	1. 5833 2. 584.32

795

TABLA 59

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5901 2. 536.29		1. 5906 2. 598.33		1. 5911 2. 603.33
	1. 5902 2. 550.3		1. 5907 2. 598.33		1. 5912 2. 609.33
	1. 5903 2. 590.32		1. 5908 2. 602.33		1. 5913 2. 609.33
	1. 5904 2. 598.33		1. 5909 2. 602.33		1. 5914 2. 610.34
	1. 5905 2. 598.33		1. 5910 2. 602.33		1. 5915 2. 612.34

796

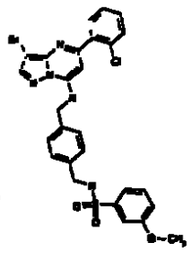
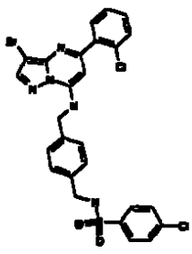
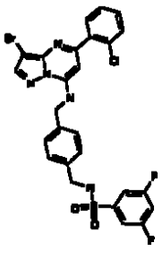
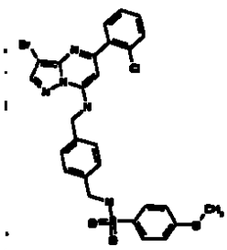
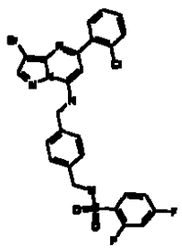
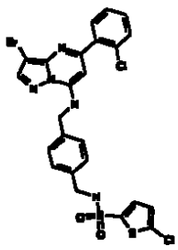
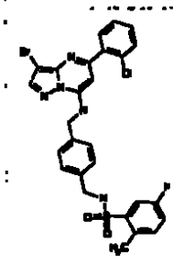
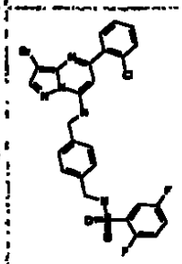
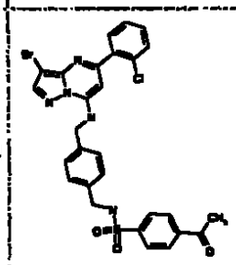
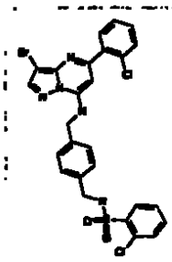
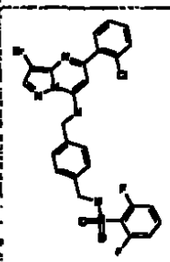
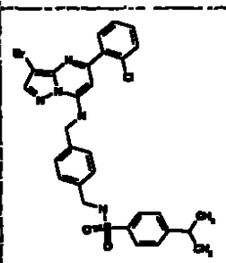
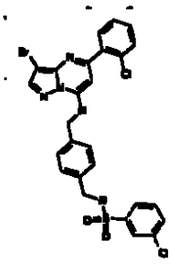
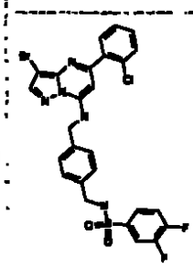
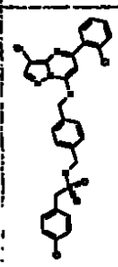
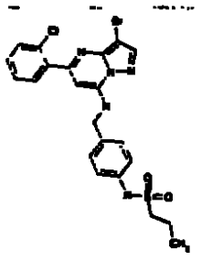
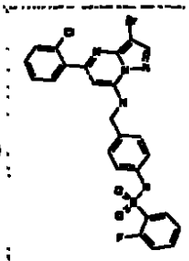
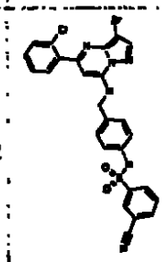
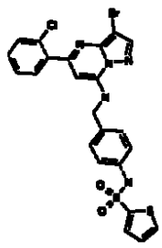
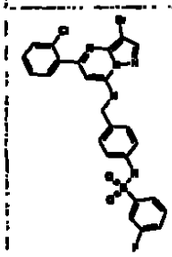
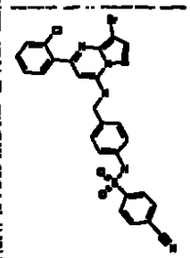
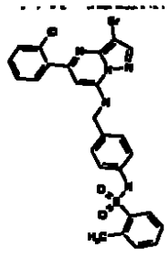
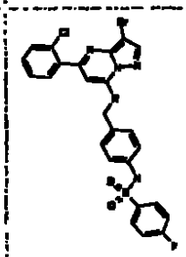
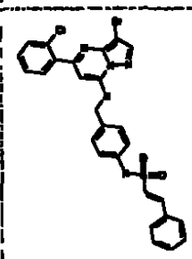
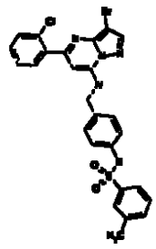
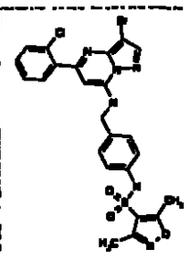
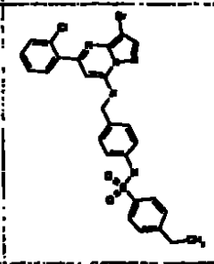
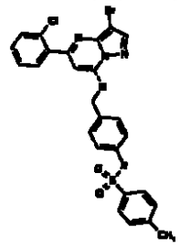
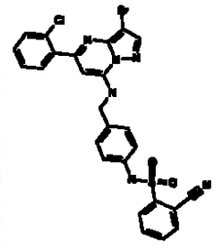
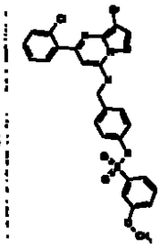
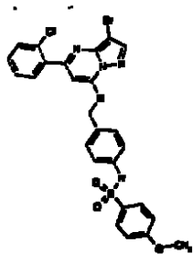
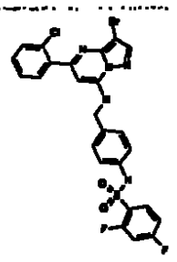
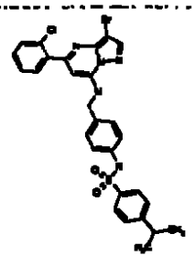
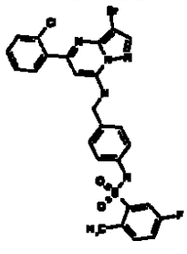
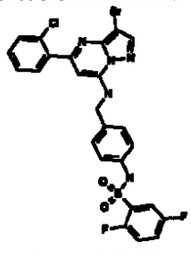
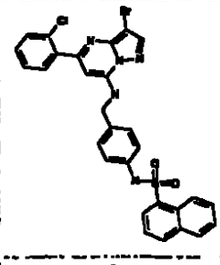
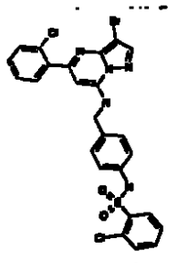
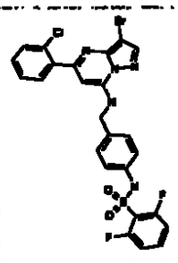
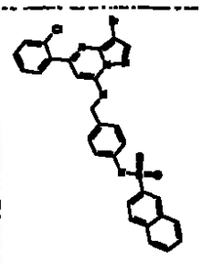
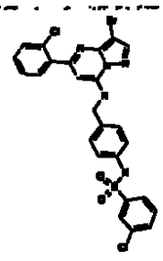
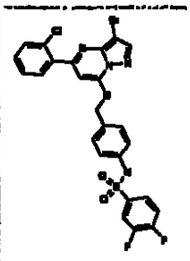
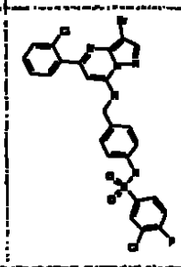
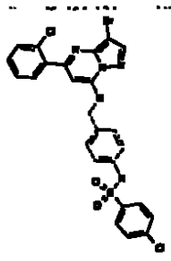
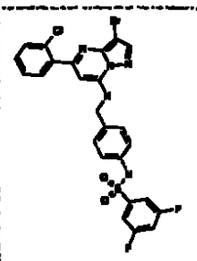
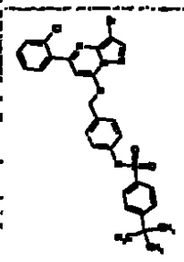
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 5916 2. 614.34		1. 5921 2. 618.34		1. 5926 2. 620.34
	1. 5917 2. 614.34		1. 5922 2. 620.34		1. 5927 2. 624.34
	1. 5918 2. 616.34		1. 5923 2. 620.34		1. 5928 2. 626.34
	1. 5919 2. 618.34		1. 5924 2. 620.34		1. 5929 2. 626.34
	1. 5920 2. 618.34		1. 5925 2. 620.34		1. 5930 2. 632.35

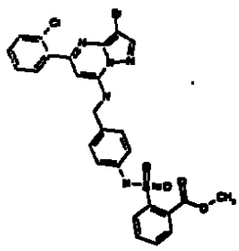
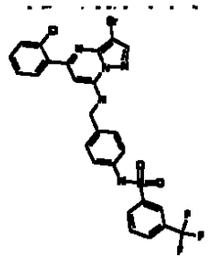
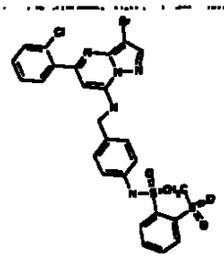
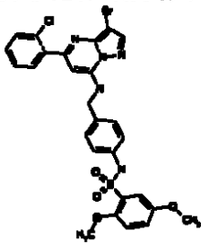
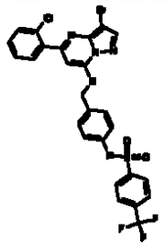
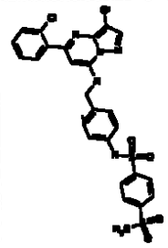
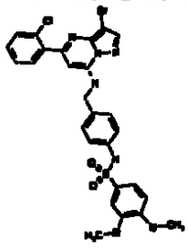
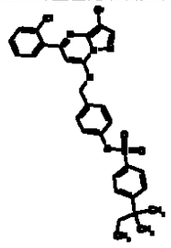
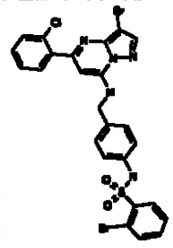
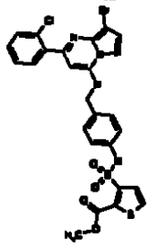
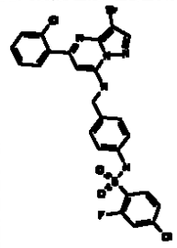
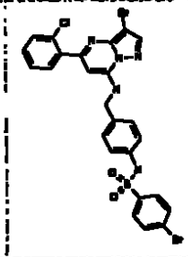
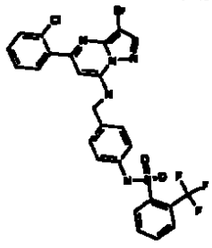
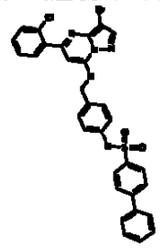
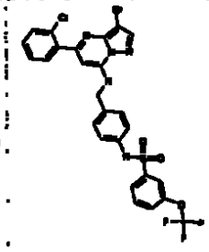
TABLA 60

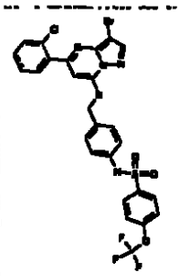
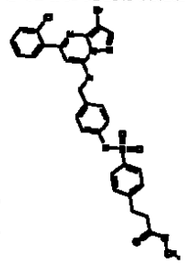
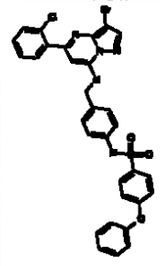
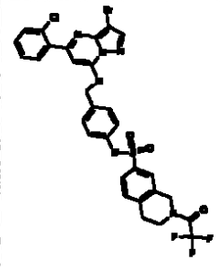
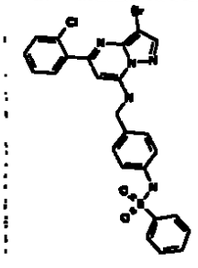
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6001 2. 536.29		1. 6006 2. 588.32		1. 6011 2. 595.33
	1. 6002 2. 576.32		1. 6007 2. 588.32		1. 6012 2. 595.33
	1. 6003 2. 584.32		1. 6008 2. 588.32		1. 6013 2. 596.33
	1. 6004 2. 584.32		1. 6009 2. 589.32		1. 6014 2. 596.33
	1. 6005 2. 584.32		1. 6010 2. 595.33		1. 6015 2. 600.33

798

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

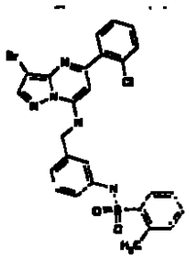
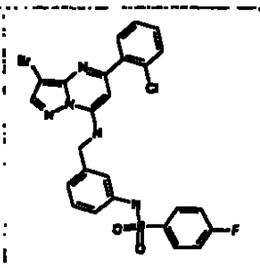
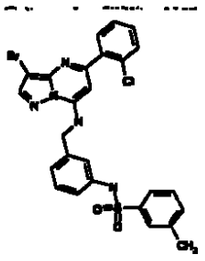
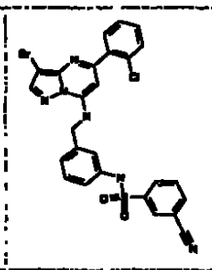
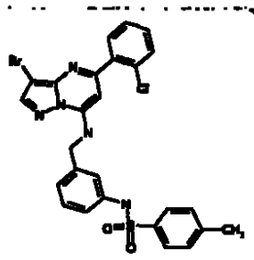
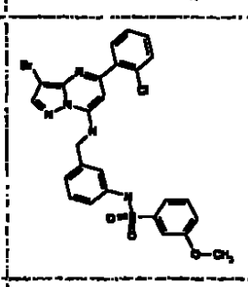
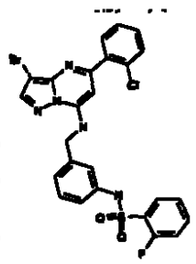
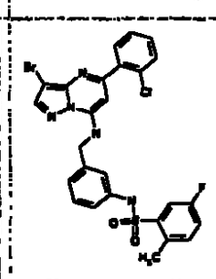
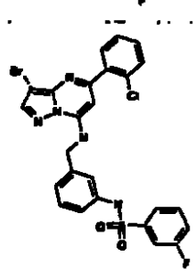
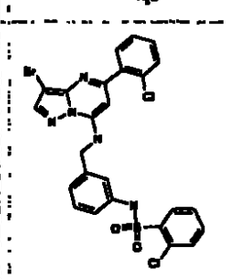
799

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6031 2. 628.35		1. 6036 2. 638.35		1. 6041 2. 648.36
	1. 6032 2. 630.35		1. 6037 2. 638.35		1. 60425 2. 648.36
	1. 6033 2. 630.35		1. 6038 2. 638.35		1. 6043 2. 648.36
	1. 6034 2. 634.35		1. 6039 2. 622.34		1. 6044 2. 648.36
	1. 6035 2. 638.35		1. 6040 2. 646.36		1. 6045 2. 654.36

Producto	1. Ej. 2. m/z
	1. 6046 2. 654.36
	1. 6047 2. 656.36
	1. 6048 2. 662.36
	1. 6049 2. 721.4
	1. 6050 2. 570.31

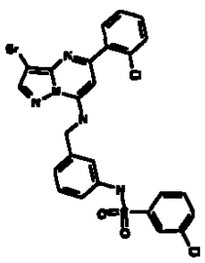
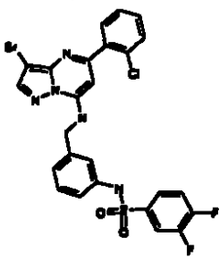
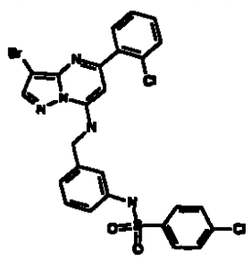
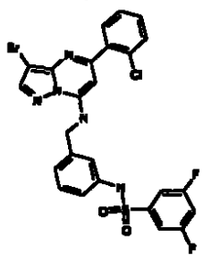
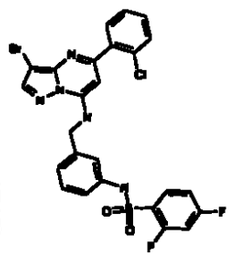
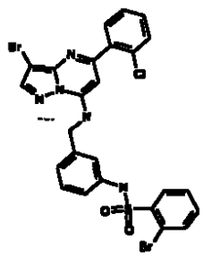
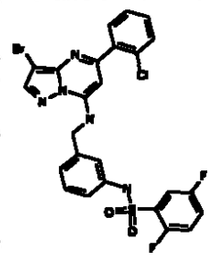
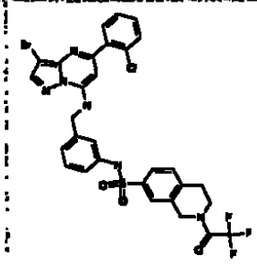
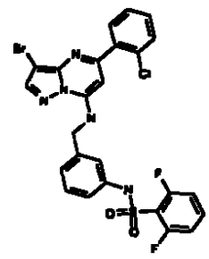
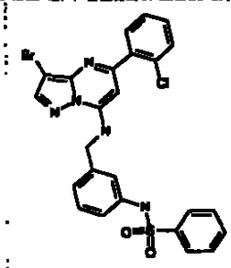
801

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

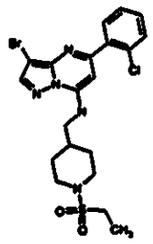
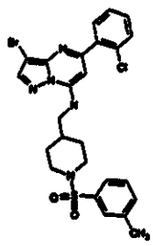
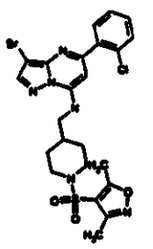
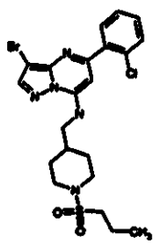
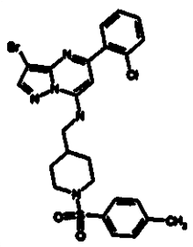
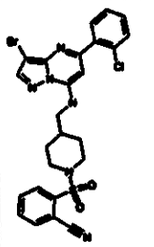
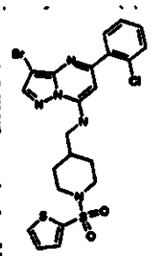
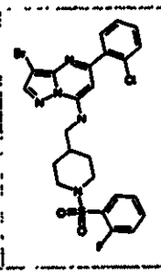
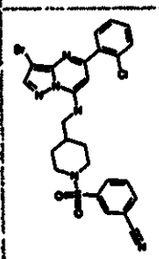
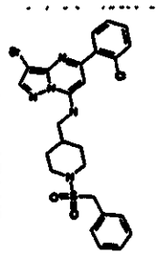
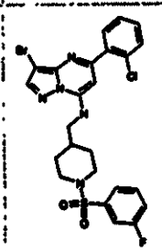
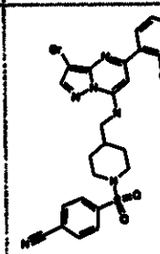
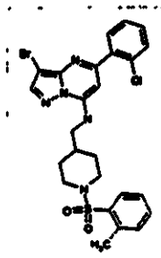
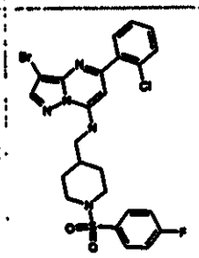
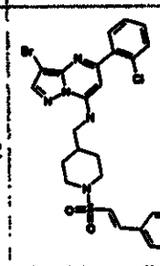
5

802

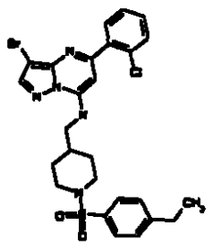
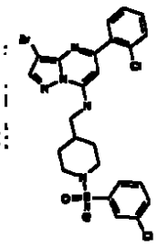
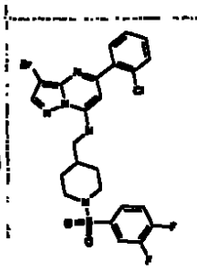
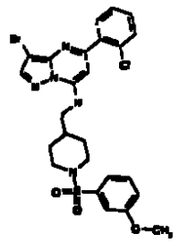
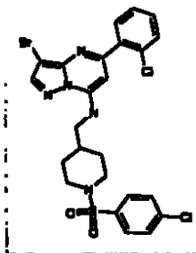
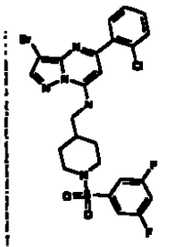
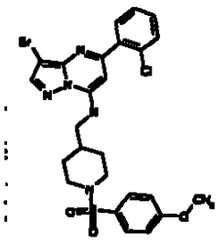
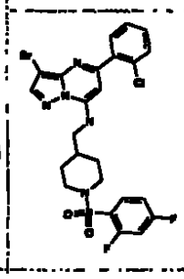
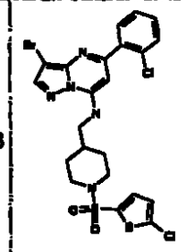
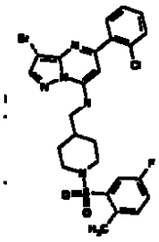
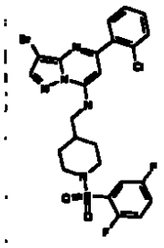
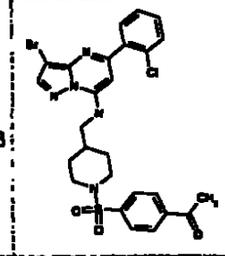
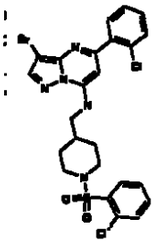
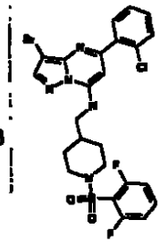
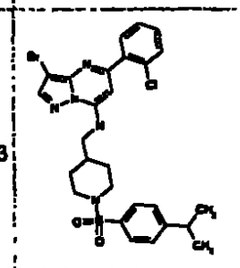
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6111 2. 604.33		1. 6116 2. 606.33
	1. 6112 2. 604.33		1. 6117 2. 606.33
	1. 6113 2. 606.33		1. 6118 2. 648.36
	1. 6114 2. 606.33		1. 6119 2. 721.4
	1. 6115 2. 606.33		1. 6120 2. 570.31

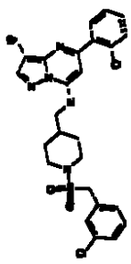
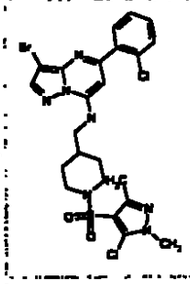
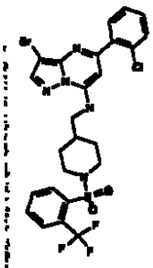
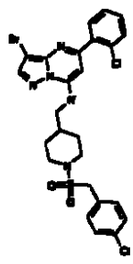
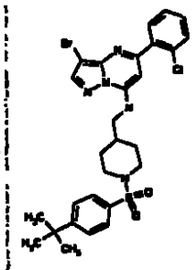
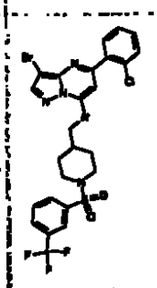
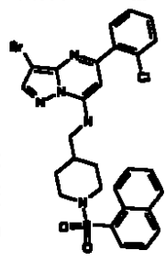
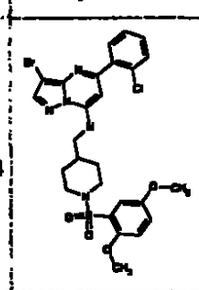
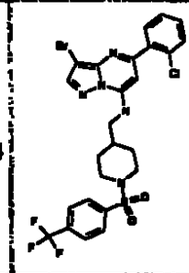
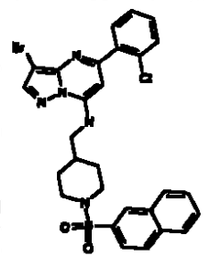
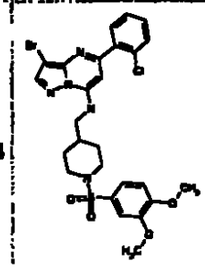
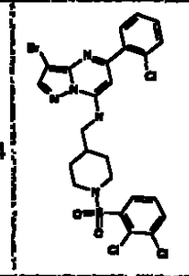
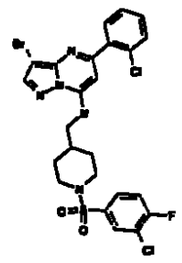
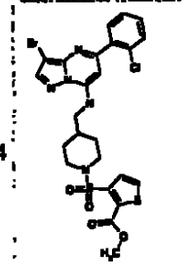
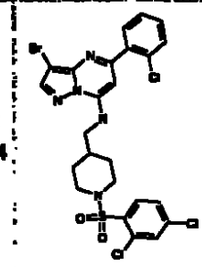
803

TABLA 62

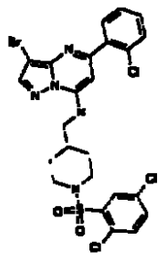
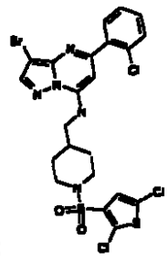
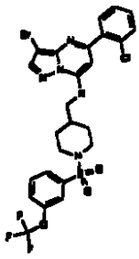
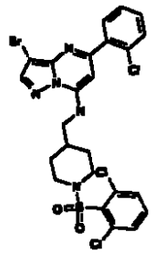
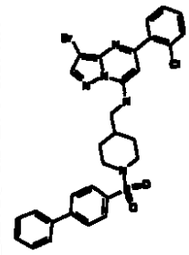
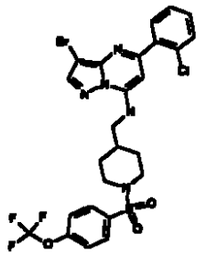
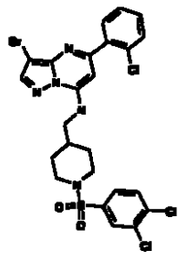
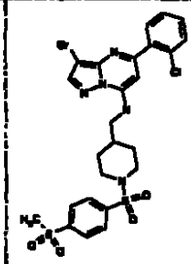
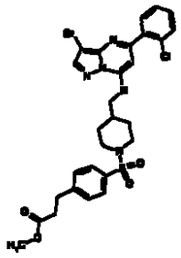
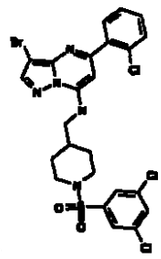
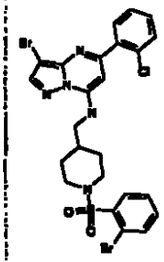
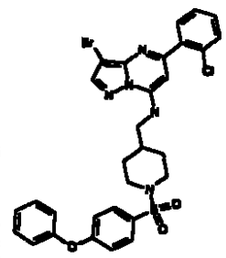
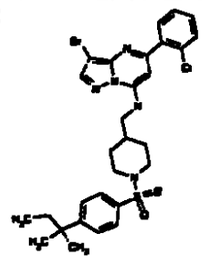
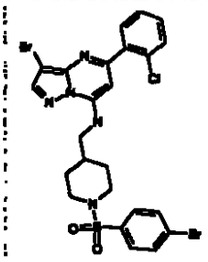
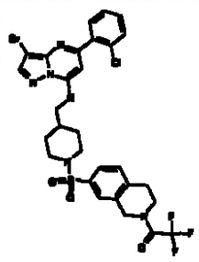
Producto	1. Ej. 2 m/z	Producto	1. Ej. 2 m/z	Producto	1. Ej. 2 m/z
	1. 6201 2. 514.28		1. 6206 2. 576.32		1. 6211 2. 581.32
	1. 6202 2. 528.29		1. 6207 2. 576.32		1. 6212 2. 587.32
	1. 6203 2. 568.31		1. 6208 2. 580.32		1. 6213 2. 587.32
	1. 6204 2. 576.32		1. 6209 2. 580.32		1. 6214 2. 587.32
	1. 6205 2. 576.32		1. 6210 2. 580.32		1. 6215 2. 588.32

804

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6216 2. 590.32		1. 6221 2. 596.33		1. 6226 2. 598.33
	1. 6217 2. 592.33		1. 6222 2. 596.33		1. 6227 2. 596.33
	1. 6218 2. 592.33		1. 6223 2. 598.33		1. 6228 2. 602.33
	1. 6219 2. 592.33		1. 6224 2. 596.33		1. 6229 2. 604.33
	1. 6220 2. 594.33		1. 6225 2. 598.33		1. 6230 2. 604.33

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6231 2. 610.34		1. 6236 2. 614.34		1. 6241 2. 630.35
	1. 6232 2. 610.34		1. 6237 2. 618.34		1. 6242 2.
	1. 6233 2. 612.34		1. 6238 2. 622.34		1. 6243 2. 630.35
	1. 6234 2. 612.34		1. 6239 2. 622.34		1. 6244 2. 630.35
	1. 6235 2. 614.34		1. 6240 2. 626.34		1. 6245 2. 630.35

806

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1 .6246 2. 630.35		1 .6251 2. 636.35		1. 6256 2. 646.36
	1. 6247 2. 630.35		1.0 6252 2. 638.35		1. 6257 2. 646.36
	1. 6248 2. 630.35		1. 6253 2. 640.35		1. 6258 2. 648.36
	1. 6249 2. 630.35		1. 6254 2. 640.35		1. 6259 2. 654.36
	1 .6250 2. 632.35		1. 6255 2. 638.35		1. 6260 2. 713.39

807

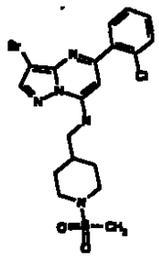
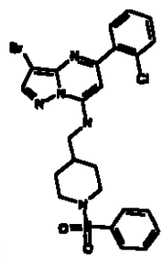
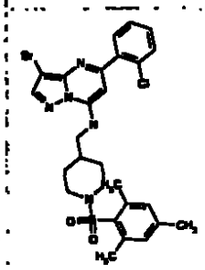
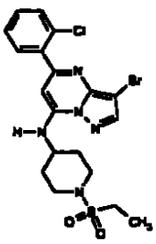
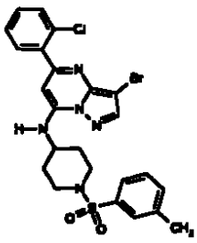
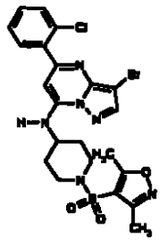
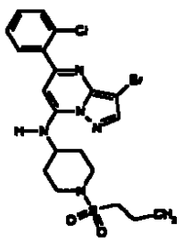
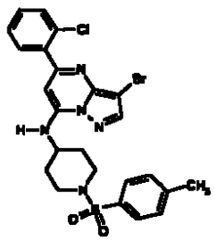
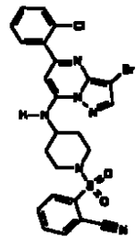
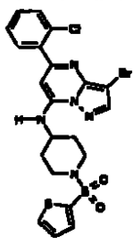
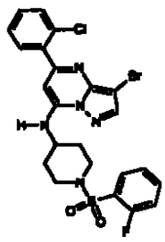
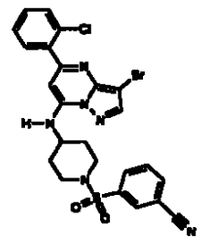
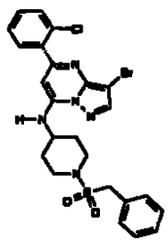
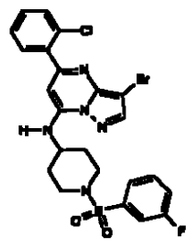
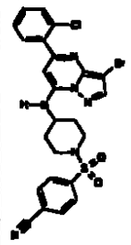
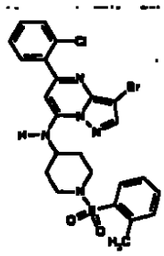
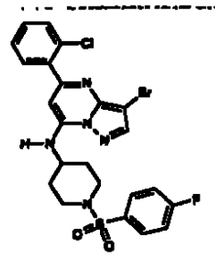
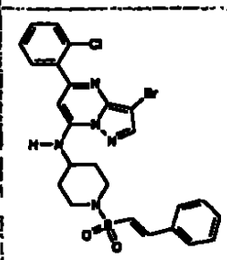
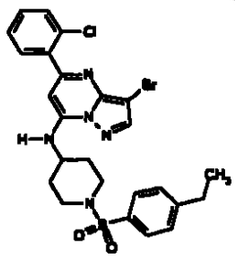
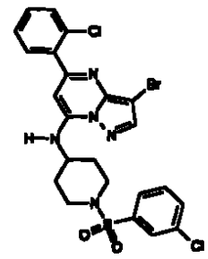
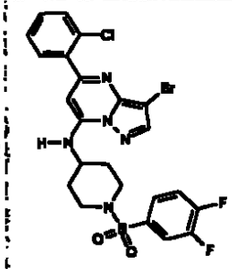
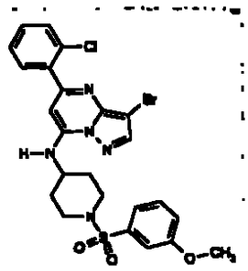
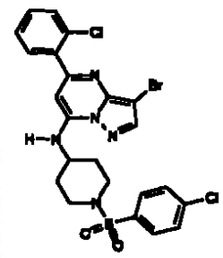
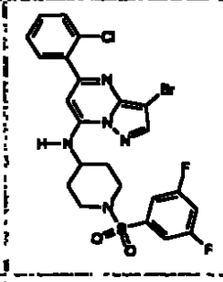
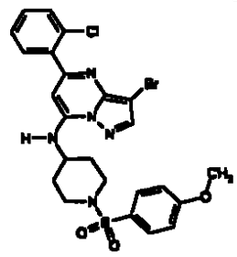
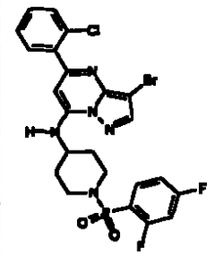
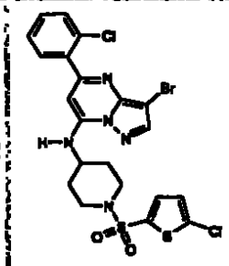
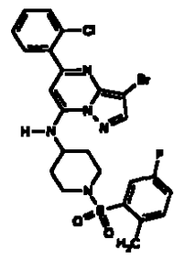
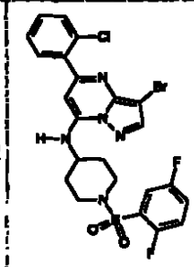
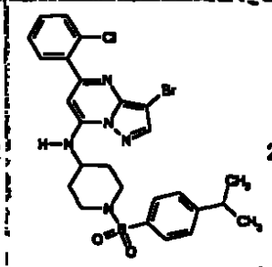
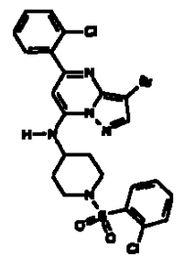
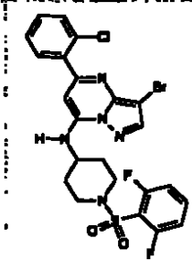
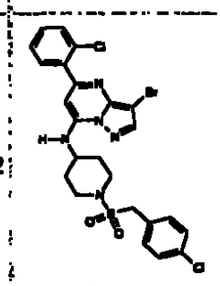
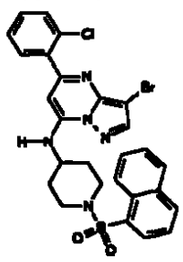
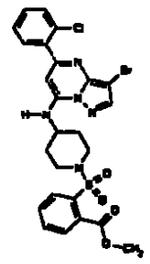
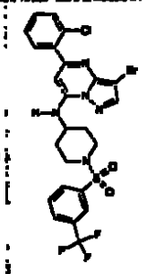
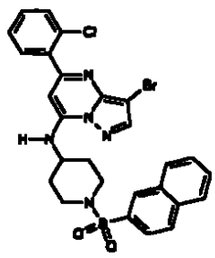
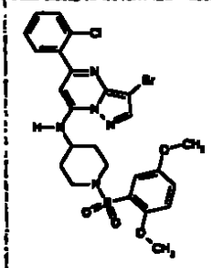
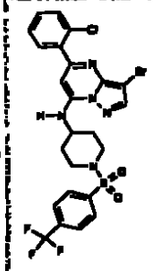
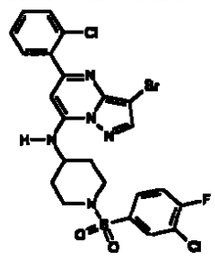
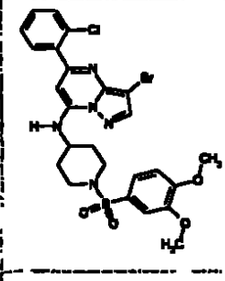
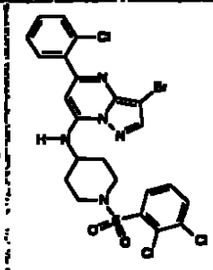
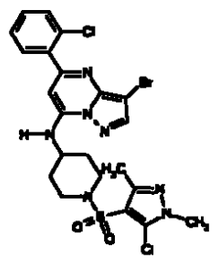
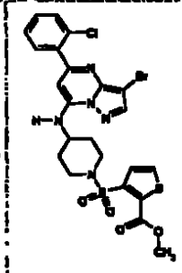
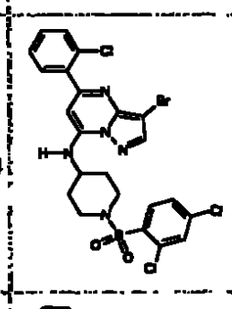
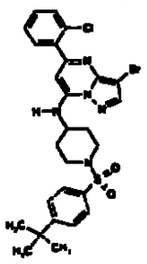
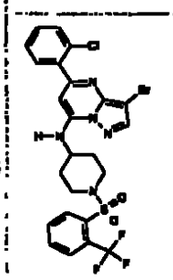
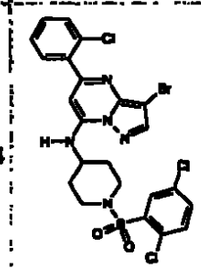
Producto	1. Ej. 2. m/z
	1. 6261 2. 500.27
	1. 6262 2. 562.31
	1. 6263 2. 604.33

TABLA 63

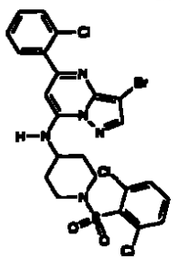
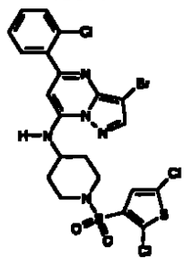
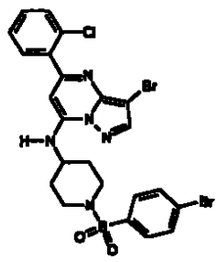
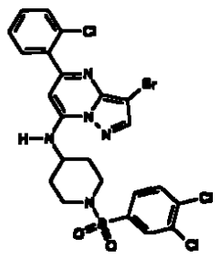
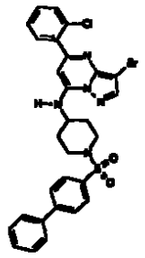
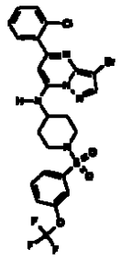
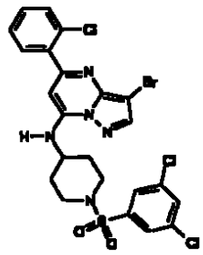
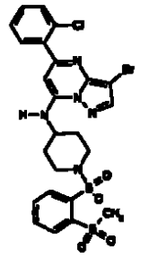
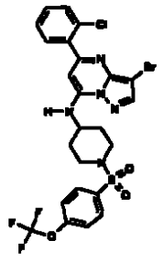
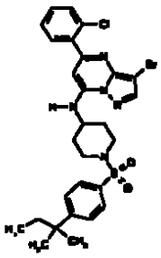
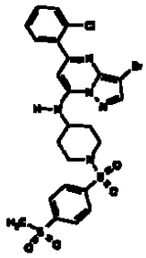
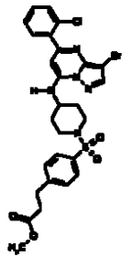
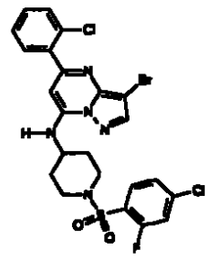
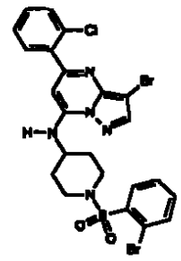
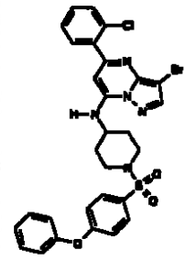
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2.m/z
	1. 6301 2. 500.27		1. 6306 2. 562.31		1. 6311 2. 567.31
	1. 6302 2. 514.28		1. 6307 2. 562.31		1. 6312 2. 573.32
	1. 6303 2. 554.3		1. 6308 2. 566.31		1. 6313 2. 573.32
	1. 6304 2. 562.31		1. 6309 2. 566.31		1. 6314 2. 573.32
	1. 6305 2. 562.31		1. 6310 2. 566.31		1. 6315 2. 574.32

606 809

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6316 2. 576.32		1. 6321 2. 582.32		1. 6326 2. 584.32
	1. 6317 2. 578.32		1. 6322 2. 582.32		1. 6327 2. 584.32
	1. 6318 2. 578.32		1. 6323 2. 584.32		1. 6328 2. 588.32
	1. 6319 2. 580.32		1. 6324 2. 582.32		1. 6329 2. 590.32
	1. 6320 2. 582.32		1. 6325 2. 584.32		1. 6330 2. 596.33

Producto	1. Ej. 2.m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6331 2. 598.33		1. 6336 2. 606.33		1. 6341 2. 616.34
	1. 6332 2. 598.33		1. 6337 2. 608.33		1. 6342 2. 616.34
	1. 6333 2. 600.33		1. 6338 2. 608.33		1. 6343 2. 616.34
	1. 6334 2. 600.33		1. 6339 2. 612.34		1.6344 2. 616.34
	1. 6335 2. 604.33		1. 6340 2. 616.34		1. 6345 2. 616.34

811

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6346 2. 616.34		1. 6351 2. 622.34		1. 6356 2. 626.34
	1. 6347 2. 616.34		1. 6352 2. 624.34		1. 6357 2. 632.35
	1. 6348 2. 616.34		1. 6353 2. 626.34		1. 6358 2. 632.35
	1. 6349 2. 618.34		1. 6354 2. 626.34		1. 6359 2. 634.35
	1. 6350 2. 600.33		1. 6355 2. 626.34		1. 6360 2. 640.35

812

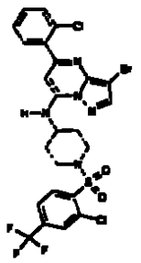
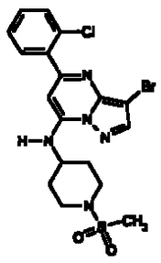
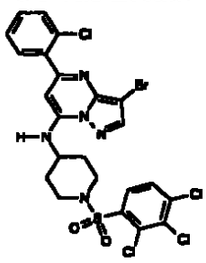
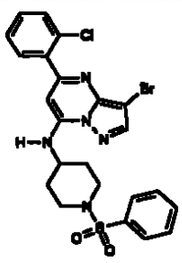
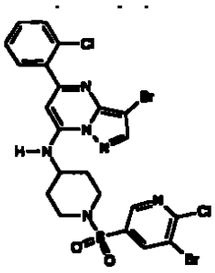
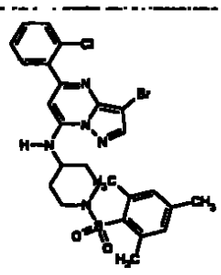
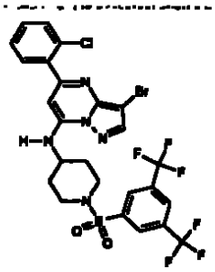
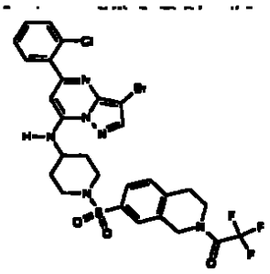
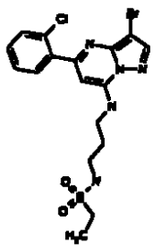
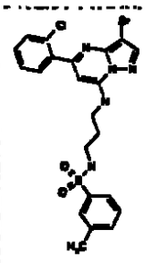
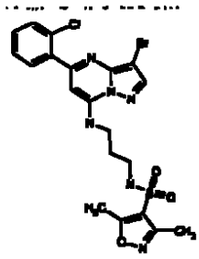
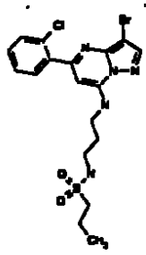
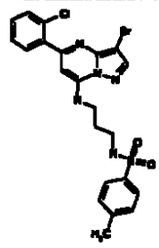
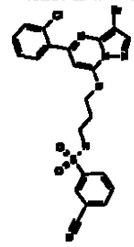
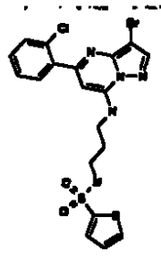
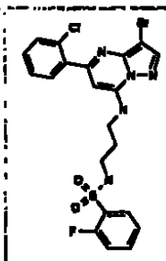
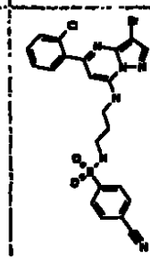
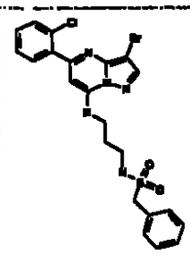
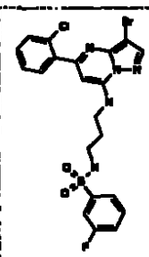
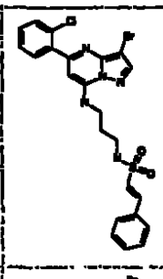
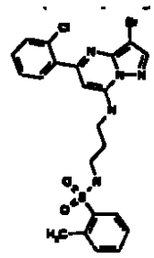
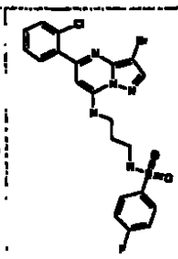
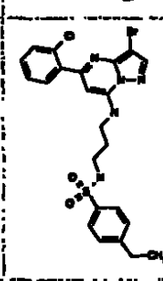
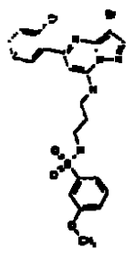
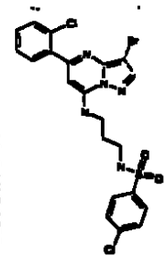
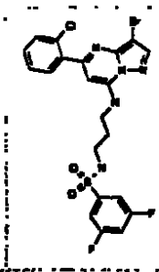
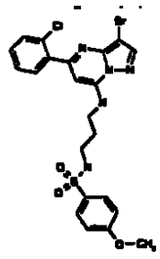
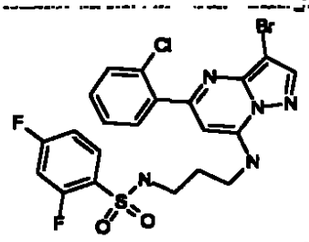
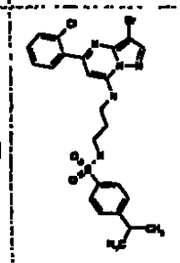
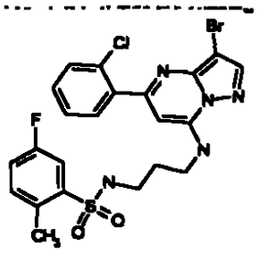
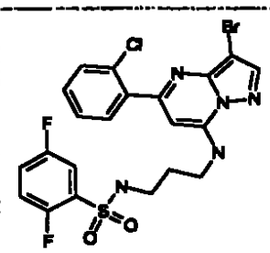
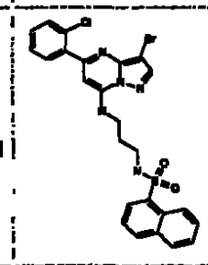
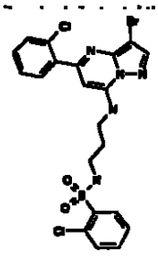
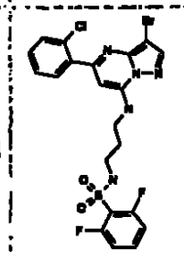
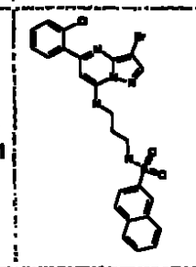
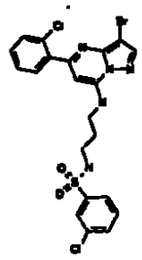
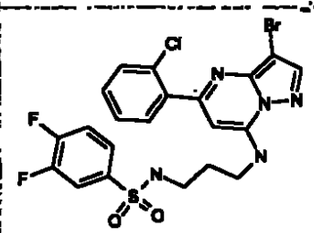
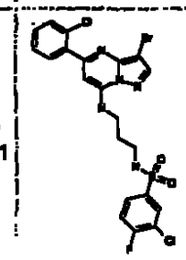
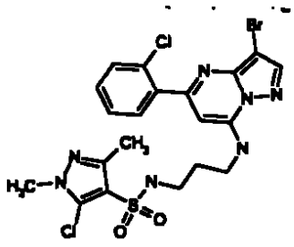
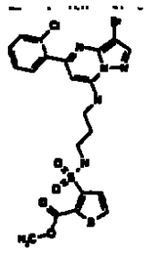
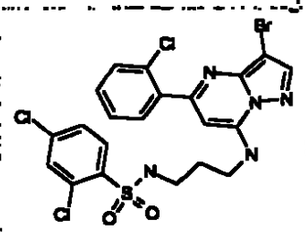
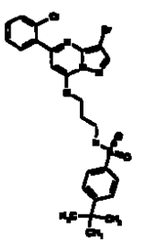
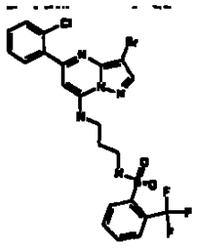
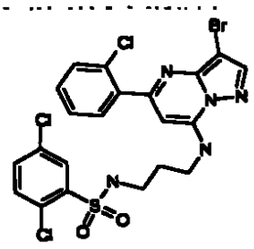
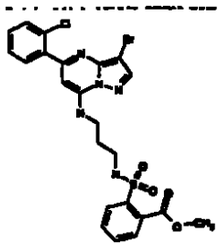
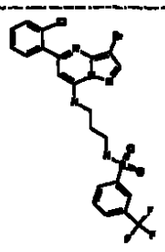
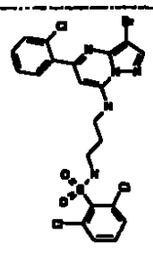
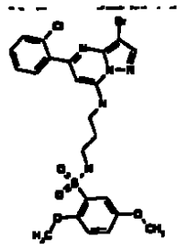
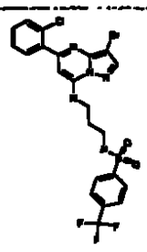
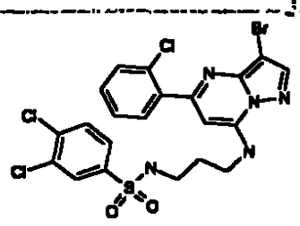
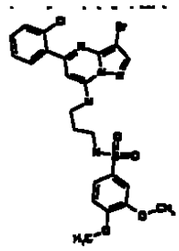
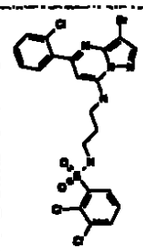
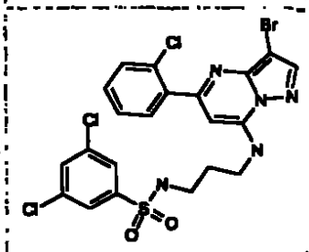
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6361 2. 650.36		1. 6366 2. 486.27
	1. 6362 2. 650.36		1. 6367 2. 548.3
	1. 6363 2. 661.36		1. 6368 2. 590.32
	1. 6364 2. 684.36		
	1. 6365 2. 699.36		

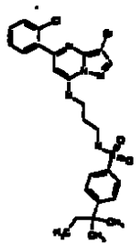
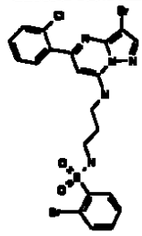
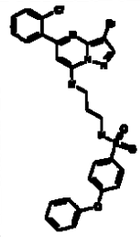
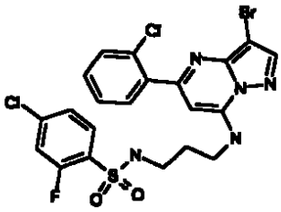
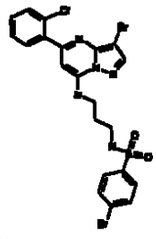
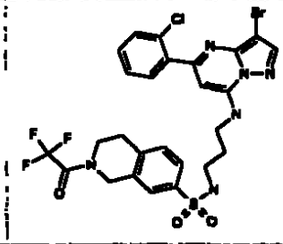
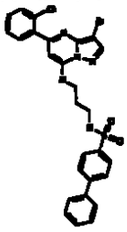
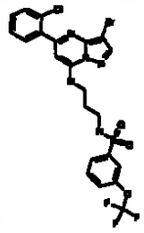
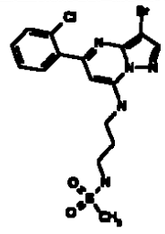
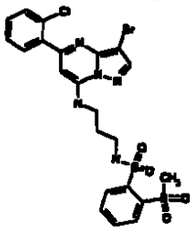
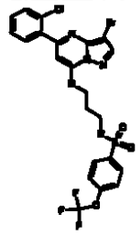
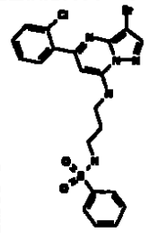
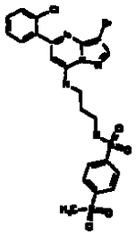
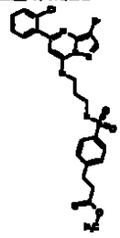
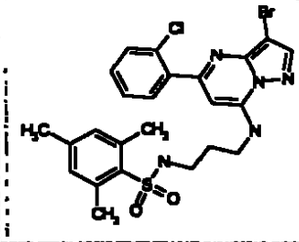
TABLA 64

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6401 2. 474.26		1. 6406 2. 536.29		1. 6411 2. 541.3
	1. 6402 2. 488.27		1. 6407 2. 536.29		1. 6412 2. 547.3
	1. 6403 2. 528.29		1. 6408 2. 540.3		1. 6413 2. 547.3
	1. 6404 2. 536.29		1. 6409 2. 540.3		1. 6414 2. 548.3
	1. 6405 2. 536.29		1. 6410 2. 540.3		1. 6415 2. 550.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6416 2. 552.3		1. 6421 2. 556.31		1. 6426 2. 558.31
	1. 6417 2. 552.3		1. 6122 2. 558.31		1. 6427 2. 564.31
	1. 6418 2. 554.3		1. 6423 2. 558.31		1. 6428 2. 572.31
	1. 6419 2. 556.31		1. 6424 2. 558.31		1. 6429 2. 572.31
	1. 6420 2. 556.31		1. 6425 2. 558.31		1. 6430 2. 574.32

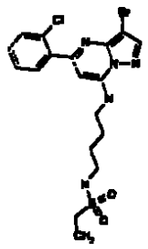
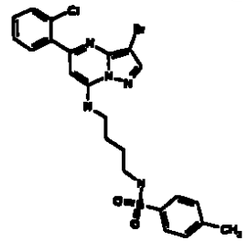
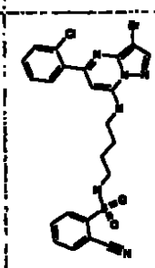
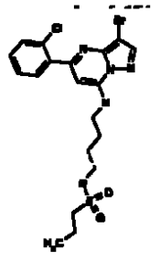
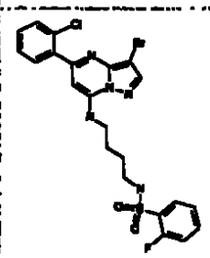
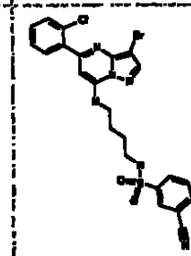
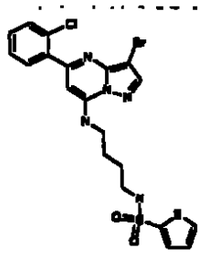
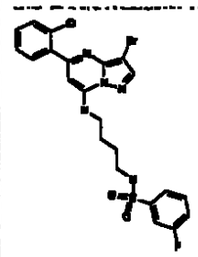
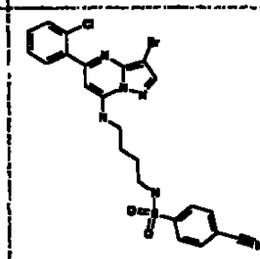
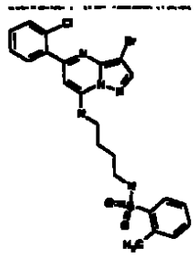
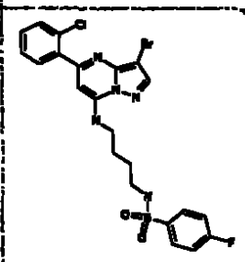
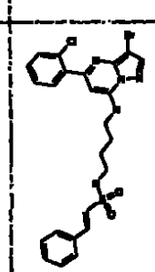
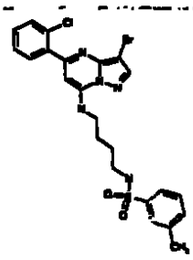
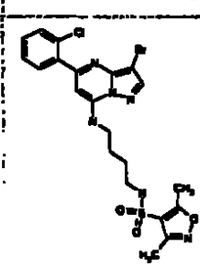
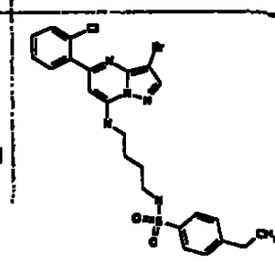
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6431 2. 574.32		1. 6436 2. 586.32		1. 6441 2. 590.32
	1. 6432 2. 578.32		1. 6437 2. 590.32		1. 6442 2. 590.32
	1. 6433 2. 580.32		1. 6438 2. 590.32		1. 6443 2. 590.32
	1. 6434 2. 582.32		1. 6439 2. 590.32		1. 6444 2. 590.32
	1. 6435 2. 582.32		1. 6440 2. 589.32		1. 6445 2. 590.32

816

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6446 2. 592.33		1. 6451 2. 600.33		1. 6456 2. 614.34
	1. 6447 2. 574.32		1. 6452 2. 600.33		1. 6447 2. 673.37
	1. 6448 2. 598.33		1. 6453 2. 606.33		1. 6458 2. 460.25
	1. 6449 2. 600.33		1. 6454 2. 606.33		6459 2.
	1. 6450 2. 600.33		1. 6455 2. 608.33		1. 6460 2. 564.31

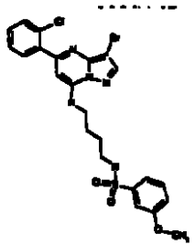
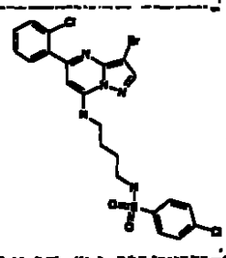
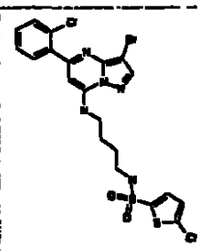
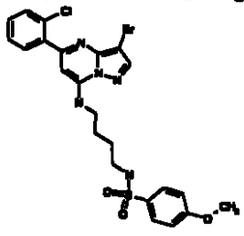
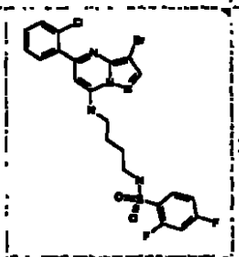
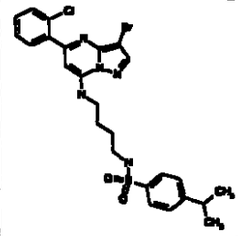
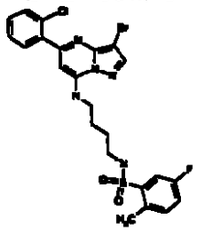
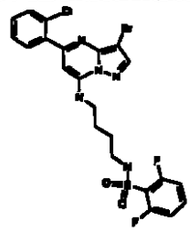
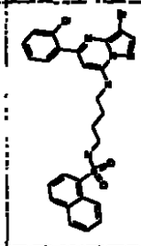
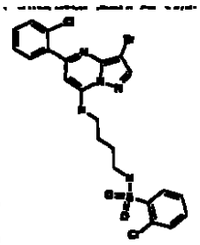
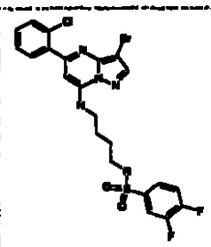
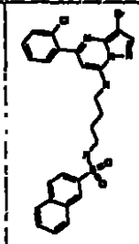
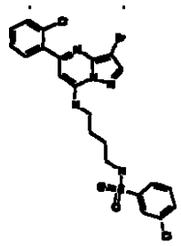
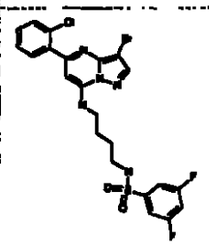
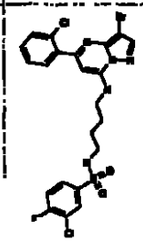
814 817

TABLA 65

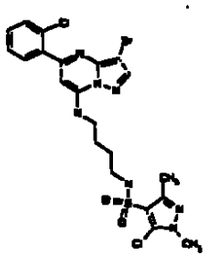
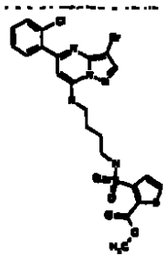
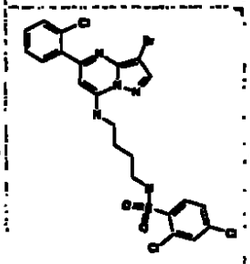
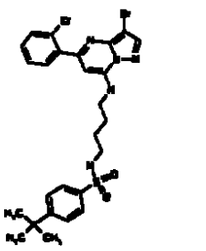
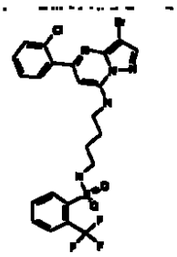
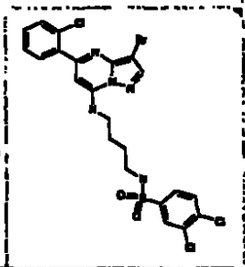
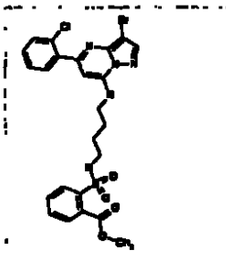
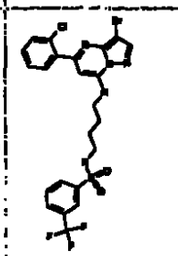
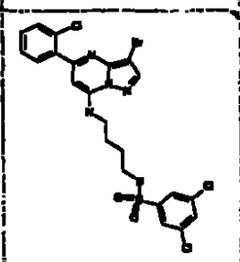
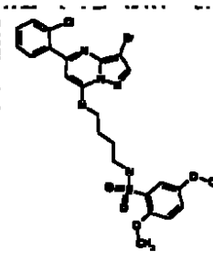
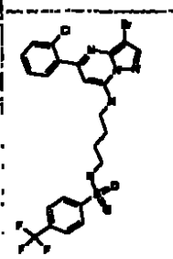
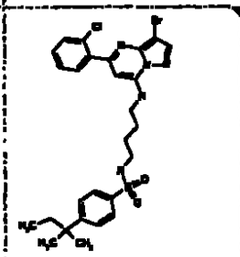
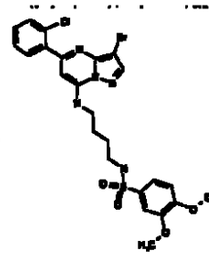
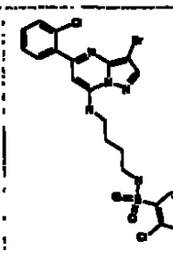
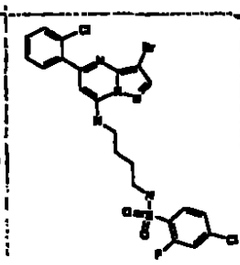
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6501 2. 488.27		1. 6506 2. 550.3		1. 6511 2. 561.31
	1. 6502 2. 502.28		1. 6507 2. 554.3		1. 6512 2. 561.31
	1. 6503 2. 542.3		1. 6508 2. 554.3		1. 6213 2. 561.31
	1. 6504 2. 550.3		1. 6509 2. 554.3		1. 6514 2. 562.31
	1. 6505 2. 550.3		1. 6510 2. 555.31		1. 6515 2. 564.31

5

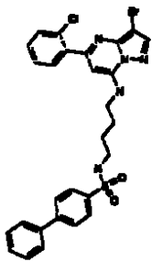
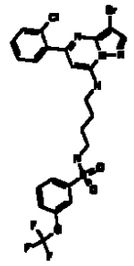
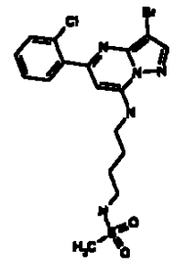
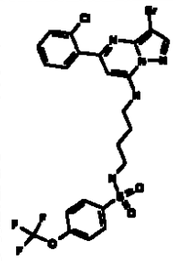
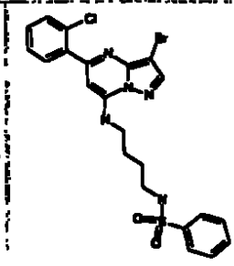
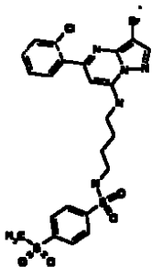
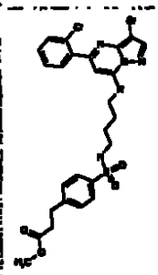
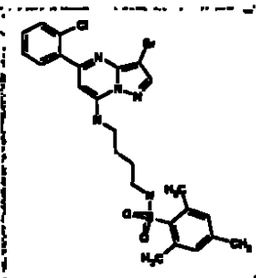
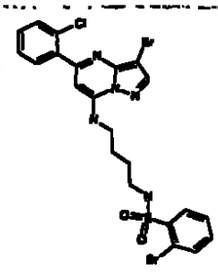
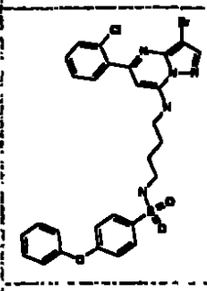
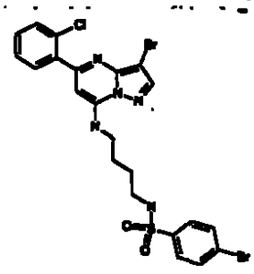
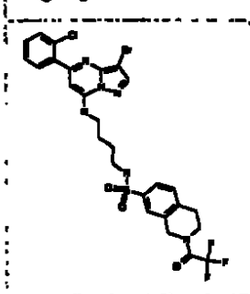
818

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6516 2. 566.31		1. 6521 2. 570.31		1. 6526 2. 576.32
	1. 6517 2. 566.31		1. 6522 2. 572.31		1. 6527 2. 578.32
	1. 6518 2. 568.31		1. 6523 2. 572.31		1. 6528 2. 586.32
	1. 6519 2. 570.31		1. 6524 2. 572.31		1. 6529 2. 586.32
	1. 6520 2. 570.31		1. 6525 2. 572.31		1. 6530 2. 586.32

819

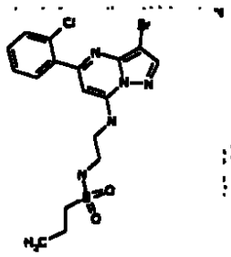
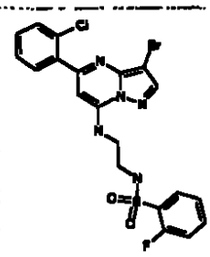
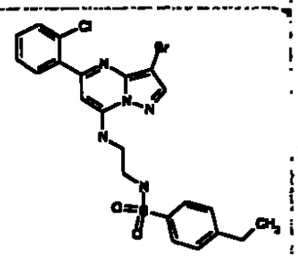
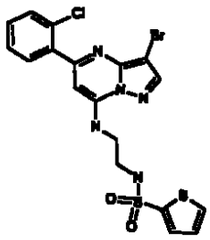
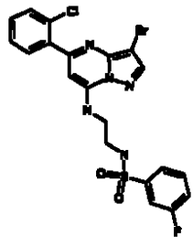
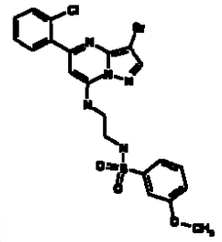
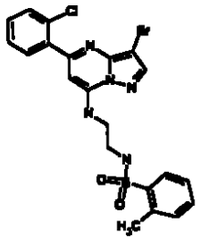
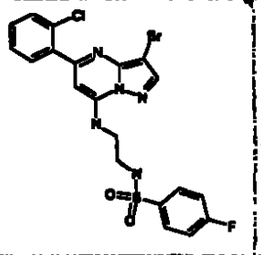
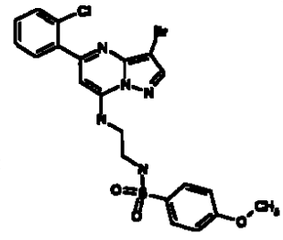
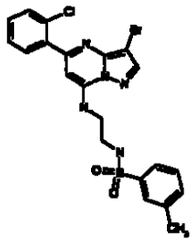
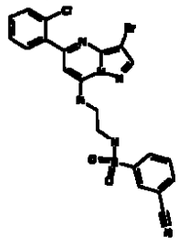
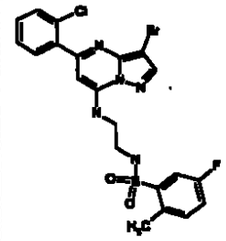
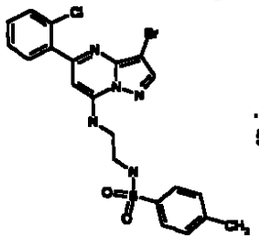
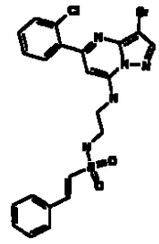
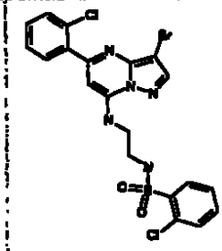
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6531 2. 588.32		1. 6536 2. 600.33		1. 6541 2. 604.33
	1. 6532 2. 592.33		1. 6537 2. 604.33		1. 6542 2. 604.33
	1. 6533 2. 594.33		1. 6538 2. 604.33		1. 6543 2. 604.33
	1. 6534 2. 596.33		1. 6539 2. 604.33		1. 6544 2. 606.33
	1. 6535 2. 596.33		1. 6540 2. 604.33		1. 6545 2. 588.32

879 820

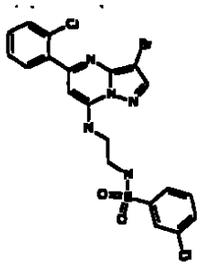
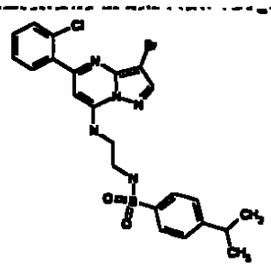
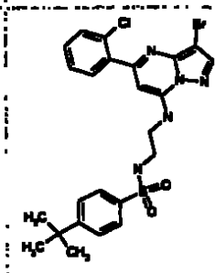
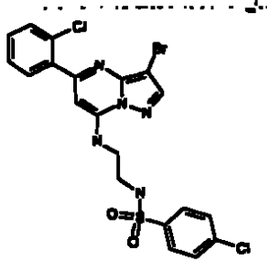
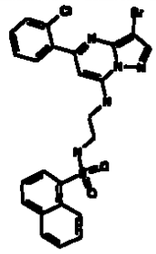
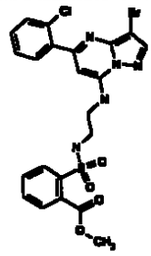
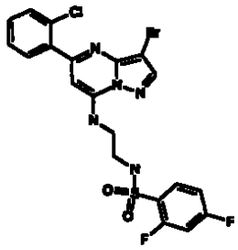
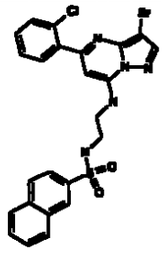
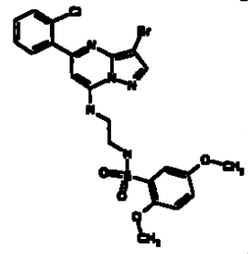
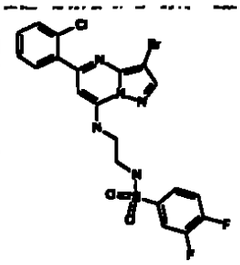
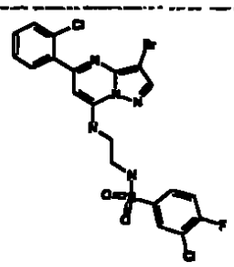
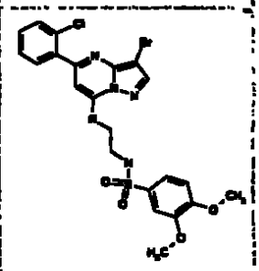
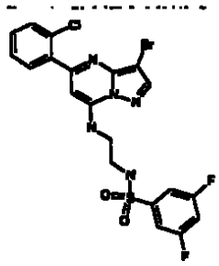
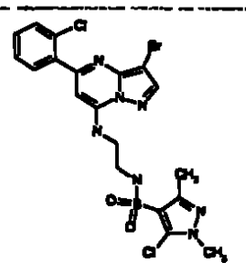
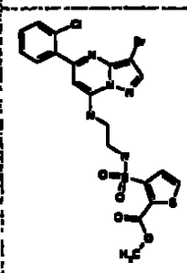
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2.m/z
	1. 6546 2. 612.34		1. 6551 2. 620.34		1. 6556 2. 474.26
	1. 6547 2. 614.34		1. 6552 2. 620.34		1. 6557 2. 536.29
	1. 6548 2. 614.34		1. 6553 2. 622.34		1. 6558 2. 578.32
	1. 6549 2. 614.34		1. 6554 2. 628.35		
	1. 6550 2. 614.34		1. 6555 2. 687.38		

821

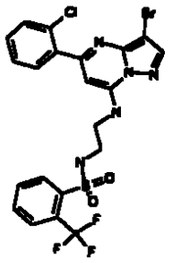
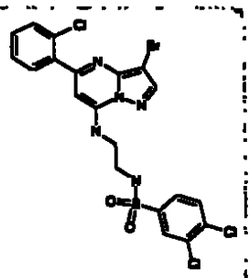
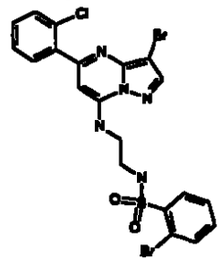
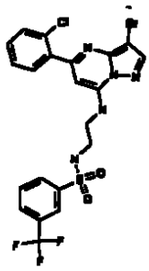
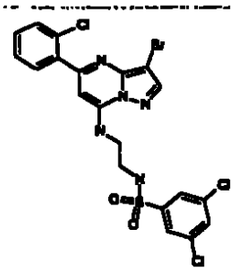
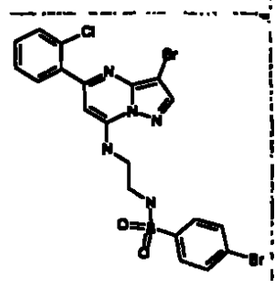
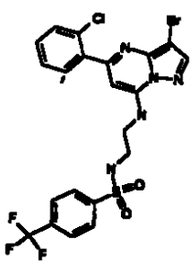
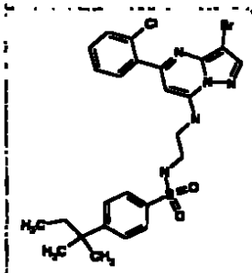
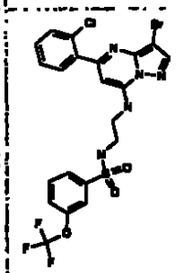
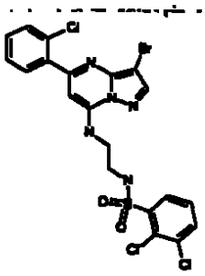
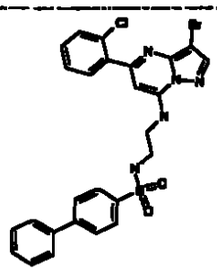
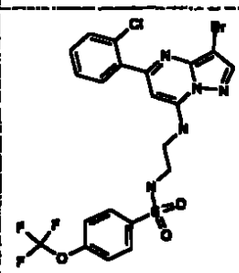
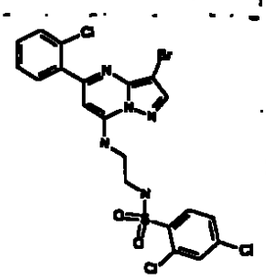
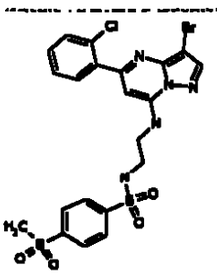
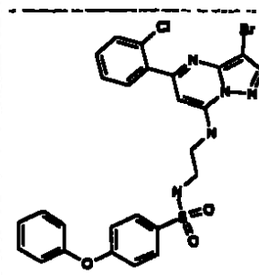
TABLA 67

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6701 2. 474.26		1. 6706 2. 526.29		1. 6711 2. 536.29
	1. 6702 2. 514.28		1. 6707 2. 526.29		1. 6712 2. 538.3
	1. 6703 2. 522.29		1. 6708 2. 526.29		1. 6713 2. 538.3
	1. 6704 2. 522.29		1. 6709 2. 533.29		1. 6714 2.
	.6705 522.29		1. 6710 2. 534.29		1. 6715 2. 542.3

822

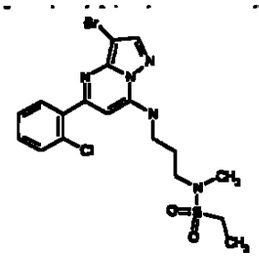
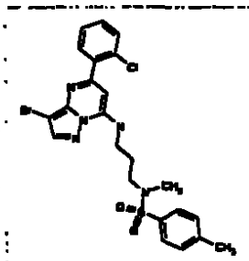
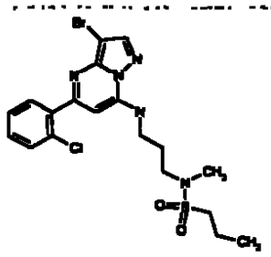
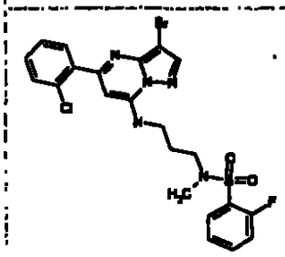
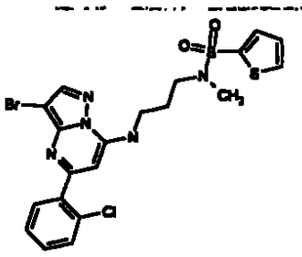
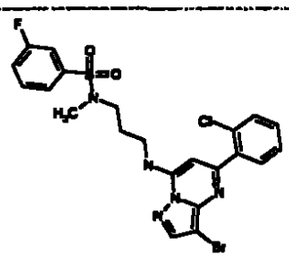
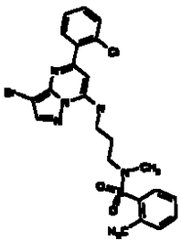
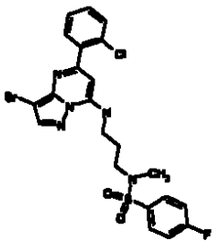
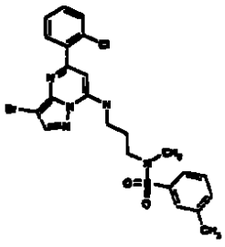
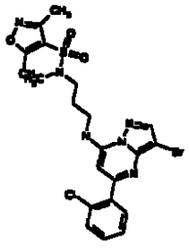
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6716 2. 542.3		1. 6721 2. 550.3		1. 6726 2. 564.31
	1. 6717 2. 542.3		1. 6722 2. 558.31		1. 6727 2. 566.31
	1. 6718 2. 544.3		1. 6723 2. 558.31		1. 6728 2. 568.31
	1. 6719 2. 544.3		1. 6724 2. 560.31		1. 6729 2. 568.31
	1. 6720 2. 544.3		1. 6725 2. 560.31		1. 6730 2. 572.31

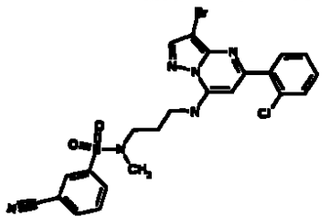
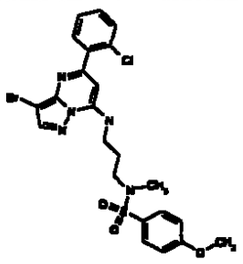
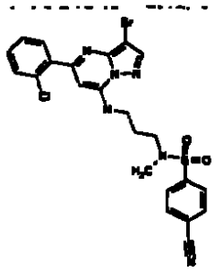
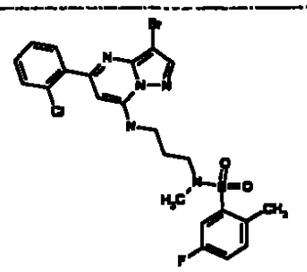
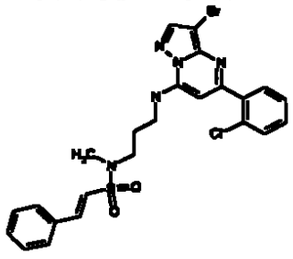
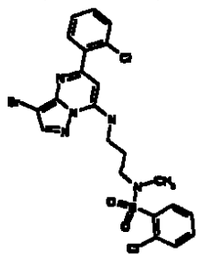
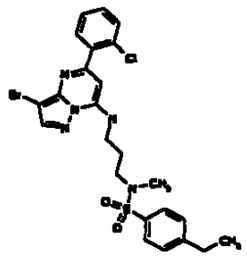
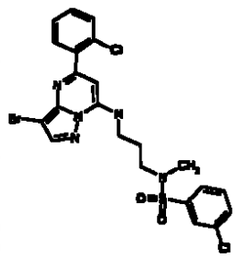
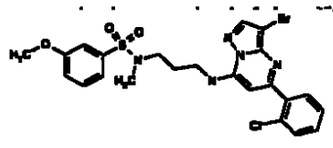
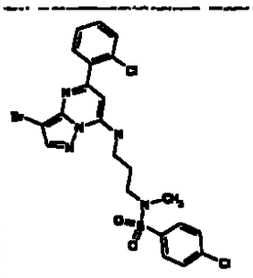
823

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

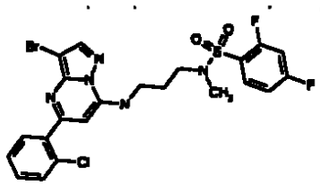
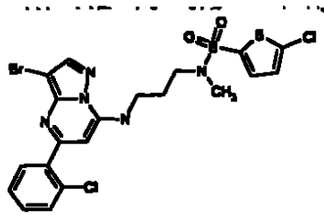
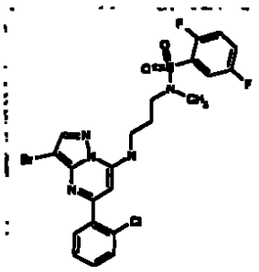
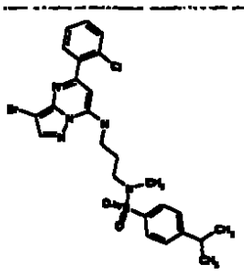
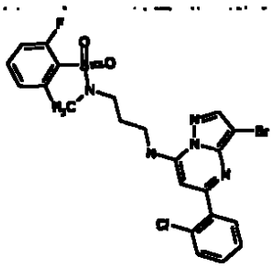
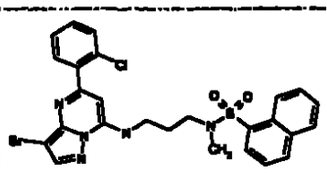
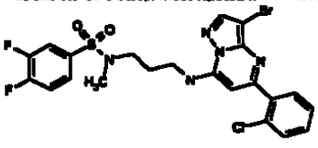
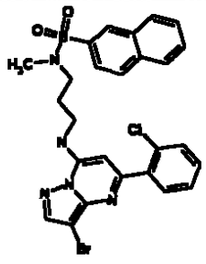
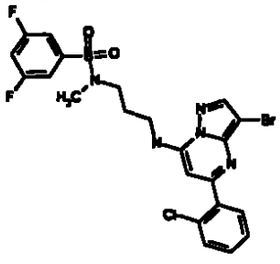
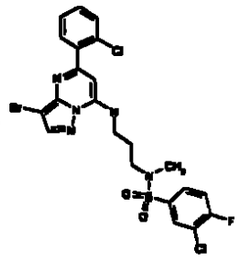
824

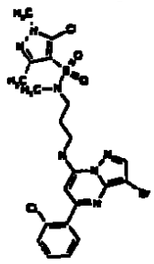
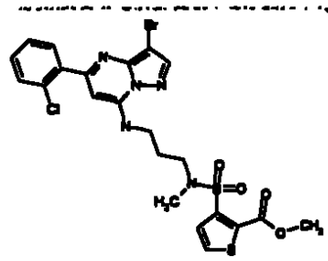
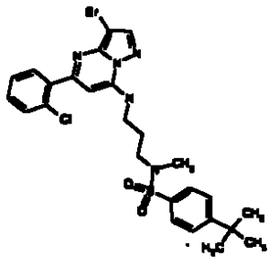
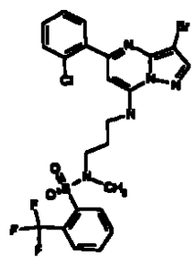
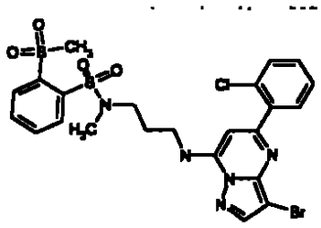
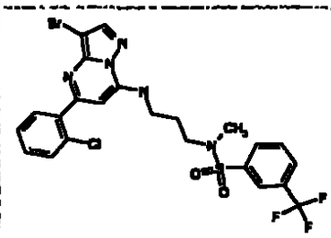
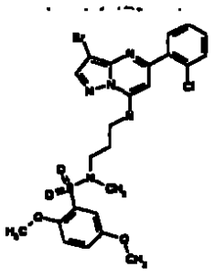
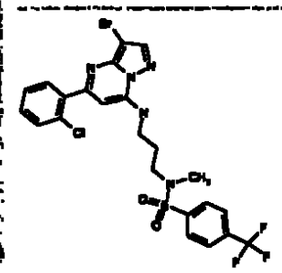
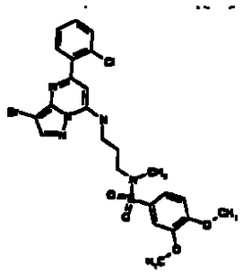
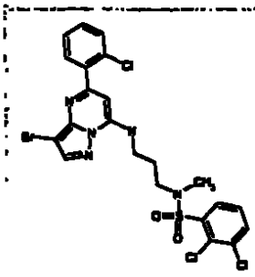
TABLA 68

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2 .m/z
	1. 6801 2. 488.27		1. 6806 2. 550.3
	1. 6802 2. 502.28		1. 6807 2. 554.3
	1. 6803 2. 542.3		1. 6808 2. 554.3
	1. 6804 2. 550.3		1. 6809 2. 554.3
	1. 68058 2. 550.3		1. 6810 2. 555.31

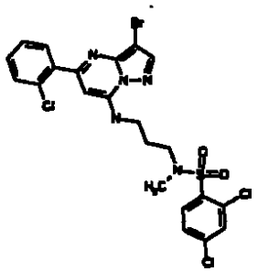
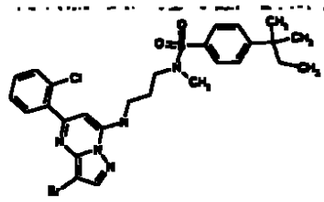
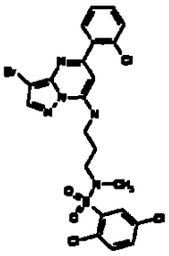
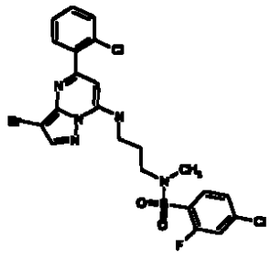
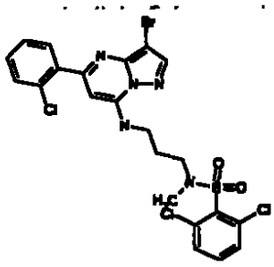
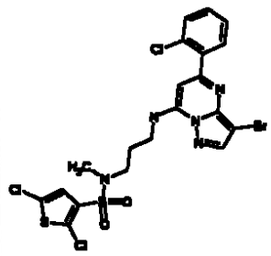
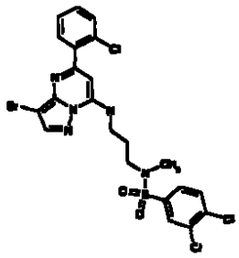
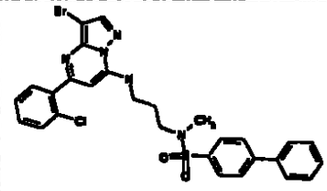
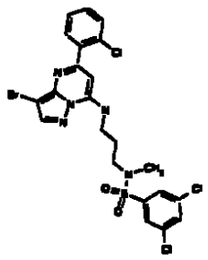
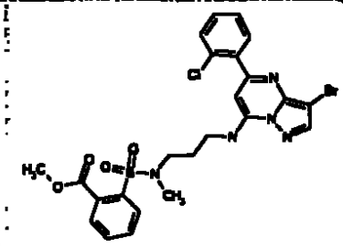
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6811 2. 561.31		1. 6816 2. 568.31
	1. 6812 2. 561.31		1. 6817 2. 568.31
	1. 6813 2. 562.31		1. 6818 2. 570.31
	1. 6814 2. 564.31		1. 6819 2. 570.31
	1. 6815 2. 566.31		1. 6820 2. 570.31

826

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6821 2. 571.31		1. 6826 2. 576.32
	1. 6822 2. 572.31		1. 6827 2. 578.32
	1. 6823 2. 572.31		1. 6828 2. 586.32
	1. 6824 2. 572.31		1. 6829 2. 586.32
	1. 6825 2. 572.31		1. 6830 2. 588.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6831 2. 588.32		1. 6836 2. 600.33
	1. 6832 2. 592.33		1. 6837 2. 602.33
	1. 6833 2. 614.34		1. 6838 2. 604.33
	1. 6834 2. 596.33		1. 6839 2. 604.33
	1. 6835 2. 596.33		1. 6840 2. 604.33

828

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6841 2. 604.33		1. 6846 2. 606.33
	1. 6842 2. 604.33		1. 6847 2. 588.32
	1. 6843 2. 605.33		1. 6848 2. 610.34
	1. 6844 2. 604.33		1. 6849 2. 612.34
	1. 6845 2. 604.33		1. 6850 2. 594.33

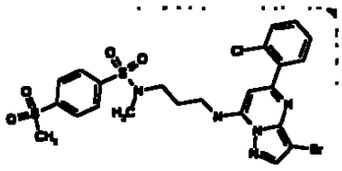
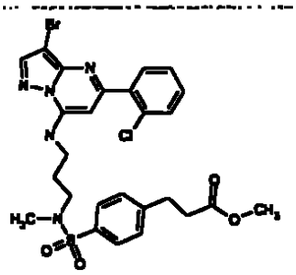
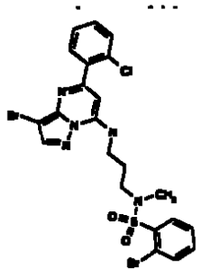
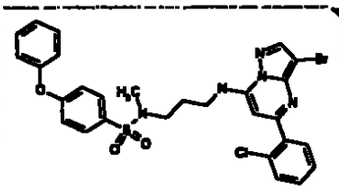
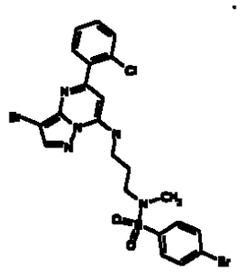
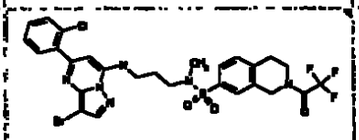
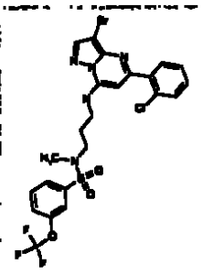
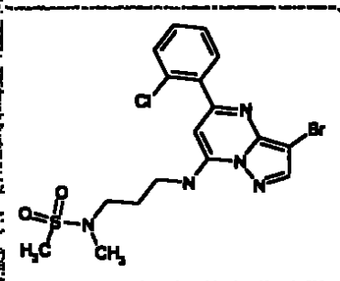
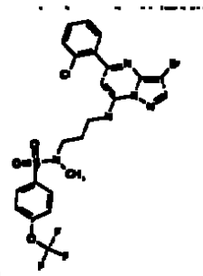
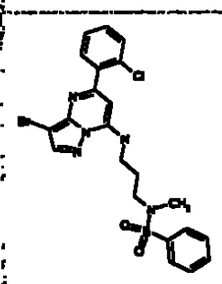
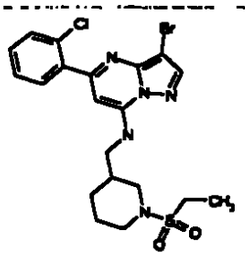
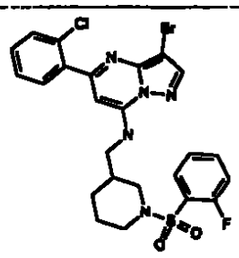
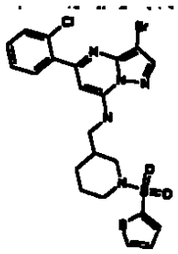
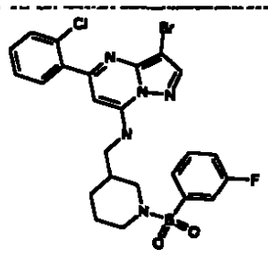
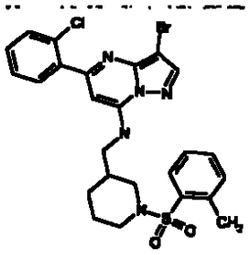
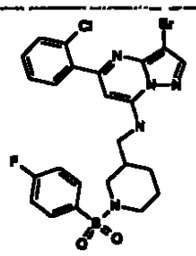
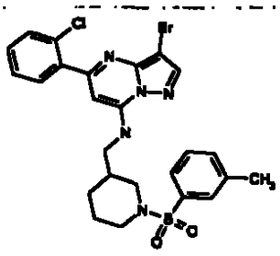
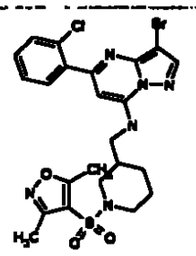
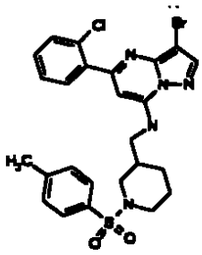
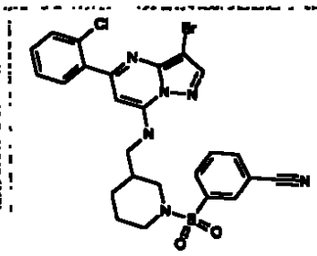
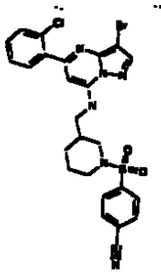
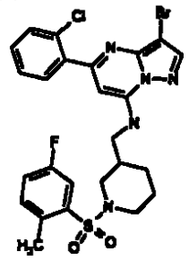
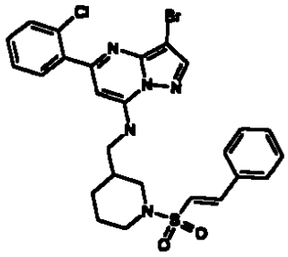
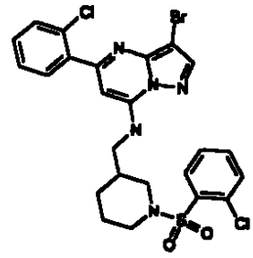
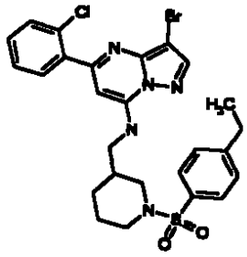
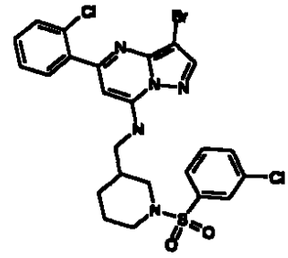
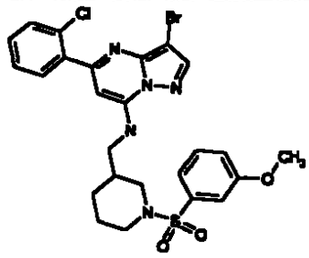
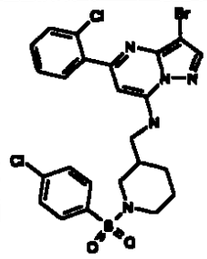
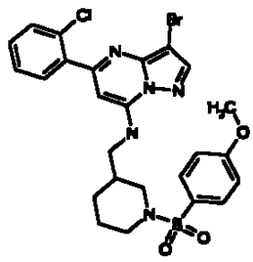
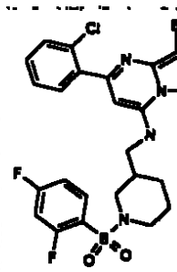
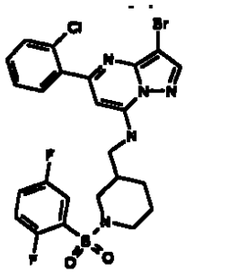
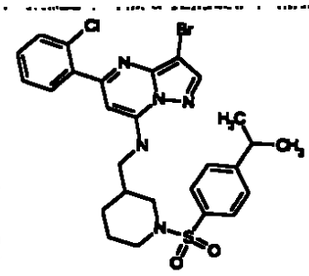
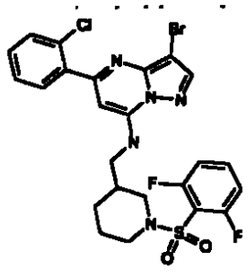
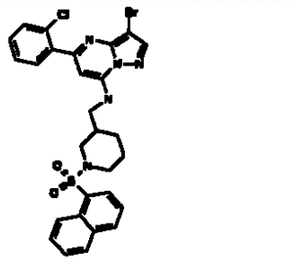
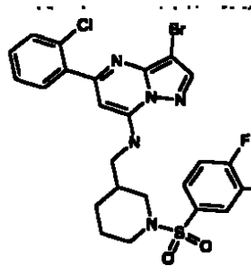
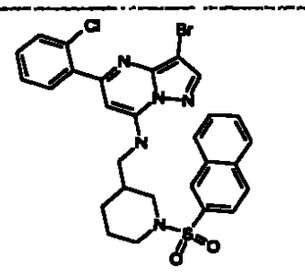
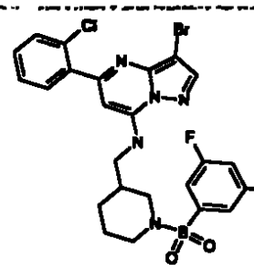
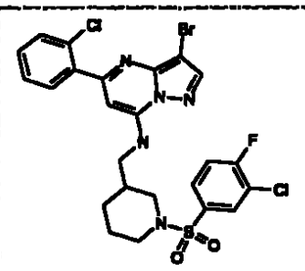
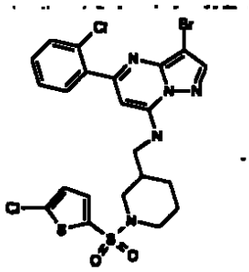
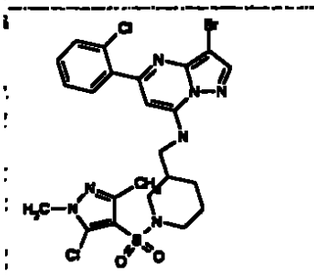
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6851 2. 614.34		1. 6856 2. 620.34
	1. 6852 2. 614.34		1. 6858 2. 628.35
	1. 6853 2. 614.34		1. 6857 2. 687.38
	1. 6854 2. 620.34		1. 6859 2. 474.26
	1. 6855 2. 620.34		1. 6860 2. 536.29

TABLA 69

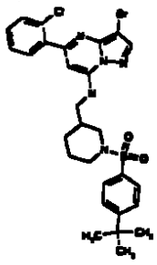
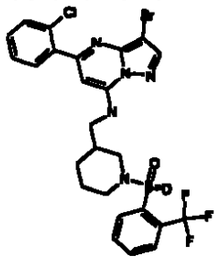
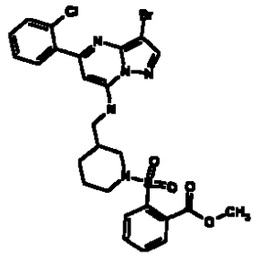
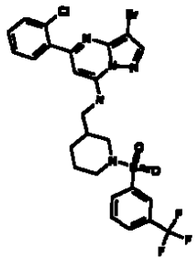
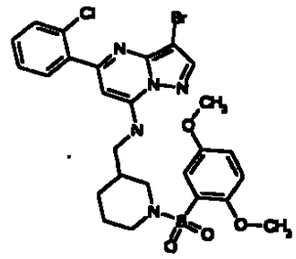
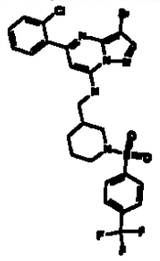
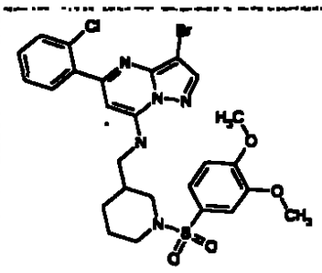
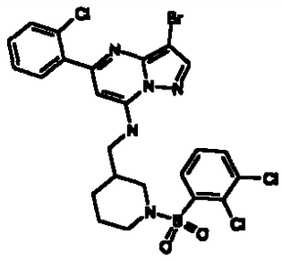
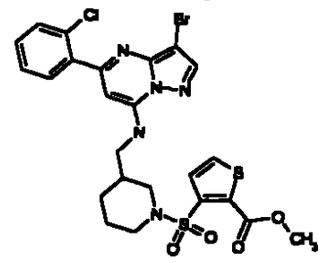
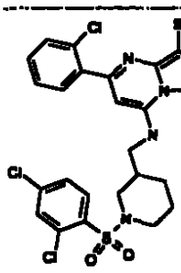
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1 .6901 2. 514.28		1. 6906 2. 580.32
	1. 6902 2. 568.31		1. 6907 2. 580.32
	1. 6903 2. 576.32		1. 6908 2. 580.32
	1. 6904 2. 576.32		1. 6909 2. 581.32
	1. 6905 2. 576.32		1. 6910 2. 587.32

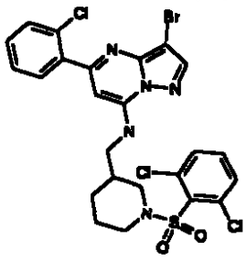
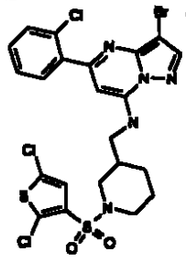
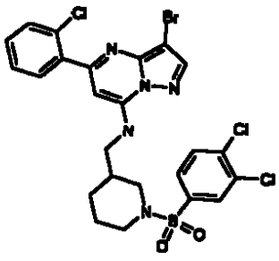
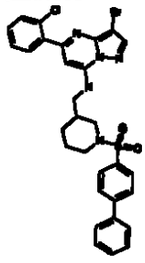
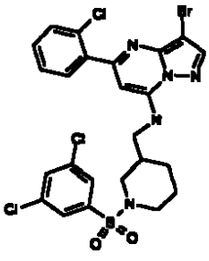
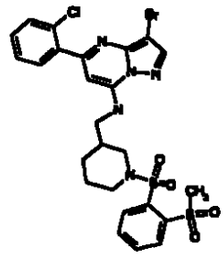
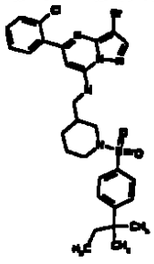
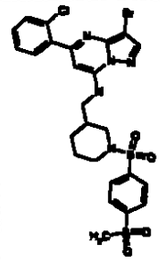
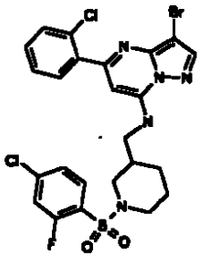
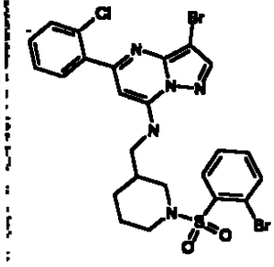
831

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6911 2. 587.32		1. 6916 2. 594.33
	1. 6912 2. 588.32		1. 6917 2. 596.33
	1. 6913 2. 590.32		1. 6918 2. 596.33
	1. 6914 2. 592.33		1. 6919 2. 596.33
	1. 6915 2. 592.33		1. 6920 2. 598.33

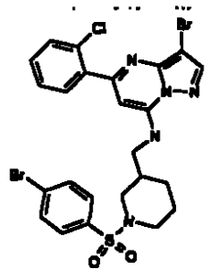
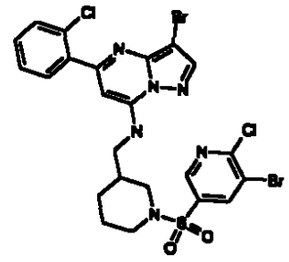
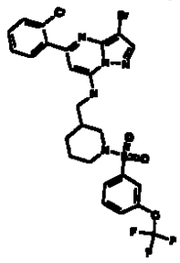
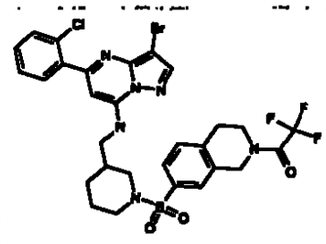
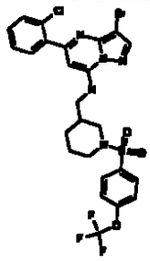
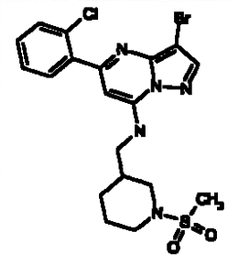
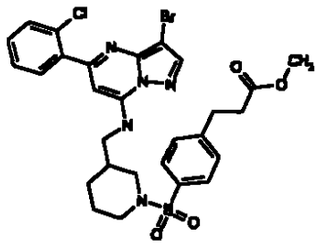
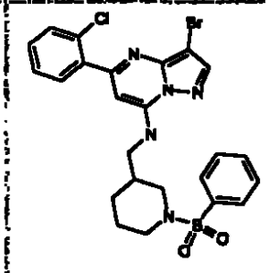
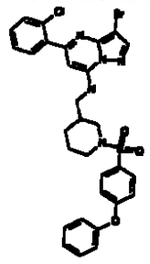
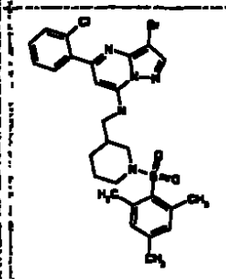
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6921 2. 598.33		1. 6926 2. 604.33
	1. 6922 2. 598.33		1. 6927 2. 612.34
	1. 6923 2. 598.33		1. 6928 2. 612.34
	1. 6924 2. 598.33		1. 6929 2. 614.34
	1. 6925 2. 602.33		1. 6930 2. 614.34

833

Producto	1. Ej. 2 .m/z	Producto	1. Ej. 2. m/z
	1. 6931 2. 618.34		1. 6936 2. 630.35
	1. 6932 2. 620.34		1. 6937 2. 630.35
	1. 6933 2. 622.34		1. 6938 2. 630.35
	1. 6934 2. 622.34		1. 6939 2. 630.35
	1. 6935 2. 626.34		1. 6940 2. 630.35

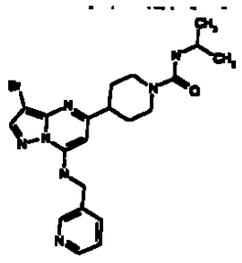
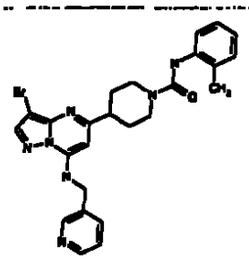
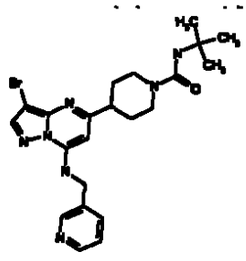
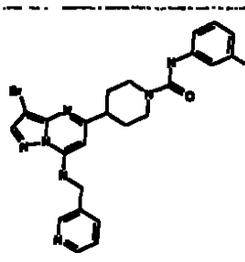
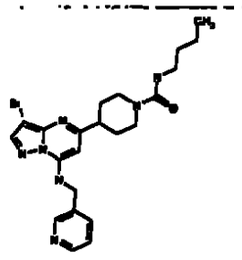
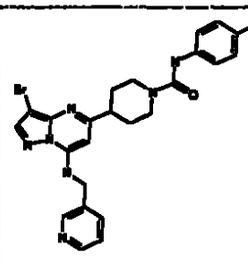
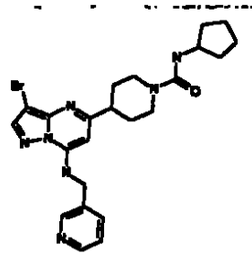
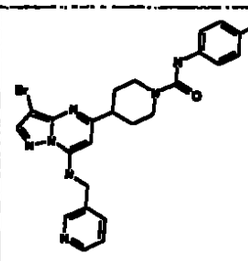
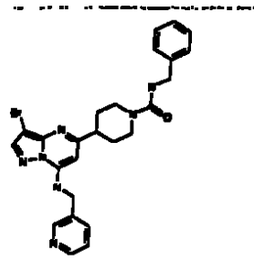
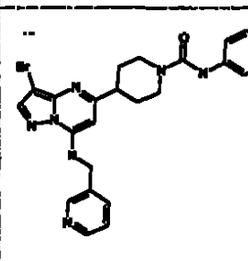
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6941 2. 630.35		1. 6946 2. 636.35
	1. 6942 2. 630.35		1. 6947 2. 638.35
	1. 6943 2. 630.35		1. 6948 2. 640.35
	1. 6944 2. 632.35		1. 6949 2. 640.35
	1. 6945 2. 614.34		1. 6950 2. 640.35

835

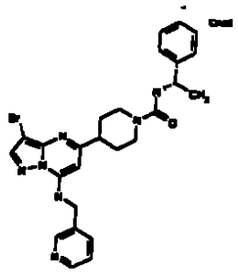
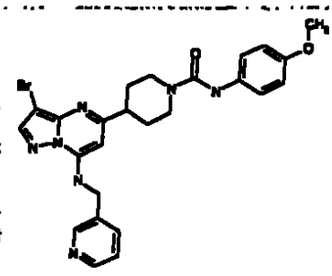
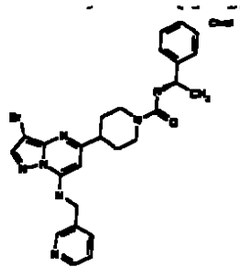
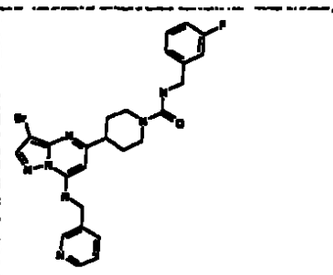
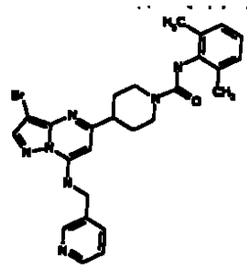
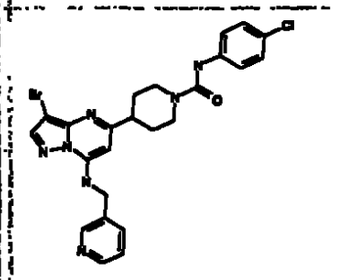
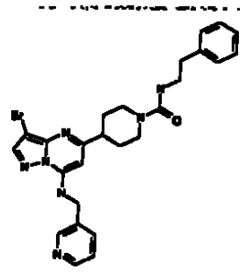
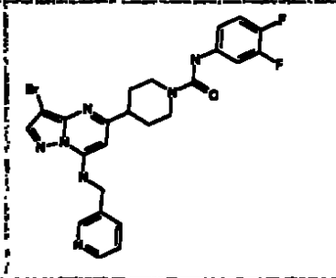
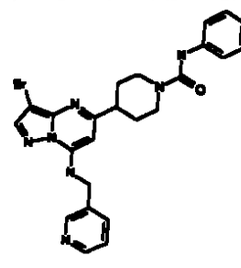
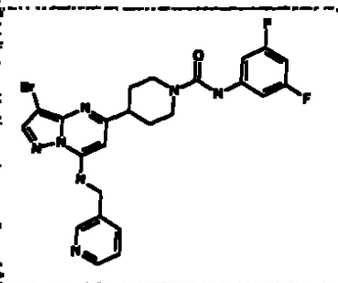
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 6951 2. 640.35		1. 6956 2. 675.23
	1. 6952 2. 646.36		1. 6957 2. 713.39
	1. 6953 2. 646.36		1. 6958 2. 500.27
	1. 6954 2. 646.36		1. 6959 2. 562.31
	1. 6955 2. 654.36		1. 6960 2. 604.33

836

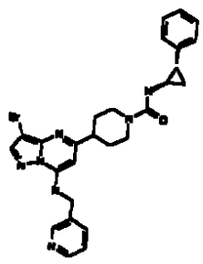
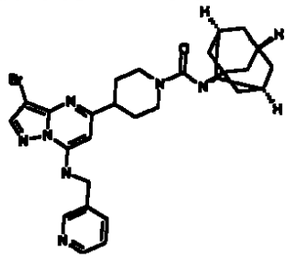
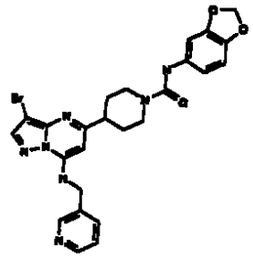
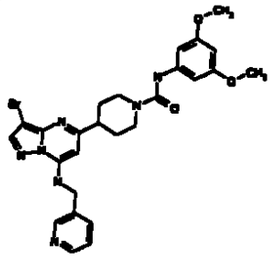
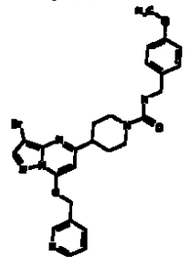
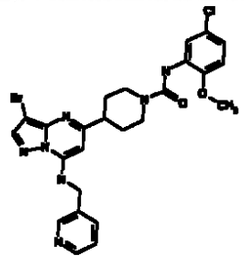
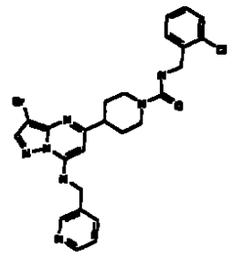
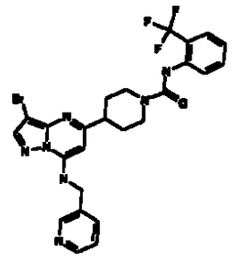
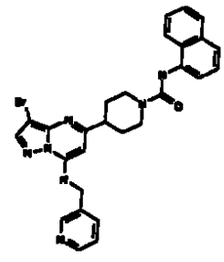
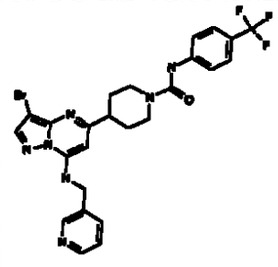
TABLA 70

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7001 2. 472.26		1. 7006 2. 522.29
	1. 7002 2. 488.27		1. 7007 2. 520.29
	1. 7003 2. 488.27		1. 7008 2. 520.29
	1. 7004 2. 500.27		1. 7009 2. 526.29
	1. 7005 2. 520.29		1. 7010 2. 533.29

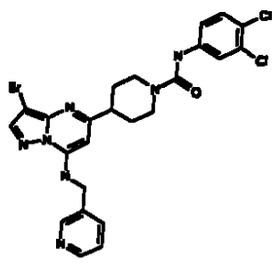
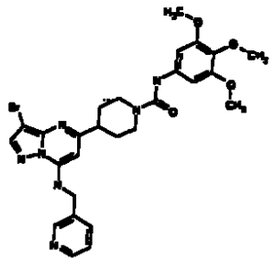
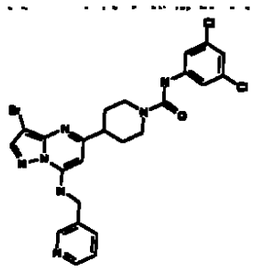
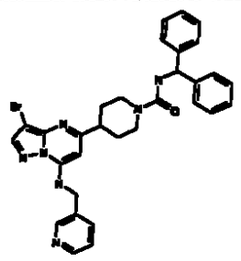
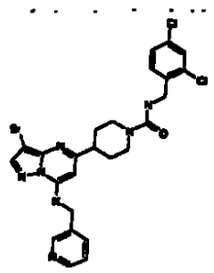
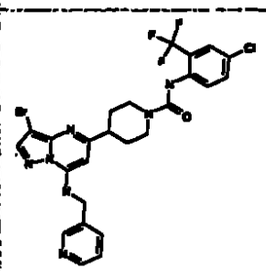
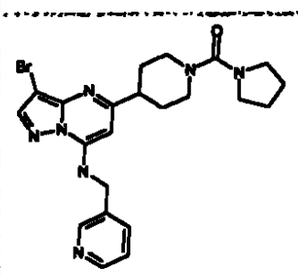
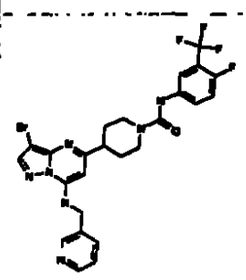
837

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

838

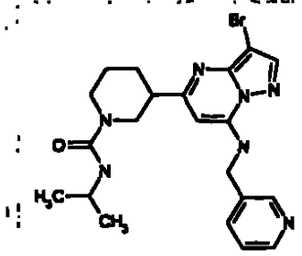
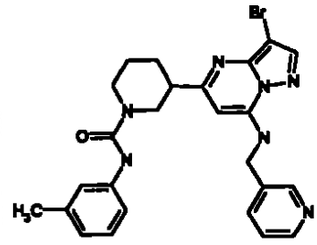
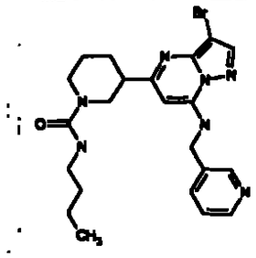
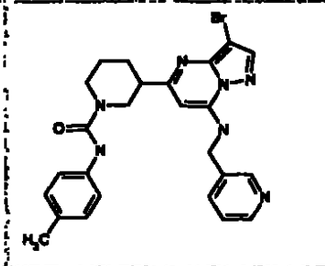
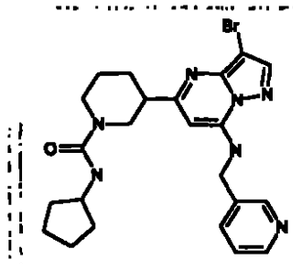
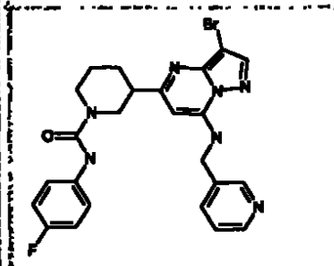
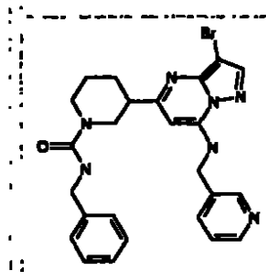
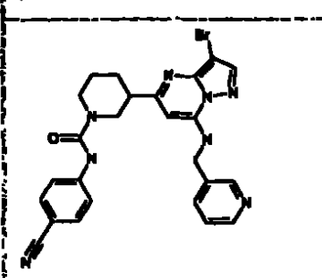
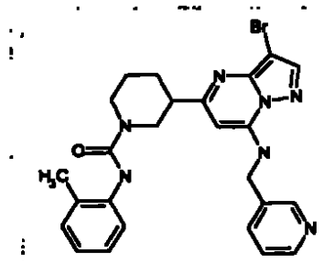
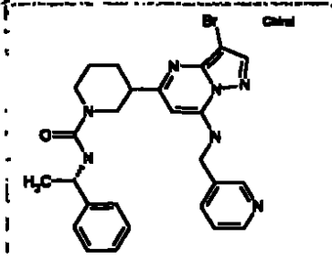
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7021 2. 548.3		1. 7026 2. 566.31
	1. 7022 2. 552.3		1. 7027 2. 568.31
	1. 7023 2. 552.3		1. 7028 2. 572.31
	1. 7024 2. 556.31		1. 7029 2. 576.32
	1. 7025 2. 556.31		1. 7030 2. 576.32

839

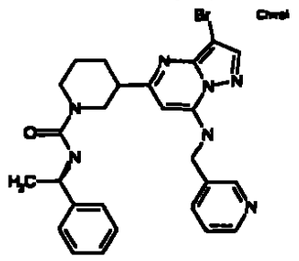
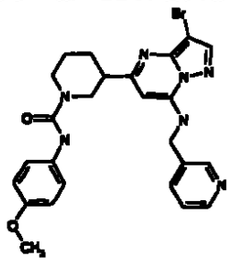
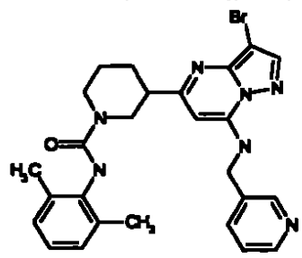
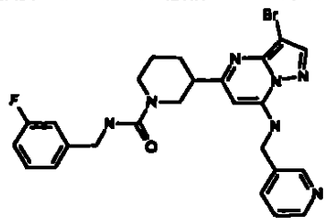
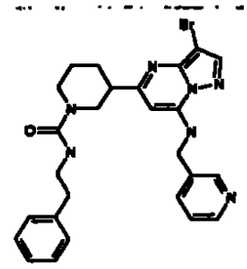
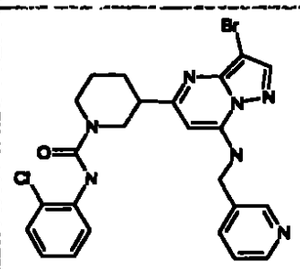
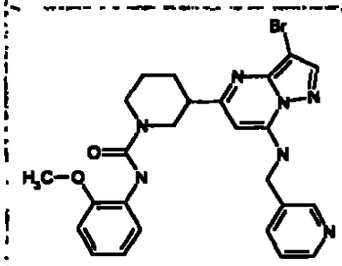
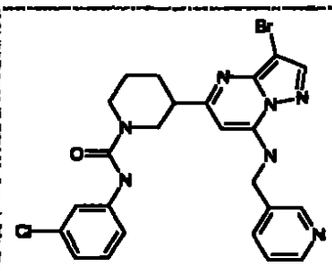
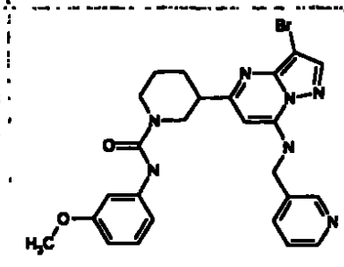
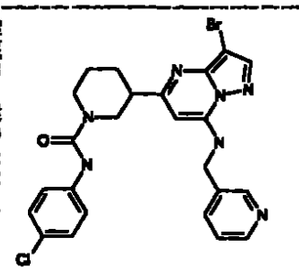
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7031 2. 576.32		1. 7036 2. 598.33
	1. 7032 2. 576.32		1. 7037 2. 598.33
	1. 7033 2. 590.32		1. 7038 2. 610.34
	1. 7034 2. 486.27		
	1. 7035 2. 594.33		

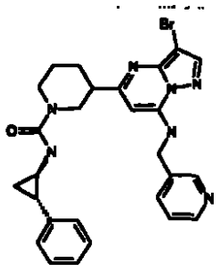
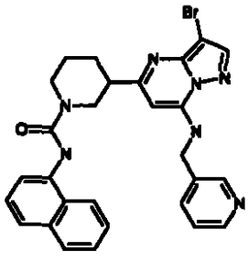
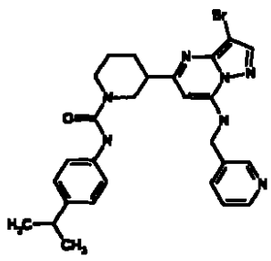
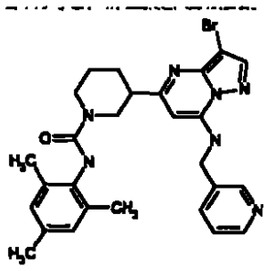
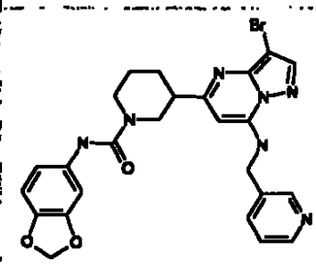
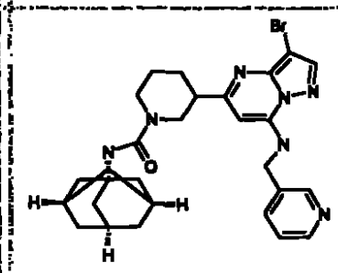
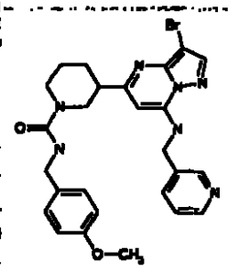
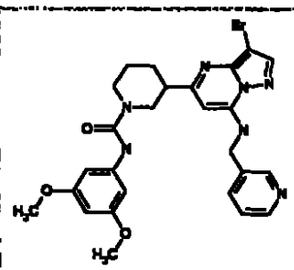
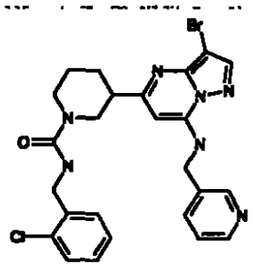
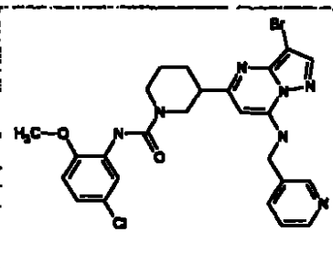
840

TABLA 71

Producto	1. EJ. 2. m/z	Producto	1. EJ. 2. m/z
	1 . 7101 2. 474.26		1. 7106 2. 522.29
	1. 7102 2. 488.27		1. 7107 2. 522.29
	1. 7103 2. 500.27		1. 7108 2. 526.3
	1. 7104 2. 522.29		1. 7109 2. 533.29
	1. 7105 2. 522.29		1. 7110 2. 536.29

841

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7111 2. 536.29		1. 7116 2. 538.3
	1. 7112 2. 536.29		1. 7117 2. 540.3
	1. 7113 2. 536.29		1. 7118 2. 542.3
	1. 7114 2. 536.29		1. 7119 2. 542.3
	1. 7115 2. 536.3		1. 7120 2. 542.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7121 2. 546.3		1. 7126 2. 558.31
	1. 7122 2. 550.3		1. 7127 2. 550.3
	1. 7123 2. 552.3		1. 7128 2. 566.31
	1. 7124 2. 552.3		1. 7129 2. 565.31
	1. 7125 2. 556.31		1. 7130 2. 572.31

843

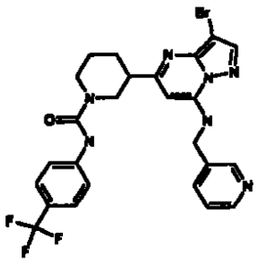
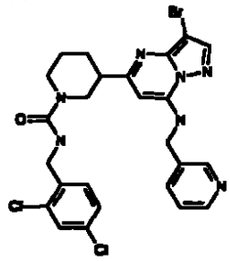
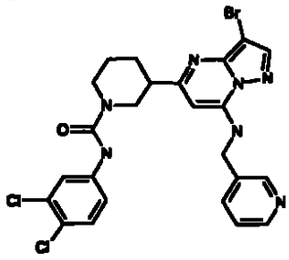
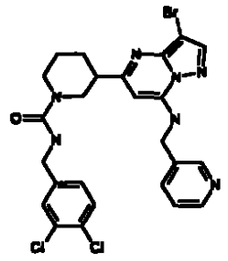
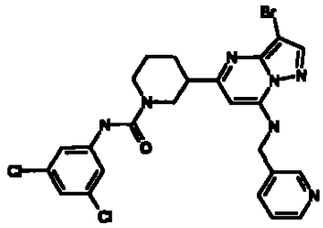
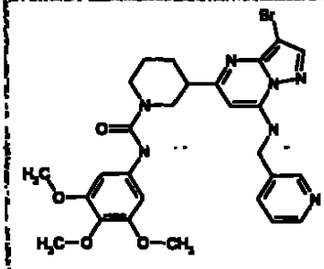
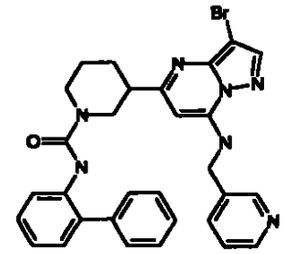
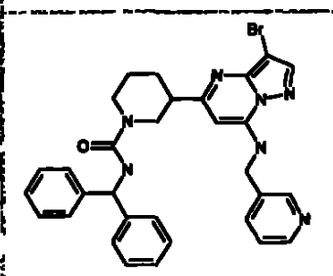
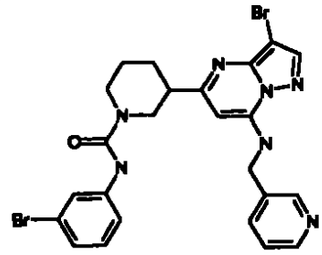
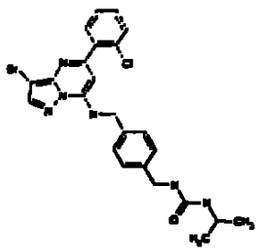
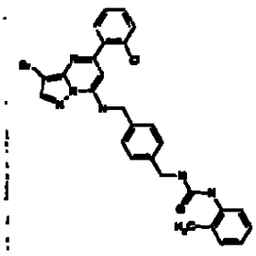
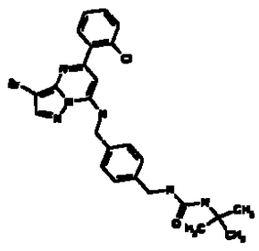
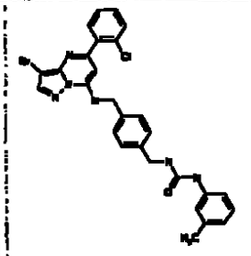
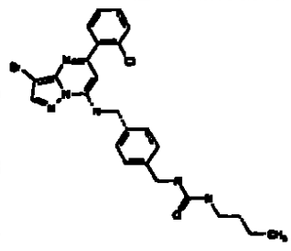
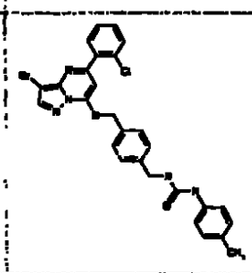
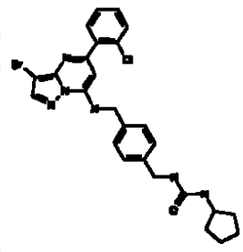
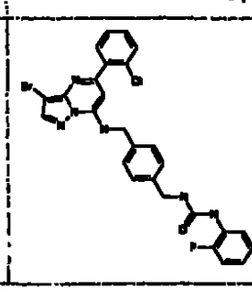
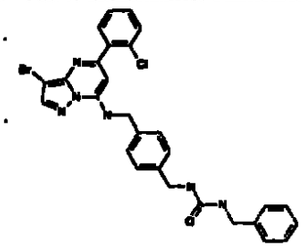
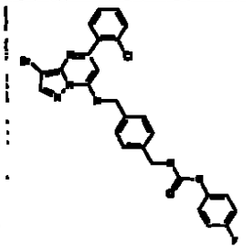
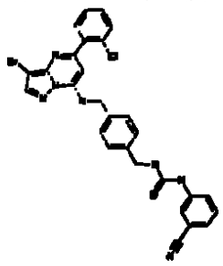
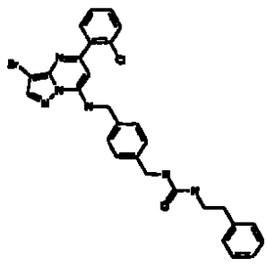
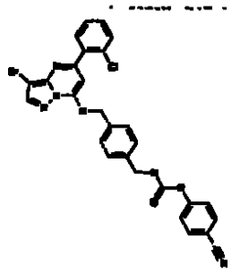
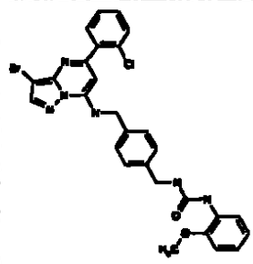
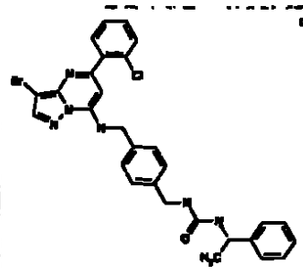
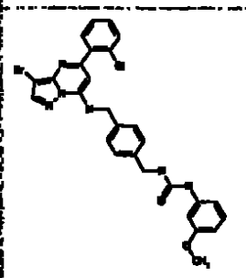
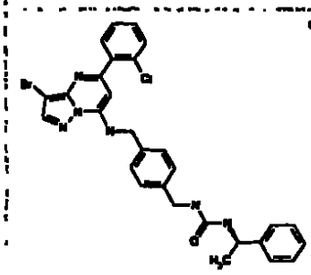
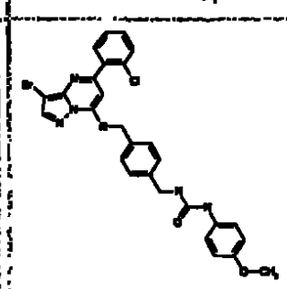
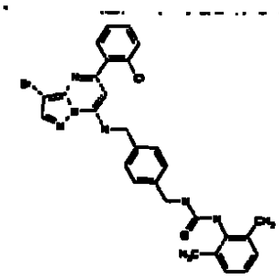
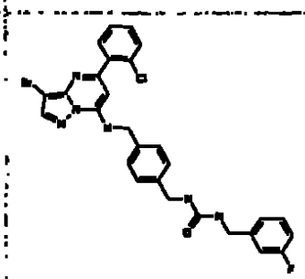
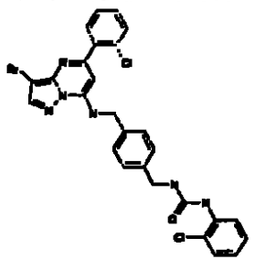
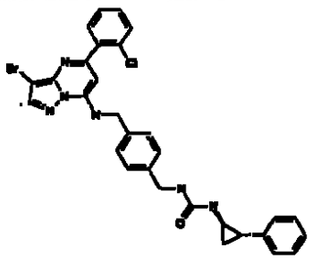
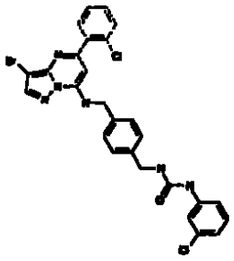
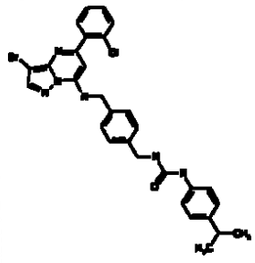
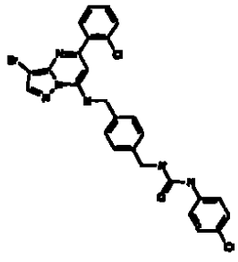
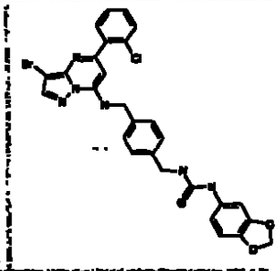
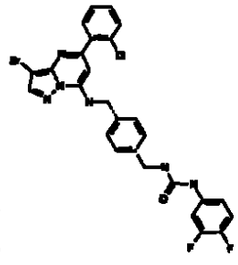
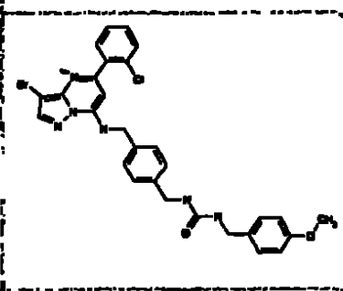
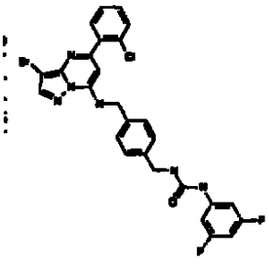
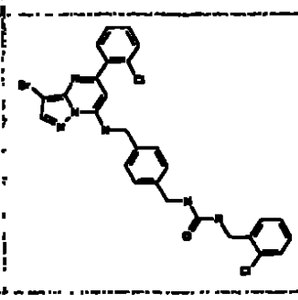
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7131 2. 576.32		1. 7136 2. 590.32
	1. 7132 2. 576.32		1. 7137 2. 590.32
	1. 7133 2. 576.32		1. 7138 2. 598.33
	1. 7134 2. 584.32		1. 7139 2. 598.33
	1. 7135 2. 585.3		

TABLA 72

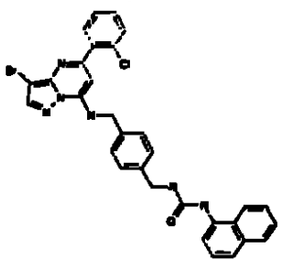
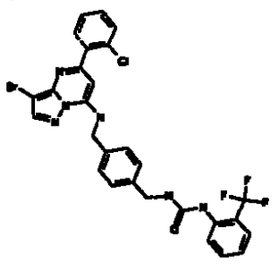
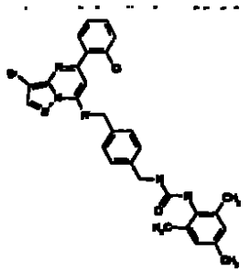
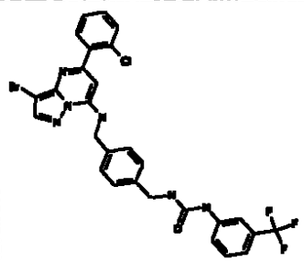
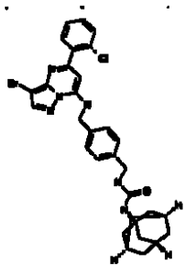
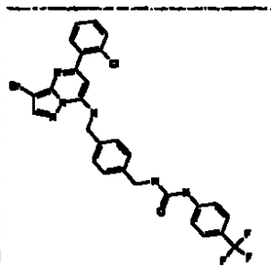
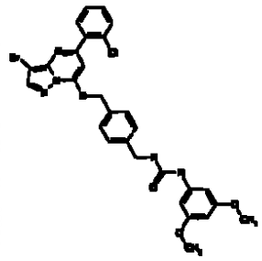
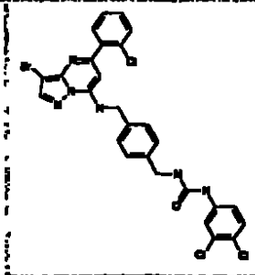
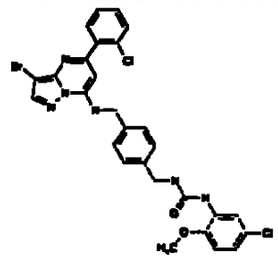
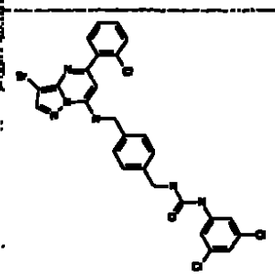
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7201 2. 529.29		1. 7206 2. 577.32
	1. 7202 2. 543.3		1. 7207 2. 577.32
	1. 7203 2. 543.3		1. 7208 2. 577.32
	1. 7204 2. 555.31		1. 7209 2. 581.32
	1. 7205 2. 577.32		1. 7210 2. 581.32

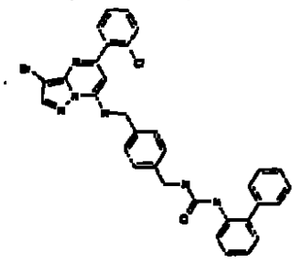
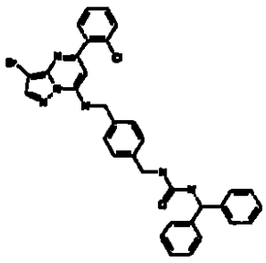
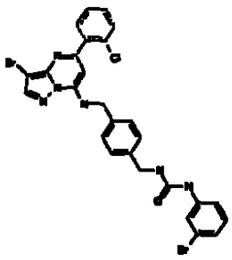
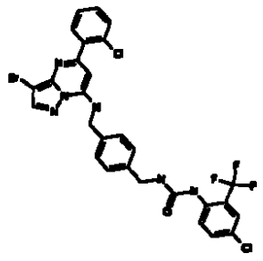
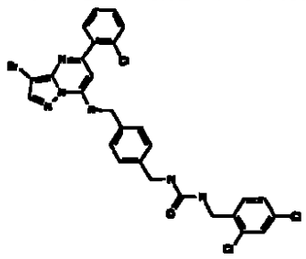
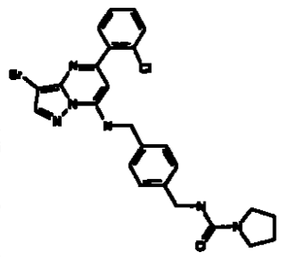
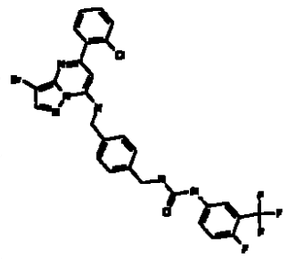
845

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7211 2. 588.32		1. 7216 2. 591.33
	1. 7212 2. 588.32		1. 7217 2. 593.33
	1. 7213 2. 591.33		1. 7218 2. 593.33
	1. 7214 2. 591.33		1. 7219 2. 593.33
	1. 7215 2. 591.33		1. 7220 2. 595.33

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7221 2. 597.33		1. 7226 2. 603.33
	1. 7222 2. 597.33		1. 7227 2. 603.33
	1. 7223 2. 597.33		1. 7228 2. 607.33
	1. 7224 2. 599.33		1. 7229 2. 607.14
	1. 7225 2. 599.33		1. 7230 2. 611.34

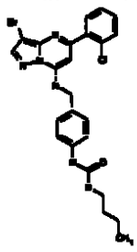
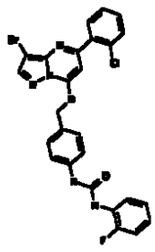
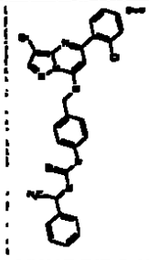
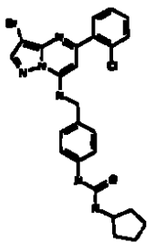
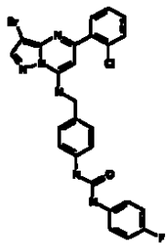
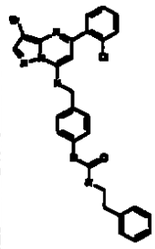
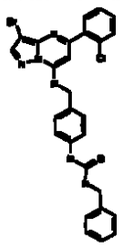
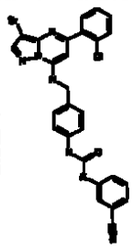
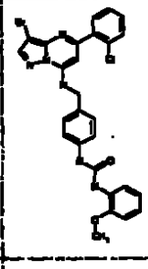
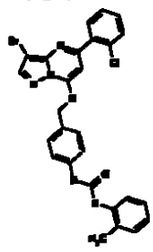
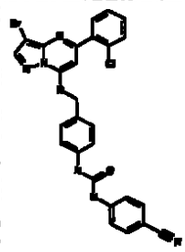
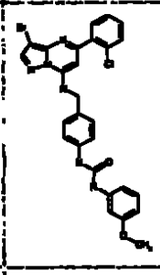
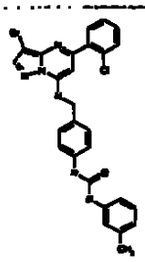
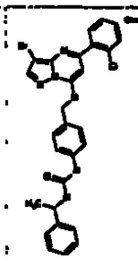
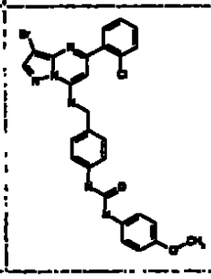
847

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7231 2. 613.34		1. 7236 2. 631.35
	1. 7232 2. 605.33		1. 7237 2. 631.35
	1. 7233 2. 621.34		1. 7238 2. 631.35
	1. 7234 2. 623.34		1. 7239 2. 631.35
	1. 7235 2. 627.34		1. 7240 2. 631.35

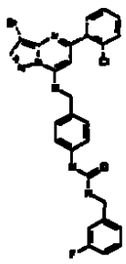
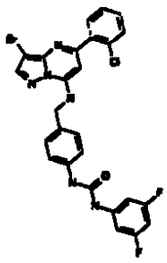
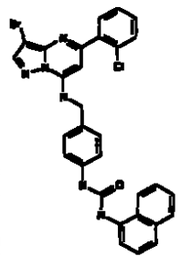
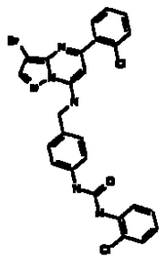
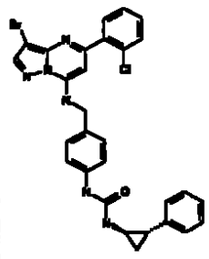
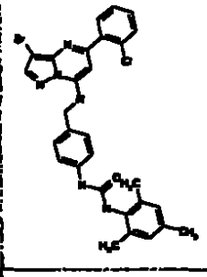
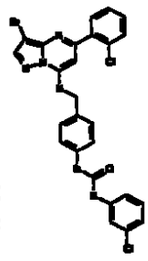
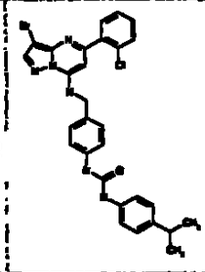
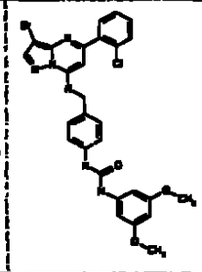
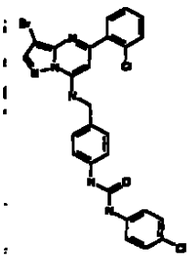
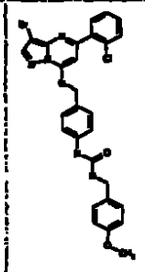
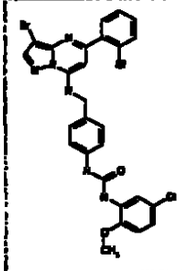
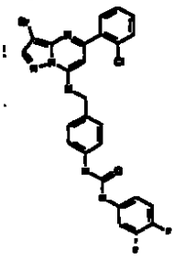
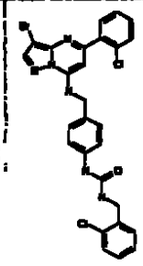
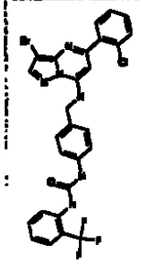
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7241 2. 639.35		1. 7246 2. 653.36
	1. 7242 2. 641.35		1. 7247 2. 665.37
	1. 7243 2. 645.35		
	1. 7244 2. 541.3		
	1. 7245 2. 649.36		

-846-
849

TABLA 73

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7301 2. 529.29		1. 7306 2. 567.31		1. 7311 2. 577.32
	1. 7302 2. 541.3		1. 7307 2. 567.31		1. 7312 2. 577.32
	1. 7303 2. 563.13		1. 7308 2. 574.32		1. 7313 2. 579.32
	1. 7304 2. 563.31		1. 7309 2. 574.32		1. 7314 2. 579.32
	1. 7305 2. 563.31		1. 7310 2. 577.32		1. 7315 2. 579.32

847
850

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7316 2. 581.32		1. 7321 2. 585.32		1. 7326 2. 599.33
	1. 7317 2. 583.32		1. 7322 2. 589.32		1. 7327 2. 591.33
	1. 7318 2. 583.32		1. 7323 2. 591.33		1. 7328
	1. 7319 2. 583.32		1. 7324 2. 593.33		1.7329 2. 613.34
	1. 7320 2. 585.32		1. 7325 2. 597.33		1. 7330 2. 617.34

848

851

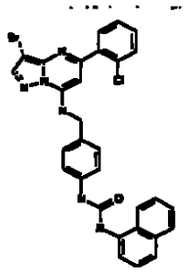
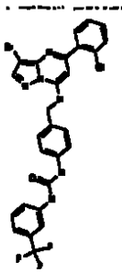
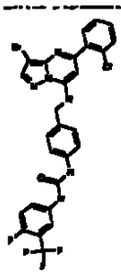
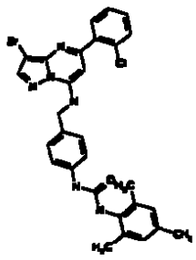
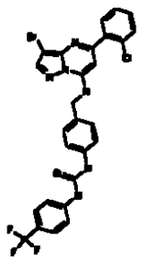
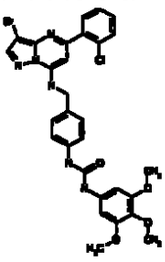
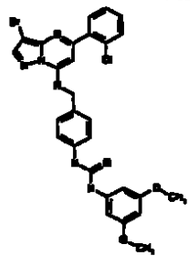
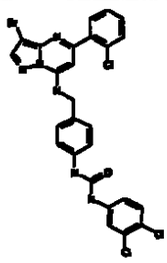
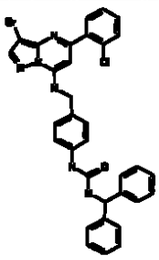
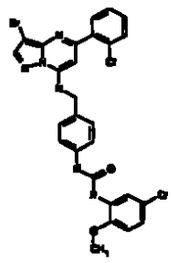
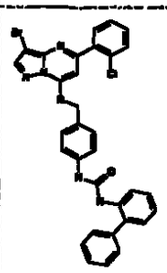
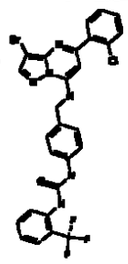
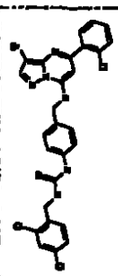
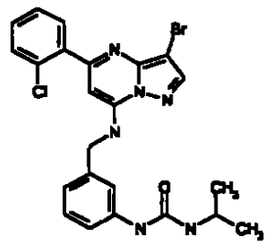
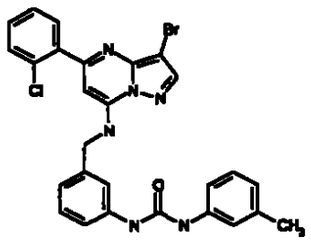
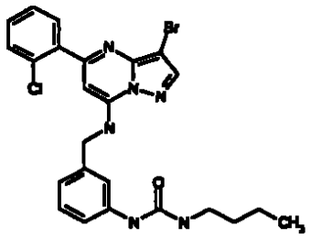
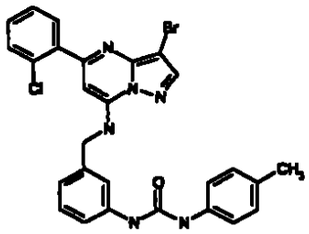
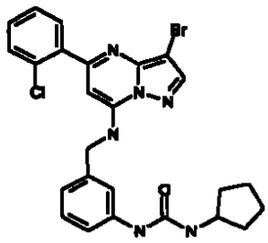
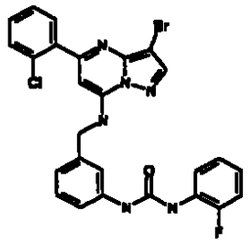
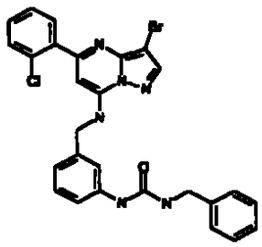
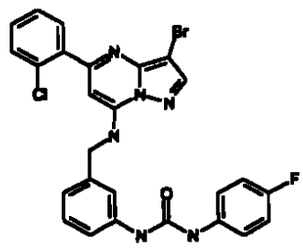
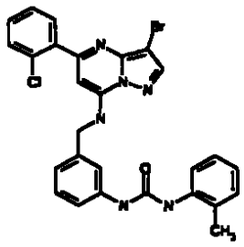
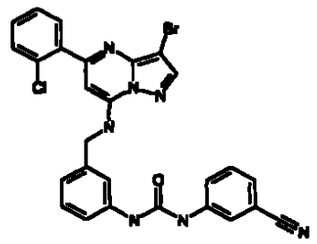
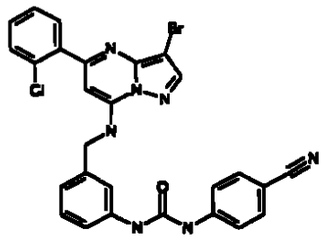
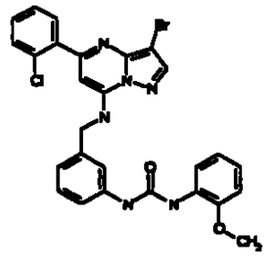
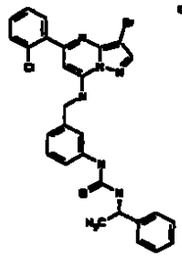
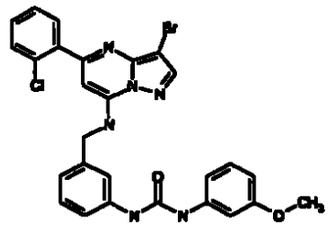
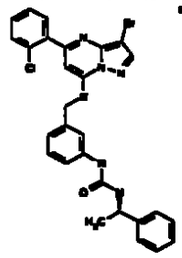
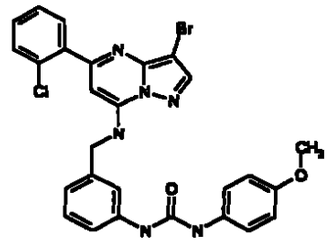
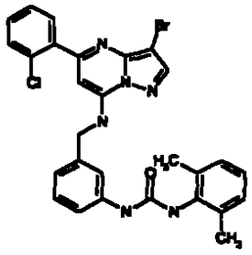
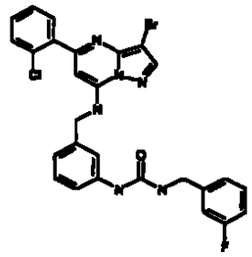
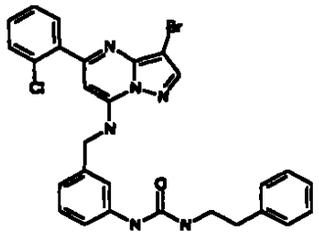
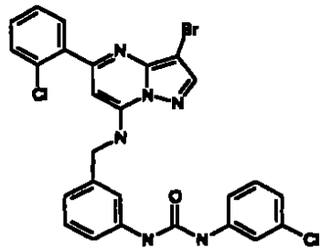
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7331 2. 599.33		1. 7336 2. 617.34		1. 73412. 635.35
	1. 7332 2. 591.33		1. 7337 2. 617.34		1. 7342 2. 639.35
	1. 7333 2. 609.33		1. 7338 2. 617.34		1. 7343 2. 639.35
	1. 7334 2. 613.34		1. 7339 2. 625.34		
	1. 7335 2. 617.34		1. 7340 2. 631.35		

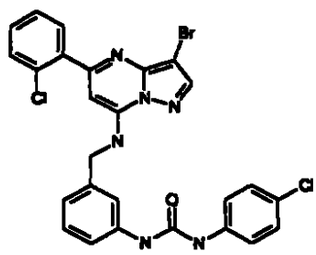
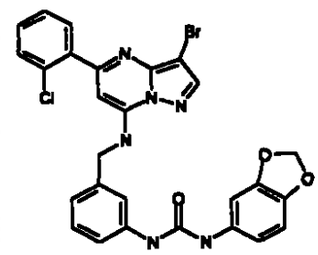
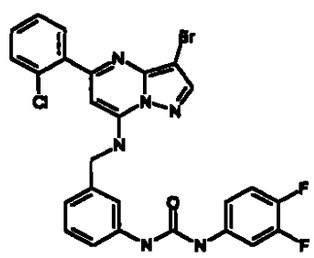
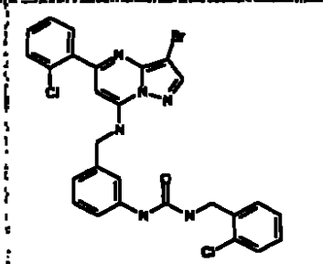
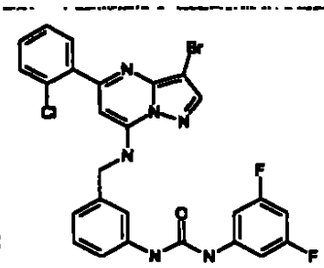
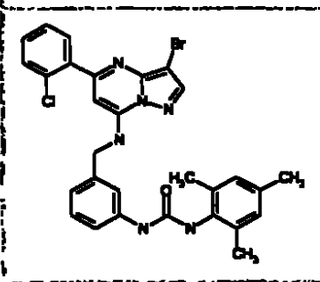
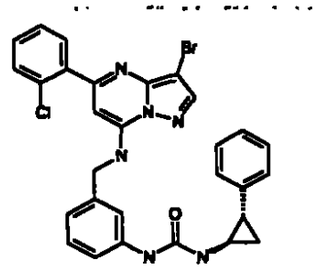
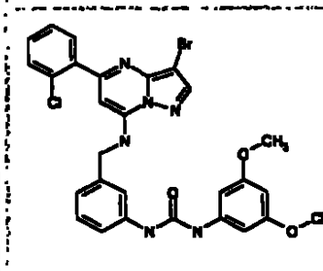
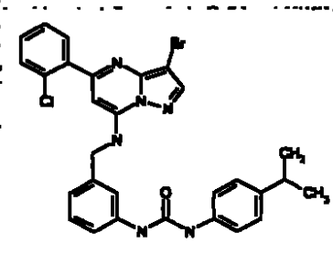
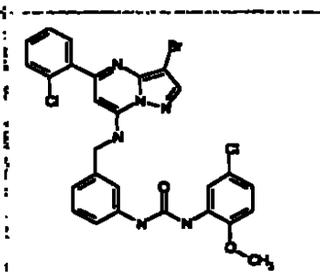
TABLA 74

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7401 2. 515.28		1. 7406 2. 563.31
	1. 7402 2. 529.29		1. 7407 2. 563.31
	1. 7403 2. 541.3		1. 7408 2. 567.31
	1. 7404 2. 563.13		1. 7409 2. 567.31
	1. 7405 2. 563.31		1. 7410 2. 574.32

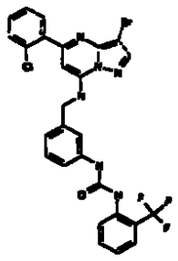
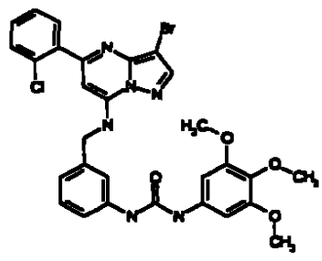
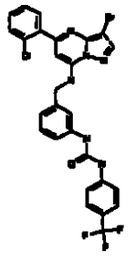
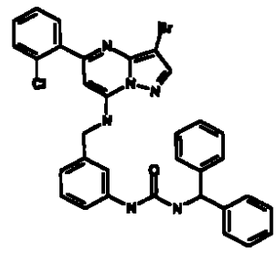
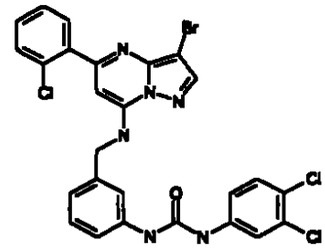
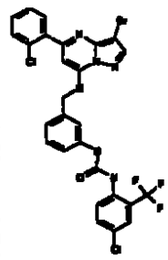
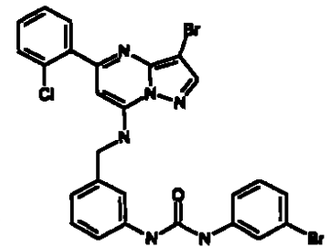
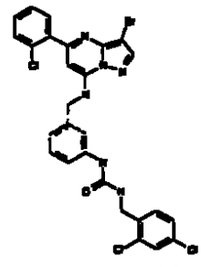
850
853

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7411 2. 574.32		1. 7416 2. 579.32
	1. 7412 2. 577.14		1. 741 7 2. 579.32
	1. 7413 2. 577.32		1. 7418 2. 579.32
	1. 7414 2. 577.32		1. 7419 2. 581.32
	1. 7415 2. 577.32		1. 7420 2. 583.32

-851
854

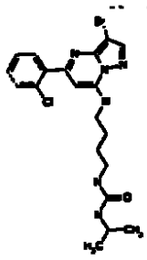
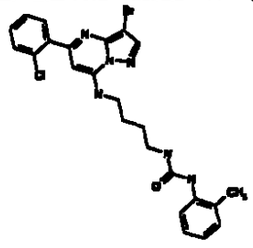
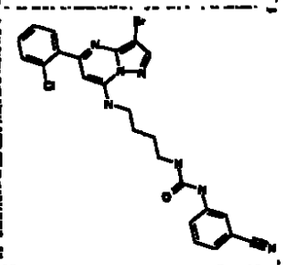
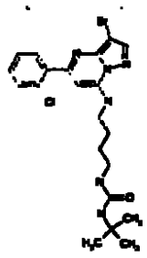
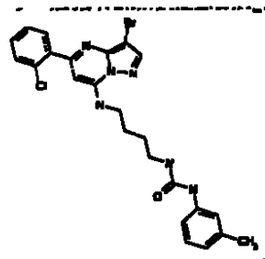
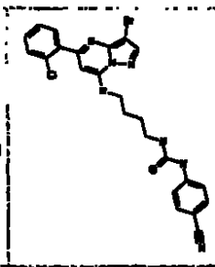
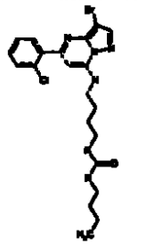
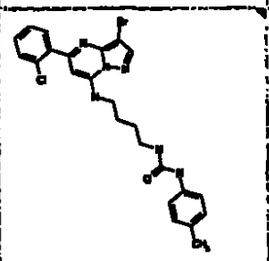
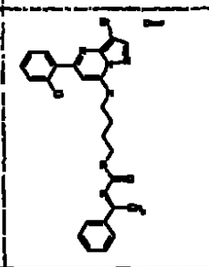
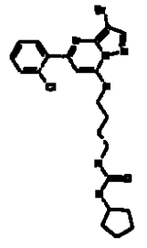
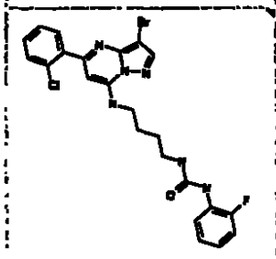
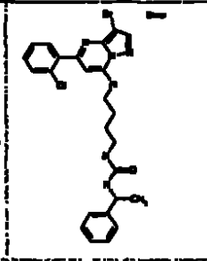
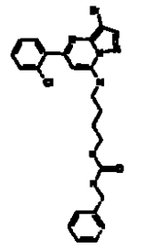
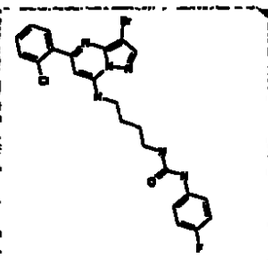
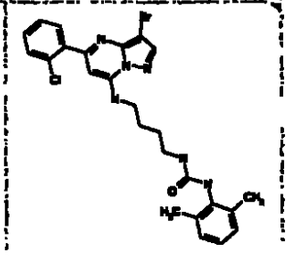
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7421 2. 583.32		1. 7426 2. 593.33
	1. 7422 2. 585.32		1. 7427 2. 597.33
	1. 7423 2. 585.32		1. 7428 2. 591.33
	1. 7424 2. 589.32		1. 7429 2. 609.33
	1. 7425 2. 591.33		1. 7430 2. 613.34

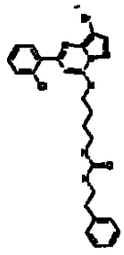
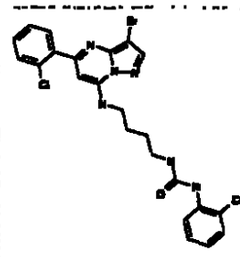
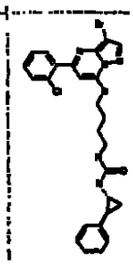
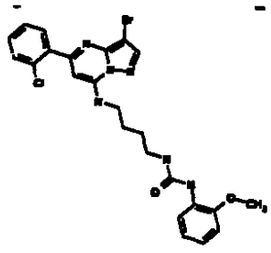
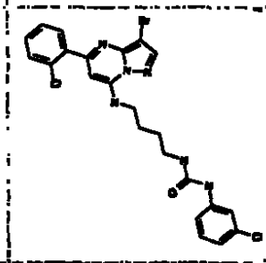
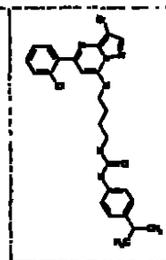
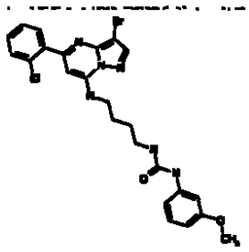
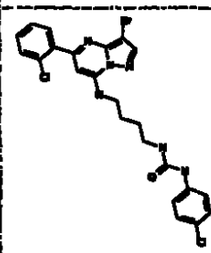
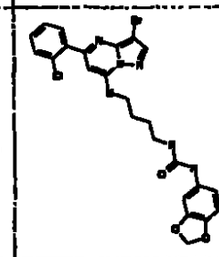
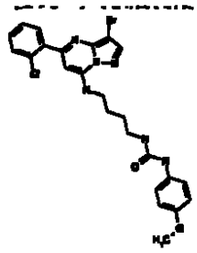
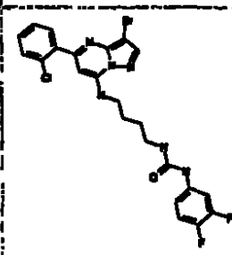
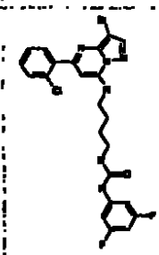
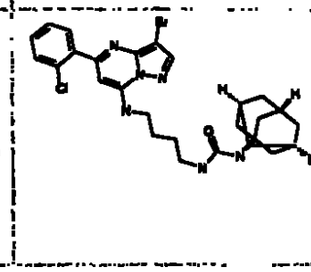
855

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7431 2. 617.34		1. 7436 2. 639.35
	1. 7432 2. 617.34		1. 7437 2. 639.35
	1. 7433 2. 617.34		1. 7438 2. 651.36
	1. 7434 2. 627.34		
	1. 7435 2. 631.35		

853
856

TABLA 75

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7501 2. 481.26		1. 7506 2. 529.29		1. 7511 2. 540.3
	1. 7502 2. 495.27		1. 7507 2. 529.29		1. 7512 2. 540.3
	1. 7503 2. 495.27		1. 7508 2. 529.29		1. 7513 2. 543.3
	1. 7504 2. 507.28		1. 7509 2. 533.29		1. 7514 2. 543.3
	1. 7505 2. 529.29		1. 7510 2. 533.29		1. 7515 2. 543.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2 .m/z
	1. 7516 2. 543.3		1. 7521 2. 549.3		1. 7526 2. 555.31
	1. 7517 2. 545.3		1. 7522 2. 549.3		1. 7527 2. 557.31
	1. 7518 2. 545.3		1. 7523 2. 549.3		1. 7528 2. 559.31
	1. 7519 2. 545.3		1. 7524 2. 551.3		1. 7529 2. 560.31
	1. 7520 2. 547.3		1. 7525 2. 551.3		1. 7530 2. 573.32

855
858

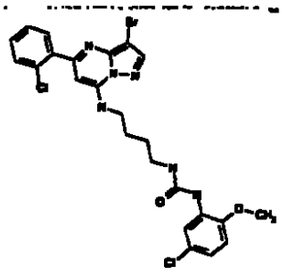
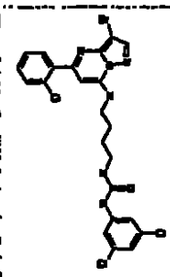
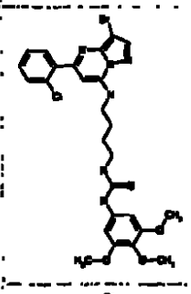
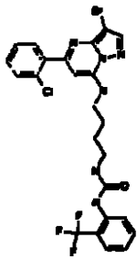
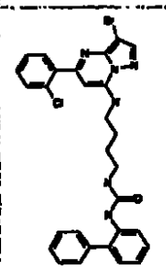
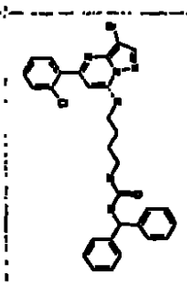
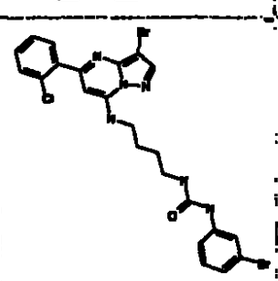
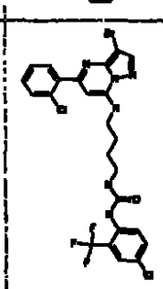
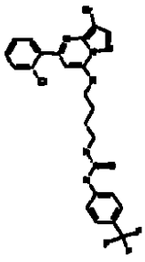
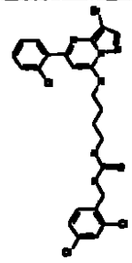
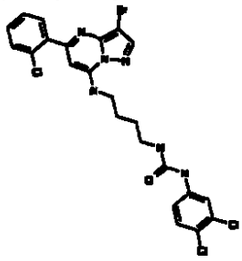
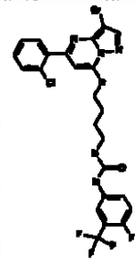
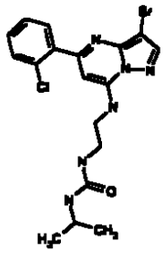
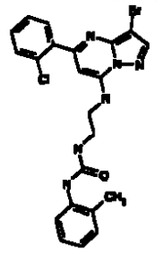
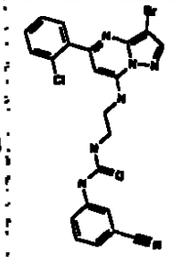
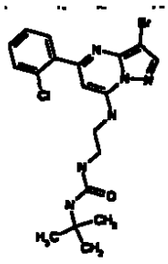
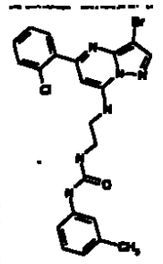
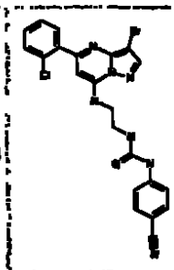
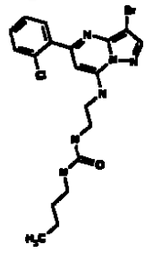
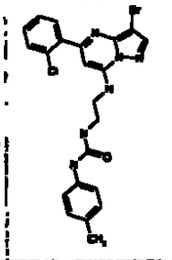
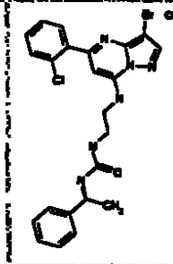
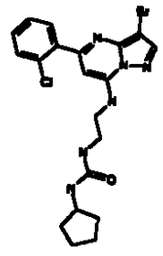
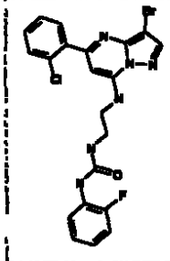
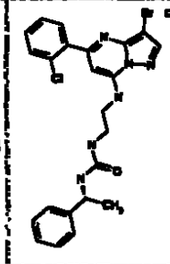
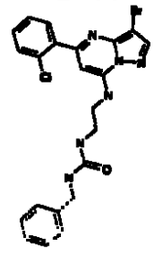
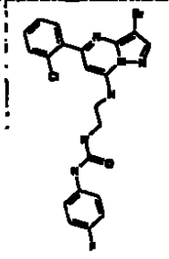
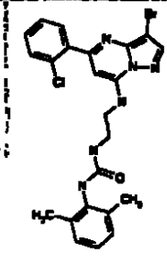
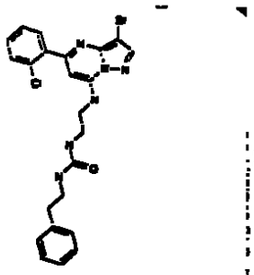
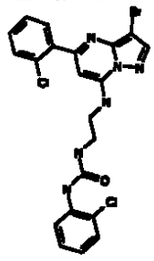
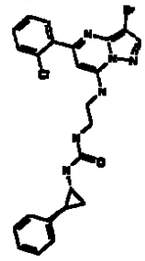
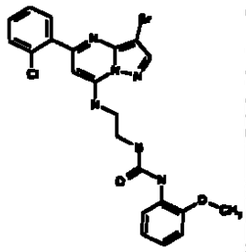
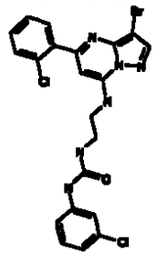
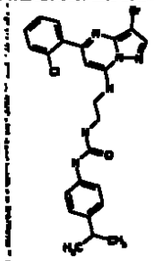
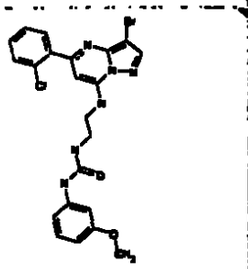
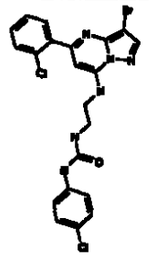
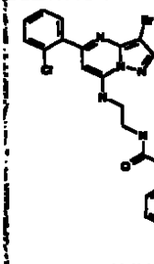
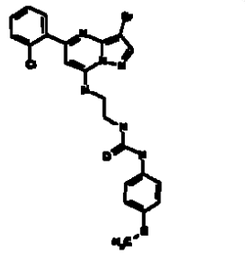
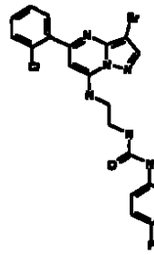
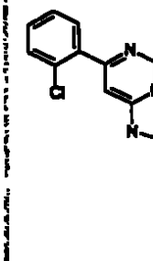
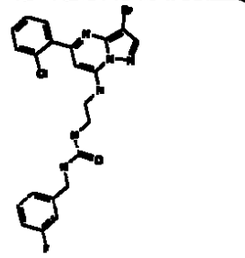
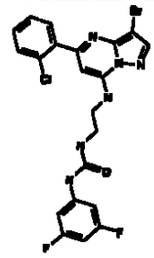
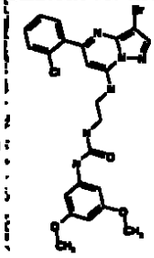
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7531 2. 579.32		1. 7536 2. 583.32		1. 7541 2. 605.33
	1. 7532 2. 583.32		1. 7537 2. 591.33		1. 7542 2. 605.33
	1. 7533 2. 583.32		1. 7538 2. 593.33		1. 7543 2. 614.34
	1. 7534 2. 583.32		1. 7539 2. 597.33		
	1. 7535 2. 583.32		1. 7540 2. 601.33		

TABLA 76

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7601 2. 453.25		1. 7606 2. 501.28		1. 7611 2. 512.28
	1. 7602 2. 467.26		1. 7607 2. 501.28		1. 7612 2. 512.28
	1. 7603 2. 467.26		1. 7608 2.501.28		1. 7613 2. 515.28
	1. 7604 2. 479.26		1. 7609 2. 505.28		1. 7614 2. 515.28
	1. 7605 2. 501.28		1. 7610 2. 505.28		1. 7615 2. 515.28

857
860

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 761 6 2. 515.28		1. 7621 2. 521.29		1. 7626 2. 527.29
	1. 7617 2. 517.28		1. 7622 2. 521.29		1. 7627 2. 529.29
	1. 7618 2. 517.28		1. 7623 2. 521.29		1. 7628 2. 541.3
	1. 7619 2. 517.28		1. 7624 2. 523.29		1. 7629 2. 545.3
	1. 7620 2. 519.29		1. 7625 2. 523.29		1. 7630 2. 547.3

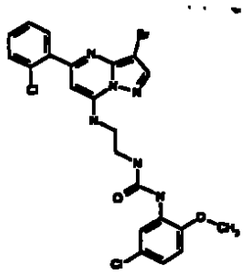
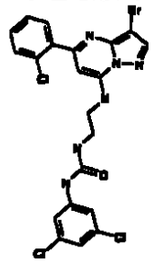
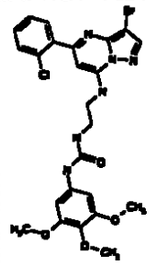
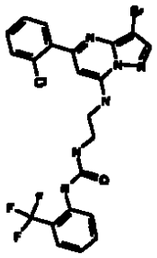
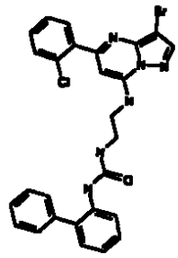
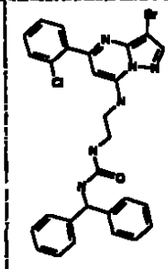
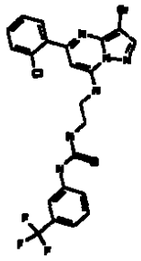
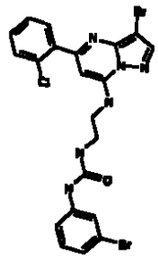
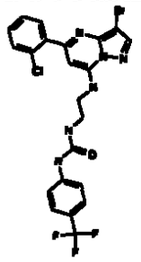
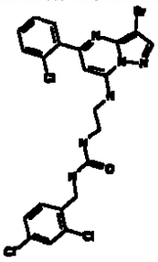
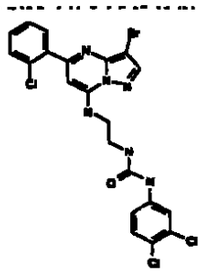
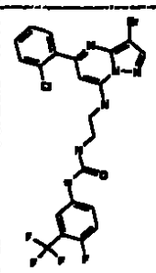
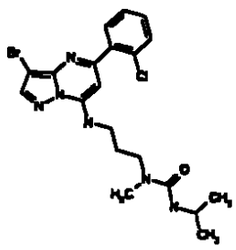
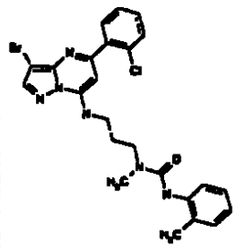
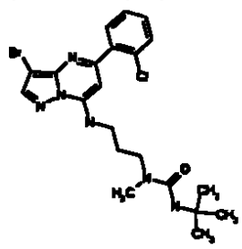
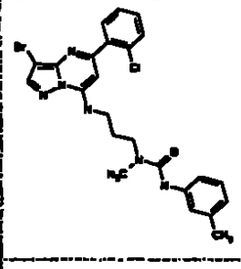
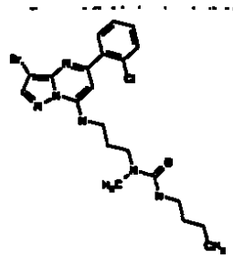
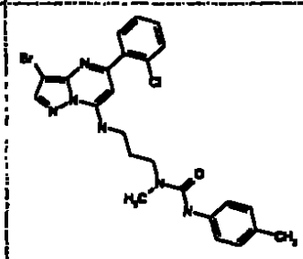
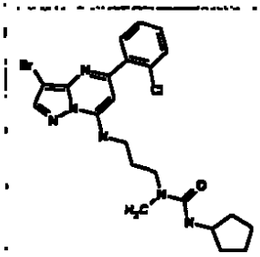
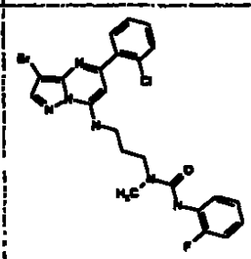
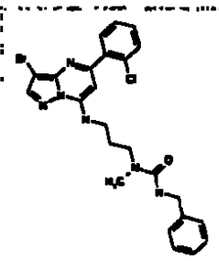
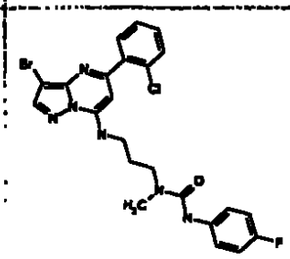
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7631 2. 551.3		1. 7636 2. 555.31		1. 7641 2. 577.32
	1. 7632 2. 555.31		1. 7637 2. 583.31		1. 7642 2. 577.32
	1. 7633 2. 555.31		1. 7638 2. 585.31		
	1. 7634 2. 555.31		1. 7639 2. 569.31		
	1. 7635 2. 555.31		1. 7640 2. 573.32		

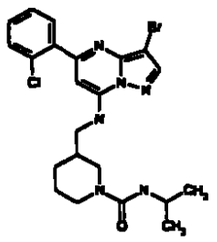
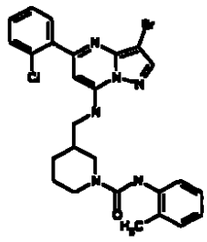
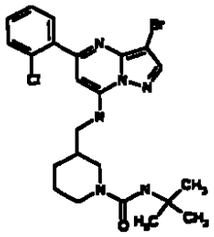
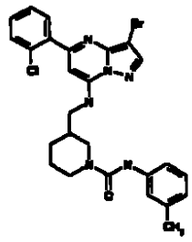
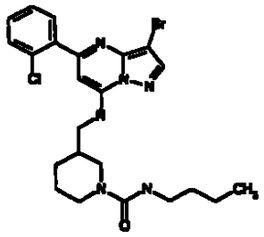
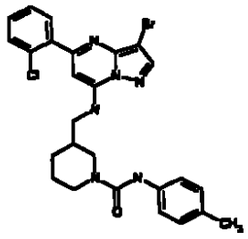
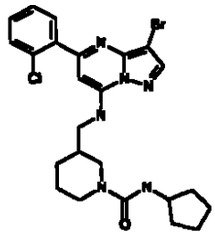
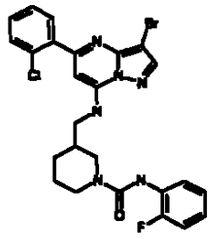
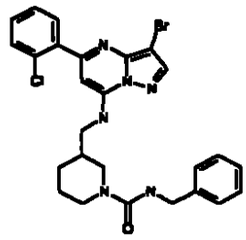
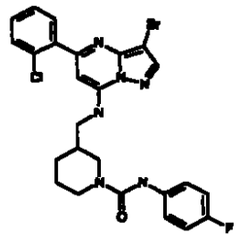
TABLA 77

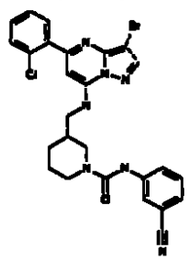
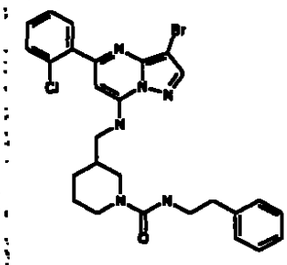
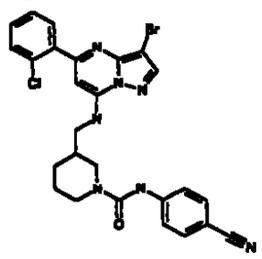
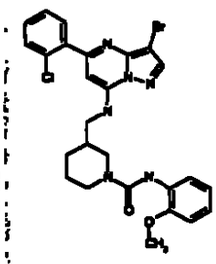
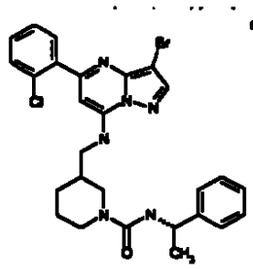
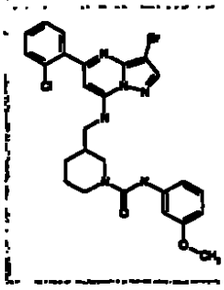
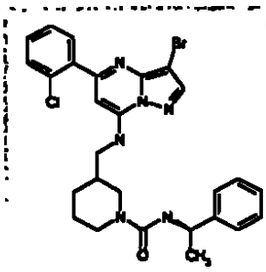
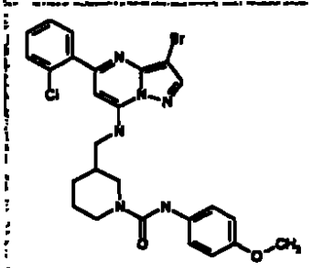
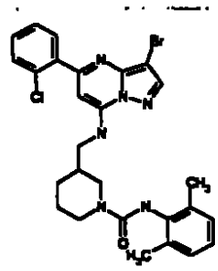
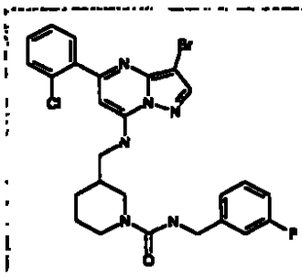
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7701 2. 481.26		1. 7706 2. 529.29
	1. 7702 2. 495.27		1. 7707 2. 529.29
	1. 7703 2. 495.27		1. 7708 2. 529.29
	1. 7704 2. 507.28		1. 7709 2. 533.29
	1. 7705 2. 529.29		1. 7710 2. 533.29

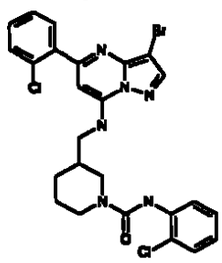
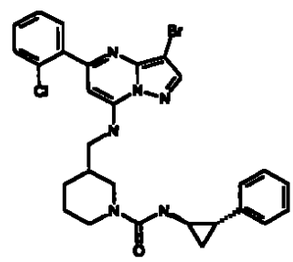
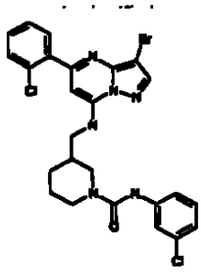
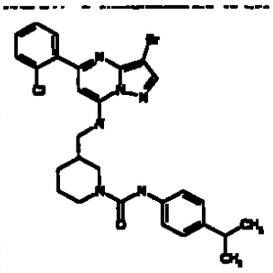
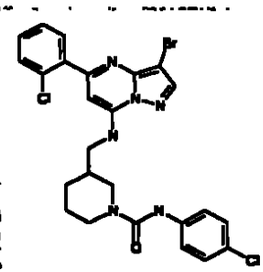
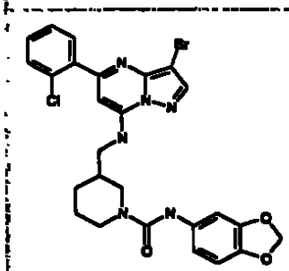
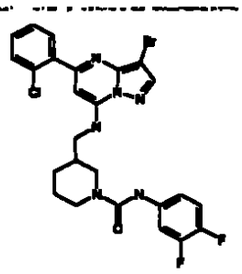
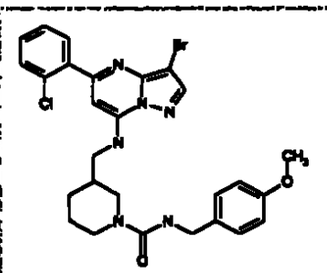
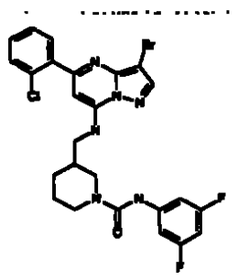
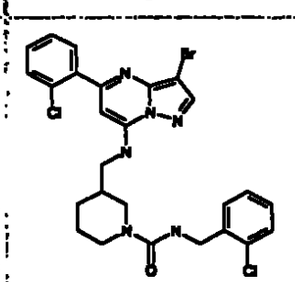
5

860
863

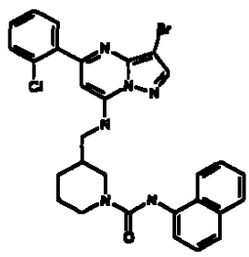
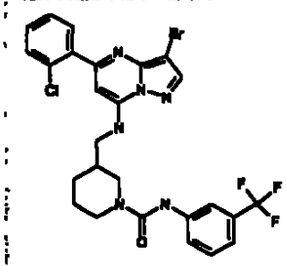
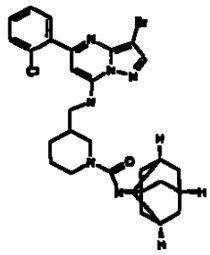
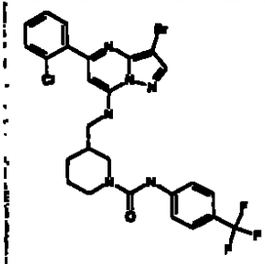
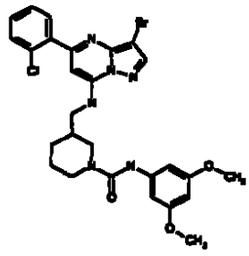
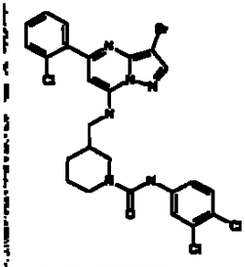
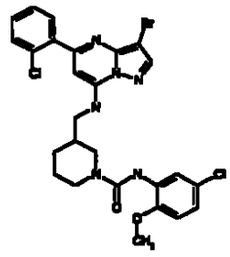
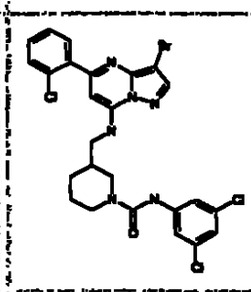
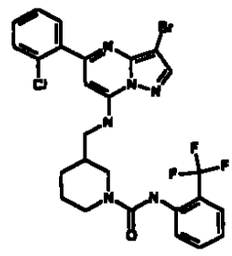
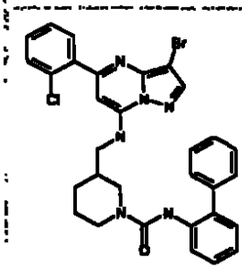
TABLA 78

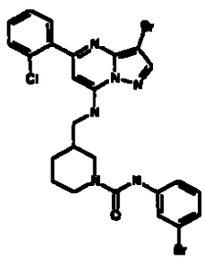
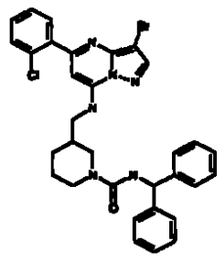
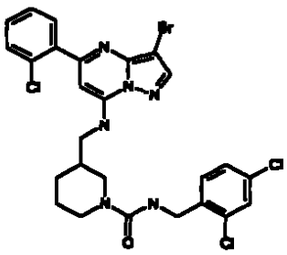
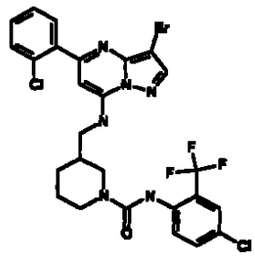
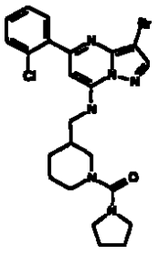
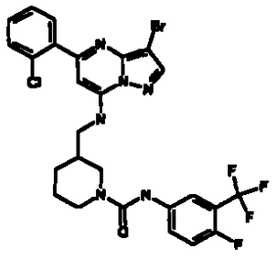
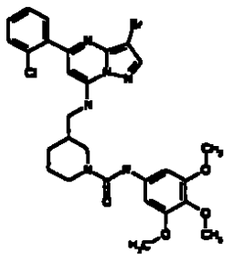
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7801 2. 507.28		1. 7806 2. 555.31
	1. 7802 2. 521.29		1. 7807 2. 555.31
	1. 7803 2. 521.29		1. 7808 2. 555.31
	1. 7804 2. 533.29		1. 7809 2. 559.31
	1. 7805 2. 555.31		1. 7810 2. 559.31

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7811 2. 566.31		1. 7816 2. 569.31
	1. 7812 2. 566.31		1. 7817 2. 571.31
	1. 7813 2. 569.31		1. 7818 2. 571.31
	1. 7814 2. 569.31		1. 7819 2. 571.31
	1. 7815 2. 569.31		1. 7820 2. 573.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7821 2. 575.32		1. 7826 2. 581.32
	1. 7822 2. 575.32		1. 7827 2. 583.32
	1. 7823 2. 575.32		1. 7828 2. 585.32
	1. 7824 2. 577.32		1. 7829 2. 585.32
	1. 7825 2. 577.32		1. 7830 2. 589.32

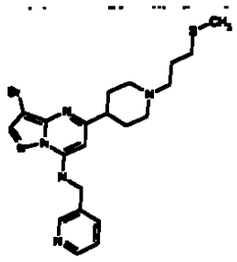
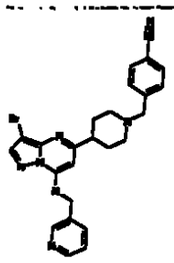
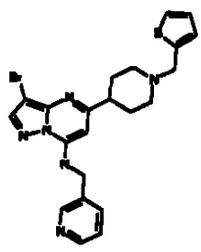
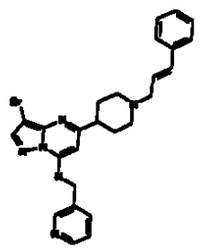
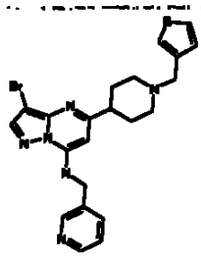
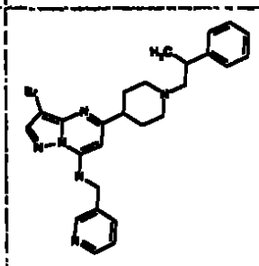
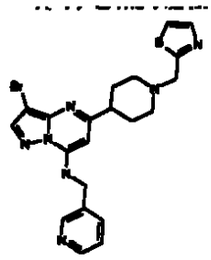
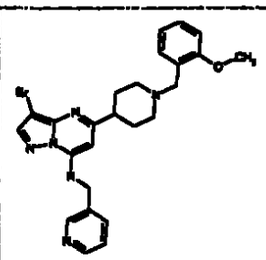
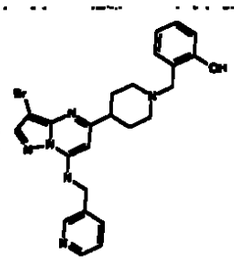
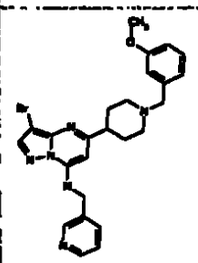
863
866

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7831 2. 591.33		1. 7836 2. 609.33
	1. 7832 2. 599.33		1. 7837 2. 609.33
	1. 7833 2. 601.33		1. 7838 2. 609.33
	1. 7834 2. 605.33		1. 7839 2. 609.33
	1. 7835 2. 609.33		1. 7840 2. 617.34

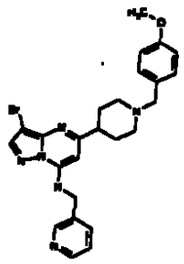
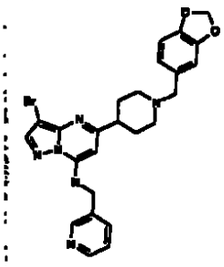
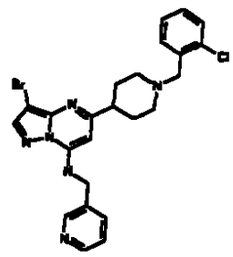
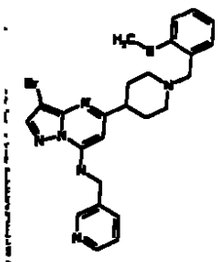
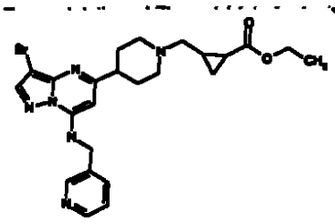
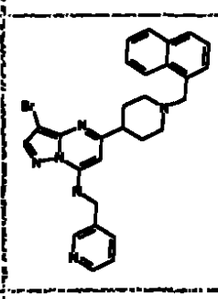
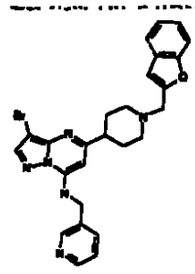
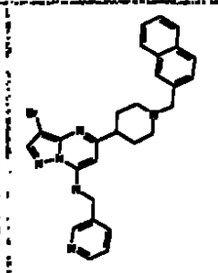
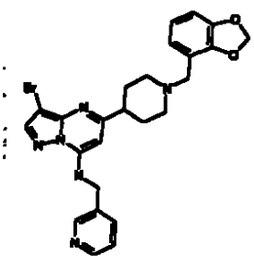
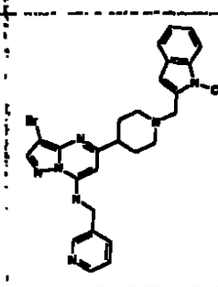
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7841 2. 619.34		1. 7846 2. 631.35
	1. 7842 2. 623.34		1. 7847 2. 643.35
	1. 7843 2. 519.29		
	1. 7844 2. 627.34		
	1. 7845 2. 631.35		

865
868

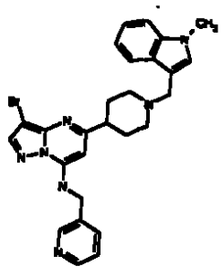
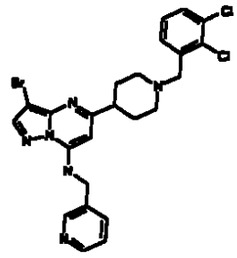
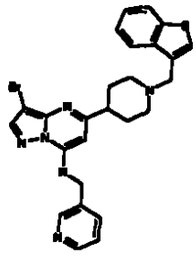
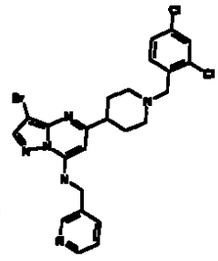
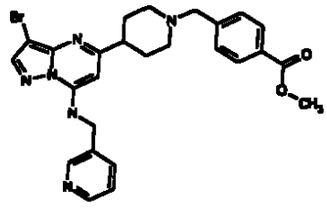
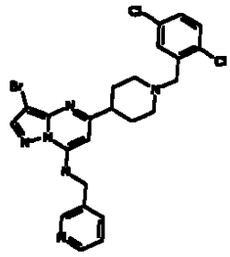
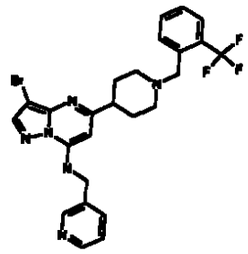
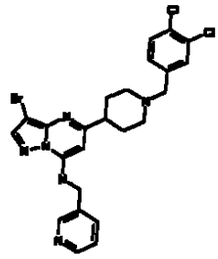
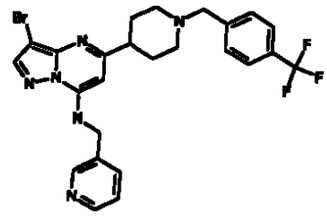
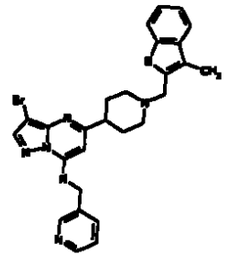
TABLA 79

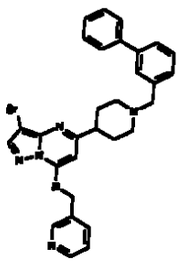
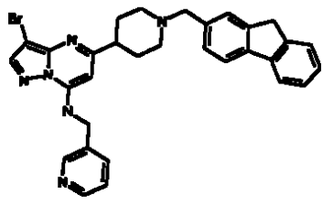
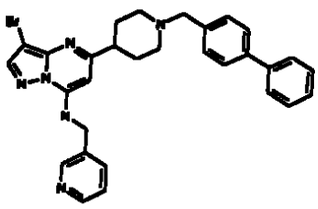
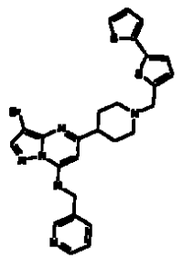
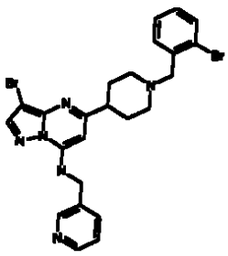
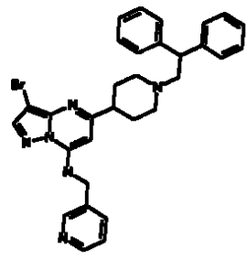
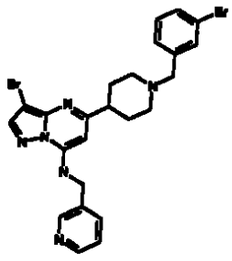
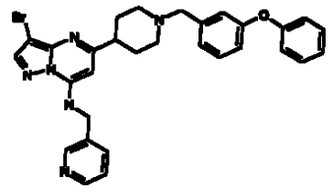
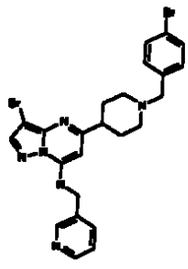
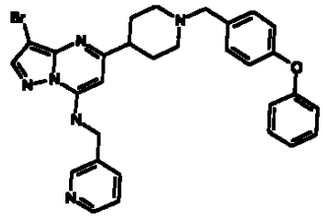
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7901 2. 477.26		1. 7906 2. 504.28
	1. 7902 2. 485.27		1. 7907 2. 505.28
	1. 7903 2. 485.27		1. 7908 2. 507.28
	1. 7904 2. 486.27		1. 7909 2. 509.28
	1. 7905 2. 495.27		1. 7910 2. 509.28

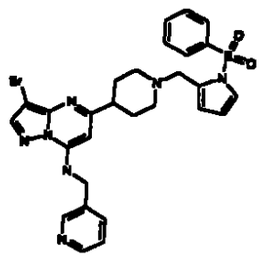
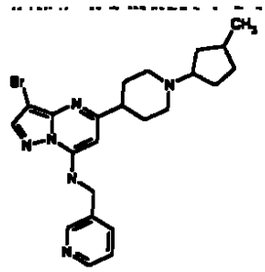
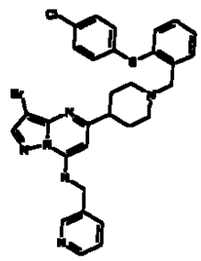
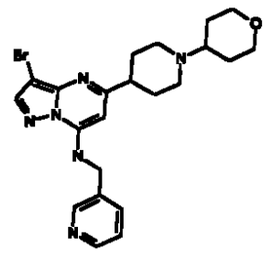
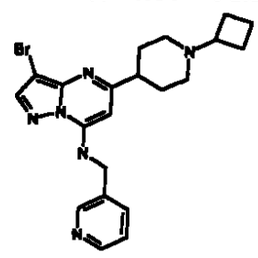
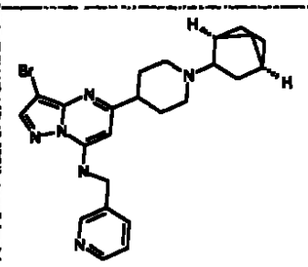
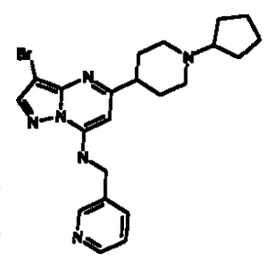
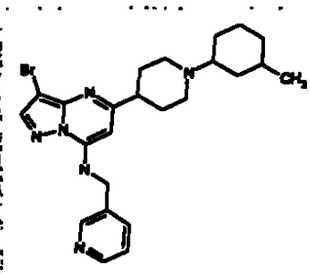
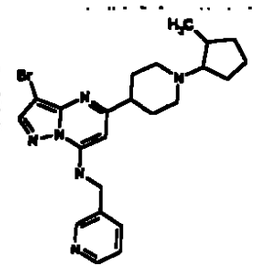
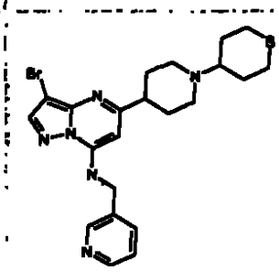
866
869

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

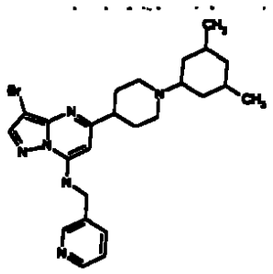
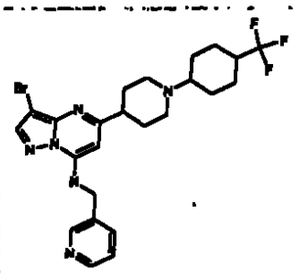
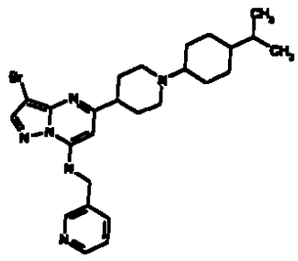
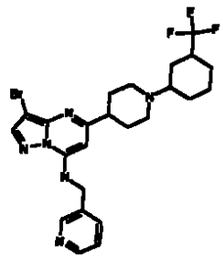
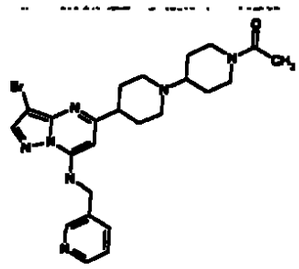
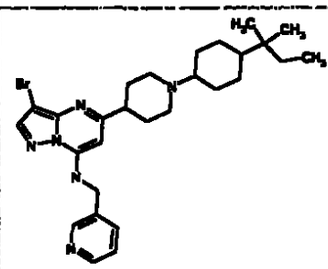
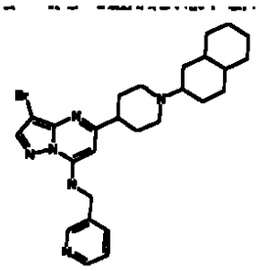
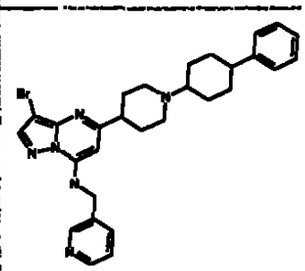
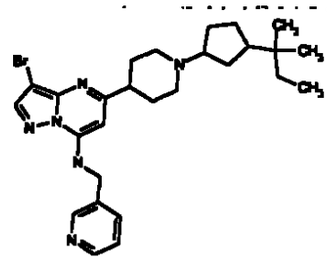
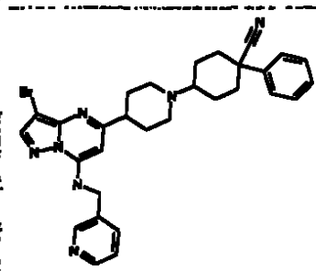
867
870

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7921 2. 530.29		1. 7926 2. 547.3
	1. 7922 2. 535.29		1. 7927 2. 547.3
	1. 7923 2. 537.3		1. 7928 2. 547.3
	1. 7924 2. 547.3		1. 7929 2. 547.3
	1. 7925 2. 547.3		1. 7930 2. 549.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7931 2. 555.31		1. 7936 2. 567.31
	1. 7932 2. 555.31		1. 7937 2. 567.31
	1. 7933 2. 557.31		1. 7938 2. 569.31
	1. 7934 2. 557.31		1. 7939 2. 571.31
	1. 7935 2. 557.31		1. 7940 2. 571.31

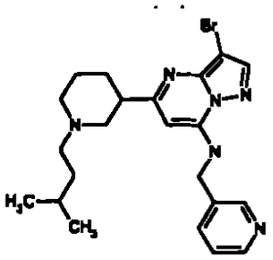
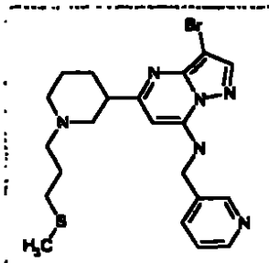
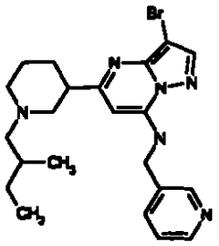
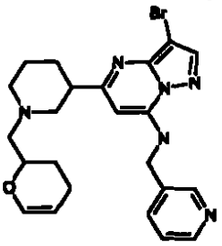
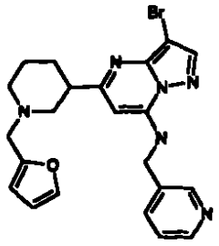
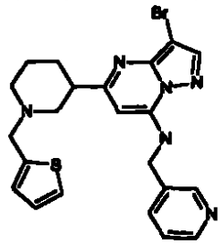
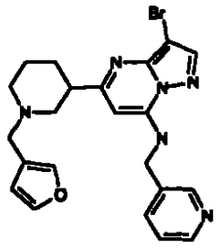
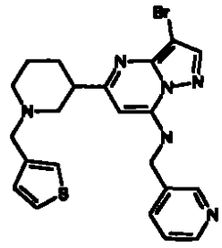
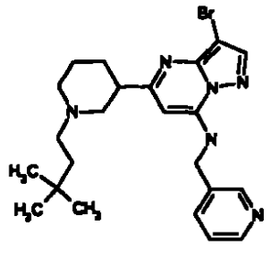
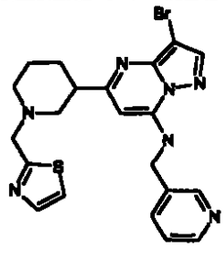
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7941 2. 608.33		1. 7946 2. 471.26
	1. 7942 2. 621.34		1. 7947 2. 473.26
	1. 7943 2. 443.24		1. 7948 2. 483.27
	1. 7944 2. 457.25		1. 7949 2. 485.27
	1. 7945 2. 471.26		1. 7950 2. 489.27

820
873

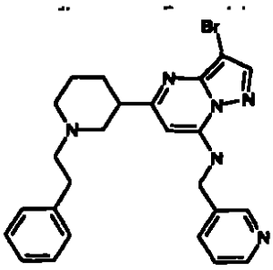
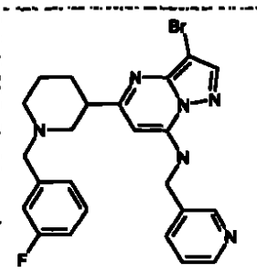
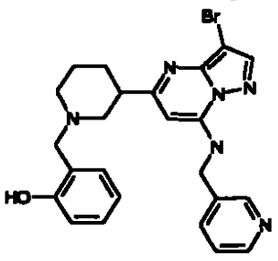
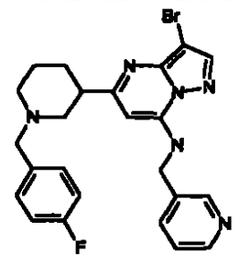
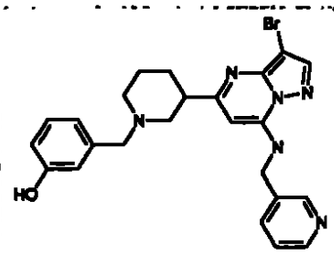
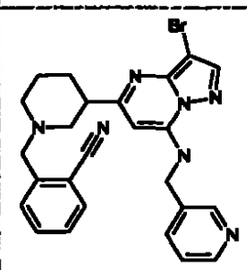
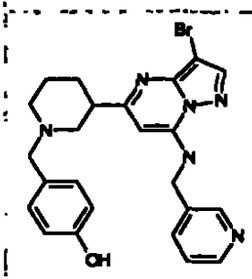
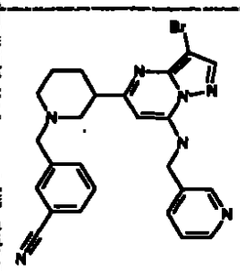
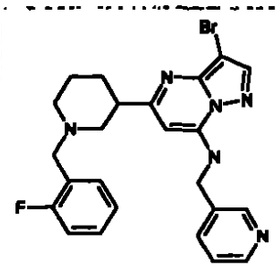
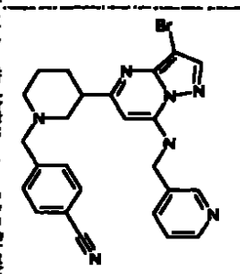
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 7951 2. 499.27		1. 7956 2. 536.29
	1. 7952 2. 513.28		1. 7957 2. 539.3
	1. 7953 2. 514.28		1. 7958 2. 541.3
	1. 7954 2. 525.29		1. 7959 2. 547.3
	1. 7955 2. 525.29		1. 7960 2. 572.31

873
874

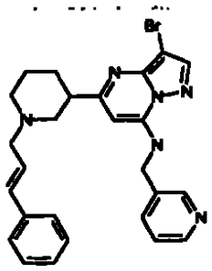
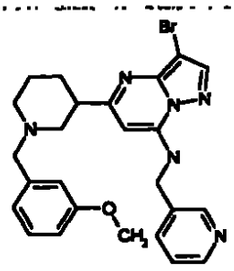
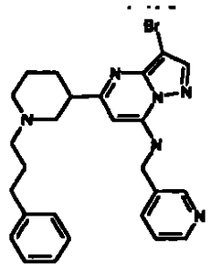
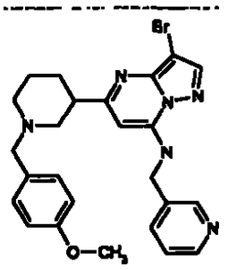
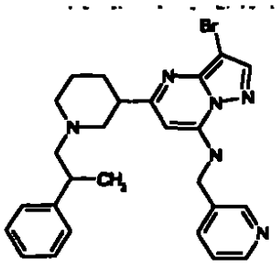
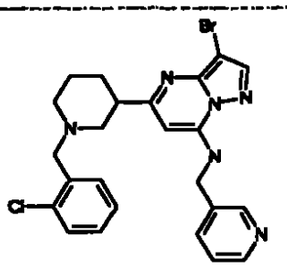
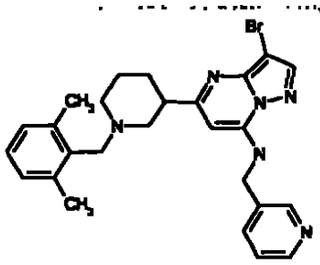
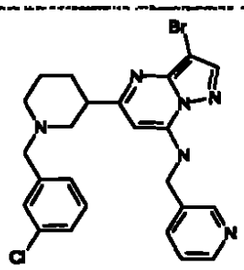
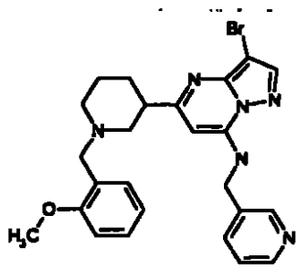
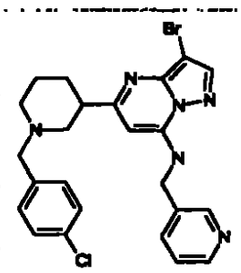
TABLA 80

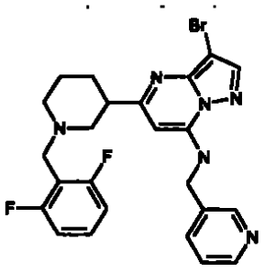
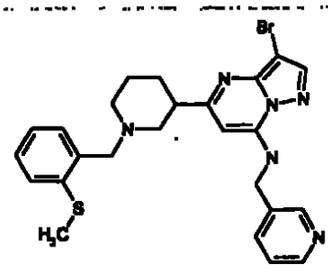
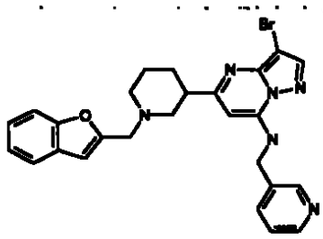
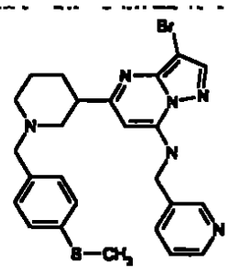
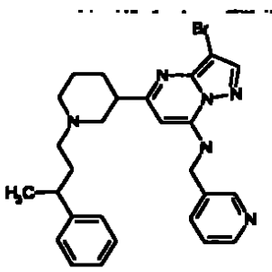
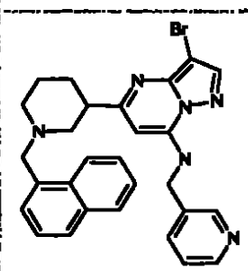
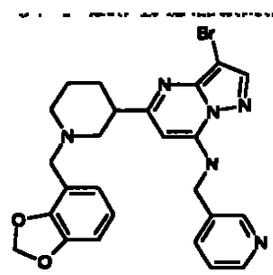
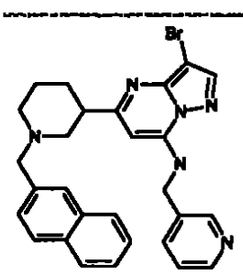
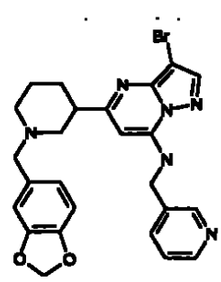
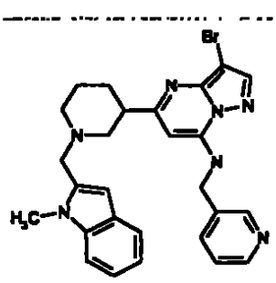
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8001 2. 459.25		1. 8006 2. 477.26
	1.8002 2. 459.25		1. 8007 2 485.27
	1. 8003 2. 469.26		1. 8008 2. 485.27
	1. 8004 2. 469.26		1. 8009 2. 485.27
	1. 8005 2. 473.26		1. 8010 2. 486.27

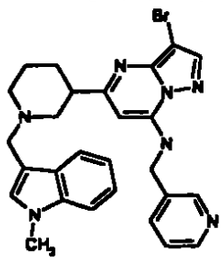
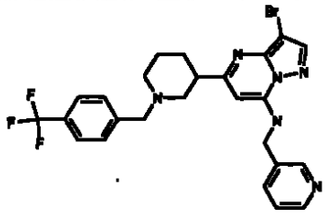
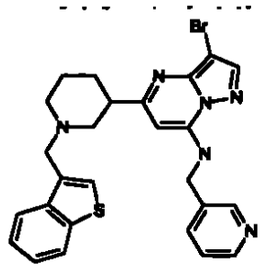
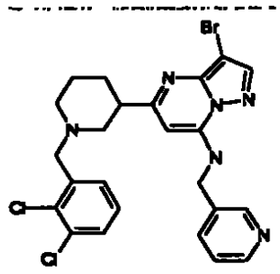
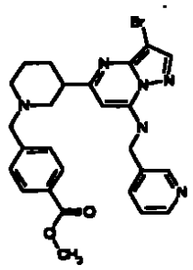
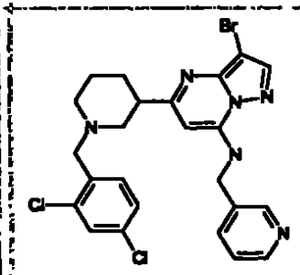
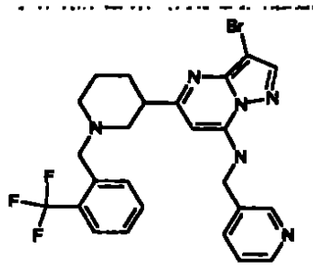
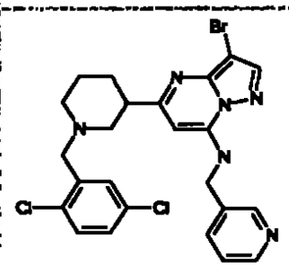
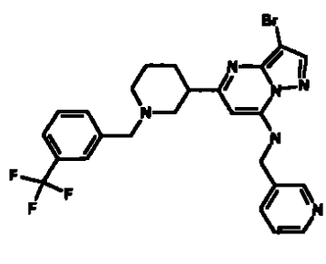
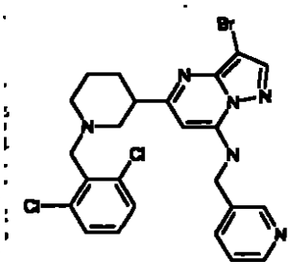
872
875

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8011 2. 493.27		1. 8016 2. 495.27
	1. 8012 2. 495.27		1. 8017 2. 495.27
	1. 8013 2. 495.27		1. 8018 2. 502.28
	1. 8014 2. 495.27		1. 8019 2. 502.28
	1. 8015 2. 495.27		1. 8020 2. 502.28

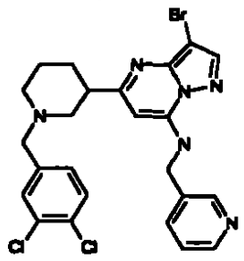
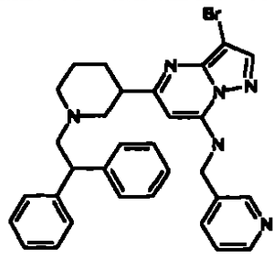
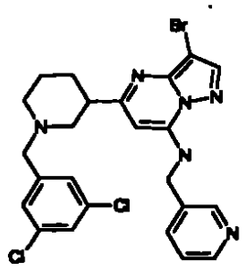
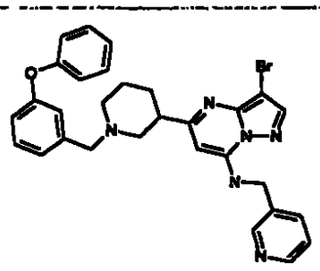
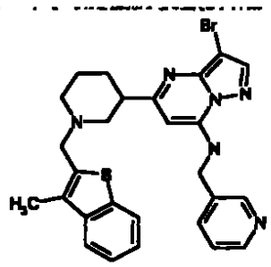
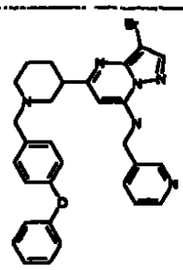
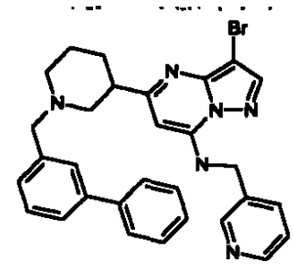
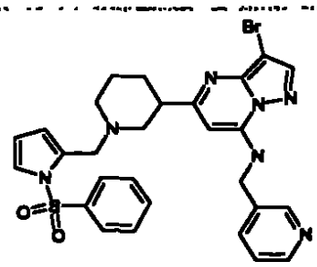
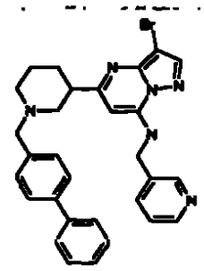
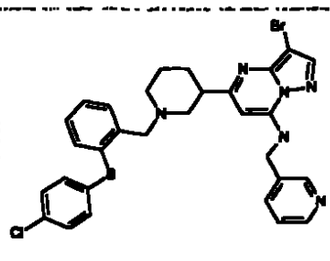
873
876

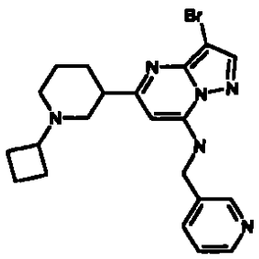
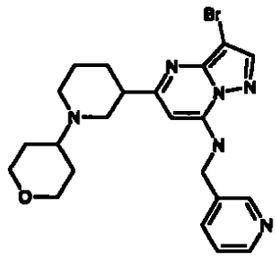
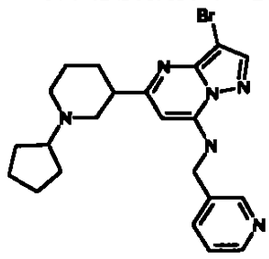
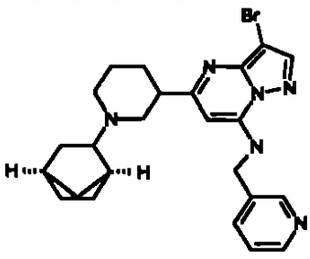
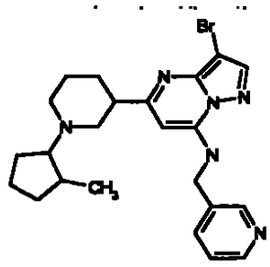
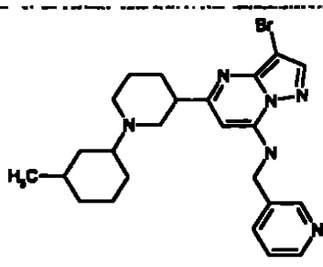
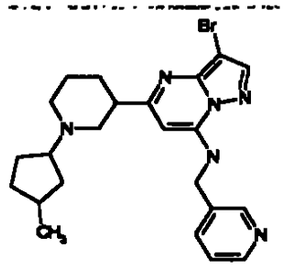
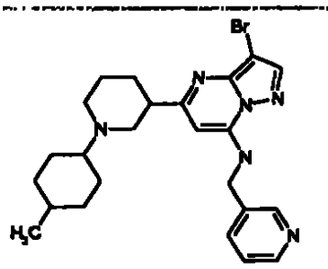
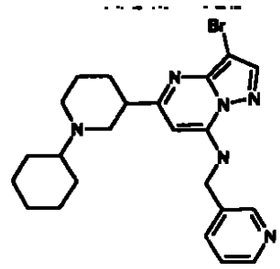
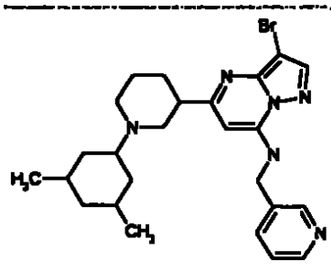
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8021 2. 505.28		1. 8026 2. 509.28
	1. 8022 2. 505.28		1. 8027 2. 509.28
	1. 8023 2. 507.28		1. 8028 2. 513.28
	1. 8024 2. 507.28		1. 8029 2. 513.28
	1. 8025 2. 507.28		1. 8030 2. 513.28

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8031 2. 515.28		1. 8036 2. 523.29
	1. 8032 2. 519.29		1. 8037 2. 525.29
	1. 8033 2. 521.29		1. 8038 2. 529.29
	1. 8034 2. 523.29		1. 8039 2. 529.29
	1. 8035 2. 523.29		1. 8040 2. 530.29

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8041 2. 530.29		1. 8046 2. 547.3
	1. 8042 2. 535.29		1. 8047 2. 544.3
	1. 8043 2. 537.3		1. 8048 2. 547.3
	1. 8044 2. 547.3		1. 8049 2. 547.3
	1. 8045 2. 547.3		1. 8050 2. 547.3

876
879

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8051 2. 548.3		1. 8056 2. 569.31
	1. 8052 2. 548.3		1. 8057 2. 569.31
	1. 8053 2. 547.3		1. 8058 2. 571.31
	1. 8054 2. 555.31		1. 8059 2. 608.33
	1. 8055 2. 553.3		1. 8060 2. 621.34

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8061 2. 443.24		1. 8066 2. 473.26
	1. 8062 2. 457.25		1. 8067 2. 483.27
	1. 8063 2. 471.26		1. 8068 2. 485.27
	1. 8064 2. 471.26		1. 8069 2. 483.27
	1. 8065 2. 469.26		1. 8070 2. 499.27

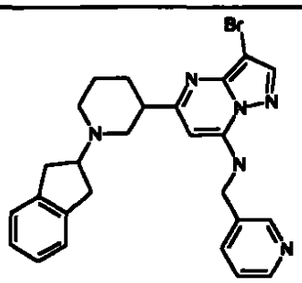
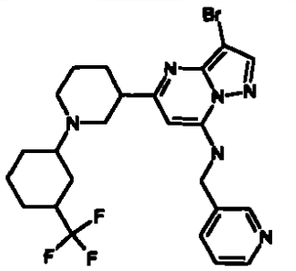
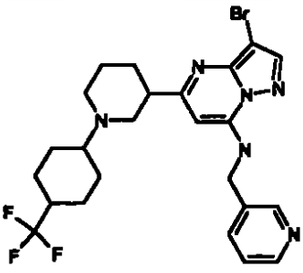
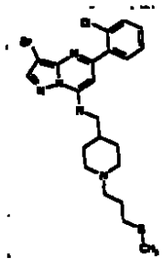
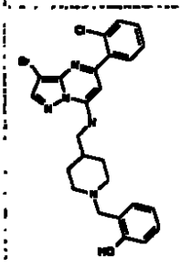
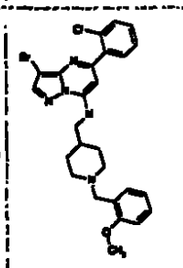
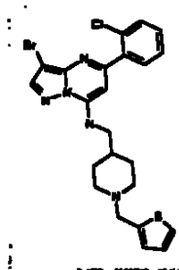
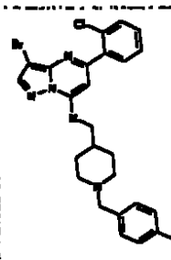
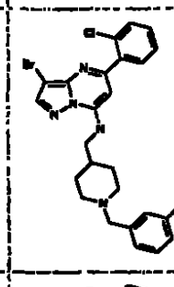
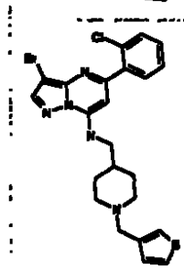
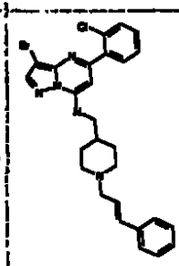
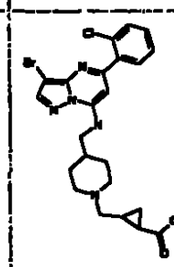
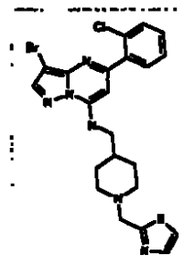
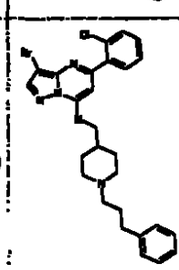
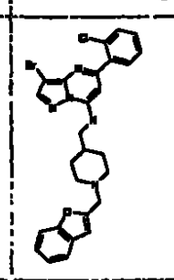
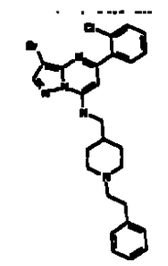
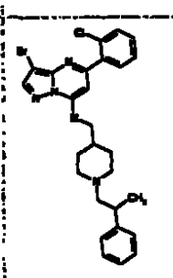
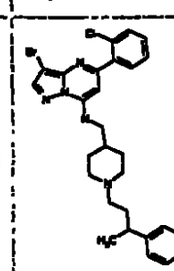
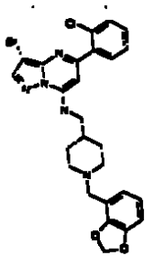
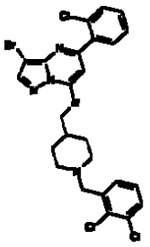
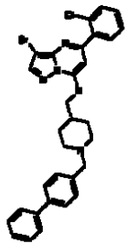
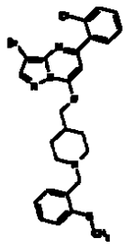
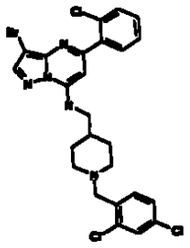
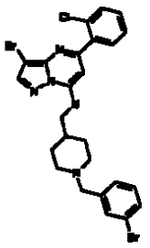
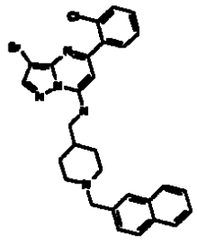
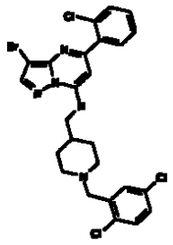
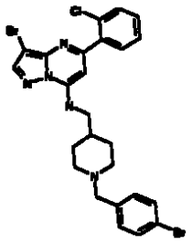
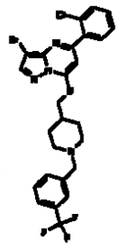
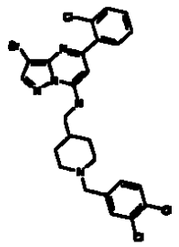
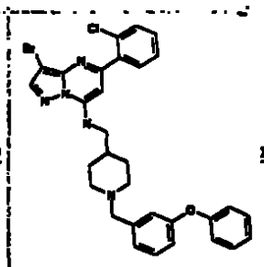
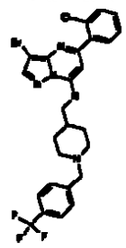
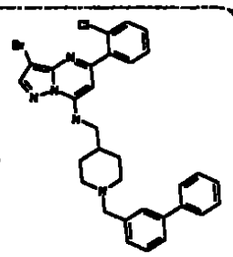
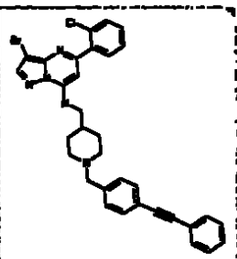
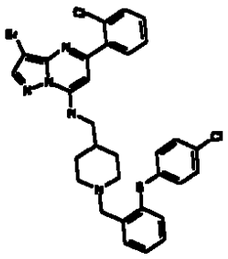
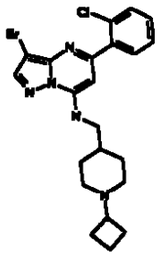
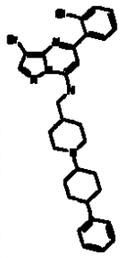
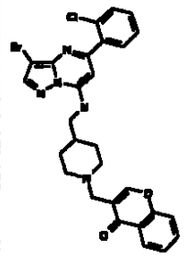
Producto	1. Ej., 2. m/z
	1. 8071 2. 505.28
	1. 8072 2. 537.3
	1. 8073 2. 537.3

TABLA 81

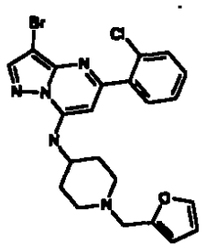
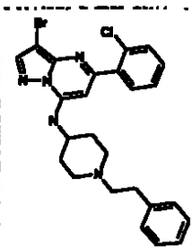
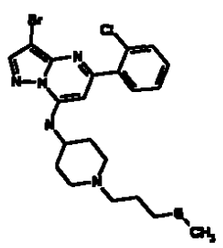
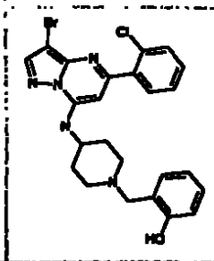
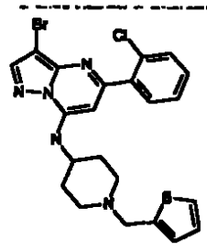
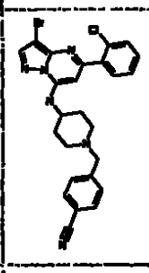
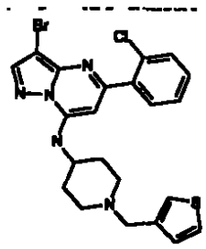
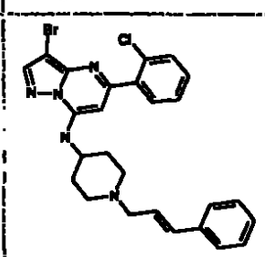
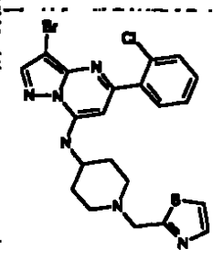
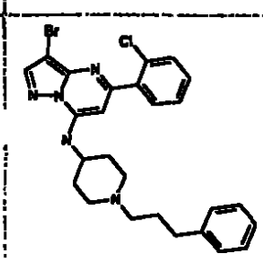
Producto	1. Ej. 2 m/z	Producto	1. Ej. 2. m/z	Product	1. Ej. 2.m/z
	1. 8101 2. 510.28		1. 8106 2. 528.29		1. 8111 2. 542.3
	1. 8102 2. 518.28		1. 8107 2. 537.3		1. 8112 2. 542.3
	1. 8103 2. 518.28		1. 8108 2. 538.3		1. 8113 2. 548.3
	1. 8104 2. 519.29		1. 8109 2. 540.3		1. 8114 2. 552.3
	1. 8105 2. 526.29		1. 8110 2. 540.3		1. 8115 2. 554.3

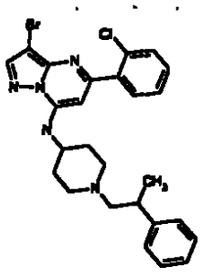
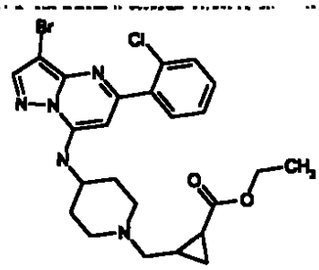
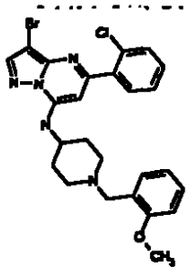
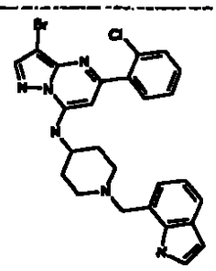
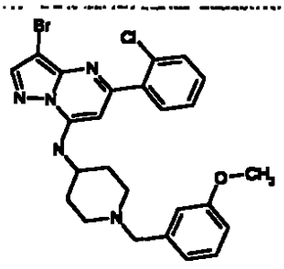
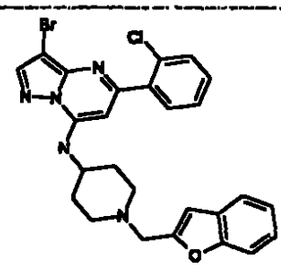
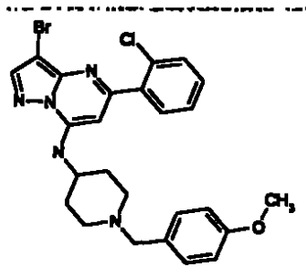
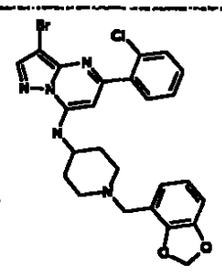
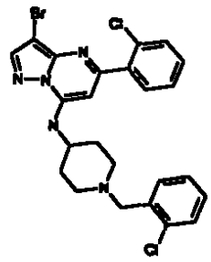
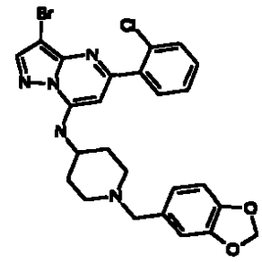
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8116 2. 556.31		1. 8121 2. 580.32		1. 8126 2. 588.32
	1. 8117 2. 558.31		1. 8122 2. 580.32		1. 8127 2. 590.32
	1. 8118 2. 562.31		1. 8123 2. 580.32		1. 8128 2. 590.32
	1. 8119 2. 580.32		1. 8125 2. 580.32		1. 8129 2. 604.33
	1. 8120 2. 580.32		1. 8126 2. 588.32		1. 8130 2. 612.34

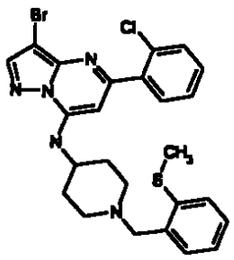
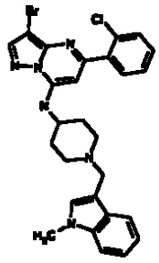
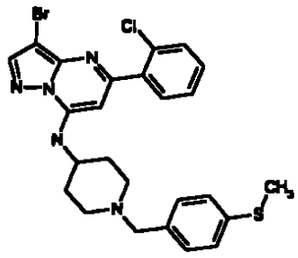
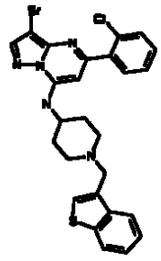
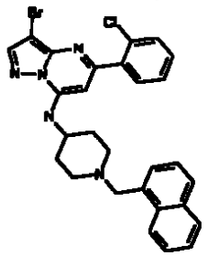
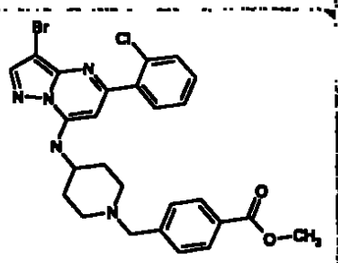
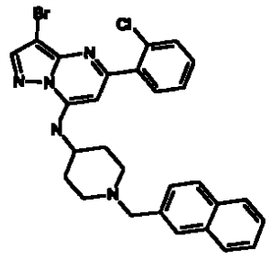
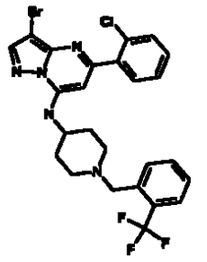
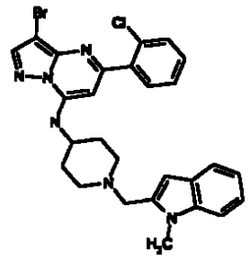
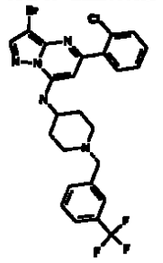
Producto	1. Ej. 2. m/z
	1. 8131 2. 654.36
	1. 8132 2. 476.26
	1. 8133 2. 580.32
	1. 8134 2. 580.32

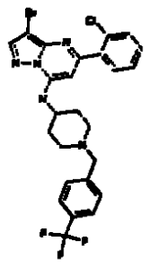
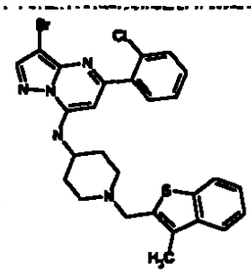
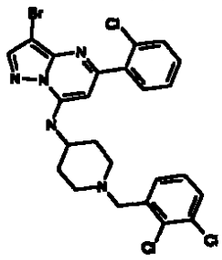
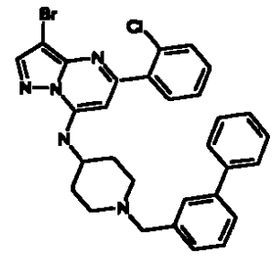
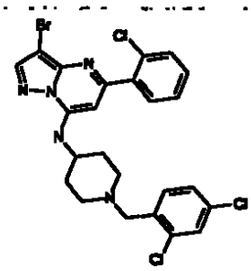
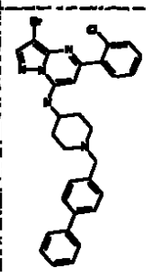
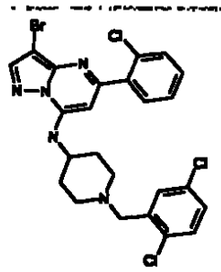
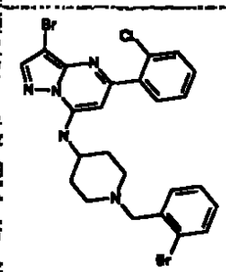
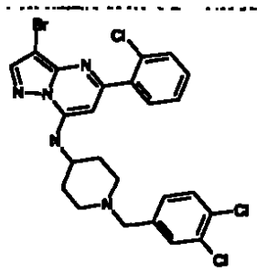
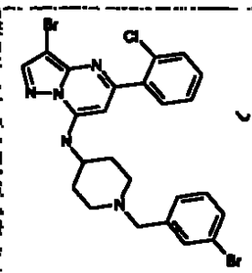
882
885

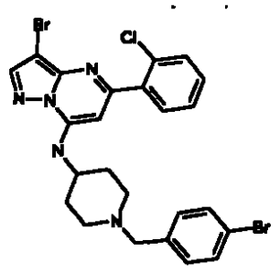
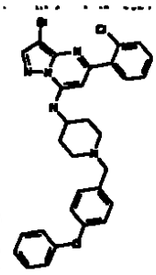
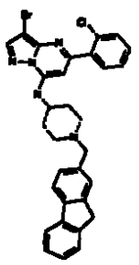
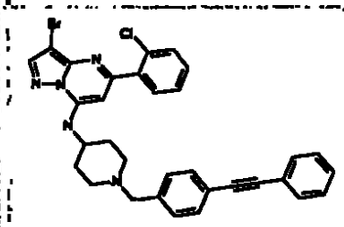
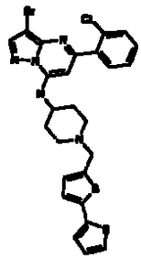
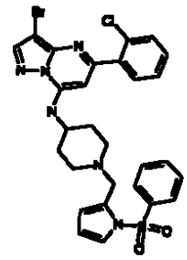
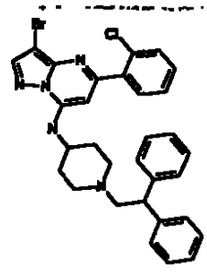
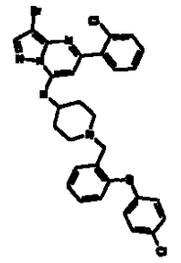
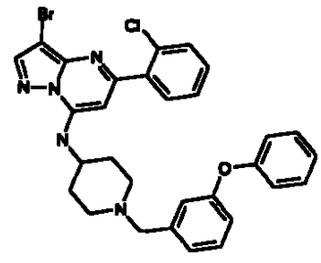
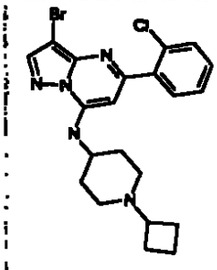
TABLA 82

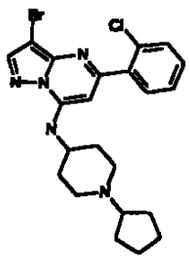
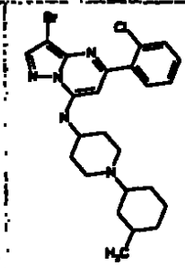
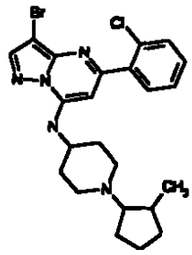
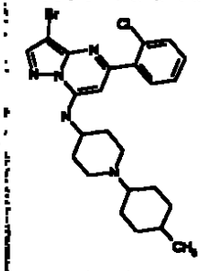
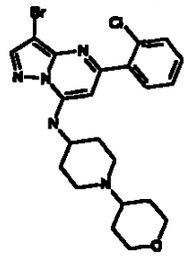
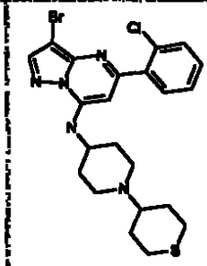
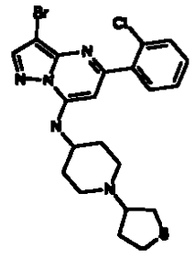
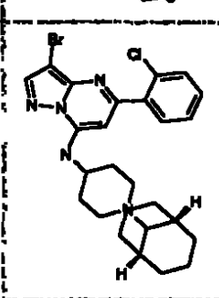
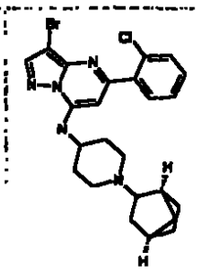
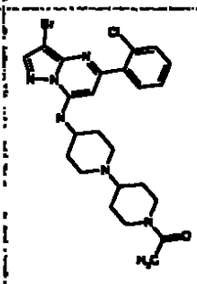
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8201 2. 488.27		1. 8206 2. 512.28
	1. 8202 2. 498.27		1. 8207 2. 514.28
	1. 8203 2. 504.28		1. 8208 2. 523.29
	1. 8204 2. 504.28		1. 8209 2. 524.29
	1. 8205 2. 505.28		1. 8210 2. 526.29

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8211 2. 526.29		1. 8216 2. 534.29
	1. 8212 2. 528.29		1. 8217 2. 537.3
	1. 8213 2. 528.29		1. 8218 2. 538.3
	1. 8214 2. 528.29		1. 8219 2. 542.3
	1. 8215 2. 532.29		1. 8220 2. 542.3

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8221 2. 544.3		1. 8226 2. 551.3
	1. 8222 2. 544.3		1. 8227 2. 554.3
	1. 8223 2. 548.3		1. 8228 2. 556.31
	1. 8224 2. 548.3		1. 8229 2. 566.31
	1. 8225 2. 551.3		1. 8230 2. 566.31

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8231 2. 566.31		1. 8236 2. 568.31
	1. 8232 2. 566.31		1. 8237 2. 574.32
	1. 8233 2. 566.31		1. 8238 2. 574.32
	1. 8243 2. 566.31		1. 8239 2. 576.32
	1. 8235 2. 566.31		1. 8240 2. 576.32

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8241 2. 576.32		1. 8246 2. 590.32
	1. 8242 2. 586.32		1. 8247 2. 598.33
	1. 8243 2. 586.32		1. 8248 2. 627.34
	1. 8244 2. 588.32		1. 8249 2. 640.35
	1. 8245 2. 590.32		1. 8250 2. 462.25

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8251 2. 476.26		1. 8256 2. 504.28
	1. 8252 2. 490.27		1. 8257 2. 504.28
	1. 8253 2. 492.27		1. 8258 2. 508.28
	1. 8254 2. 492.27		1. 8259 2. 530.29
	1. 8255 2. 502.28		1. 8260 2. 533.29

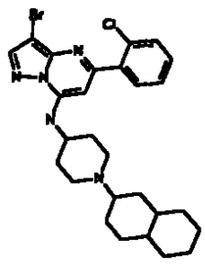
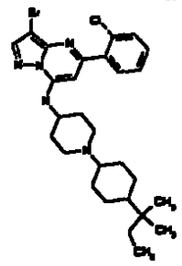
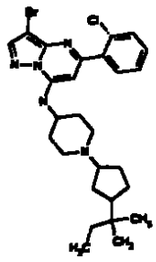
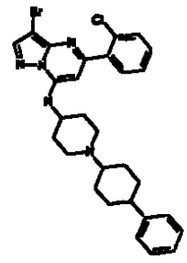
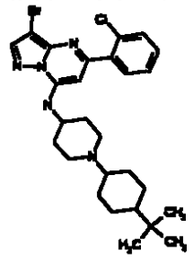
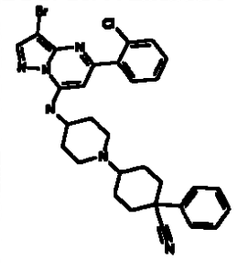
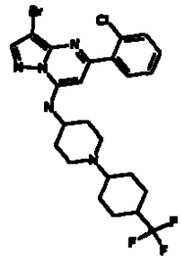
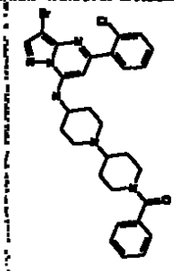
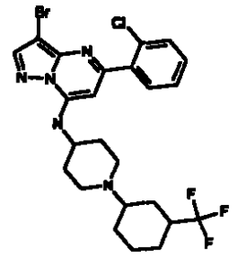
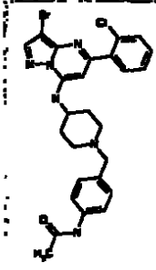
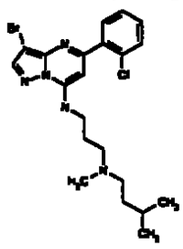
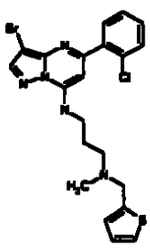
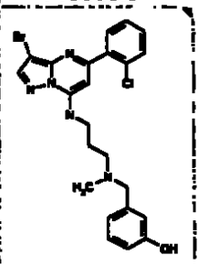
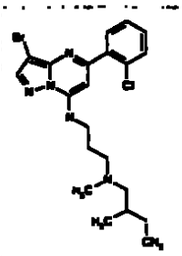
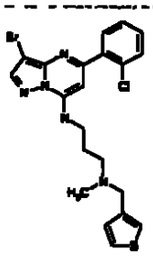
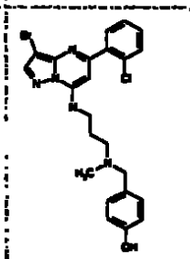
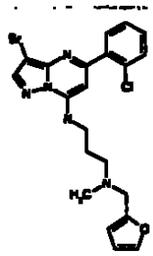
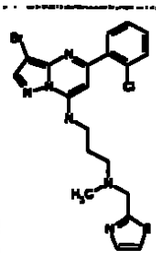
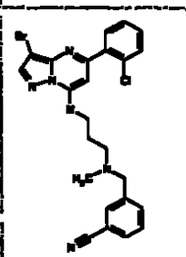
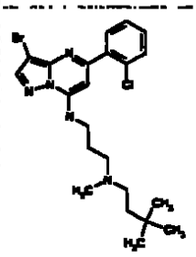
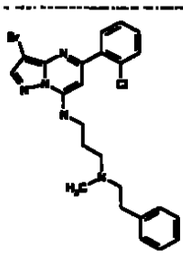
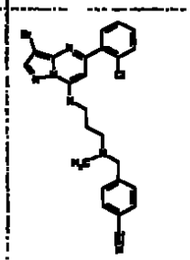
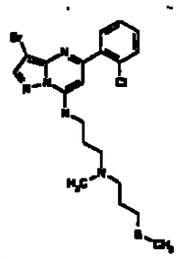
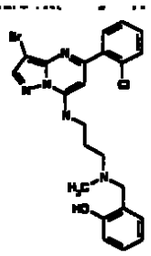
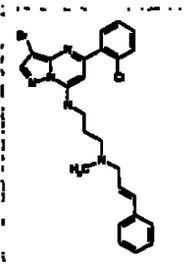
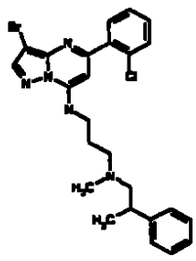
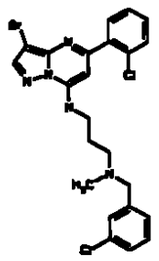
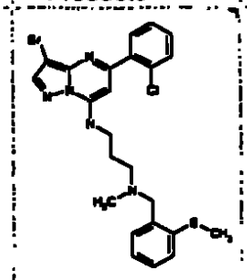
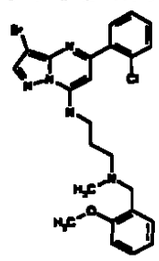
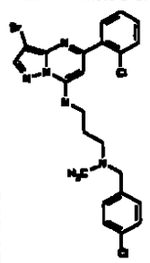
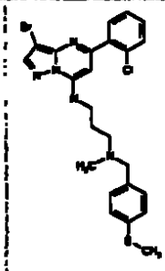
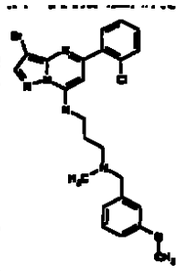
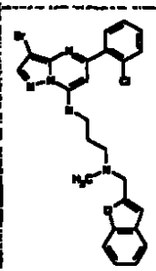
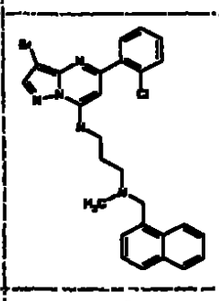
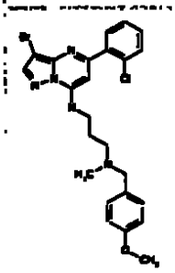
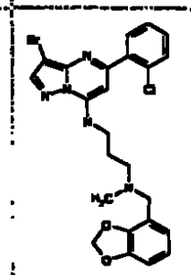
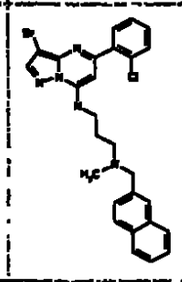
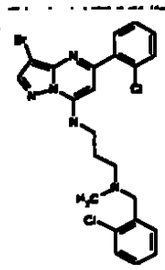
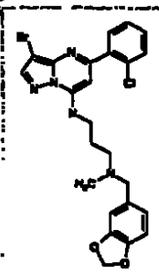
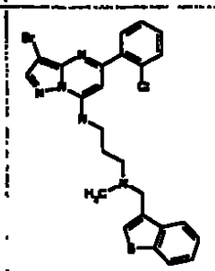
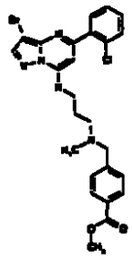
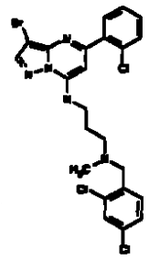
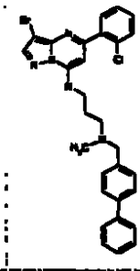
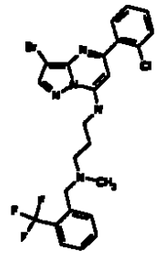
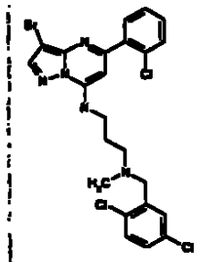
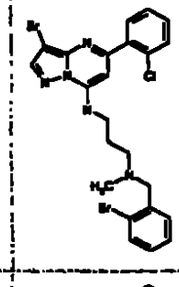
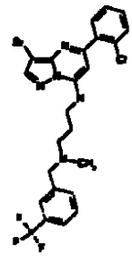
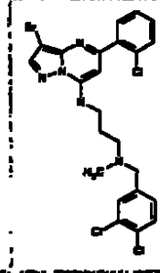
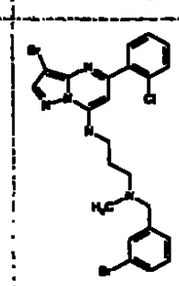
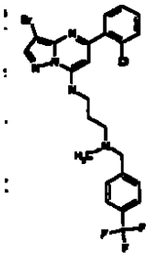
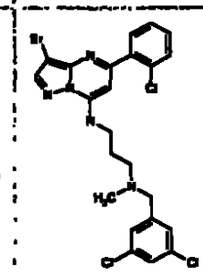
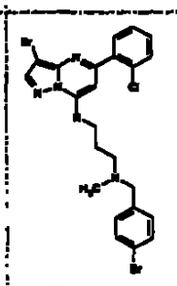
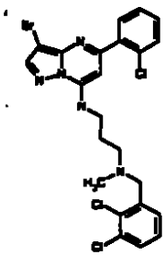
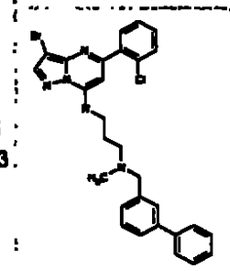
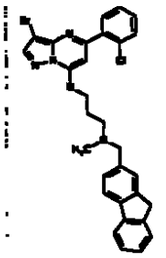
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8261 2. 544.3		1. 8266 2. 560.31
	1. 8262 2. 546.3		1. 8267 2. 586.31
	1. 8263 2. 546.3		1. 8268 2. 591.33
	1. 8264 2. 558.31		1. 8269 2. 595.33
	1. 8265 2. 558.31		1. 8270 2. 555.31

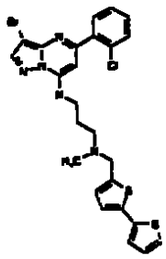
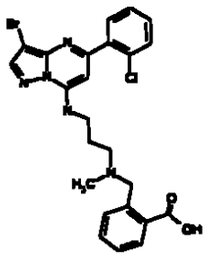
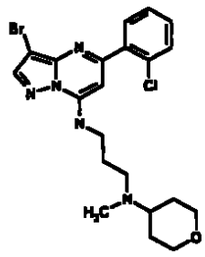
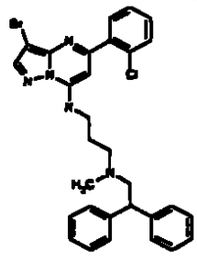
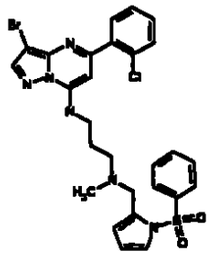
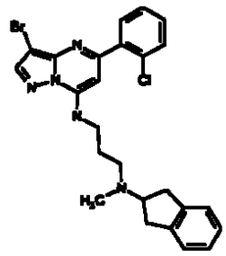
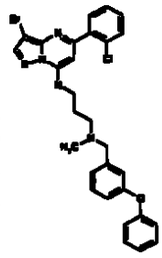
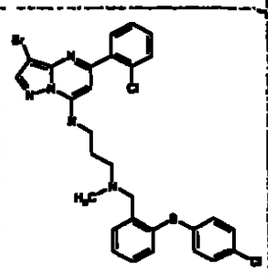
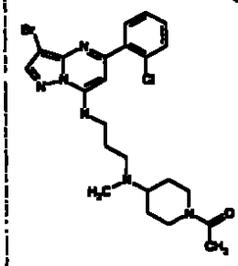
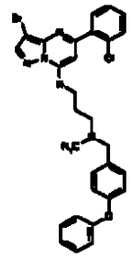
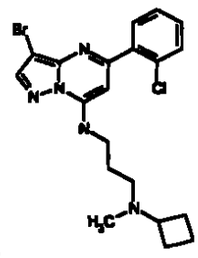
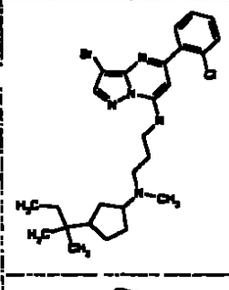
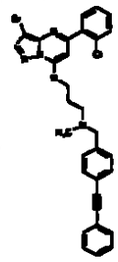
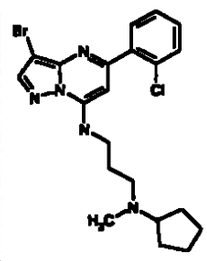
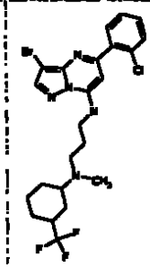
TABLA 83

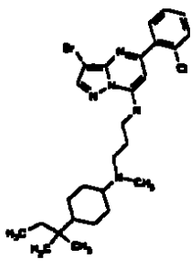
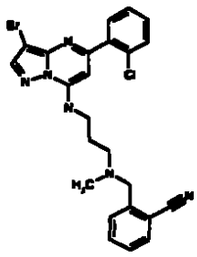
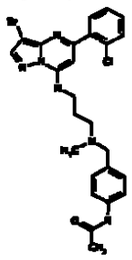
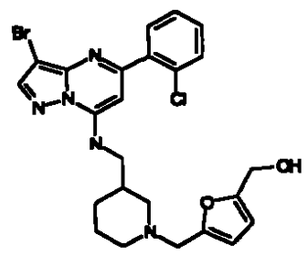
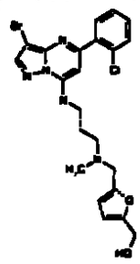
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2.m/z	Producto	1. Ej. 2. m/z
	1. 8301 2. 465.882		1. 8306 2. 491.79		1. 8311 2. 501.825
	1. 8302 2. 465.885		1. 8307 2. 491.792		1. 8312 2. 501.833
	1. 8303 2. 475.827		1. 8308 2. 492.787		1. 8313 2. 510.822
	1. 8304 2. 479.89		1. 8309 2. 499.846		1. 8314 2. 510.821
	1. 8305 2. 483.829		1. 8310 2. 501.826		1. 8315 2. 511.841

890
893

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8316 2. 513.855		1. 8321 2. 519.783		1. 8326 2. 531.804
	1. 8317 2. 515.832		1. 8322 2. 519.781		1. 8327 2. 531.812
	1. 8318 2. 515.832		1. 8323 2. 525.813		1. 8328 2. 535.83
	1. 8319 2. 515.837		1. 8324 2. 529.806		1. 8329 2. 535.831
	1. 8320 2. 519.782		1. 8325 2. 529.81		1. 8330 2. 541.788

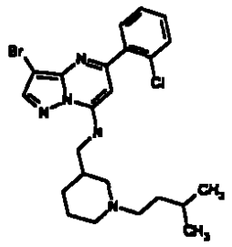
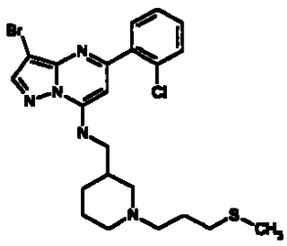
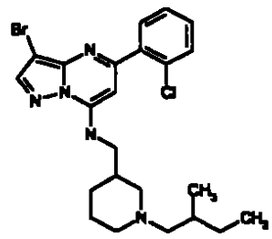
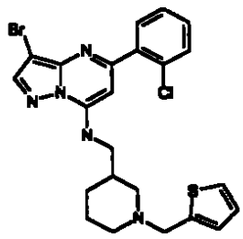
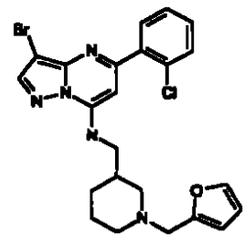
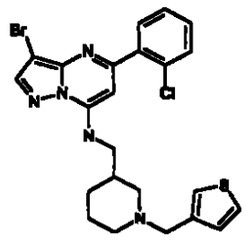
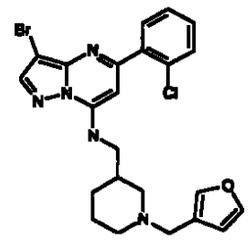
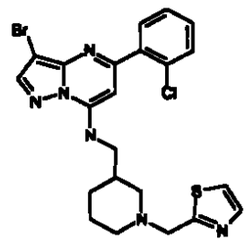
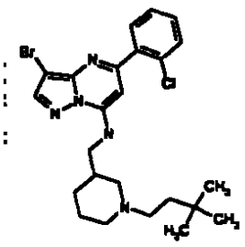
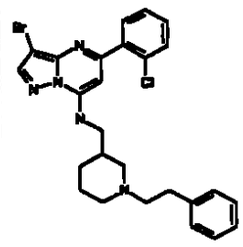
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8331 2. 543.821		1. 8336 2. 554.727		1. 8341 2. 561.838
	1. 8332 2. 553.797		1. 8337 2. 554.738		1. 8342 2. 564.714
	1. 8333 2. 553.796		1. 8338 2. 554.738		1. 8343 2. 564.704
	1. 8334 2. 553.795		1. 8339 2. 554.727		1. 8344 2. 564.72
	1. 8335 2. 554.73		1. 8340 2. 561.836		1. 8345 2. 573.823

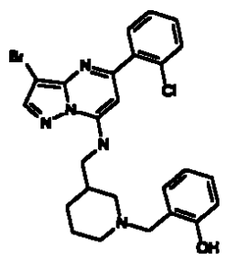
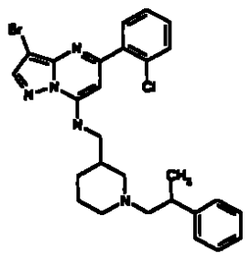
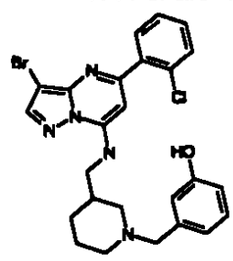
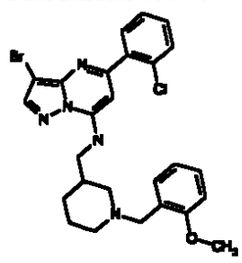
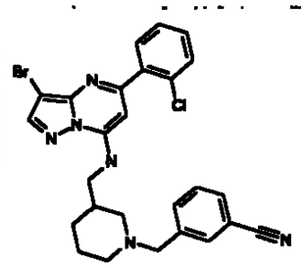
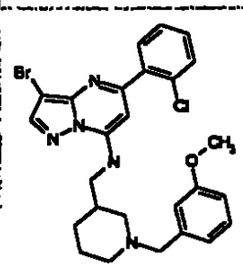
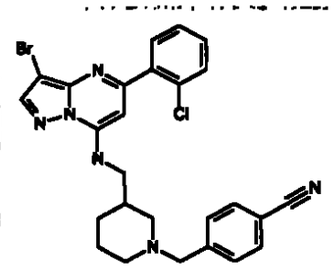
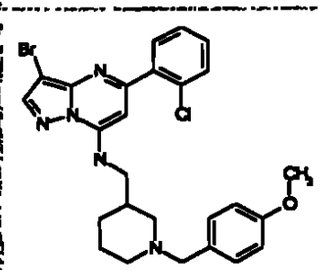
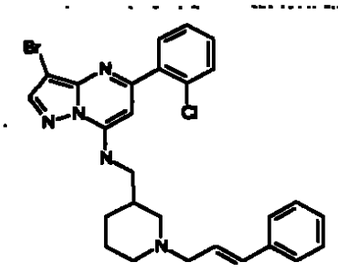
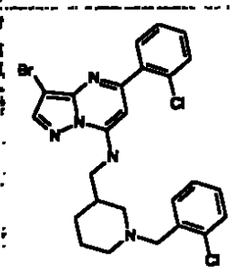
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8346 2. 573.735		1. 8351 2. 529.808		1. 8356 2. 479.856
	1. 8347 2. 575.839		1. 8352 2. 614.763		1. 8357 2. 511.842
	1. 8348 2. 577.818		1. 8353 2. 628.727		1. 8358 2. 520.859
	1. 8349 2. 577.814		1. 8354 2. 449.857		1. 8359 2. 533.903
	1. 9350 2. 585.818		1. 8355 2. 463.867		1. 8360 2. 545.823

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

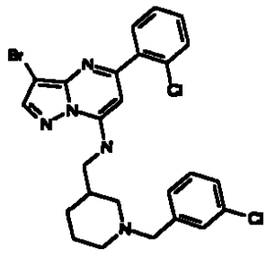
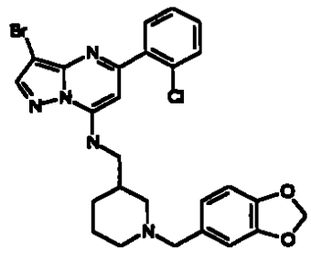
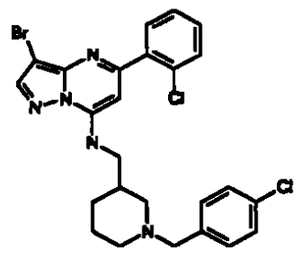
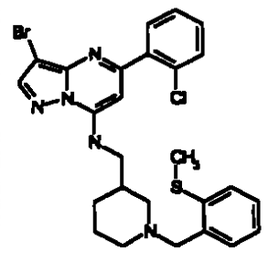
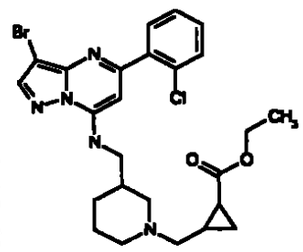
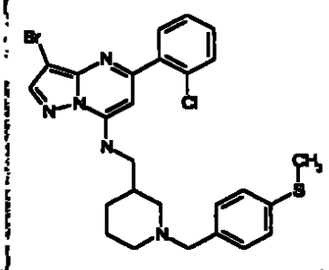
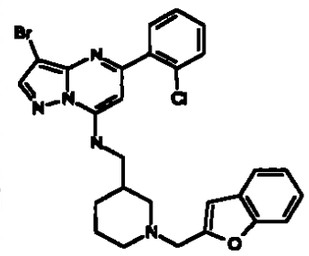
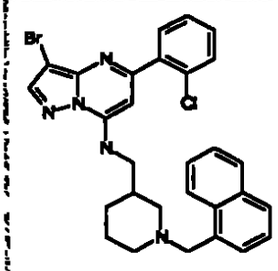
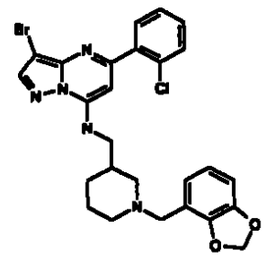
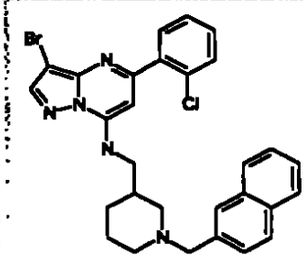
894
897

TABLA 84

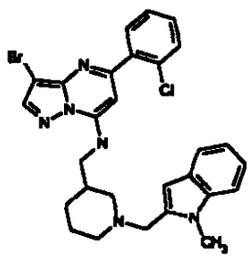
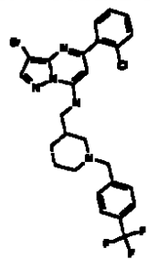
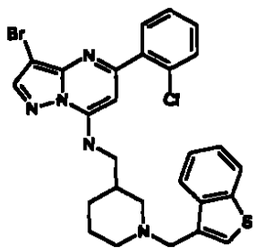
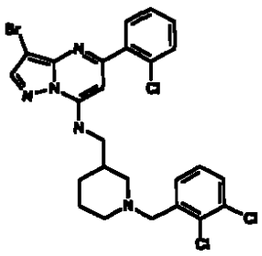
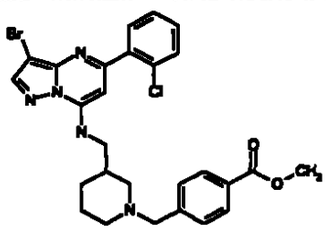
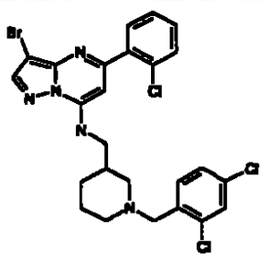
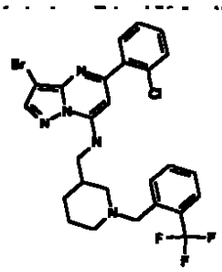
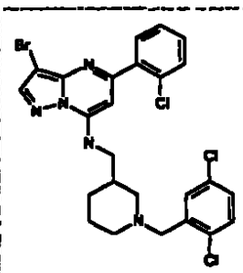
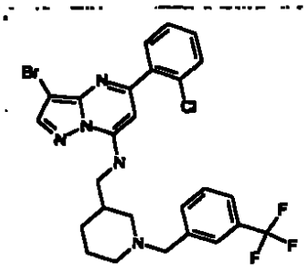
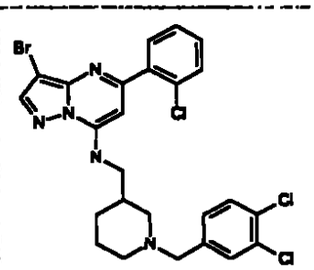
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8401 2. 491.883		1. 8406 2. 509.829
	1. 8402 2. 491.883		1. 8407 2. 517.795
	1. 8403 2. 501.823		1. 8408 2. 517.799
	1. 8404 2. 501.827		1. 8409 2. 518.796
	1. 8405 2. 505.89		1. 8410 2. 525.851

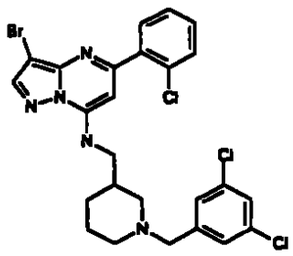
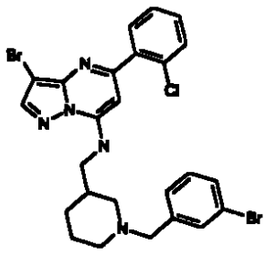
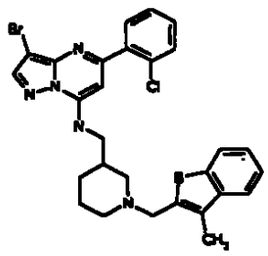
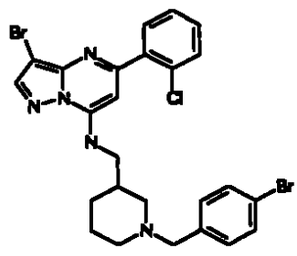
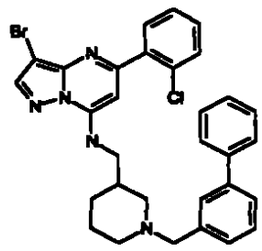
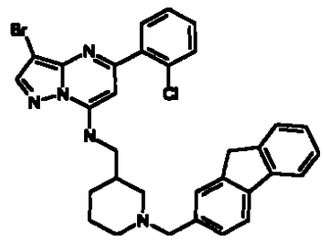
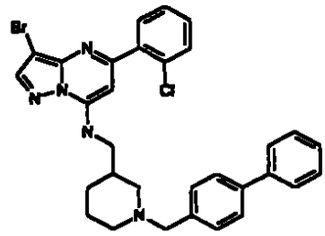
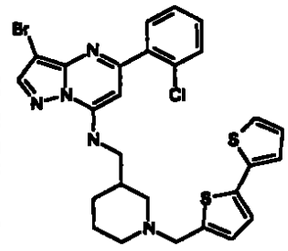
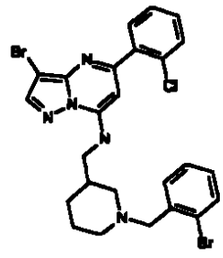
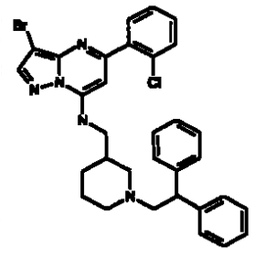
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8411 2. 527.831		1. 8416 2. 539.859
	1. 8412 2. 527.833		1. 8417 2. 541.84
	1. 8413 2. 536.833		1. 8418 2. 541.843
	1. 8414 2. 536.829		1. 8419 2. 541.843
	1. 8415 2. 537.845		1. 8420 2. 546.788

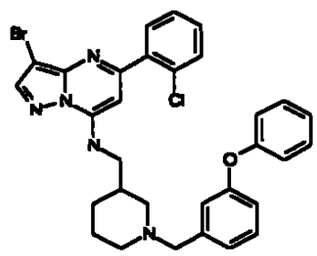
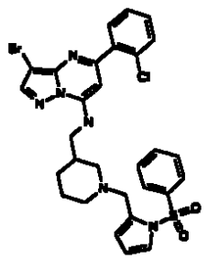
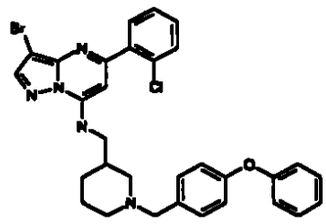
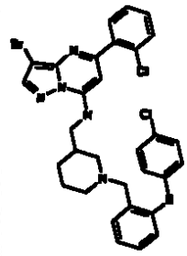
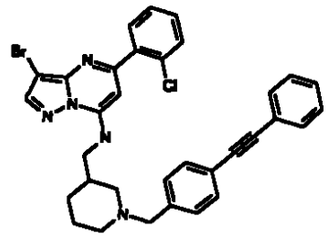
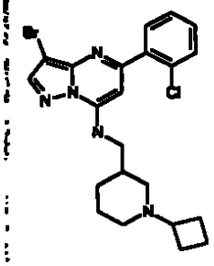
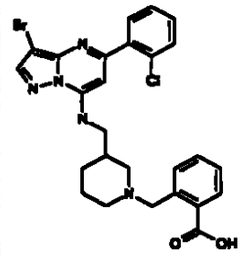
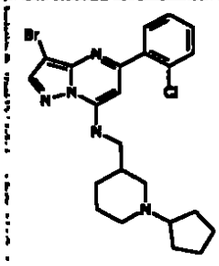
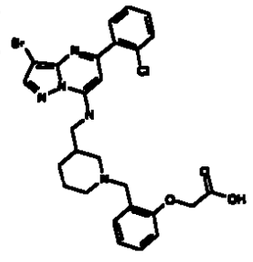
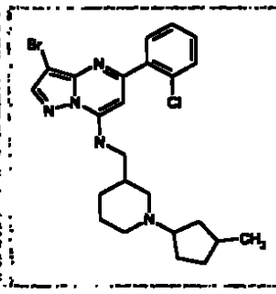
896
899

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

897
900

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8431 2. 564.841		1. 8436 2. 579.794
	1. 8432 2. 567.795		1. 8437 2. 580.738
	1. 8433 2. 569.823		1. 8438 2. 580.732
	1. 8434 2. 579.797		1. 8439 2. 580.733
	1. 8435 2. 579.796		1. 8440 2. 580.734

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8441 2. 580.726		1. 8446 2. 590.726
	1. 8442 2. 581.805		1. 8447 2. 590.724
	1. 8443 2. 587.844		1. 8448 2. 599.834
	1. 8444 2. 587.835		1. 8449 2. 599.749
	1. 8445 2. 590.723		1. 8450 2. 601.854

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8451 2. 603.831		1. 8456 2. 640.779
	1. 8452 2. 603.83		1. 8457 2. 654.746
	1. 8453 2. 611.83		1. 8458 2. 475.871
	1. 8454 2. 555.824		1. 8459 2. 489.879
	1. 8455 2. 585.817		1. 8460 2. 503.885

400
903

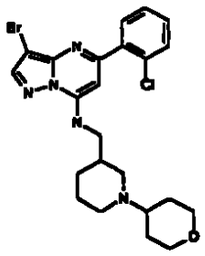
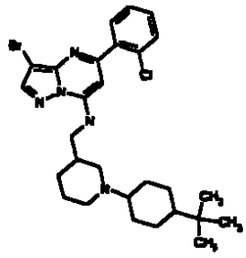
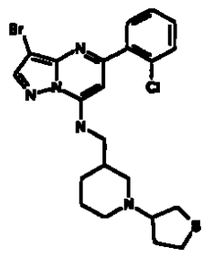
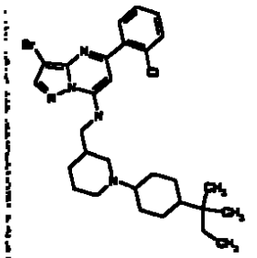
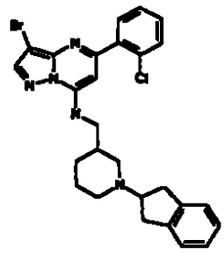
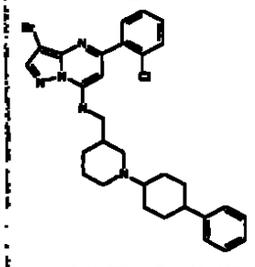
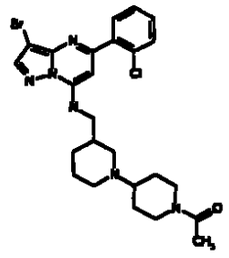
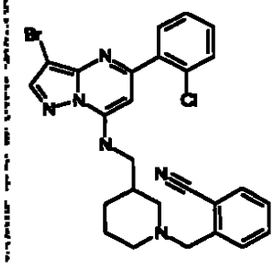
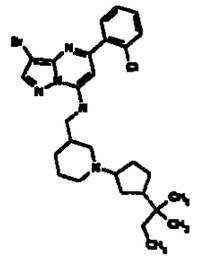
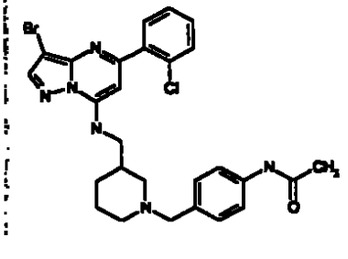
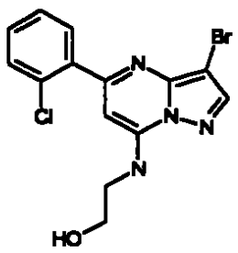
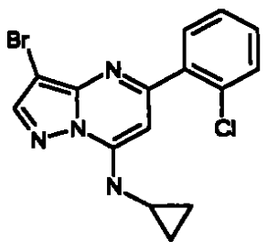
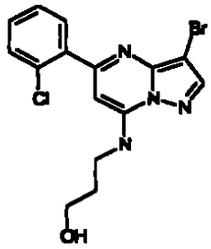
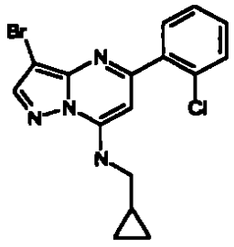
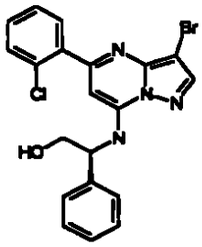
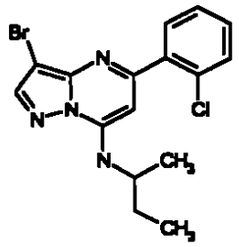
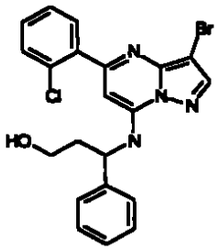
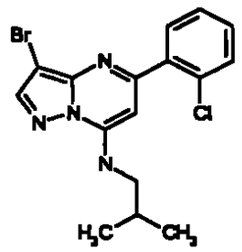
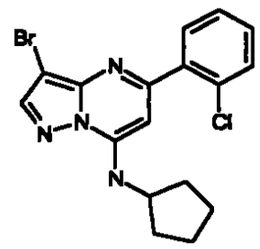
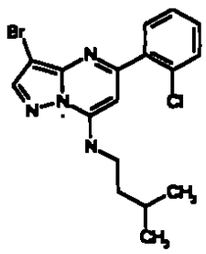
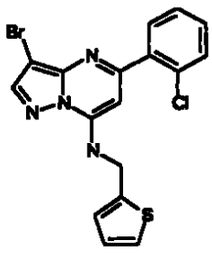
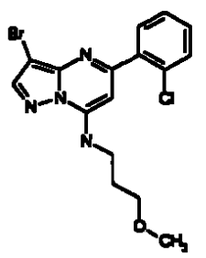
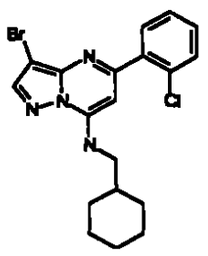
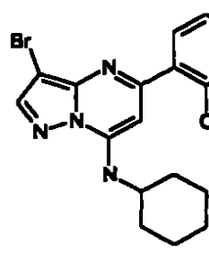
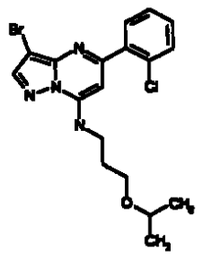
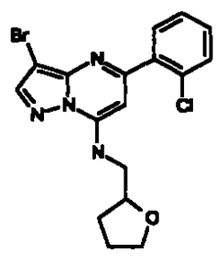
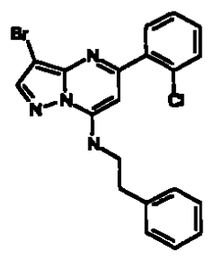
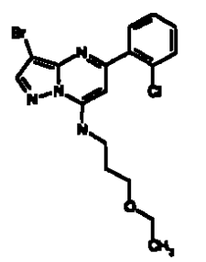
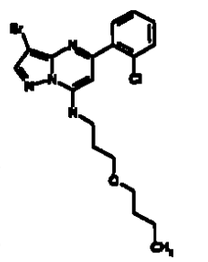
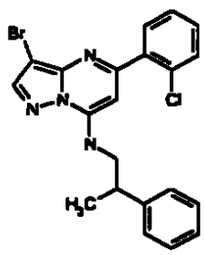
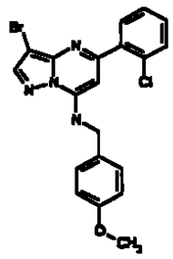
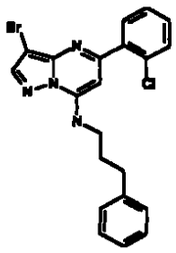
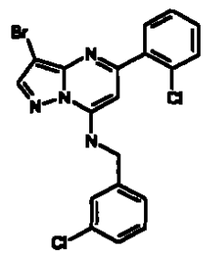
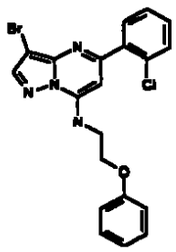
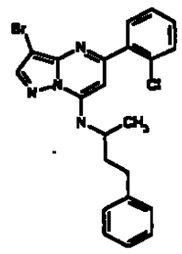
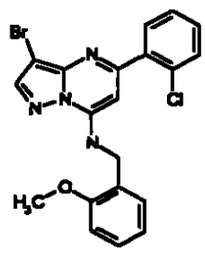
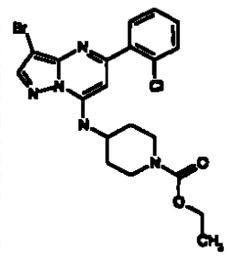
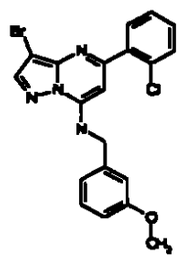
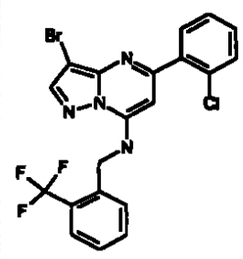
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8461 2. 505.866		1. 8466 2. 559.919
	1. 8462 2. 507.828		1. 8467 2. 573.925
	1. 8463 2. 537.859		1. 8468 2. 579.876
	1. 8464 2. 546.877		1. 8469 2. 536.831
	1. 8465 2. 559.921		1. 8470 2. 568.843

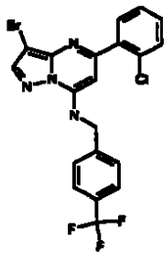
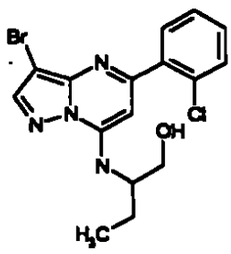
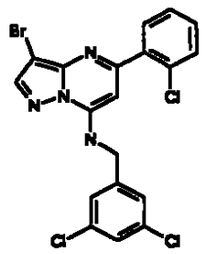
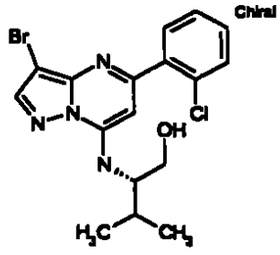
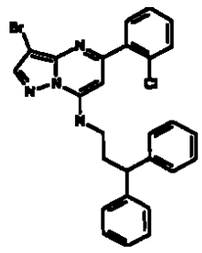
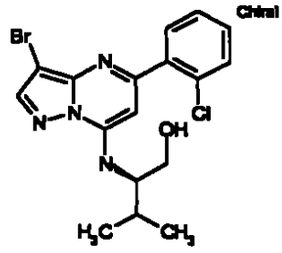
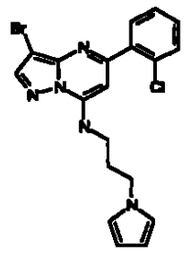
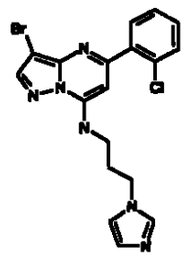
TABLA 85

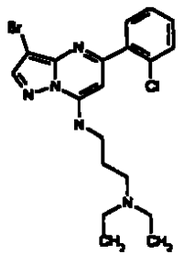
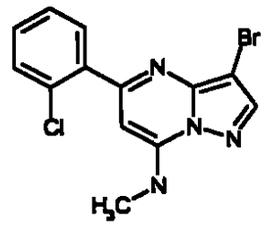
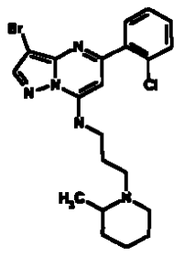
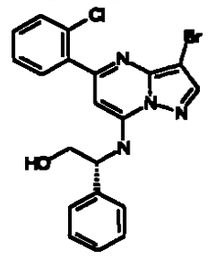
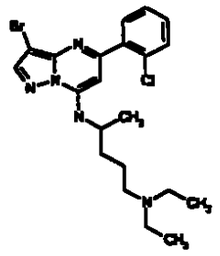
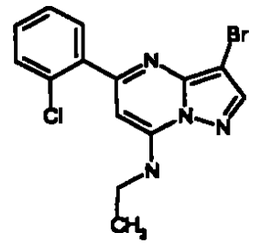
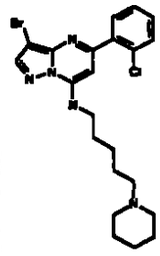
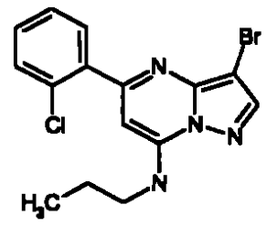
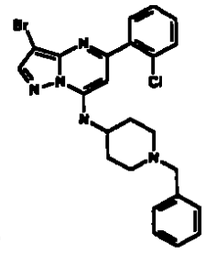
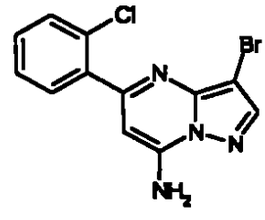
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1.8501 2. 367.2		1. 8506 2. 443.1
	1. 8502 2. 381.2		1. 8507 2. 323.1
	1. 8503 2. 443.2		1. 8508 2. 385.2
	1. 8504 2. 457.3		1. 8509 2. 379.21
			1. 8510 2. 381.21

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8511 2. 381.21		1. 8516 2. 409.22
	1. 8512 2. 393.22		1. 8517 2. 411.23
	1. 8513 2. 395.22		1. 8518 2. 421.23
	1. 8514 2. 397.22		1. 8519 2. 421.23
	1. 8515 2. 407.22		1. 8520 2. 425.23

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

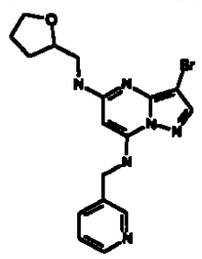
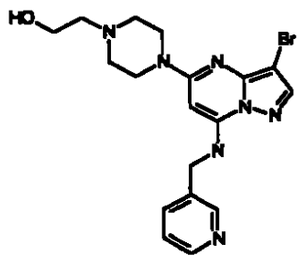
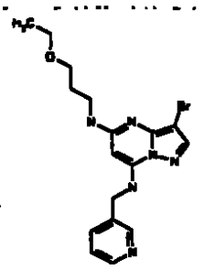
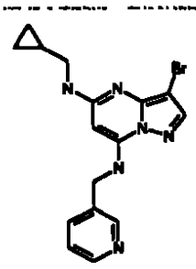
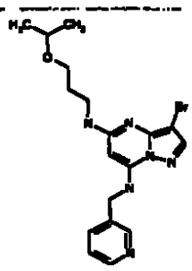
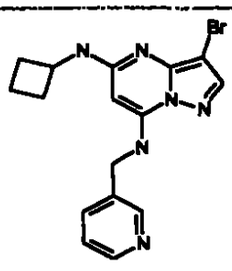
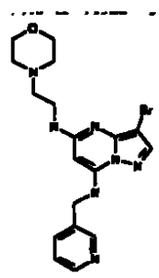
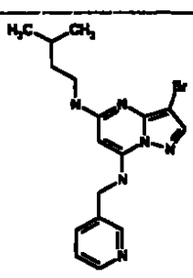
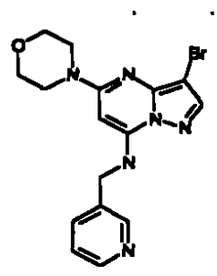
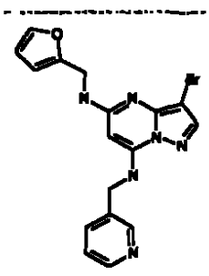
904
907

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

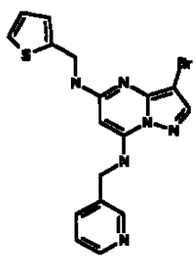
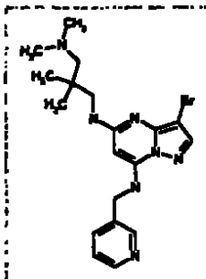
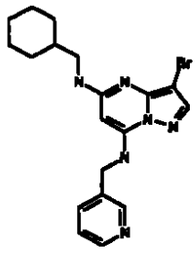
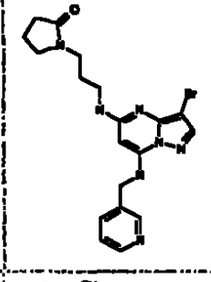
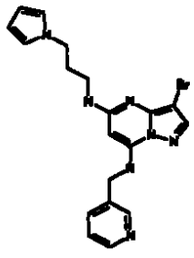
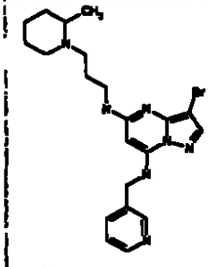
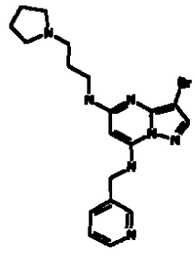
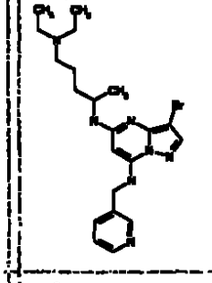
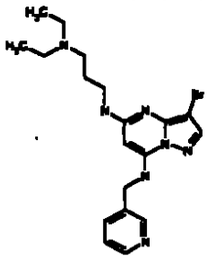
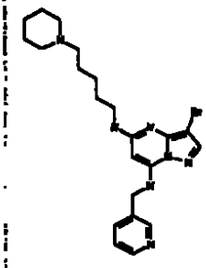
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8541 2. 432.24		1. 8547 2. 478.26
	1. 8542 2. 433.24		1. 8548 2. 498.27
	1. 8543 2. 438.24		1. 8549 2. 365.1
	1. 8545 2. 464.28		1. 8549 2. 337.1
	1. 8546 2. 466.26		1. 8550 2. 351.1

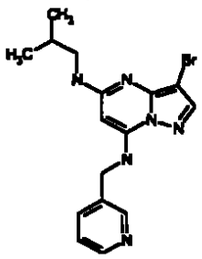
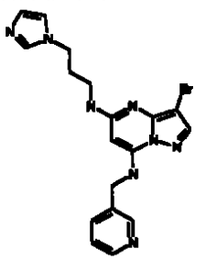
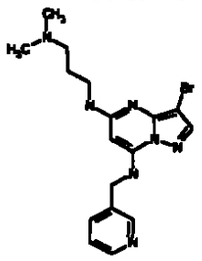
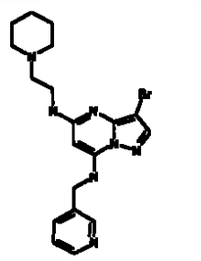
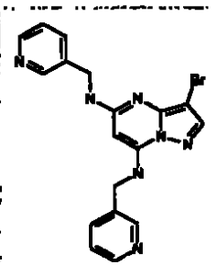
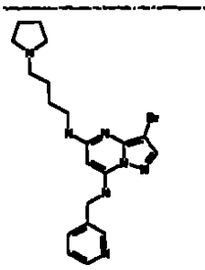
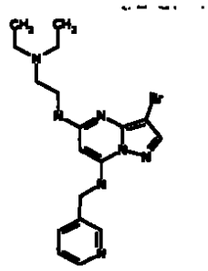
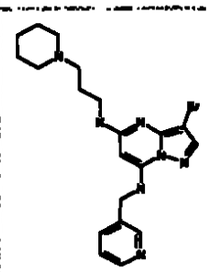
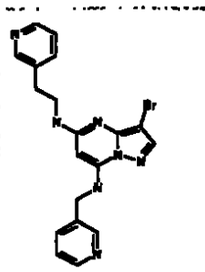
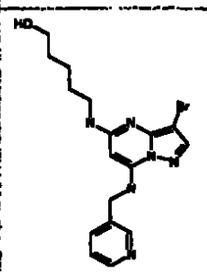
906
909

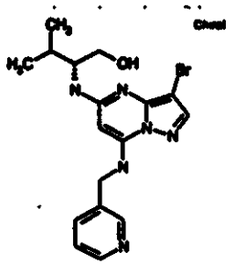
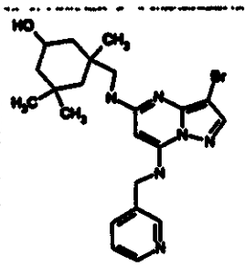
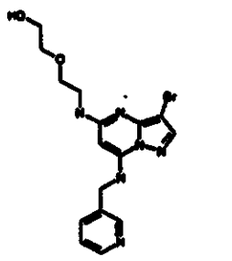
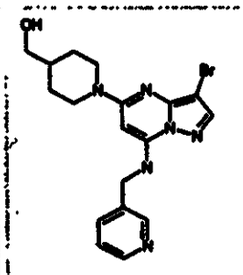
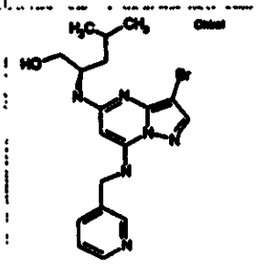
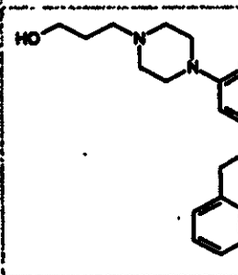
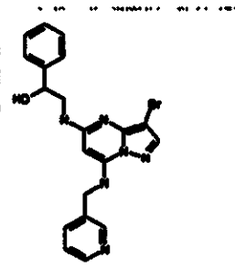
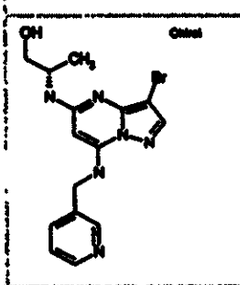
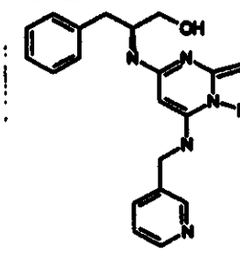
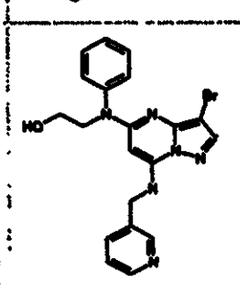
TABLA 86

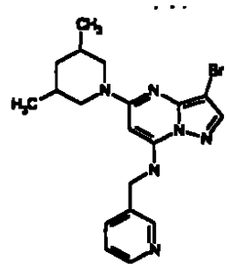
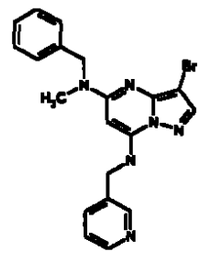
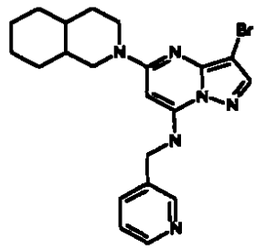
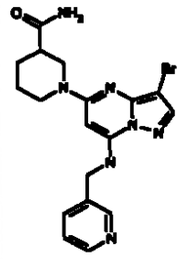
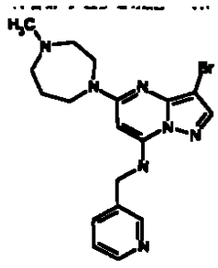
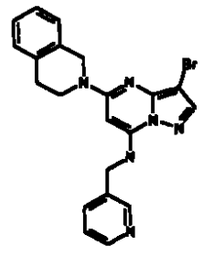
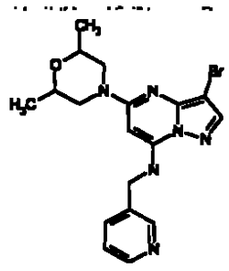
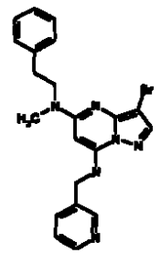
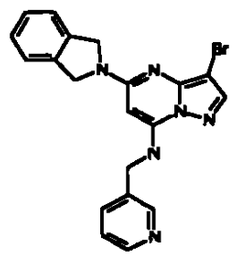
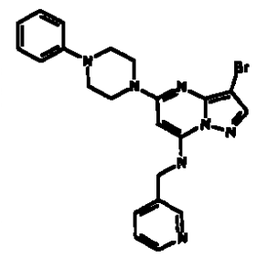
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8601 2. 403.22		1. 8606 2. 434.24
	1. 8602 2. 407.22		1. 8607 2. 375.21
	1. 8603 2. 421.23		1. 8608 2. 375.21
	1. 8604 2. 434.24		1. 8609 2. 391.22
	1. 8605 2. 391.22		1. 8610 2. 399.22

909
910

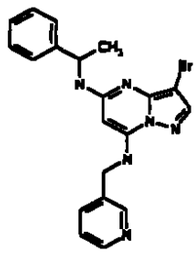
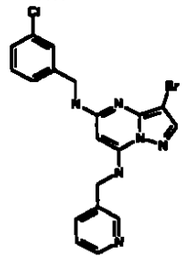
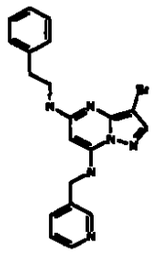
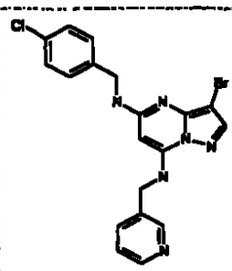
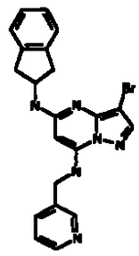
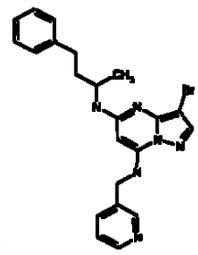
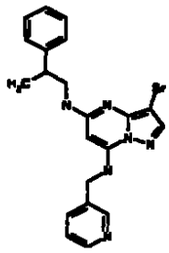
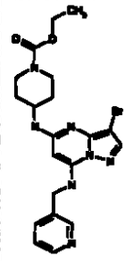
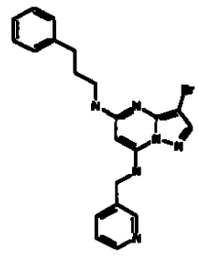
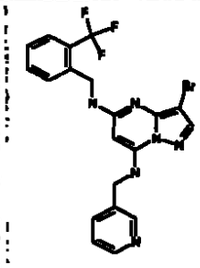
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8611 2. 417.23		1. 8616 2. 434.24
	1. 8612 2. 415.23		1. 8617 2. 446.25
	1. 8613 2. 428.24		1. 8618 2. 460.25
	1. 8614 2. 430.24		1. 8619 2. 459.25
	1. 8615 2. 434.24		1. 8620 2. 474.26

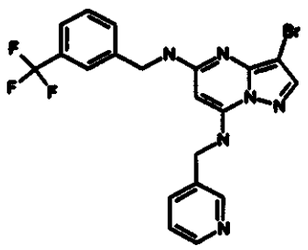
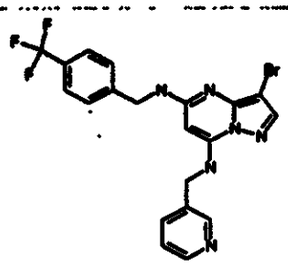
Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8621 2. 377.21		1. 8626 2. 427.23
	1. 8622 2. 406.22		1. 8627 2. 431.24
	1. 8623 2. 412.23		1. 8628 2. 446.25
	1. 8624 2. 420.23		1. 8629 2. 446.25
	1. 8625 2. 426.23		1. 8630 2. 407.2

Producto	1. Ej. 2. m/z	Producto	1. Ej. 2. m/z
	1. 8631 2. 407.2		1. 8636 2. 475.3
	1. 8632 2. 409.2		1. 8637 2. 419.2
	1. 8633 2. 421.2		1. 8638 2. 448.2
	1. 8634 2. 439.2		1. 8639 2. 379.2
	1. 8635 2. 455.3		1. 8640 2. 437.2

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

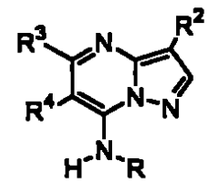
911
914

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

Producto	1. Ej. 2. m/z
	1. 8661 2. 477.26
	1. 8662 2. 479.26

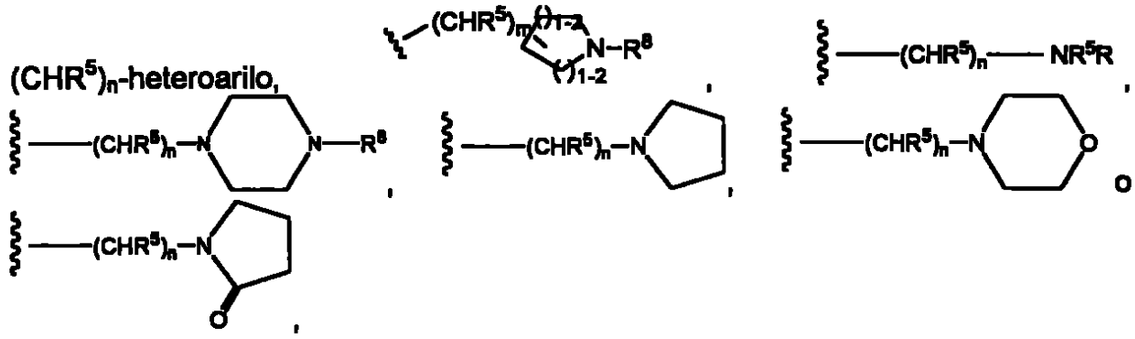
REIVINDICACIONES

1. Un compuesto representado por la fórmula estructural:



o una sal o solvato farmacéuticamente aceptable de dicho compuesto, donde:

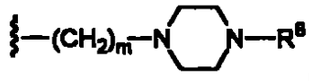
R is H, alquilo, alquenilo, alquinilo, arilalquilo, arilalquenilo, cicloalquilo, cicloalquilalquilo, alquenilalquilo, alquinilalquilo, heterociclilo, heterociclilalquilo, heteroarilalquilo (incluyendo el N-óxido de dicho heteroarilo), -$(CHR^5)_n$-arilo, -$(CHR^5)_n$-heteroarilo,

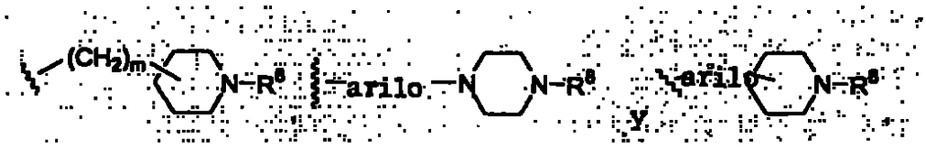


donde cada uno de dichos alquilo, alquenilo, alquinilo, arilo, cicloalquilo, heterociclilo, y heteroarilo pueden estar no sustituidos o pueden estar opcionalmente insustituidos con una o más porciones que pueden ser iguales o diferentes, donde cada porción está independientemente seleccionada del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, heterociclilalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^{10}$, $-C(R^4R^5)_p-R^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^{10}$, $-SO_3H$, $-SR^{10}$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^{10}$;

R^2 está seleccionado del grupo que consiste en R^8, alquilo, alquenilo, alquinilo, CF_3, heterociclilo, heterociclilalquilo, halógeno, haloalquilo, arilo, arilalquilo, heteroarilalquilo, alquinilalquilo, cicloalquilo, heteroarilo alquilo

sustituido con 1-6 grupos R^9 que pueden ser iguales o diferentes y que están independientemente seleccionados de la lista de R^9 que se muestra en lo que sigue, arilo sustituido con 1-3 grupos arilo o heteroarilo que pueden ser iguales o diferentes y que están independientemente seleccionados entre los grupos fenilo, piridilo, tiofenilo, furanilo y tiazolo, arilo fusionado con un grupo arilo o heteroarilo, heteroarilo sustituido con 1-3 grupos arilo o heteroarilo que pueden ser iguales o diferentes y que están independientemente seleccionados de los grupos que consisten en fenilo, piridilo, tiofenilo, furanilo y tiazolo, heteroarilo fusionado con

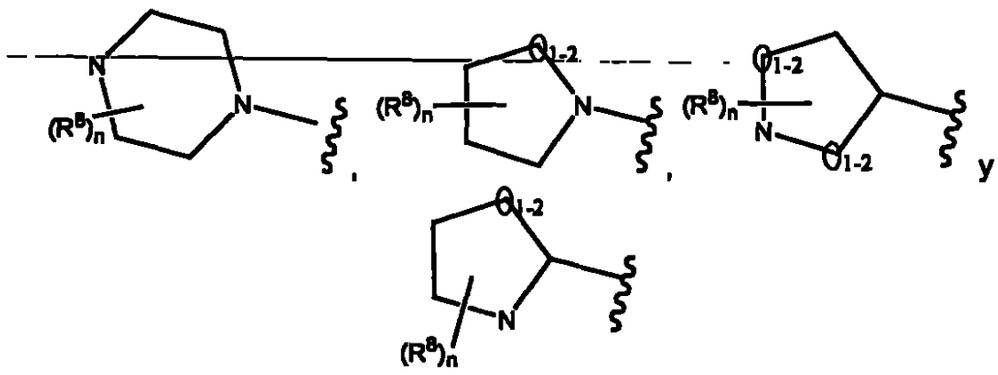
un grupo arilo o heteroarilo,  ,



donde uno o más de los arilo y/o uno o más de los heteroarilo en las definiciones previamente indicadas para R^2 puede estar no sustituido o puede estar opcionalmente sustituido con una o más porciones que pueden ser iguales o diferentes, estando cada porción independientemente seleccionada del grupo que consiste en halógeno, -CN, $-OR^5$, $-SR^5$, $-S(O_2)R^6$, $-S(O_2)NR^5R^6$, $-NR^5R^6$, $-C(O)NR^5R^6$, CF_3, alquilo, arilo y OCF_3;

R^3 está seleccionado del grupo que consiste en H, halógeno, $-NR^5R^6$, $-OR^6$, $-SR^6$, $-C(O)N(R^5R^6)$, alquilo, alquinilo, cicloalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heteroarilo y heteroarilalquilo,

05-20516 915 918



donde cada uno de dichos alquilo, cicloalquilo, arilo, arilalquilo, heterociclilo, heterociclilalquilo, heteroarilo y heteroarilalquilo para R^3 y las porciones heterociclilo cuyas estructuras se muestran inmediatamente en lo que antecede para R^3 pueden estar no sustituidas o pueden estar opcionalmente sustituidas independientemente con una o más porciones que pueden ser iguales o diferentes, donde cada porción está independientemente seleccionada del gurpo 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 condición de que ningún carbono adyacente a un átomo de nitrógeno en un anillo heterociclilo es portador de una porción– OR^5;

R^4 es H, halo o alquilo;

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

R^6 está seleccionado 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 pueden estar no sustituidos o pueden estar opcionalmente sustituidos con una o más porciones las cuales pueden ser iguales o diferentes, estando cada porción independientemente seleccionada del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, heterociclilalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^{10}$, $-C(R^4R^5)_p-R^9$, $-N(R^5)Boc$, -

OS-20516 916 919

$(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)R^5$, $-C(O)NR^5R^{10}$, $-SO_3H$, $-SR^{10}$, $-S(O_2)R^7$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^5R^{10}$;

R^{10} está seleccionado del grupo que consiste en H, alquilo, arilo, arilalquilo, cicloalquilo, heterociclilo, heterociclilalquilo, heteroarilo, y heteroarilalquilo, donde cada uno de dichos alquilo, arilo, arilalquilo, cicloalquilo, heterociclilo, heterociclilalquilo, heteroarilo y heteroarilalquilo pueden estar no sustituidos o pueden estar opcionalmente sustituidos con una o más porciones que pueden ser iguales o diferentes, estando cada porción independientemente seleccionada del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, heterociclilalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^4R^5$, $-C(R^4R^5)_p-R^9$, $-N(R^5)Boc$, $-(CR^4R^5)_pOR^5$, $-C(O_2)R^5$, $-C(O)NR^4R^5$, $-C(O)R^5$, $-SO_3H$, $-SR^5$, $-S(O_2)R^7$, $-S(O_2)NR^4R^5$, $-N(R^5)S(O_2)R^7$, $-N(R^5)C(O)R^7$ y $-N(R^5)C(O)NR^4R^5$;

u opcionalmente (i) R^5 y R^{10} en la porción $-NR^5R^{10}$, o (ii) R^5 y R^6 en la porción $-NR^5R^6$, pueden estar unidos conjuntamente para formar una porción cicloalquilo o heterociclilo, donde cada porción cicloalquilo o heterociclilo está no sustituida o está opcionalmente independientemente sustituida con uno o más grupos R^9;

R^7 está seleccionado del grupo que consiste en alquilo, cicloalquilo, arilo, arilalquenilo, heteroarilo, arilalquilo, heteroarilalquilo, heteroarilalquenilo y heterociclilo, donde cada uno de dichos alquilo, cicloalquilo, heteroarilalquilo, arilo, heteroarilo, y arilalquilo pueden estar no sustituidos o pueden estar opcionalmente independientemente sustituidos con una o más porciones que pueden ser iguales o diferentes, estando cada porción independientemente seleccionada del grupo que consiste en halógeno, alquilo, arilo, cicloalquilo, CF_3, OCF_3, CN, $-OR^5$, $-NR^5R^{10}$, $-CH_2OR^5$, $-C(O_2)R^5$, $-C(O)NR^5R^{10}$, $-C(O)R^5$, $-SR^{10}$, $-S(O_2)R^{10}$, $-S(O_2)NR^5R^{10}$, $-N(R^5)S(O_2)R^{10}$, $-N(R^5)C(O)R^{10}$ y $-N(R^5)C(O)NR^5R^{10}$;

977
920

R^8 está seleccionado del grupo que consiste en halógeno, R^6, $-OR^6$, $-C(O)NR^5R^{10}$, $-S(O_2)NR^5R^{10}$, $-C(O)R^7$, $-C(=N-CN)-NH_2$, $-C(=NH)-NHR^5$, heterociclilo, y $-S(O_2)R^7$;

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

m es 0 a 4;

n es 1 a 4; y

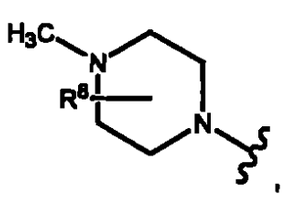
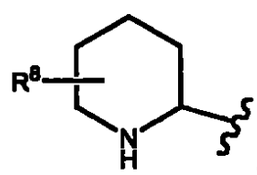
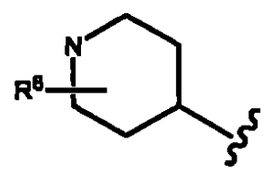
p es 1 a 4,

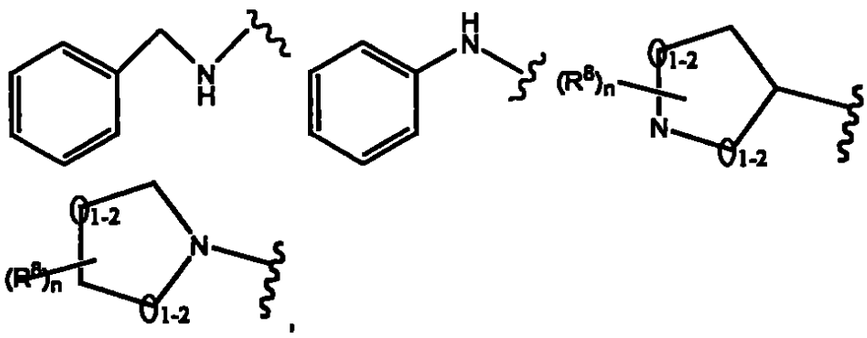
con la condición de que cuando R^2 es fenilo, R^3 no sea alquilo, alquinilo o halógeno, y que cuando R^2 es arilo, R no sea $\sim\!\!\sim\!\!-(CHR^5)_n-NR^5R$, y con la condición adicional de que cuando R es arilalquilo, entonces cualquier sustituyente heteroarilo en el arilo de dicho arilalquilo contenga por lo 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 pueden estar no sustituidos o pueden estar opcionalmente sustituidos con una o más porciones tal como se indica en la reivindicación 1;

R^2 es halógeno, alquilo, haloalquilo, CN, cicloalquilo, heterociclilo o alquinilo;

R^3 es H, alquilo inferior, arilo, heteroarilo, cicloalquilo, $-NR^5R^6$,


,

,

,



o

donde dicho alquilo, arilo, heteroarilo, cicloalquilo y las estructuras heterociclilo que se muestran inmediatamente en lo que antecede para R^3 están opcionalmente sustituidas con una o más porciones que pueden ser iguales o diferentes, donde cada porción está independientemente seleccionada del grupo que consiste en halógeno, CF_3, OCF_3, alquilo inferior, CN, $-C(O)R^5$, $-S(O_2)R^5$, $-C(=NH)-NH_2$, $-C(=CN)-NH_2$, hidroxialquilo, alcoxicarbonilo, $-SR^5$, y OR^5, con la condición de que ningún carbono adyacente a un átomo de nitrógeno en un anillo heterociclilo es portador de una porción $-OR^5$;

R^4 es H o alquilo inferior;

R^5 es H, alquilo inferior o cicloalquilo;

n es 1 a 2; y

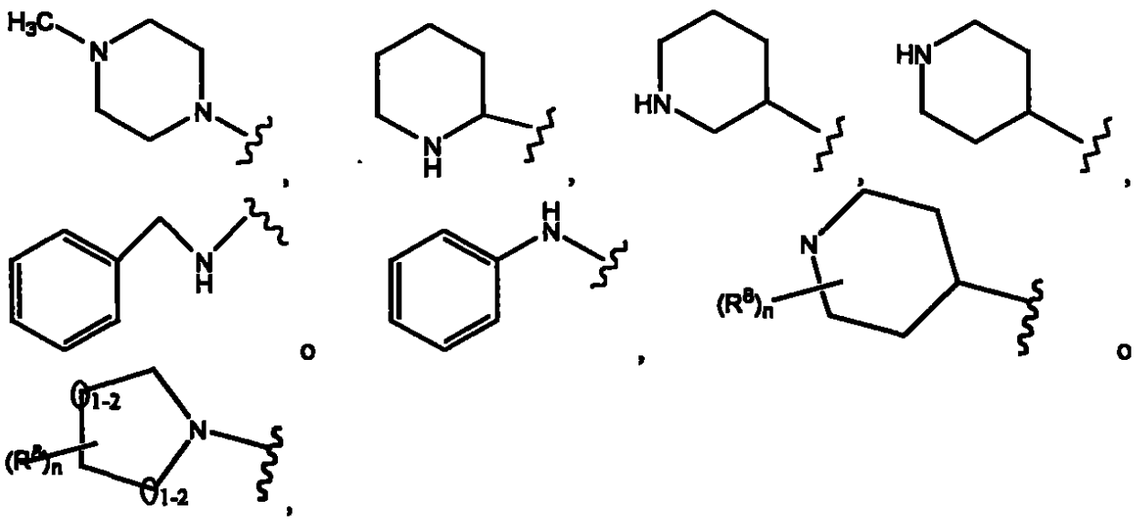
p es 1 ó 2.

3. El compuesto de la reivindicación 2, en el cual R es hidroxialquilo, $-(CHR^5)_n$-arilo, $-(CHR^5)_n$-heteroarilo, donde cada uno de dichos arilo y heteroarilo está no sustituido o sustituido con uno o más grupos que pueden ser iguales o diferentes, donde cada grupo está independientemente seleccionado 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.

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, donde R^3 es H, alquilo inferior, arilo,

heteroarilo, cicloalquilo,



donde cada uno de dichos alquilo, arilo, heteroarilo, cicloalquilo y las estructuras heterociclilo que se muestran inmediatamente en lo que antecede para R^3 están opcionalmente sustituidas con una o más porciones donde dichas porciones pueden ser iguales o diferentes, y cada porción está independientemente seleccionada del grupo que consiste en halógeno, CF_3, OCF_3, alquilo inferior, CN y OR^5, con la condición de que ningún carbono adyacente a un átomo de nitrógeno en un anillo heterociclilo es portador de una porción $-OR^5$.

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.

11. El compuesto de la reivindicación 2, en el cual R es pirid-3-ilmetilo, en el cual dicho piridilo puede estar no sustituido o puede estar independientemente

920
923

opcionalmente sustituido con una o más porciones tal como se indica en la reivindicación 1.

12. El compuesto de la reivindicación 2, en donde R es pirid-4-ilmetilo, donde dicho piridilo puede estar no sustituido o puede estar opcionalmente independientemente sustituido con una o más porciones tal como se indica en la reivindicación 1.

13. El compuesto de la reivindicación 2, en el cual R es el N-óxido de pirid-2-ilmetilo, pirid-3-ilmetilo, o pirid-4-ilmetilo, donde cada uno de dichos piridilo puede estar no sustituido o puede estar opcionalmente independientemente sustituido con una o más porciones tal como se indica 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, donde R^3 es isopropilo.

21. El compuesto de la reivindicación 19, donde R^3 es ciclohexilo o norbornilo donde cada uno de dicho ciclohexilo o norbornilo puede estar no sustituido o puede estar sustituido con una o más porciones que pueden ser iguales o diferentes, estando cada porción independientemente seleccionada del grupo que consiste en alquilo e hidroxialquilo.

22. El compuesto de la reivindicación 19, donde R^3 es fenilo no sustituido.

23. El compuesto de la reivindicación 19, donde R^3 es un fenilo sustituido con una o más porciones que pueden ser iguales o diferentes, donde cada porción está independientemente seleccionada del grupo que consiste en F, Br, Cl y CF_3.

924

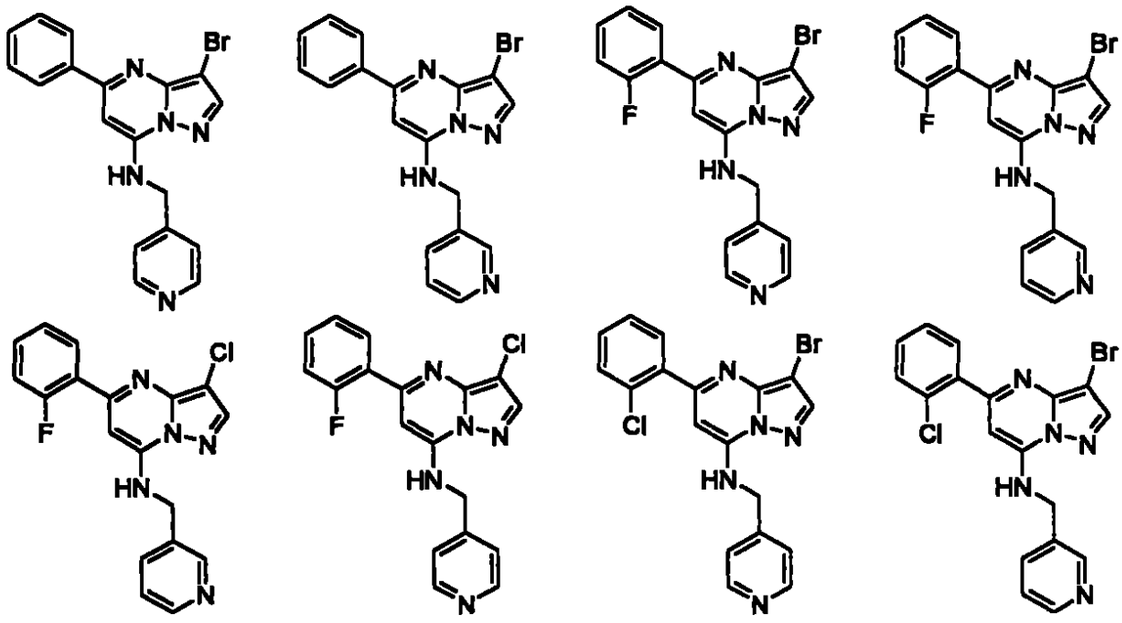
924

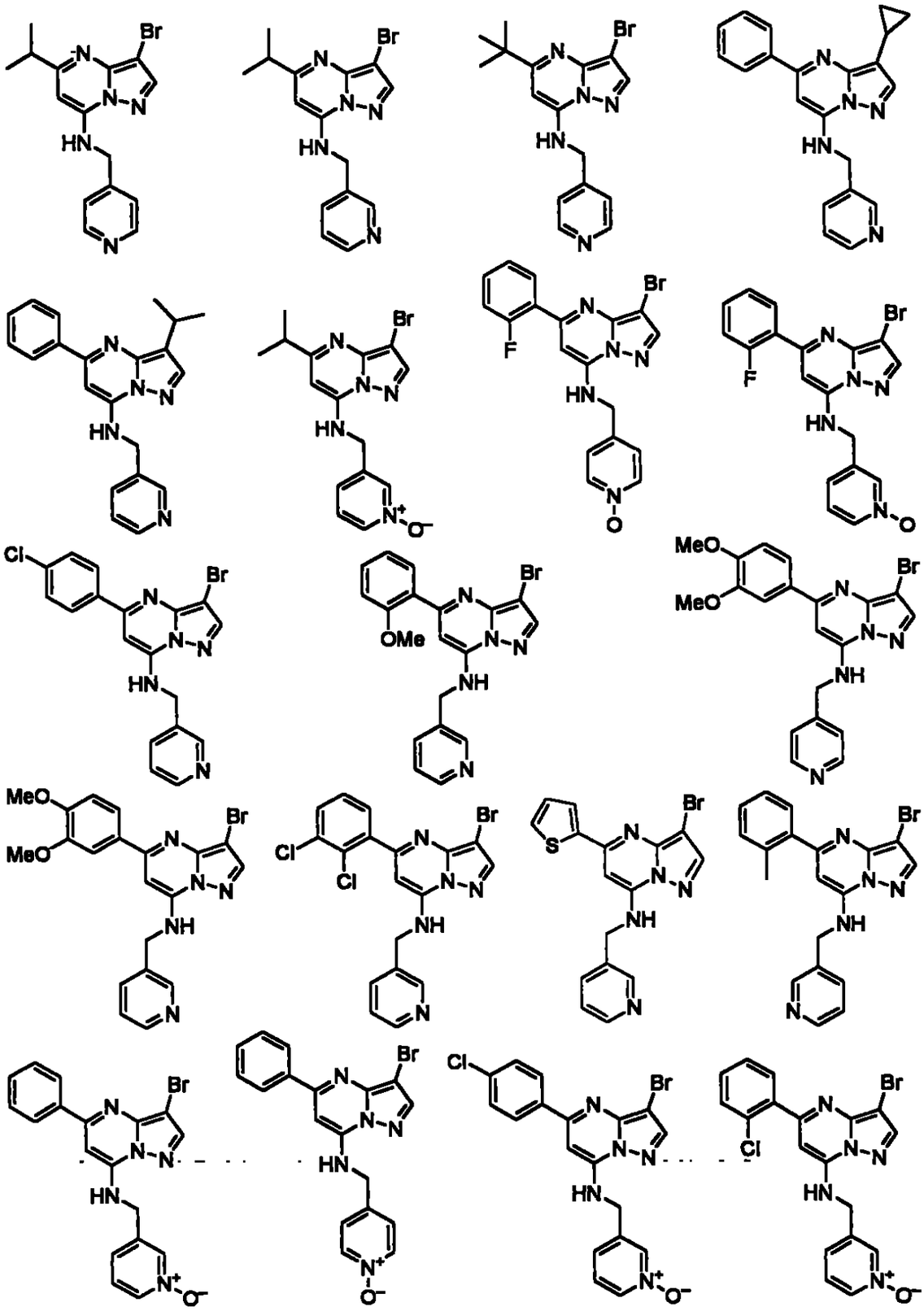
24. El compuesto de la reivindicación 19, donde R^5 de dicho $-N(R^5R^6)$ es H o hidroxialquilo, y R^6 de dicho $-N(R^5R^6)$ está seleccionado del grupo que consiste en alquilo, hidroxialquilo, cicloalquilo y metilendioxi, donde cada uno de dichos alquilo y cicloalquilo puede estar no sustituido o puede estar sustituido con una o más porciones que pueden ser iguales o diferentes, estando cada porción independientemente seleccionada del grupo que consiste en amina, etoxicarbonilo, amida, hidroxialquilo, hidroxi.

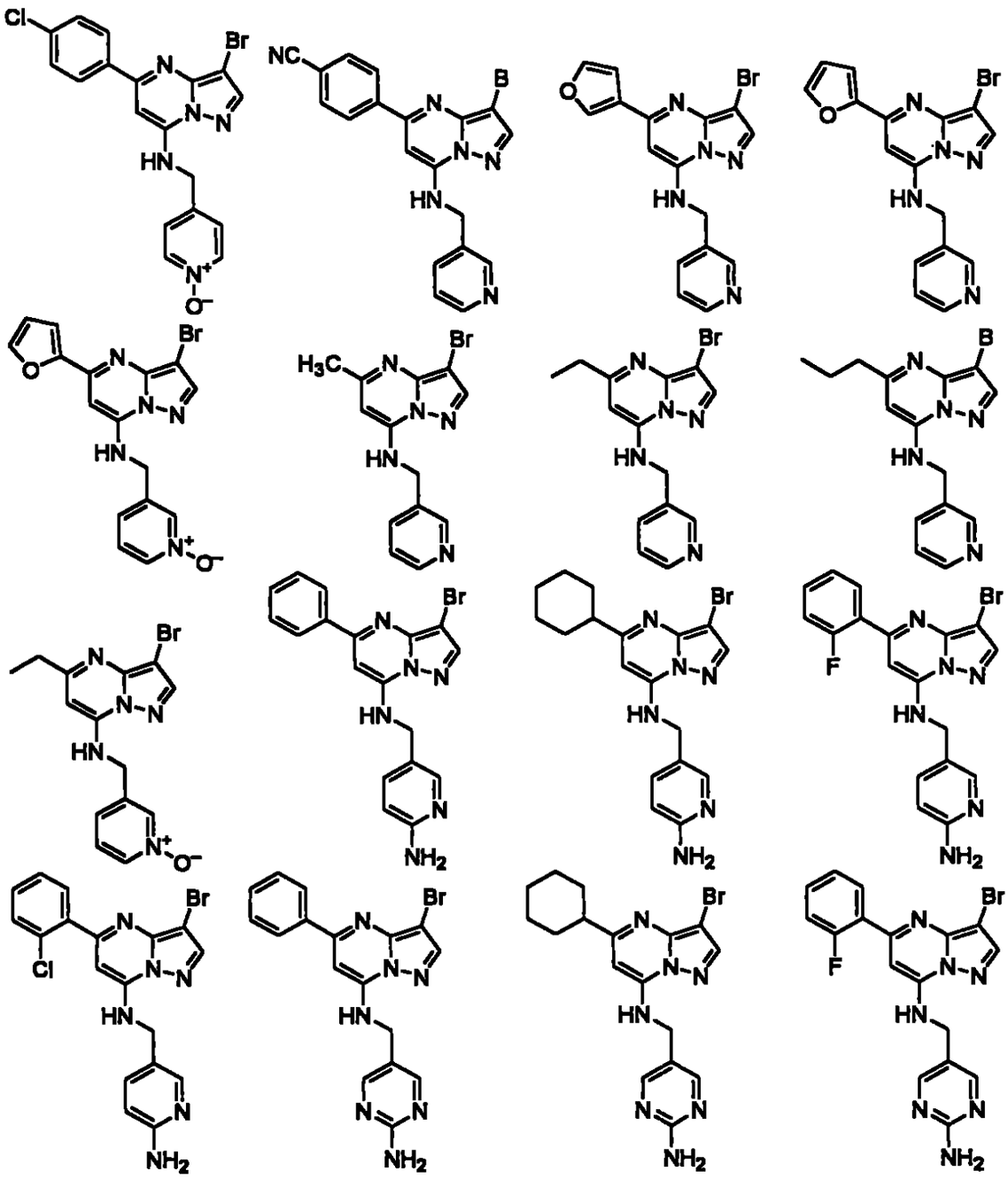
25. El compuesto de la reivindicación 19, donde R^5 y R^6 de dicho $-N(R^5R^6)$ están unidos conjuntamente para formar una porción heterociclilo, donde dicha porción heterociclilo puede estar no sustituida o puede estar opcionalmente independientemente sustituida con uno o más grupos que pueden ser iguales o diferentes, estando cada grupo seleccionado 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 $-C(=N\text{-}CN)N(R^5R^6)$.

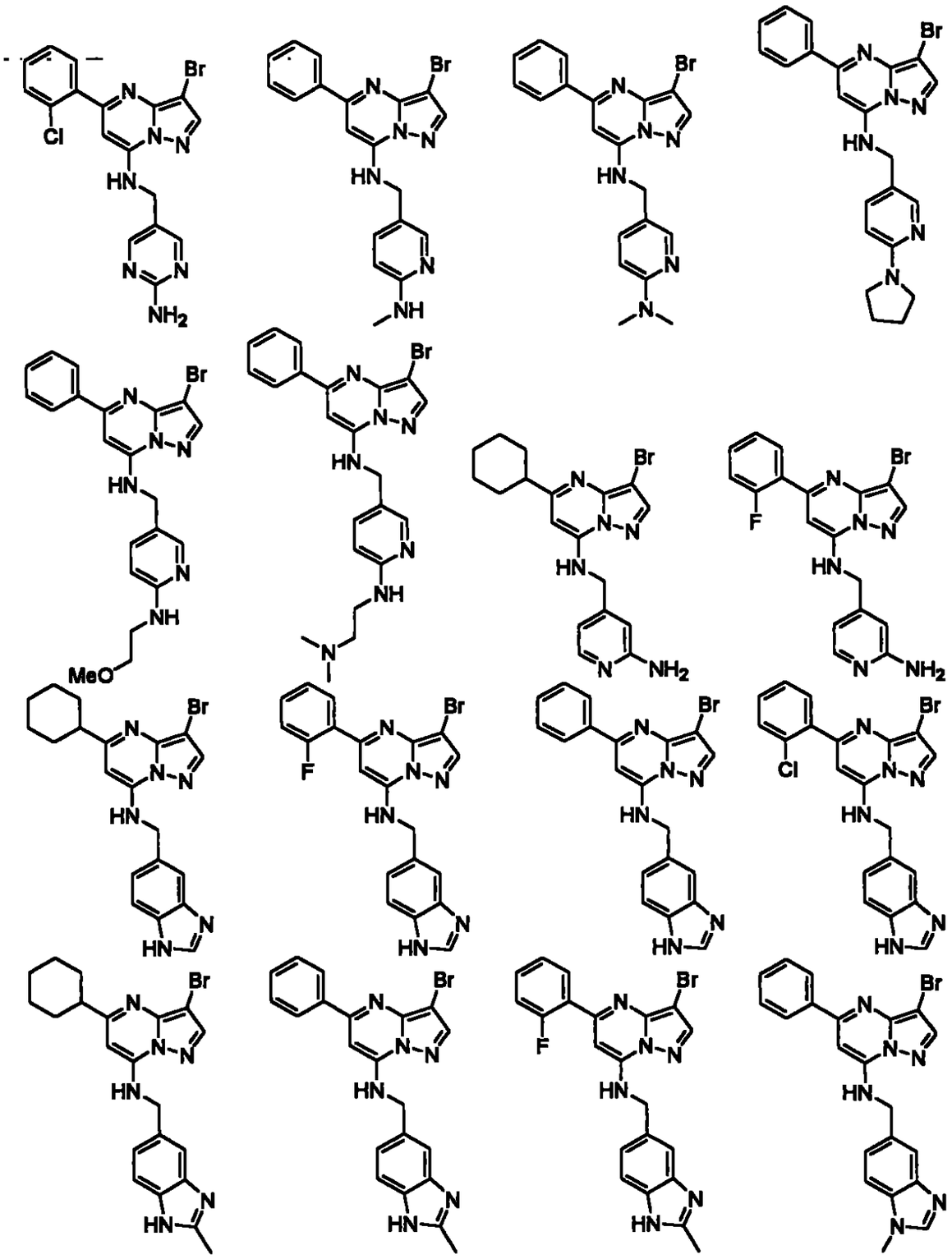
26. El compuesto de la reivindicación 25, en el cual dicha porción heterociclilo formada por R^5 y R^6 es un anillo pirrolidina o piperidina.

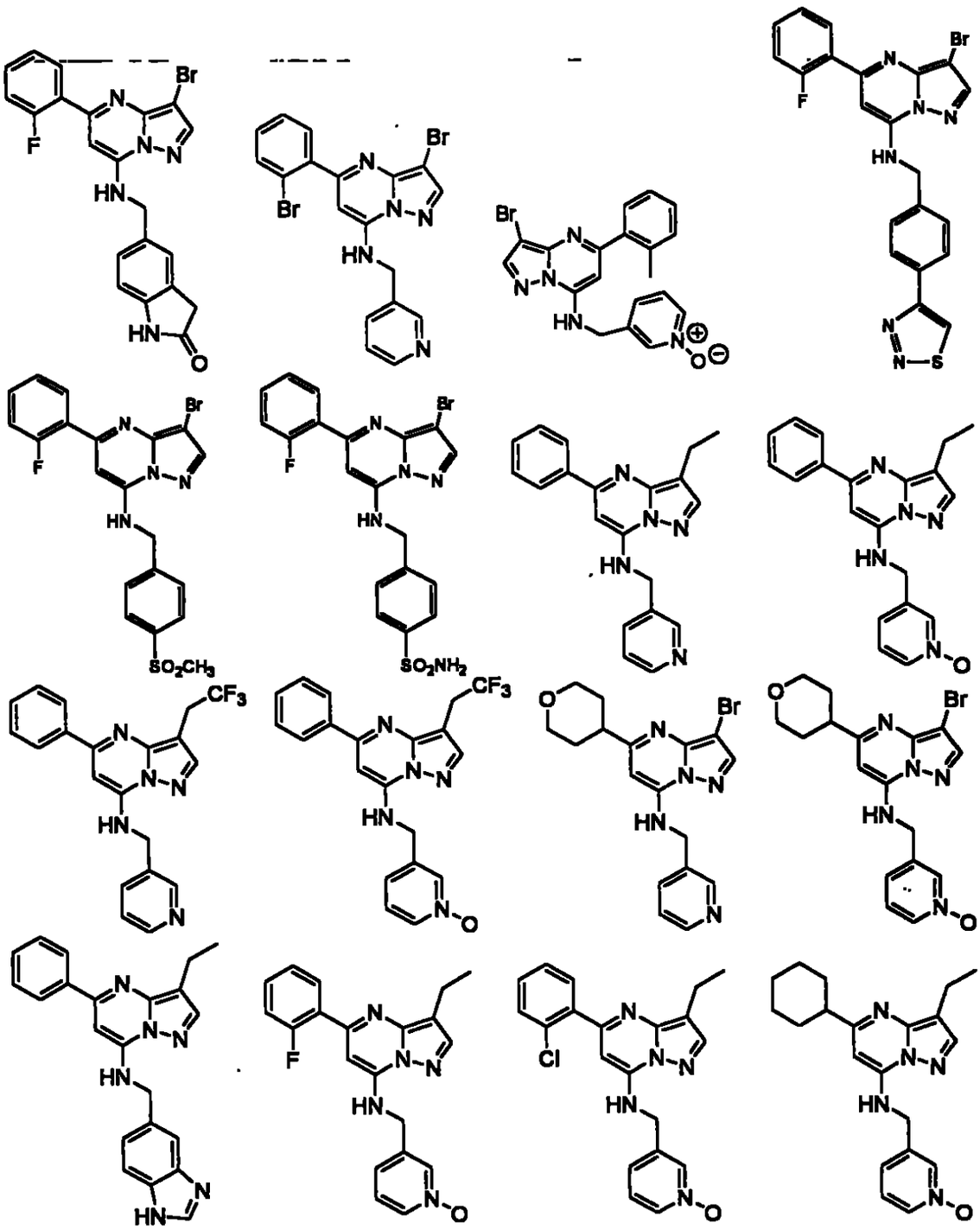
27. Un compuesto de la fórmula:

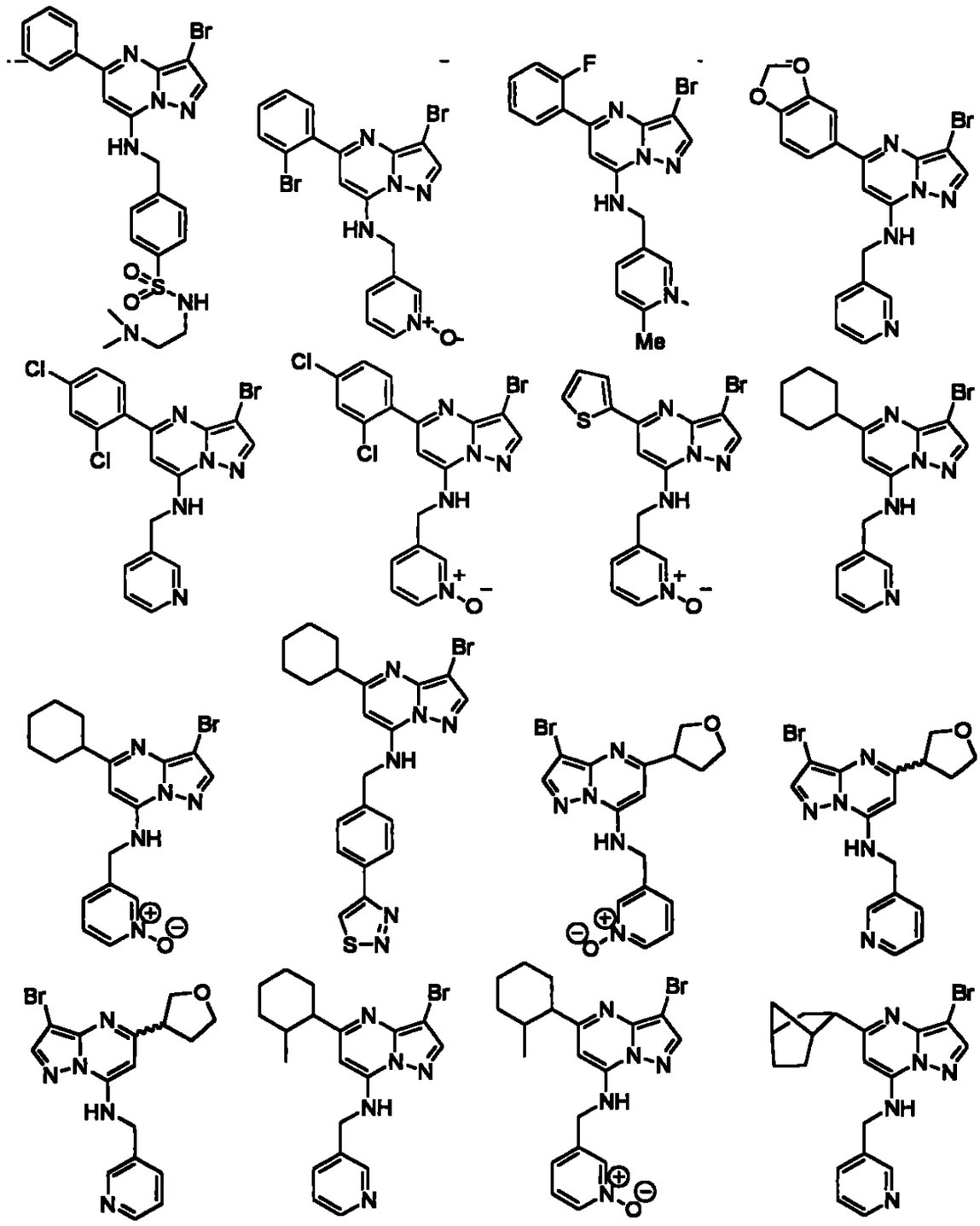


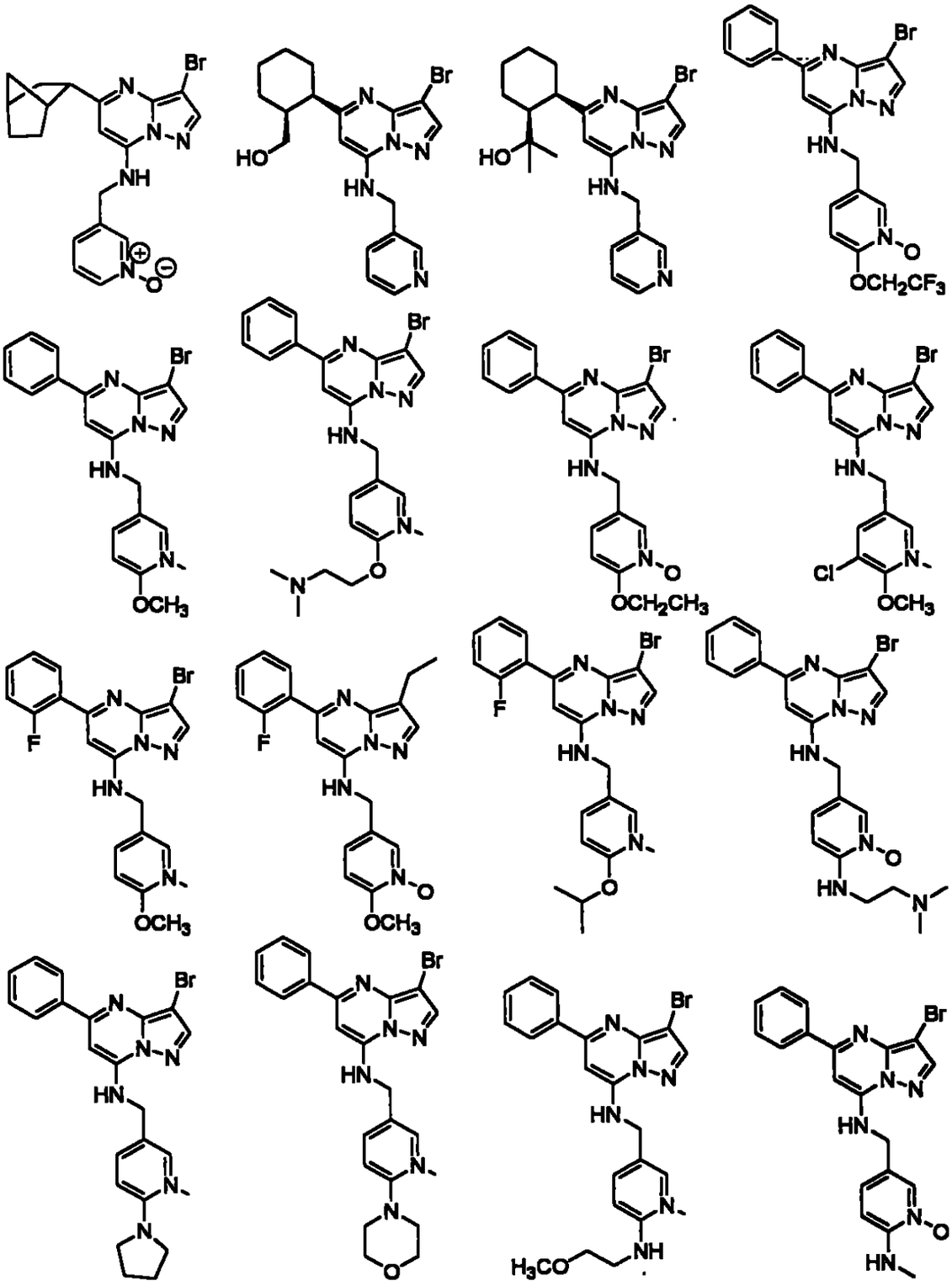


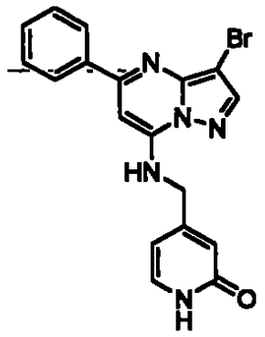
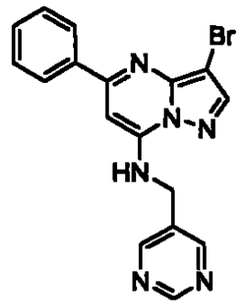
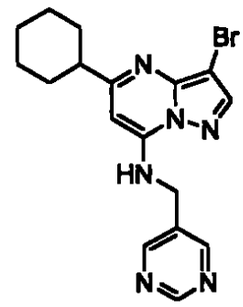
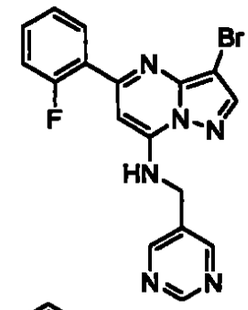
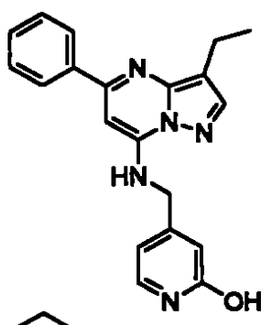
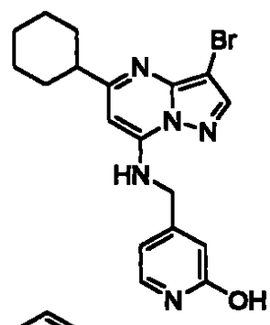
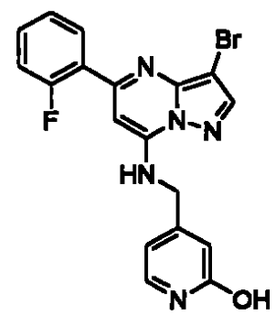
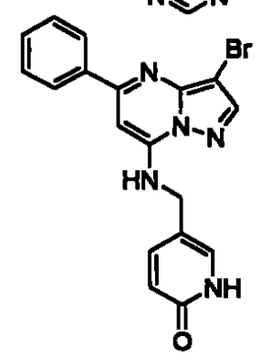
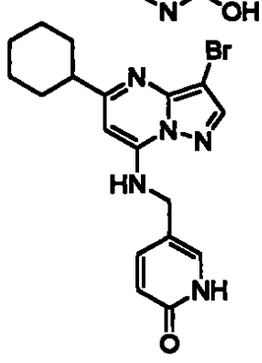
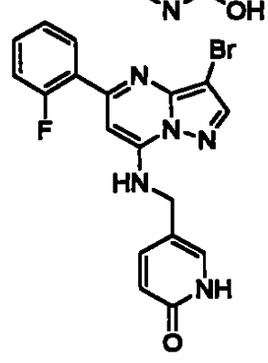
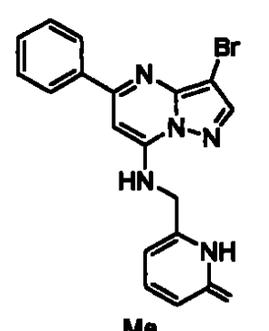
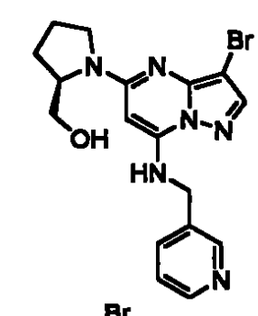
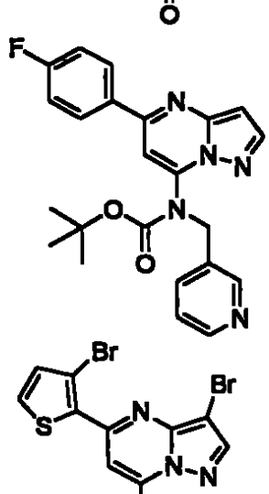
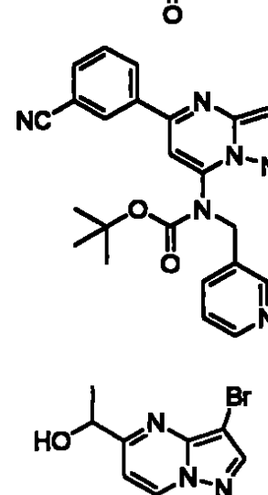
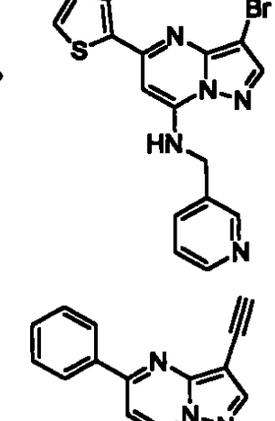
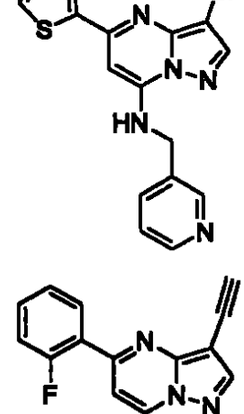
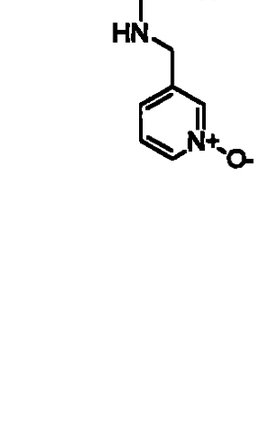
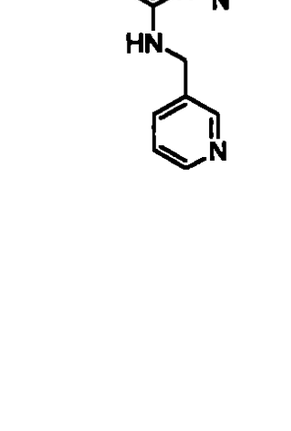
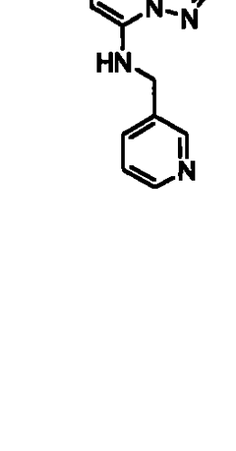
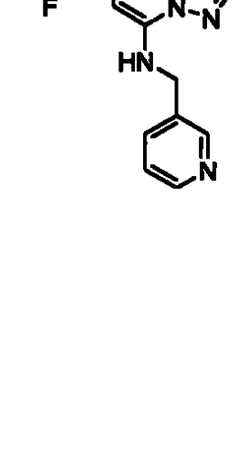


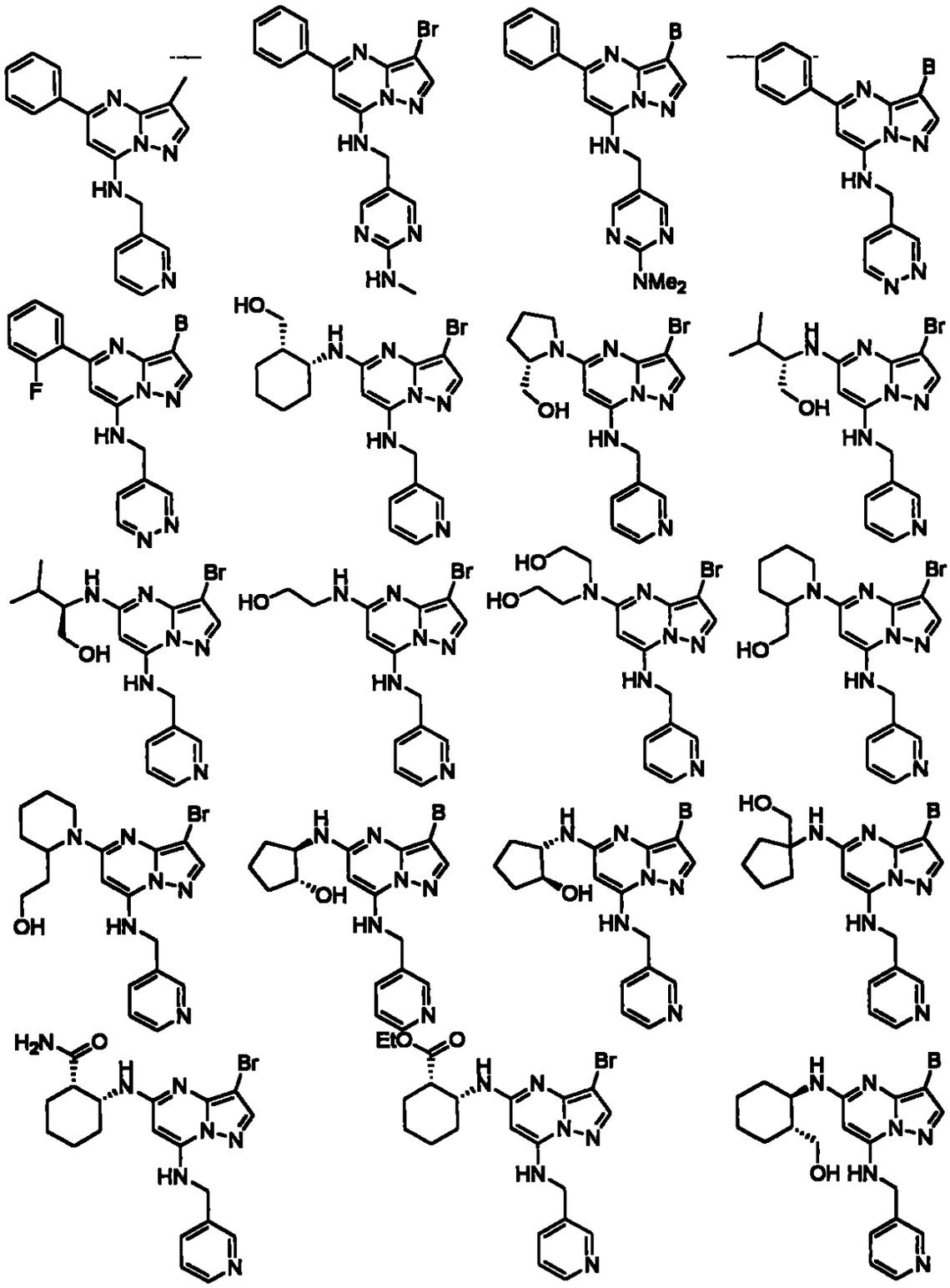


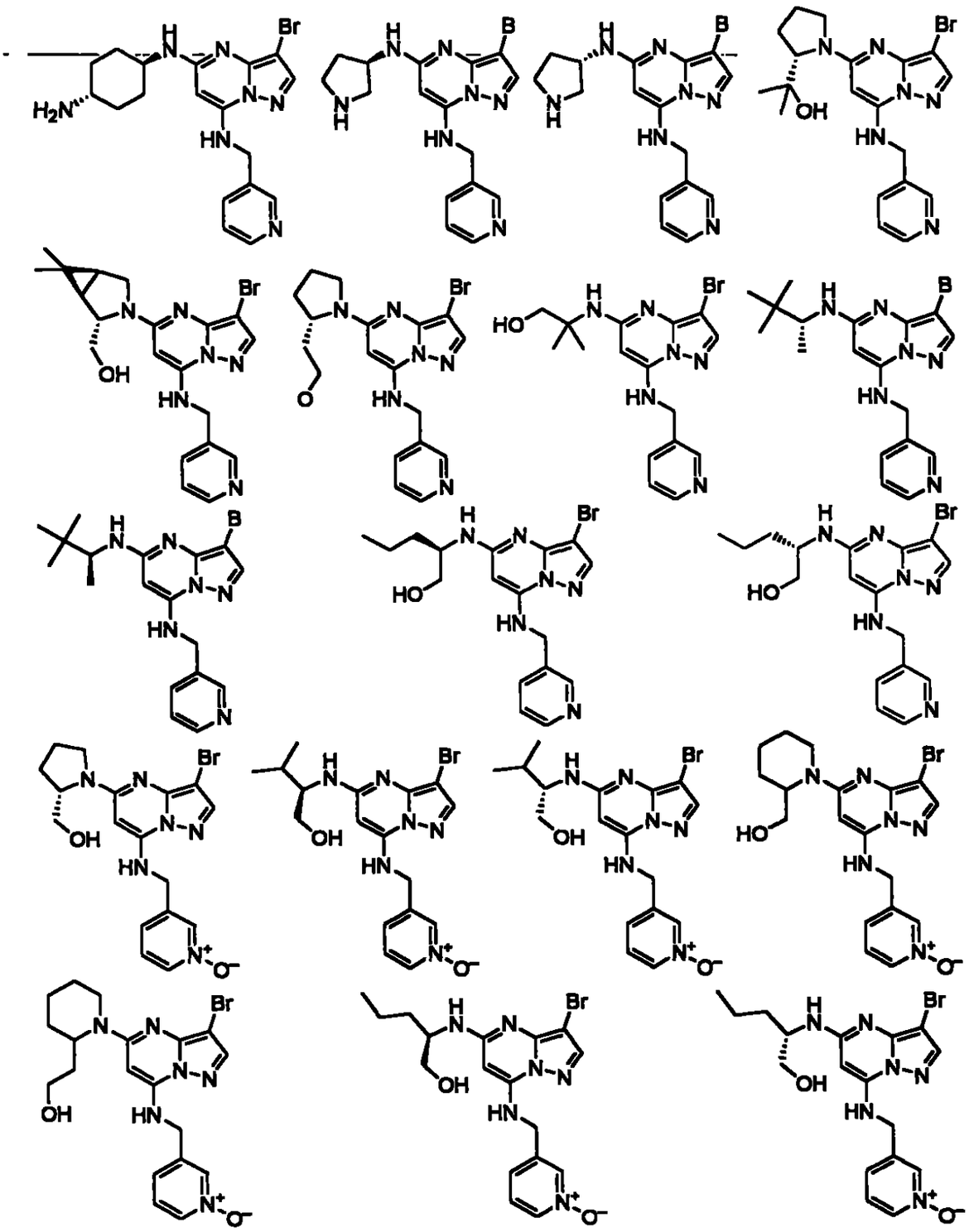


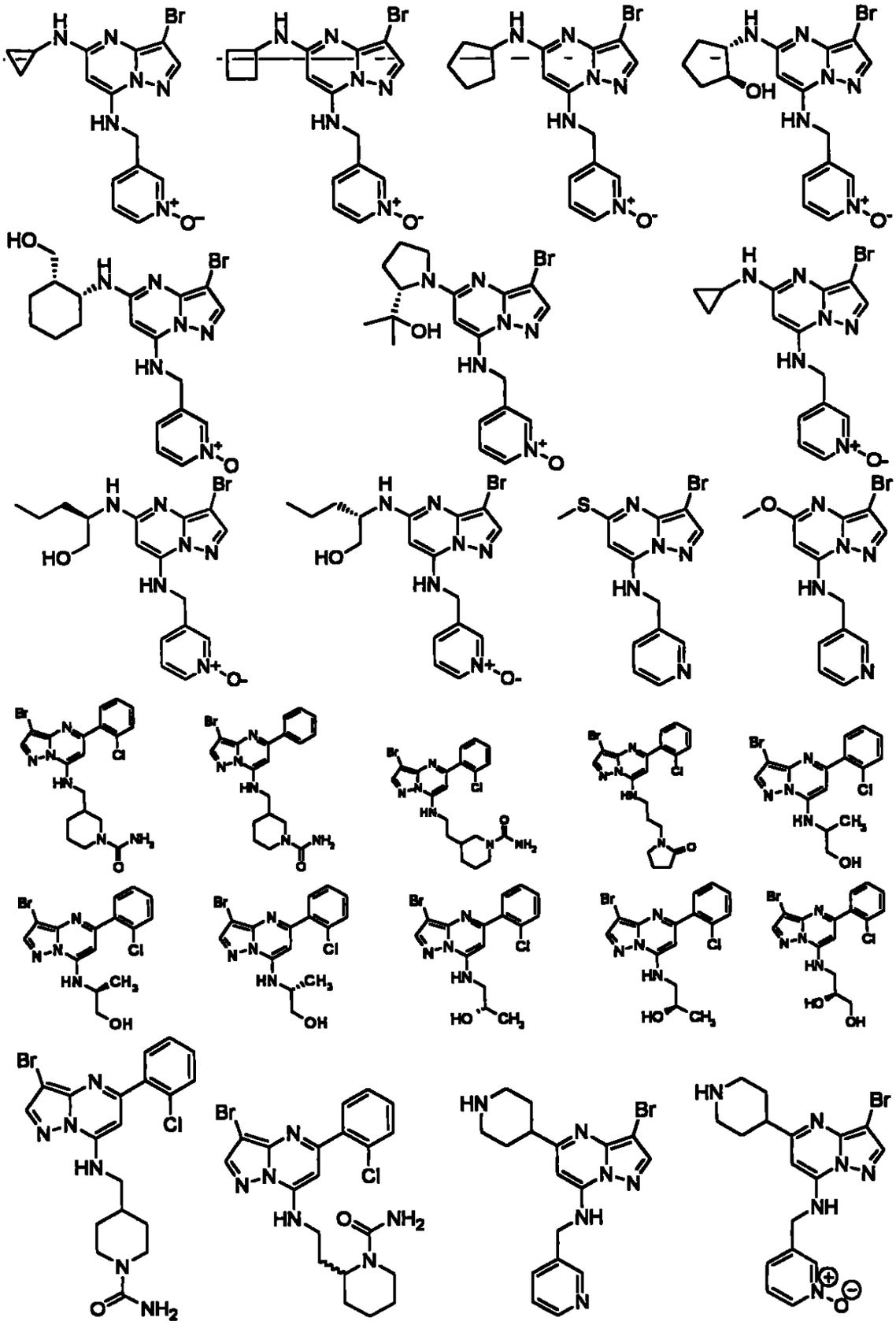


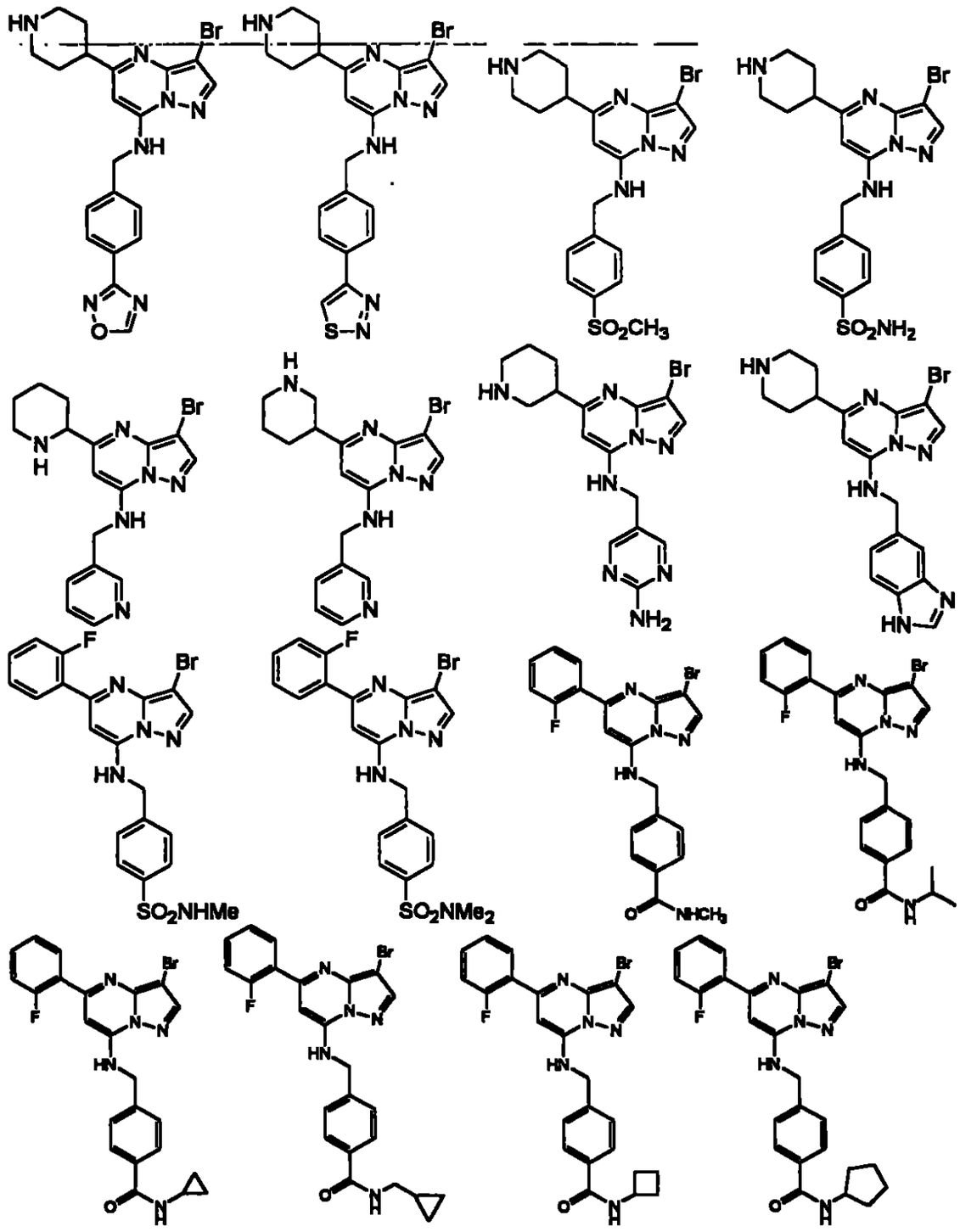


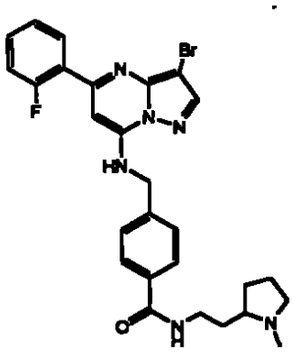





















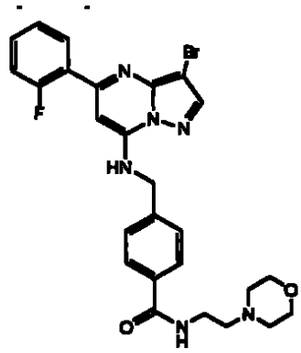


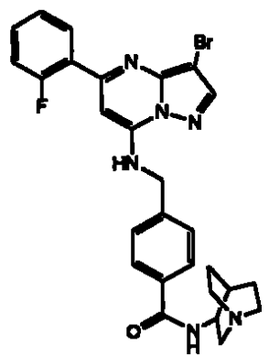


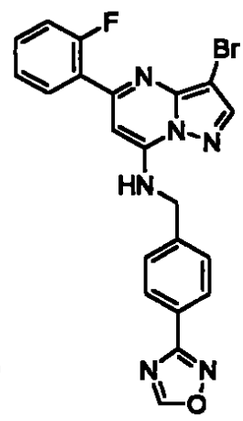


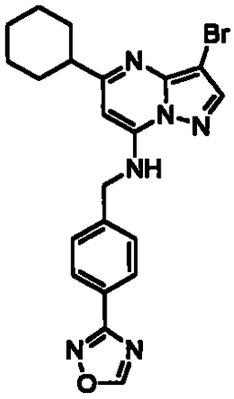

HN
Br
N
N-N
NH
N
O
N
HN
Br
N
N-N
NH
S-N
HN
Br
N
N-N
NH
SO2CH3
HN
Br
N
N-N
NH
SO2NH2
N
H
Br
N
N-N
NH
N
H
N
Br
N
N-N
NH
N
HN
Br
N
N-N
HN
N
NH2
HN
Br
N
N-N
HN
N
HN
F
Br
N
N-N
HN
SO2NHMe
F
Br
N
N-N
HN
SO2NMe2
F
Br
N
N-N
HN
O
NHCH3
F
Br
N
N-N
HN
O
N
H
F
Br
N
N-N
HN
O
N
H
F
Br
N
N-N
HN
O
N
H
F
Br
N
N-N
HN
O
N
H
F
Br
N
N-N
HN
O
N
H

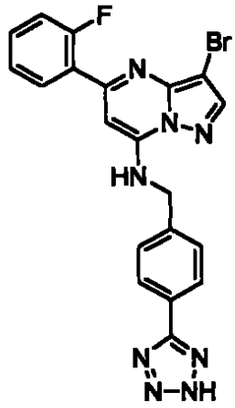


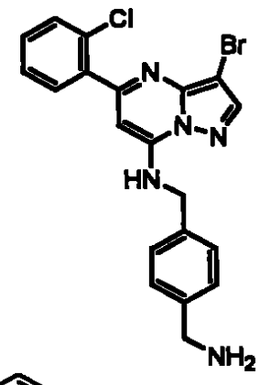


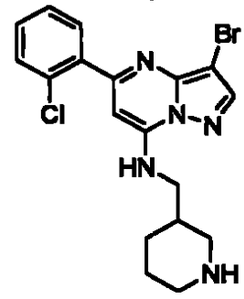


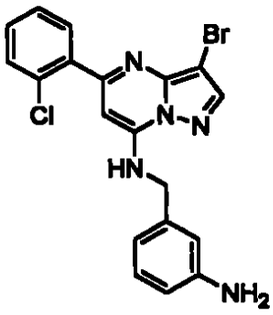


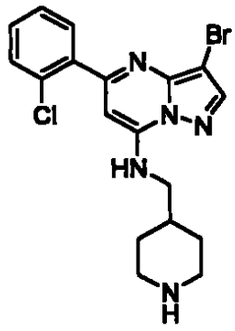


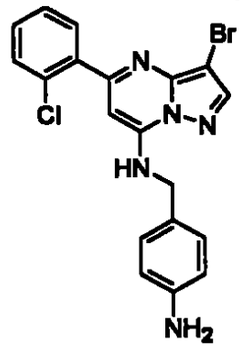


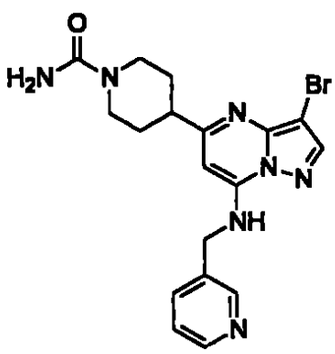


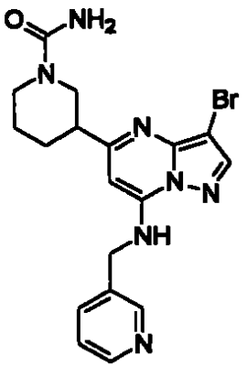


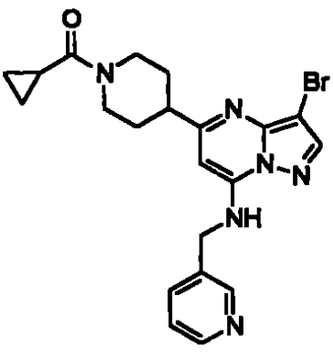


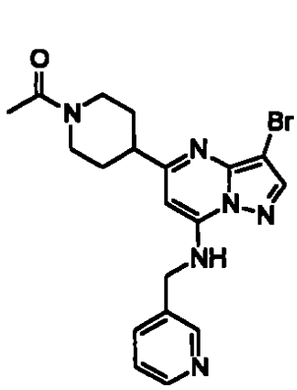


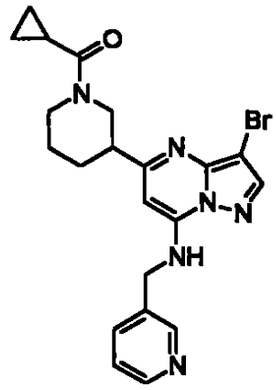


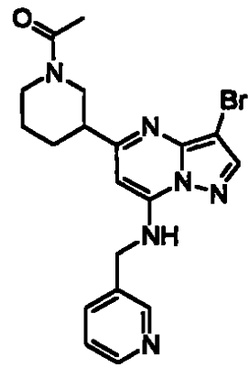


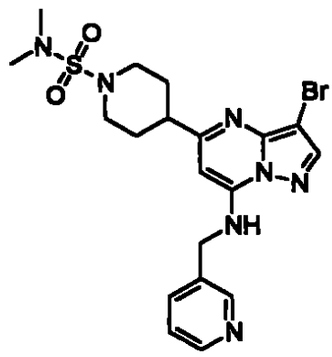


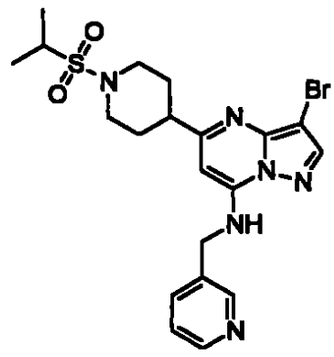


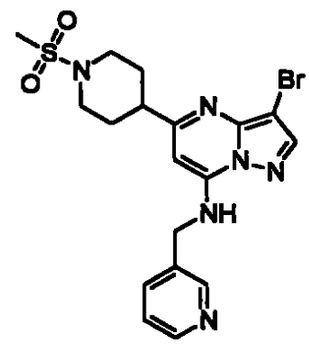


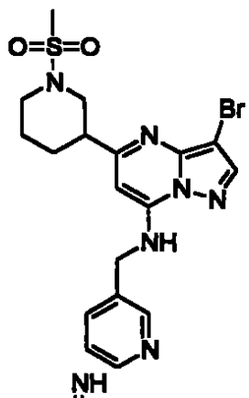


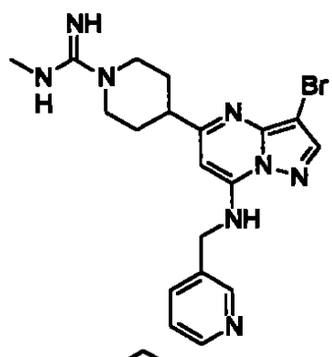


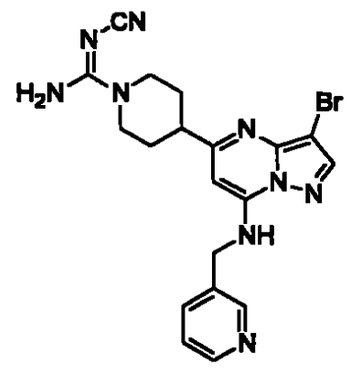


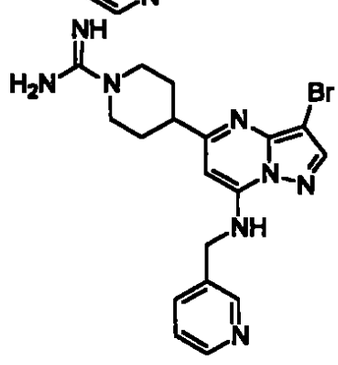


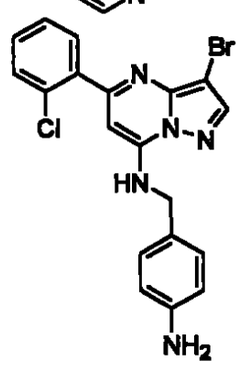


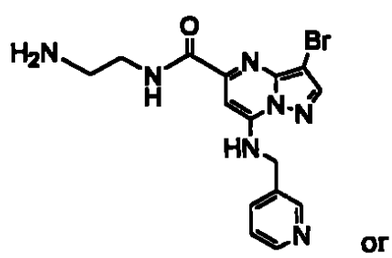




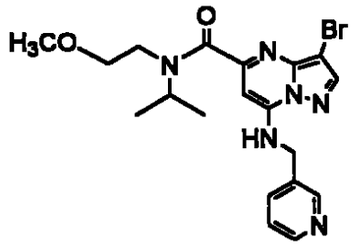


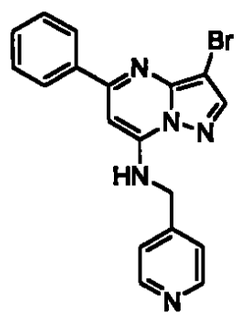


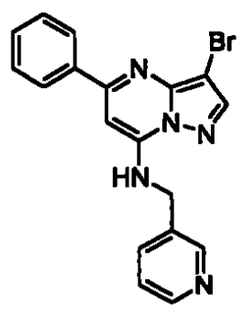


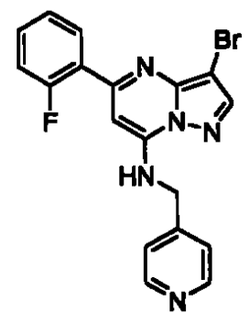


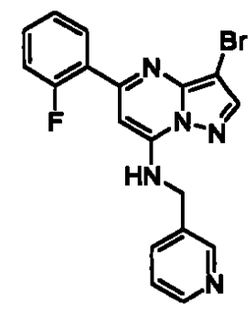
or

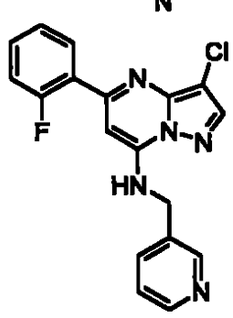


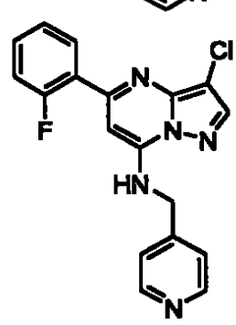


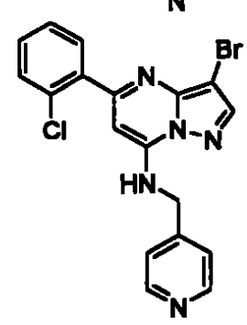


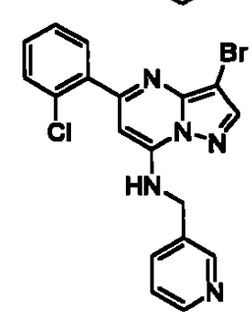


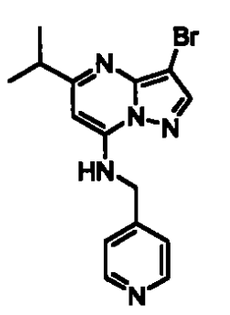


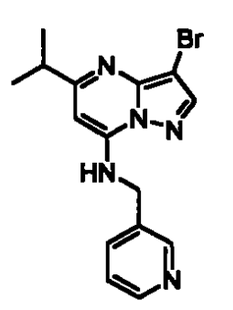


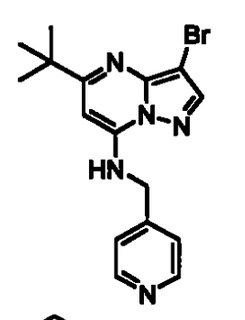


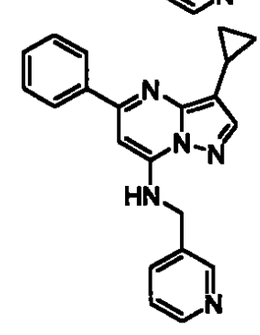


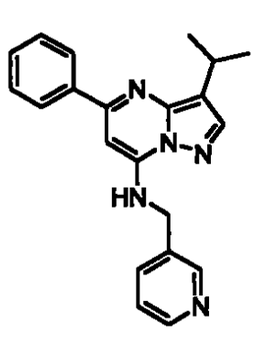


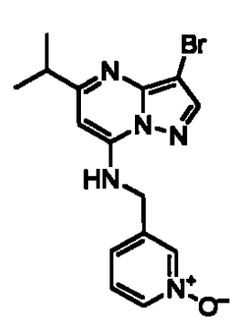


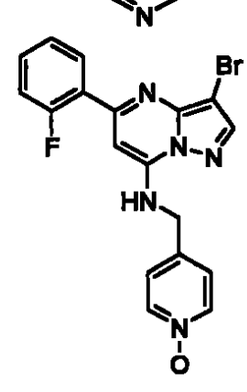


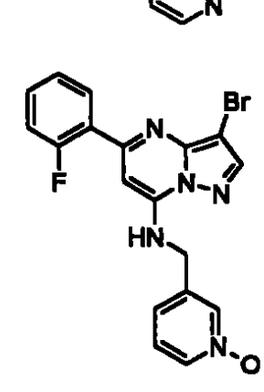


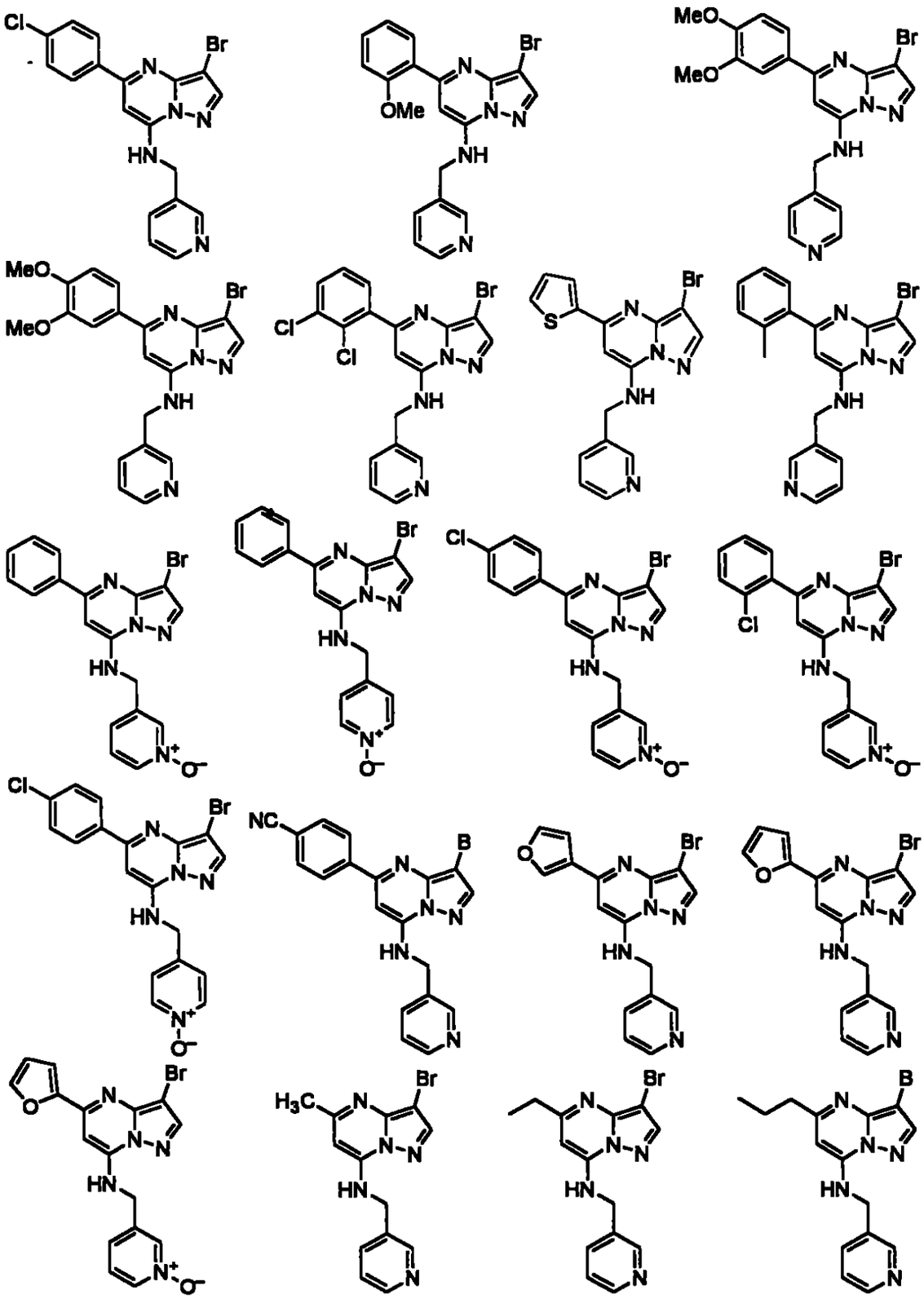


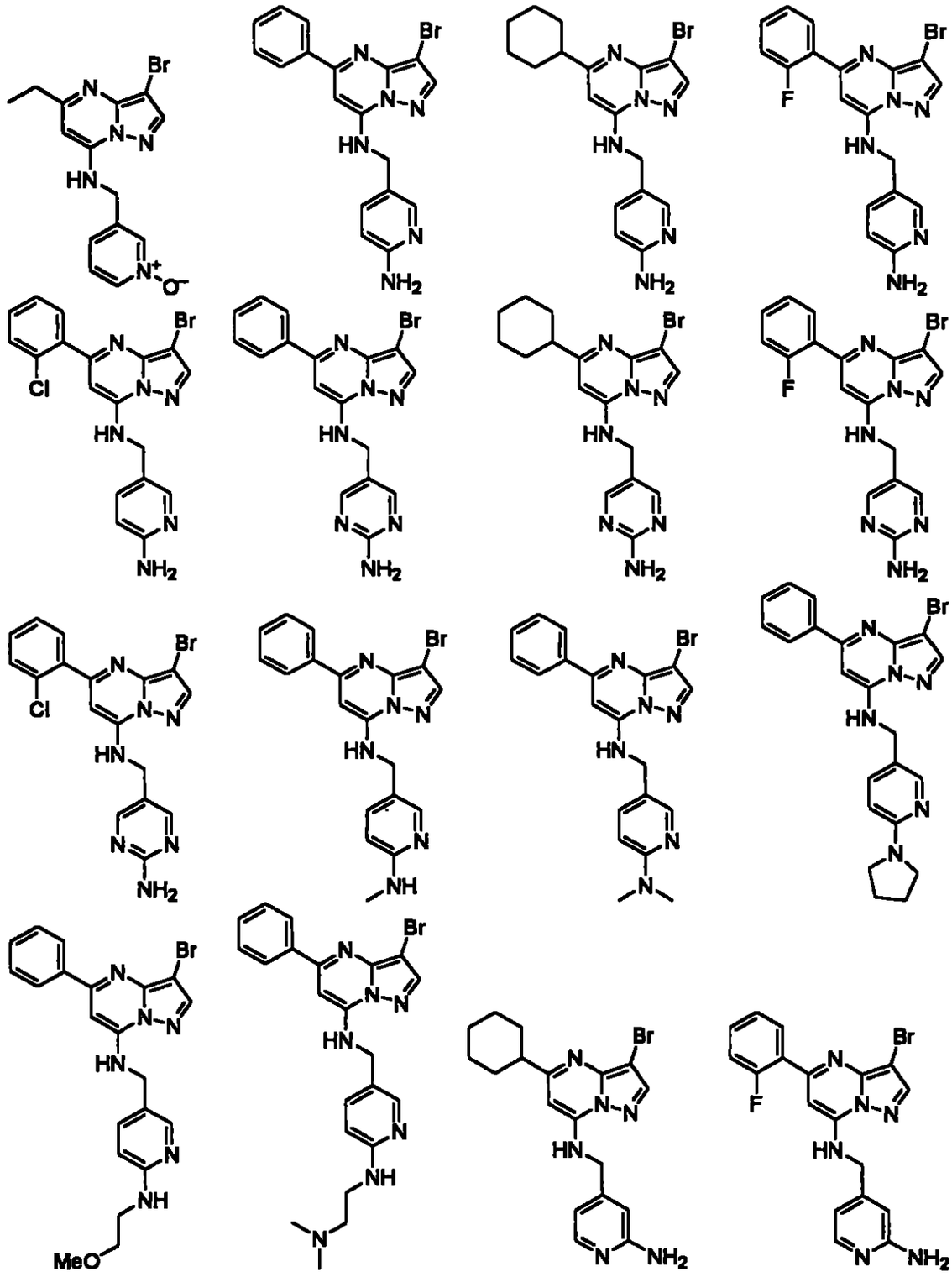


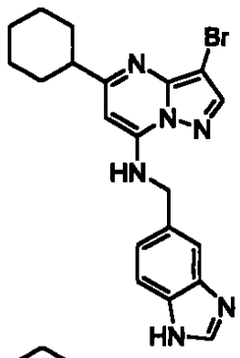
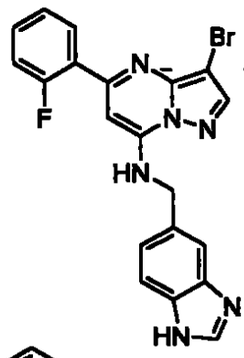
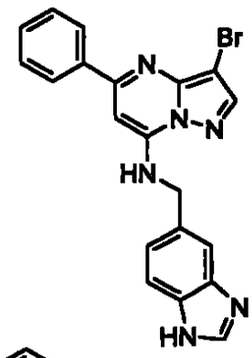
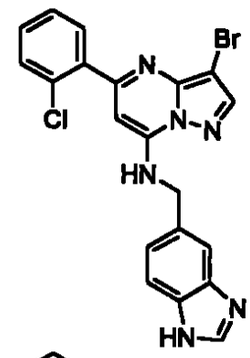
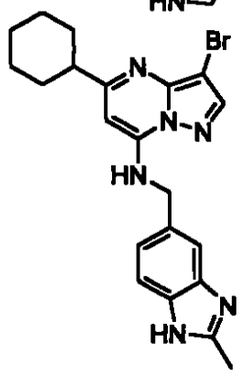
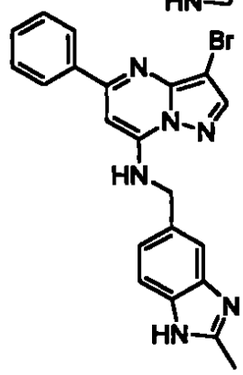
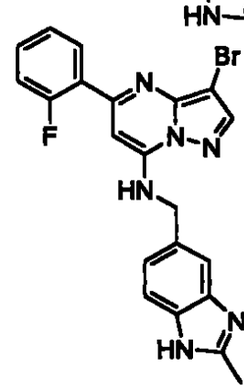
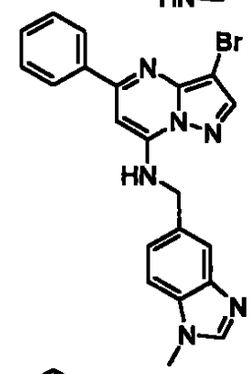
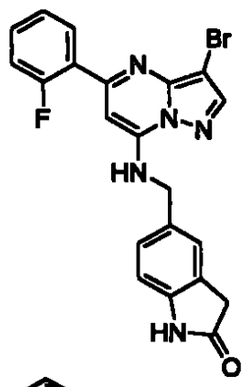
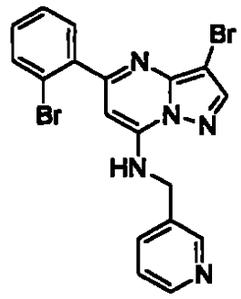
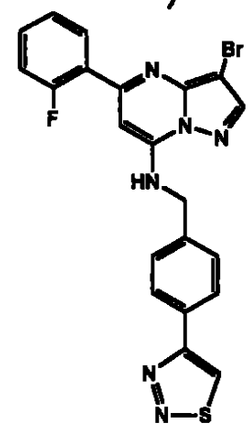
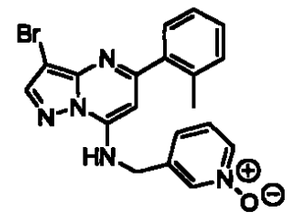
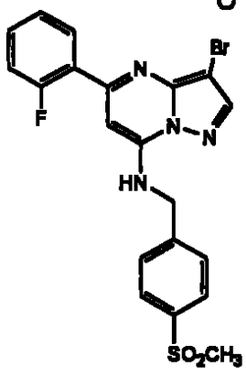
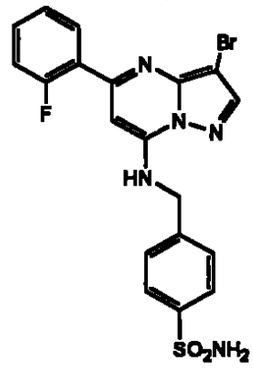
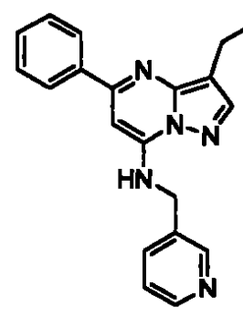
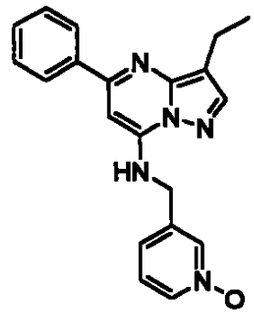


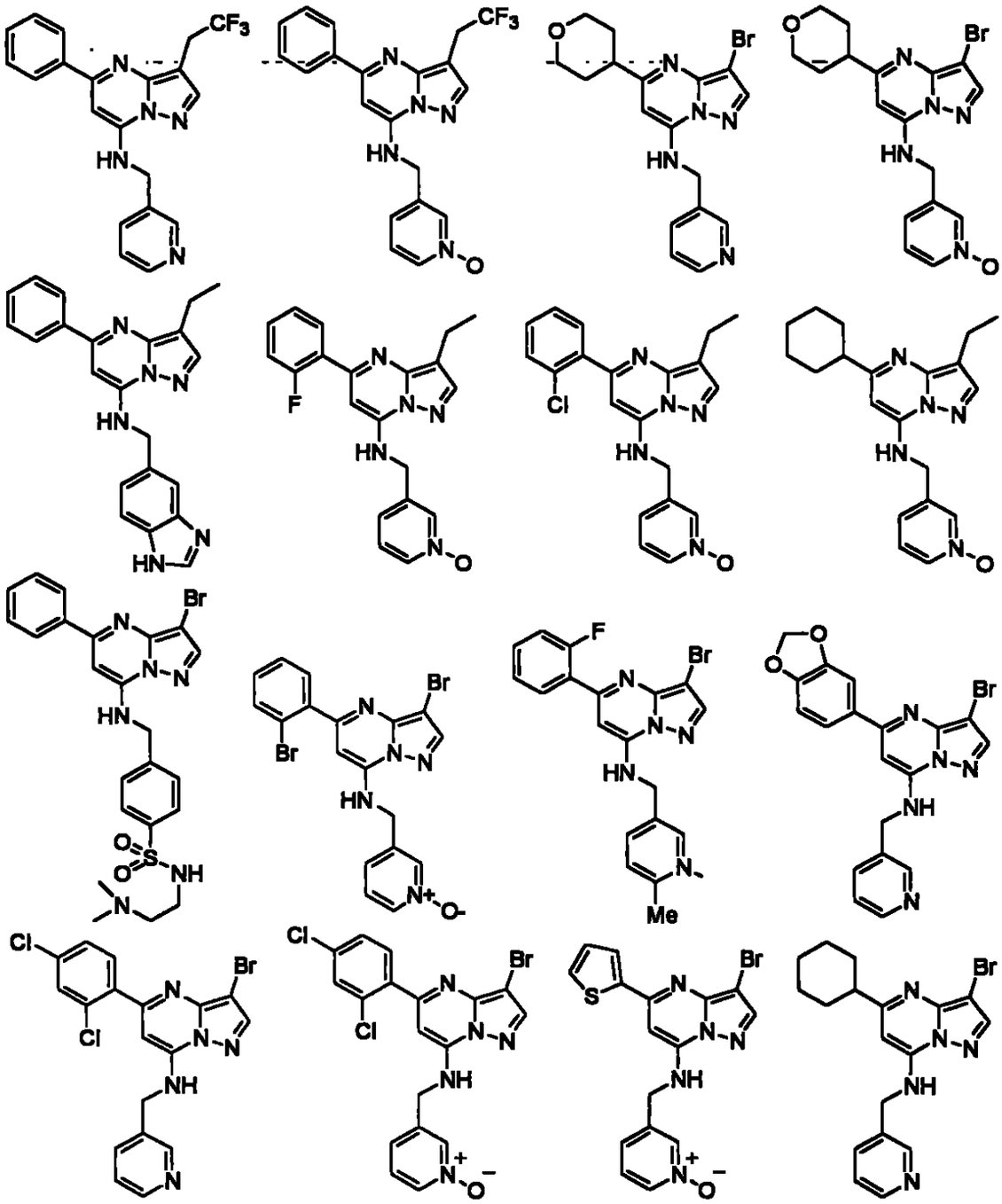


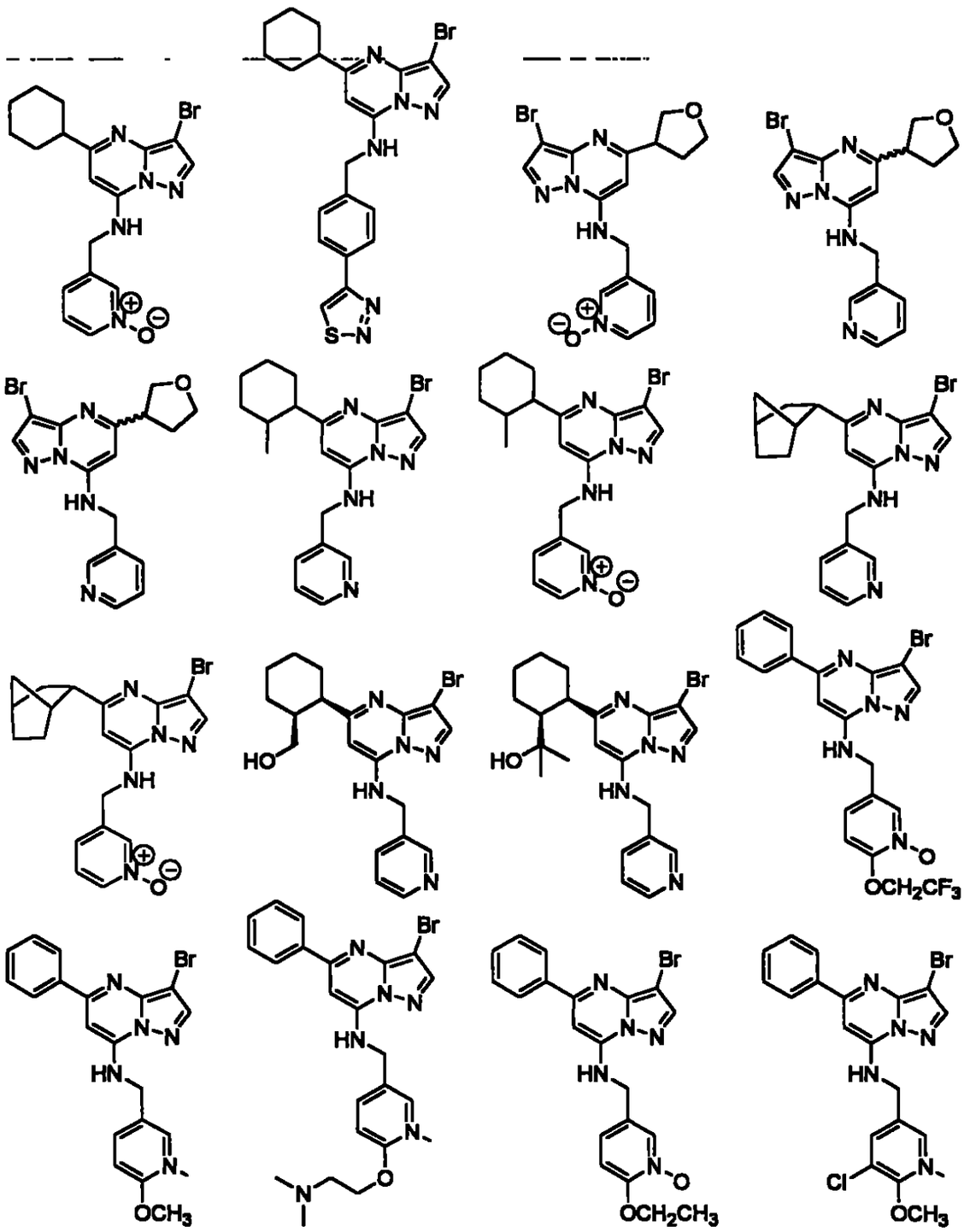


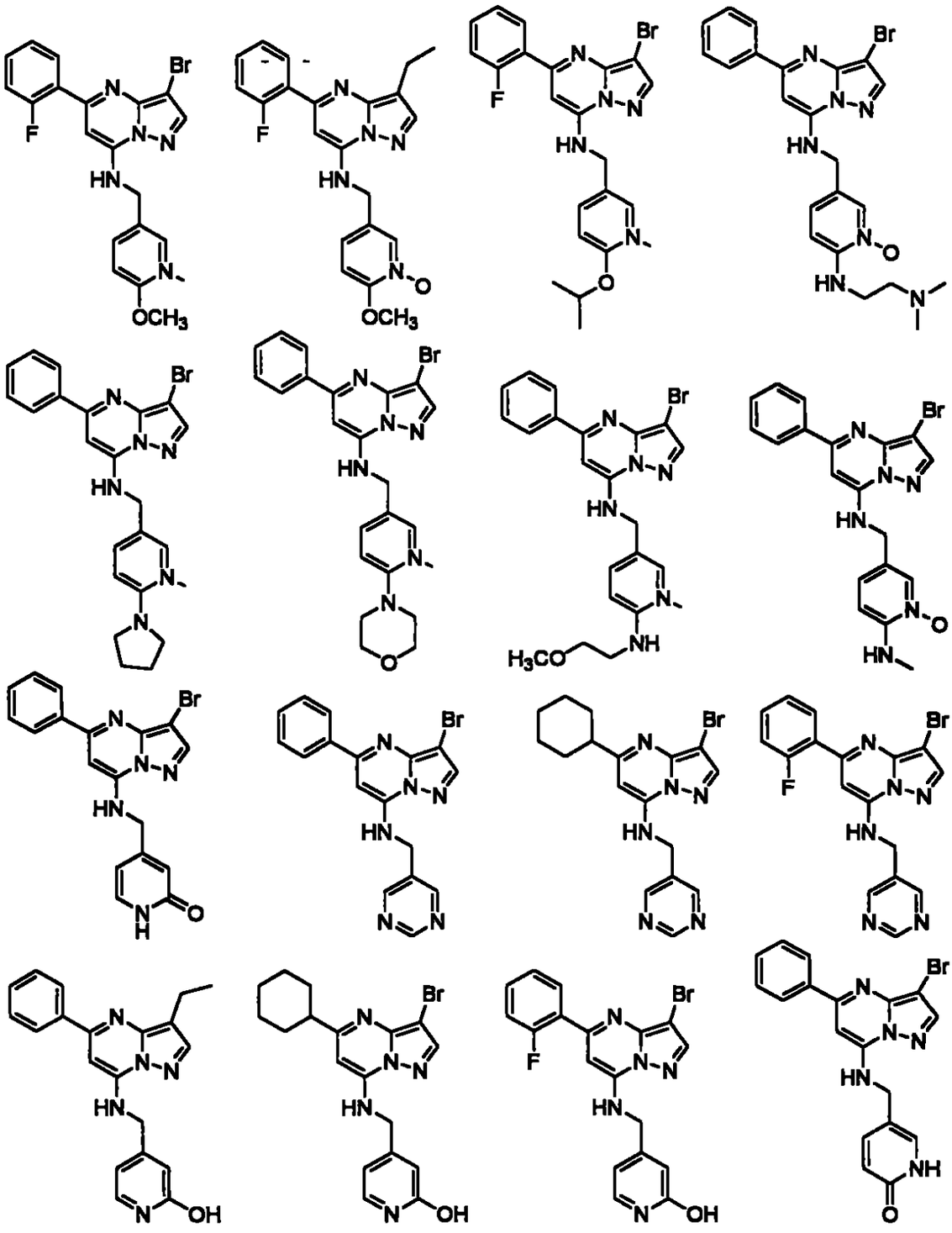


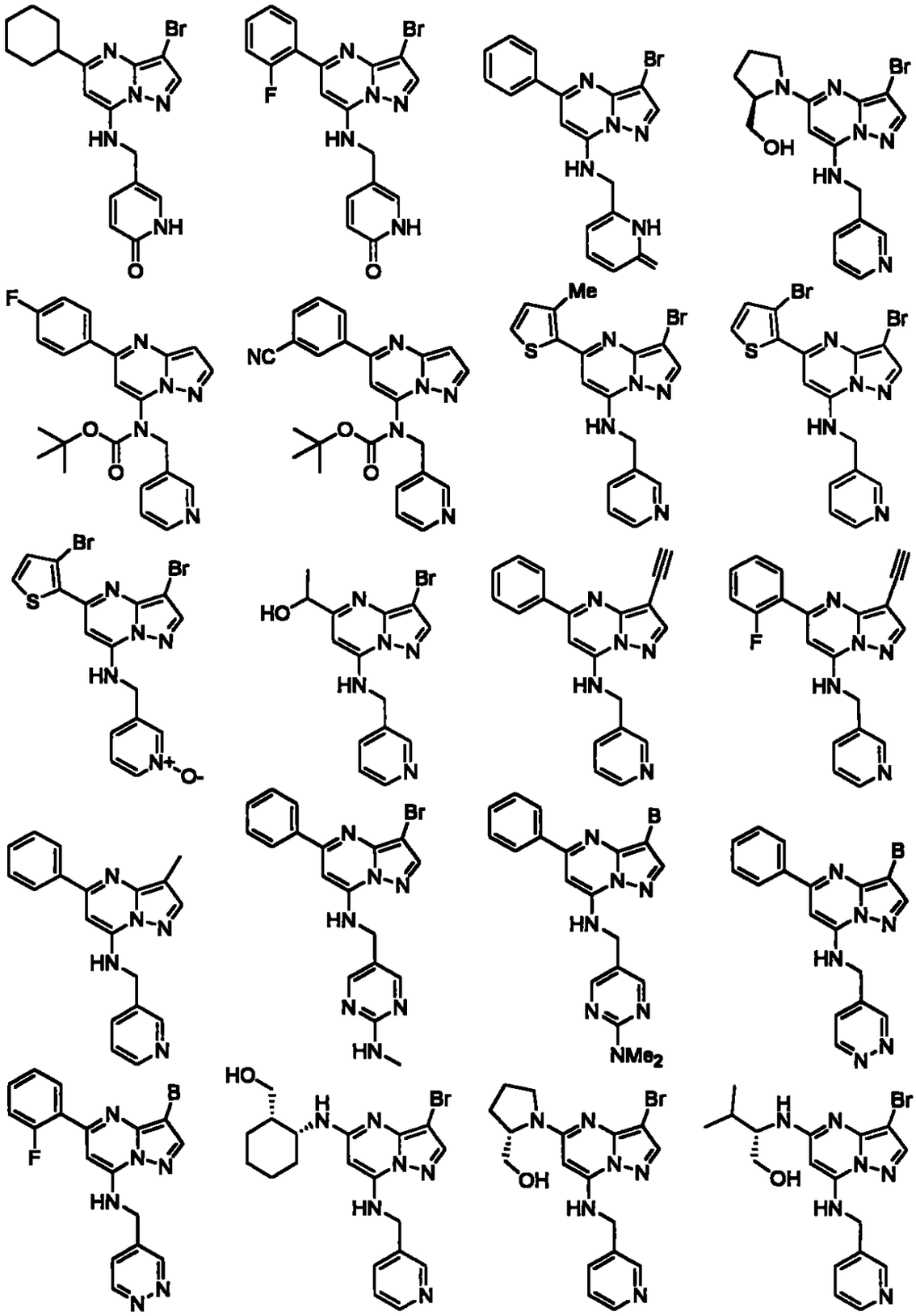


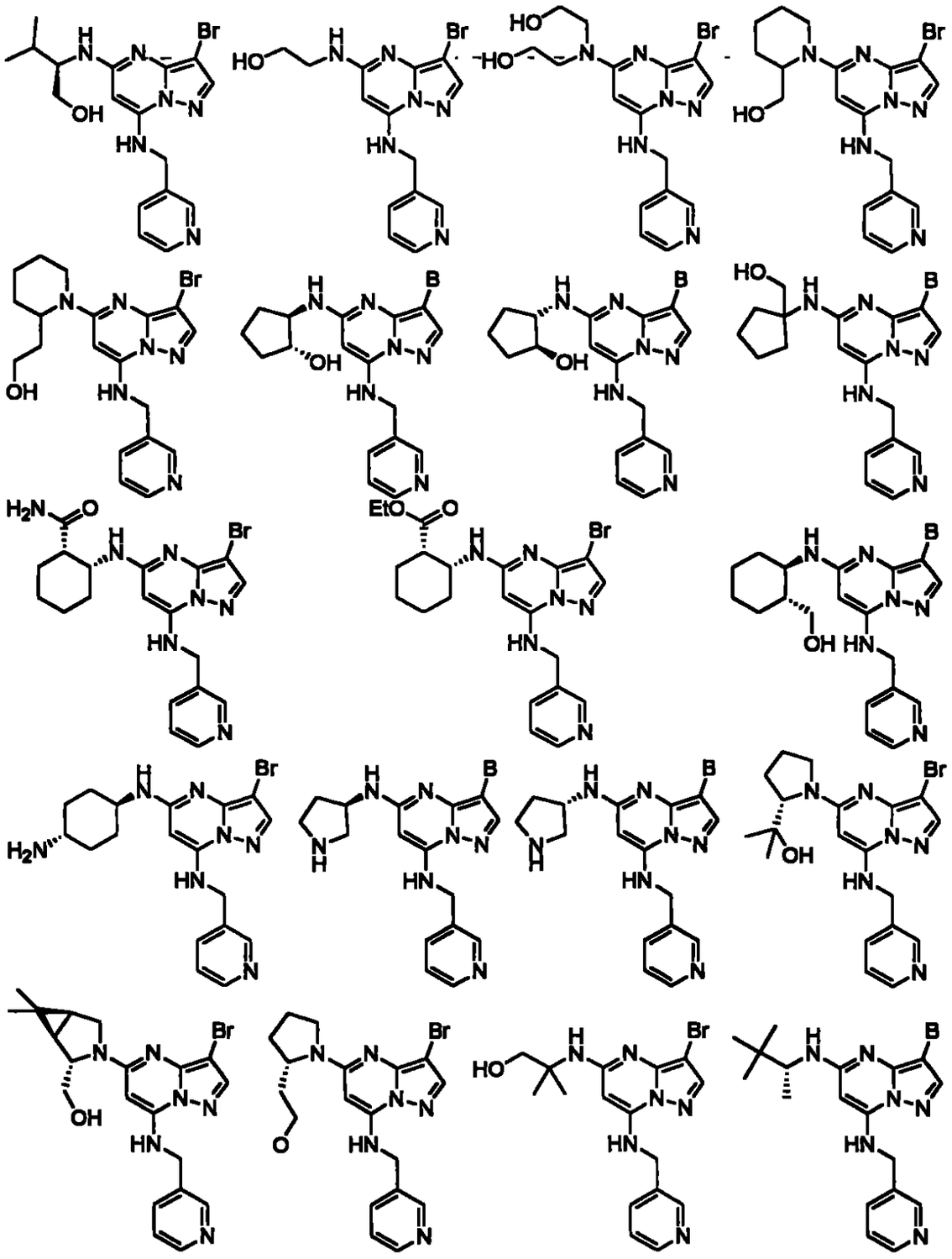

















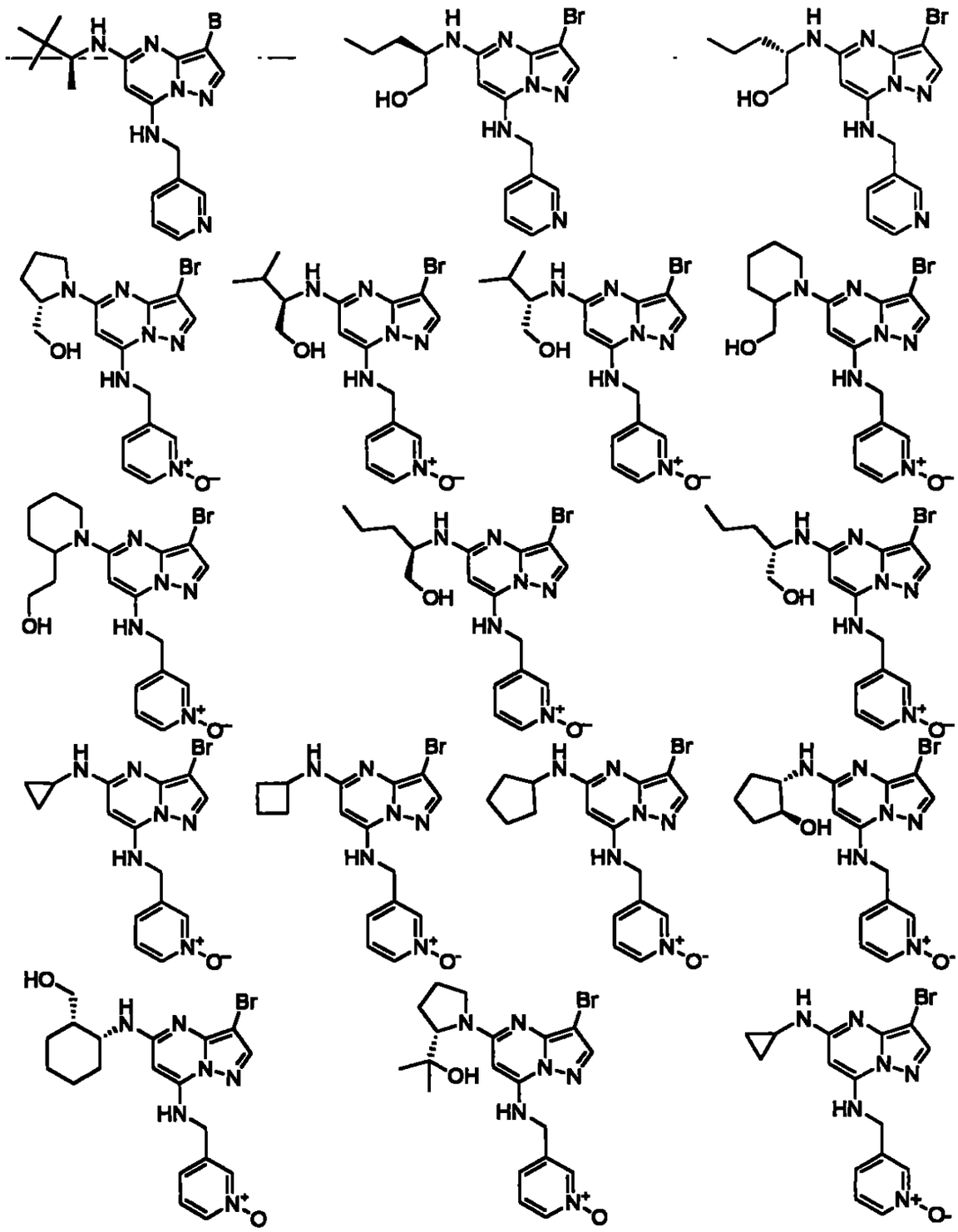


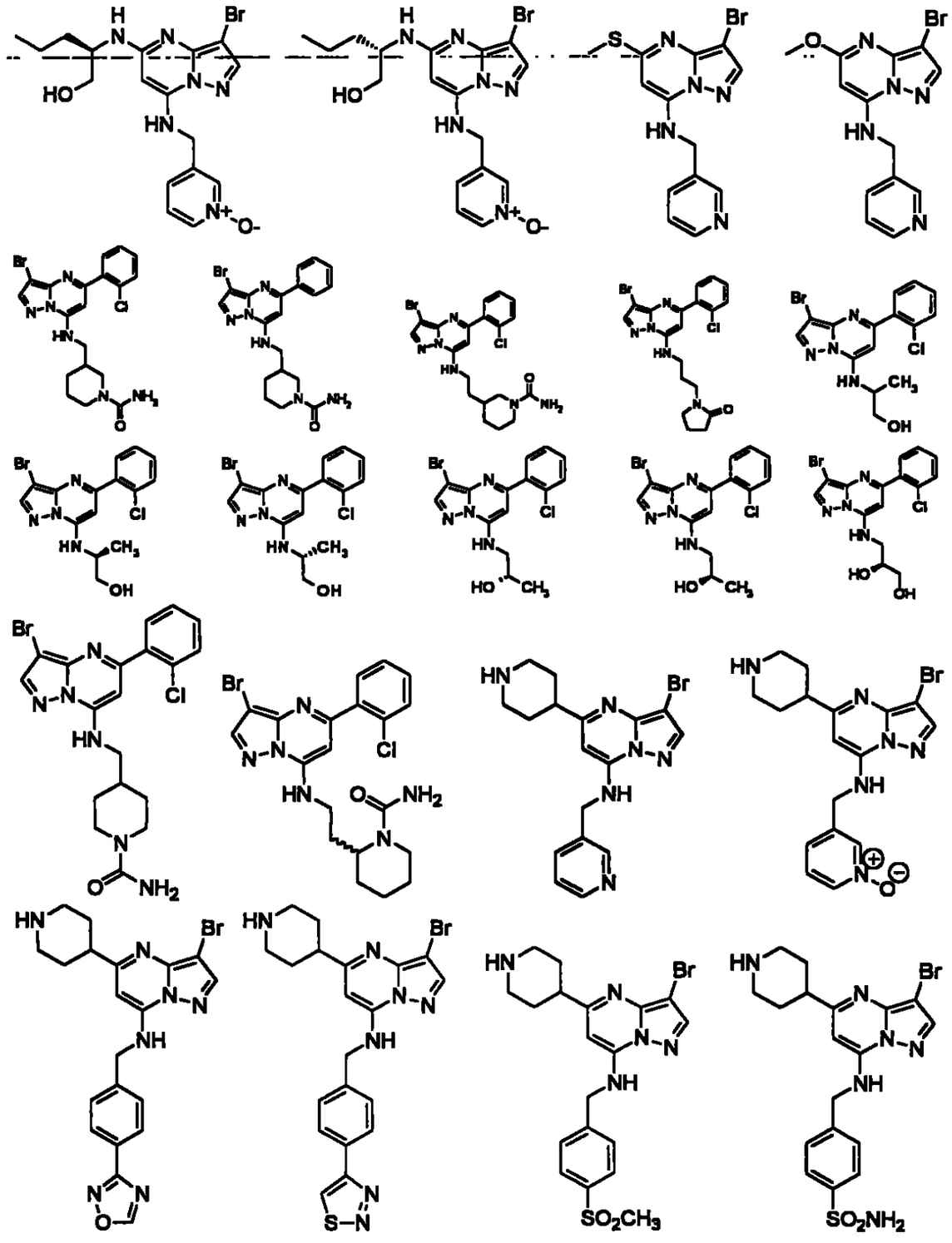


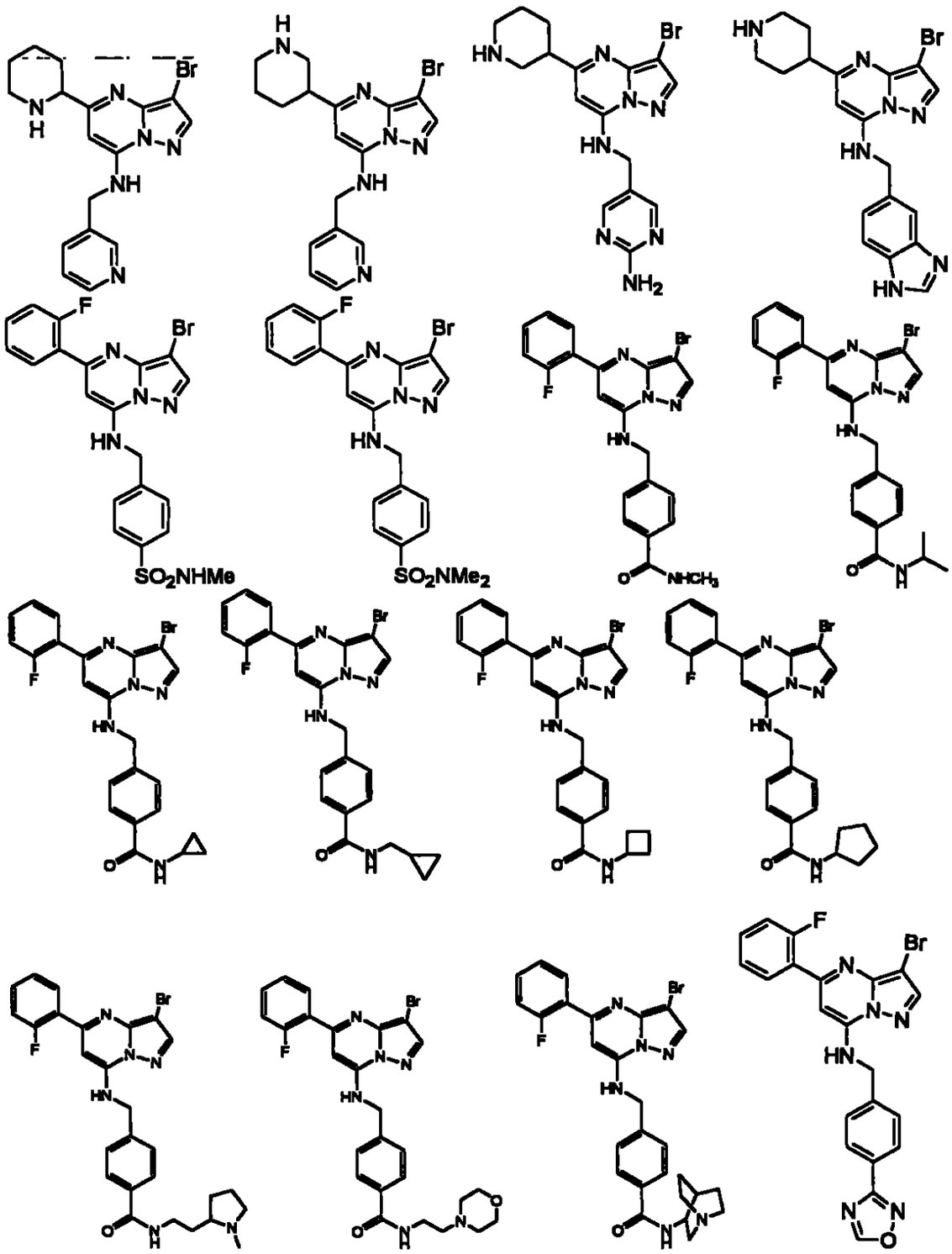


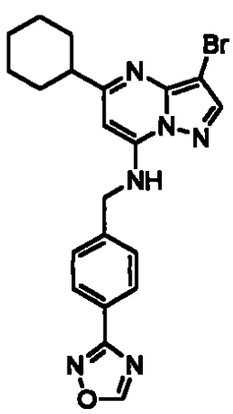
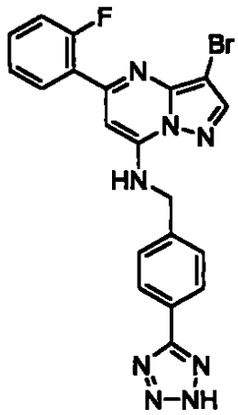
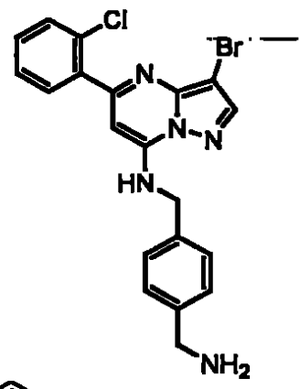
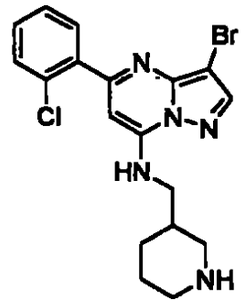
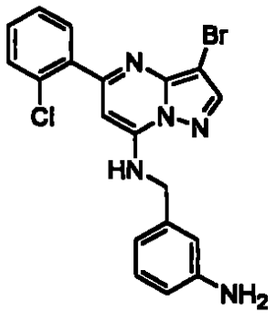
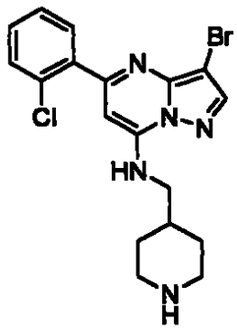
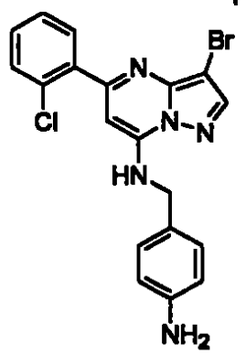
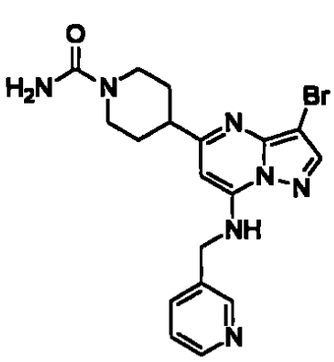
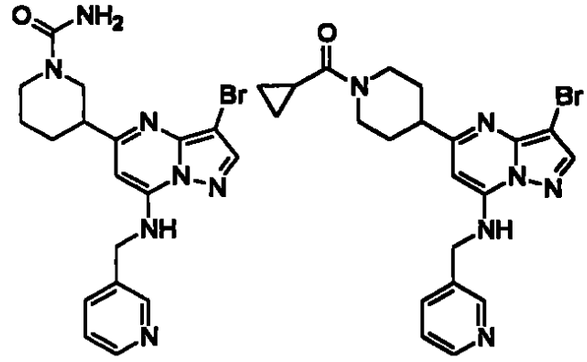
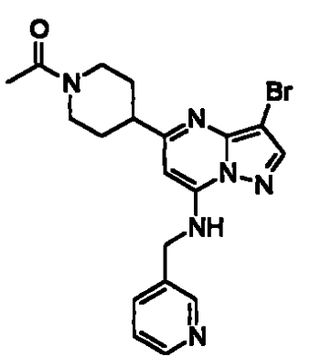
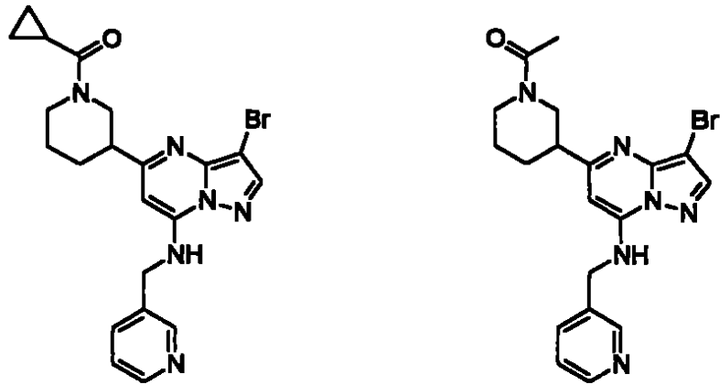


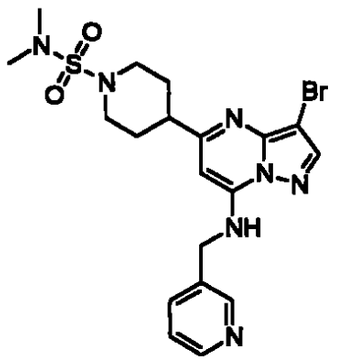
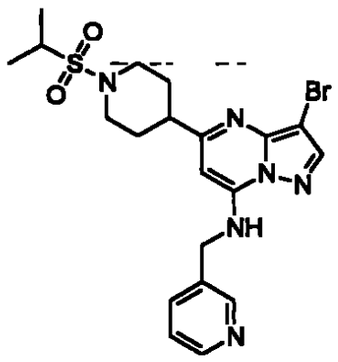
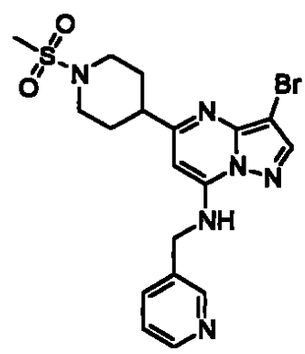
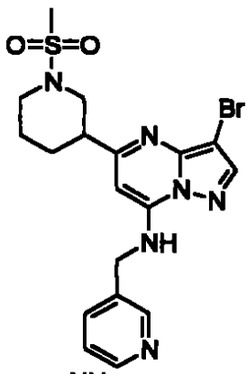
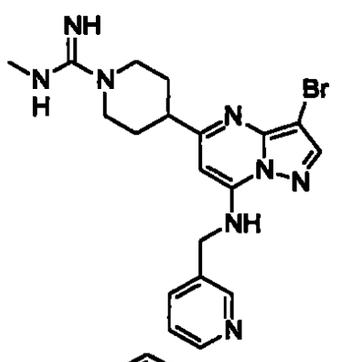
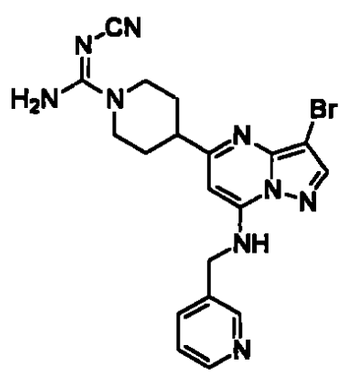
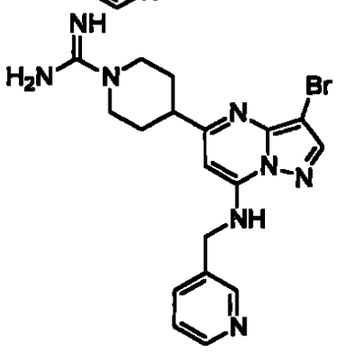
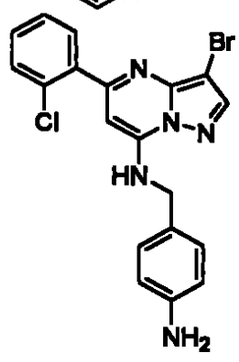
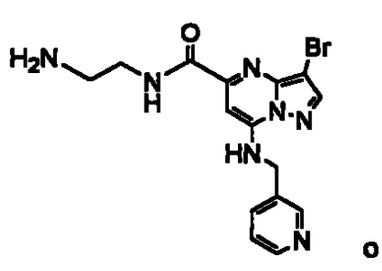
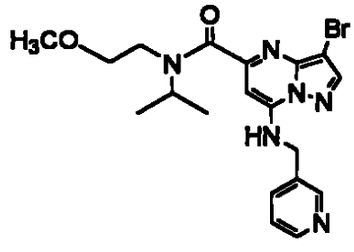






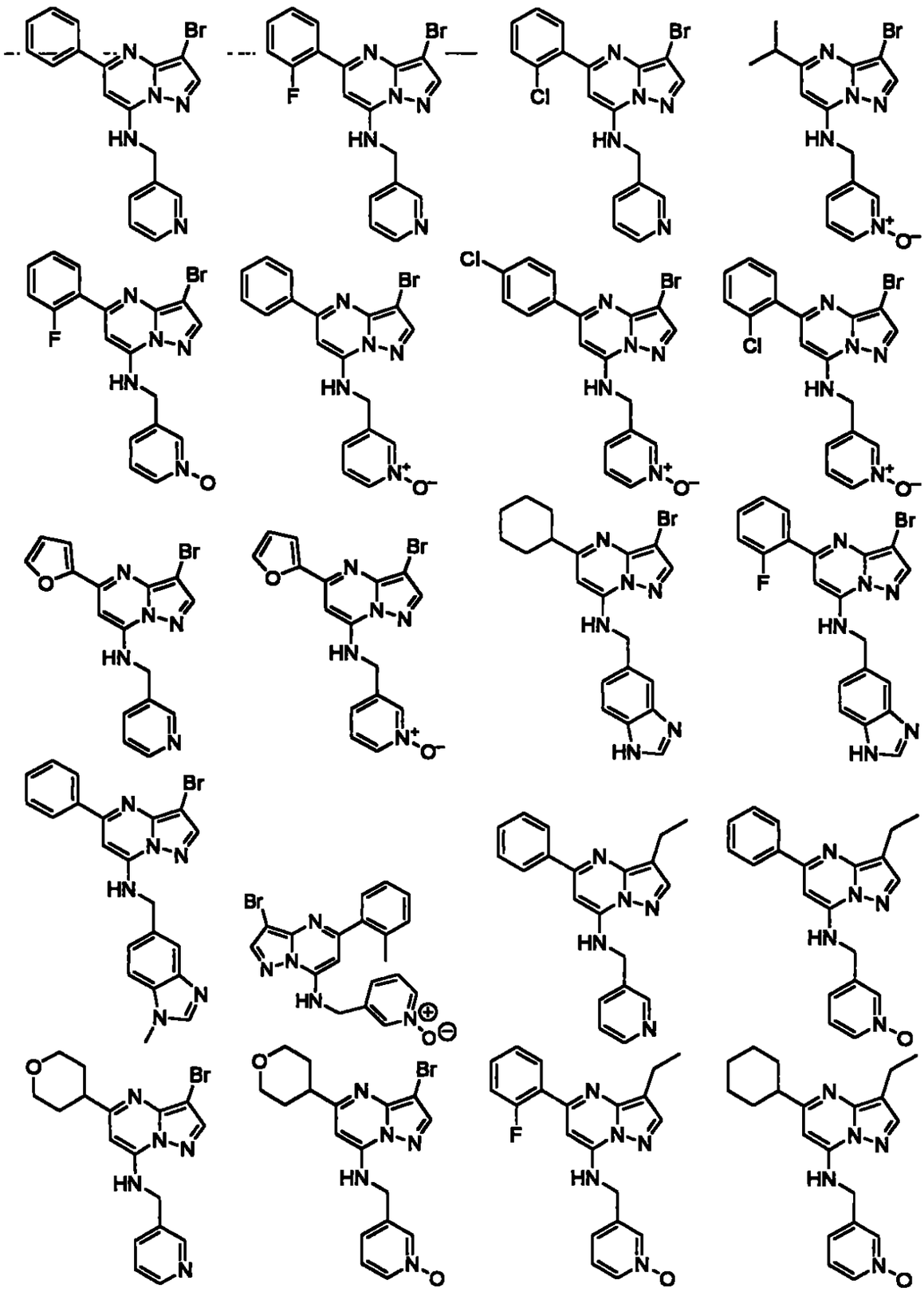


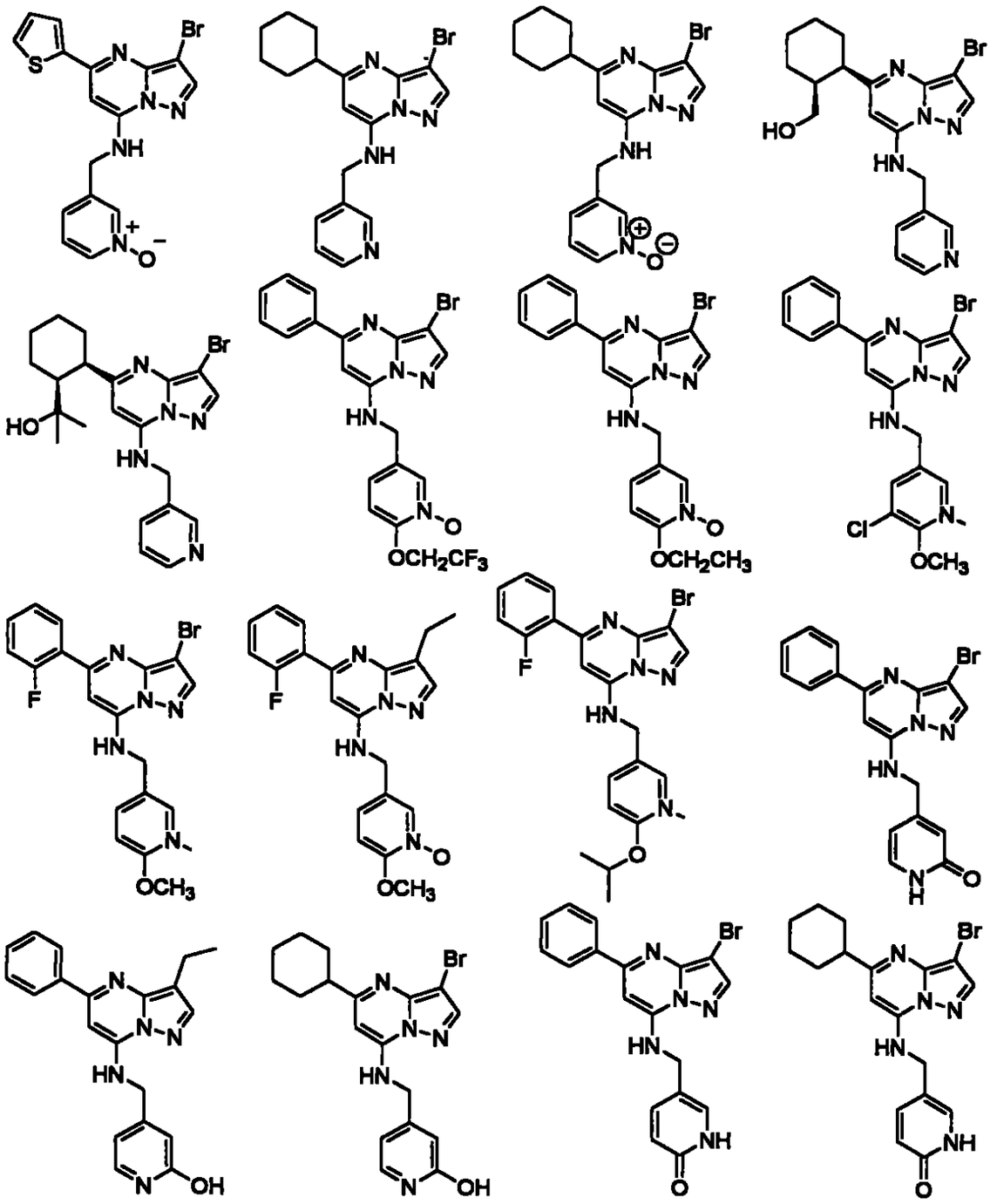












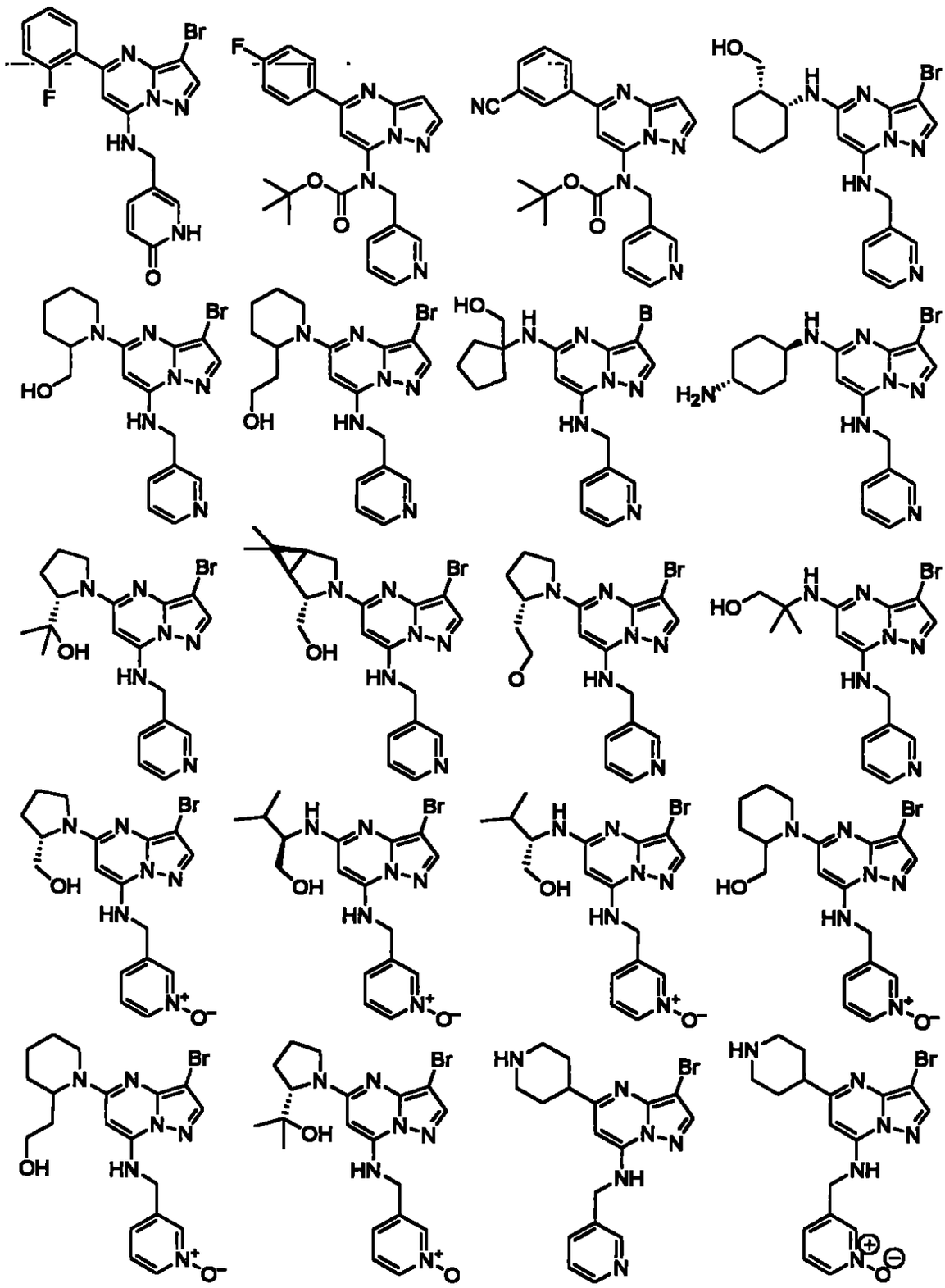











o una sal o solvato del mismo farmacéuticamente aceptable.

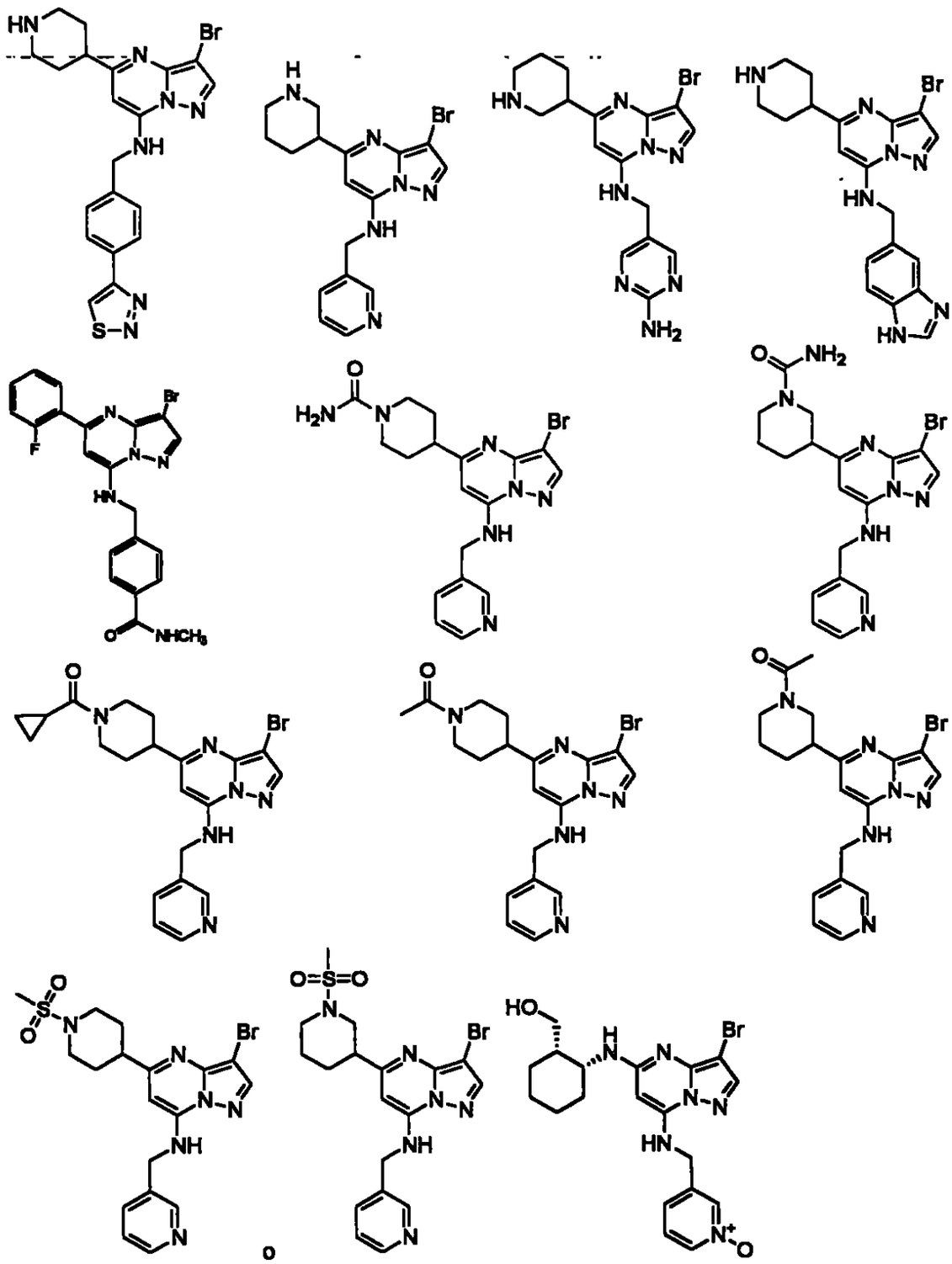
28. Un compuesto que tiene la fórmula:





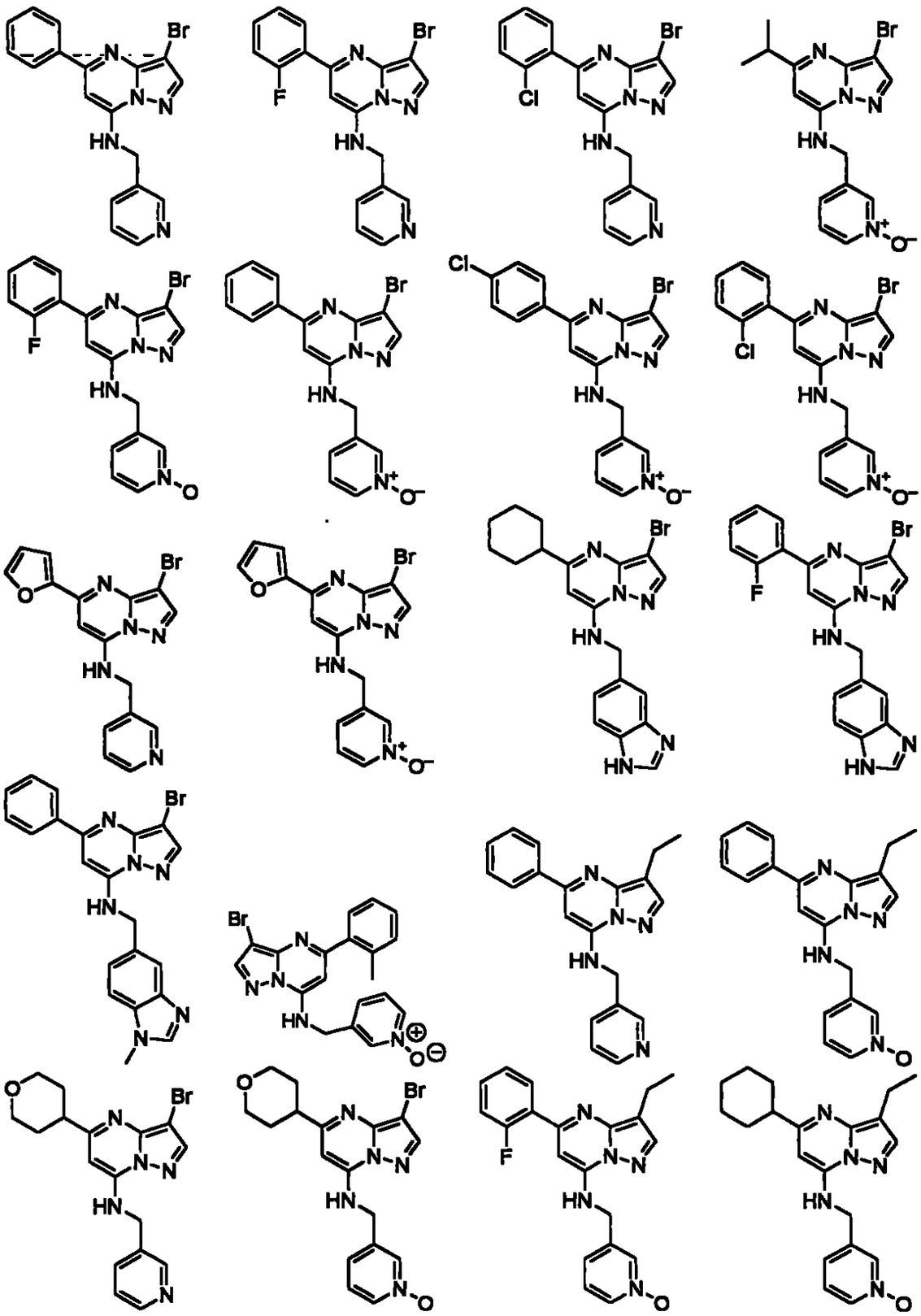


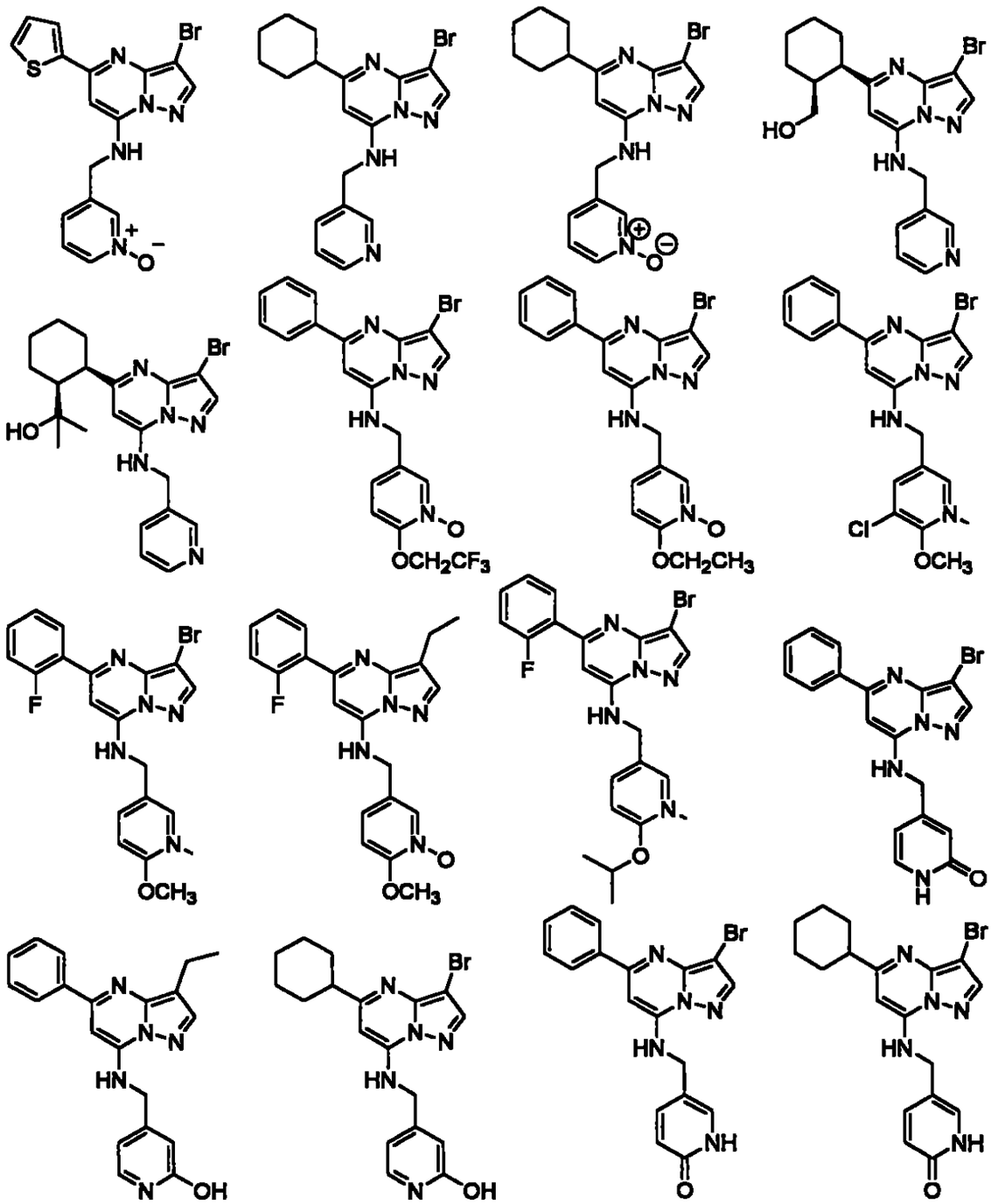
952
955

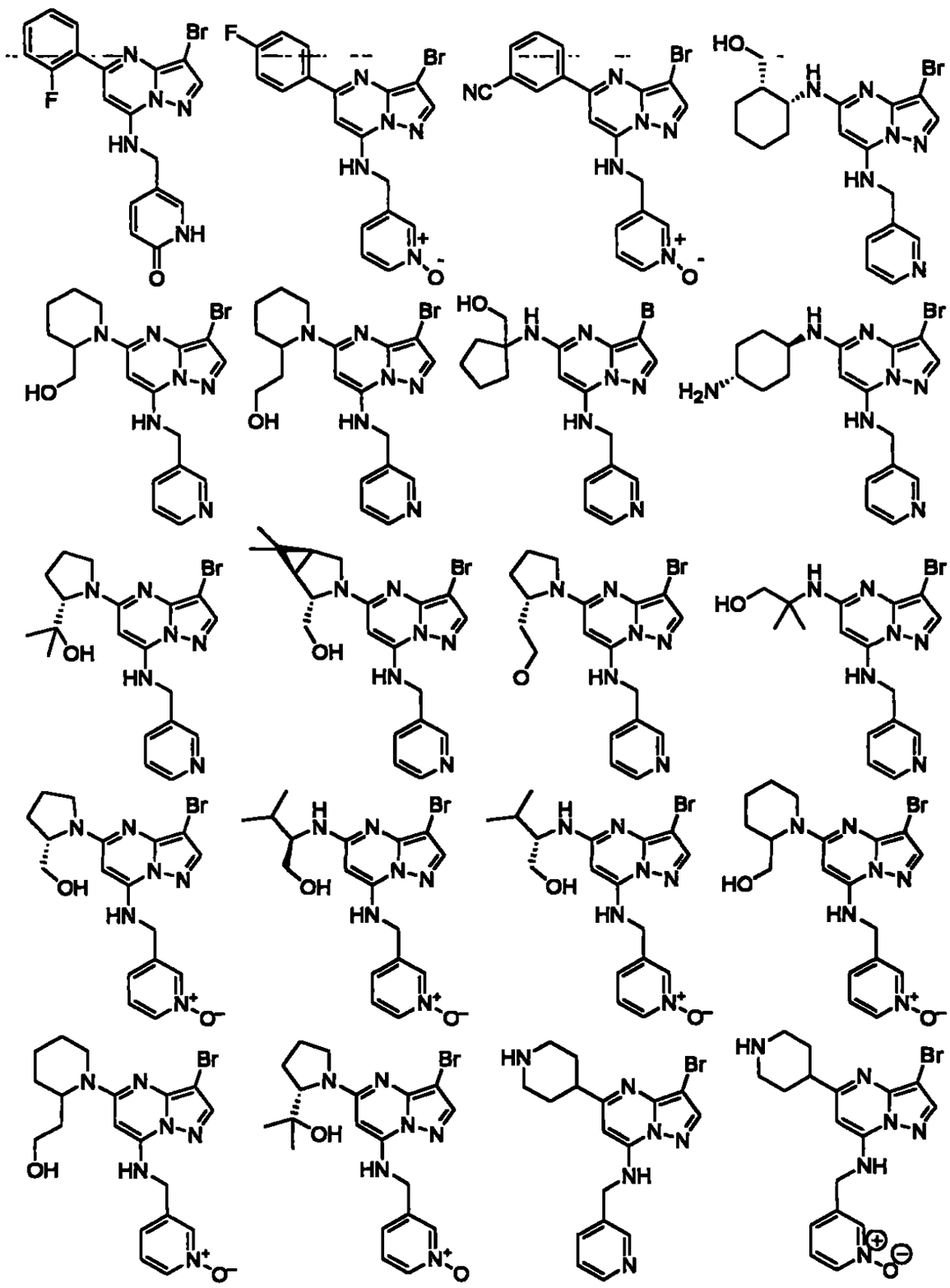


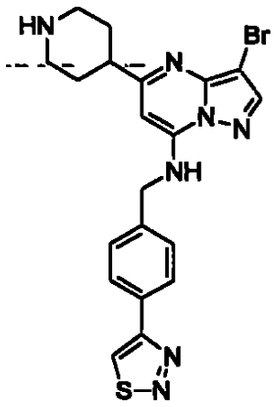
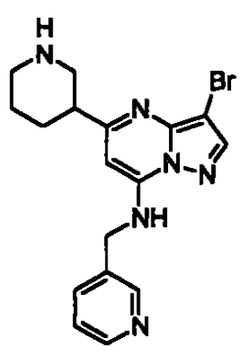
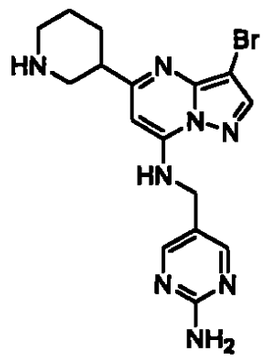
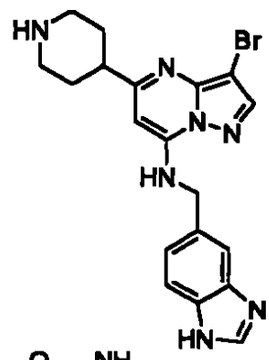
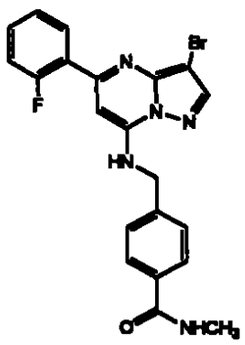
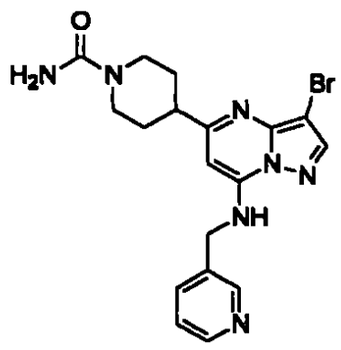
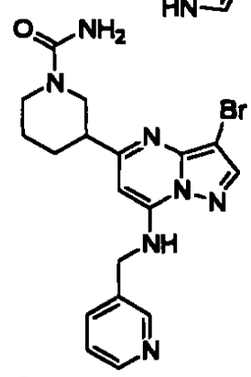
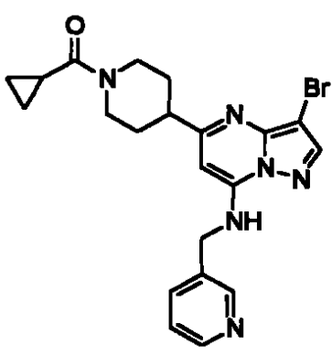
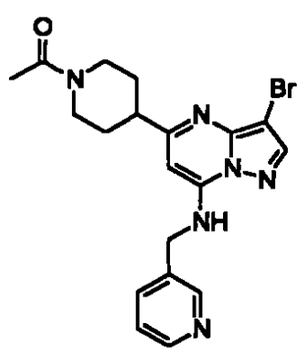
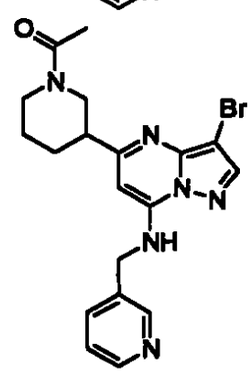
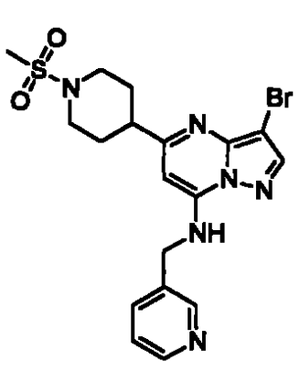
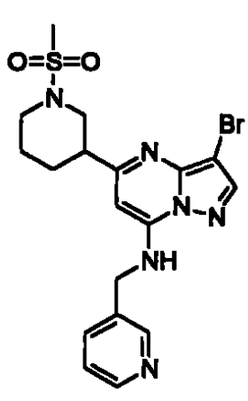
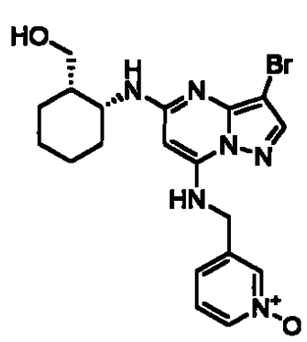
o una sal o solvato farmacéuticamente aceptable del mismo.

29. Un compuesto de la fórmula:



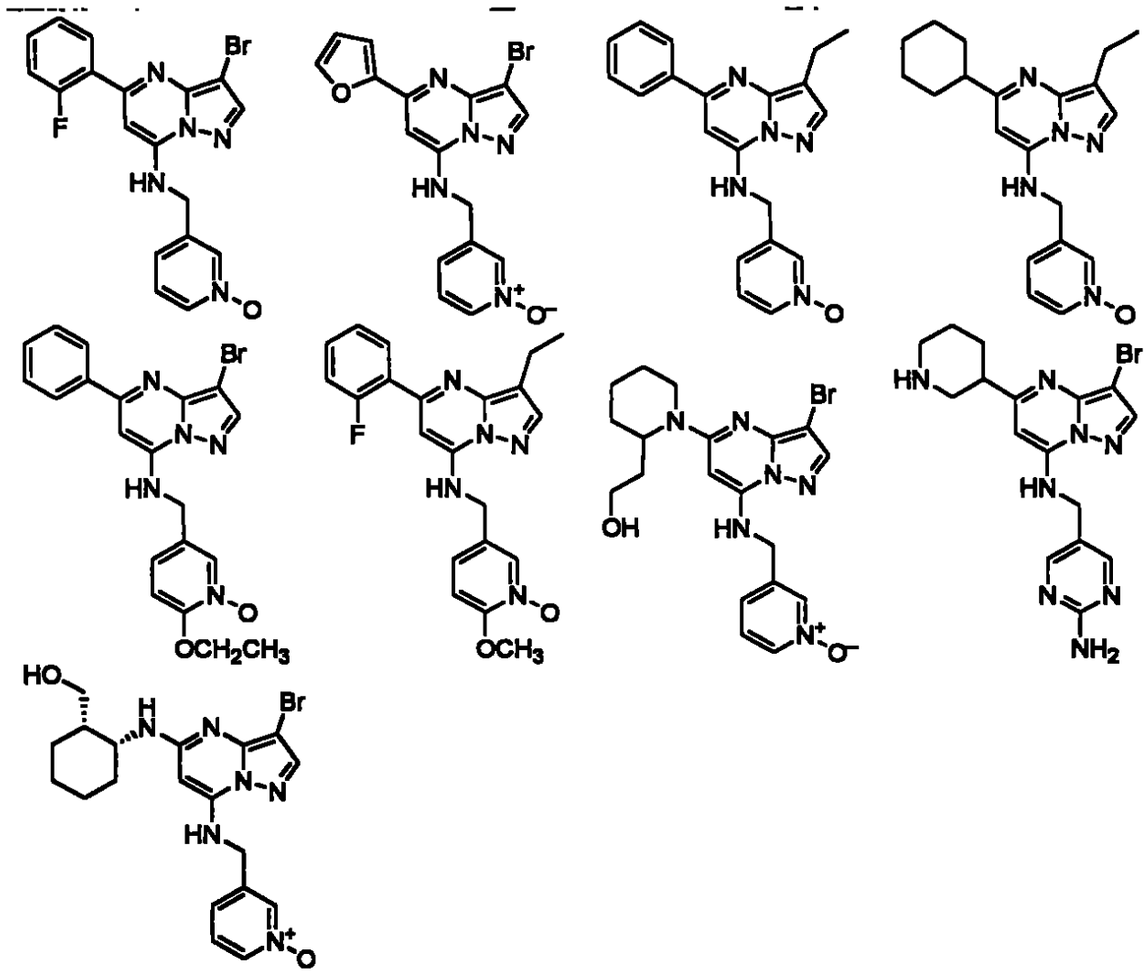




o una sal o solvato farmacéuticamente aceptable del mismo.

30. Un compuesto de la fórmula:



o una sal o solvato farmacéuticamente aceptable del mismo.

31. Un método para inhibir una o más quinasas dependientes de ciclina, que comprende administrar una cantidad terapéuticamente eficaz de por lo menos un compuesto de la reivindicación 1 a un paciente que necesita dicha inhibición.

32. Un método para tratar una o más enfermedades asociadas con la quinasa dependiente de ciclina, que comprende administrar una cantidad terapéuticamente eficaz de por lo menos un compuesto de la reivindicación 1, a un paciente que necesita dicho tratamiento.

33. El método de la reivindicación 32, donde dicha quinasa dependiente de ciclina es CDK2.

34. El método de la reivindicación 32, donde dicha quinasa dependiente de ciclina es la proteína quinasa activada por mitógeno (MAPK/ERK).

35. El método de la reivindicación 32, donde dicha quinasa dependiente de ciclina es la glicógeno sintasa quinasa 3 (GSK3beta).

36. El método de la reivindicación 32, donde dicha enfermedad está seleccionada del grupo que consiste en:

cáncer de vejiga, mama, colon, riñón, hígado, pulmón, células pequeñas de pulmón, carcinoma de esófago, de vesícula, de ovario, de páncreas, de estómago, de cuello uterino, de tiroides, de próstata, y de piel incluyendo carcinoma de células escamosas;

leucemia, leucemia linfocítica aguda, leucemia linfoblástica aguda, linfoma de células B, linfoma de células T, linfoma de Hodgkins, linfoma no Hodgkiniano, tricoleucemia y linfoma de Burkett;

leucemia mielógeno agudo y crónico, síndrome mielodisplástico y leucemia promielocítica;

fibrosarcoma, rabdomiosarcoma;

astrocitoma, neuroblastoma, glioma y schwannomas;

melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderoma pigmentosa, queratoctantoma, cáncer folicular de tiroides y sarcoma de Kaposis.

37. Un método para el tratamiento o de una o más enfermedades asociadas con quinasa dependiente de ciclina, que comprende administrar a un mamífero que necesita dicho tratamiento

una cantidad de un primer compuesto, que es un compuesto de la reivindicación 1, o una sal o solvato del mismo farmacéuticamente aceptable; y

una cantidad de por lo menos un segundo compuesto, donde dicho segundo compuesto es un agente anti-cáncer;

donde las cantidades del primer compuesto y de dicho segundo compuesto

962

dan como resultado un efecto terapéutico.

38. El método de la reivindicación 37, que comprende además terapia de radiación.

39. El método de la reivindicación 37, donde dicho agente anti-cáncer está seleccionado del grupo que consiste en un agente citostático, cisplatina, doxorubicin, taxotere, taxol, etoposide, CPT-11, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epofilones, tamoxifen, 5-fluoruracilo, metoxtrexato, 5FU, temozolomida, ciclofosfamida, SCH 66336, R115777, L778,123, BMS 214662, Iressa, Tarceva, anticuerpos para EGFR, Gleevec, intron, ara-C, adriamicina, citoxan, gemcitabine, Uracilo mostaza, Clormetina, Ifosfamida, Melfalan, Clorambucil, Pipobroman, Trietilenmelamina, Trietientiofosforamina, Busulfan, Carmustina, Lomustina, Ereptozocina, Dacarbazina, Floxuridina, Citarabina, 6-Mercaptopurina, 6-Tioguanina, fosfato de Fludarabina, oxaliplatina, leucovirina, ELOXATIN™, Pentostatina, Vinblastina, Vincristina, Vindesina, Bleomicina, Dactinomicina, Daunorubicina, Doxorubicina, Epirubicina, Idarubicina, Mitramicina, Desoxicoformicina, Mitomicina-C, L-Asparaginasa, Teniposida 17α-Etinilestradiol, Dietilstilbestrol, Testosterona, Prednisona, Fluoximesterona, propionato de Dromostanolona, Testolactona, Megestrolacetato, Metilprednisolona, Metiltestosterona, Prednisolona, Triamcinolona, Clorotrianiseno, Hidroxiprogesterona, Aminoglutetimida, Estramustina, acetato de Medroxiprogesterona, Leuprolida, Flutamida, Toremifeno, goserelina, Cisplatina, Carboplatina, Hidroxiurea, Amsacrina, Procarbazina, Mitotano, Mitoxantrona, Levamisol, Navelbeno, CPT-11, Anastrazol, Letrazol, Capecitabina, Reloxafina, Droloxafina, o Hexametilmelamina.

40. Una composición farmacéutica que comprende una cantidad terapéuticamente eficaz de por lo menos un compuesto de la reivindicación 1, en combinación con por lo menos un portador farmacéuticamente aceptable.

41. La composición farmacéutica de la reivindicación 38, que comprende adicionalmente uno o más agentes anti-cáncer seleccionados del grupo que consiste en un agente citostático, cisplatina, doxorubicina, taxotere, taxol, etoposida, CPT-11, irinotecan, camptostar, topotecan, paclitaxel, docetaxel, epotilonas, tamoxifen, 5-fluoruracilo, metoxtrexato, 5FU, temozolomida,

960
963

ciclofosfamida, SCH 66336, R115777, L778,123, BMS 214662, Iressa, Tarceva, anticuerpos para EGFR, Gleevec, intron, ara-C, adriamicina, citoxan, gemcitabina, Uracilo mostaza, Clormetina, Ifosfamida, Melfalan, Clorambucil, Pipobroman, Trietilenmelamina, Trietilentiofosforamina, Busulfan, Carmustina, Lomustina, Estreptozocina, Dacarbazina, Floxuridina, Citarabina, 6-Mercaptopurina, 6-Thioguanina, fosfato de Fludarabina, Pentostatina, Vinblastina, Vincristina, Vindesina, Bleomicina, Dactinomicina, Daunorubicina, Doxorubicina, Epirubicina, Idarubicina, Mitramicina, Desoxicoformicina, Mitomicina-C, L-Asparaginasa, Teniposida 17α-Etinilestradiol, Dietilstilbestrol, Testosterona, Prednisona, Fluoximesterona, propionato de Dromostanolona, Testolactona, Megestrolacetato, Metilprednisolona, Metiltestosterona, Prednisolona, Triamcinolona, Clorotrianiseno, Hidroxiprogesterona, Aminoglutetimida, Estramustina, acetato de Medroxiprogesterona, Leuprolida, Flutamida, Toremifeno, goserelina, Cisplatina, Carboplatina, Hidroxiurea, Amsacrina, Procarbazina, Mitotano, Mitoxantrona, Levamisol, Navelbeno, CPT-11, Anastrazol, Letrazol, Capecitabina, Reloxafina, Droloxafina, o Hexametilmelamina.

42. Un compuesto de la reivindicación 1, en forma purificada.

p: SCHERING CORPORATION * PHARMACOPEIA, INC.

Resumen de la Invención

En sus muchas realizaciones, la presente invención provee una nueva clase de compuestos de pirazolo[1,5-a]pirimidina como inhibidores de las quinasas dependientes de ciclina, métodos para preparar dichos compuestos, composiciones farmacéuticas que contienen uno o más de dichos compuestos, métodos para la preparación de formulaciones farmacéuticas que comprenden uno o más de dichos compuestos, y métodos para el tratamiento, prevención, inhibición, o mejoría de una o más enfermedades asociadas con las CDK usando dichos compuestos o composiciones farmacéuticas.

PATENT DEPARTMENT
962
965

PATENT COOPERATION TREATY

APR 07 2004

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
Kalyanaraman, P.S.
SCHERING CORPORATION
PATENT DEPARTMENT K-6-1-1990
2000 Galloping Hill Road
Kenilworth, NJ 07033-0530
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

CHECK FILE

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	06/04/2004
Applicant's or agent's file reference: OC01617K	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US03/27555	03/09/2003	04/09/2002

Applicant

SCHERING CORPORATION et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report 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 examination report. 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 invention 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 IPEA/

European Patent Office, Gitschiner Str. 103
D-10969 Berlin - Germany
Tel.: (+49-30) 25901-0
Fax: (+49-30) 25901-840

Authorized officer

HALBARTSCHLAGER M
Tel. (+49-89) 2399 2828

Office européen des brevets · Europäisches Patentamt · European Patent Office

962
966

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
OC01617K		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US03/27555	03/09/2003	04/09/2002
International Patent Classification (IPC) or national classification and IPC		
C07D487/04		
Applicant		
SCHERING CORPORATION et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 2 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consists of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/03/2004	01/04/2004
Name and mailing address of the IPEA/	Authorized officer
European Patent Office, Gitschiner Str. 103 D-10969 Berlin - Germany Tel.: (+49-30) 25901-0 Fax: (+49-30) 25901-840	DE BUNDEL E R J Tel. (+49-89) 2399 2828

Form PCT/IPEA/409 (cover sheet) P20476 (October 2002)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US03/27555

I. Basis of the report

The basis of this international preliminary examination is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT); see also international search report).

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in the independent claims, which have been the subject of an international search report, meets the criteria mentioned in Article 33(1) PCT, i.e. appears to be novel, to involve an inventive step and to be industrially applicable.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/27555

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/519 //(C07D487/04,239:00,231:00)

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

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)
CHEM ABS Data, EPO-Internal, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 628 559 A (BEIERSDORF LILLY GMBH) 14 December 1994 (1994-12-14) cited in the application page 3, formula (I) page 4, partial structure (A) page 7, partial structure (L) page 8, line 46 - line 48	27-30
A	US 6 107 305 A (BURSUKER ISIA ET AL) 22 August 2000 (2000-08-22) cited in the application column 1, formula (I) column 1, line 24 - line 25 column 11, line 19	27-30

-/—

[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
17 December 2003	29/12/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hoepfner, W

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 03/27555

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 413 974 B1 (BORCHERDING DAVID R ET AL) 2 July 2002 (2002-07-02) cited in the application abstract column 15, formula (I) claim 26	27-30
A	WO 02 50079 A (ULIBARRI GERARD ;LONCHAMPT MARIE-ODILE (FR); THURIEAU CHRISTOPHE () 27 June 2002 (2002-06-27) cited in the application page 1, line 1 - line 3 page 5, formula (I) page 8, line 21	27-30

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

Continuation of Box I.2

Claims Nos.: 1-26,31-42

Present claims 1-26 and 31-42 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a relatively limited proportion of the compounds 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.

In particular:

the vast number of values for most of the variables, in conjunction with their cascading meanings and especially the presence of open definitions such as "alkyl", "arylalkyl" or "heterocyclyl" and the like render the scope of the invention, for which protection is sought, ill-defined and obscure. Consequently, an exhaustive and complete search is precluded for practical and economical reasons. The search was based upon though not limited to examples and tables given in the description and to the subject-matter of claims 27-30 (cf. Arts. 6, 15 and Rule 33 PCT).

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 03/27555

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 31-39 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 1-26,31-42
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No
PCT/US 03/27555

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0628559 A	14-12-1994	EP 0628559 A1	14-12-1994
		CA 2125458 A1	11-12-1994
		DE 69430279 D1	08-05-2002
		DE 69430279 T2	06-03-2003
		ES 2174863 T3	16-11-2002
		JP 7002860 A	06-01-1995
		US 5571813 A	05-11-1996
		US 5602136 A	11-02-1997
		US 5602137 A	11-02-1997
US 6107305 A	22-08-2000	AU 747705 B2	23-05-2002
		AU 1629799 A	05-07-1999
		CA 2314355 A1	24-06-1999
		EP 1043998 A1	18-10-2000
		JP 2002508324 T	19-03-2002
		WO 9930710 A1	24-06-1999
		ZA 9811178 A	07-06-2000
US 6413974 B1	02-07-2002	NONE	
WO 0250079 A	27-06-2002	FR 2818278 A1	21-06-2002
		AU 2509602 A	01-07-2002
		CA 2432417 A1	27-06-2002
		EP 1345941 A1	24-09-2003
		WO 0250079 A1	27-06-2002

968
971

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

		USUARIO	RADICADOR
PATENTE DE INVENCIÓN	MODELO DE UTILIDAD	( )	( )
- Indicación de que se solicita la concesión de una patente.		( )	( )
- Datos de identificación del solicitante o de la persona que se 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 o 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 solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solcitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable:

SUPERINDUSTRIA Y COMERCIO
Radicacion : 05020516 00000000
Fecha (AMD): 2005-03-04 17:26:23 Folios: 967
Tramite : 411 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Fecha:

Industria y Comercio
SUPERINTENDENCIA

Folio 969 Folio 969

2020
Bogotá, D.C.,

Doctor(a)
CARLOS R. OLARTE

Oficio Nº 12670

ASUNTO:		
	Radicación Nº	05-20516
	Solicitud internacional	PCT/US2003/027555
	Fecha inicio fase nacional	04/04/2003
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

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:

- La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente de los inventores a los solicitantes o a sus causantes. Art. 26-k) Decisión 486/00.

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 Única Nº 10 de 2001.

ALIX CARRENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 29 ABR. 2005

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador: 382 0840
Fax: 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia